Depression and cardiovascular disease:

The role of diet, lifestyle, and health

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Depressie en hart- en vaatziekten:

De rol van voeding, leefstijl en gezondheid

(met een samenvatting in het Nederlands)

Proefschrift

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Een dag niet gelachen, is een dag niet geleefd.

Voor mijn ouders

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Manuscripts not presented in this thesis

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Contents

Chapter 1	**General introduction**	1
Chapter 2	**Depression and cardiovascular disease**	
	Depressive symptoms as risk factor of cardiovascular mortality in older European men.	9
Chapter 3	**Diet and lifestyle**	
3.1	Dietary intake of B-vitamins, serum homocysteine levels and their association with depressive symptoms.	29
3.2	Depression and cardiovascular mortality: a role for n-3 fatty acids?	41
3.3	Depressive symptoms, physical inactivity and risk of cardiovascular mortality in European elderly.	55
Chapter 4	**Health**	
4.1	Autonomic dysfunction: the link between depression and cardiovascular mortality?	71
4.2	The association of depressive symptoms with cardiovascular mortality is partly explained by subjective health status.	87
Chapter 5	**General discussion**	
	Depression and cardiovascular disease: cause, consequence, or innocent bystander?	101
Chapter 6	**Summary**	115
	Samenvatting	121
	Dankwoord	127
	Curriculum Vitae	133

Chapter 1

General introduction

Depression and cardiovascular disease

The results of the 'Global Burden of Disease Study', initiated by the World Health Organization (WHO), show that cardiovascular diseases (CVD), including ischemic heart disease and cerebrovascular disease, are the top contributors of mortality world wide **(Figure 1)**. Moreover, it is predicted that mortality from cardiovascular diseases will increase steeply from 23.8 million deaths in 2002 to 34.4 million in 2030.[1] At the same time, patients with CVD will live longer because of improved treatment possibilities. As a result, CVDs are expected to become a major cause of disability world wide **(Table 1)**.[1]

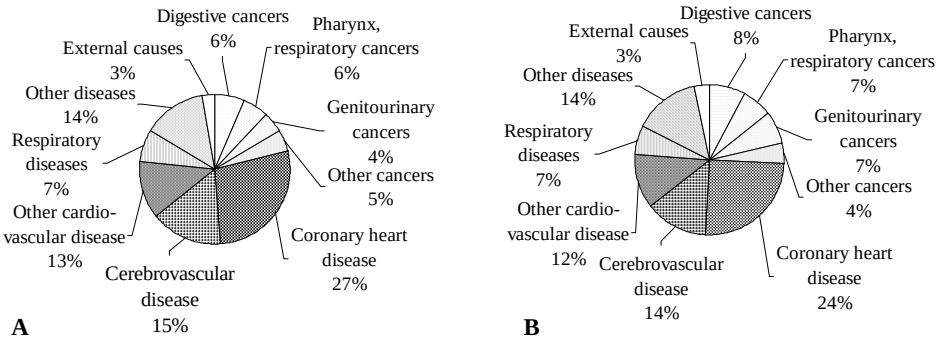

Figure 1: Causes of mortality for **(A)** European older men and **(B)** the Finland, Italy and Netherlands Elderly Study.

Another major contributor to global disability are major depressive disorders **(Table 1)**. The two core symptoms of major depressive disorder are depressed mood or a feeling of sadness and loss of interest. In order to meet the criteria for a diagnosis of major depressive disorder, one or both of these symptoms have to be present most of the day for a period of at least two weeks, as well as three or four other symptoms, such as weight loss, fatigue, feelings of guilt, or suicidal thoughts. It has been estimated that 16% of the adult population will have an episode of major depressive disorder during his or her lifetime, and about 6.6% may have had a major depressive disorder in the past 12 months.[2] Estimates from Europe indicate that the prevalence of major depressive disorder in the elderly is much lower (1.8%), but that minor depression (9.8%) and subthreshold depressive symptoms (13.5%) are very common in the elderly.[3]

Table 1: Change in rank order of DALYs for the ten leading causes of disease or injuries world wide 2002-2030

2002 *disease or injury*	*%*	*rank*	*rank*	*%*	*2030* *disease or injury*
Perinatal disorders	6.6	1	1	10.3	HIV/AIDS
Lower respiratory infections	6.3	2	2	5.3	Unipolar major depression
HIV/AIDS	5.7	3	3	4.4	Ischemic heart disease
Unipolar major depression	4.5	4	4	3.8	COPD
Diarrhoeal diseases	4.3	5	5	3.8	Perinatal disorders
Ischemic heart disease	4.0	6	6	3.7	Cerebrovascular disease
Cerebrovascular disease	3.3	7	7	3.6	Road-traffic accidents
Road-traffic accidents	2.6	8	8	2.9	Cataracts
Malaria	2.3	9	9	2.8	Lower respiratory infections
Tuberculosis	2.3	10	10	2.5	Tuberculosis

Abbreviations: DALYs, disability adjusted life years; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; COPD, Chronic obstructive pulmonary disease. Source: Updated projections of global mortality and burden of disease, 2003-2030: data sources, methods and results

Depression and CVD are not only highly prevalent and major contributors of disability, they are also more closely related. The first evidence for a relation between depression and CVD came from studies in patients with myocardial infarction (MI). These studies showed that about one-third of post-MI patients had minor or major depression.[4,5] In addition, these patients had a worse prognosis than patients who were not depressed after a MI.[5]

More recently, it has been hypothesized that depression not only leads to poor prognosis in patients with established CVD, but also increases the risk of CVD in apparently healthy persons. Recent reviews support the view that depression is a risk factor for CVD and cardiovascular mortality. The evidence comes not only from studies that used clinical diagnoses of depressive disorder, but also from studies that used questionnaires to estimate the presence and degree of depressive symptoms.[6]

Possible explanations

Several explanations have been put forward to explain why depression may be a risk factor for cardiovascular events. Indirectly an unhealthy diet or -lifestyle in depressed persons and medication non-adherence in depressed cardiac patients may increase their risk of CVD. Potential direct mechanisms include dysregulation of the hypothalamic-pituitary-adrenocortical axis, inflammation, platelet reactivity and autonomic dysfunction.[7] While these factors have been linked to depression and vascular events, no studies have examined the

relative contribution of each factor alone in the relation between depression and CVD.[8] In this thesis, we will focus on diet, lifestyle, autonomic dysfunction and general subjective health status as potential explanations for the relation between depression and CVD.

Diet and lifestyle

Persons who become depressed may adapt an unhealthy lifestyle including a poor diet and may therefore be at increased risk of CVD. Research has suggested that a low dietary intake of B-vitamins, especially folate and n-3 fatty acids may be involved in the etiology of both depression and CVD.[9] Studies have also shown that depressed persons may be less physically active.[10] Since physical inactivity is a major risk factor for CVD and cardiovascular mortality,[11] it may be an intermediate factor in the relation between depression and CVD. In addition, depression and physical inactivity may interact in the development of CVD, possibly through their impact on adverse atherosclerotic and thrombotic processes.

Health

One of the biological explanations for the increased risk of CVD associated with depression is through autonomic dysfunction.[12] Indicators of autonomic dysfunction such as elevated resting heart rate, low heart rate variability (HRV) and prolonged QTc-intervals are associated with depression in cardiac patients but also in persons without CVD.[13,14] Since autonomic dysfunction is associated with increased cardiovascular- and all-cause mortality,[15,16] it has been hypothesized that autonomic dysfunction may explain why depression increases risk for CVD. An alternative explanation for the increased risk of depression on CVD is that depression reflects a general poor health status, in particular if the depression is mild or asymptomatic. This would imply that depression is not a true risk factor for CVD but rather reflects underlying disease.

Aim of this thesis

The main aim of this thesis is to investigate the relation between depression and CVD. The objectives of this thesis are, first, to investigate whether depressive symptoms are a risk factor for cardiovascular mortality in a population of healthy older men; second, to investigate the role of dietary and lifestyle factors in the relation between depressive symptoms and cardiovascular mortality; and third, to investigate to what extent autonomic dysfunction and subjective health status can explain the association between depressive symptoms and cardiovascular mortality. Finally, we discuss whether the results of the studies described in

this point at a role for depression as a cause, a consequence, or an innocent bystander of CVD.

Study population

The data for the studies described in this thesis are from the Finland, Italy and Netherlands Elderly (FINE) study. FINE is a prospective population-based cohort study on risk factors of CVD in elderly men. FINE started in 1984 as a continuation of the Seven Countries Study, which was originally initiated in 1958 as a cardiovascular risk factor survey among middle-aged men born between 1900 and 1920. In the Netherlands, the surviving cohort was extended with a new random sample of men of the same age, also living in Zutphen but not belonging to the original cohort (The Zutphen Elderly Study). In 1989-1991, the second round of FINE took place, and measures of depression were added. In the Zutphen Elderly Study extensive data on diet was also collected. Mortality data were collected until the year 2000.

Our primary risk factor of interest is depression. We used the Zung Self-rating Depression Scale (SDS) to assess depressive symptoms. This scale was developed to assess depressive disorders among patients admitted to a psychiatric hospital and has frequently been used in non-institutionalized elderly.[17] The questionnaire contains 20 either positively or negatively formulated items, based on clinical diagnostic criteria commonly used to characterize depressive disorders. It contains mood items as ‘I feel down and sad’ and ‘I still do with pleasure things I used to do’ but also more somatic items as’ My heart beats faster than usually’ and ‘I notice myself to have lost weight’. Although no formal diagnosis of depressive disorder can be made with the Zung SDS, a high score represents a greater risk of depression, and cut-off values are generally used to indicate mild depression, moderate depression, and severe depression.

Our primary outcome of interest is incidence of CVD. We defined incidence of CVD as mortality from CVD during ten years of follow-up in persons without a history of CVD and diabetes, and coded according to the International Classification of Diseases. They include coronary heart disease, stroke, heart failure, and other degenerative heart diseases. The causes of death in the FINE study are comparable with the figures of 2002 in older European men presented on the website of the WHO.[18] Also, in older men, ischemic heart disease and cerebrovascular disease are the top two contributors to mortality **(Figure 1)**.

Outline of this thesis

In **chapter 2** we investigated whether depressive symptoms are a risk factor for cardiovascular mortality in older men who had no history of CVD and diabetes at baseline. We examined specific cardiovascular mortality endpoints and excluded men who died from CVD in the first five years after the start of the study to minimize the possibility of reversed causality. In **chapter 3.1** we explored the association between dietary intake of B-vitamins, serum levels of homocysteine and depressive symptoms. In **chapter 3.2** the role of n-3 fatty acids in the relation between depressive symptoms and cardiovascular mortality was examined. In **chapter 3.3** we studied the role of physical inactivity in the association between depressive symptoms and cardiovascular mortality. In **chapter 4.1** we set out to determine whether indicators of autonomic dysfunction could explain the relation between depressive symptoms and cardiovascular mortality. In **chapter 4.2** we addressed the extent to which the association between depressive symptoms and cardiovascular mortality could be explained by subjective health status. In **chapter 5** we discussed the results of the studies described in this thesis and revisited the question whether depression is a cause, a consequence, or an innocent bystander of CVD in the context of the results presented in this thesis and the literature. A summary of the results presented in this thesis is provided in **chapter 6**.

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Chapter 2

Depression and cardiovascular disease

Depressive symptoms as risk factor of cardiovascular mortality in older European men.

Abstract

Background: Depressive symptoms have been suggested to increase the risk of cardiovascular diseases (CVD), but this may reflect reversed causality. We investigated to what extent depressive symptoms are a true risk factor for cardiovascular mortality in elderly men.

Methods: Data were used from the population-based prospective Finland, Italy and the Netherlands Elderly (FINE) Study. Depressive symptoms were measured with the Zung Self-rating Depression Scale in 799 elderly men, aged 70-90 years, free from CVD and diabetes. Using Cox models, hazard ratios (HR) were calculated for specific cardiovascular mortality endpoints. The analyses were adjusted for potential confounders, stratified by country and repeated after exclusion of men who died from CVD up to five years after baseline.

Results: During 10-year follow-up 224 (28%) men died from CVD. The adjusted hazard for a 5-point increase in depressive symptoms was 1.15 (95% CI 1.08-1.23) for cardiovascular mortality. This risk was stronger for mortality from stroke (HR 1.35; 95% CI 1.19-1.53) and heart failure (HR 1.16; 95% CI 1.00-1.35) in comparison with mortality from coronary heart disease (HR 1.08; 95% CI 0.97-1.20) and other degenerative heart diseases (HR 1.06; 95% CI 0.91-1.23). Exclusion of men who died from CVD within five years after baseline did not change the strength of the associations. There were no significant differences in hazard ratios between Northern and Southern Europe.

Conclusions: This study provides further and more convincing prospective evidence for depressive symptoms as a risk factor for cardiovascular mortality in elderly men.

