# Relationship of non-melancholic and melancholic depressive symptoms with all-cause mortality: A prospective study in a primary care population

**Running title: Depressive symptoms and all-cause mortality**

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# Relationship of non-melancholic and melancholic depressive symptoms with all-cause mortality: A prospective study in a primary care population


## Abstract

**Objective:** To assess relationship of non-melancholic and melancholic subtypes of depressive symptoms with all-cause mortality among cardiovascular risk persons.

**Methods:** A population-based prospective study of 2522 Finnish middle-aged persons with elevated cardiovascular risk was conducted. Depressive symptoms were assessed by the Beck´s Depression Inventory. Data on mortality were obtained from the official statistics after 11-year follow-up.

**Results:** At baseline, the prevalence of non-melancholic and melancholic depressive symptoms was 14.9% and 5.2%, respectively. During the mean follow-up time of 11 years, 8.1% (n = 164) of those without, 13.9% (n = 52) of those with non-melancholic, and 10.7% (n = 14) of those with melancholic depressive symptoms died. Compared to non-depressive subjects, the hazard ratio for time to all-cause mortality was 1.67 (95 % CI: 1.21-2.32, p = 0.002) in non-melancholically depressive and 1.01 (95 % CI: 0.56-1.83, p = 0.97) in melancholically depressive subjects, when adjusted for age, gender, education, smoking, alcohol use, BMI, hypertension, dyslipidaemia, and glucose disorders. In comparison to the mortality rate in the general population throughout Finland over the same period, non-depressiveness was associated with a decreased standardized mortality rate.

**Conclusion:** Non-melancholic depressive symptoms seem to be associated with excess all-cause mortality. In clinical settings, recognition of non-melancholic depressive symptoms should be emphasised.



## Keywords

All-cause mortality; Beck's Depression Inventory; melancholic depressive symptoms; non-melancholic depressive symptoms

## Introduction

Depression and increased depressive symptoms have been associated with excess mortality [1–3]. It has been proposed that the increased mortality risk is similar in major and subthreshold depression [3], and in the general population and specific patient groups [2]. However, two recent reviews of meta-analyses [4,5] suggest evidence of a causal relationship between depression and all-cause mortality ~~is~~ to be still inconclusive, partly due to inadequate adjusting for confounding variables such as cardiovascular disease (CVD) risk factors and health behaviours [4,5]. Machado et al. [4] have stated that only 40 % of the studies included in the meta-analyses controlled for at least age and sex. Considering depression has repeatedly been associated with poor health behaviours such as smoking [6] and low physical activity [7], other major health risk factors such as obesity [8,9], and global leading cause of death, CVD [10,11], taking these factors into account seems essential when studying depression and mortality. Moreover, there is extensive literature on the association of depression and mortality among subjects with established CVD [12], but we are not aware that the association of depression and mortality would have previously been studied namely among CVD risk subjects.

In addition, the multifaceted nature of depression [13] has rarely been considered in studies assessing depressive symptomatology and mortality, although subtyping depression has been proposed to be useful [14]. Depressive symptoms can be divided into melancholic, i.e. typical, and non-melancholic, i.e. atypical subtypes [15] which might be attributable to different biological dysregulations [15], and thus differently relate to somatic diseases and mortality. Specifically, non-melancholic depressive symptoms including mood reactivity, interpersonal rejection sensitivity, hypersomnia, fatigue, increased appetite, and weight gain [16] have been associated with CVD risk factor clustering [17] and increased risk for incident CVD [18]. This could highlight the importance of subtyping depressive symptoms also in clinical practice.

To the best of our knowledge, the association of atypicality of depression and mortality has only once been studied in a prospective setting [19]. In this study, Lasserre et al. aimed to assess the effect of clinical and course characteristics of depression on all-cause mortality, and found no association between atypical depression and increased mortality risk. Among their study population (n = 3668), only 1.6 % (n = 56) died during the 5-year follow-up, and the prevalence of atypical depression among the depressed subjects (n = 1971) was 16.5 %, probably attenuating the possibility to detect differences between the subgroups.

Due to this lack of research on the subtypes of depressive symptoms and mortality risk our study aims to provide more evidence on the association of subtypes of depressive symptoms and all-cause mortality. Furthermore, we previously found that specifically non-melancholic depressive symptoms increased risk for CVD [18]. Now, after a longer follow-up, we aimed to assess whether non-melancholically and melancholically depressive middle-aged CVD risk subjects, who were apparently healthy at baseline, have an increased risk for all-cause mortality, and whether this risk differs according to the depressive subtype.

