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Depressive symptoms and smoking: Effect on mortality in a primary care cohort

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ABSTRACT

Objective: Depressive symptoms have been suggested to increase mortality risk but causality remains unproven. Depressive symptoms increase likelihood of smoking which is thus a potential factor modifying the effect of depressive symptoms on mortality. This study aims to assess if the association of depressive symptoms and all-cause mortality is affected by smoking.

Methods: A prospective cohort study in Finnish primary care setting was conducted among 2557 middle-aged cardiovascular disease (CVD) risk persons identified in a population survey. Baseline depressive symptoms were assessed by Beck's Depression Inventory (BDI) and current smoking by self-report. Data on mortality was obtained from the official statistics. Effect of depressive symptoms and smoking on all-cause mortality after 14-year follow-up was estimated.

Results: Compared to non-depressive non-smokers, the adjusted hazard ratio (HR) for all-cause mortality was 3.10 (95% CI 2.02 to 4.73) and 1.60 (95% CI 1.15 to 2.22) among smoking subjects with and without depressive symptoms, respectively. Compared to the general population, relative survival was higher among non-depressive non-smokers and lower among depressive smokers. Relative standardized mortality ratio (SMR) for all-cause mortality was 1.78 (95% CI 1.31 to 2.44) and 3.79 (95% CI 2.54 to 6.66) among non-depressive and depressive smokers, respectively, compared to non-depressive non-smokers. The HR for all-cause mortality and relative SMR of depressive non-smokers were not increased compared to non-depressive non-smokers.

Conclusion: Current smoking and increased depressive symptoms seem to additively contribute to excess mortality.

1. Introduction

Depression and subthreshold depressive symptoms have been related to increased mortality risk [1]. This is plausible as depression intervenes with somatic diseases in complex biological pathways [2] and is considered as a risk factor for major causes of mortality, CVD [3] and cancer [4,5]. Depression and depressive symptoms are also associated with other risk factors such as hypertension [6], metabolic disturbances [7,8], sedentary and unhealthy lifestyle including smoking [9–11], and low socioeconomic status [12]. Nevertheless, there is still controversy weather depressive symptoms *per se* are associated with mortality. Depression can been considered to namely cause excess mortality through its effect on physical health, social factors, and lifestyle [13]. However, two recent meta-analyses concluded that causality remains unproven, in part due to inadequate adjustments for confounding factors [14,15].

Depression and depressive symptoms increase likelihood of smoking [11] and decrease odds to successful quitting [16]. Current smokers have 2 to 3 times higher mortality than never-smokers [17], and although prevalence of smoking has decreased during the past decades, it still accounts for a substantial loss of life-years [18]. This excess mortality has been attributed to at least 26 different disease categories including several cancers, many cardiovascular (CVD) and respiratory diseases, diabetes, renal failure, and some infections [17].

Smoking has previously been reported to affect the association of depression and CVD [19,20], and it appears a potential factor modifying the effect of depressive symptoms on mortality. We are not aware that this interaction would have been previously studied among subjects

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with CVD risk. This study aims to assess if the association of depressive symptoms and all-cause mortality is affected by smoking among CVD risk persons, and to compare their mortality, stratified by depression and smoking status, to the general population. We assume to find a modifying effect on all-cause mortality.