Introduction

Cardiovascular diseases (CVD), including coronary heart disease (CHD) and stroke, are still the major causes of death in most European countries and account for 32% of all deaths.[1] There is increasing evidence that besides classical risk factors, such as hypertension, hypercholesterolemia, diabetes and smoking, psychosocial factors and depression also play a role in the occurrence of CVD.[2]

In patients with CVD depression is common. For instance, one in five patients with newly diagnosed coronary disease is depressed.[3] Depression is not only common in patients with CVD, it may also worsen the prognosis and may lead to a higher mortality from CVD.[4,5] Several explanations have been put forward for a worse prognosis associated with depression, such as higher disease severity, unhealthy behavior, non-adherence to cardiac treatment, antidepressant cardiotoxicity, more cardiovascular risk factors, inflammation, autonomic dysfunction and increased platelet activation.[6]

More recently, it has been hypothesized that depression not only leads to poor prognosis in patients with established CVD, but also increases the risk of CVD in initially healthy persons. Recent reviews show evidence for the hypothesis that depression is a risk factor for CVD.[2,7] However, due to heterogeneity between studies, results of these studies are difficult to compare. For instance, most of the studies reviewed used different cardiovascular endpoints. In addition, most of the studies were performed in middle-aged persons. In elderly men the results are less conclusive. For instance, mild and major depression have been associated with increased total mortality[8] and cardiovascular mortality[9-11] but the results are not conclusive for CHD,[9,12] stroke[13] and heart failure (HF) incidence.[14,15] Also, depression may still be a consequence of subclinical disease, thus indicating reversed causality.[16-19]

We investigated the relation between depressive symptoms and risk of cardiovascular mortality in a population-based sample of older men in three European countries. We investigated specific cardiovascular mortality endpoints, and excluded men who died from CVD in the first five years after baseline to minimize the possibility of reversed causality.

Methods

The FINE study

The FINE (acronym for Finland, Italy and the Netherlands Elderly) Study is a prospective population-based cohort study on risk factors and health in elderly men. The study design and measurements have been described in detail elsewhere.[20] In brief, the FINE study started in 1984 as a continuation of the Seven Countries Study (SCS), which was originally initiated in 1958 by Keys as a cardiovascular risk factor survey among 12,763 middle-aged

men, born between 1900 and 1920.[21] In the Netherlands, the surviving cohort was enlarged in 1985 to an elderly cohort of 939 men, by inviting a random sample of men born between 1900 and 1920 who had not participated in the study before. In total, 2285 men from Finland (n=716), Italy (n=682) and the Netherlands (n=887) participated in the baseline examination of the study in 1985. Informed consent was obtained from all study participants. Data collection followed the international protocol used in previous surveys of the SCS.[21] In 1989-1991 the second round of the FINE Study took place. In this round, measures on depression, functional status, cognitive function and self-reported health were added. Around 1995 and 2000 the third and fourth round of examinations where carried out. Mortality data were collected until the year 2000.

Depressive symptoms

Depressive symptoms were measured using the Self-rating Depression Scale (SDS), developed by Zung.[22] This scale was used to assess depression among patients admitted to a psychiatric hospital, but also for non-institutionalized elderly,[23] and was found to be highly comparable among different countries.[24] The reliability of the SDS is good in elderly men (Cronbach alpha 0.75)[25] and has been validated repeatedly with other questionnaires on depressive symptoms, such as CESD (r=0.69),[26] the Geriatric Depression Scale (r=0.59)[27] and the Hamilton Depression scale (r=0.80).[28] The questionnaire contained 20 either positively or negatively formulated items, based on clinical diagnostic criteria commonly used to diagnose depressive disorders. The answers on those items were coded on a four-point Likert-type scale varying from 'none or sometimes' to 'most or always'. Positive items on the absence of depressive symptoms were recoded, so that a higher score indicated more depressive symptoms, with total scores ranging from 20 to 80. Men with more than two missing items were excluded for the analysis. If one or two items were missing, the mean score of the valid items of the subject was calculated and the missing item(s) was (were) replaced by this mean score. An index for the SDS was derived by dividing the sum of the answers by 80 times 100 (range 25-100), with a higher score indicating more depressive symptoms. The original clinical cut-off values are: no depression (< 50); mild depression (50-59) and moderate-severe depression (≥ 60).[23] To increase power a continuous measure of the SDS was used (5-point increase) and the SDS was categorized into country-specific tertiles.

Cardiovascular endpoints

Mortality data were collected during ten years of follow-up and obtained through official death certificates. One person was lost to follow-up. He was included in the analyses, but censored at the date of the examination round that he was lost to follow-up (after 3.6 years).

Men who died from other causes than CVD were censored at date of death; for men who were still alive in 2000 the censor date was set at the examination date of the last round. In Finland, information on the causes of death was obtained from Finnish death registers; in Italy and the Netherlands the information was obtained from hospital registries and/or general practitioners. Original coding was done locally and checked by one clinical epidemiologist, who was blinded for the risk factor status of the subject. All diagnoses were coded according to the International Classification of Diseases, ninth Revision (ICD-9). The following ICD codes were used: CVD (390-459), coronary heart disease (CHD) (410-414), stroke (430-438), heart failure (HF) (428) and other degenerative heart disease (oDHD) (401-405, 426-427 and 429). For the analyses, both primary and secondary causes of death were considered.

Cardiovascular risk factors

The self-administered questionnaire contained questions on demographic characteristics, educational level, lifestyle habits, past and current morbidity. Participants were classified as current, past or never smokers. Alcohol consumption was derived from the cross-check dietary history in the Netherlands, and in Finland and Italy assessed with self-administered questionnaires.[29] A part of the Finnish men (n=62) had no information of alcohol consumption, because in 1990 a reduced questionnaire was used. For these men the alcohol consumption from 1985 was used. Alcohol consumption was expressed as grams of alcohol per day (g/d), and classified into three categories (0 g/d, 1-29 g/d and $\geq$ 30 g/d).[29] body mass index (BMI) was calculated from weight and height (kg/m^2), which were measured while the participant was standing in light clothing without shoes. Physical activity was assessed with a self-administered validated questionnaire designed for retired men[30] and expressed as minutes of total physical activity per week (min/wk). Self-reported disability was measured using a standardized questionnaire about routine daily activities and classified as moderate to severe disabilities, compared with no to mild disabilities, following a hierarchical disability coding scheme.[31]

Arterial blood pressure was measured twice on the right arm after five minutes of rest, with the man in a supine position. In Finland and Italy standard mercury sphygmomanometers were used, while in the Netherlands a random zero sphygmomanometer was used. The average of two readings of both systolic and diastolic blood pressure (fifth Korotkoff phase) was calculated. Venous blood samples (fasting in Finland and non-fasting in Italy and the Netherlands) were taken and total- and high density lipoprotein (HDL) cholesterol (mmol/L) were determined using standardized procedures according to the criteria of the World Health Organization's Lipid Reference Laboratories in Prague, Czechoslovakia, or Atlanta, Georgia.[29] History of myocardial infarction was obtained using the London School of Hygiene and Tropical Medicine questionnaire,[32] verified by information from general

practitioners or hospital registries. The clinical history of stroke, HF and diabetes was based on the doctor's conclusion using the questionnaire information and the results of the physical examination.

Study sample

Depressive symptoms were measured for the first time during the second round of the FINE study, between October 1989 and November 1991, when in total 1416 men (82%) participated of the 1734 men still alive. At that time, 909 (64%) were free of CVD and diabetes. We excluded 85 men with more than two missing items in the SDS as well as 25 men with missing values in covariates. Thus, a study sample of 799 men remained for analysis, 229 men from Finland, 332 men from the Netherlands and 238 men from Italy.

Statistical analysis

Means and standard deviations (SD) were computed for continuous baseline variables, and medians and 10-90 percentiles for continuous variables with a skewed distribution. Frequency distributions were given for categorical variables according to country specific tertiles of the SDS index score. Differences between SDS tertiles were tested for each country, with ANOVA, Kruskal-Wallis (in case of skewed distribution) or X^2-test.

To investigate the association between depressive symptoms and cardiovascular mortality, Cox proportional hazard analyses were performed. By censoring on type of events we could analyze different cardiovascular mortality endpoints separately. Age was used as the time scale in the proportional hazards models to optimally adjust for age.[33] Age at entry was assigned as the age at the date of examination in 1990. Censoring age was defined as age at death or end of study. A hazard curve of the follow-up years versus the percentage of subjects who died of CVD was made, according to tertiles of depressive symptoms. With a log minus log plot the assumptions of proportional hazards were checked. The assumptions of proportionality were not violated. Analyses were performed for 5-point increase- and tertiles of baseline depressive symptoms. In the first model we adjusted for age (as time scale). In the second model analyses we also adjusted for possible confounders, i.e. country (Finland vs the Netherlands and Italy vs the Netherlands), years of education, BMI (kg/m^2), smoking (past vs never and current vs never), alcohol consumption (1-29 g/d vs 0 g/d and $\geq$ 30 g/d vs 0 g/d), systolic blood pressure SBP (mmHg), total- and HDL cholesterol levels (mmol/L) and physical activity (min/wk). Analyses were additionally adjusted for disability and repeated with clinical categories of depressive symptoms (no (< 50)/mild (50-59)/moderate-severe ($\geq$ 60)). To evaluate whether country modified the association between depressive symptoms and cardiovascular mortality, analyses were also done after stratification by country and interaction terms of country and the SDS index

score were included. Analyses were repeated after exclusion of men who died from CVD in the subsequent five years after baseline.

All analyses were performed with SPSS version 12.0.1 and the SAS statistical software package, version 8.2.[34] Point estimates are given with corresponding 95% confidence intervals (CI).

Results

After ten years of follow-up, 396 (50%) men had died and 403 men were still alive. Two-hundred and twenty-four (28%) men died from CVD, 93 from CHD, 66 from stroke, 45 from HF and 46 from oDHD. The total number of person years was 5893 and the mean follow-up time was 7.4 years (SD=3.0). The average SDS score was 49.2 (SD=11) in Italy, 45.4 (SD=10) in Finland and 42.6 (SD=10) in the Netherlands.

Table 1 presents the baseline characteristics of the men (n=799) for each country and for the whole study population, according to country specific tertiles of the SDS score. Men with more depressive symptoms had received shorter education, were more disabled and less physically active. Although not statistically significant, men from Finland and Italy with more depressive symptoms seemed to have lower total- and HDL cholesterol levels. One-hundred and ten men (8%) who were excluded from the analyses due to missing values in the SDS or other covariates were older, less educated and less physically active, more disabled and had a higher mortality rate in comparison with men who were not excluded (results not shown).

Table 2 presents hazard ratios (HR) for a 5-point increase and tertiles of depressive symptoms and different cardiovascular mortality endpoints. The age-adjusted hazard ratio for the continuous SDS score and cardiovascular mortality was 1.14 (95% CI 1.08-1.22), indicating that for each increase of five points on the SDS (range 25-100) the risk of mortality from CVD increased with 14%. This hazard ratio did not change after additional adjustments for demographical and other cardiovascular risk factors (model 2). In addition, the association was slightly attenuated after adjustment for disability (HR 1.12; 95% CI 1.05-1.20). The associations were stronger for mortality due to stroke (HR 1.35; 95% CI 1.19-1.53) and HF (HR 1.16; 95% CI 1.00-1.35) in comparison with mortality due to CHD (HR 1.08; 95% CI 0.97-1.20) and oDHD (HR 1.06; 95% CI 0.91-1.23).

Table 1: Baseline characteristics per country and tertiles of the Zung SDS index score (n=799)

	Finland			The Netherlands		
	Depressive symptoms			Depressive symptoms		
	Low	Middle	High	Low	Middle	High
	< 42	42-49	> 49	< 37	37-45	> 45
Characteristic	**n=79**	**n=74**	**n=76**	**n=104**	**n=123**	**n=105**
Age, mean (SD), y	75 (5)	77 (5)	77 (5)	75 (4)	75 (4)	76 (5)
Education, mean (SD), y	4.6 (3.0)	4.9 (3.6)	3.8 (2.4)	11.1 (4.3)	11.1 (4.7)	9.2 (3.3)*
Alcohol consumption						
0 g/d (%)	41	26	24	31	22	23
1-29 g/d (%)	56	67	71	48	59	65
≥ 30 g/d (%)	3	7	5	21	19	12
Smoking						
current (%)	13	14	12	24	23	23
past (%)	47	58	54	58	58	60
never (%)	40	28	34	18	19	17
Physical activity, median,	630	480	415*	603	540	420†
P10-P90, min/wk	210-2760	75-1500	60-1395	180-1335	105-1190	32-910
Disability (%)	5	10	19*	5	14	16*
BMI, mean (SD), kg/m^2	26.1 (3.7)	26.1 (3.9)	26.0 (3.9)	25.5 (2.9)	25.3 (2.9)	26.1 (3.0)
SBP, mean (SD), mmHg	153 (20)	161 (23)	158 (22)	150 (19)	147 (20)	153 (21)
DBP, mean (SD), mmHg	83 (11)	87 (11)	84 (11)	81 (10)	81 (11)	84 (13)
Hypertension (%)	51	64	57	43	35	44
Total cholesterol, mean (SD), mmol/L	5.7 (1.1)	5.6 (0.9)	5.6 (1.2)	6.1 (1.2)	6.1 (1.1)	6.1 (1.1)
HDL cholesterol, mean (SD), mmol/L	1.1 (0.2)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.1 (0.3)

Abbreviations: SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein. Disability is defined as moderate to severe, compared to no to mild, following the hierarchical disability score. Hypertension was defined as a systolic blood pressure of ≥ 160 mmHg, or a diastolic blood pressure of ≥ 95 mmHg or use of medication *P < 0.05 †P < 0.001

