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

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Abstract

Objective: To assess the independent and combined associations of long-term changes in depressive symptoms (DSs) and estimated cardiorespiratory fitness (eCRF) with all-cause mortality.

Participants and Methods: This is a longitudinal cohort study of 15,217 middle-aged and older individuals attending both the second (from August 15, 1995, through June 18, 1997) and third (from October 3, 2006, through June 25, 2008) health surveys of the Nord-Trøndelag Health Study, Norway, and followed until December 31, 2014. Depressive symptoms were estimated using the validated Hospital Anxiety and Depression Scale, and a validated nonexercise model estimated eCRF. Hazard ratios (HRs) were computed using Cox regression. All-cause mortality was ascertained using the Norwegian Cause of Death Registry.

Results: The mean age was 63.3 ± 8.9 years, and 7932 (52.1%) were women. During the follow-up period of 7.1 ± 1.1 years, 1157 participants (7.6%) died. Multivariable-adjusted analyses revealed that persistently low DSs were independently associated with a 28% risk reduction of all-cause mortality (HR, 0.72; 95% CI, 0.56-0.92; P = .008) as compared with persistently high DSs. Persistently high eCRF independently predicted a 26% lower risk of death (HR, 0.76; 95% CI, 0.66-0.88; P < .001) relative to low eCRF. Analyses of changes in DSs and eCRF revealed that persistently high eCRF combined with decreased or persistently low DSs 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.

Conclusion: Maintaining low DSs and high eCRF was independently associated with a lower risk of all-cause mortality. The lowest mortality risk was observed for persistently high eCRF combined with decreased or persistently low DSs. These results emphasize the effect of preventing DSs and maintaining high CRF on long-term mortality risk, which is potentially important for long-term population health.

Depression is among the top 3 leading causes of years lived with disability and affects approximately 350 million people worldwide, with increasing prevalence with increasing age. Depression and depressive symptoms (DSs) have been linked with cardiovascular disease (CVD) and risk of premature mortality. 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.

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. A recent statement from the American Heart Association suggests assessing CRF in clinical practice to optimize the prevention and treatment of CVD. Nonexercise models for the estimation of CRF (estimated CRF [eCRF]) have been developed, which provide a rough estimate of objectively measured from the Department of Public Health and Nursing (T.C., ØS, LE) and K.G. Jebsen Center for Exercise in Medicine, Department of Circulation and Medical Imaging (T.C., U.W.), Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway; Department of Exercise Science, Arnold School of Public Health, University of

Affiliations continued at the end of this article.
More importantly, eCRF models are associated with all-cause and CVD mortality. Therefore, eCRF is a valid estimate of CRF in population-based studies. Studies investigating the relationship between DSs and CRF suggest that higher CRF is associated with lower DSs. Furthermore, in men with emotional distress, a higher CRF was associated with a lower risk of premature death, independent of other important mortality predictors.

Despite the established protective effect of CRF on mortality and the association of CRF with DSs, few studies investigating the relationship between DSs and mortality account for the possible influence of CRF. A prospective study (the Aerobics Center Longitudinal Study) reported that low levels of negative emotions reduced the all-cause mortality risk by 30% after adjusting for confounding factors, including CRF. More interestingly, the combination of low levels of negative emotions and high CRF reduced the risk of all-cause mortality by 63% as compared with the combination of high levels of negative emotions and low CRF.

There are few longitudinal studies considering the changing nature of DSs and mortality risk. Among the studies investigating this relationship, Geerlings et al reported that middle-aged and older people with persistently high DSs were more than twice as likely to suffer from premature death as those with consistently low DSs. Schoevers et al reported a 38% higher risk of mortality in middle-aged and older community living people depressed at both baseline and at 3-year follow-up as compared with nondepressed counterparts. Both studies adjusted for demographic characteristics, chronic diseases, and functional limitations, but neither considered CRF.

Therefore, how the direction of change in DSs 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 DSs change and premature death. In the present study, we determined the independent associations of changes in DSs and eCRF with all-cause mortality in middle-aged and older adults. We further investigated how combinations of changes in DSs and eCRF were associated with long-term survival.

