Long-term Changes in Depressive Symptoms and Estimated Cardiorespiratory Fitness and Risk of All-Cause Mortality: The HUNT Study

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Conflict of interest

None known.

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ABSTRACT

OBJECTIVE: To assess the independent and combined associations of long-term changes in DS and estimated CRF (eCRF) with all-cause mortality.

PATIENTS AND METHODS: Longitudinal cohort study of 15 217 middle-aged and older individuals attending both the second (1995-97) and third (2006-08) waves of the Nord-Trøndelag Health Study, Norway, and followed until December 31, 2014. DS were assessed with the validated Hospital Anxiety and Depression Scale, and a validated non-exercise model estimated eCRF. Hazard ratios were computed using Cox regression. All-cause mortality was ascertained using The Norwegian Cause of Death Registry.

RESULTS: Mean age (SD) was 63.3 (8.9) years and 52.1% were women. During the follow-up period of 7.1±1.1 years, 1157 (7.6%) participants died. Multivariable adjusted analyses showed that persistently low DS was independently associated with a 28% risk reduction of all-cause mortality (hazard ratio [HR], 0.72; 95% CI 0.56-0.92, p=.008) compared to persistently high DS. Persistently high eCRF independently predicted 26% lower risk of death (HR 0.76; 95% CI 0.66-0.88, p<.001) relative to low eCRF. Analyses of changes in DS and eCRF showed that persistently high eCRF combined with decreased or persistently low DS decreased mortality risk by 49% (HR 0.51; 95% CI 0.28-0.91, p=.02) and 47% (HR 0.53; 95% CI 0.37-0.76, p=.001), respectively.

CONCLUSIONS: Improving or maintaining low DS and high eCRF was independently associated with a lower risk of all-cause mortality. The lowest mortality risk was observed persistently high eCRF combined with decreased or persistently low DS. These results emphasize the impact

of preventing DS and maintaining high CRF on long-term mortality risk, which is potentially important for long-term population health.

ABBREVIATIONS

CI – Confidence Interval

CRF – Cardiorespiratory Fitness

CVD – Cardiovascular Disease

DS – Depressive Symptoms

eCRF – Estimated Cardiorespiratory Fitness

HADS – Hospital Anxiety and Depression Scale

HADS-D - Hospital Anxiety and Depression Scale, depression sub-scale.

HR – Hazard Ratio

HUNT – Nord-Trøndelag Health Study

PA – Physical Activity

RHR – Resting Heart Rate

SBP – Systolic Blood Pressure

WC – Waist Circumference

INTRODUCTION

Depression is among the top three leading causes of years lived with disability [1] and affects approximately 350 million people worldwide [2] with increasing prevalence with increasing age [3]. Depression and depressive symptoms (DS) have been linked with cardiovascular disease (CVD) [4-6] and risk of premature mortality [7-9]. In addition, as physical and mental health are intimately related, people with depression face a higher risk of onset of physical conditions such as CVD, hypertension, and type 2 diabetes mellitus [10].

Cardiorespiratory fitness (CRF) is a physiological measure reflecting the body's ability to transport and utilize oxygen to perform physical work and is a strong predictor of mortality, independent of traditional risk factors, such as smoking, type 2 diabetes mellitus, and hypertension [11-13]. A recent statement from the American Heart Association suggests assessing CRF in clinical practice to optimize the prevention and treatment of CVD [14]. Non-exercise models for estimation of CRF (eCRF) have been developed [15-17] and provides a rough estimate of objectively measured CRF [15]. More importantly, eCRF models are associated with all-cause and CVD mortality [17-19]. Therefore, eCRF is a valid estimate of CRF in population-based studies.