Table 1: Continued

	Italy			All countries		
	Depressive symptoms			Depressive symptoms		
	Low	Middle	High	Low	Middle	High
	< 43	43-53	> 53			
Characteristic	**n=78**	**n=81**	**n=79**	**n=261**	**n=278**	**n=260**
Age, mean (SD), y	77 (4)	78 (4)	78 (4)	76 (4)	76 (4)	77 (5)
Education, mean (SD), y	5.6 (3.2)	4.9 (2.6)	4.1 (1.7)*	7.5 (4.7)	7.6 (5.0)	6.1 (3.7)
Alcohol consumption						
0 g/d (%)	19	17	23	31	22	23
1-29 g/d (%)	50	52	35	51	59	58
≥ 30 g/d (%)	31	31	42	18	19	19
Smoking						
current (%)	18	11	22	19	17	20
past (%)	44	54	47	50	57	54
never (%)	38	35	31	31	26	26
Physical activity, median,	978	680	245†	795	540	390†
P10-P90, min/wk	180-2400	90-1905	0-1830	1180-1985	90-1575	25-1200
Disability (%)	5	9	33†	5	11	22
BMI, mean (SD), kg/m^2	26.3 (3.4)	26.3 (3.6)	25.8 (4.1)	25.9 (3.3)	25.8 (3.4)	25.9 (3.6)
SBP, mean (SD), mmHg	164 (19)	164 (19)	159 (19)	155 (20)	156 (22)	156 (21)
DBP, mean (SD), mmHg	86 (10)	87 (8)	85 (9)	84 (11)	85 (11)	84 (11)
Hypertension (%)	73	69	65	54	53	54
Total cholesterol, mean (SD), mmol/L	5.6 (1.2)	5.5 (1.0)	5.4 (0.9)	5.8 (1.2)	5.8 (1.1)	5.7 (1.1)
HDL cholesterol, mean (SD), mmol/L	1.38 (0.4)	1.32 (0.3)	1.33 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)

Abbreviations: SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein. Disability is defined as moderate to severe, compared to no to mild, following the hierarchical disability score. Hypertension was defined as a systolic blood pressure of ≥ 160 mmHg, or a diastolic blood pressure of ≥ 95 mmHg or use of medication *P < 0.05 †P <0.001

Table 2: Hazard ratios for a 5-point increase- and country specific tertiles of depressive symptoms and mortality from specific cardiovascular diseases

		Cases (PY)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Cardiovascular disease				
Depressive symptoms:	5-point increase		1.14 (1.08-1.22)	1.15 (1.08-1.23)
	low	51 (2083)	reference	reference
	middle	76 (2087)	1.39 (0.97-1.99)	1.35 (0.84-1.94)
	high	97 (1723)	2.15 (1.53-3.03)	2.07 (1.46-2.94)
	P for trend		< 0.0001	< 0.0001
Coronary heart disease				
Depressive symptoms:	5-point increase		1.07 (0.97-1.17)	1.08 (0.97-1.20)
	low	25 (2083)	reference	reference
	middle	31 (2087)	1.18 (0.70-2.01)	1.19 (0.70-2.04)
	high	37 (1723)	1.71 (1.03-2.84)	1.68 (0.99-2.84)
	P for trend		0.04	0.05
Stroke				
Depressive symptoms:	5-point increase		1.30 (1.17-1.45)	1.35 (1.19-1.53)
	low	11 (2083)	reference	reference
	middle	21 (2087)	1.78 (0.85-3.72)	1.65 (0.78-3.47)
	high	34 (1723)	3.50 (1.77-6.91)	3.41 (1.69-6.90)
	P for trend		< 0.0001	0.0003
Heart Failure				
Depressive symptoms:	5-point increase		1.16 (1.01-1.33)	1.16 (1.00-1.35)
	low	8 (2083)	reference	reference
	middle	15 (2087)	1.56 (0.65-3.73)	1.56 (0.64-3.57)
	high	22 (1723)	2.91 (1.29-6.56)	2.77 (1.19-6.42)
	P for trend		0.006	0.01
Other degenerative heart disease				
Depressive symptoms:	5-point increase		1.14 (1.00-1.31)	1.06 (0.91-1.23)
	low	16 (2083)	reference	reference
	middle	14 (2087)	0.80 (0.38-1.66)	0.71 (0.34-1.50)
	high	16 (1723)	1.14 (0.57-2.28)	0.93 (0.45-1.92)
	P for trend		0.73	0.85

Abbreviations: PY, person years; HR, hazard ratio; CI, confidence interval

Model 1: Adjusted for age (as time scale) Model 2: Additionally adjusted for country (Finland, Italy, the Netherlands (reference)), years of education, BMI (kg/m^2), smoking (never (reference), past, current), alcohol consumption (0 g/d (reference), 1-29 g/d, ≥ 30 g/d), systolic blood pressure (mmHg), total- and HDL cholesterol levels (mmol/L) and physical activity (min/wk)

Figure 1 illustrates a fully adjusted cumulative hazard curve for cardiovascular mortality according to country specific tertiles of depressive symptoms. The death rate increased with the number of depressive symptoms. In addition, when using the clinical cut-off scores, the adjusted hazard ratios for cardiovascular mortality were 1.72 (95% CI 1.25-2.37) for men with mild depression (50-59) and 1.87 (95% CI 1.25-2.80) for moderate-severe depression (≥ 60), compared to men without depression (< 50). Analyses with the primary death causes showed the same estimates with wider CIs (results not shown).

Exclusion of early CVD deaths did not materially change the results **(Table 3)**. After exclusion of 144 men who died within five years after baseline, the hazard ratio for a 5-point increase was 1.16 (95% CI 1.03-1.30).

After stratification by country the adjusted hazard ratios for cardiovascular mortality did not differ between countries and none of the interaction terms were statistically significant (results not shown).

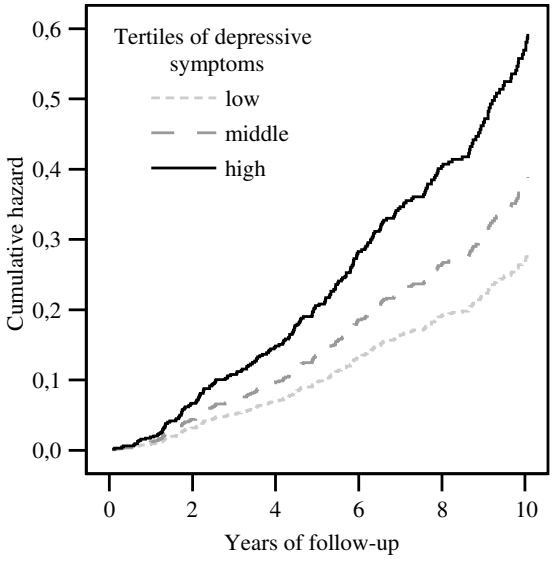

Figure 1: Hazard curves for cardiovascular mortality according to country specific tertiles of depressive symptoms, adjusted for age (years), country (Finland, Italy, the Netherlands (reference)), years of education, BMI (kg/m^2), smoking (never (reference), past, current), alcohol consumption (0 g/d (reference), 1-29 g/d, ≥ 30 g/d), systolic blood pressure (mmHg), total- and HDL cholesterol levels (mmol/L) and physical activity (min/wk)

Table 3: Adjusted hazard ratios for 5-point increase and country specific tertiles of depressive symptoms and cardiovascular mortality, after exclusion of men who died from cardiovascular diseases in the five following years after baseline

	Years of exclusion after baseline				
	1	**2**	**3**	**4**	**5**
Number excluded	41	64	85	112	144
Depressive symptoms:					
5-point	1.16 (1.08-1.25)	1.16 (1.07-1.26)	1.17 (1.08-1.28)	1.14 (1.04-1.26)	1.16 (1.03-1.30)
low	reference	reference	reference	reference	reference
middle	1.28 (0.85-1.92)	1.24 (0.80-1.92)	1.24 (0.78-2.06)	1.30 (0.78-2.17)	1.43 (0.77-2.66)
high	2.18 (1.48-3.20)	2.22 (1.47-3.26)	2.21 (1.46-3.55)	2.06 (1.25-3.40)	2.52 (1.38-4.60)
P for trend	< 0.0001	< 0.0001	0.0002	0.004	0.002

Hazard ratios are adjusted for age (as time scale), country (Finland, Italy, the Netherlands (reference)), years of education, BMI (kg/m^2), smoking (never (reference), past, current), alcohol consumption (0 g/d (reference), 1-29 g/d, ≥ 30 g/d), systolic blood pressure (mmHg), total- and HDL cholesterol levels (mmol/L) and physical activity (min/wk)

Discussion

The results of this prospective study among elderly men without CVD at baseline show that depressive symptoms are associated with an increased risk of future cardiovascular mortality. The risk is highest for mortality due to stroke and HF. There are no risk differences observed between Northern and Southern Europe.

A major strength of this study is its prospective longitudinal design, which made it possible to determine depressive symptoms before onset of CVD. Furthermore, the long follow-up period and large sample size enabled us to examine specific causes of death and to exclude subjects who died from CVD in the first five years after baseline, making the possibility of reversed causality even more unlikely. In addition, the estimated effects were not disturbed by a selective loss to follow-up, because the mortality follow-up was complete. Finally, to investigate the independent effect of depressive symptoms, we were able to adjust for many potential confounding variables, in particular lifestyle- and CVD risk factors.

We observed a dose-response relationship between depressive symptoms at baseline and cardiovascular mortality providing further evidence of a causal relationship. Also, we extensively adjusted for possible confounding variables, in particular lifestyle and CVD risk factors. These factors explained only a small part of the association between depressive symptoms and cardiovascular mortality. Additional adjustment for disability attenuated the

strength of the association a little further, but there was still an independent effect of depressive symptoms.

Our results provide further and more convincing evidence of depression as a true risk factor for CVD[2,7] The strength of the association for CHD mortality that we observed is highly similar to the risk ratio of 1.64 that was found in two systematic reviews.[17,35] In the present study we found stronger associations for depressive symptoms and mortality from stroke and HF, in comparison with mortality from CHD and oDHD. To date, in the elderly results of specific cardiovascular endpoints as CHD[9,12] and stroke[13] have been inconclusive. In addition, increased risks on HF incidence were observed in elderly women and hypertensive patients.[14,15] Our study is the first to observe an increased risk for HF mortality in elderly men without CVD at baseline.

In the present study we did not have clinical diagnoses of depressive disorder. As a result, this study thus cannot draw conclusions on the relation between clinical diagnoses of depression and CVDs mortality. However, the analyses with depressive symptoms classified according to the original clinical cut-off values showed similar results as the analyses with tertiles of depressive symptom scores. Moreover, the linear and dose-response relationship we observed suggests that there is no clinical threshold to increase the risk of cardiovascular mortality.

Several mechanisms have been hypothesized to explain the relationship between depression and CVD.[6] First, dietary habits or nutrients might play a role. Depressed persons might have a higher saturated-fat intake or a lower omega-3 fatty acid intake compared with controls.[36] Second, neuro-endocrine changes during depression may accelerate the development of CVD. For instance, dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, with its elevated cortisol levels is often present in depression and may lead to atherosclerosis-inducing actions such as injury of vascular endothelial cells, hypertension, hypercholesterolemia and inflammation.[37] Depression is also associated with excessive sympathetic and diminished parasympathetic nervous system activity, which may influence the progression of HF by impaired left ventricular function and renal sodium retention.[38,39] Autonomic dysfunction may also lead to decreased heart rate variability,[40] which in turn is associated with arrhythmia's and sudden cardiac death.[41] Some mechanisms or factors such as dietary omega-3 fatty acid intake[36] or inflammation[42] are also associated with an increased risk of depression, indicating that they might be common causes for depression as well as CVD. In the present study, we were not able to discern these potential mechanisms. However, our rigorous exclusion of men with prevalent CVD and diabetes at baseline and our extensive adjustment for classical cardiovascular and lifestyle risk factors indicate that the relation between depression and cardiovascular mortality cannot be explained by unhealthy behaviour or severity of disease. The relatively high risk we observed for mortality from stroke associated with depressive symptoms may be supportive for the hypothesis that vascular pathology of the brain precedes depression.[43]

Finally, some methodological issues of the current study must be considered. First, selective participation of healthier respondents and exclusion of men with missing values who had a worse health profile may have led to a dilution of the observed hazard ratios. Second, the use of death certificates may have resulted in misclassification of some of the mortality endpoints. However, to minimize misclassification, in the Netherlands and Italy the death certificates were verified with clinical records and in Finland they were linked with the death registers. Furthermore, because the classification of mortality outcome was blinded for baseline status, possible misclassification of the outcome was not related to depression, and will therefore only have resulted in dilution of the associations. Finally, in an observational study the possibility of residual confounding cannot be excluded. However, we adjusted for many known classical cardiovascular risk factors to minimize this possibility.

In conclusion, the results of the present longitudinal study among elderly men provide strong support for the hypothesis that depressive symptoms are a true risk factor for the occurrence of cardiovascular disease. Future studies should investigate what the underlying mechanisms are and which factors may be intermediates or common causes. They may suggest what preventive or therapeutic strategies may be effective to reduce depression in the elderly, who are often undertreated, and consequently the risk of cardiovascular disease.

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Chapter 3

Diet and lifestyle

Chapter 3.1

Diet and lifestyle

Dietary intake of B-vitamins, serum homocysteine levels and their association with depressive symptoms.

Abstract

Background: Research has indicated that low dietary intake of B-vitamins and high levels of serum homocysteine are related to depression, but the results of studies thus far are inconclusive. We investigated whether a low dietary intake of B-vitamins and high levels of serum homocysteine are associated with depressive symptoms in elderly men.

Methods: The Zutphen Elderly Study is a population-based prospective cohort study conducted in the Netherlands. In 332 men, aged 70-90 years and free from cardiovascular diseases and diabetes at baseline, depressive symptoms were measured with the Zung Self-rating Depression Scale. Information on dietary factors was obtained with a cross-check dietary history method. Multiple linear- and logistic regression analyses were performed.