**PARTICIPANTS AND METHODS**

**The Nord-Trøndelag Health Study**

The Nord-Trøndelag Health (HUNT) Study is a population-based health study conducted in the county of Nord-Trøndelag in Norway, with the first wave conducted in 1984 to 1986 (HUNT1, from January 16, 1984, through April 15, 1986). The HUNT Study is a collaboration between HUNT Research Centre [Faculty of Medicine, Norwegian University of Science and Technology], Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health. The participants in the present study attended both the second (HUNT2, from August 15, 1995, through June 18, 1997) and third (HUNT3, from October 3, 2006, through June 25, 2008) waves and survived up to the age of 50 years in HUNT3 (n=26,208). Participants with missing data were excluded in the following order: DSs HUNT2, n=545; eCRF HUNT2, n=1869; DSs HUNT3, n=3162; eCRF HUNT3, n=3510; and any of the other confounders (age, sex, education, marital status, smoking status, alcohol consumption, heart disease, stroke/brain hemorrhage, diabetes, and cancer) collected in 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 because of missing data (n=10,991). On average, the excluded group had somewhat higher DSs and lower eCRF than did the included group.

**Depressive Symptoms**

Depressive symptoms were assessed by a Norwegian translation of the Hospital Anxiety and Depression Scale (HADS). The basic psychometric properties of the Norwegian version of the HADS were found to be acceptable based on HUNT2 data. The HADS consists of 14 items assessing psychological symptoms of depression (HADS — depression [HADS-D] subscale) and anxiety during the past week. The HADS-D subscale covers 7 items. Each item scores 0 to 3 points, with the highest...
score reflecting the most symptomatic load. If participants filled in 5 or 6 items only, the total score multiplied by 7/5 or 7/6, respectively, replaced missing values. A cutoff score of 8 or more defined high DSs, which has previously shown a sensitivity and specificity of 0.8 for caseness of depression.\(^{30}\) We classified change into 4 categories: persistently high, increased, decreased, and persistently low. Change measured as a continuous variable was the difference between HUNT2 and HUNT3.

**Estimated CRF**

Estimated CRF was calculated using a validated nonexercise prediction model based on data from HUNT2.\(^{17}\) The sex-specific models included age, physical activity (PA) level, resting heart rate (RHR), and waist circumference (WC). The following models were used to estimate each participant’s CRF (in milliliters per kilogram per minute):

**Women:**

\[
78.00 - (0.297 \times \text{age}) - (0.270 \times \text{WC}) - (0.110 \times \text{RHR}) + (2.674 \times \text{PA level})
\]

**Men:**

\[
105.91 - (0.334 \times \text{age}) - (0.402 \times \text{WC}) - (0.144 \times \text{RHR}) + (3.102 \times \text{PA level})
\]

The self-administered questionnaire provided information on the average weekly duration and intensity of leisure time PA during the past year. Participants were asked to specify the average number of hours of low (no sweating or being out of breath)—and vigorous (sweating/out of breath)—intensity PA per week during the past year (separate questions for low- and vigorous-intensity PA), with response options “none,” “less than an hour,” “1 to 2 hours,” and “3 hours or more.” To enable the estimation of eCRF, participants were divided into 2 categories: (1) meeting (PA level=1) recommended amount of minutes of PA per week (vigorous-intensity PA for a total of \(\geq 75\) min/wk or moderate-intensity PA for \(\geq 150\) min/wk, or a combination of both) or (2) not meeting (PA level=0) PA recommendations.\(^{17,31}\) The resting heart rate was measured using a Critikon Dinamap 845XT automatic monitor after 2 minutes of rest in the seated position,\(^{32}\) and WC was measured to the nearest centimeter using a band placed horizontally at the height of the umbilicus.\(^{27}\) Estimated CRF above an age- and sex-specific (based on 10-year age categories) median value indicated higher eCRF. We categorized change according to the median value into 4 categories: persistently high, increased, decreased, and persistently low. Change measured as a continuous variable was the difference between HUNT2 and HUNT3.

**Confounders**

Self-administered questionnaires and clinical measurements from HUNT3 provided data on 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 the average number of alcoholic beverages (beer, wine, and liquor) over a typical 2-week period. Smoking habits were categorized into never, former smoker, 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 or no response for each disease. Systolic blood pressure (SBP; in millimeters of mercury) was measured using a Critikon Dinamap 845XT automatic monitor after a 2-minute rest in the seated position. Statistics Norway provided educational data.