Studies investigating the relationship between DS and CRF suggest that higher CRF is associated with lower DS [20-22]. Further, among men with emotional distress, higher CRF was associated with lower risk of premature death, independent of other important mortality predictors [23]. Despite the established protective effect of CRF on mortality and the association with DS, few studies investigating the relationship between DS and mortality account for the possible influence of CRF. A prospective study (The Aerobics Center Longitudinal Study) demonstrated that low

levels of negative emotions reduced the all-cause mortality risk by 30%, after adjusting for confounding factors, including CRF [24]. More interestingly, the combination of low levels of negative emotions and high CRF reduced the risk of all-cause mortality by 63% compared to participants with high levels of negative emotions and low CRF [24].

There are few longitudinal studies considering the changing nature of DS and mortality risk. Among the studies investigating the latter relationship, Geerlings et al [25] reported that middle-aged and older people with persistently high DS were more than twice as likely to suffer from premature death compared to those with consistently low DS. Schoevers and colleagues [26] reported a 38% increased risk of mortality among middle-aged and older community living people depressed at both baseline and at three-year follow-up compared with non-depressed counterparts. Both studies adjusted for demographics, chronic diseases and functional limitations, but neither considered CRF.

Therefore, how the direction of change in DS over time contributes to the association with mortality and how simultaneous eCRF changes influence this association remain unclear. To our knowledge, no studies have considered eCRF change when investigating the association between DS change and premature death. In the present study, we determined the independent associations of changes in DS and eCRF with all-cause mortality in middle-aged and older adults. We further investigated how combinations of changes in DS and eCRF were associated with long-term survival.

METHODS

Study Population

HUNT is a population-based health study conducted in the Nord-Trøndelag county in Norway, with the first wave (HUNT1) conducted in 1984-86 [27]. The participants in the present study attended both HUNT2 (1995-97) and HUNT3 (2006-08) and survived up to the age of 50 in HUNT3 (n=26 208). Participants with missing data were excluded in the following order: DS HUNT2 (n=545), eCRF HUNT2 (n=1869), DS HUNT3 (n=3162), eCRF HUNT3 (n=3510) and on any of the other confounders (age, sex, education, marital status, smoking status, alcohol consumption, heart disease, stroke/brain hemorrhage, diabetes, cancer) collected at HUNT3 (n=1905). The final cohort comprised 15 217 participants. All HUNT participants provided written consent. Participants included in the present study were compared with those excluded due to missing data (n=10 991). On average, the excluded group had somewhat higher depressive symptoms and lower eCRF, compared with those included.

Depressive Symptoms

DS were assessed by a Norwegian translation of the Hospital Anxiety and Depression Scale (HADS) [28]. The basic psychometric properties of the Norwegian version of HADS were found to be acceptable based on HUNT2 data [29]. HADS consists of 14 items assessing psychological symptoms of depression (HADS-D) and anxiety during the last week. HADS-D sub-scale covers seven items. Each item scores 0-3 points with the highest score reflecting most symptomatic load. If participants filled in five or six items only, the total score multiplied by 7/5 or 7/6, respectively, replaced missing values. A cut-off score of ≥8 defined high DS, and has previously shown a sensitivity and specificity of 0.8 for caseness of depression [30]. We classified change into four categories: persistently high, increased, decreased, and persistently low. Change over time was

130 calculated as the difference between HADS-D score between HUNT2 and HUNT3.

131 **Estimated Cardiorespiratory Fitness**

132 Estimated CRF was calculated using a validated, non-exercise prediction model based on HUNT2 [17]. The sex-specific models included age,
133 physical activity (PA) level, resting heart rate (RHR) and waist circumference (WC). The following models were used to estimate each
134 participant's CRF in ml/kg/min:

135 Women: 78.00 − (0.297·age) − (0.270·WC) − (0.110·RHR) + (2.674·PA)

136 Men: 105.91 − (0.334·age) − (0.402·WC) − (0.144·RHR) + (3.102·PA)

137 Self-administered questionnaire provided information about average, weekly duration and intensity of leisure-time PA during the last year.
138 Participants were asked to specify the average number of hours of low (no sweating or being out of breath) and vigorous (sweating/out of
139 breath) PA per week during the last year (separate questions for low and vigorous PA), with response options "none", "less than an hour", "1-2
140 hours" and "3 hours or more". To enable eCRF estimation, participants were divided into two categories according to meeting (PA=1) or not
141 meeting (PA=0) PA recommendations [17, 31]. RHR was measured using a Critikon Dinamap 845XT (GE Medical Systems) after two minutes of rest
142 in the seated position [32] and WC was measured to the nearest centimeter using a band placed horizontally at the height of the umbilicus [27].
143 Estimated CRF above a sex- and age-specific (based on ten-year age categories) median value indicated higher levels of eCRF. We categorized

change according to median value into four categories: persistently high, increased, decreased and persistently low. Change measured as a continuous variable was the difference between HUNT2 and HUNT3.

Confounders

Self-administrated questionnaires and clinical measurements from HUNT3 provided data on the confounders. Confounders were obtained from the later time point to include any changes in health status between HUNT2 and HUNT3. Marital status was categorized into married, unmarried, divorced/separated and widow(er). Alcohol consumption was assessed by asking about average number of alcoholic beverages (beer, wine, liquor) over a typical two-week period. Smoking habits were categorized into never, former and current smoker. Disease status/history was assessed by asking about the following diseases; myocardial infarction, angina pectoris, stroke/brain hemorrhage, diabetes or cancer, with a yes/no response for each disease. Systolic blood pressure (SBP, mmHg) was measured using a Critikon Dinamap 845XT (GE Medical Systems) after a two-minute rest in the seated position. Statistics Norway provided educational data.

End point and Mortality Surveillance

Outcome variable was all-cause mortality. We followed participants from date of participation in HUNT3 through the date of death or study end December 31, 2014. Matching of the unique 11-digit Norwegian person identification number with The National Cause of Death Register ensured complete follow-up.

Statistical Analysis

Participant characteristics at HUNT3 are presented as mean (95% confidence interval (CI)) and numbers (percentage) for continuous and categorical variables, respectively, and compared using Pearson X^2 test for categorical variables and one-way analysis of variance for continuous variables. The associations between change in DS, change in eCRF, and all-cause mortality were assessed using Cox regression, and hazard ratios (HR) and 95% CI were computed. Two models were fitted to assess the association between change in DS measured as a categorical variable and mortality, and between change in eCRF measured as a categorical variable and mortality. For both models, time variable was attained age. The basic model (model 1) was adjusted for sex. The multivariable model (model 2) was further adjusted for change in eCRF (in the analysis with DS as the independent variable), change in DS (in the analysis with eCRF as the independent variable), education, marital status, smoking, alcohol consumption, SBP, heart disease, stroke/brain hemorrhage and diabetes. Stratifying variable in model 2 was cancer because of apparent violation of the proportional hazard assumption. Those having persistently high DS and those having persistently low eCRF were set as reference categories for the separate analyses of the association between change in DS and eCRF with mortality, respectively.

Analyses of change measured as a continuous variable were adjusted for the same variables as in the analyses of change as a categorical variable. In addition, the analyses of change in DS was adjusted for DS at HUNT2, and the analyses of change in eCRF was adjusted for eCRF at HUNT2.

The final analysis assessed the association between combined patterns of change in DS and eCRF on all-cause mortality. By combining the two categorical variables, we created 16 new combinations. The combination of persistently high DS and persistently low eCRF was set as reference category.

Test of linear trend was performed separately for change in DS and eCRF by adding the four-category variables as an ordinal variable in the multivariable-adjusted regression model.

Proportional hazard assumptions for the confounders were examined by Schoenfeld residuals. Interactions were tested between change in DS and change in eCRF, change in DS and sex, and change in eCRF and sex by the likelihood ratio test. Statistical analyses were performed using Stata statistical software, v13.1 (StataCorp). Two-sided p-values <.05 were considered statistically significant.