Results: Dietary intake of folate (-1.19, 95% CI -2.03; -0.36) and vitamin B6 (-2.10, 95% CI -2.92; -1.27) per standard deviation increase was associated with lower levels of serum homocysteine, while vitamin B12 was not associated with serum homocysteine. Intake of folate, vitamin B6, vitamin B12 and levels of serum homocysteine were not related to depressive symptoms.

Conclusions: Our results do not support the hypothesis that a low dietary intake of B-vitamins and high levels of serum homocysteine are related to depression in healthy elderly men.

Introduction

Research has indicated that a low intake of folate, vitamin B6, vitamin B12 (B-vitamins) and high levels of serum homocysteine may be related to depression. B-vitamins are co-enzymes and cofactors in the methylation of homocysteine to methionine. Methionine is a precursor of S-adenosylmethionine (SAM) and a necessary factor for the production of monoamine transmitters. Low levels of monoamine transmitters are associated with depression.[1]

Support for this hypothesis originated from studies, which showed that major depression is associated with lower blood levels of folate and vitamin B12 in psychiatric patients.[2] In addition, depressed patients with low blood levels of folate had a poorer response to antidepressive treatment.[3] These results suggest that low blood levels of B-vitamins may be involved in the etiology of depression.

Thus far, population-based studies have not been conclusive. Studies that investigated the association of blood levels of B-vitamins and homocysteine with depression in the elderly showed inconsistent results.[4-9] Studies in middle aged men found that dietary intake of folate was associated with fewer depressive symptoms and with a lower risk of developing depression,[10,11] while the intake of vitamin B6 and B12 was not associated with depression.[10] To our knowledge, no studies examined the association between dietary intake of B-vitamins, homocysteine levels and depressive symptoms in the elderly.

In the present study, we first investigated whether dietary intake of folate, vitamin B6, and vitamin B12 was associated with serum levels of homocysteine. Second, we determined whether dietary intake of folate, vitamin B6 and vitamin B12 and serum levels of homocysteine were related to depressive symptoms in elderly men. Data were used from a population-based cohort study of elderly men.

Methods

The Zutphen Elderly Study

The Zutphen Elderly Study is a population-based prospective cohort study on risk factors and health in elderly men. The study design and measurements have been described in detail elsewhere.[12] In brief, it started in 1985 as a continuation of the Zutphen Study, the Dutch contribution to the Seven Countries Study (SCS)[13] and was extended with a new random sample of men of the same age, also living in Zutphen but not belonging to the original cohort. In total, 939 men aged 65-84 years participated in the study. Data collection followed the international protocol used in previous surveys of the SCS.[13] In 1990, the second round of the Zutphen Elderly Study took place. In that round, measures of depression,

functional status, and self-rated health were added. Informed consent was obtained from all study participants.

Dietary factors and homocysteine levels

Information on habitual food consumption was obtained with the cross-check dietary history method, adapted to the Dutch situation,[14] which has been described in detail elsewhere.[15] In brief, both in 1985 and 1990 each participant, and if possible in the presence of the person who prepared the hot meal, was interviewed by a trained dietician about his average food consumption pattern in the two weeks before the interview. A checklist of foods and quantities of food bought per week was used to calculate and verify the participant's food consumption pattern. The energy intake and the intake of folate, vitamin B6 and vitamin B12 was calculated with corresponding Dutch food tables that contained updated information on folate.[16] Homocysteine was measured in non-fasting venous blood samples, collected at the examinations in 1985 and stored at -20°C until determination in 1995.[17]

Depressive symptoms

Depressive symptoms were measured using the Self-rating Depression Scale (SDS), developed by Zung.[18] This scale was developed to assess depression among patients admitted to a psychiatric hospital and has frequently been used in non-institutionalized elderly.[19] The reliability of the SDS is reasonable in elderly men (Cronbach alpha 0.75)[20] and has been validated repeatedly with other questionnaires on depressive symptoms, such as the CESD (r=0.69),[21] the GDS (r=0.59)[22] and the Hamilton Depression scale (r=0.80).[23] The questionnaire contains 20 either positively or negatively formulated items, based on clinical diagnostic criteria commonly used to diagnose depressive disorders. The answers on those items are coded on a four-point Likert-type scale varying from 'none or sometimes' to 'most or always'. Positive items on the absence of depressive symptoms were recoded, so that a higher score indicated more depressive symptoms, with total scores ranging from 20 to 80. Men with more than two missing items were excluded from the analysis. If one or two items were missing, a mean score of the present items of the subject was calculated to replace the missing item(s). An index for the SDS was derived by dividing the sum of the answers by 80 times 100 (range 25-100), with a higher score indicating more depressive symptoms. The original cut-off values are: no depressive symptoms (< 50) versus mild, moderate, and severe depressive symptoms (≥ 50).[19]

Other variables

The self-administered questionnaire comprised questions on demographic characteristics, educational level, lifestyle habits, and past and current morbidity. Education was classified in years of education. Marital status was classified as living alone (yes versus no). Alcohol consumption was assessed in the dietary survey, expressed in grams per day, and classified as users and non-users.[24] Participants were classified as current or non-smokers. Body mass index (BMI) was calculated from weight and height (kg/m^2), which were measured while the participant was standing in light clothing without shoes. Physical activity was assessed with a self-administered validated questionnaire designed for retired men.[25] All types of activity with an intensity of more than two kilocalories energy expended per kilogram of body weight during one hour, were summed and expressed as minutes of total physical activity per week (min/wk). Self-rated health was assessed with a single-item question: 'We would like to know what you think about your health, with four answer categories: 1) healthy, 2) rather healthy, 3) moderately healthy, 4) not healthy. For the analyses self-rated health was categorized into healthy versus rather healthy versus moderately- or not healthy.

Study sample

Depressive symptoms were measured during the second round of the Zutphen Elderly study, when in total 556 men (77%) participated of the 718 men still alive in 1990. Of these, 380 (68%) were free of cardiovascular diseases (CVD) and diabetes. We excluded 43 men with more than two missing items in the SDS as well as five men with missing values in covariates. Thus, a study sample of 332 men remained for analysis.

Data analysis

All micronutrients were adjusted for energy intake using the regression residual method.[26] Multiple linear regression analysis was used to estimate the cross-sectional relationship between daily intake of B-vitamins (entered as a continuous independent variable) and levels of serum homocysteine (entered as a continuous dependent variable). For these analyses we used the measures of B-vitamins and homocysteine in 1985. In the first model we adjusted for age. In the second model we additionally adjusted for BMI (kg/m^2), current smoking (no vs yes), coffee consumption (cups/d), alcohol consumption (yes vs no) and energy intake (kcal).

Means and standard deviations (SD) were computed for continuous baseline variables, and medians and 10-90 percentiles for continuous variables with a skewed distribution. Frequency distributions were given for categorical variables according to the presence or absence of depressive symptoms based on the cut-off score of 50. Differences

between categories of depressive symptoms were tested with ANOVA, Kruskal-Wallis (in case of skewed distribution) or X^2-test.

The risk of having depressive symptoms associated with dietary intake of B-vitamins and serum homocysteine levels was examined with logistic regression analysis. Presence or absence of depressive symptoms dichotomized at a SDS-score of 50 was the dependent variable, and tertiles of dietary intake of B-vitamins and tertiles of homocysteine level were entered as the independent variables. Since no data on homocysteine levels in 1990 were available, we used the levels from 1985. In the first model we adjusted for age. In the second model we additionally adjusted for years of education, living alone (yes vs no), physical activity (min/wk), energy intake (kcal) and self-rated health (rather healthy vs healthy and moderately- not healthy vs healthy). Additional adjustments for BMI, current smoking, alcohol consumption, and coffee consumption did not change the risks.

All analyses were performed with the SAS statistical software package, version 9.1.2.[27] Point estimates are given with corresponding 95% confidence intervals (CI).

Results

The average energy-adjusted daily intake of folate (194 µg; ± 97) was below the recommended daily intake of 300 µg, the average intake of vitamin B6 (1.65 mg; ± 0.30) was also lower than the recommended daily intake (1.8 mg). In contrast, the average intake of vitamin B12 (5.34 µg; ± 3.14) was much higher than the recommended intake of 2.8 µg per day. Twenty-nine percent of the subjects had increased levels of serum homocysteine (≥ 15 µmol/l).

Higher dietary intake of folate and vitamin B6 was inversely associated with levels of homocysteine (per SD increase -1.19, 95% CI -2.03 to -0.36, and -2.09, 95% CI -2.92 to -1.26, respectively). Intake of vitamin B12 was not related to levels of serum homocysteine (**Table 1**).

Table 1: Average daily intake of B-vitamins and their relationships with serum levels of homocysteine (µmol/l) (n=318)

	Average daily intake (SD)	Model 1* beta (95% CI)	Model 2† beta (95% CI)
Folic acid per SD (µg)	194 (97)	-1.25 (-2.09; -0.41)	-1.19 (-2.03; -0.36)
Vitamin B6 per SD (mg)	1.65 (0.30)	-2.27 (-3.09; -1.46)	-2.09 (-2.91; -1.26)
Vitamin B12 per SD (µg)	5.34 (3.14)	0.00 (-0.82; 0.82)	-0.08 (-0.89; 0.74)

Abbreviations: SD, standard deviation; CI, confidence interval

*Model 1: Adjusted for age (years)

†Model 2: Additionally adjusted for BMI (kg/m^2), current smoking (no vs yes), coffee consumption (cups/d), alcohol consumption (yes vs no), energy intake (kcal)

The average depression score was 42.6 (SD ± 10), which is low in comparison with the cut-off value for mild depression (50-59). The prevalence of mild to severe depressive symptoms was 22% (14% mild,- 7% moderate,- and 1% severe depressive symptoms). **Table 2** presents the baseline characteristics of the study sample. Men with mild to severe depressive symptoms (≥ 50) were less physically active, less well educated, had a higher BMI, were more likely to live alone and reported a worse self-rated health in comparison to men with no depressive symptoms.

Table 2: Baseline characteristics of the study sample according to depressive symptoms (n=332)

		Depressive symptoms	
	Total	**No (< 50)**	**Mild-severe (≥ 50)**
Characteristic	**n=332**	**n=260**	**n=72**
Age, mean (SD), years	75 (4)	75 (4)	76 (5)
Education, mean (SD), years	10.5 (4.2)	11.0 (4.4)	8.7 (2.7)*
Physical activity, median (P10-P90), min/wk	488 (105-1170)	540 (115-1223)	420 (32-900)*
Alcohol consumption (%)	75	74	79
Current smoking (%)	24	23	23
Coffee use, median (P10-P90), cups/d	4 (1-6)	4 (1-6)	4 (2-6)
Living alone (%)	20	18	31*
BMI, mean (SD), kg/m^2	25.6 (2.9)	25.4 (2.9)	26.2 (2.9)*
Self-reported health			
healthy (%)	59	65	40
rather healthy (%)	34	31	45
moderately-not healthy (%)	7	4	15*
Daily intake of			
energy, mean (SD), kcal	2144 (459)	2150 (457)	2123 (472)
folic acid, median (P10-P90), µg	176 (129-239)	178 (129-240)	169 (130-238)
vitamin B6, mean (SD), mg	1.58 (0.31)	1.58 (0.30)	1.60 (0.34)
vitamin B12, median (P10-P90), µg	4.3 (2.6-7.1)	4.3 (2.6-7.1)	4.4 (2.8-7.5)
Serum homocysteine , median (P10-P90), µmol/l	13.0 (10.0-20.0)	13.0 (9.0-19.5)	14.0 (10.0-20.0)

Abbreviations: SD, standard deviation; BMI, body mass index *p < 0.05

Table 3 presents the odds ratios (OR) for depressive symptoms in relation to dietary intake of B-vitamins and levels of serum homocysteine. The intake of folate, vitamin B6 and vitamin B12 was not associated with depressive symptoms. Also, the levels of serum homocysteine were not associated with depressive symptoms.

Table 3: Odds ratios of depressive symptoms (≥ 50) in 1990 for intake of B vitamins in 1990 and serum homocysteine levels in 1985 (n=332)

Daily intake of	Model 1* OR (95% CI)	Model 2† OR (95% CI)
Folate		
low (< 158 µg)	reference	reference
middle (158-193 µg)	0.85 (0.45-1.58)	0.88 (0.45-1.72)
high (≥ 194 µg)	0.73 (0.38-1.39)	0.85 (0.43-1.70)
P for trend	0.33	0.62
Vitamin B6		
low (< 1.46 mg)	reference	reference
middle (1.46-1.69 mg)	1.09 (0.58-2.04)	1.21 (0.61-2.39)
high (≥ 1.70 mg)	0.83 (0.43-1.60)	0.84 (0.42-1.71)
P for trend	0.59	0.65
Vitamin B12		
low (3.6 µg)	reference	reference
middle (3.6-4.9 µg)	0.84 (0.44-1.63)	1.15 (0.56-2.35)
high (≥ 5.0 µg)	1.18 (0.63-2.22)	1.24 (0.63-2.44)
P for trend	0.6	0.54
Serum homocysteine levels		
low (< 12µmol/l)	reference	reference
middle (12-15 µmol/l)	1.09 (0.57-2.08)	1.05 (0.52- 2.11)
high (≥ 16 µmol/l)	1.19 (0.60-2.39)	0.97 (0.46-2.06)
P for trend	0.62	0.94

Abbreviations: OR, odds ratio; CI, confidence interval

*Model 1: adjusted for age (years)

†Model 2: additionally adjusted for years of education, living alone (yes vs no), physical activity (min/wk), energy intake (kcal) and self-reported health (healthy (reference), rather healthy, moderately-not healthy)

Discussion

In the present study dietary intake of folate and vitamin B6 was inversely related with serum homocysteine levels, while the intake of vitamin B12 was not associated with serum homocysteine levels. A low dietary intake of folate, vitamin B6 or vitamin B12 and high levels of serum homocysteine were not associated with depressive symptoms.