## Methods

### Study population

The study sample was drawn from the Harjavalta Risk Monitoring for Cardiovascular Disease (Harmonica) Project, a population survey aiming to assess CVD risk factors and risk for type 2 diabetes (T2D) in middle-aged subjects, conducted in the semirural towns of Harjavalta and Kokemäki with only Caucasian population from autumn 2005 to autumn 2007. All non-institutionalized 45- to 70-year-old inhabitants (n = 6013) were invited. They were mailed a CVD risk factor survey (Table 1), a tape for waist circumference measurement, and a T2D risk assessment form (FINDRISC, Finnish Diabetes Risk Score, available from www.diabetes.fi/english)

[20]. The CVD risk factor survey was developed by the investigators of the Harmonica Project, and it included assessment of well-established CVD risk factors. The FINDRISC is a validated instrument for assessing risk for T2D [20]. Its total score ranges from 0 to 26, and it represents the risk for developing T2D within ten years (categorized as low risk: < 7 points, estimated 1 in 100 will develop T2D; slightly elevated risk: 7-11 points, estimated 1 in 25 will develop T2D; moderate risk: 12-14 points, estimated 1 in 6 will develop T2D; high risk: 15-20 points, estimated 1 in 3 will develop T2D; very high risk: > 20 points, estimated 1 in 2 will develop T2D). Of those responding (n = 4450, 74%), we included subjects with at least one CVD risk factor assessed by the CVD risk factor survey (n = 3072). Considering inclusion criteria, different cut-off values for the FINDRISC score in Harjavalta and Kokemäki were used for logistical reasons: due to limited financial resources and the surprisingly high response rate with FINDRISC score ≥ 12 in Kokemäki. Of the 3072 subjects meeting the inclusion criteria, 2752 attended the study visit. In the present analysis, only subjects with completed Beck´s Depression Inventory (BDI) [21] were included (n = 2522). Exclusion criteria were a previously established CVD (ischemic heart disease (IHD), cerebrovascular disease (CeVD), or peripheral artery disease (PAD)), chronic kidney disease or T2D, determined by medical records.

**Table 1.** Cardiovascular risk factor survey: Factors considered and definition for cardiovascular risk.

| FACTOR | RISK DEFINITION |
|---|---|
| Waist circumference | ≥ 80 cm in women and ≥ 94 cm in men* |
| Use of antihypertensive medication | Yes |
| Latest blood pressure measurement | ≥ 140/90 mmHg |
| Family history of T2D, IHD, myocardial infarction, or stroke | Yes |
| History of gestational diabetes or hypertension | Yes |
| FINDRISC-score | ≥ 12*/15** points |

* In Harjavalta, ** In Kokemäki. FINDRISC, Finnish Diabetes Risk Score; IHD, ischemic heart disease; T2D, type 2 diabetes. Different cut-off values for FINDRISC-score were used for logistic reasons.

**Measurements**

Subjects attended an enrolment examination performed by a trained nurse. First, self-administered questionnaires were completed. Subjects were asked to report their gender, age, education years, cohabiting (yes/no), and current smoking (yes/no). Level of leisure-time physical activity (LTPA) was determined, and categorized as low (LTPA for ≥ 30 minutes at a time for maximum of three times a week), moderate (LTPA for ≥ 30 minutes at a time for four to five times a week), and high (LTPA ≥ 30 minutes at a time for six or more times a week). Alcohol consumption was assessed by Alcohol Use Disorders Identification Test (AUDIT) [22], and AUDIT score was handled as a continuous variable (range 0-40 points). Beck's Depression Inventory, version BDI-1A [21] was used to assess depressive symptoms. A BDI score ≥ 10 [23] was used as the definition of increased depressive symptoms. The subjects with increased depressive symptoms were divided into melancholic and non-melancholic subgroups by comparing means of summary scores of melancholic and non-melancholic items in the BDI [17,24–26]. Items considered melancholic based on Diagnostic and Statistical Manual for Mental Disorders (DSM)-defined criteria were sadness, past failure, loss of pleasure, guilty feelings, punishment feelings, irritability, loss of interest, change in sleeping, and change in appetite. Other items were considered non-melancholic. A subject was classified into the melancholic subtype if the mean of the summary score of the melancholic items was higher than that of the non-melancholic items, and vice versa. If the means were equal, depressiveness was considered melancholic.