RESULTS

The mean age of the 15 217 included participants was 63.3±8.9 years at HUNT3 and 52.1% were women. During the 7.1±1.1 years of follow-up, 1157 (7.6%) died from all causes. The interactions between change in DS and change in eCRF, change in DS and sex, and change in eCRF and sex were not statistically significant. HUNT3 characteristics are presented in **Table 1** and **Table 2** according to categories of change in DS and eCRF, respectively.

Change in Depressive Symptoms

Table 3 shows the HRs for change in DS measured as a categorical variable and all-cause mortality. In model 1, those having persistently low DS

had 29% lower risk of all-cause mortality compared to those with persistently high DS over the 7 years of follow-up. After additional adjustments for confounders (model 2), the risk remained nearly the same. Linear test for trend suggested an inverse dose-response relationship (p=.005) across the categories of change in DS.

In the multivariable adjusted analysis of DS as a continuous variable (data not shown) each 1 unit increase in DS was associated with 4% higher risk of all-cause mortality (HR 1.04, 95%CI 1.01-1.06) over the 7 years of follow-up.

Change in eCRF

Model 1 with change in eCRF as a categorical variable showed that over the 7 years of follow-up, those with persistently high eCRF had 28% lower risk of all-cause mortality compared to those with persistently low eCRF (**Table 4**). Further adjustment for confounders (model 2), revealed that those having persistently high eCRF had 24% lower all-cause mortality risk compared to those with persistently low eCRF (**Table 4)**. The linear test for trend indicated an inverse dose-response relationship (p=0.001) across the categories of eCRF change and all-cause mortality.

In the multivariable adjusted analysis of mortality risk from change in eCRF measured as a continuous variable (data not shown), each 1 ml/kg/min improvement in eCRF was associated with a 2% lower risk of all-cause mortality (HR 0.98, 95%CI 0.96-0.99) over the 7 years of follow-up.

Combined Groups

For the combined patterns of change in DS and eCRF (**Figure 1**), the largest risk reduction was observed among those with persistently high eCRF who decreased DS (HR 0.51, 95%CI 0.28-0.91) or had persistently low DS (HR 0.53, 95%CI 0.37-0.76), compared to those having persistently low eCRF and persistently high DS. The combination of persistently high eCRF and persistently high DS was not associated with mortality risk reduction (HR 0.89, 95%CI 0.51-1.55) compared to those with persistently low median eCRF and persistently high DS. Persistently low DS was associated with reduced mortality risk, irrespective of persistently low eCRF (HR 0.69, 95%CI 0.49-0.98). The results also tended towards a reduced risk for those having persistently low DS regardless of increasing or decreasing eCRF (increased eCRF, HR 0.70, 95%CI 0.48-1.03; decreased eCRF, HR 0.71, 95%CI 0.49-1.02).

DISCUSSION

Our main finding was that improving or maintaining low DS was associated with lower risk of all-cause mortality during seven years of follow-up compared to those with persistently high DS. The most favorable combination of DS and eCRF for lowered risk of mortality was seen among those maintaining high eCRF who either decreased or had persistently low DS. All observed associations were independent of confounding factors (age, sex, education, marital status, smoking, alcohol consumption, SBP, heart disease, stroke/brain hemorrhage, and diabetes), including concurrent change in eCRF (for DS change) and DS (for eCRF change).

Our results suggest that preventing increased DS and high DS over time may play an important role in the association with all-cause mortality. In line with our findings, data on nearly 2000 participants from The Amsterdam Study of the Elderly showed that chronic depression (diagnosed

using Geriatric Mental State-AGECAT) over a three-year period increased risk of ten-year mortality by 38% [26]. On the other hand, Penninx et al [33] (n=3701; Established Populations for Epidemiologic Studies of the Elderly) found that the association between persistently high DS over three and/or six years (measured on the Center for Epidemiologic Studies Depression scale) and mortality was fully attenuated after adjustment for differences in lifestyle factors and health conditions including physical disability [33]. The use of different diagnostic approaches, different covariates, differences in follow-up time, time between assessments and number of included participants in the present and above-mentioned studies make comparisons difficult.