Before discussing the results we first will consider some aspects of the present study. A strength of this population-based study is the use of the dietary history method to obtain information on the *usual* food consumption of the participants. This is a reproducible[14] and valid dietary survey method[28] which reduces the possibility of random misclassification.

Second, we were able to investigate the dietary intake of several B-vitamins, besides homocysteine levels, in relation to depressive symptoms.

Some methodological limitations of the current study need also be considered. First, selective participation of healthier elderly respondents and exclusion of men with missing values from the baseline sample may, to some extent, have led to a dilution of the observed associations. Second, we only had serum homocysteine values available in 1985 and information on depressive symptoms in 1990. Earlier studies showed that serum homocysteine levels measured one (r=0.85) to three (r=0.78) years apart correlated strongly.[29] Therefore, we assumed that these homocysteine values measured in 1985 were also representative for the values in 1990. Third, although we hypothesized that a low intake of B-vitamins may lead to depressive symptoms, we were not able to determine the prospective relation between the intake of B-vitamins and depressive symptoms. As a result, we cannot exclude the possibility that depressive symptoms may lead to a low intake of B-vitamins due to loss of appetite and decreased food consumption. Since energy intake was not materially lower in depressed subjects and we adjusted for intake of energy, reversed causality is less likely.

Our observation that dietary intake of folate and vitamin B6 was inversely associated with levels of serum homocysteine agrees with the hypothesis that several B-vitamins are involved in the metabolism of homocysteine. In contrast, intake of vitamin B12 was not associated with homocysteine levels. This could be due to malabsorption of vitamin B12 in elderly people.[30] The intake of vitamin B12 was high compared to the recommended daily intake, however, and it was comparable with the intake in another Dutch older population. In this latter study a substantial part of the population had a deficiency of vitamin B12 despite the high intake.[31] In addition, the results of a previous study on dietary intake of B-vitamins and levels of homocysteine in middle aged men, showed that intake of folate, vitamin B-6 and vitamin B12 was associated with levels of homocysteine univariately, however, in the multivariate analyses only dietary intake of folate was associated with levels of homocysteine.[32] In addition, randomized controlled trials showed that use of B-vitamin supplements lowered homocysteine levels.[33,34]

Our observation of no association between dietary intake of folate and depressive symptoms is in contrast to the results of a study carried out in middle aged men from Finland, which showed an inverse relation between dietary intake of folate and depressive symptoms.[10,11] An explanation why we showed no, or at best a very weak but imprecise, association between dietary intake of folate and depressive symptoms could be that the intake of folate was low compared to the recommended daily intake of folate in the Netherlands. This low intake may have decreased the power to detect an effect. In addition, it might be possible that the association between dietary intake of folate and depressive symptoms weakens with age. This agrees with the results of studies that investigated the association between blood markers of folate and depressive symptoms. One study in a middle-aged sample showed that low folate status was associated with depressive symptoms.[8] Two studies in the elderly did not find an inverse association between plasma folate and

depression.[5,9] In addition, one study in an older population did observe an inverse association between folate status and depression, but this was due to physical comorbidity and cardiovascular diseases.[4]

In our study, dietary intake of vitamin B6 was also not associated with depressive symptoms. The intake of vitamin B6 was below the recommended daily intake, which could have diminished the power to find an association. Our results are, however, in line with findings of the study carried out in middle-aged men in Finland. In this study the intake of vitamin B6 was adequate, but they could also not disclose an association between dietary intake vitamin B6 and depressive symptoms.[10] In contrast, the results of a study on blood markers of vitamin B6 and depressive symptoms did show an inverse association.[5] However, a recent review concluded that there was no treatment effect of vitamin B6 for depression, except for hormone related depression in women.[7]

Our results on dietary intake of vitamin B12 and depressive symptoms confirm the results of the study carried out in middle-aged men in Finland, which also showed no association between dietary intake of vitamin B12 and depressive symptoms.[10] Furthermore, in a randomized controlled trial in the elderly, treatment with vitamin B12 was not associated with a decrease in depressive symptoms.[35] Remarkably, studies on the blood status of vitamin B12, did show an inverse association between vitamin B12 and depression in the elderly.[4,5,9] An explanation could be that dietary intake of vitamin B12 may not be reflected in serum levels of vitamin B12, because we also showed that dietary intake of vitamin B12 was not associated with homocysteine levels. Further studies should compare dietary intake of vitamin B12 with the blood status of vitamin B12, and their relation to depression.

Finally, we did not find an association between serum homocysteine levels and depression. Studies on blood levels of homocysteine and depression have shown inconsistent results.[4-6,8,9,36-38] The results of one of these studies suggests that the association between homocysteine levels and depression could be confounded by cardiovascular morbidity.[4] Two studies that did show a positive association did not account for prevalent CVD in the analyses.[6,8] However, two other studies did find a positive association, independent of vascular status[37] or history of myocardial infarction.[36] In our study, men with prevalent CVD and diabetes at baseline were excluded, which may explain why we did not find an association between homocysteine levels and depressive symptoms.

In conclusion, our findings confirm that dietary intake of folate and vitamin B6 are important correlates of serum homocysteine levels. However, the results of the present study do not provide evidence that dietary intake of B-vitamins and levels of serum homocysteine are related to depression in the elderly.

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Chapter 3.2

Diet and lifestyle

Depression and cardiovascular mortality: a role for n-3 fatty acids?

Abstract

Background: Recent studies indicate that depression plays an important role in the occurrence of cardiovascular diseases (CVD). Underlying mechanisms are not well understood. We investigated whether dietary intake of the n-3 fatty acids (FAs) eicosapentaenic acid (EPA) and docosahexaenoic acid (DHA) could explain the relation between depressive symptoms and cardiovascular mortality.

Methods: The Zutphen Elderly Study is a prospective cohort study conducted in the Netherlands. Depressive symptoms were measured with the Zung Self-rating Depression Scale in 332 men, aged 70-90 years, and free of CVD and diabetes in 1990. Dietary factors were assessed with a cross-check dietary history method in 1990. Mortality data were collected between 1990 and 2000. Logistic- and Cox regression analyses were performed adjusting for demographics and CVD risk factors.

Results: Compared to a low intake (mean: 21 mg/d), a high intake (mean: 407 mg/d) of n-3 FAs was associated with fewer depressive symptoms (OR 0.46; 95% CI 0.22-0.95) at baseline, and with a non-significant reduced risk of 10-year cardiovascular mortality (HR 0.88; 95% CI 0.51-1.50). The adjusted HR for an increase in depressive symptoms with one standard deviation for cardiovascular mortality was 1.28 (95% CI 1.03-1.57), and did not change after additional adjustment for the intake of n-3 FAs.

Conclusions: An average intake of about 400 mg n-3 FAs per day may decrease the risk of depression. Our results, however, do not support the hypothesis that the intake of n-3 FAs explains the relationship between depression and CVD.

Introduction

By the year 2020, ischemic heart disease and cerebrovascular disease will be the leading causes of death in the world. Moreover, ischemic heart disease and depression are also projected to be the top two contributors of the global burden of disease.[1] Recent studies indicate that depression plays an important role in the occurrence of cardiovascular diseases (CVD), both in patients with CVD as well as in the general population without CVD.[2,3] Several mechanisms to explain the association have been proposed but remain insufficiently understood. These mechanisms may act directly through pathophysiologically linked pathways, or indirectly through shared cardiovascular risk factors, lifestyle factors and diet.[4,5]

One of the explanations for the association between depression and CVD is a low intake of the omega (n)-3 fatty acids (FAs) eicosapentaenic acid (EPA) and docosahexaenoic acid (DHA), which main source is fish consumption. Low fish consumption is a well established risk factor for cardiovascular mortality[6,7] and may also predispose to depression.[8,9] Although there is indirect support for a low intake of n-3 FAs as a common cause for depression and CVD, it has not been investigated whether this could also explain the increased risk of depression for CVD. This requires the examination of intake of n-3 FAs in relation to both the risk of depression and CVD.

We determined, first, whether intake of the n-3 FAs EPA and DHA was related to the risk of depressive symptoms, and second, whether intake of these n-3 FAs could explain the increased risk of depressive symptoms on 10-year cardiovascular mortality. Data of the Zutphen Elderly Study were used, a population-based prospective cohort study of healthy elderly men in the Netherlands.

Methods

The Zutphen Elderly study

The Zutphen Elderly Study is a population-based prospective cohort study on diet, risk factors for cardiovascular disease and health in elderly men. The study design and measurements have been described in detail elsewhere.[10] In brief, the study started in 1985 as a continuation of the Zutphen Study, the Dutch contribution to the Seven Countries Study (SCS).[11] In 1985, the 555 survivors of the original cohort were invited for the examinations. In addition, a random sample of 711 men of the same age, and living in Zutphen but not belonging to the original cohort, was invited to participate. Of these 1266 men, 887 (70%) gave informed consent and participated in the baseline examinations. Data collection followed the international protocol used in previous surveys of the SCS,[11] extended with gerontologic variables. In 1990, the second round of the Zutphen Elderly Study took place.

In that round, information on depression, functional status, cognitive function and self-reported health were added. In 1995 and 2000, the third and fourth rounds of examinations were carried out. Mortality data were collected until the year 2000.

Depressive symptoms

Depressive symptoms were measured using the Self-rating Depression Scale (SDS), developed by Zung.[12] This scale was developed to assess depression among patients admitted to a psychiatric hospital, but also for non-institutionalized elderly,[13] and was found to be highly comparable among different countries.[14] The reliability of the SDS is good in elderly men (Cronbach alpha 0.75)[15] and has been validated repeatedly with other questionnaires on depressive symptoms such as the CESD (r=0.69),[16] the GDS (r=0.59)[17] and the Hamilton Depression scale (r=0.80).[18] The questionnaire contains 20 either positively or negatively formulated items, based on clinical diagnostic criteria commonly used to diagnose depressive disorders. The answers on those items are coded on a four-point Likert-type scale varying from 'none or sometimes' to 'most or always'. Positive items on the absence of depressive symptoms were recoded, so that a higher score indicated more depressive symptoms, with total scores ranging from 20 to 80. Men with more than two missing items were excluded from the analyses. If one or two items were missing, a mean score of the present items of the subject was calculated to replace the missing item(s). An index for the SDS was derived by dividing the sum of the answers by 80 times 100 (range 25-100), with a higher score indicating more depressive symptoms. The original clinical cut-off values are: no depression (< 50) and mild-severe depression (≥ 50).[13]

Dietary factors

Information on habitual food consumption was obtained with the cross-check dietary history method, which was adapted to the Dutch situation[19] and has been described in detail elsewhere.[20] In brief, each participant, and if possible in the presence of the person who prepared the hot meal, was interviewed by a trained dietician about his average food consumption pattern in the two weeks before the interview. A checklist of foods and quantities of food bought per week was used to calculate and verify the participant's food consumption pattern. Total fish consumption was computed by adding the number of grams of all fish consumed per day. Fish is the main source (71%) of the n-3 FAs: EPA and DHA. Other sources of n-3 FAs are meat, eggs and plant foods such as leek.[21] Nutrient intake, including the intake of EPA and DHA was calculated with the Dutch food table.

Cardiovascular endpoints

Mortality data were collected during ten years of follow-up and obtained through general practitioners verified with information from hospital registries. No persons were lost to follow-up. Coding of causes of death was done by one clinical epidemiologist who was blinded for the risk factor status of the subjects. Mortality from CVD was coded according to the International Classification of Diseases, ninth Revision (ICD-9: 390-459). In the analyses, both primary (n=78) and secondary (n=44) causes of death were used. The number of patients with at least one cardiovascular cause of death was 92. Men who died from other causes than CVD were censored at date of death. Men who were still alive at the end of the study were censored at the date of the last examination round in 2000.

Other variables

The self-administered questionnaire contained questions on demographic characteristics, educational level and lifestyle habits. Marital status was classified as living alone (unmarried, separated or widow) or together. Alcohol consumption was assessed in the dietary survey, expressed in absolute grams of alcohol per day , and classified into three categories (0 g/d, 1-29 g/d and $\geq$ 30 g/d).[22] Participants were classified as current, past or never smokers. Body mass index (BMI) was calculated from weight and height (kg/m^2), which were measured while the participant was standing in light clothing without shoes. Physical activity was assessed with a self-administered validated questionnaire designed for retired men.[23] All types of activity with an intensity of more than two kilocalories energy expended per kilogram of body weight during one hour, were summed and expressed as minutes of total physical activity per week (min/wk).

Arterial blood pressure was measured twice on the right arm after five minutes of rest with a random zero sphygmomanometer, with the man in a supine position. The average of two readings of both systolic and diastolic blood pressure (fifth Korotkoff phase) was calculated. Non-fasting venous blood samples were taken and total- and high density lipoprotein (HDL) cholesterol (mmol/L) were determined using standardized procedures according to the criteria of the World Health Organization's Lipid Reference Laboratory in Atlanta, Georgia.[22]

History of myocardial infarction was obtained using the Rose questionnaire,[24] verified by information from general practitioners and/or hospital registries. A clinical history of stroke, heart failure and diabetes was based on the doctor's conclusion using questionnaire information and the results of the physical examination, verified by information from general practitioners or hospital registries.

