

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

2 Trude Carlsen<sup>1,2</sup>, MSc; Øyvind Salvesen<sup>1</sup>, PhD; Xuemei Sui<sup>3</sup>, MD, MPH, PhD; Carl J. Lavie<sup>4</sup>, MD; Steven N. Blair<sup>3</sup>, PhD; Ulrik Wisløff<sup>2,5</sup>, PhD; Linda  
3 Ernstsens<sup>1</sup>, RN, PhD.

4 <sup>1</sup>) Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology,  
5 Trondheim, Norway

6 <sup>2</sup>) K.G. Jebsen Center of Exercise in Medicine, Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences,  
7 Norwegian University of Science and Technology, Trondheim, Norway

8 <sup>3</sup>) Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC, United States

9 <sup>4</sup>) Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland  
10 School of Medicine, New Orleans, LA, United States

11 <sup>5</sup>) School of Human Movement & Nutrition Sciences, University of Queensland, Australia

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19 **Conflict of interest**

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21 **Corresponding author:** Linda Ernsten, RN, PhD

22 Department of Public Health and Nursing, Norwegian University of Science and Technology, Postbox 8905, 7491 Trondheim, Norway.

23 Phone +4773413036, Fax +4773597577

24 E-mail: linda.ernsten@ntnu.no

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41 **ABSTRACT**

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

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

48 **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  
49 died. Multivariable adjusted analyses showed that persistently low DS was independently associated with a 28% risk reduction of all-cause  
50 mortality (hazard ratio [HR], 0.72; 95% CI 0.56-0.92, p=.008) compared to persistently high DS. Persistently high eCRF independently predicted  
51 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  
52 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  
53 0.53; 95% CI 0.37-0.76, p=.001), respectively.

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

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

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69 **ABBREVIATIONS**

70 CI – Confidence Interval

71 CRF – Cardiorespiratory Fitness

72 CVD – Cardiovascular Disease

73 DS – Depressive Symptoms

74 eCRF – Estimated Cardiorespiratory Fitness

75 HADS – Hospital Anxiety and Depression Scale

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

77 HR – Hazard Ratio

78 HUNT – Nord-Trøndelag Health Study

79 PA – Physical Activity

80 RHR – Resting Heart Rate

81 SBP – Systolic Blood Pressure

82 WC – Waist Circumference

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## 85 INTRODUCTION

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

90 Cardiorespiratory fitness (CRF) is a physiological measure reflecting the body's ability to transport and utilize oxygen to perform physical work  
91 and is a strong predictor of mortality, independent of traditional risk factors, such as smoking, type 2 diabetes mellitus, and hypertension <sup>11-13</sup>.

92 A recent statement from the American Heart Association suggests assessing CRF in clinical practice to optimize the prevention and treatment  
93 of CVD <sup>14</sup>. Non-exercise models for estimation of CRF (eCRF) have been developed <sup>15-17</sup> and provides a rough estimate of objectively measured  
94 CRF <sup>15</sup>. More importantly, eCRF models are associated with all-cause and CVD mortality <sup>17-19</sup>. Therefore, eCRF is a valid estimate of CRF in  
95 population-based studies.

96 Studies investigating the relationship between DS and CRF suggest that higher CRF is associated with lower DS <sup>20-22</sup>. Further, among men with  
97 emotional distress, higher CRF was associated with lower risk of premature death, independent of other important mortality predictors <sup>23</sup>.

98 Despite the established protective effect of CRF on mortality and the association with DS, few studies investigating the relationship between DS  
99 and mortality account for the possible influence of CRF. A prospective study (The Aerobics Center Longitudinal Study) demonstrated that low

100 levels of negative emotions reduced the all-cause mortality risk by 30%, after adjusting for confounding factors, including CRF <sup>24</sup>. More  
101 interestingly, the combination of low levels of negative emotions and high CRF reduced the risk of all-cause mortality by 63% compared to  
102 participants with high levels of negative emotions and low CRF <sup>24</sup>.