Second, a trained nurse measured height, weight, waist circumference, and blood pressure (BP). Body mass index (BMI) was calculated. In fasting blood samples, glucose values, total cholesterol, high-density lipoprotein cholesterol, and triglycerides were determined. Low-density lipoprotein was calculated according to Friedewald's formula. In addition, an oral glucose tolerance test was performed. Glucose metabolism disorders were categorized into T2D (fasting

glucose ≥ 7.0 mmol/l or 2-hour postload plasma glucose ≥ 12.2 mmol/l), impaired glucose tolerance (2-hour postload plasma glucose 8.9-12.2 mmol/l), and impaired fasting glucose (fasting glucose 6.1-6.9 mmol/l). Subjects with newly diagnosed glucose metabolism disorders were included in the analyses of this study.

**Interventions on CVD risk factors**

The study nurse gave lifestyle counselling to all subjects attending the enrolment examination. If hypertension, diabetes, impaired glucose tolerance, metabolic syndrome, obesity (BMI ≥ 30.0 $kg/m^2$), or ≥ 5% ten-year risk for CVD death estimated by the SCORE (Systematic Coronary Risk Evaluation) [27] was found at the nurse's appointment (n = 1928), subjects were further invited to a physician's appointment. Preventive medication (an antihypertensive drug, a lipid lowering agent, or low dose aspirin) was started if the ten-year risk for developing a fatal CVD event was ≥ 5% estimated by the SCORE. According to national guidelines at that time, antihypertensive medication was initiated if systolic BP was ≥ 160 mmHg or diastolic BP ≥ 100 mmHg, or target organ damage was diagnosed. Ongoing antihypertensive medication was intensified if systolic BP was ≥ 140 mmHg or diastolic BP ≥ 85 mmHg (≥ 80 mmHg in patients with diabetes). However, prospective data on adherence to these interventions were not available.

**Mortality**

Data on mortality were obtained from the official statistics provided by Statistics Finland. The coverage of this data is virtually 100 % [28]. Causes of death were classified according to the International Statistical Classification of Diseases and Related Health Problems, $10^{th}$ Revision (ICD-10). The underlying causes of deaths were classified as follows: malignant neoplasms (C00-C97), diseases of the nervous system (G00-G99), diseases of the circulatory system (I00-I99), diseases of

the digestive system (K00-K93), external causes of death (V01-X84 accidents and intentional self-harm), and other causes of death (diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-89), endocrine, nutritional and metabolic diseases (E00-E90), mental and behavioural disorders (F00-F99), diseases of the respiratory system (J00-J99), diseases of the musculoskeletal system and connective tissue (M00-M99), diseases of the genitourinary system (N00-N99), symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)).

A subject's follow-up time started at the time of the enrolment examination, and ended on December 31$^{st}$, 2017, or on the date of death.

**Statistical analysis**

Data are presented as means with standard deviation (SD) or as counts with percentages. Statistical comparisons between categories of depressive symptoms were made by using analysis of variance (ANOVA) and Pearson's chi-square. The bootstrap method was used when the theoretical distribution of the test statistics was unknown, or in the case of violation of the assumptions (e.g. non-normality). The Kaplan-Meier method was used to estimate the cumulative mortality. Adjusted survival curves and hazard ratios (HR) were based on a stratified Cox model using baseline age, gender, education years, smoking, alcohol use, LTPA, BMI, hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, or antihypertensive medication), dyslipidaemia (total cholesterol ≥ 5.0 mmol/l or medication for lipid disorders), and glucose disorders as covariates. The possible non-linear relationship between BDI and all-cause mortality was modelled using restricted cubic splines with three knots at the 10$^{th}$, 50$^{th}$, and 90$^{th}$ percentiles. Spline functions were estimated using flexible parametric survival models, including baseline age, gender, education years, smoking, alcohol use, LTPA, BMI, hypertension, dyslipidaemia, and

glucose disorders as covariates. The proportional hazards assumption was tested graphically and by use of a statistical test based on the distribution of Schoenfeld residuals. The ratio of observed to expected number of deaths, the standardized mortality ratio (SMR) for all-cause deaths, was calculated using subject-years methods with 95% confidence intervals, assuming a Poisson distribution. The expected number was determined by multiplying the person-years of observation by the appropriate mortality rate in the general population according to categories of gender, 1-year age group and calendar period. Probabilities of survival in an age- and gender-matched sample of the general population were calculated from data of the official statistics from Statistics Finland. Hommel's multiple comparison procedure was used to correct significance levels for post hoc testing. The normality of variables was evaluated graphically and using the Shapiro–Wilk W test. Stata 16.0 (StataCorp LP, College Station, TX, USA) was used for the analysis.