Study sample

Depressive symptoms were measured for the first time between March and June 1990, when in total 556 men (77%) participated of the 718 men still alive since the start of the study in 1985. Of these, 380 (68%) were free of CVD and diabetes. We excluded 43 men with more than two missing items in the SDS as well as five men with missing values in covariates. Thus, a study sample of 332 men remained for statistical analysis.

Data analysis

The intake of n-3 FAs was adjusted for energy intake using the regression residual method.[25] Means and standard deviations (SD) were computed for continuous baseline variables, and medians and 10-90 percentiles for continuous variables with a skewed distribution. Frequency distributions were given for categorical variables according to categories of depressive symptoms (no (< 50) and mild-severe (≥ 50)). Differences between categories of depressive symptoms were tested with ANOVA, Kruskal-Wallis (in case of skewed distribution) or X^2-test.

Cross-sectional associations between intake of n-3 FAs and depressive symptoms in 1990 were examined with logistic regression analysis. Depression was the dependent variable, and daily intake of n-3 FAs (middle vs low and high vs low) was the independent variable. In the first model we adjusted for age. In the second model we also adjusted for years of education, BMI (kg/m^2), smoking (past vs never and current vs never), alcohol consumption (1-29 g/d vs 0 g/d and ≥ 30 g/d vs 0 g/d), systolic blood pressure (SBP) (mmHg), physical activity (min/wk), living alone (yes vs no) and energy intake (kcal).

The prospective associations between daily intake of n-3 FAs (middle vs low and high vs low) and cardiovascular mortality were estimated with Cox proportional hazard models. With a log minus log plot the assumptions of proportional hazards were checked. The assumptions of proportionality were not violated. In the first model we adjusted for age (as the time scale). In the second model we also adjusted for years of education, BMI, smoking, alcohol consumption, SBP, total- and HDL cholesterol levels, physical activity, living alone and energy intake.

Finally, we investigated with Cox proportional hazard models whether the daily intake of n-3 FAs could explain the relation between depressive symptoms and cardiovascular mortality. Tertiles of n-3 FAs were added to the model containing depressive symptoms (per SD), age and classical CVD risk factors as independent variables and cardiovascular mortality as dependent variable.

All analyses were performed with the SAS statistical software package, version 9.1.2.[26] Point estimates are given with corresponding 95% confidence intervals (CI).

Results

At baseline, the average depression score was 42.6 (SD=10), which is low in comparison with the clinical cut-off value for mild depression (50-59). About 22% of the elderly men had mild to severe depressive symptoms. **Table 1** presents the baseline characteristics of the study sample by categories of depressive symptoms. Men with mild to severe depressive symptoms (SDS ≥ 50) were less well educated, less physically active, had a higher BMI and were more likely to live alone in comparison to men with no depressive symptoms.

Table 1: Baseline characteristics of the study sample according to depressive symptoms in 1990 (n=332)

	Depressive symptoms 1990	
	No (< 50)	**Mild -severe (≥ 50)**
Characteristic	**n=260**	**n=72**
Age, mean (SD), years	75 (4)	76 (5)
Education, mean (SD), years	11.0 (4.4)	8.7 (2.7)*
Physical activity, median (P10-P90), min/wk	540 (115-1223)	420 (32-900)*
Alcohol consumption		
0 g/day (%)	26	21
1-29 g/day (%)	55	68
≥ 30 g/day (%)	19	11
Smoking		
current (%)	23	23
past (%)	57	64
never (%)	20	13
Living alone (%)	18	31*
BMI, mean (SD), kg/m^2	25.4 (2.9)	26.2 (2.9)*
SBP, mean (SD), mmHg	149 (20)	151 (20)
DBP, mean (SD), mmHg	82 (11)	84 (12)
Total cholesterol, mean (SD), mmol/L	6.1 (1.1)	6.0 (1.1)
HDL cholesterol, mean (SD), mmol/L	1.2 (0.3)	1.1 (0.2)
Daily intake of		
energy, mean (SD), kcal	2150 (457)	2123 (472)
n-3 FAs: EPA + DHA, median (P10-P90), mg	105.0 (8-463)	87 (6-355)

Abbreviations: SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; FA, fatty acids; EPA, eicosapentaenic acid; DHA, docosahexaenoic acid *$p < 0.05$

Cross-sectional analyses showed that men in the highest tertile of n-3 FAs (mean daily intake: 407 mg) had a 54% (OR 0.46; 95% CI 0.22; 0.95) lower risk of depressive symptoms compared to men in the lowest tertile of n-3 FAs (mean daily intake: 21 mg) **(Table 2)**. In addition, an increase of 50 mg in daily intake of n-3 FAs was associated with a 7% (OR 0.93; 95% CI 0.87-1.01) reduction in risk of depressive symptoms. Compared to no fish consumption, consumption of at least 20 g fish per day was associated with a 37% lower risk of depressive symptoms (OR 0.63; 95% CI 0.30-1.34).

Table 2: Odds ratios of depressive symptoms (≥ 50) in 1990 for intake of n-3 FAs in 1990 (n=332)

Daily intake of	Model 1* OR (95% CI)	Model 2† OR (95% CI)
N-3 FAs: EPA+ DHA		
low (< 59 mg/d)	reference	reference
middle (59.0-156 mg/d)	0.86 (0.47-1.58)	0.84 (0.43-1.64)
high (≥ 156 mg/d)	0.52 (0.27-1.03)	0.46 (0.22-0.95)
P for trend	0.06	0.04

Abbreviations: OR, odds ratio; CI, confidence interval; FA, fatty acids; EPA, eicosapentaenic acid; DHA, docosahexaenoic acid

*Model 1: adjusted for age (years)

†Model 2: additionally adjusted for years of education, BMI (kg/m^2), smoking (never (reference), past, current), alcohol consumption (0 g/d (reference), 1-19 g/d and ≥ 30 g/d), systolic blood pressure (mmHg), physical activity (min/wk), living alone (yes vs no), and energy intake (kcal)

After ten years of follow-up, 170 of the 332 men (51%) had died, of whom 92 (28%) had died from CVD. The total number of person years was 2574 and the mean follow-up period was 7.8 years (SD=3.1). **Table 3** presents the prospective association for daily intake of n-3 FAs for cardiovascular mortality. The fully adjusted hazard ratios of cardiovascular mortality associated with medium and high daily intake of n-3 FAs were 0.85 (95% CI 0.51-1.42) and 0.88 (95% CI 0.51-1.50), respectively.

Table 4 presents the hazard ratios of an increase in depressive symptoms per SD and cardiovascular mortality before and after adjustment for daily intake of n-3 FAs. The adjusted HR for an increase in the SDS index with one SD for cardiovascular mortality was 1.28 (95% CI 1.03-1.57), and did not change after additional adjustment for n-3 FAs. Analyses with CVD as primary cause of death showed similar results.

Table 3: Adjusted hazard ratios for 10-year cardiovascular mortality and intake of n-3 FAs (n=332)

Daily intake of	Cases/ PY	Model 1* HR (95% CI)	Model 2† HR (95% CI)
N-3 FAs: EPA+ DHA			
low (<59 mg/d)	32/ 820	reference	reference
middle (59-156 mg/d)	32/ 897	0.94 (0.58-1.54)	0.85 (0.51-1.43)
high (≥ 156 mg/d)	28/ 857	0.91 (0.54-1.51)	0.88 (0.51-1.50)
P for trend		0.71	0.63

Abbreviations: HR, hazard ratios; CI, confidence interval; PY, person years; FA, fatty acids; EPA, eicosapentaenic acid; DHA, docosahexaenoic acid

*Model 1: adjusted for age (as time scale)

†Model 2: additionally adjusted for years of education, BMI (kg/m^2), smoking (never (reference), past, current), alcohol consumption (0 g/d (reference), 1-29 g/d, ≥ 30 g/d), systolic blood pressure (mmHg), total- and HDL cholesterol levels (mmol/L), physical activity (min/wk), living alone (yes vs no), and energy intake (kcal)

Discussion

Lack of n-3 FAs in the diet has been suggested to explain the relationship between depression and CVD. The results of our study, however, while confirming that a high intake of n-3 FAs was associated with fewer depressive symptoms, do not support the view that intake of n-3 FAs explains the relationship between depression and the occurrence of CVD.

To interpret the findings, different aspects of the present study need to be addressed. Major strengths of this study are its prospective design with a long follow-up period, and the study sample of elderly men who were free of CVD and diabetes at baseline. Second, selective loss to follow-up could not have disturbed our results, because the mortality follow-up was complete. Third, food consumption was obtained with a dietary history method. This extensive method estimates the habitual food consumption and reduces random misclassification.

The current study has also methodological limitations that need to be considered. First, selective participation of healthier respondents and exclusion of men with missing values from the baseline sample, who had a worse health profile and higher mortality rates (results not shown), may have diluted the associations. Moreover, the present study population consisted of older Caucasian men and the results may not be generalisable to women and non-Caucasian populations. Second, in an observational study the possibility of residual confounding cannot be ruled out. We tried to minimize this possibility by adjusting for several known risk factors of depression and CVD in the analyses, including education, physical activity, BMI and living status. Unfortunately, we did not have information on depression treatment. It should be noted though that the average SDS score was below the clinical cut point for mild depression (≥ 50). There were only two men with a SDS score that was indicative of major depression (SDS score ≥ 70). Therefore, treatment for

Table 4: Hazard ratios of 10-year cardiovascular mortality for depressive symptoms at baseline, additionally adjusted for intake of n-3 FAs (n=332)

	HR (95% CI)
Depressive symptoms (per SD)	
Model 1*	1.28 (1.03-1.57)
Additional adjustment:	
Daily intake of N-3 FAs: EPA+DHA	1.28 (1.03-1.58)

Abbreviations: HR, hazard ratios; CI, confidence interval; FA. fatty acids; EPA, eicosapentaenic acid; DHA, docosahexaenoic acid

*Model 1: adjusted for age (as time scale), BMI (kg/m^2), smoking (never (reference), past, current), alcohol consumption (0 g/d (reference), 1-29, ≥ 30 g/d), systolic blood pressure (mmHg), total- and HDL cholesterol levels (mmol/L), physical activity (min/wk), living alone (yes vs no), and energy- intake (kcal)

depression is not an issue in our study. In addition, we did not collect data on supplemental use of n-3 fatty acids. However, use of n-3 fatty acids supplements was non-existent in 1990 in the Netherlands. Third, the association between the intake of n-3 FAs and depressive symptoms was observed in a cross-sectional analysis and is not necessarily causal. Reversed causality is an alternative explanation, because the presence of depressive symptoms may cause a low intake of n-3 FAs due to loss of appetite and decreased food consumption. However, energy intake was not materially lower in depressed subjects; moreover we adjusted for intake of energy. Finally, it can be argued that depressive symptoms are markers of subclinical CVD, therefore reflecting reversed causality. We tried to minimize this possibility by excluding men with prevalent CVD. Furthermore, in a previous paper we made a plausible argument against reversed causality.[27]

A low intake of n-3 FAs may predispose to depression through several biological mechanisms.[8,9] High concentrations of n-3 FAs in neuronal membranes are hypothesized to play a role in synaptic neurotransmission through mechanisms involving the metabolism, release, uptake and receptor functioning of neurotransmitters.[8] For instance, low levels of the essential n-3 FAs are associated with reduced production of 5-hydroxy-indolacetic acid (5-HIAA) which is the major metabolite of serotonin and an indicator of reduced serotonin turnover.[28] Neurotransmission is thought to be impaired in depressed patients. Second, low levels of n-3 FAs are associated with increased levels of inflammatory markers,[29] which are associated with both depression[30,31] and atherosclerosis.[32]

Our results agree with previous observational studies that showed an inverse association between intake of fish and depression,[33-35] blood levels of n-3 FAs and depression,[36,37] and n-3 FAs in adipose tissue and depression,[38] although two studies did not find an association between intake of n-3 FAs and depression.[39,40] To our knowledge, thus far no

prospective studies have investigated association between intake of n-3 FAs and the incidence of depression. However, preliminary results of randomized controlled trials suggest that an additional intake of n-3 FAs (0.5-9.6 g/d) leads to a larger reduction in depressive symptoms compared to standard treatment in depressed patients.[41,42]

Two meta-analyses calculated relative risks of the incidence of stroke and mortality from coronary heart disease for weekly consumption of fish, the main source of n-3 FAs, compared to consumption less than once per month. The risks of the incidence of stroke and mortality from coronary heart disease were 0.87 (95% CI 0.72-0.94) and 0.85 (95% CI 0.76-0.96), respectively.[6,7] These estimates are comparable with our results of 0.85 and 0.88 for total cardiovascular mortality, which may have not been statistically significant due to lack of power. Although we did show an association between intake of n-3 FAs and depressive symptoms, and to lesser extent with cardiovascular mortality, intake of n-3 FAs did not explain the increased risk of depressive symptoms on cardiovascular mortality in elderly men.

If lack of consumption of n-3 FAs cannot explain the increased cardiovascular mortality risk associated with depression in elderly men, what other explanations are possible? An alternative mechanism is that dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, often present in depression, promotes atherosclerosis through injury of vascular endothelial cells, hypertension, and inflammation.[4] Depression has also been associated with autonomic dysfunction.[43] In patients with myocardial infarction depression was associated with decreased heart rate variability, which contributed to their increased mortality risk compared to patients who were not depressed.[44]

In conclusion, although a low intake of n-3 FAs may increase the risk of depression, the results of the present study do not support the view that a low intake of n-3 FAs explains the relation between depression and CVD in elderly men.

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Chapter 3.3

Diet and lifestyle

Depressive symptoms, physical inactivity and risk of cardiovascular mortality in European elderly.