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

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

## 113 **METHODS**

### 114 **Study Population**

115 HUNT is a population-based health study conducted in the Nord-Trøndelag county in Norway, with the first wave (HUNT1) conducted in 1984-  
116 86<sup>27</sup>. 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  
117 (n=26 208). Participants with missing data were excluded in the following order: DS HUNT2 (n=545), eCRF HUNT2 (n=1869), DS HUNT3  
118 (n=3162), eCRF HUNT3 (n=3510) and on any of the other confounders (age, sex, education, marital status, smoking status, alcohol  
119 consumption, heart disease, stroke/brain hemorrhage, diabetes, cancer) collected at HUNT3 (n=1905). The final cohort comprised 15 217  
120 participants. All HUNT participants provided written consent. Participants included in the present study were compared with those excluded  
121 due to missing data (n=10 991). On average, the excluded group had somewhat higher depressive symptoms and lower eCRF, compared with  
122 those included.

### 123 **Depressive Symptoms**

124 DS were assessed by a Norwegian translation of the Hospital Anxiety and Depression Scale (HADS)<sup>28</sup>. The basic psychometric properties of the  
125 Norwegian version of HADS were found to be acceptable based on HUNT2 data<sup>29</sup>. HADS consists of 14 items assessing psychological symptoms  
126 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  
127 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,  
128 replaced missing values. A cut-off score of  $\geq 8$  defined high DS, and has previously shown a sensitivity and specificity of 0.8 for caseness of  
129 depression<sup>30</sup>. 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<sup>17</sup>. 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:  $78.00 - (0.297 \cdot \text{age}) - (0.270 \cdot \text{WC}) - (0.110 \cdot \text{RHR}) + (2.674 \cdot \text{PA})$

136 Men:  $105.91 - (0.334 \cdot \text{age}) - (0.402 \cdot \text{WC}) - (0.144 \cdot \text{RHR}) + (3.102 \cdot \text{PA})$

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<sup>17, 31</sup>. RHR was measured using a Critikon Dinamap 845XT (GE Medical Systems) after two minutes of rest  
142 in the seated position<sup>32</sup> and WC was measured to the nearest centimeter using a band placed horizontally at the height of the umbilicus<sup>27</sup>.  
143 Estimated CRF above a sex- and age-specific (based on ten-year age categories) median value indicated higher levels of eCRF. We categorized

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

#### 146 **Confounders**

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

#### 154 **End point and Mortality Surveillance**

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

#### 158 **Statistical Analysis**

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

170 Analyses of change measured as a continuous variable were adjusted for the same variables as in the analyses of change as a categorical  
171 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  
172 HUNT2.

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

176 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  
177 multivariable-adjusted regression model.

178 Proportional hazard assumptions for the confounders were examined by Schoenfeld residuals. Interactions were tested between change in DS  
179 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  
180 Stata statistical software, v13.1 (StataCorp). Two-sided p-values <.05 were considered statistically significant.

## 181 **RESULTS**

182 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,  
183 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  
184 were not statistically significant. HUNT3 characteristics are presented in **Table 1** and **Table 2** according to categories of change in DS and eCRF,  
185 respectively.

### 186 **Change in Depressive Symptoms**

187 **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

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

191 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  
192 risk of all-cause mortality (HR 1.04, 95%CI 1.01-1.06) over the 7 years of follow-up.

### 193 **Change in eCRF**

194 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%  
195 lower risk of all-cause mortality compared to those with persistently low eCRF (**Table 4**). Further adjustment for confounders (model 2),  
196 revealed that those having persistently high eCRF had 24% lower all-cause mortality risk compared to those with persistently low eCRF (**Table**  
197 **4**). The linear test for trend indicated an inverse dose-response relationship ( $p=0.001$ ) across the categories of eCRF change and all-cause  
198 mortality.

199 In the multivariable adjusted analysis of mortality risk from change in eCRF measured as a continuous variable (data not shown), each 1  
200 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  
201 follow-up.

### 202 **Combined Groups**

203 For the combined patterns of change in DS and eCRF (**Figure 1**), the largest risk reduction was observed among those with persistently high  
204 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  
205 persistently low eCRF and persistently high DS. The combination of persistently high eCRF and persistently high DS was not associated with  
206 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  
207 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  
208 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-  
209 1.03; decreased eCRF, HR 0.71, 95%CI 0.49-1.02).