The non-significant association between increased or decreased DS and mortality risk observed in this study was in accordance with other studies [25, 26, 33] and could possibly be due to the fluctuating nature of DS. In the present study, depressive symptoms were measured at two time points (ten years apart). The Norwegian HADS-D assesses symptom load during the last week. Thus, participants classified as having high DS may have experienced lower DS sometime between the two HUNT assessments, and vice versa for participants classified as having low DS. The study by Schoevers et al assessed depression three years after baseline evaluation and found no association between remitted or incident depression and mortality risk [26]. Further, no association was shown between participants with high degree of instability of DS (measured eight times over a three-year period) and mortality risk, compared to those with persistently low DS [25].

In our combined analyses, compared to those with persistently high DS and persistently low eCRF, we found that participants maintaining high eCRF had a lower risk of all-cause mortality, regardless of DS change, except for the combination of persistently high eCRF and persistently high

DS. Surprisingly, those who had persistently high DS and at the same time maintained high eCRF did not show reduced mortality risk. The latter indicates the detrimental influence persistently high DS might impose on long-term health. Furthermore, our results indicated that maintaining low DS lowered the risk of all-cause mortality, regardless of eCRF change status, compared to the reference group. However, we underline the borderline significant finding for those having persistently low DS in combination with increasing or decreasing eCRF. The small number of participants in some of the combination groups should be noted, and is reflected by wider CIs and overlapping CIs within each category. We therefore suggest caution when drawing conclusions from the combined analyses.

We found that those who increased and maintained high eCRF had lower all-cause mortality risk compared to those with persistently low eCRF, which is in line with previous studies [34-36]. The reduced risk for those with persistently high eCRF was still evident after adjusting for confounding factors, including concurrent change in DS. Ortega and co-workers highlighted the importance of considering psychological well-being in their study of CRF and mortality risk [24], showing that additional adjustment for negative emotions slightly reduced the influence of CRF on mortality, but the association remained statistically significant [24]. However, the latter study was based on a single measurement of DS, thus no changes in relevant variables were considered.

Strengths and Limitations

We had a large number of participants with complete follow-up data, extensive control of data on psychosocial, lifestyle and biological factors, and most importantly, controlling for eCRF, which strengthens our findings. Adjustments for DS were included for eCRF analysis and vice versa,

recognizing the close relation between mental and physical health. To our knowledge, this is the first study to assess the combined association of change in DS and eCRF with mortality. However, we acknowledge several limitations with our study. Due to missing data on relevant variables at HUNT2, and differences in some questions on lifestyle factors at HUNT2 and HUNT3, we did not consider changes in any medical conditions or lifestyle factors other than DS and eCRF.

Furthermore, population-based studies are vulnerable to selection bias and non-participation studies from HUNT2 show that older age, and mental health issues are related to non-participation [32, 37]. If a significant number of the non-participants eligible for the present study did not participate due to mental health issues, we recognize the possibility of an underestimation of the measured associations. The eCRF model used in the present study is based on cross-sectional data. It is shown that CRF declines in a nonlinear manner with age [38] which the eCRF model does not take into account. The latter might influence the results of our study as the eCRF model is used in a longitudinal design. On the other hand, the algorithm is specific for the present population as it is based on a sample of study participants from HUNT2 [17]. In addition, Nauman and colleagues found the current used eCRF model to be associated with all-cause and CVD mortality [17]. The present results expand the eCRF and mortality relationship by showing an association between eCRF change status and mortality. However, future studies on changes in eCRF should use eCRF models based on longitudinal data to confirm the latter statement [16, 39]. Future research should aim to assess DS and eCRF at several closer time points to capture the changing nature of DS and the influence lifestyle factors and disease status have on eCRF.