### Ethical approval

The ethics committee of Satakunta Hospital District reviewed and approved the study protocol and consent forms. All participants provided written informed consent for the project and subsequent research.

## Results

### Characteristics of the study population

The baseline characteristics of the subjects according to depressive symptoms are presented in Table 2. At baseline, 2522 CVD risk subjects were evaluated. The mean age was 58.1 (SD 6.9) years and 55.7% were females. Increased depressive symptoms (BDI ≥ 10) were detected in 506 (20.1%) subjects. Of them, 375 (14.9%) had non-melancholic and 131 (5.2%) melancholic depressive

symptoms. Those with non-melancholic depressive symptoms had metabolic risk factors more often: higher BMI and larger waist circumference (only women) compared to the other groups, and more glucose disorders and higher triglyceride level compared to those without depressive symptoms. They also performed less LTPA than subjects without depressiveness. Those with melancholic depressive symptoms had a higher mean AUDIT score compared to the two other groups. At baseline, antihypertensive medication was more often used in subjects with non-melancholic depressive symptoms. Medication for depression/anxiety was more often used by subjects with depressive symptoms compared to non-depressive subjects.

**Table 2.** Characteristics of the study population according to the categories of depressive symptoms.

| | BDI <10 | BDI ≥10 | | |
|---|---|---|---|---|
| | I<br>n= 2016 | NMeD<br>II<br>n=375 | MeD<br>III<br>n=131 | P-value*<br>[multiple comparison] |
| Age, mean, years (SD) | 58 (7) | 59 (7) | 58 (7) | <0.001 [I/II] |
| Females, n (%) | 1078 (53) | 257 (69) | 70 (53) | <0.001 [I/II, II/III] |
| Education years, mean (SD) | 10.4 (2.7) | 10.1 (2.7) | 10.8 (3.1) | 0.013 [I/II, II/III] |
| Cohabiting, n (%) | 1587 (79) | 279 (74) | 102 (78) | 0.18 |
| Body mass index, kg/m$^2$, mean (SD) | 28.6 (4.7) | 30.0(5.9) | 28.9(5.6) | <0.001 [I/II, II/III] |
| Waist circumference, cm, mean (SD)<br>women<br>men | <br>91 (12)<br>101 (11) | <br>96 (15)<br>104 (13) | <br>92 (15)<br>101 (13) | <br><0.001 [I/II, II/III]<br>0.046 [I/II] |
| Current smoking, n (%) | 343 (17) | 74 (20) | 30 (23) | 0.12 |
| AUDIT-score, mean (SD) | 4.5 (4.6) | 4.8 (5.2) | 6.9 (7.1) | <0.001 [I/III, II/III] |
| Leisure-time physical activity level, n (%)<br>low | <br>333 (17) | <br>95(25) | <br>29(22) | <0.001 [I/II] |

| | | | | |
|---|---|---|---|---|
| moderate | 1020 (51) | 182(49) | 59(46) | |
| high | 653 (33) | 97(26) | 41(32) | |
| Blood pressure, mmHg, mean (SD) | | | | |
| systolic | 141(19) | 140(18) | 139(17) | 0.57 |
| diastolic | 84(10) | 84(10) | 86(10) | 0.29 |
| Plasma lipids, mmol/l, mean (SD) | | | | |
| total cholesterol | 5.4 (1.0) | 5.5 (1.1) | 5.5 (1.0) | 0.068 |
| HDL cholesterol | 1.6 (0.4) | 1.6 (0.5) | 1.5 (0.4) | 0.84 |
| LDL cholesterol | 3.2 (0.9) | 3.3 (1.0) | 3.3 (0.9) | 0.30 |
| triglycerides | 1.4 (0.7) | 1.6 (0.9) | 1.5 (0.7) | <0.001 [I/II] |
| Plasma glucose, mmol/l, mean (SD) | | | | |
| fasting | 5.6 (1.1) | 5.7 (1.3) | 5.6 (1.7) | 0.14 |
| 2h glucose | 7.3 (2.2) | 7.7 (2.7 ) | 7.5 (2.2) | 0.040 [I/II] |
| Glucose disorder, n (%) | | | | 0.040 [I/II] |
| impaired fasting glucose | 202 (10) | 40 (11) | 14 (11) | |
| impaired glucose tolerance | 265 (13) | 50 (13) | 16 (12) | |
| type 2 diabetes | 153 (8) | 50 (13) | 13 (10) | |
| BDI score, mean (SD) | 3.8 (2.7) | 15.1 (5.5) | 14.8. (5.5) | .. |
| Medication, n (%) | | | | |
| Hypertension | 623(31) | 165 (44) | 47 (36) | <0.001 [I/II] |
| Lipid disorders | 242 (12) | 47 (13) | 16 (12) | 0.96 |
| Depression/anxiety | 39 (2) | 50 (13) | 15 (11) | <0.001 [I/II, I/III] |

