

1 **Global myocardial longitudinal strain in a general population. Associations**
2 **with blood pressure and subclinical heart failure. The Tromsø Study**

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18

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21

1 **Abstract**

2 **Purpose:** The early detection of subclinical myocardial dysfunction can contribute to the treatment and
3 prevention of heart failure (HF). The aim of the study was to (i) describe myocardial global longitudinal strain
4 (GLS) patterns in a large general population sample from Norway and their relation to established cardiovascular
5 disease (CVD) risk factors; (ii) to determine its normal thresholds in healthy individuals and (iii) ascertain the
6 relation of myocardial GLS to stage A subclinical heart failure (SAHF).

7 **Methods:** Participants (n=1855) of the 7th survey of the population-based Tromsø Study of Norway (2015-2016)
8 with GLS measurements were studied. Linear and logistic regression models were used for assessment of the
9 associations between CVD risk factors and GLS.

10 **Results:** Mean GLS (SD) in healthy participants was -15.9 (2.7)% in men and -17.8 (3.1)% in women. Among
11 healthy subjects, defined as those without known cardiovascular diseases and comorbidities, GLS declined with
12 age. An increase of systolic blood pressure (SBP) of 10 mm Hg was associated with a 0.2% GLS reduction.
13 Myocardial GLS in individuals with SAHF was 1.2% lower than in participants without SAHF (p<0.001).

14 **Conclusion:** Mean myocardial GLS declines with age in both sexes, both in a general population and in the
15 healthy subsample. SBP increase associated with GLS decline in women. Our findings indicate high sensitivity
16 of GLS for early subclinical stages of HF.

17

18 **Key words:** Global longitudinal strain, heart failure, systole, arterial hypertension, echocardiography,
19 epidemiology

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21

1 **Introduction**

2 Cardiovascular disease (CVD) is a leading cause of death worldwide [1]. Global myocardial longitudinal strain
3 (GLS) is a derived deformation parameter, enabling detection of subtle left ventricular (LV) function
4 abnormalities. GLS is superior to LV ejection fraction (LVEF) in prediction of cardiovascular mortality in
5 patients with chronic kidney disease [2], all-cause mortality in patients with systolic heart failure (HF) [3] and
6 atrial fibrillation [4]. Furthermore, myocardial GLS was found to be an independent predictor of the adverse
7 outcomes after acute myocardial infarction (MI) [5], infective endocarditis [6], aortic stenosis [7], hypertrophic
8 cardiomyopathy [8] and stroke [9]. The role of myocardial GLS in CVD mortality prediction in populations with
9 low CVD risk has also been investigated [10]. In patients with arterial hypertension, myocardial GLS was related
10 to structural remodeling of the LV [11]. Kuznetsova et al. have recently shown that high mean arterial pressure
11 was associated with a decline in GLS over a follow-up of 4.7 years [12]. However, there are few studies of the
12 associations between systolic blood pressure (SBP), hypertension treatment and GLS in general unselected
13 populations.

14 To date there is no consensus, and thus no established clinical guidelines [13,14], as to what constitutes cut
15 points for normal myocardial GLS, however peak GLS level of -20% mentioned as expected in healthy persons
16 [13]. Assessment of cut off points of normal myocardial GLS in healthy individuals have produced varying
17 results. Most population studies find higher reference values in healthy subjects [15,16].

18 Stage A subclinical HF (SAHF) define individuals with absence of clinical symptoms or structural heart disease
19 but presence of risk factors for HF [17]. SAHF progression is associated with impairment of structural and
20 functional state of the heart over time with progression to the next stage of HF [18]. Myocardial GLS has
21 improved prediction of subsequent clinical HF in patients with Stage B subclinical HF [19] and myocardial GLS
22 is already known to be related to SAHF in high risk groups [20-22]. However, whether this applies to the whole
23 SAHF group is, to the best of our knowledge, unknown. Whether GLS adds information in SAHF group beyond
24 CVD risk factors and self-reported dyspnea symptoms in a general population has yet to be elucidated.

25 The main aim of our study is to describe peak-myocardial GLS in a large general population sample from
26 Norway and their relation to established CVD risk factors. Secondary aims are to determine GLS normal
27 thresholds in healthy individuals and the relation of myocardial GLS to SAHF.

28

1 **Methods**

2 **Study population**

3 The Tromsø Study is a prospective cohort study, which was initiated in 1974 with the aim of assessing the role
4 of known modifiable risk factors for CVD in Northern Norway and detection of new targets for prevention of
5 CVD. The design of the study was described in previous publications [23]. Seven consecutive surveys have been
6 conducted. Our study sample included 840 men and 1015 women from 7th survey in the Tromsø Study who
7 underwent echocardiography and had myocardial GLS data (Fig. 1). We excluded those with missing values on
8 risk factors (n=108) leaving 1747 individuals aged 40-99 years for the main analyses.

9

10 **Data collection**

11 Self-reported history of MI, HF, atrial fibrillation, angina, stroke, diabetes, chronic obstructive pulmonary
12 disease was collected by questionnaires. Additionally, we included those who experienced atrial fibrillation
13 during echocardiography as atrial fibrillation “positive” individuals. Participants with HbA1c $\geq 6.5\%$ were
14 treated as having diabetes regardless of self-reported status. Breathlessness was assessed by the modified UK
15 Medical Research Council (mMRC) breathlessness/dyspnea scale [24].

16 Blood pressure (BP) was measured three times with 1-minute intervals using an automated device Dinamap Pro
17 care 300 Monitor (GE Medical Systems Information Technologies, Tampa, FL, USA). The mean of the last two
18 readings was used in the analysis. Hypertension was defined as SBP ≥ 140 mm Hg, diastolic blood pressure
19 (DBP) ≥ 90 mm Hg or self-reported use of antihypertensive medication. Metabolic syndrome was defined
20 according to American Heart Association (AHA)/National Heart, Lung and Blood Institute statement [25].

21 **Study groups definitions**

22 Healthy persons were defined as those without known cardiovascular diseases and comorbidities. We excluded
23 those with hypertension, diabetes, atrial fibrillation, HF, angina, MI, stroke, chronic obstructive pulmonary
24 disease and ejection fraction of the left ventricle (LV EF) $< 50\%$ leaving a “healthy” subsample of 1068
25 individuals (Fig. 1). To assess the effect of increasing echocardiographic pathology by age we additionally
26 excluded from the healthy subsample those with severe valve dysfunction, LV or left atrial (LA) enlargement or
27 severe tricuspid regurgitation (> 2.8 m/s).

1 For defining the SAHF individuals we excluded subjects (n=1146) with known CVD (previous history of MI,
2 HF or stroke) and echocardiographic geometric LV abnormalities (Left ventricular myocardial mass index
3 (LVMMi) >50 in men and >47 in women; relative LV wall thickness (rwt) >0.42 or rwt ≤0.42 with LVMMi >50
4 in men and >47 in women), LV EF <50%, and severe valve dysfunction (mitral and aortic stenosis and
5 regurgitation ≥ grade 3) (Fig. 1). Thus, we identified a subset of 709 individuals who may include those with
6 SAHF. In the American College of Cardiology Foundation/AHA guidelines [17], SAHF is defined as
7 the presence of at least one of the following conditions: diabetes, metabolic syndrome, obesity, arterial
8 hypertension or angina. Applying these criteria, we identified 220 individuals with SAHF (Fig. 1).

10 **Echocardiography imaging**

11 In the Tromsø 7 study echocardiography was performed by a qualified sonographer using a GE Vivid E9 (GE
12 Medical, Horten, Norway) ultrasound scanner. Offline image reading using EchoPac software (EchoPac version
13 113; GE Medical, Horten, Norway) was performed by one reader (M.S.).