**End Point and Mortality Surveillance**

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

**Statistical Analyses**

The characteristics of participants from HUNT3 are presented as mean (95% CI) and number (percentage) for continuous and categorical variables, respectively, and compared using the Pearson chi-square test for categorical variables and 1-way analysis of variance for continuous variables. The associations between change in DSs, change in eCRF, and all-cause mortality were assessed using Cox regression, and hazard
ratios (HRs) and 95% CI were computed. Two models were used to assess the association between change in DSs measured as a categorical variable and mortality and the association 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 DSs as the independent variable), change in DSs (in the analysis with eCRF as the independent variable), education, marital status, smoking, alcohol consumption, SBP, heart disease, stroke/brain hemorrhage, and diabetes. The stratifying variable in model 2 was cancer because of the apparent violation of the proportional hazard assumption. Those having persistently high DSs and those having persistently low eCRF were set as reference categories for the separate analyses of the association of change in DSs and change in eCRF with mortality, respectively. Analyses of change measured as a continuous variable were adjusted for the same variables as in the analyses of change measured as a categorical variable. In addition, the analysis of change in DSs was adjusted for DSs in HUNT2 and the analysis of change in eCRF was adjusted for eCRF in HUNT2. The final analysis assessed the association of the combined patterns of changes in DSs and eCRF with all-cause mortality. By combining the 2 categorical variables, we created 16 new combinations. The combination of persistently high DSs and persistently low eCRF was set as the reference category.

### TABLE 1. Characteristics of Participants in HUNT3 by Categories of Change in DSs From HUNT2 (1995–1997) to HUNT3 (2006–2008)a,b

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Persistently low</th>
<th>Decreased</th>
<th>Increased</th>
<th>Persistently high</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants with data</td>
<td>12,776 (84.0)</td>
<td>926 (6.1)</td>
<td>913 (6.0)</td>
<td>602 (4.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63.0 (62.9-63.2)</td>
<td>64.1 (63.6-64.7)</td>
<td>65.0 (64.3-65.6)</td>
<td>64.5 (63.8-65.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Women</td>
<td>6740 (52.8)</td>
<td>484 (52.3)</td>
<td>427 (46.8)</td>
<td>281 (46.7)</td>
<td>.001</td>
</tr>
<tr>
<td>HADS-D score</td>
<td>2.8 (2.7-2.8)</td>
<td>4.5 (4.4-4.7)</td>
<td>9.3 (9.2-9.4)</td>
<td>9.8 (9.7-10.0)</td>
<td>.001</td>
</tr>
<tr>
<td>eCRF (mL/kg per minute)</td>
<td>32.9 (32.8-33.1)</td>
<td>32.1 (31.6-32.5)</td>
<td>31.9 (31.4-32.3)</td>
<td>31.7 (31.2-32.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Tertiary</td>
<td>2980 (23.3)</td>
<td>151 (16.3)</td>
<td>135 (14.8)</td>
<td>77 (12.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Secondary</td>
<td>7230 (56.6)</td>
<td>538 (58.1)</td>
<td>525 (57.5)</td>
<td>345 (57.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Primary</td>
<td>2566 (20.1)</td>
<td>237 (25.6)</td>
<td>253 (27.7)</td>
<td>180 (29.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Married</td>
<td>9484 (74.2)</td>
<td>627 (67.7)</td>
<td>618 (67.7)</td>
<td>386 (64.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Unmarried</td>
<td>709 (5.6)</td>
<td>62 (6.7)</td>
<td>70 (7.7)</td>
<td>72 (12.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>1204 (9.4)</td>
<td>112 (12.1)</td>
<td>115 (12.6)</td>
<td>77 (12.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Widow(er)</td>
<td>1379 (10.8)</td>
<td>125 (13.5)</td>
<td>110 (12.1)</td>
<td>67 (11.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>Never</td>
<td>4846 (37.9)</td>
<td>296 (32.0)</td>
<td>337 (36.9)</td>
<td>189 (31.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Former</td>
<td>5416 (42.4)</td>
<td>396 (42.8)</td>
<td>364 (39.9)</td>
<td>264 (43.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Current</td>
<td>2514 (19.7)</td>
<td>234 (25.3)</td>
<td>212 (23.2)</td>
<td>149 (24.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Alcohol consumption (units/2 wk)</td>
<td>4.6 (4.5-4.7)</td>
<td>4.2 (3.8-4.6)</td>
<td>3.9 (3.5-4.2)</td>
<td>3.7 (3.3-4.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Physically activec</td>
<td>7997 (62.6)</td>
<td>545 (58.9)</td>
<td>466 (51.0)</td>
<td>305 (50.7)</td>
<td>.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>94.9 (94.7-95.1)</td>
<td>96.4 (95.6-97.2)</td>
<td>97.0 (96.2-97.8)</td>
<td>97.8 (96.9-98.8)</td>
<td>.001</td>
</tr>
<tr>
<td>RHR (beats/min)</td>
<td>67.6 (67.4-67.8)</td>
<td>67.6 (66.9-68.4)</td>
<td>68.1 (67.4-68.9)</td>
<td>68.0 (67.1-68.9)</td>
<td>.44</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>135.9 (135.6-136.2)</td>
<td>135.1 (133.9-136.3)</td>
<td>134.6 (133.4-135.8)</td>
<td>134.8 (133.3-136.3)</td>
<td>.09</td>
</tr>
<tr>
<td>Diabetes</td>
<td>723 (5.7)</td>
<td>66 (7.1)</td>
<td>64 (7.0)</td>
<td>43 (7.1)</td>
<td>.06</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>951 (7.4)</td>
<td>108 (11.7)</td>
<td>109 (11.9)</td>
<td>63 (10.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Stroke/brain hemorrhage</td>
<td>417 (3.3)</td>
<td>45 (4.9)</td>
<td>51 (5.6)</td>
<td>31 (5.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>996 (7.8)</td>
<td>64 (6.9)</td>
<td>86 (9.4)</td>
<td>39 (6.5)</td>
<td>.12</td>
</tr>
</tbody>
</table>