2. Materials and methods

2.1. Study population

The study sample was drawn from the Harjavalta Risk Monitoring for Cardiovascular Disease (Harmonica) Project that was conducted in years 2005–2007 in Harjavalta and Kokemäki, Finland. It aimed to find subjects in increased CVD risk and provide primary prevention. All home-dwelling inhabitants who were 45–70 years old (n = 6013) were invited. They received an invitation letter, a CVD risk factor survey, a type 2 diabetes (T2D) risk assessment form (FINDRISC, Finnish Diabetes Risk Score) [21], and a tape for waist circumference (WC) measurement. Response rate was 74% (n = 4450). In accordance with the aims of the project, only subjects with increased CVD risk (n = 3072) but without previously established CVD, chronic kidney disease, or T2D were included. Criteria for increased CVD risk was having at least one of the following assessed risk factors: WC ≥80 cm in women and ≥ 94 cm in men (only in Harjavalta), use of antihypertensive medication, latest blood pressure (BP) measurement ≥140/90 mmHg, family history of ischemic heart disease, myocardial infarction, or stroke, history of gestational diabetes or hypertension, or FINDRISC-score ≥ 12 in Harjavalta or ≥ 15 in Kokemäki. Different FINRISC-scores were used for logistic reasons. The risk subjects were further invited for laboratory tests and an appointment with a study nurse. 2752 subjects participated. In this study, only subjects with adequate information on depressive symptoms and smoking status were included (n = 2557).

2.2. Questionnaires and measurements

Information on subjects' health and lifestyle habits was gathered by self-administered questionnaires before the study visit. Beck's Depression Inventory (BDI) [22] was used to measure depressive symptoms with a cut-off value ≥10 indicating increased depressive symptoms [23]. Subjects were asked if they currently smoke and were dichotomized to current smokers and non-smokers. Information on alcohol consumption was inquired by Alcohol Use Disorders Identification Test (AUDIT) [24], and subjects were also asked to report current frequency of leisure-time physical activity (LTPA) for at least 30 min at a time. LTPA was categorized as low, moderate, or high as follows: at most three, four to five, at least six times a week, respectively.

The study visit, conducted by a trained nurse, included the following measurements: height and weight with subjects in a standing position without shoes and outer garments, WC at the level midway between the lower rib margin and the iliac crest, and BP. BMI was calculated by dividing weight (kg) by height squared (m^2). Also, a 2-h oral glucose tolerance test was performed, and fasting plasma lipids were determined.

2.3. Intervention for primary prevention

At the study visit subjects received lifestyle counselling. In addition, high risk subjects (n = 1928) were further referred to a physician's appointment. Definition for high risk was 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 Systematic Coronary Risk Evaluation (SCORE) [25]. Then, preventive medication for hypertension or dyslipidaemia, or low dose aspirin, was initiated if SCORE indicated ≥5% ten-year risk for fatal CVD event. In addition, antihypertensive medication was initiated if systolic BP was ≥160 mmHg, diastolic BP was ≥100 mmHg, or target organ damage was diagnosed, and it was intensified if systolic BP was ≥140 mmHg or diastolic BP was ≥85 mmHg (≥80 mmHg in patients with diabetes).

2.4. Mortality

Data on mortality was obtained from the Official Statistics of Finland provided by Statistics Finland. Causes of death were classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). A subject's follow-up time started at the time of the study visit (9/2005 to 3/2008) and ended on December 31st, 2019.

2.5. Statistical analysis

Summary statistics were described using mean and standard deviation (SD), median and interquartile range (IQR), or numbers as percentages. The baseline characteristics were evaluated using generalized linear models (*e.g.* analysis of variance or logistic models) with appropriate distribution and link function. Crude cumulative rate of all-cause mortality was estimated using Kaplan-Meier method and compared between groups with the log-rank test. Cox proportional hazards regression was used to estimate the adjusted hazard ratios (HR) and their 95% confidence intervals (CIs). Age, sex, education years, BMI, total cholesterol, LTPA, AUDIT score, the presence of glucose disorders, and hypertension were used as covariates in these models. The proportional-hazards assumption was evaluated by Schoenfeld residuals and log–log plots. A possible nonlinear relationship between smoking (smoking per non-smoking) and the BDI summary score was assessed by using 3-knot restricted cubic spline Cox regression models. The length of the distribution of knots were located at the 10th, 50th, and 90th percentiles. For restricted cubic splines, also known as natural splines, knot locations are based on Harrell's recommended percentiles [26]. Relative survival, the ratio between the observed survival proportion in a patient group and the expected survival proportion was calculated by the Ederer II method [27]. The ratio between observed and expected numbers, standardized mortality ratio (SMR), was calculated using subject-years methods with 95% confidence intervals (CI), assuming a Poisson distribution. The expected number of deaths was calculated on the basis of sex-, age- and calendar-period-specific mortality rates in the Finnish population (Official Statistics of Finland). 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 sex, 1-year age group and calendar period. Relative standardized mortality ratios were calculated using Poisson regression model. No adjustment was made for multiple testing, but this information can be obtained by multiplying the actual p value by the number of comparisons made. All analyses were performed using STATA 17 0.0 (StataCorp LP, College Station, TX).