Abstract

Background: Studies indicate that depression may increase risk of cardiovascular disease (CVD), in addition to classical risk factors. One of the hypotheses to explain this relation is that depressed subjects become physical inactive. We set out to determine the role of physical inactivity in the relation between depressive symptoms and cardiovascular mortality.

Methods: Data were used from the population-based prospective Finland, Italy and the Netherlands Elderly (FINE) Study. Depressive symptoms were measured with the Zung Self-rating Depression Scale in 909 elderly men, aged 70-90 years, free of CVD and diabetes at baseline in 1990. Physical activity was assessed with a questionnaire for retired men. Hazard ratios (HR) for 10-year cardiovascular mortality were calculated, adjusting for demographics and cardiovascular risk factors.

Results: At baseline, men with more depressive symptoms were less physically active (722 min/wk; 95% CI 642-802) than men with few depressive symptoms (919 min/wk; 95% CI 823-1015). During ten years of follow-up 256 (28%) men died from CVD. The adjusted HR of cardiovascular mortality for a decrease of 30 min/d in physical activity was 1.09 (95% CI 1.04-1.14). An increase in depressive symptoms with one standard deviation was associated with a higher cardiovascular mortality risk (HR 1.42; 95% CI 1.26-1.60). After additional adjustment for physical activity the risk decreased (9%), but an independent risk remained (HR 1.37; 95% CI 1.21-1.56). The excess risk on cardiovascular mortality attributable to the combined effect of depressive symptoms with inactivity was 1.47 (95% CI -0.17-3.11).

Conclusions: The increased risk of depressive symptoms on cardiovascular mortality could not be explained by physical inactivity. However, depressive symptoms and physical inactivity may interact to increase cardiovascular mortality risk.

Introduction

Cardiovascular diseases (CVD), including coronary heart disease (CHD) and stroke, are still the major causes of death in European countries and account for 33% of all deaths.[1] Besides classical risk factors, such as high blood pressure and cholesterol, depressive symptoms and physical inactivity have been associated with increased risk of CVD.[2,3]

One of the hypotheses to explain the relationship between depression and CVD risk is that depressed persons adapt an unhealthy lifestyle. For instance, prospective studies indicate that depressed persons develop a more sedentary lifestyle and become less physically active.[4,5] Physical inactivity may increase the risk of developing CVD in depressed subjects. Therefore physical inactivity may be an intermediate factor in the relation between depressive symptoms and CVD. In addition, depression and physical inactivity may interact, possibly via atherosclerotic processes, in the development of CVD.

Although several population-based studies adjusted for physical activity in their analyses,[6-9] they did so by adding this variable to the model in the same step as other covariates. Only two studies examined the independent effect of physical inactivity (sedentary behavior) on the relation between depressive symptoms and cardiovascular disease or mortality. One study observed that physical inactivity partly explained the relation between depression and cardiovascular mortality, and that there was no interaction between depression and physical inactivity.[10] In contrast, the second study showed that depression did not explain the association between exercise and all cause mortality and cardiovascular events.[11] These studies were carried out in patients with CHD. It is not known to what extent physical inactivity explains the association between depressive symptoms and cardiovascular mortality in subjects without prevalent CVD at baseline, and whether depressive symptoms and physical inactivity may interact in the development of CVD.

In the present study, we set out to determine the prospective independent and combined effects of depressive symptoms and physical inactivity on the 10-year cardiovascular mortality in a population-based sample of European elderly men.

Methods

The FINE study

The FINE (acronym for Finland, Italy and the Netherlands Elderly) Study is a prospective population-based cohort study on risk factors and health in elderly men. The study design and measurements have been described in detail elsewhere.[12] In brief, the FINE study started in 1984 as a continuation of the Seven Countries Study (SCS), which was originally initiated in 1958 by Keys as a cardiovascular risk factor survey among 12,763 middle-aged men.[13] In total, 2285 men from Finland (n=716), Italy (n=682) and the Netherlands (n=887)

participated in the baseline examination of the study in 1985. Informed consent was obtained from all study participants. Data collection followed the international protocol used in previous surveys of the SCS.[13] In 1989-1991 the second round of the FINE Study took place. In this round, depressive symptoms were assessed. Mortality data were collected until the year 2000.

Depressive symptoms

Depressive symptoms were measured using the Self-rating Depression Scale (SDS), developed by Zung.[14] This scale was developed to assess depression among patients admitted to a psychiatric hospital, but also for non-institutionalized elderly,[15] and was found to be highly comparable among different countries.[16] The reliability of the SDS is good in elderly men (Cronbach alpha 0.75)[17] and has been validated repeatedly with other questionnaires on depressive symptoms, such as the CESD (r=0.69),[18] the GDS (r=0.59)[19] and the Hamilton Depression Scale (r=0.80).[20] The questionnaire contains 20 either positively or negatively formulated items, based on clinical diagnostic criteria commonly used to diagnose depressive disorders. The answers on those items are coded on a four-point Likert-type scale varying from 'none or sometimes' to 'most or always'. Positive items on the absence of depressive symptoms were recoded, so that a higher score indicated more depressive symptoms. An index for the SDS was derived by dividing the sum of the answers by 80 times 100 (range 25-100), with a higher score indicating more depressive symptoms. For the analyses a continuous measure was used (per standard deviations (SD); Finland SD=10.6, Italy SD=11.3 and the Netherlands SD=9.6) and the SDS was categorized into country-specific tertiles. The cut-off values for the middle and high tertile were 42 and 51 for Finland, 45 and 54 for Italy, and 39 and 46 for the Netherlands.

Physical activity

Physical activity was assessed with a self-administered validated questionnaire, designed for retired men.[21] The questionnaire consisted of items on the frequency, durations, and pace of walking and bicycling during the previous week, the average amount of time spent weekly on hobbies and gardening (in both summer and winter), and the average amount of time spent monthly on odd jobs and sports. Type of odd jobs, sports and hobbies (e.g., dancing or fishing) were also assessed. The Finnish and the Italian questionnaires further contained items on farming in summer and winter. All types of activity with an intensity of > 2 kilocalories energy expended per kilogram of body weight during one hour (kcal/kg-h), e.g. fishing and billiards, reflecting multiples of resting oxygen consumption, were summed to obtain the total duration of physical activity expressed in minutes per week (min/wk).[12] For the analyses, duration of physical activity was used as continuous variable (30 min/d)

and categorized into country-specific tertiles. The cut-off values for the middle and high tertile were 315 and 795 for Finland, 330 and 685, 335 and 965 for Italy, and 308 and 675 for the Netherlands.

Cardiovascular endpoints

Mortality data were collected during ten years of follow-up. In Finland, information on causes of death was obtained from the Finnish death register, while in Italy and the Netherlands information was obtained from hospital registries and/or general practitioners. One person from Finland, one from Italy and one from the Netherlands were lost to follow-up. They were included in the analyses, but censored at the date of the examination round after which they were lost to follow-up. Coding of causes of death for all countries was done by one clinical epidemiologist who was blinded for the risk factor status of the subject. Mortality from CVD was coded according to the International Classification of Diseases, ninth Revision (ICD-9: 390-459). In the analyses, primary (n=214) and secondary (n=120) causes of death were combined and 256 men died from CVD. Men who died from other causes than CVD (n=215) were censored at date of death. Men who were still alive at the end of the study were censored at the last examination date.

Other variables

The self-administered questionnaire contained questions on marital status, educational level, alcohol consumption, smoking habits, past and current morbidity. Marital status was classified as living alone (unmarried, separated or widowed) or together. Educational level was expressed as years of education. In Finland and Italy habitual alcohol consumption was assessed with a self-administered questionnaire, while in the Netherlands it was assessed in the dietary survey while, and classified as consumers versus non-consumers. Participants were classified as non-smokers versus current smokers.

Body mass index (BMI) was calculated from weight and height (kg/m^2), which were measured while the participant was standing in light clothing without shoes. Arterial blood pressure was measured twice on the right arm after five minutes of rest, with the man in a supine position. In Finland and Italy standard mercury sphygmomanometers were used, while in the Netherlands a random zero sphygmomanometer was used. The average of two readings of both systolic and diastolic blood pressure (fifth Korotkoff phase) was calculated. Venous blood samples (fasting in Finland and non-fasting in Italy and the Netherlands) were taken and total- and high density lipoprotein (HDL) cholesterol (mmol/L) were determined using standardized procedures according to the criteria of the World Health Organization's Lipid Reference Laboratories in Prague, Czechoslovakia, or Atlanta, Georgia.[22]

Study sample

Depressive symptoms were measured during the second round of the FINE study, between October 1989 and November 1991, when in total 1416 men (82%) participated of the 1734 men still alive. Of these, 909 (64%) were free of CVD and diabetes. Thus a study sample of 909 men remained for analysis, 268 men from Finland, 261 men from Italy, and 380 men from the Netherlands.

Data analysis

To enlarge power and to prevent bias from missing values in a selective group, of respondents a single imputation procedure in SPSS version 12.0.1 was used. We imputed missing values on the items of the SDS (on average 7%), physical activity (3%) and the other covariates (on average 2%). All information of the baseline examination in 1990 and follow-up examinations were used to fill in missing values.

Frequency distributions are given for categorical variables for each country. Means SDs were computed for continuous baseline variables, and medians and 10-90 percentiles for continuous variables with a skewed distribution.

Cross-sectional associations between depressive symptoms and physical activity at baseline were examined with multiple linear regression analyses. Depression was the independent variable (tertiles) and physical activity was the dependent variable, and adjustments were made for demographics and lifestyle factors. Robust standard errors were calculated to account for the violation of normality assumption.

Cox proportional hazard analyses were performed to estimate the prospective association between a decrease in physical activity with 30 minutes per day and cardiovascular mortality. Analyses were adjusted for potential confounding or intermediate factors such as age (as the time scale), country (Finland vs the Netherlands and Italy vs the Netherlands), years of education, living alone (yes vs no), current smoking (no vs yes), alcohol consumption (yes vs no), BMI (kg/m^2), systolic blood pressure (SBP) (mmHg), total- and HDL cholesterol levels (mmol/L).

The prospective associations between depressive symptoms (per SD) and cardiovascular mortality were estimated using Cox proportional hazard models. In the first model, hazard ratios were adjusted for confounding or intermediate factors such as age, country, years of education, living alone, current smoking, alcohol consumption, BMI, systolic blood pressure, and total- and HDL cholesterol levels. In the second model, additional adjustment was made for duration of physical inactivity (continuously) to examine to what extent physical inactivity could be an intermediate or confounding factor in the relation between depression and cardiovascular mortality. The percentage reduction was calculated by one minus the estimate of depressive symptoms in the model with health status divided

by the estimate of depressive symptoms in the model without subjective health status. Accompanying confidence limits were also calculated.[23]

Finally, we investigated whether depressive symptoms and physical inactivity interacted on the risk of cardiovascular mortality. Interaction was estimated on an additive scale[24] and dummy variables were created for the combination of tertiles of depressive symptoms with tertiles of physical activity. Subjects with depressive symptoms in the low tertile and duration of physical activity in the high tertile served as the reference group. Departure from additivity was calculated using the formula for the relative excess risk due to interaction (RERI=RR(AB) – RR(A) – RR (B) + 1)[24] and a 95% confidence limit was calculated.[25] All analyses were repeated within strata of country.

All analyses were performed with the SAS statistical software package, version 9.1.2.[26] Point estimates are given with corresponding 95% confidence intervals (CI).

Results

Table 1 presents the baseline characteristics for each country. The average depression score was highest in Italy (49.6; SD=11) and lowest in the Netherlands (43.2; SD=10). Men in Italy were older, more physically active, and had higher HDL-cholesterol levels than men

Table 1: Baseline characteristics for each country (n=909)

Characteristic	Finland n=268	Italy n=261	The Netherlands n=380
Age, mean (SD), years	76.7 (5.0)	77.4 (3.9)	75.6 (4.5)
Depressive symptoms, mean (SD)	46.6 (10.6)	49.6 (11.3)	43.2 (9.6)
Education, mean (SD), years	4.2 (3.0)	4.7 (2.6)	10.4 (4.2)
Living alone (%)	30	26	21
Physical activity, median	492	580	480
(P10-P90), min/wk	(60-1890)	(20-2100)	(63-1165)
Alcohol consumption (%)	80	80	74
Current smoking (%)	13	17	24
BMI, mean (SD), kg/m^2	26.0 (3.8)	26.1 (3.8)	25.5 (3.1)
SBP, mean (SD), mmHg	156 (22)	162 (19)	150 (21)
DBP, mean (SD), mmHg	84 (11)	86 (9)	82 (12)
Total cholesterol, mean (SD), mmol/L	5.6 (1.1)	5.5 (1.1)	6.1 (1.1)
HDL cholesterol, mean (SD), mmol/L	1.2 (0.3)	1.3 (0.3)	1.2 (0.3)

Abbreviations: SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein

in Finland and the Netherlands, while men in the Netherlands had higher levels of education, were more likely to smoke, had a lower systolic and diastolic blood pressure, and higher total cholesterol levels compared to those in Finland and Italy ($p<0.05$).

Multiple linear regression analyses, adjusted for age, country and living alone showed that men in the middle and high tertile of depressive symptoms were less physically active (562 min/wk; 95% CI 466-658 and 722 min/wk; 95% CI 642-802, respectively) compared to men in the low tertile of depressive symptoms (919 min/wk; 95% CI 823-1015) (**Figure 1**). Additional adjustment for education, current smoking and alcohol consumption did not change these estimates.