14 **Conventional Echocardiography**

15 Cine-loops were recorded using standard 4-chamber, 2-chamber and long-axis apical views according to a
16 prespecified protocol [26]. We obtained the images at a framerate of 50-70 frames per second. Ultrasound
17 examinations were performed according to American Society of Echocardiography (ASE) and European
18 Association of Cardiovascular Imaging (EACVI) guidelines [13] in the left lateral decubitus position. M-Mode
19 images were aligned in the parasternal long axis view and recorded in the short axis view. LV myocardial mass
20 was calculated according to ASE guidelines and indexed by height^{2.7} [13]. LVEF and LA volume were
21 calculated using the biplane Simpson's method. LA volume was indexed (LAVi) by body surface area (BSA)
22 [27]. Mitral valve Doppler measurements were performed with a Doppler sample volume of 2-mm placed
23 between the tip of the mitral leaflets in the apical 4-chamber view. We adjusted the spectral gain until the flow
24 curves became clear [28]. The insonation angle for Doppler measurements was kept perpendicular toward the
25 mitral inflow. Maximal velocity flow was measured in early diastole and after atrial p-wave.

26 Tissue Doppler parameters such as peak septal and lateral e' were derived from apical 4-chamber view with 2-
27 mm sample volume located at the septal and lateral side of the mitral annulus. Abnormal echo parameters
28 considered as tricuspid regurgitation velocity >2.8 m/s; LAVi >34 ml/m² [29].

29

1 **Two-Dimensional strain**

2 Two-dimensional strain was analyzed according to EACVI/ASE common standards for 2D speckle tracking
3 echocardiography [30]. The endo- and epicardial borders were initially traced with the use of automated function
4 imaging. Myocardial GLS values were obtained from averaging of endo- mid- and epicardial layer's GLS values
5 from three apical views based on 17-segment model. Images were checked visually for clear visibility of the
6 endo- and epicardial border during the entire cardiac cycle. Attention was paid to accurate placement of region
7 of interest (ROI) with the aim of avoiding inclusion of extracardiac structures. Furthermore, we paid attention
8 not to include papillary muscles in contour of LV or the fibrous part of the basal inferoseptum or LV outflow
9 tract [31]. ROI was visually assessed and manually adjusted in case of inappropriate tracking. Views with more
10 than two segments with inappropriate tracking were excluded from the analysis.

11 **Statistical methods**

12 The study population included individuals aged from 40 to 99 years divided in 10-year age groups. Baseline
13 characteristics of the study participants were described with the use of means with standard deviations and
14 proportions. For analyses of associations between myocardial GLS and SBP we divided study population by the
15 following SBP groups: <120, 120-129, 130-139, 140-159, 160-169, 170-179 and \geq 180 mm Hg.

16 According to the sex-specific SBP groups, means for myocardial GLS were adjusted for age using linear
17 regression analysis. Absolute means were tabulated for those aged 63 years. Comparisons between groups were
18 performed by analysis of variance (ANOVA), χ^2 test and Fisher's exact test. For analysis of GLS change by age
19 we used weighted linear regression. The "Weight" variable for regression equation was estimated from number
20 of individuals in each age group. Lower limit of normal (LLN) myocardial GLS for "healthy" subpopulation was
21 defined as absolute mean GLS minus 1.96*standard deviation. Bootstrapping with 1000 samples was used to
22 define upper 97.5th and lower 2.5th percentiles for LLN with confidence intervals [32]. We used quantile
23 regression for estimation of the p-value for trend of LLN change by age. Logistic regression models were
24 applied to estimate odds ratios (OR) for different risk factors of myocardial GLS below age and sex-specific
25 LLN (abnormal GLS). The OR for each of the following predictors (BMI, history of: MI, atrial fibrillation,
26 angina, diabetes, stroke, arterial hypertension and breathlessness scale) were estimated separately.

27 Intra- and inter-reader variability of myocardial GLS was assessed in recordings of 27 of 30 randomly selected
28 participants. Three individuals were excluded due to inappropriate image quality. Intra-reader variability was
29 assessed in repeated GLS measurements by one reader (M.S) with 3-months intervals. To assure external

1 validity of measurements as well as internal inter-reader variability was assessed with two readers (M.S. and A.R.
2 and presented as intra-class correlation coefficients (ICC) and mean difference \pm SD. Coefficient of repeatability
3 (CR) was calculated using the formula $2.77*SD_w$ with SD_w as the within-subject standard deviation. Visual
4 assessment of inter-observer variability was performed with use of a Bland-Altman plot.

5 A two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS
6 statistical package, version 9.4 (SAS Institute, Cary, NC).

7 **Ethical considerations**

8 The Tromsø Study protocol was approved by the Regional Committee for Medical and Health Research Ethics,
9 North Norway (2014/940/REK Nord) and was performed according ethical standards outlined in the 1964
10 Declaration of Helsinki. All participants of the study provided signed informed consent.

11

1 **Results**

2 **Descriptive characteristics**

3 The descriptive echocardiographic and clinical characteristics of the study population are presented in 10-year
4 age groups (Table 1). Study sample included 840 (45.3%) men and 1015 (54.7%) women. The prevalence of
5 self-reported pathology increased across the entire age range except for MI, diabetes and angina pectoris which
6 have the highest prevalence in 70-79 years individuals. Of the echocardiographic characteristics: LVMMi,
7 LAVi, Mitral E-wave deceleration time (DT), E/e' ratio showed a linear relation to age, while LVEF and E/A
8 ratio did not.

10 **Myocardial GLS in The Tromsø 7 Study**

11 In our general population sample, mean myocardial GLS declined with age in both men and women (Fig. 2).

13 **Myocardial GLS of the healthy participants**

14 The prevalence of healthy individuals by age from the Tromsø 7 study sample according to the
15 healthy/unhealthy criteria is presented in Table 2. We found that the prevalence of healthy women was stable
16 between 40 and 59 with a decline after 60 years of age (p for change of healthy proportions by age <0.001). In
17 men the decrease of healthy individuals starts earlier than in women but then follows the same slope by age
18 ($p<0.001$). There was no interaction between age group and sex ($p=0.457$).

19 Mean myocardial GLS (SD) in healthy participants ($n=1068$) was -15.9 (2.7)% in men ($n=451$) and -17.8 (3.1)%
20 in women ($n=617$). Fig. 2 describes mean levels of myocardial GLS in healthy participants according to age and
21 sex. Healthy women had higher values of myocardial GLS than men in all age groups. Significant change of
22 mean myocardial GLS by age was observed for both sexes ($p=0.001$ and <0.001 in men and women
23 respectively). In the healthy subgroup without echo abnormalities the age effect on GLS was no longer
24 significant in men (p -value for men 0.179, for women <0.001).

25 The comparison of GLS in healthy versus unhealthy individuals is demonstrated in Online Resources 2 (for men)
26 and 3 (for women) as well as the numbers of individuals with measured myocardial GLS (Online Resource 4).

27 **Abnormal myocardial GLS in the Tromsø 7 Study sample**

28 With the use of mean myocardial GLS values in the healthy individuals aged 40-99 years, myocardial GLS LLN
29 equaled -10.6% for men and -11.7% for women. Data shown in table 3 estimates LLN with bootstrapped 2.5th
30 and 97.5th CI by age groups and sex. A tendency of declining LLN with the age was still present in both men and

1 women, however the differences were non-significant (p-value for age trend were 0.522 and 0.801 for men and
2 women respectively).

3

4 **Abnormal myocardial GLS and risk factors**

5 We estimated OR for factors possibly associated with abnormal myocardial GLS (Table 4). Individuals with
6 diabetes had 2.91-fold (95% CI 1.52, 5.55) increased risk of having abnormal myocardial GLS. All other
7 predictors had significant effect on abnormal GLS excluding hypertension and mMRC scale ≥ 2 . Table 5 shows
8 the difference in GLS for each of the significant predictors of GLS. The lowest myocardial GLS (SD) of -14.3
9 (3.5)% was found in individuals with self-reported HF.