2.6. 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.

3. Results

3.1. Characteristics of the subjects

At baseline, 20.6% (106/515) of the subjects with increased depressive symptoms smoked and 16.8% (344/2042) were non-depressive smokers (p = 0.047). The probability of smoking increased from BDI score 10 onwards (Fig. 1).

Baseline characteristics of the subjects are presented in Table 1. Subjects with depressive symptoms were more often women, slightly older, and were living alone more often than non-depressive subjects.

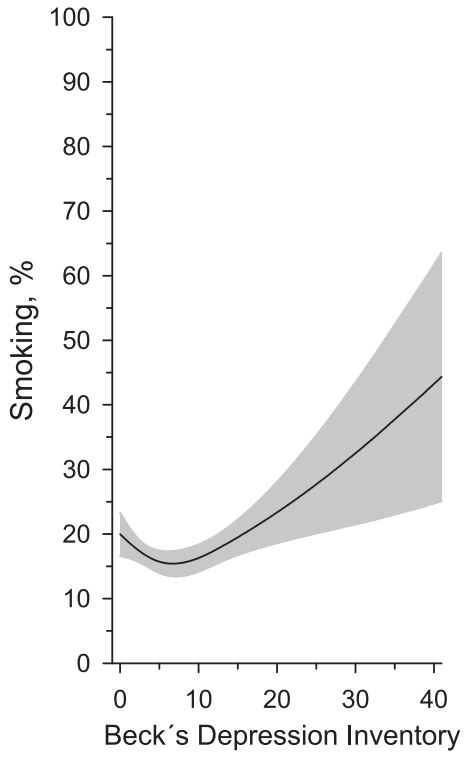

Fig. 1. Probability of smoking as a function of the Beck's Depression Inventory. The curve was derived from a 3-knot restricted cubic splines logistic model. The 95% confidence intervals of percentage are denoted by the grey area.

They also performed less LTPA, had higher mean AUDIT score, higher BMI and larger WC, higher triglyceride levels, higher 2-h glucose, and more glucose disorders than those without depressive symptoms.

3.2. Mortality

In total, 304 deaths occurred during the 14-year follow-up. Data on number of deaths, person-years followed-up, and crude mortality according to depressive symptoms and smoking are displayed in Table 2. At the end of the follow-up period, the crude mortality rate differed between the study groups ($p < 0.001$).

3.2.1. Hazard ratio for all-cause mortality

Unadjusted and adjusted hazard ratios (HR) for all-cause mortality

Table 2
Mortality data according to depressive symptoms and smoking.

	BDI < 10		BDI ≥ 10	
	Non-smoking $N = 1698$	Current smoking $N = 344$	Non-smoking $N = 409$	Current smoking $N = 106$
Person-years followed-up, total	21,965	4399	5161	1250
Person-years followed-up, median (IQR)	13.3 (12.8–13.9)	13.3 (12.7–13.9)	13.2 (12.7–13.9)	13.0 (12.4–13.6)
Number of deaths	170	51	55	28
Crude mortality, % (95% CI)	11.2 (9.4 to 13.3)	15.6 (12.0 to 20.1)	14.5 (11.3 to 18.7)	26.4 (19.1 to 35.9)

BDI, Beck's Depression Inventory.

Table 1
Characteristics of the subjects according to depressive symptoms and smoking.