*aDSs = depressive symptoms; eCRF = estimated cardiorespiratory fitness; HADS-D = Hospital Anxiety and Depression Scale — depression; HUNT = Nord-Trøndelag Health Study; HUNT2 = 1995–1997; HUNT3 = 2006–2008; RHR = resting heart rate; SBP = systolic blood pressure; WC = waist circumference.

bData are presented as mean (95% CI) or as No. (percentage).

cPhysically active according to current physical activity recommendations: vigorous-intensity physical activity for a total of ≥75 min/wk or moderate-intensity physical activity for ≥150 min/wk, or a combination of both.
A test of linear trend was performed separately for changes in DSs and eCRF by adding the 4-category variable as an ordinal variable in the multivariable-adjusted regression model.

Proportional hazard assumptions for the confounders were examined using Schoenfeld residuals. Interactions were tested between the change in DSs and the change in eCRF, between the change in DSs and sex, and between the change in eCRF and sex by using the likelihood ratio test. Statistical analyses were performed using Stata version 13.1 (StataCorp LLC). Two-sided $P$ values less than .05 were considered statistically significant.

**RESULTS**

The mean age of the 15,217 included participants was $63.3\pm8.9$ years in HUNT3, and 7932 (52.1%) were women. During the follow-up period of $7.1\pm1.1$ years, 1157 (7.6%) died of all causes. The likelihood ratio tests showed that the models with the interactions between (1) change in CSs and change in eCRF, (2) change in DSs and sex, and (3) change in eCRF and sex, did not fit the data better than the models which did not include the interactions ($P=0.33$, $P=0.96$, and $P=0.66$, respectively). The characteristics of participants in HUNT3 are presented in Tables 1 and 2 according to categories of change in DSs and change in eCRF, respectively.
persistently low DSs had a 29% (HR, 0.71; 95% CI, 0.56-0.91) lower risk of all-cause mortality than did those with persistently high DSs during the 7 years of follow-up. After additional adjustments for confounders (model 2), the risk remained nearly the same. The test for linear trend suggested an inverse dose-response relationship (P = .005) across the categories of change in DSs.

In the multivariable-adjusted analysis of DSs as a continuous variable (data not shown), each 1-unit increase in DSs was associated with a 4% higher risk of all-cause mortality than did those with persistently low DSs during the 7 years of follow-up (Table 4). Further adjustment for confounders (model 2) revealed that those having persistently high eCRF had a 24% (HR, 0.76; 95% CI, 0.66-0.88) lower risk of all-cause mortality than did those with persistently low eCRF (Table 4). The test for linear trend indicated an inverse dose-response relationship (P = .001) across the categories of eCRF change and all-cause mortality.