*Hommel's multiple comparison procedure was used to correct significance levels for post hoc testing ($p<0.05$).

AUDIT, Alcohol Use Disorders Identification Test; BDI, Beck's Depression Inventory; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MeD, increased (BDI ≥ 10) melancholic depressive symptoms; NMeD, increased non-melancholic depressive symptoms.

## Mortality

### *Cumulative all-cause mortality*

Unadjusted cumulative all-cause mortality over 5, 10 and 12 years were as follows: 3.4% (95% CI: 2.7-4.3), 5.8% (95% CI: 4.9-7.0), and 9.2% (95% CI: 7.9-10.8) in non-depressive; 5.9% (95% CI: 3.9-8.8), 12.0% (95% CI: 9.1-15.7), and 14.4% (95% CI: 11.0-18.7) in non-melancholically depressive; and 2.2% (95% CI: 0.7-6.9), 9.2% (95% CI: 5.3-15.6), and 11.4% (95% CI: 6.8-18.7) in melancholically depressive subjects.

When BDI score ten was set as the reference level, adjusted HR for time to all-cause mortality rose with higher and declined with lower BDI score levels (Figure 1).

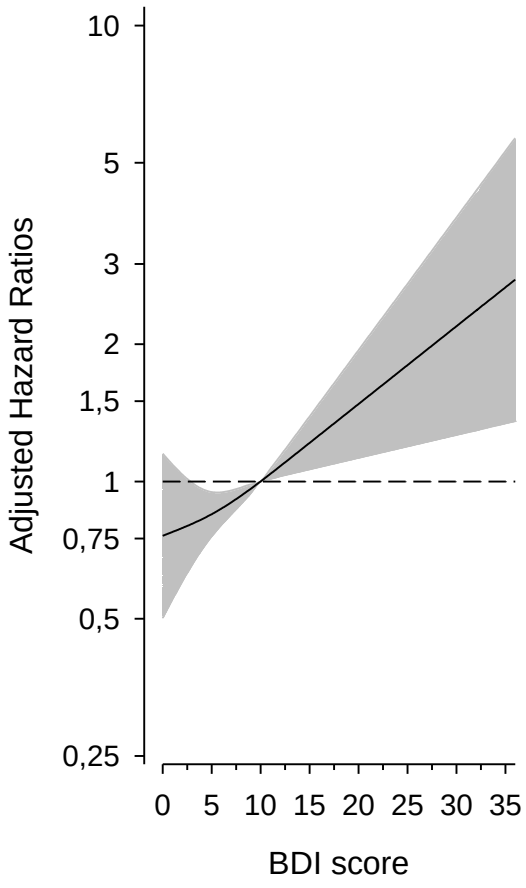

**Figure 1.** Adjusted (age, gender, education, current smoking, alcohol use, BMI, hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, or antihypertensive medication), dyslipidaemia (total cholesterol ≥ 5.0 mmol/l or medication for lipid disorders), and glucose disorders) hazard ratios for time to all-cause mortality according to Beck's Depression Inventory (BDI) summary score. Hazard ratios were derived from a 3-knot restricted cubic flexible parametric survival models, with BDI score 10 as the reference value. The 95 per cent confidence intervals are denoted by the grey area.

Adjusted (age, gender, education, current smoking, alcohol use, BMI, hypertension, dyslipidaemia, and glucose disorders) survival according to depressive symptoms is presented in Figure 2. Compared to non-depressive subjects, the HR for time to all-cause mortality was 1.67 (95% CI: 1.21-2.32, p=0.002) in non-melancholically depressive and HR 1.01 (95% CI: 0.56-1.83, p=0.97) in melancholically depressive subjects.