	BDI < 10		BDI ≥ 10		*P*-value	
	Non-smoking	Current smoking	Non-smoking	Current smoking	Main effect	
	$N = 1698$	$N = 344$	$N = 409$	$N = 106$	BDI	Smoking
Women, n (%)	950(56)	140(41)	267(65)	63(59)	<0.001	<0.001
Age, years, mean (SD)	58(7)	55(7)	60(7)	57(6)	0.001	<0.001
Education years, mean (SD)	10.4(2.7)	10.4(2.3)	10.3(2.9)	10.4(2.5)	0.78	0.76
Cohabiting, n (%)	1356(80)	256(74)	319(78)	69(65)	0.042	<0.001
Leisure-time physical activity, n (%)					0.022	<0.001
Low	251(15)	86(25)	92(22)	33(31)		
Moderate	859(51)	180(52)	196(48)	50(47)		
High	588(35)	78(23)	121(30)	23(22)		
AUDIT score, mean (SD)	4.0(4.1)	7.2(5.8)	4.6(5.1)	8.2(7.3)	0.003	<0.001
Body mass index, kg/m^2, mean (SD)	28.7(4.7)	28.0(4.5)	30.0(5.8)	28.7(6.0)	0.002	0.002
Waist circumference, cm, mean (SD)						
Women	91(12)	90(12)	96(15)	94(15)	<0.001	0.36
Men	101(11)	101(12)	103(12)	101(14)	0.39	0.29
Blood pressure, mmHg, mean (SD)						
Systolic	141(19)	138(19)	140(18)	139(18)	0.96	0.16
Diastolic	84(10)	85(10)	84(10)	84(12)	0.75	0.61
Hypertension, n (%)	822(48)	155(45)	226(55)	52(49)	0.080	0.12
Plasma lipids, mmol/l, mean (SD)						
Total cholesterol	5.33(0.94)	5.49(1.01)	5.50(1.05)	5.41(1.10)	0.50	0.58
LDL cholesterol	3.20(0.86)	3.36(0.91)	3.30(0.92)	3.30(1.03)	0.69	0.14
HDL cholesterol	1.56(0.44)	1.50(0.44)	1.56(0.43)	1.49(0.49)	0.92	0.019
Triglycerides	1.34(0.70)	1.47(0.77)	1.51(0.87)	1.56(0.80)	0.004	0.046
Fasting glucose, mmol/l, mean (SD)	5.57(1.06)	5.75(1.24)	5.66(1.31)	5.93(1.62)	0.070	0.002
2-h glucose, mmol/l, mean (SD)	7.41(2.12)	6.93(2.28)	7.65(2.47)	7.68(3.04)	<0.001	0.13
Glucose disorder					0.005	0.001
No glucose disorder	1349(79)	251(73)	308(75)	68(64)		
Prediabetes	229(13)	64(19)	54(13)	20(19)		
Diabetes	120(7)	29(8)	47(11)	18(17)		
Antidepressive medication, n (%)	31(2)	8(2)	47(11)	18(17)	<0.001	0.16

BDI, Beck's Depression Inventory, AUDIT, Alcohol Use Disorders Identification Test; LDL, low-density lipoprotein; HDL high-density lipoprotein.

according to smoking status and presence of depressive symptoms are displayed in Table 3. Full adjustment did not change the results notably. Compared to non-smoking non-depressive subjects, higher risk for all-cause mortality was detected among smoking non-depressive subjects and among smoking depressive subjects in the adjusted analysis. Fig. 2 shows unadjusted and adjusted hazard ratios for all-cause mortality between smokers and non-smokers as a function of the Beck's Depression Inventory (BDI) summary score.

3.2.2. Relative survival and standardized mortality ratio

Relative survival and standardized mortality (SMR) ratio according to smoking and depressive symptoms during the 14-year follow-up is presented in Fig. 3. Compared to the general population, relative survival was higher among non-smoking subjects without depressive symptoms and lower among smoking subjects with depressive symptoms. Table 4 shows SMRs according to smoking status and presence of depressive symptoms. Smoking subjects had higher relative SMR compared to non-depressive non-smoking subjects.