10

11 **Myocardial GLS and SBP**

12 Myocardial GLS in women declines as SBP increase (Fig. 3). In men with and without antihypertensive
13 treatment differences in myocardial GLS between SBP groups were non-significant (p=0.206 and p=0.276 for
14 untreated and treated men respectively). Men and women with BP treatment had lower values of myocardial
15 GLS than those without treatment. In linear regression analysis adjusted for age and sex, 10 mmHg increase of
16 SBP resulted in a 0.2% decrease of myocardial GLS ($\beta=0.235$; p<0.001). After adjustment for age, sex, BMI,
17 history of: MI, atrial fibrillation, angina, diabetes, stroke, arterial hypertension and breathlessness scale, SBP
18 remained an independent predictor of myocardial GLS decline ($\beta=0.146$; p<0.001).

19

20 **Subclinical HF and myocardial GLS**

21 In the subgroup without LV echocardiographic abnormalities (total n=709), 120 (29.1%) of women and 100
22 (33.8%) of men were categorized as SAHF individuals. Mean myocardial GLS (SD) (n) in those with SAHF
23 were -16.7 (2.5)% (n=220) and -17.9 (2.6)% (n=489) in participants without SAHF (p<0.001). In the SAHF
24 positive group 3.2% reported dyspnea by exertion (mMRC scale ≥ 2 , versus 1.6% in individuals without SAHF
25 (p=0.257).

26

27 **Inter-observer variability of GLS**

28 We benchmarked the single reader (MS) against another clinical echocardiographer (AR) who had extensive
29 experience of routine measurement of myocardial GLS. Analyses of myocardial GLS reproducibility (Online

1 Resource 1) and Bland-Altman plots visual assessment (Fig. 4) showed good to excellent intra- and inter-
2 observer agreement levels.

3

4 **Discussion**

5 This is the first study to our knowledge to explore GLS patterns and its associations to CVD risk factors and
6 SAHF in a general population. The main results of this study were the following: (1) mean GLS in healthy
7 participants aged 40-99 years was -15.9 (2.7)% in men and -17.8 (3.1)% in women with significant change of
8 GLS by age in both sexes; (2) GLS LLN was estimated as -10.6% for men and -11.7% for women aged 40-99
9 years; (3) GLS declines in women with increase of SBP; (4) Increase of SBP by 10 mm Hg results in 0.2% GLS
10 reduction in age and sex adjusted regression model; (5) Myocardial GLS in individuals with SAHF was 1.2%
11 lower ($p < 0.001$) than in participants without SAHF.

12 **Myocardial GLS in general population**

13 Our findings of a decline in myocardial GLS with age confirmed previous studies describing the same age and
14 sex related myocardial GLS patterns [15,33]. However, there was a number of controversial reports with no
15 detected myocardial GLS age change in general or healthy samples [34-36]. Additionally, we found that change
16 in myocardial GLS by age disappears in men when individuals with echo abnormalities were excluded from the
17 “healthy” subgroup.

18 Mean myocardial $GLS \pm SD$ values derived from averaging of endo- mid- and epicardial layer's GLS values in
19 healthy participants in the Tromsø 7 study sample were similar to those published in Dalen et al. work (-
20 $15.9 \pm 2.3\%$ in men and $-17.4 \pm 2.3\%$ in women) based on data of 1266 healthy individuals participated in HUNT
21 study of Norway [37]. However, other authors found significantly higher absolute values of mean myocardial
22 GLS in healthy subjects. One of the possible reasons of different GLS values found in healthy individuals among
23 the studies is the use of the different myocardial layers (endo- midwall or epicardial layer) for calculating the
24 GLS since recent reports show endocardial GLS approximately 30% higher than epicardial GLS [35]. In the
25 guidelines GLS level of -20% is considered as the borderline in healthy subjects [13]. Guideline based GLS LLN
26 values by vendor (GE Software) were higher than values we found. It is also important that myocardial GLS
27 values of our study were derived using EchoPac version (EchoPac ver. 113) which was newer than these listed in
28 the guidelines [13]. Castel et al. reported that upgrades of speckle tracking software were associated with
29 significant changes in GLS values [38]. It is worth to mention that sample sizes in HUNT and Tromsø studies

1 were much larger than in the other studies. Thus, Alcidi et al. reported myocardial GLS \pm SD level of $-22.7\pm 1.8\%$
2 in a sample of 266 healthy individuals [15]. The authors found significant change of myocardial GLS by age
3 even though the participants age (mean \pm SD) was 39.2 ± 17.5 years compared with 63.0 ± 10.8 in Tromsø 7
4 population sample.

5 Taking into the account the small sample size of “healthy” individuals in higher age groups, we assessed
6 bootstrapped 95% CI for myocardial GLS LLN. We found no significant change of LLN by age neither in men
7 nor women.

8 Our results indicate that subclinical myocardial dysfunction assessment should not be limited to considering
9 hypertension alone, as myocardial GLS is influenced by other comorbidities and risk factors as well. We found
10 that BMI was associated with presence of myocardial GLS below LLN. It was consistent with previous research
11 of Bendiab et al. [39] where most of the risk factors were inversely correlated with myocardial GLS. The BMI
12 has been described as an independent factor for low myocardial GLS, previously [39]. However, the associations
13 between myocardial GLS and self-reported dyspnea symptoms are more complicated. Relatively low myocardial
14 GLS (SD) -14.8 (3.5)% in those with mMRC scale ≥ 2 can be explained by the characteristics of the selected
15 sample and association of abnormal myocardial GLS with diastolic dysfunction and LV filling pressures [40].
16 Another explanation of the low myocardial GLS levels in patients with dyspnea could be the unrecognized
17 systolic dysfunction which prevalence according to earlier reports reaches 15.7% (95% CI 12.9–19.0) in
18 individuals aged 65 years or older [41].

19 **Myocardial GLS and BP**

20 In our study we tried to expand the current knowledge about factors contributing to myocardial GLS decline.
21 SBP was chosen as such as a factor due to its known association to myocardial GLS in different patient groups
22 [16] and the high prevalence of arterial hypertension worldwide. Another important aspect is that myocardial
23 GLS decline in hypertensives reflects subclinical damage of LV structure and function due to early
24 microscarring of the subendocardium, especially in the highly hypertrophied muscles [42]. Furthermore,
25 increased afterload is known to prolong contraction and delay active relaxation [43] and reduce longitudinal
26 strain and strain-rate [44].

27 We have found mean myocardial GLS decline up to -15.9% in patients with arterial hypertension. This value
28 was higher than GLS LLN in both men and women with the significant difference with those without arterial
29 hypertension (GLS = -16.6% , $p < 0.001$). Adjusted for age and sex 10 mm Hg SBP increase was responsible for

1 0.2% of myocardial GLS decrease. This confirmed the association between SBP and myocardial GLS found in
2 earlier studies [45].

3 We assessed the sex-related LV function in hypertensive individuals. Previous reports have found contradicting
4 results [46]. We found that in women myocardial GLS declined from -18.4% in SBP group of <120 mm Hg to -
5 17.1% in those within SBP >180 mmHg (p<0.001). We revealed a similar decline among men, however without
6 significant difference between SBP groups. Presumable cause could be the small number of men with the highest
7 SBP levels (only 9 persons in the SBP >180 mm Hg group). Mean myocardial GLS was lower in the high-
8 normal SBP group of 130-139 mmHg compare to normal SBP groups in both men and women, showing that
9 longitudinal function of LV was already impaired in these groups of study participants. The previous report by
10 Tadic et al. showed that myocardial GLS was lower in high-normal BP individuals with no such BP effect on
11 radial LV function [47]. We revealed that women have larger values of myocardial GLS in both healthy
12 individuals as well as in those with CVD risk factors. Partly it could be explained by pathophysiological
13 diversities between men and women reflected in complex relationships between LV mechanics and sex
14 hormones. Thus, Salem et al. showed that higher levels of testosterone in men were associated with decreased
15 myocardial GLS [48].