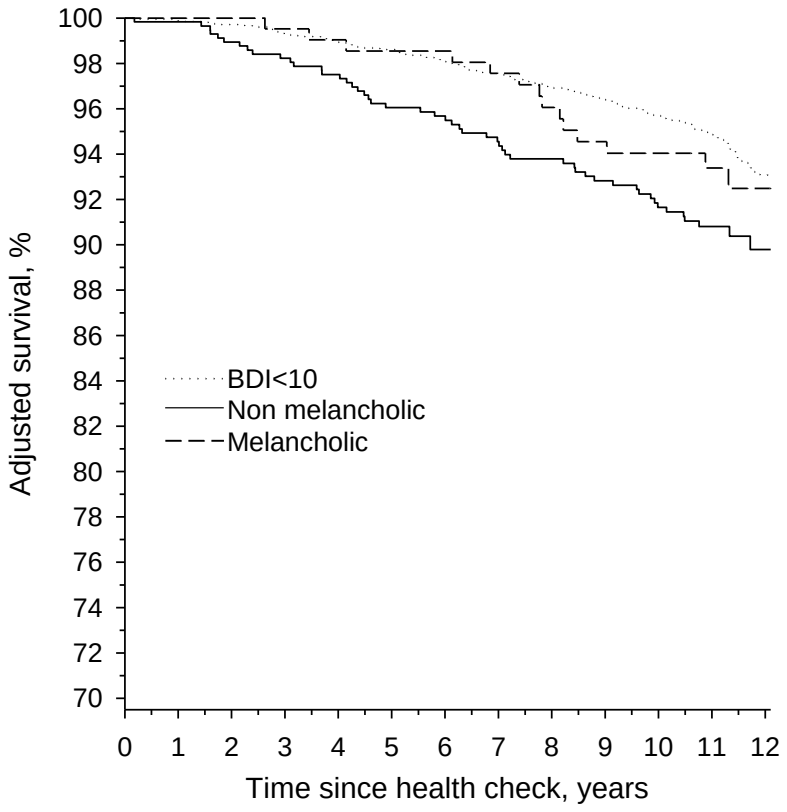


**Figure 2.** Survival according to depressive symptoms. Adjusted for age, gender, education, smoking, age, gender, education, current smoking, alcohol use, BMI, hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, or antihypertensive medication), dyslipidaemia (total cholesterol ≥ 5.0 mmol/l or medication for lipid disorders), and glucose disorders. BDI, Beck's Depression Inventory.

***Causes of death***

In the whole cohort, a total of 27681 person-years (mean 11.0) was followed up, and 230 deaths occurred: 164 (8.1%) among those without increased depressive symptoms, 52 (13.9%) among those with non-melancholic depressive symptoms, and 14 (10.7%) among those with melancholic depressive symptoms. The most prevalent cause of death was cancer (42% of all deaths), followed by CVD (28% of all deaths). The causes of death according to depressiveness are presented in Table 3.

**Table 3.** Causes of death according to depressive symptoms.

| | **All** | **BDI < 10** | **NMeD** | **MeD** |
|---|---|---|---|---|
| Cause of death, n (%) | n = 230 | n = 164 | n = 52 | n = 14 |
| **Malignant neoplasms** | 97 (42) | 63 (38) | 26 (50) | 8 (57) |
| **Nervous system** | 16 (7) | 12 (7) | 4 (7) | 0 (0) |
| **Circulatory system** | 64 (28) | 48 (29) | 12 (23) | 4 (29) |
| **IHD** | 31 (13) | 23 | 8 | 0 |
| **CeVD** | 17 (7) | 15 | 0 | 2 |
| **Other** | 16 (7) | 10 | 4 | 2 |
| **Digestive system** | 13 (6) | 7 (4) | 5 (10) | 1 (7) |
| **External cause** | 23 (10) | 20 (12) | 3 (4) | 0 (0) |
| **Other** | 17 (7) | 14 (9) | 2 (4) | 1 (7) |

BDI, Beck's Depression Inventory; CeVD, cerebrovascular disease; IHD, ischaemic heart disease; MeD, increased (BDI≥ 10) melancholic depressive symptoms; NMeD, increased non-melancholic depressive symptoms

***Standardized mortality rate***

In comparison to the mortality rate in the general population throughout Finland over the same period, the standardized mortality ratio (SMR) among women and men in our study was 0.73 (95% confidence interval (CI): 0.62-0.86) and 0.70 (95% CI: 0.57-0.86), respectively. Non-depressiveness was associated with a decreased SMR (0.64, 95% CI: 0.55-0.74), whereas those with increased depressive symptoms did not differ from the general population: SMR 1.14 (95% CI: 0.87-1.50) in non-melancholically depressive and SMR 0.85 (95% CI: 0.50-1.43) in melancholically depressive subjects. There was a statistically significant difference in the SMR of those with non-melancholic depressive symptoms and non-depressive subjects ($p<0.001$).