4. Discussion

To our knowledge, this is the first study to investigate the effect of smoking on the association between depressive symptoms and all-cause mortality during a 14-year follow-up in middle-aged CVD risk population. Among this population, current smoking and increased depressive symptoms seem to additively contribute to excess mortality. Current smokers who had increased depressive symptoms had 3–4-times higher risk for all-cause mortality compared to all non-smoking participants even if they were depressive. Their relative survival was lower and SMR higher than that of the general population, whereas relative survival and SMR of depressive non-smokers and non-depressive smokers was comparable to the general population.

4.1. Strengths and limitations

There was some special strengths in our study. We studied a sample of middle-aged subjects commonly treated in primary care in Finland. Mortality data was highly reliable and comprehensive. To our knowledge, the association of depressive symptoms and mortality has not previously been studied stratified by smoking. However, limitations have to be noted. All our study participants were selected because of their elevated CVD risk. Thus, sampling bias may have an effect on our results. We also excluded 515 study subjects who had not completed the BDI questionnaire or whose smoking status was not reliable. Hence, generalizability of our results to primary care populations is limited. We assessed depressive symptoms and smoking only at baseline, and thus weren't able to consider their variation in time. We have previously detected that especially non-melancholic depressive symptoms seem to increase mortality risk [28] but, in this study, we could not make further division of the data according to depressive subtypes because the number of smoking subjects was too small. We dichotomized smoking to current and non-current smokers, the latter including both former smokers and never-smokers. Furthermore, we could not take into consideration frequency or heaviness of smoking. The mortality risk associated with smoking has been shown to vary whether smoking is daily or not, and by cigarettes smoked per day [29]. Lastly, we tested only for additive interaction of depressive symptoms and smoking on mortality. However, additive interaction, compared to multiplicative, is sometimes regarded more relevant in studies having public health significance [30].

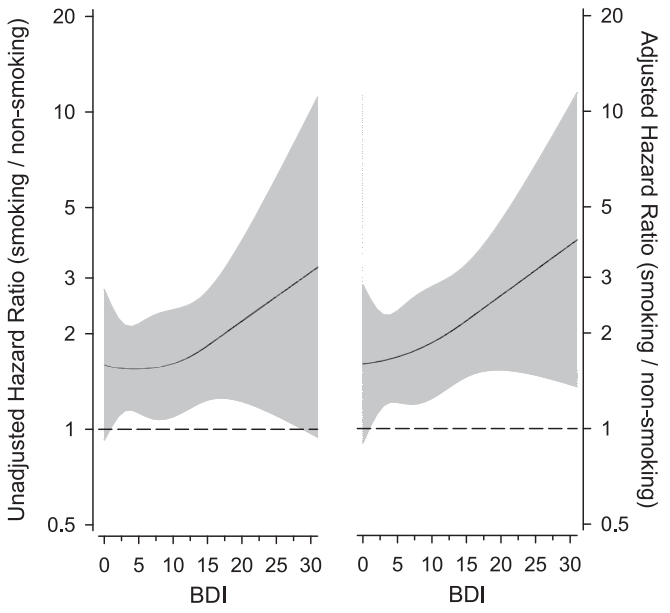

Fig. 2. Unadjusted and adjusted hazard ratio for all-cause mortality between smokers and non-smokers as a function of the Beck's Depression Inventory (BDI) summary score. The curves were derived from a 3-knot restricted cubic splines Cox proportional hazards model. The model was adjusted for age, sex, education years, body mass index, total cholesterol, leisure-time physical activity, AUDIT score, the presence of glucose disorders, and hypertension. The 95% confidence intervals of hazard ratios are denoted by the grey area.

Table 3
Unadjusted and adjusted hazard ratios (HR) for all-cause mortality in persons with smoking status (smoking) and presence of depressive symptoms. Models include BDI and smoking interaction (additive) terms.