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

**Combined Groups**
For the combined patterns of change in DSs and change in eCRF (Figure), the largest risk

<table>
<thead>
<tr>
<th>TABLE 3. Hazard Ratios for All-Cause Mortality by Categories of Change in DSs From HUNT2 (1995-1997) to HUNT3 (2006-2008)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Categories of DSs change</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Persistently high (n=602)</td>
</tr>
<tr>
<td>Increased (n=913)</td>
</tr>
<tr>
<td>Decreased (n=926)</td>
</tr>
<tr>
<td>Persistently low (n=12,776)</td>
</tr>
<tr>
<td>Test for trend</td>
</tr>
</tbody>
</table>

*DSs = depressive symptoms; HR = hazard ratio; HUNT = Nord-Trøndelag Health Study; HUNT2 = 1995-1997; HUNT3 = 2006-2008.
1Adjusted for sex, attained education, marital status, smoking status, systolic blood pressure, alcohol consumption, heart disease, stroke/brain hemorrhage, diabetes, and change in estimated cardiorespiratory fitness, with attained age as the time variable.
2Model 2 was stratified by cancer.

<table>
<thead>
<tr>
<th>TABLE 4. Hazard Ratios for All-Cause Mortality by Categories of Change in eCRF From HUNT2 (1995-1997) to HUNT3 (2006-2008)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Categories of eCRF change</strong></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Persistently low (n=4435)</td>
</tr>
<tr>
<td>Decreased (n=1717)</td>
</tr>
<tr>
<td>Increased (n=3174)</td>
</tr>
<tr>
<td>Persistently high (n=5891)</td>
</tr>
<tr>
<td>Test for trend</td>
</tr>
</tbody>
</table>

*eCRF = estimated cardiorespiratory fitness; HR = hazard ratio; HUNT = Nord-Trøndelag Health Study; HUNT2 = 1995-1997; HUNT3 = 2006-2008.
1Adjusted for sex, with attained age as the time variable.
2Adjusted for sex, attained education, marital status, smoking status, systolic blood pressure, alcohol consumption, heart disease, stroke/brain hemorrhage, diabetes, and change in depressive symptoms, with attained age as the time variable.
3Model 2 was stratified by cancer.
reduction was observed in those with persistently high eCRF who had decreased DSs (HR, 0.51; 95% CI, 0.28-0.91) or had persistently low DSs (HR, 0.53; 95% CI, 0.37-0.76) as compared with those having persistently low eCRF and persistently high DSs. The combination of persistently high eCRF and persistently high DSs was not associated with mortality risk reduction (HR, 0.89; 95% CI, 0.51-1.55) as compared with the combination of persistently low eCRF and persistently high DSs. Persistently low DSs were associated with reduced mortality risk, irrespective of persistently low eCRF (HR, 0.69; 95% CI, 0.49-0.98).

DISCUSSION
The main findings of the present study were that (1) maintaining low DSs was associated with a lower risk of all-cause mortality during the 7 years of follow-up as compared to persistently high DSs; (2) the most

FIGURE. Hazard ratios and 95% CIs for all-cause mortality by combinations of changes in DSs and eCRF from HUNT2 (1995-1997) to HUNT3 (2006-2008) in the total study population (n=15,217). All data were adjusted for age (as timescale), sex, marital status, education, smoking status, alcohol consumption, systolic blood pressure, heart disease, stroke/brain hemorrhage, and diabetes in HUNT3 and stratified by cancer. The number of participants (number of all-cause deaths) in the persistently low, decreased, increased, and persistently high eCRF groups, respectively, were 297 (35), 99 (10), 66 (6), and 140 (20) in the persistently high DSs group; 425 (58), 194 (14), 85 (15), and 209 (28) in the increased DSs group; 395 (32), 171 (19), 115 (12), and 245 (17) in the decreased DSs group; and 4774 (373), 2710 (153), 1451 (128), and 3841 (237) in the persistently low DSs group. DSs = depressive symptoms; eCRF = estimated cardiorespiratory fitness; HUNT = Nord-Trøndelag Health Study; HUNT2 = 1995-1997; HUNT3 = 2006-2008.
favorable combination of DSs and eCRF for lower risk of mortality was seen in those maintaining high eCRF who had either decreased or persistently low DSs; (3) the combination of persistently high eCRF and persistently high DSs was not associated with mortality risk reduction. 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 DSs change) and change in DSs (for eCRF change).