## Discussion

In our follow-up study (mean follow-up time 11 years) of 2522 apparently healthy CVD risk subjects, the most prevalent causes of death were cancer (42%) and CVD (28%). Compared to the general population, those without depressive symptoms had a decreased standardized mortality rate. Non-melancholic depressive symptoms were associated with an increased risk for all-cause mortality compared to those without depressive symptoms, whereas melancholic depressive symptoms were not.

In recent studies assessing depressive symptoms and all-cause or cause-specific mortality in general middle-aged or older populations, depressive symptoms have generally been associated with an increased mortality risk. In a study of over 29000 US adults (≥ 45 years old), Moise et. al [29] found that time-varying depressive symptoms increased the risk for all-cause mortality by 24% and for non-CVD mortality by 29%. In their study, depressive symptoms were not associated with increased CVD mortality. In line with Moise's and our study, Kozela et. al [30] found depressive symptoms to independently predict all-cause mortality. Furthermore, in their

study of over 24000 middle-aged subjects in Central and Eastern Europe, depressive symptoms were also associated with CVD mortality. However, conflicting results have also been published. For example, in a study among over 11 000 UK adults (≥ 50 years old) even low levels of depressive symptoms seemed to be associated with increased mortality risk, but adjustment for physical activity, illnesses, and impairments in functioning fully attenuated the association [31]. This emphasises the importance of adequate adjustments, but the mixed results might also be attributable to the diversity of depressive symptoms.

Yet, studies on the association of subtypes of depressive symptoms and all cause-mortality are scarce. Lasserre et al. [19] found depression to increase the risk for all-cause mortality more than 3-fold compared to those without depressive symptoms. However, in contrast to our results, atypicality of depression was not associated with increased all-cause mortality risk. A profound difference between the studies is that we assessed depressive symptoms and divided them into melancholic and non-melancholic subgroups when Lasserre et al. based their depression diagnosis on a semi-structured diagnostic interview and assessed the atypicality of depression based on DSM-defined criteria, although not requiring mood reactivity. Still, the means of the assessment of depression have not been found to substantially affect the found association of depressive symptomatology and all-cause mortality [2].

Many possible explanations for the excess mortality risk among depressed subjects have been proposed. As the increased mortality risk has been found to be similar in community samples and specific patient groups, it has been suggested that this association is driven by generic mechanisms [2]. These might include lifestyle associated factors and biological mechanisms. In addition, depression is a major risk factor for self-harm [32].However, in our study population, there were fewer deaths from external causes among those with depressive symptoms than among those without.

Depression and depressive symptoms are associated with unhealthy lifestyle such as smoking [6] and low physical activity [33], and poorer adherence to medical treatment [34]. These factors inevitably contribute to mortality risk. If subjects with non-melancholic and melancholic depressive symptoms would remarkably differ considering lifestyle, different mortality risk could be partly explained by that. However, previous research does not provide consistent evidence of different lifestyles among these subgroups [17,35–37]. In our study population, melancholically depressive subjects had higher AUDIT mean score than those with non-melancholic depressive symptoms but otherwise they seemed rather alike considering lifestyle. In addition, we adjusted for important socio-demographic, lifestyle associated and clinical factors, thus suggesting the association found is not only driven by them.