CONCLUSION

In conclusion, our results showed that maintaining low or improving DS are associated with a decreased mortality risk after accounting for eCRF change. Maintaining high eCRF and at the same time possessing high or increasing DS did not significantly reduce all-cause mortality risk. This study suggest that efforts should be made on assessing both DS and eCRF, and emphasize modalities to reduce long-term high DS and improve fitness, as improvements in both are associated with considerable improvement in long-term survival.

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Figure 1: Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality by combinations of changes in depressive symptoms and estimated cardiorespiratory fitness from HUNT 2 (1995-97) to HUNT 3 (2006-08) in the total study population (n=15 217). All data were adjusted for age, sex, marital status, attained education, smoking status, alcohol consumption, SBP, heart disease, stroke/brain hemorrhage and diabetes at baseline in HUNT 3. DS=depressive symptoms, eCRF=estimated cardiorespiratory fitness, SBP=systolic blood pressure. The number of participants (number of all-cause deaths) in the persistently low, decreased, increased and persistently high eCRF groups were 297 (35), 99 (10), 66 (6) and 140 (20) in the persistently high DS group; 425 (58), 194 (14), 85 (15) and 209 (28) in the increased DS group; 395 (32), 171 (19), 115 (12) and 245 (17) in the from decreased DS group; and 4774 (373), 2710 (153), 1451 (128) and 3841 (237) in the persistently low DS group, respectively. *Depressive symptoms=DS, **Estimated cardiorespiratory fitness=eCRF.

373 **Table 1**: Unadjusted HUNT3 Characteristics by Categories of Change in Depressive Symptoms from HUNT2 (1995-97) to HUNT3 (2006-08)

Depression Symptoms	**Persistently low**	**Decreased**	**Increased**	**Persistently high**	p-value
No. (%) with data	12776 (84.0)	926 (6.1)	913 (6.0)	602 (4.0)	
Age, mean (95% CI), y	63.0 (62.9-63.2)	64.1 (63.6-64.7)	65.0 (64.3-65.6)	64.5 (63.8-65.2)	<.001
Women	6740 (52.8)	484 (52.3)	427 (46.8)	281 (46.7)	<.001
HADS-D score, mean (95% CI)	2.8 (2.7-2.8)	4.5 (4.4-4.7)	9.3 (9.2-9.4)	9.8 (9.7-10.0)	<.001
eCRF, mean (95% CI), ml/kg/min	32.9 (32.8-33.1)	32.1 (31.6-32.5)	31.9 (31.4-32.3)	31.7 (31.2-32.3)	<.001
Education					<.001
Tertiary	2980 (23.3)	151 (16.3)	135 (14.8)	77 (12.8)	
Secondary	7230 (56.6)	538 (58.1)	525 (57.5)	345 (57.3)	
Primary	2566 (20.1)	237 (25.6)	253 (27.7)	180 (29.9)	
Marital Status					<.001
Married	9484 (74.2)	627 (67.7)	618 (67.7)	386 (64.1)	

Unmarried	709 (5.6)	62 (6.7)	70 (7.7)	72 (12.0)	
Divorced/Separated	1204 (9.4)	112 (12.1)	115 (12.6)	77 (12.8)	
Widow(er)	1379 (10.8)	125 (13.5)	110 (12.1)	67 (11.1)	
Smoking status					<.001
Never	4846 (37.9)	296 (32.0)	337 (36.9)	189 (31.4)	
Former	5416 (42.4)	396 (42.8)	364 (39.9)	264 (43.9)	
Current	2514 (19.7)	234 (25.3)	212 (23.2)	149 (24.8)	
Alcohol consumption, mean (95% CI), units/2w	4.6 (4.5-4.7)	4.2 (3.8-4.6)	3.9 (3.5-4.2)	3.7 (3.3-4.1)	<.001
Physically active[1]	7997 (62.6)	545 (58.9)	466 (51.0)	305 (50.7)	<.001
WC, mean (95% CI), cm	94.9 (94.7-95.1)	96.4 (95.6-97.2)	97.0 (96.2-97.8)	97.8 (96.9-98.8)	<.001
RHR, mean (95% CI), bpm	67.6 (67.4-67.8)	67.6 (66.9-68.4)	68.1 (67.4-68.9)	68.0 (67.1-68.9)	.44
SBP, mean (95% CI), mmHg	135.9 (135.6-136.2)	135.1 (133.9-136.3)	134.6 (133.4-135.8)	134.8 (133.3-136.3)	.09
Diabetes	723 (5.7)	66 (7.1)	64 (7.0)	43 (7.1)	.06