16 It is worth to mention that hypertensive individuals are characterized by increased afterload which leads to
17 thickening of the LV wall and LV hypertrophy development [49] as a compensatory mechanism. Some studies
18 demonstrated that decreased longitudinal systolic function cannot be attributed to the afterload increase in
19 patients with arterial hypertension and LV hypertrophy [50], which might be due to low effect of increased
20 blood-pressure on the compensatory hypertrophied ventricle, where the smaller ventricle and thicker walls lead
21 to reduced wall stress. Kim at al. in a study of 145 hypertensive patients [11] showed that different ventricular
22 regions have different susceptibility for stress induced afterload with inhomogeneous development of ventricular
23 hypertrophy. Myocardial GLS has been shown to be lower in ventricular regions with more pronounced LV
24 hypertrophy. Concerning the fact that in our study sample individuals with 70+ years of age had mean LVMMi >
25 47 g/m^{2.7}, we assume that arterial hypertension exerts its negative influence on myocardial GLS through
26 microscarring and insufficient myocardial perfusion in LV hypertrophy.

27 **Myocardial GLS and SAHF**

28 Identification of individuals with SAHF who are at risk of developing advanced HF stages appears to be a
29 promising CVD primary prevention strategy. In most of the cases patients without symptoms are rarely involved

1 in screening procedures until development of later HF stages. In our study we found that mean GLS (SD) in
2 individuals with SAHF -16.7% (2.5)% was lower compared to those without - 17.9% (2.6) ($p<0.001$). The
3 components defining SAHF (elevated SBP, diabetes, obesity or atherosclerosis) were found to be associated with
4 abnormal GLS, possibly indicating the presence of subclinical damage of the myocardium [20,21]. It is worth to
5 mention that myocardial GLS may have benefits in early HF detection because symptoms of HF are not always
6 present in even more advanced HF stages (Stage B HF). Thus, Redfield et al. reported that 14% of patients with
7 dilated cardiomyopathy and LVEF $<50\%$ had never experienced any of HF symptoms [51].

8 **Myocardial GLS and vendor-specific software**

9 Different vendor-specific image postprocessing algorithms were earlier considered as an issue which could
10 potentially limit clinical use of the strain imaging [52]. However, launching of EACVI/ASE Strain
11 Standardization Task Force [30] resulted in increased number of evidence on improvement of concordance in
12 strain imaging between vendors [53]. Yingchoncharoen et al. reported no significant difference of GLS
13 variability in healthy individuals between EchoPac and non-EchoPac software ($p=0.98$) [16]. Based on these
14 findings we assume that values of myocardial GLS in healthy population of our study is valid not only for
15 EchoPac but also for another vendor's software.

16 **Strengths and limitations**

17 This is a large population-based study with a large age range providing a good power to estimate the normal
18 range of normal strain values. Strain is reduced with increasing afterload. Possible use of afterload adjustment
19 for example, indexing myocardial GLS to the population-based average BP may solve the issue, however data on
20 SBP and DBP during echo examination in the Tromsø 7 study is lacking. Single center study design could be a
21 possible source of reduced validity of the findings. Another limitation is the low sample size above 80 years of
22 age. Data on use of cardiotoxic drugs is not available in The Tromsø study and accordingly not included as risk
23 factor in SAHF definition.

24 **Clinical implications**

25 The results we demonstrated could potentially be used in control of the patients with SAHF with help of GLS
26 monitoring over time. Age-related GLS LLN is a promising parameter for clinical follow-up in group of patients
27 with subclinical HF due to its sensitivity for early myocardial function impairment.

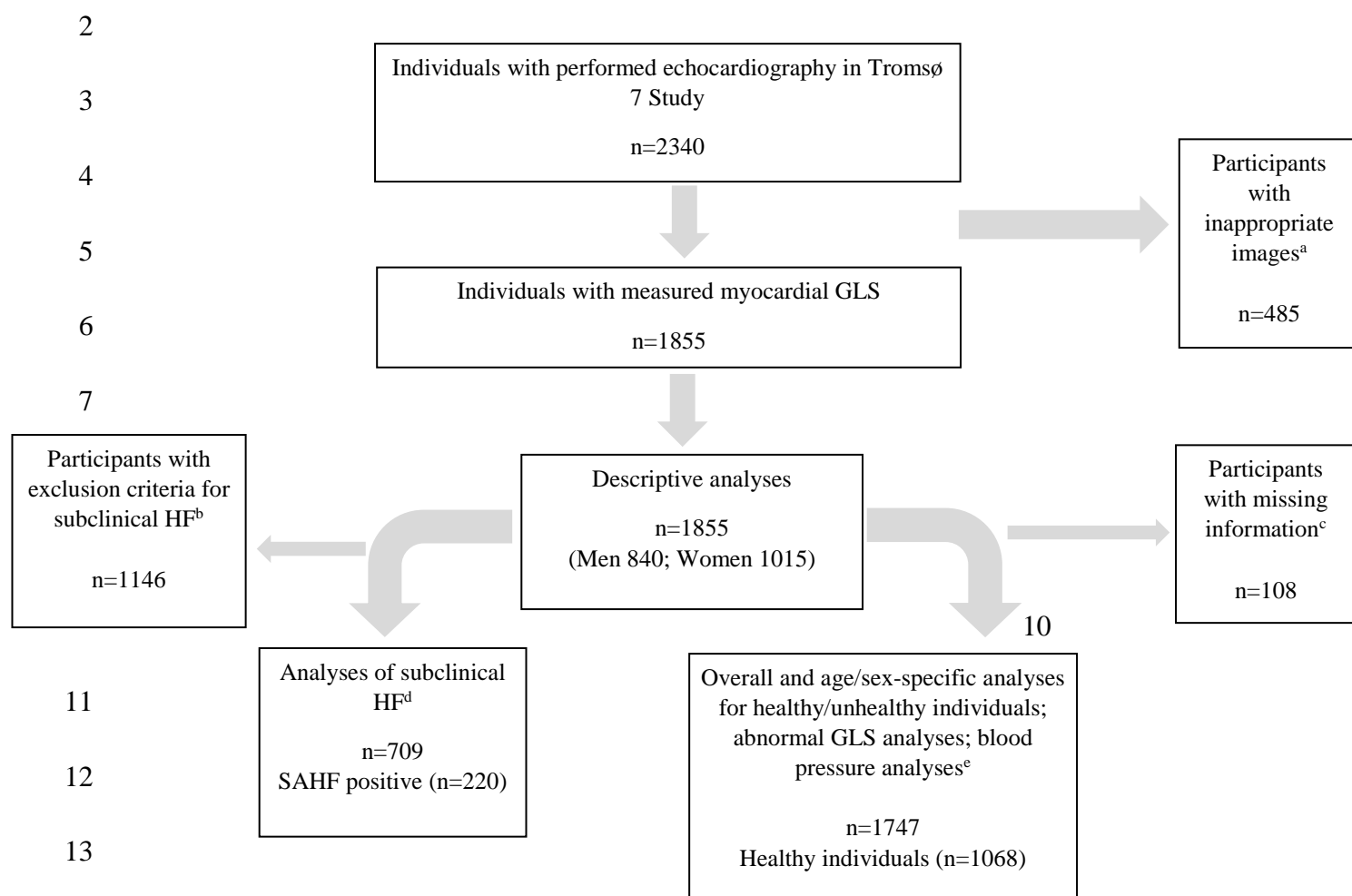
28 **Conclusions**

1 In large unselected samples from the general population myocardial GLS values were found both in the total and
2 healthy subsamples. Mean myocardial GLS declined with age in both sexes in general and in healthy
3 participants. SBP increase was associated with GLS decline in women. GLS was decreased in subjects with
4 subclinical HF. The close association of GLS to SAHF parameters indicates its importance for subclinical heart
5 disease diagnostics.

6 **Conflict of interest**

7 Authors declare no conflict of interest.

1 **Fig. 1** Flowchart of the study participants. The Tromsø Study (2015-2016).



15 ^aParticipants excluded from GLS analysis due to inappropriate imaging quality.

16 ^bIndividuals with any of the following: left ventricle geometry abnormalities, left ventricle ejection fraction < 50%, severe valvular heart disease, history of myocardial infarction, heart failure or stroke.