Smoking	Beck's Depression Inventory (BDI)			
	Unadjusted Hazard Ratios		Adjusted analyses Hazard Ratios*	
	<10 HR (95% CI)	≥10 HR (95% CI)	<10 HR (95% CI)	≥10 HR (95% CI)
No	1.00 (Reference)**	1.39 (1.02 to 1.88)	1.00 (Reference)**	1.21 (0.59 to 1.65)
Yes	1.50 (1.10 to 2.05)	2.98 (2.00 to 4.45)	1.60 (1.15 to 2.22)	3.10 (2.02 to 4.73)
P-value: Main effects:				
BDI	<0.001		0.003	
Smoking	<0.001		<0.001	
Interaction	0.039		0.032	

* The models were adjusted for age, sex, education years, body mass index, total cholesterol, leisure-time physical activity, AUDIT score, the presence of glucose disorders, and hypertension.
** Denominator of Hazard ratios (HR).

4.2. Comparison with existing literature

Almost 20% of our study population were current smokers at baseline. Smoking was more prevalent among subjects who had increased depressive symptoms than among non-depressed individuals, consistent with previous research [16]. Compared to never-smokers and former smokers, current smoking has been associated with 1.50 to 1.76 times higher odds for depression in cross-sectional studies [11]. In a large population study among US adults, daily smoking was found to over double risk of depression [31]. Psychological mechanisms including affective disturbances and cognitive impairment have been suggested to underlie motivation to smoke in depression [32]. For example, among Finnish middle-aged twins, smoking dependence and dependence motives related to heavy, automatic use, and use to regulate affective states have been found to be associated with depression [33]. Among our study population, the probability of smoking increased with increasing severity of depressive symptoms (BDI score ≥ 10). It has previously been

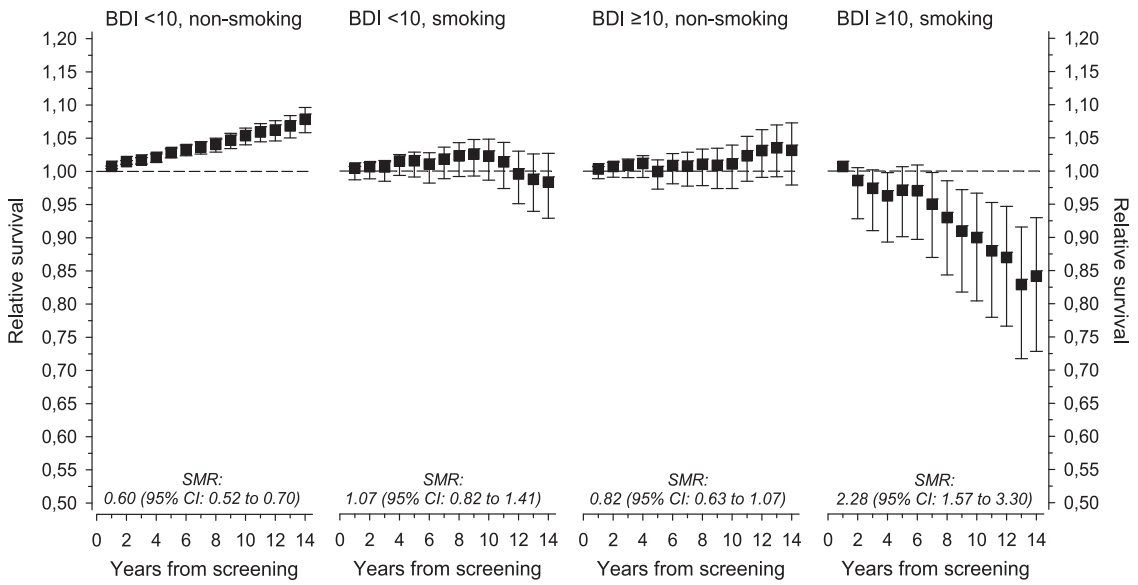

Fig. 3. Relative survival and standardized mortality ratios (SMR) according to smoking and depressive symptoms. BDI, Beck's Depression Inventory.