The results of the present study suggest that preventing increased DSs and high DSs 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 indicated that chronic depression (diagnosed using the Geriatric Mental State-AGECAT) over a 3-year period increased the risk of 10-year mortality by 38%. In contrast, Penninx et al (n=3701; Established Populations for Epidemiologic Studies of the Elderly) found that the association between persistently high DSs over 3 and/or 6 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. 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 makes comparisons difficult.

The nonsignificant association between increased or decreased DSs and mortality risk observed in this study was in accordance with other studies and could possibly be due to the fluctuating nature of DSs. In the present study, DSs were measured at 2 time points (10 years apart). The Norwegian HADS-D assesses symptom load during the past week. Thus, participants classified as having high DSs may have experienced lower DSs sometime between the 2 HUNT assessments, and vice versa, for participants classified as having low DSs. The study by Schoevers et al assessed depression 3 years after baseline evaluation and found no association between remitted or incident depression and mortality risk. Furthermore, no association was found between participants with high degree of instability of DSs (measured 8 times over a 3-year period) and mortality risk compared to those with persistently low DSs.

In our combined analyses, compared with participants with persistently high DSs and persistently low eCRF, those maintaining high eCRF had a lower risk of all-cause mortality, regardless of DSs change, except for the combination of persistently high eCRF and persistently high DSs. Surprisingly, those who had persistently high DSs and at the same time maintained high eCRF did not exhibit reduced mortality risk, which indicates the strong detrimental influence persistently high DSs might have on long-term health.

The literature shows a link between cardiovascular health and brain function and structure, but the underlying potential pathophysiological mechanisms of the association between CRF and DSs have not been entirely elucidated. Potential mechanisms include both social and biological explanations. Therefore, whether the association between CRF and DSs works through these pathways is at present unclear. Our observation that persistently high eCRF did not reduce the all-cause mortality risk in individuals with persistently high DSs indicates that the association between DSs and all-cause mortality works through pathways other than the cardiovascular system. Our results indicated that maintaining low DSs lowered the risk of all-cause mortality, regardless of eCRF change status, in comparison to the reference group. The small number of participants in some of the combination groups should be noted, and it 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 than did those with persistently low eCRF, which is in line with previous studies. The reduced risk for those with persistently high eCRF was still evident after adjusting for confounding factors, including concurrent change in DSs. Ortega et al
highlighted the importance of considering psychological well-being in their study of CRF and mortality risk, revealing that additional adjustment for negative emotions slightly reduced the influence of CRF on mortality, but the association remained statistically significant. However, that study was based on a single measurement of DSs; thus, no changes in relevant variables were considered.

The strengths of our study were a large number of participants with complete follow-up data; extensive control of data on psychosocial, lifestyle, and biological factors; and, most importantly, control of eCRF which strengthens our findings. Adjustments for DSs were included for eCRF analysis, and vice versa, recognizing the close relationship between mental and physical health. To our knowledge, this is the first study to assess the combined association of change in DSs and change in eCRF with mortality. However, we acknowledge several limitations of our study. Because of missing data on relevant variables in HUNT2 and HUNT3, we did not consider changes in some questions on lifestyle factors in HUNT2 and HUNT3, we did not consider changes in any medical conditions or lifestyle factors other than DSs and eCRF. Furthermore, no register-based or self-reported measures on current antidepressant medication use or other medications that may influence DSs and/or eCRF were available.

Population-based studies are vulnerable to selection bias, and nonparticipation studies from HUNT2 found that older age and mental health issues are related to nonparticipation.\(^{32,42}\) If a significant number of the nonparticipants eligible for the present study did not participate because of 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,\(^ {43}\) 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. In contrast, the algorithm is specific for the present population, as it is based on a sample of study participants from HUNT2.\(^ {17}\) In addition, Nauman et al\(^ {17}\) found the currently used eCRF model to be associated with all-cause and CVD mortality. The present results expand the eCRF and mortality relationship by exhibiting 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 last statement.\(^ {10,44}\)

Future research should aim to assess DSs and eCRF at several closer time points to capture the changing nature of DSs and the influence lifestyle factors and disease status have on eCRF.

**CONCLUSION**

The results of the present study indicated that maintaining low or improving DSs are associated with a decreased mortality risk after accounting for eCRF change. Maintaining high eCRF and at the same time having high or increasing DSs were not associated with reduced all-cause mortality risk. This study suggests that efforts should be made to assess both DSs and eCRF and emphasizes modalities to reduce long-term high DSs and improve fitness, as improvements in both are associated with considerable improvement in long-term survival.
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REFERENCES