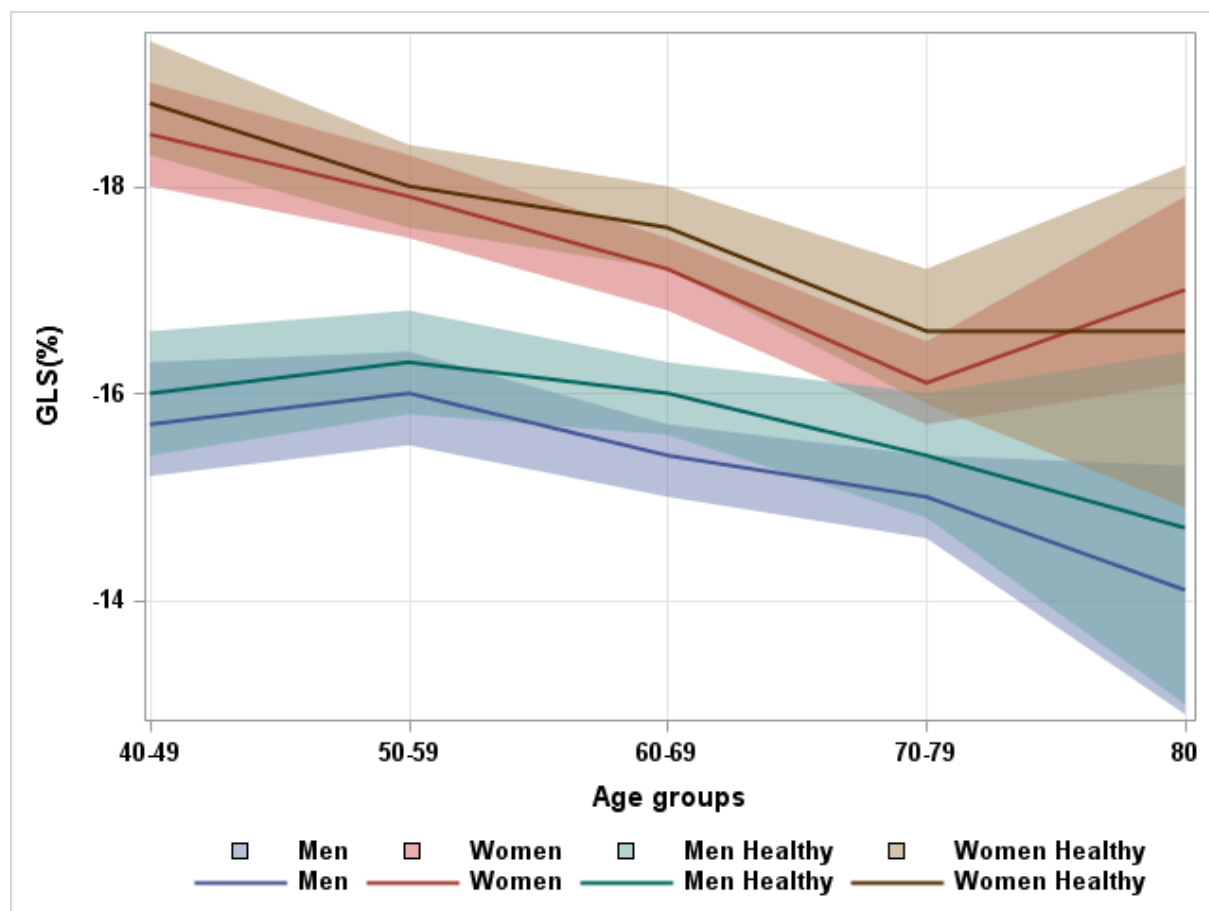
18 ^cMissing information on any of the following variables: myocardial infarction, angina, stroke, bronchitis, hypertension, diabetes, atrial fibrillation, heart failure, Hb1ac, left ventricle ejection fraction.

20 ^dIncluded those with the present at least one of the following: diabetes, metabolic syndrome, obesity, arterial hypertension, angina.

22 ^eFive individuals with missing information were excluded from GLS analyses according to SBP groups. One individual excluded from logistic regression analysis.

24

1 **Fig. 2** Age and sex-specific myocardial GLS means with 95% CI bands in general and healthy subsamples
 2 (n=1747). The Tromsø Study (2015-2016)



3
 4 *For “General” subsample: p-value (Difference between men and women by age groups): 40-49: $p < 0.001$; 50-
 5 59: $p < 0.001$; 60-69: $p < 0.001$; 70-79: $p < 0.001$; 80+: $p < 0.001$

6 *p-value (for change of mean myocardial GLS by age) Men: $p < 0.001$; Women: $p < 0.001$

7 ^aNumbers for men and women: 40-49 (M99;W144) 50-59 (M144;W188) 60-69 (M314;W345) 70-79
 8 (M200;W225); 80+ (M39;W49); Total n=1747

9
 10 *For “Healthy” subsample: p-value (Difference between men and women by age groups) 40-49: $p < 0.001$; 50-59:
 11 $p < 0.001$; 60-69: $p < 0.001$; 70-79: $p = 0.009$; 80+: $p = 0.115$

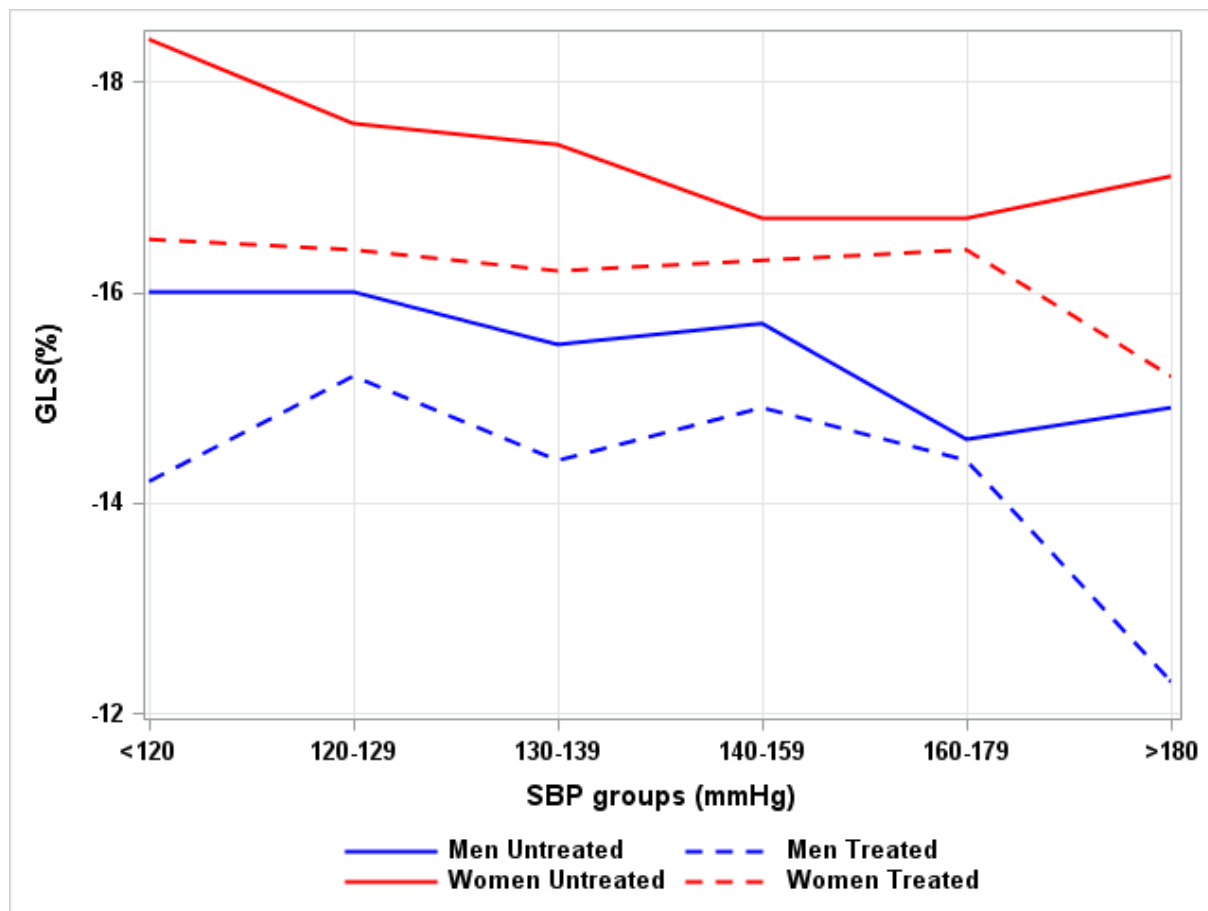
12 *p-value (for change of mean myocardial GLS by age) Men: $p = 0.001$; Women: $p < 0.001$

13 ^bNumbers for healthy: 40-49 (M81;W119); 50-59 (M109;W155); 60-69 (M170;W230); 70-79 (M72;W98); 80+
 14 (M19;W15); Total n=1068

15 ^cGLS: Global longitudinal strain; CI: confidence interval

16

1 **Fig. 3** Mean myocardial GLS levels stratified by SBP, sex and antihypertensive treatment. The Tromsø Study
 2 (2015-2016)



3

4

5 ^aMeans are adjusted for age and estimated for a mean age of 63 years using linear regression.