The pathophysiology of depression is complex and not fully understood, but most importantly dysregulations of immuno-inflammatory, metabolic, and autonomic systems, and hypothalamic-pituitary-adrenal (HPA) axis have been associated with depression [15]. They can all contribute to somatic diseases and thus affect mortality risk. First, inflammation is also a crucial factor in the pathogenesis of malignant neoplasms, and it has been proposed as a connecting pathway between depression and cancer [38]. Similarly, inflammation is a core component in atherosclerosis [39], and it plausibly at least partly mediates the association of depression and CVD. In addition, dysregulations of the autonomic system and HPA axis are also important possible pathways connecting depression to especially CVD [40,41]. Moreover, there is some evidence that different subtypes of depressive symptoms are associated with different biological disturbances [42] which could explain differences in mortality risks found. It has been suggested that inflammation might be associated with certain depressive symptoms [43], such as sleep problems, tiredness/lack of energy, and changes in appetite [44], and may play a significant role namely in atypical depression [45]. This could explain increased all-cause mortality, driven by inflammation's

associations with cancer and CVD, among non-melancholically depressed subjects. Atypical depression and non-melancholic depressive symptoms have also been associated with an increased risk for metabolic disturbances [17,35,37,46,47] which lends support to our finding that those with non-melancholic depressive symptoms had more metabolic risk factors. We have also previously found that non-melancholically depressive subjects have an increased risk for CVD morbidity, although independently of major CVD risk factors hypertension and dyslipidaemia [18]. However, increased odds for metabolic dysregulations probably partly mediate increased mortality among those with non-melancholic depressive symptoms. It might be that inflammation and metabolic dysregulations are stronger contributors to mortality than HPA axis dysfunction that has been associated with melancholic depression [48].

Consistent with previous research [17,49], non-melancholic depressive symptoms were more prevalent than melancholic among our study population. This, however, causes differential statistical power for non-melancholic and melancholic depressiveness~~, and may contribute to the found associations~~. Women had more often depressive symptoms than men in our study population. The gender difference in depression risk is comprehensively documented also previously, and women have been suggested to have 1.5-fold risk for depressive symptoms compared to men[50].

Unfortunately, in our study, there was a lack of statistical power to analyse the association of the subtypes of depressive symptoms and CVD mortality due to few CVD deaths (n = 4) among those with melancholic depressive symptoms. In addition, it has to be noted that our study population was drawn from a population survey aimed at diminishing CVD risk. Preventive medication for hypertension and lipid disorders or low dose aspirin was initiated for those at high CVD risk. Subjects with established CVD were excluded at baseline, so the manifested CVD were apparently new. Although we do not know how adherent subjects were to the preventive

medication, these factors assumedly contribute to the severity of the manifested CVD and accordingly, to the CVD mortality found in our study population, as well as to the finding that non-depressiveness was associated with decreased standardized mortality rate. In addition, depression has been associated with poorer adherence to medical treatment such as antihypertensive medication [51], diabetes self-care [52], and medication after acute coronary syndrome [53].

This was one of the first studies to assess the association of different subtypes of depressive symptoms and all-cause mortality, and it has some specific strengths: A representative sample of middle-aged CVD risk subjects who were apparently healthy at baseline was well evaluated. Data on mortality were obtained from a comprehensive and reliable register. However, our study also has limitations. The mean age of the study population at the start of the follow-up was 58 years, resulting in a limited number of deaths during the follow-up, and probably affecting the prevalence of the causes of death. Depressive symptoms were assessed only at baseline, so we were not able to control for changes in depressive status. There is inconsistent evidence on the stability of depressive subtypes: In Finland, the stability of especially melancholic features has previously been suggested to be rather weak (only one in five of melancholically depressive subjects presented with melancholic features at following episodes during 18-month follow-up) [49] but in the Netherlands, the stability of a melancholic, an atypical, and a moderate subtype was over 75 % during a two-year follow-up [54]. Similarly, the course trajectories of melancholic and atypical depression have sometimes been found to be rather similar [49,55] but in some studies melancholic depression has been associated with higher severity and lower rates of remission [56,57]. We also acknowledge that there is a limitation in assessing the depressive symptoms with BDI. Neither the depressive symptom group nor the subtype groups fully represent clinical depression. Beck et al. have reported a mean correlation of 0.72 between BDI-IA and clinical depression ratings in psychiatric patients, and 0.60 in a non-psychiatric sample such as

in our study [58]. There were few (n = 14) deaths among those with melancholic depressive symptoms which can undermine the association of melancholic depressive symptoms with all-cause mortality.

In conclusion, non-melancholic depressive symptoms seem to be associated with excess all-cause mortality. In clinical settings, recognition of non-melancholic depressive symptoms such as mood reactivity, fatigue and increased appetite should thus be emphasised. However, this finding should be confirmed in a larger sample and with a more robust definition of depression. In addition, a longer follow-up time would probably reveal specific causes of death.

## Declaration of interest

None.

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