## 210 **DISCUSSION**

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

216 Our results suggest that preventing increased DS and high DS over time may play an important role in the association with all-cause mortality.

217 In line with our findings, data on nearly 2000 participants from The Amsterdam Study of the Elderly showed that chronic depression (diagnosed

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

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

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

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

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

#### 245 **Strengths and Limitations**

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

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

252 Furthermore, population-based studies are vulnerable to selection bias and non-participation studies from HUNT2 show that older age, and  
253 mental health issues are related to non-participation <sup>32, 37</sup>. If a significant number of the non-participants eligible for the present study did not  
254 participate due to mental health issues, we recognize the possibility of an underestimation of the measured associations. The eCRF model used  
255 in the present study is based on cross-sectional data. It is shown that CRF declines in a nonlinear manner with age <sup>38</sup> which the eCRF model  
256 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  
257 hand, the algorithm is specific for the present population as it is based on a sample of study participants from HUNT2 <sup>17</sup>. In addition, Nauman  
258 and colleagues found the current used eCRF model to be associated with all-cause and CVD mortality <sup>17</sup>. The present results expand the eCRF  
259 and mortality relationship by showing an association between eCRF change status and mortality. However, future studies on changes in eCRF  
260 should use eCRF models based on longitudinal data to confirm the latter statement <sup>16, 39</sup>. Future research should aim to assess DS and eCRF at  
261 several closer time points to capture the changing nature of DS and the influence lifestyle factors and disease status have on eCRF.

## 262 **CONCLUSION**

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

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270 Public Health.

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357 **Figure 1:** Hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality by combinations of changes in depressive symptoms and  
358 estimated cardiorespiratory fitness from HUNT 2 (1995-97) to HUNT 3 (2006-08) in the total study population (n=15 217). All data were  
359 adjusted for age, sex, marital status, attained education, smoking status, alcohol consumption, SBP, heart disease, stroke/brain  
360 hemorrhage and diabetes at baseline in HUNT 3. DS=depressive symptoms, eCRF=estimated cardiorespiratory fitness, SBP=systolic  
361 blood pressure. The number of participants (number of all-cause deaths) in the persistently low, decreased, increased and persistently  
362 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  
363 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  
364 (128) and 3841 (237) in the persistently low DS group, respectively. \*Depressive symptoms=DS, \*\*Estimated cardiorespiratory  
365 fitness=eCRF.

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

<b>Depression Symptoms</b>	<b>Persistently low</b>	<b>Decreased</b>	<b>Increased</b>	<b>Persistently high</b>	<b>p-value</b>
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 <sup>1</sup>	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-

375 Trøndelag

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

377 <sup>1</sup>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)

<b>Fitness</b>	<b>Persistently high</b>	<b>Increased</b>	<b>Decreased</b>	<b>Persistently low</b>	<b>p-value</b>
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 <sup>1</sup>	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-

390 Trøndelag

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

392 <sup>1</sup>according to current physical activity recommendations.

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401 **Table 3:** Hazard Ratios of All-Cause Mortality by Categories of Change in Depressive Symptoms from

402 HUNT2 (1995-97) to HUNT3 (2006-08)

			<b>Model 1</b>	<b>Model 2</b>
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

403 abbreviations: CI, confidence interval; DS, depressive symptoms; eCRF, estimated cardiorespiratory fitness;

404 HR, hazard ratio; HUNT, Nord-Trøndelag Health Survey; SBP, systolic blood pressure.

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

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

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

408 model 2 was stratified by cancer.

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423 **Table 4:** Hazard Ratio of All-Cause Mortality by Categories of Change in Estimated Cardiorespiratory Fitness

424 from HUNT2 (1995-97) to HUNT3 (2006-08)

			<b>Model 1</b>	<b>Model 2</b>
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

425 abbreviations: CI, confidence interval; DS, depressive symptoms; eCRF, estimated cardiorespiratory fitness;

426 HR, hazard ratio; HUNT, Nord-Trøndelag Health Survey; SBP, systolic blood pressure.

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

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

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

430 model 2 was stratified by cancer.

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