6 *p-value between SBP groups: Men (Untreated)=0.206; Women (Untreated)<0.001; Men (Treated)=0.276;

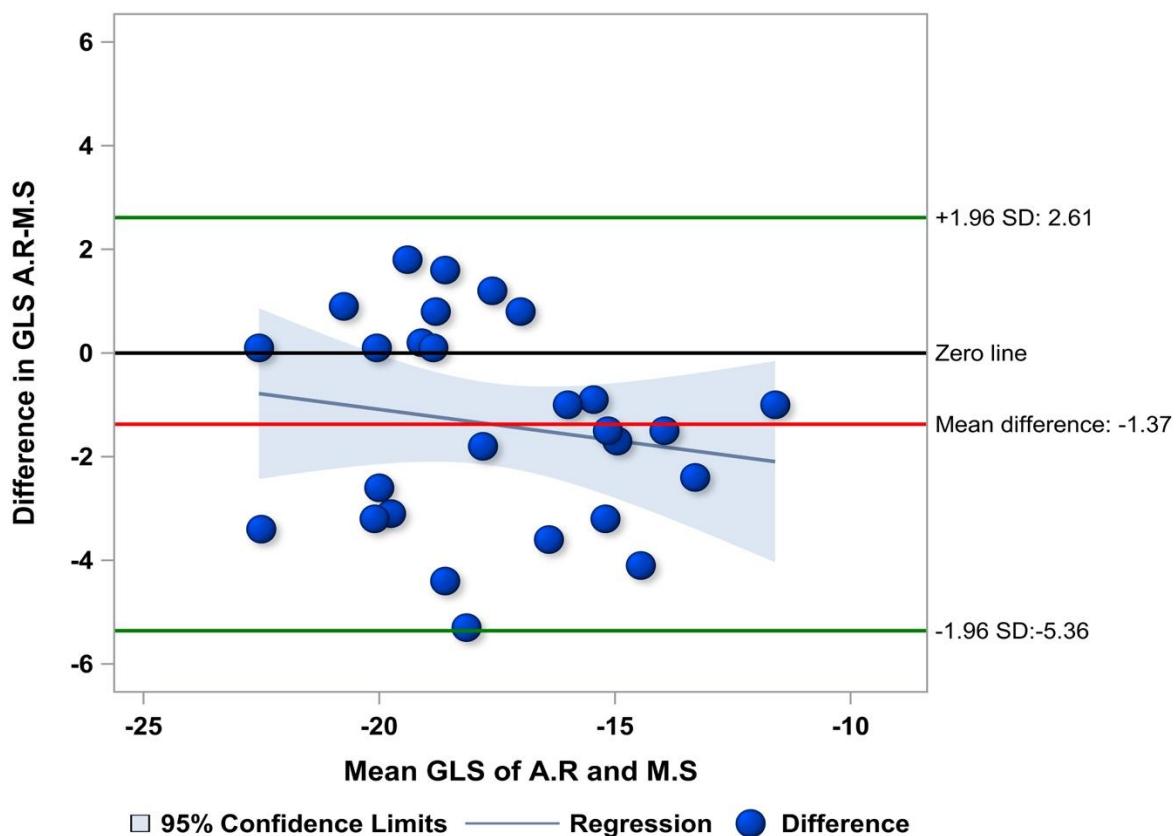
7 Women (Treated)=0.898.

8 ^cSBP: Systolic blood pressure; GLS: Global longitudinal strain; SD: Standard deviation.

9

10

1 **Fig. 4** Bland-Altman plot for inter-observer study. The Tromsø 7 Study.



2

3

4 ^aDifference in GLS: difference between observer A.R and observer M.S measurements (A.R minus M.S);

5 ^bMean GLS: mean GLS of two observers A.R and M.S; SD: standard deviation; GLS: Global longitudinal strain;

6 A.R: observer 1; M.S: observer 2

7 *P-value for linear regression model (y (difference in GLS) = x (mean GLS)) = 0.408

8

9

10

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Tables

Table 1 Descriptive characteristics of the participants who underwent echocardiography and had their myocardial GLS measured. The Tromsø Study (2015-2016)

Characteristics	Total	Age-group (yrs)				
		40-49	50-59	60-69	70-79	80+
<i>n</i> (%)	1855 (100)	247 (13.3)	338 (18.2)	694 (37.4)	467 (25.2)	109 (5.9)
BMI, kg/m ² (SD)	26.9 (4.1)	27.1 (5.0)	26.6 (4.1)	26.8 (3.8)	27.3 (4.2)	26.0 (3.5)
SBP, mm Hg (SD)	133.8 (20.5)	121.2 (15.6)	126.9 (18.2)	133.9 (19.3)	141.3 (19.8)	150.9 (22.0)
DBP, mm Hg (SD)	75.2 (9.9)	74.0 (9.9)	76.1 (9.6)	76.1 (9.8)	74.3 (10.0)	73.5 (9.8)
Antihypertensive treatment, <i>n</i> (%)	612 (33.4)	24 (9.8)	51 (15.2)	229 (33.4)	248 (54.0)	60 (58.3)
Hypertension, <i>n</i> (%)	549 (29.7)	24 (9.8)	45 (13.3)	209 (30.2)	212 (45.5)	59 (54.1)
mMRC						
scale grade 0-1, <i>n</i> (%)	1778 (95.9)	239 (96.8)	333 (98.5)	673 (97.0)	436 (93.4)	97 (89.0)
grade ≥2, <i>n</i> (%)	77 (4.2)	8 (3.2)	5 (1.5)	21 (3.0)	31 (6.6)	12 (11.0)
History of MI, <i>n</i> (%)	106 (5.9)	2 (0.8)	2 (0.6)	35 (5.2)	60 (13.4)	7 (7.5)
History of HF, <i>n</i> (%)	67 (3.6)	2 (0.8)	4 (1.2)	20 (2.9)	27 (5.8)	14 (13.2)
History of Stroke, <i>n</i> (%)	59 (3.3)	2 (0.8)	4 (1.2)	22 (3.3)	22 (5.0)	9 (9.2)
History of Angina, <i>n</i> (%)	74 (4.1)	4 (1.6)	1 (0.3)	23 (3.4)	39 (8.8)	7 (7.5)
History of Afib, <i>n</i> (%)	127 (6.9)	9 (3.6)	14 (4.1)	47 (6.8)	45 (9.6)	12 (11.0)
History of Diabetes, <i>n</i> (%)	114 (6.2)	9 (3.6)	7 (2.1)	43 (6.2)	51 (10.9)	4 (3.7)