Ischemic Heart Disease	951 (7.4)	108 (11.7)	109 (11.9)	63 (10.5)	<.001
Stroke/brain hemorrhage	417 (3.3)	45 (4.9)	51 (5.6)	31 (5.2)	<.001
Cancer	996 (7.8)	64 (6.9)	86 (9.4)	39 (6.5)	0.12

374 abbreviations: bpm, beats per minute; eCRF, estimated cardiorespiratory fitness; HADS, Hospital Anxiety and Depression Scale; HUNT, Nord-

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376 Health Study; RHR, resting heart rate; SBP, systolic blood pressure; WC, waist circumference; 2w, two weeks.

377 [1]according to current physical activity recommendations.

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387 **Table 2**: Unadjusted HUNT3 Characteristics by Categories of Change in Estimated Cardiorespiratory Fitness from HUNT2 (1995-97) to HUNT3

388 (2006-08)

Fitness	**Persistently high**	**Increased**	**Decreased**	**Persistently low**	p-value
No. (%) with data	4435 (29.2)	1717 (11.3)	3174 (20.9)	5891 (38.7)	
Age, mean (95% CI), y	64.5 (64.2-64.7)	65.2 (64.8-65.7)	60.2 (59.9-60.5)	63.5 (63.3-63.7)	<.001
Women	2901 (65.4)	1065 (62.0)	1065 (33.6)	2901 (49.2)	<.001
HADS-D score, mean (95% CI)	3.3 (3.2-3.4)	3.5 (3.3-3.6)	3.4 (3.3-3.5)	3.8 (3.8-3.9)	<.001
eCRF, mean (95% CI), ml/kg/min	34.8 (34.6-34.9)	33.5 (33.2-33.7)	35.7 (35.5-36.0)	29.4 (29.2-29.5)	<.001
Education					<.001
Tertiary	1278 (28.8)	353 (20.6)	773 (24.4)	939 (15.9)	
Secondary	2338 (52.7)	965 (56.2)	1850 (58.3)	3485 (59.2)	
Primary	819 (18.5)	399 (23.2)	551 (17.4)	1467 (24.9)	
Marital Status					<.001
Married	3292 (74.2)	1273 (74.1)	2312 (72.8)	4238 (71.9)	

Unmarried	199 (4.5)	81 (4.7)	234 (7.4)	399 (6.8)	
Divorced/Separated	434 (9.8)	132 (7.7)	382 (12.0)	560 (9.5)	
Widow(er)	510 (11.5)	231 (13.5)	246 (7.8)	694 (11.8)	
Smoking status					<.001
Never	1812 (40.9)	628 (36.6)	1186 (37.4)	2042 (34.7)	
Former	1768 (39.9)	716 (41.7)	1332 (42.0)	2624 (44.5)	
Current	855 (19.3)	373 (21.7)	656 (20.7)	1225 (20.8)	
Alcohol consumption, mean (95% CI), units/2w	4.5 (4.3-4.7)	3.8 (3.6-4.0)	5.4 (5.2-5.6)	4.1 (4.0-4.2)	<.001
Physically active[1]	3502 (79.0)	1389 (80.9)	1706 (53.8)	2716 (46.1)	<.001
WC, mean (95% CI), cm	85.8 (85.5-86.0)	90.2 (89.8-90.5)	95.6 (95.3-95.9)	103.7 (103.4-103.9)	<.001
RHR, mean (95% CI), bpm	63.9 (63.6-64.1)	65.1 (64.7-65.6)	67.1 (66.7-67.5)	71.5 (71.2-71.8)	<.001
SBP, mean (95% CI), mmHg	133.0 (132.5-133.6)	135.7 (134.8-136.6)	134.3 (133.6-134.9)	138.5 (138.1-139.0)	<.001