Table 4
Relative standardized mortality ratio for all-cause mortality in persons with smoking status (smoking) and presence of depressive symptoms.

Smoking	Beck's Depression Inventory	
	<10 Relative SMR (95% CI)*	≥10 Relative SMR (95% CI)*
No	1.00 (Reference)*	1.36 (1.00 to 1.84)
Yes	1.78 (1.31 to 2.44)	3.79 (2.54 to 6.66)

* Denominator of Standard Mortality Ratio (SMR).

reported that at least nicotine-dependent smokers have higher levels of depressive symptoms compared to non-smokers or non-dependent smokers [34], and that higher smoking frequency and volume is associated with higher risk of depression [31]. It might be that depressive smokers in our study population were those with heaviest smoking and most severe depression.

Our results indicate that smoking has a modifying effect in the relationship of depressive symptoms and all-cause mortality risk. We are not aware of previous similar studies, but one earlier study investigated the effect of smoking on the association between depressive symptoms and mortality from coronary artery disease [35]. It was then concluded that smoking might mediate but not moderate this relationship. Nevertheless, the association of depressive symptoms and all-cause mortality has previously been shown to attenuate when sociodemographic characteristics, smoking and other lifestyle associated factors, and chronic diseases are taken into account [13,36]. Our previous analysis among this same study population has shown that the effect of increased depressive symptoms on all-cause mortality risk varies with BMI [37]. We found that the elevated mortality risk was especially apparent among depressive individuals with normal weight, among whom smoking was most prevalent. However, we adjusted for many socio-demographic, lifestyle associated and metabolic risk factors. In this study, adjustments did not change the results notably.

In our study population, non-depressive non-smokers had higher survival compared to the general population, whereas smokers without depressive symptoms and depressive non-smokers had relative survival and SMR similar to the general population. As our study population was drawn from a CVD prevention program, higher survival of non-depressive non-smokers is understandable. It was also previously reported that this multifactorial CVD intervention is associated with significantly lower mortality rate compared to the general population [38]. It might be that a portion of the current smokers at baseline quit smoking after receiving lifestyle counselling, enhancing their survival. Our 14-year follow-up is likely long enough to show this. In Finland, the prevalence of smoking declined during the follow-up, from 22% in year 2005 to 13% in year 2019 [39]. Compared to current smokers, all-cause mortality risk of former smokers have been shown to decline after at least five years since quitting smoking [29]. On the other hand, baseline increased depressive symptoms might have affected non-smoking and smoking subjects' abilities to engage in preventive actions [9,10]. In addition, depressive symptoms might negatively affect adherence to medical treatment [40]. Similarly, psychological issues among depressed smokers affecting abilities to smoking cessation [16] and to engage in healthy lifestyle in general [41], in conjunction with possible heavier smoking [31], probably partly underlie excess mortality among baseline current smokers with increased depressive symptoms.

Another plausible explanation for the found relationship between depressive symptoms and smoking on all-cause mortality is that both depressive symptoms and smoking are associated with risk factor clustering. Depressive symptoms are associated with low socio-economic status [12], sedentary and unhealthy lifestyle [9,10] and biological dysregulations [2], all of which might contribute to the association of depressive symptoms and physical health. Depression might indeed predispose to hypertension [6], obesity [42], metabolic syndrome [7], and DM [8]. Similarly, it is known that smoking is often accompanied with other risk factors such as poorer lifestyle [41] and social disadvantages [43], and that it predisposes to metabolic disturbances [44]. Concordantly, burden of risk factors among smokers and depressive subjects was detected among our study population. In addition to more prevalent smoking among depressive subjects, those who smoked compared to non-smokers and those with depressive symptoms compared to non-depressive individuals, performed less leisure-time physical activity, had higher AUDIT score, and more often some metabolic disturbances. However, as pointed out earlier, adjustments for these factors did not notably affect our findings [44].