History of Bronchitis, n (%)	16 (0.9)	2 (0.8)	3 (0.9)	4 (0.6)	3 (0.7)	4 (4.2)
LVMMi, g/m ^{2.7} , n (SD)	43.9 (14.1)	38.4 (10.8)	40.2 (11.3)	44.4 (13.3)	47.7 (15.9)	50.0 (18.0)
LV EF (Biplane), % (SD)	54.5 (7.8)	55.1 (7.2)	55.7 (6.8)	54.6 (7.8)	53.3 (8.5)	54.0 (8.9)
LAVi, ml/m ² (SD)	34.3 (12.0)	31.3 (8.6)	32.6 (9.8)	33.4 (11.3)	36.4 (12.7)	43.0 (19.4)
DT, ms (SD)	189.9 (58.0)	158.6 (37.3)	172.5 (40.7)	191.0 (53.0)	210.5 (68.6)	219.7 (71.5)
E/e' ratio (SD)	8.0 (3.3)	6.3 (1.6)	7.0 (1.8)	7.9 (2.8)	9.1 (4.0)	11.3 (5.3)
E/A ratio (SD)	1.0 (1.6)	1.3 (0.4)	1.1 (0.3)	0.9 (0.3)	0.8 (0.4)	1.5 (6.4)
Myocardial GLS, % (SD)	-16.3 (3.2)	-17.4 (3.2)	-17.1 (2.9)	-16.3 (3.2)	-15.5 (3.1)	-15.7 (3.6)
Myocardial GLS, % (SD)	-15.3 (2.9)	-15.7 (2.7)	-16.0 (2.8)	-15.4 (2.9)	-14.9 (2.8)	-14.2 (3.6)
Men						
Myocardial GLS, % (SD)	-17.2 (3.2)	-18.5 (3.1)	-17.9 (2.8)	-17.1 (3.2)	-16.1 (3.2)	-16.9 (3.0)
Women						

^aBMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVMMi: Left ventricle myocardial mass index; LV EF: Left ventricle ejection fraction; LAVi: left atrial volume index; DT: mitral peak E deceleration time; E/e' ratio: mitral peak E to tissue Doppler peak e' ratio; E/A ratio: mitral peak E to peak A ratio; GLS: global longitudinal strain; MI: myocardial infarction; HF: heart failure; Afib: atrial fibrillation; mMRC: modified Medical Research Council (mMRC) breathlessness/dyspnea scale; SD: standard deviation.

^bDue to missing observations, numbers (n) for the variables may be marginally less (within 1.0%).

Table 2 Healthy individuals (%) in by age groups and sex. The Tromsø Study (2015-2016)

Age group (years)	Proportion of healthy individuals	
	Men n/total (%)	Women n/total (%)
40-49	81/99 (81.8)	119/144 (82.6)
50-59	109/144 (75.7)	155/188 (82.5)
60-69	170/314 (54.1)	230/345 (66.7)
70-79	72/200 (36.0)	98/225 (43.6)
80+	19/39 (48.7)	15/49 (30.6)
p for trend	<0.001	<0.001

^aHealthy individuals: all excluding those with hypertension, diabetes, atrial fibrillation, heart failure, angina, myocardial infarction, stroke, chronic bronchitis and ejection fraction of the left ventricle <50%

Table 3 LLN for myocardial GLS expressed as percentage (95% CI). The Tromsø Study (2015-2016)

Age group (years)	Men		Women	
	LLN (%)	95% CI*	LLN (%)	95% CI*
40-49	-10.9	-12.0, -10.1	-12.7	-14.2, -11.5
50-59	-11.0	-11.9, -9.9	-12.7	-13.7, -11.6
60-69	-10.9	-11.6, -10.3	-11.5	-12.4, -10.7
70-79	-10.5	-11.5, -9.5	-10.1	-11.5, -8.7
80+	-7.8	-11.0, -5.4	-10.9	-13.8, -9.0
All ages (40-99)	-10.7	-11.2, -10.2	-11.7	-12.2, -11.2
P for trend	0.522		0.801	

^aLLN: Lower limit of normal; GLS: global longitudinal strain; CI: confidence interval.

*95% confidence intervals were calculated using bootstrapping with 1000 samples.

Table 4 Odds ratios for factors associated with abnormal myocardial GLS. The Tromsø Study (2015-2016)

Odds ratio (Models with various predictors ^a)			
Parameter	Point estimates	Wald 95% CI limits	p-value
Diabetes	2.91	1.52, 5.55	0.001
BMI, kg/m ²	1.23	1.17, 1.29	<0.001
Angina	2.68	1.24, 5.80	0.012
MI	2.47	1.24, 4.96	0.011
Atrial fibrillation	2.04	1.02, 4.06	0.043
Stroke	2.67	1.11, 6.43	0.029
Hypertension	1.52	0.96, 2.39	0.072
mMRC scale ≥ 2	1.93	0.81, 4.59	0.138

^aFor each risk factor the OR for having an age and sex-specific abnormal GLS was estimated in a separate model.

^bn of observations used 1746; Abnormal myocardial GLS (n=100), Normal myocardial GLS (n=1646).

^cBMI: Body mass index; MI: Myocardial Infarction; GLS: global longitudinal strain; mMRC scale: modified Medical Research Council breathlessness/dyspnea scale.

Table 5 Mean myocardial GLS (SD) (95% CI) (n) adjusted for age and sex according to the history of the different risk factors. The Tromsø Study (2015-2016)

HF Risk Factors (Total n=1747)	Mean GLS (SD) (95% CI) (n)		p-value
	Present	Absent	
Self-reported HF	-14.3 (3.5) (-15.1; -13.4) (51)	-16.4 (3.1) (-16.6; -16.3) (1696)	<0.001
Diabetes	-14.8 (3.2) (-15.4; -14.2) (101)	-16.5 (3.1) (-16.6; -16.3) (1646)	<0.001
mMRC scale ≥ 2	-14.8 (3.5) (-15.5; -14.1) (69)	-16.5 (3.1) (-16.6; -16.3) (1678)	<0.001
MI	-15.2 (3.1) (-15.8; -14.6) (95)	-16.5 (3.2) (-16.6; -16.3) (1652)	<0.001
Angina	-15.5 (3.5) (-16.3; -14.8) (70)	-16.4 (3.1) (-16.6; -16.3) (1677)	0.017
Hypertension	-15.9 (3.0) (-16.1; -15.6) (487)	-16.6 (3.2) (-16.8; -16.4) (1260)	<0.001
Stroke	-15.8 (3.3) (-16.6; -15.0) (52)	-16.4 (3.2) (-16.5; -16.3) (1695)	0.138
Atrial fibrillation	-15.9 (3.3) (-16.5; -15.4) (112)	-16.4 (3.2) (-16.6; -16.3) (1635)	0.090

^aGLS: global longitudinal strain; MI: myocardial infarction; HF: Heart Failure; mMRC scale: modified Medical Research Council breathlessness/dyspnea scale; CI: confidence interval; SD: standard deviation.

Online Resource 1 Intra and Inter-observer variability of myocardial GLS. The Tromsø Study (2015-2016).