Diabetes	122 (2.8)	105 (6.1)	92 (2.9)	577 (9.8)	<.001
Ischemic Heart Disease	361 (8.1)	153 (8.9)	169 (5.3)	548 (9.3)	<.001
Stroke/brain hemorrhage	148 (3.3)	51 (3.0)	97 (3.1)	248 (4.2)	.008
Cancer	375 (8.5)	159 (9.3)	208 (6.6)	443 (7.5)	.002

389 abbreviations: bpm, beats per minute; eCRF, estimated cardiorespiratory fitness; HADS, Hospital Anxiety and Depression Scale; HUNT, Nord-

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391 Health Study; RHR, resting heart rate; SBP, systolic blood pressure; WC, waist circumference; 2w, two weeks.

392 [1]according to current physical activity recommendations.

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Table 3: Hazard Ratios of All-Cause Mortality by Categories of Change in Depressive Symptoms from HUNT2 (1995-97) to HUNT3 (2006-08)

			Model 1	**Model 2**
Categories of DS change	Person-years	Deaths n (%)	HR (95% CI)	HR (95% CI)
Persistently high (n=602)	4255	71 (11.8)	1.00 (Reference)	1.00 (Reference)
Increased (n=913)	6383	115 (12.6)	0.94 (0.70-1.27)	0.84 (0.62-1.13)
Decreased (n=926)	6588	80 (8.6)	0.83 (0.60-1.14)	0.77 (0.56-1.06)
Persistently low (n=12 776)	91544	891 (7.0)	0.71 (0.56-0.91)	0.72 (0.56-0.92)
Test for trend			P<.001	P=.005

abbreviations: CI, confidence interval; DS, depressive symptoms; eCRF, estimated cardiorespiratory fitness; HR, hazard ratio; HUNT, Nord-Trøndelag Health Survey; SBP, systolic blood pressure.

model 1: adjusted for sex with the attained age as the time variable.

model 2: adjusted for sex, attained education, marital status, smoking status, SBP, alcohol consumption, heart disease,

stroke/brain hemorrhage, diabetes and change in eCRF, with the attained age as the time variable.

model 2 was stratified by cancer.

Table 4: Hazard Ratio of All-Cause Mortality by Categories of Change in Estimated Cardiorespiratory Fitness from HUNT2 (1995-97) to HUNT3 (2006-08)

			Model 1	**Model 2**
Categories of eCRF change	Person-years	Deaths n (%)	HR (95% CI)	HR (95% CI)
Persistently low (n=4435)	42002	498 (8.5)	1.00 (Reference)	1.00 (Reference)
Decreased (n=1717)	22897	196 (6.2)	0.98 (0.83-1.16)	1.02 (0.87-1.21)
Increased (n=3174)	12072	161 (9.4)	0.93 (0.78-1.11)	1.00 (0.83-1.19)
Persistently high (n=5891)	31798	302 (6.8)	0.72 (0.62-0.83)	0.76 (0.66-0.88)
Test for trend			P<.001	P=.001

abbreviations: CI, confidence interval; DS, depressive symptoms; eCRF, estimated cardiorespiratory fitness; HR, hazard ratio; HUNT, Nord-Trøndelag Health Survey; SBP, systolic blood pressure.

model 1: adjusted for sex with the attained age as the time variable.

model 2: adjusted for sex, attained education, marital status, smoking status, SBP, alcohol consumption, heart disease, stroke/brain hemorrhage, diabetes and change in DS, with the attained age as the time variable.

model 2 was stratified by cancer.