As also already noted, we are not aware of studies assessing a modifying effect of smoking on the relationship of depressive symptoms and all-cause mortality, but many studies have explored if depression and other risk factors, including smoking, interact on CVD incidence. These studies have had inconsistent findings. For example, in a Chinese study among over 7700 adults, the association of depressive symptoms and incident CVD (precisely stroke) was significant only in non-smokers [20]. This contradicts findings based on Data from National

Epidemiologic Survey on Alcohol and Related Conditions which suggested that depression in fact amplifies the harmful effects of smoking, as well as that of hypertension and BMI, in concordance with our findings [19]. Specifically, among over 26,000 US adults, a significant interaction between current smoking and lifetime depressive disorder on CVD incidence was found. Current tobacco use was associated with higher risk of incident CVD among individuals with a lifetime depressive disorder than those without (OR 1.78 (95% CI 1.36 to 2.32) and 1.41 (95% CI 1.24 to 1.6), respectively) [19].

Related to risk factor clustering, also other risk factors than smoking might interact with depressive symptoms, giving a further explanation for depressive smokers being at highest risk. However, for example Hamieh et al. [45] did not find evidence that hypertension, DM, or dyslipidemia would have a modifying effect on the association of depression and CVD during a 20-year follow-up among over 10,000 middle-aged French subjects. Also, a Korean study among almost 200,000 adults did not find statistically significant interactions between depression and hypertension, DM, and lifestyle (smoking included) on incident CVD, although comorbid depression with diabetes or overweight was associated with higher risk than these risk factors alone [46]. Furthermore, also smoking has been suggested to interact with other risk factors than depression [47–50]. For example, smoking and hypertension have been reported to have a synergistic effect on CVD risk [47,48]. Among Chinese population, an interaction of smoking and metabolic syndrome and diabetes on CVD incidence have been reported [49,50]. Thus, it might be that even we adjusted for other risk factors, clustering of these risk factors and their amplifying effects on each other contribute to the excess mortality risk of depressive smokers.

Taken together, there are several mechanisms explaining the interaction between depressive symptoms and smoking on all-cause mortality, and it is plausible that depressive smokers are those at highest risk. The relationship of increased depressive symptoms and mortality is complex, and can be explained by social or lifestyle factors [13,51], and biological dysregulation involved in pathogenesis of depression [2]. Smoking affects these same biological processes [52], and it might be that when both are present, these effects are even stronger. Moreover, depressive smokers may be more exposed to the harmful effects of smoking due to its heaviness [31]. They may also suffer from more severe depression [34]. It should however be noted that the association of depressive symptoms and mortality have been found to exist even with subthreshold depressive symptoms [1]. Finally, one reason for this interaction could also be lower treatment adherence associated with both depressive symptoms [40] and smoking [53].

4.3. Implications for research and practice

Our findings suggest that depressive symptoms seem to increase mortality risk especially in conjunction with smoking, as the survival of depressive smokers was remarkably worse than that of non-depressive smokers or depressive non-smokers. We believe this was one of the first studies assessing the relationship of depressive symptoms and mortality stratified by smoking and there is need for replication of this study design. All in all, in future studies on depressive symptoms and mortality, consideration of smoking seems to be essential. Considering clinical practice, smoking is a robustly established risk factor for mortality [17] and a key target in health promotion. Our findings emphasise that special efforts for smoking cessation should be made among depressive smokers. However, it is known that depressive symptoms may impair the ability to quit smoking [16], and in studies assessing interventions aimed to smoking cessation, it could be useful to study the impact of depressive symptoms on the likelihood of successful withdrawal. It is plausible that effective treatment of depression plays an important role in actions aiming to improve lifestyle of depressive individuals.

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CRediT authorship contribution statement

Ansa Talvikki Rantanen: Writing – original draft. **Hannu Kautiainen:** Visualization, Methodology, Formal analysis. **Mikael Oskari Ekblad:** Writing – review & editing. **Päivi Elina Korhonen:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets analysed during the current study are available on reasonable request.

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