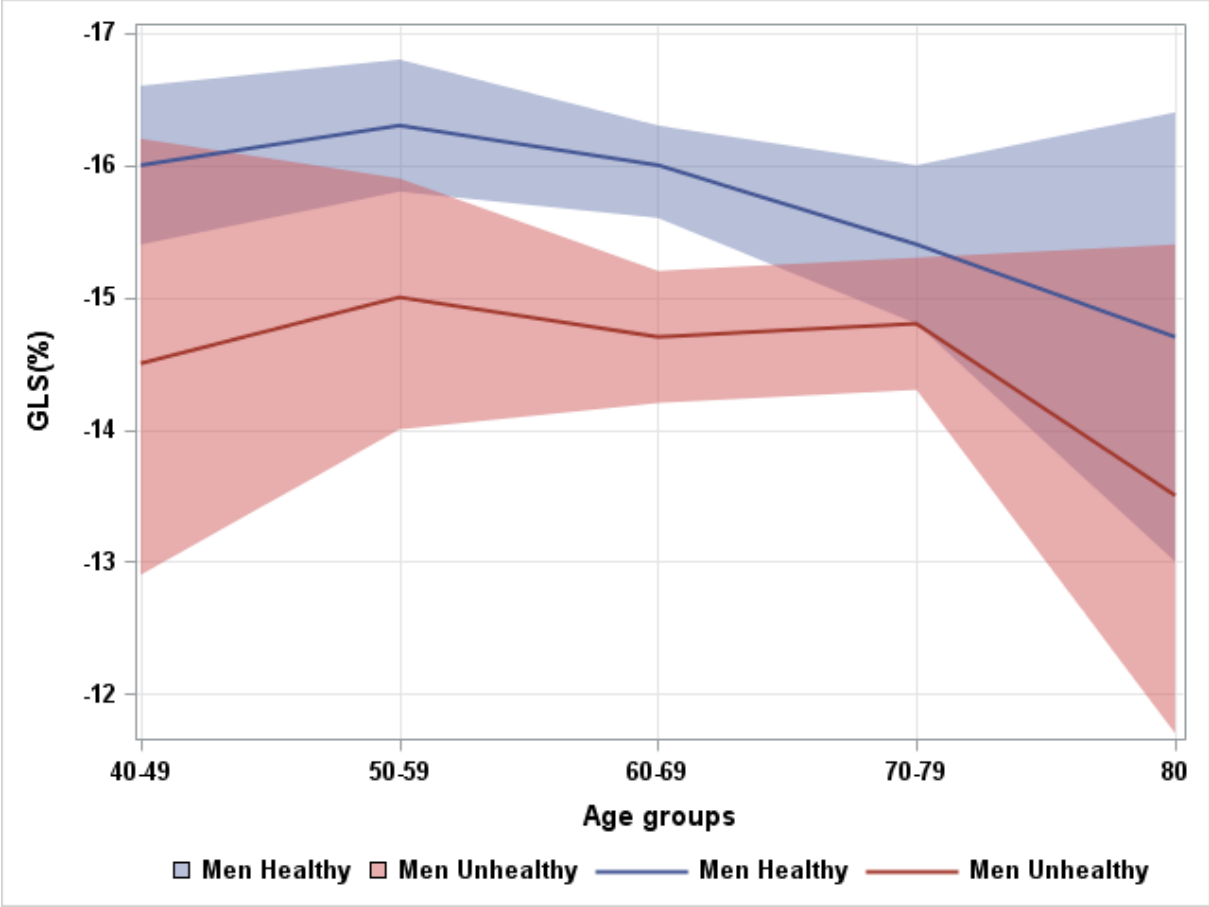
Intra-observer variability ^b			Inter-observer variability ^c		
ICC (95% CI)	Mean difference between observers (SD) (p for difference)	CR	ICC (95% CI)	Mean difference between observers (SD) (p for difference)	CR
0.96 (0.89-0.98)	0.53 (2.02) (p=0.274)	5.60	0.82 (0.47-0.93)	-1.37 (1.99) (p=0.001)	5.51

^aGLS: global longitudinal strain; ICC: intraclass correlation; SD: standard deviation; CI: confidence interval; CR: coefficient of repeatability

^bMeasurements were made by the same observer (M.S) with 3-months interval in between.

^cMeasurements made by A.R and M.S

Online Resource 2 Age and sex-specific myocardial GLS means with 95% CI bands in healthy and unhealthy men (n=796). The Tromsø Study (2015-2016)

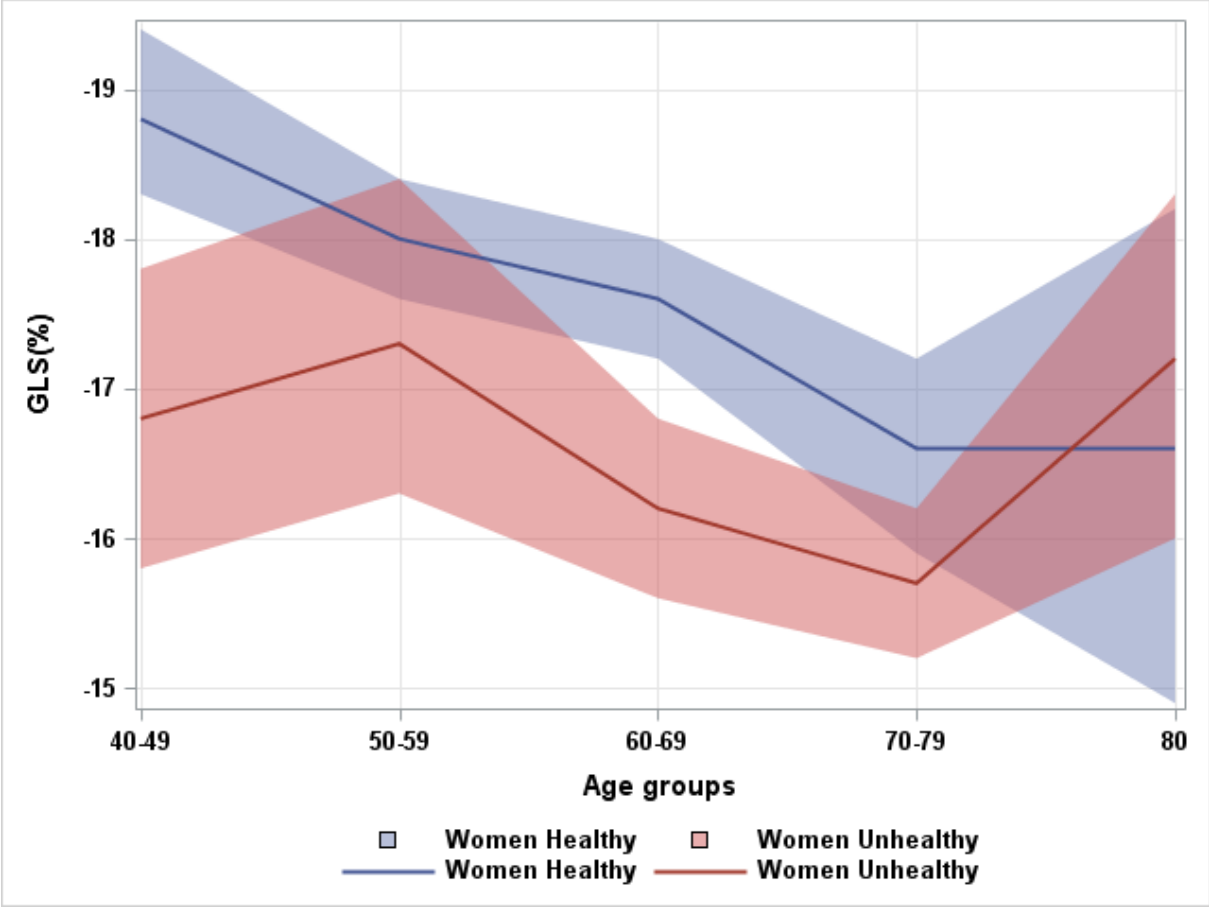


*p-value (Difference in GLS between healthy and unhealthy men by age groups): 40-49: p=0.041; 50-59: p=0.013; 60-69: p<0.001; 70-79: p=0.119; 80+: p=0.325

*p-value (for change of mean myocardial GLS by age) Healthy men: p=0.001; Unhealthy men: p=0.070

^aGLS: Global longitudinal strain; CI: confidence interval

Online Resource 3 Age and sex-specific myocardial GLS means with 95% CI bands in healthy and unhealthy women (n=951). The Tromsø Study (2015-2016)



*p-value (Difference in GLS between healthy and unhealthy women by age groups): 40-49: p=0.002; 50-59: p=0.219; 60-69: p<0.001; 70-79: p=0.033; 80+: p=0.529

*p-value (for change of mean myocardial GLS by age) Healthy women: p<0.001; Unhealthy women: p=0.070

^aGLS: Global longitudinal strain; CI: confidence interval

Online Resource 4 Healthy and unhealthy individuals with measured mean myocardial GLS according to age and sex. The Tromsø Study (2015-2016)

	Age (y)	40-49	50-59	60-69	70-79	80+	Total (n)
Healthy men (n)		81	109	170	72	19	451
Unhealthy men (n)		18	35	144	128	20	345
Healthy women (n)		119	155	230	98	15	617
Unhealthy women (n)		25	33	115	127	34	334

^aGLS: Global longitudinal strain