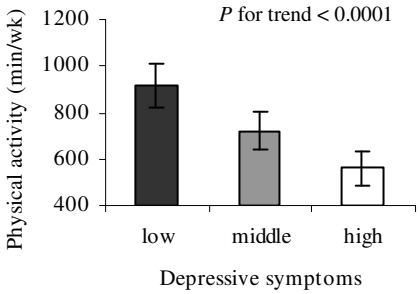

Figure 1: Physical activity (min/wk) across tertiles of depressive symptoms, adjusted for age (years), country (Finland, Italy, the Netherlands (reference)), living alone (yes vs no)

After ten years of follow-up, 471 (52%) of the 909 men had died. Two-hundred and fifty-six men (28%) had died from CVD. The total number of person years was 6550 and the mean follow-up duration was 7.2 years (SD=3.1). A decrease in physical activity with 30 minutes per day showed an increased risk of cardiovascular mortality with 9% (95% CI 1.04-1.14), after adjusting for age. Additional adjustment for demographical and cardiovascular risk factors did not change this risk.

Table 2 presents the hazard ratios estimated from the Cox proportional hazards analyses of depressive symptoms and risk of cardiovascular mortality. An increase in depressive symptoms with one SD was associated with a 42% higher risk of cardiovascular mortality (95% CI 1.26-1.60), after adjusting for age, country, education and living alone. Adjustment for current smoking, alcohol consumption, BMI, SBP, total- and HDL cholesterol did not change this risk. After additional adjustment for physical inactivity the risk decreased to some extent (9%; 95% CI 0.01-0.18), but an independent risk remained (HR 1.37; 95% CI 1.21-1.56). There were no significant differences between countries. Analyses with the primary death causes showed the same estimates with wider confidence intervals (results not shown).

Table 2: Hazard ratios of cardiovascular mortality according to depressive symptoms (n=909)

	HR (95% CI)	Beta explained (95% CI)
depressive symptoms per SD		
model 1*	1.42 (1.26-1.60)	
Additional adjustment:		
physical activity	1.37 (1.21-1.56)	0.09 (0.01-0.18)

Abbreviations: HR, hazard ratio; CI, confidence interval; SD, standard deviation

* Model 1: Adjusted for age (as time scale), country (Finland, Italy, the Netherlands (reference)), years of education, living alone (yes vs no)

Figure 2 shows the combined effect of depressive symptoms and physical inactivity on cardiovascular mortality adjusted for age, country, education and living alone. Men with more depressive symptoms (high tertile) and a low level of physical activity (low tertile) had an increased risk of cardiovascular mortality (HR 4.22; 95% CI 2.56-6.91) in comparison with men with few depressive symptoms (low tertile) and a high level of physical activity (high tertile). The HR for non-depressed but inactive men was 1.69 (95% CI 0.89-3.18), and 2.06 (95% CI 1.12-3.80) for the depressed and active men. The excess risk of cardiovascular mortality that could be attributed to the interacting effect of depressive symptoms and physical inactivity was 4.22 – 1.69 – 2.06 + 1 = 1.47 (95% CI; -0.17 to 3.11). The proportion of cardiovascular mortality among men with more depressive symptoms and low physical activity that could be due to the interaction of these factors was 1.47 / 4.22 = 33%. There were no differences for the combined effects between countries (results not shown).

Discussion

The results of this study show that depressive symptoms in elderly men are associated with reduced physical activity, and that depressive symptoms and physical inactivity both increase the risk of cardiovascular mortality. However, physical inactivity does not materially explain the relation between depressive symptoms and cardiovascular mortality. Instead, depressive symptoms and physical inactivity may interact to increase the risk of cardiovascular mortality.

Major strengths of this study are its prospective design with a long follow-up period, and the almost 100% complete mortality follow-up that minimizes the possibility of bias due to selective loss to follow-up. Also, this is the first study that examines the independent and combined effects of depressive symptoms and physical inactivity on cardiovascular mortality in initially healthy older men. In addition, physical activity was measured with a

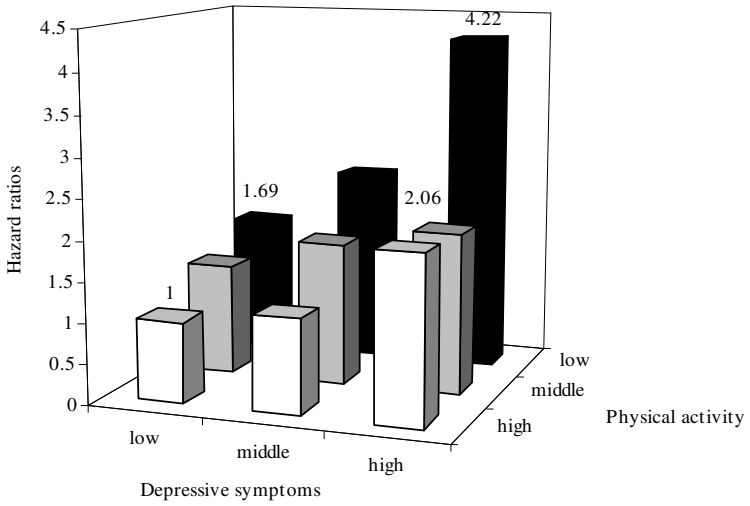

Figure 2: Hazard ratios of cardiovascular mortality for subgroups of depressive symptoms and physical activity. Persons with few depressive symptoms (low tertile) and a high physical activity (high tertile) are the reference category. Hazard ratios are adjusted for age (as time scale), country (Finland, Italy, the Netherlands (reference)), years of education, living alone (yes vs no)

questionnaire specifically designed for older men, and different types and duration of activity were assessed in detail. This will have made misclassification less likely.

Some methodological limitations of the current study need also be considered. First, the selective participation of healthier respondents may have led to a dilution of the observed associations. Second, in an observational study the possibility of residual confounding can never be excluded. We tried to minimize this possibility by adjusting for many known classical cardiovascular risk factors in the analyses. Third, it could be argued that depressive symptoms and physical inactivity are markers of subclinical CVD, therefore reflecting reversed causality. We tried to minimize this possibility by excluding men with prevalent CVD at baseline. In addition, in a previous paper we showed that reversed causality was unlikely.[9]

Our results show an increased risk of cardiovascular mortality with more depressive symptoms in elderly men free of CVD at baseline. This is concordant with the risk estimates observed in other studies in the elderly.[27-29] In addition, we observed a lower duration of physical activity to be associated with an increased risk of cardiovascular mortality, which is concordant with consistent reports of an inverse association between physical activity and coronary heart disease and cardiovascular mortality in the elderly.[30,31] Following from the literature,[4,5] we hypothesized that physical inactivity could be an intermediate

or confounding factor in the relation between depressive symptoms and cardiovascular mortality. At baseline, men with more depressive symptoms were indeed less physically active, but this did not materially explain the association between depressive symptoms and cardiovascular mortality. Therefore, it is not likely that in older men physical inactivity is an intermediate or confounding factor in this relation.

The combined effects of physical activity and depression on cardiovascular mortality have not been investigated before in the elderly. Although the confidence interval indicated borderline significance, the results of the present study suggest that depression and physical inactivity interact on an additive scale, indicating that the combination of the two risk factors has a greater effect than the sum of the two separate effects. This is suggestive for a possible biological interaction between depression and physical inactivity. This indicates that, in addition to other classical risk factors, depression and physical inactivity are necessary, although not sufficient, factors in a proportion of CVD deaths.[24]

What are the possible mechanisms through which this interaction may occur? It has been hypothesized that depression increases risk of CVD by dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, which may lead to atherosclerosis-inducing actions, such as injury of vascular endothelial cells, hypertension, hypercholesterolemia and inflammation.[32] Physical activity, on the other hand, might slow down the atherosclerotic process.[3] The hypothesized anti-depressive effects of physical activity include increased aerobic capacity;[33] increase in circulating concentrations of brain amines and beta-endorphin;[34] increased feelings of mastery or self-efficacy;[35] distraction; a reduction in negative thought patterns;[36] and reduced activity of the HPA axis and decreased cortisol levels.[37] One explanation for a possible interaction between depression and physical inactivity to increase CVD risk may be that depressed persons who are inactive are more prone to atherosclerotic processes than depressed persons who remain active. Another explanation may be that depressed persons may become less active[5] and that this inactivity may also lead to persistence or worsening of the depression, thereby increasing the risk of CVD even further.

In summary, the results of the present study show that physical inactivity does not explain the association between depressive symptoms and cardiovascular mortality. However, the combination of depressive symptoms and physical inactivity may result in an excess risk of cardiovascular mortality, suggesting that a proportion of the cardiovascular mortality cases is dependent on the joint presence of depression and physical inactivity. Further research is needed to confirm these results and explain the possible underlying mechanisms.

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Chapter 4

Health

Chapter 4.1

Health

Autonomic dysfunction: the link between depression and cardiovascular mortality?

Abstract

Background: Depression is associated with an increased risk of cardiovascular diseases (CVD) in vascular patients as well as in the general population. Mechanisms underlying this relationship are not fully understood. We investigated whether autonomic dysfunction could explain this relationship.

Methods: Data were used from the Finland, Italy and the Netherlands Elderly (FINE) Study. Depressive symptoms were measured with the Zung Self-rating Depression Scale in 870 men, aged 70-90 years, free of CVD and diabetes in 1990. Resting heart rate was determined from a 15-30 second resting electrocardiogram in the Netherlands and Italy and as pulse rate in Finland. In addition, in the Netherlands, heart rate variability (HRV) and QTc-interval were determined.

Results: At baseline, depressive symptoms were associated with an increase in resting heart rate, and non-significantly with low HRV and prolonged QTc-interval. After ten years of follow-up, 233 (27%) men died from CVD. Prospectively, an increase in resting heart rate with one standard deviation (SD) was associated with an increased risk of cardiovascular mortality (HR 1.22; 95% CI 1.08-1.38). In addition, low HRV (HR 0.78; 95% CI 0.61-1.01) and prolonged QTc-interval (HR 1.28; 95% CI 1.06-1.53) per SD were associated with cardiovascular mortality. The increased risk of depressive symptoms for cardiovascular mortality (HR 1.38; 95% CI 1.21-1.58) did not change after adjustments for several indicators of autonomic dysfunction.

Conclusions: This study suggests that mild depressive symptoms are associated with autonomic dysfunction in old men. The increased risk of cardiovascular mortality with increasing magnitude of depressive symptoms could, however, not be explained by autonomic dysfunction.

Introduction

Depression is associated with an increased risk of cardiovascular mortality in patients with cardiovascular diseases (CVD) as well as middle-aged and elderly persons without CVD.[1,2] Several mechanisms to explain this association have been proposed, such as higher prevalence of cardiovascular risk factors in depressed persons, anti-depressant cardiotoxicity, induction of the hypothalamic-pituitary-adrenocortical (HPA) axis, inflammation and increased platelet reactivity.[3] Ongoing studies are performed to gain more insight in these mechanisms.

Another explanation for the relationship between depression and increased cardiovascular mortality is through autonomic dysfunction.[4] This reflects reduced parasympathetic and increased sympathetic nervous system activity, which are involved in the pathophysiology of myocardial ischemia, heart failure, diabetes, ventricular tachycardia, ventricular fibrillation and sudden cardiac death.[5] Indicators of autonomic dysfunction are elevated resting heart rate, low heart rate variability (HRV) and prolonged QTc-intervals. These indicators are associated with increased cardiovascular and all cause mortality in patients with and without myocardial infarction.[6-10]

In depressed patients, autonomic dysfunction was first demonstrated by elevated levels of plasma and urinary cathecholamines, primarily norepinephrine (NE), which are markers of increased sympathetic nervous system activation.[11,12] More recently, elevated resting heart rates and low HRV have been associated with depressive symptoms in cardiac patients as well as in older primary care patients and older women without CVD.[5,13-17]

To investigate whether autonomic dysfunction may explain the relationship between depression and cardiovascular mortality, contribution of autonomic dysfunction on the relationship between depression and cardiovascular mortality should be investigated. Reduced HRV may partly explain the relationship between depression and mortality in cardiac patients.[18] Whether autonomic dysfunction may also explain the increased risk of depressive symptoms for cardiovascular mortality in men without cardiac disease, has not been investigated thus far.

In the present study we investigated whether depressive symptoms were associated with autonomic dysfunction, indicated by resting heart rate, HRV and QTc-intervals in old men without prevalent CVD or diabetes. Furthermore, we studied whether the increased risk of depressive symptoms on 10-year cardiovascular mortality[2] could be explained by autonomic dysfunction.

Methods

The FINE study

The FINE (acronym for Finland, Italy and the Netherlands Elderly) Study is a prospective population-based cohort study on risk factors and health in elderly men. The study design and measurements have been described in detail elsewhere.[19] In brief, the FINE Study started in 1984 as a continuation of the Seven Countries Study (SCS), which was originally initiated in 1958 by Keys as a cardiovascular risk factor survey among 12,763 middle-aged men.[20] In total, 2285 men from Finland (n=716), Italy (n=682) and the Netherlands (n=887) participated in the baseline examination of the study in 1985. Informed consent was obtained from all study participants. Data collection followed the international protocol used in previous surveys of the SCS,[20] extended with gerontologic variables. In 1989-1991 the second round of the FINE Study took place. In this round, measures on depression were added. Mortality data were collected until the year 2000.

Depressive symptoms

Depressive symptoms were measured using the Self-rating Depression Scale (SDS), developed by Zung.[21] This scale was developed to assess depression among patients admitted to a psychiatric hospital, but also for non-institutionalized elderly,[22] and was found to be highly comparable among different countries.[23] The reliability of the SDS is good in elderly men (Cronbach alpha 0.75)[24] and has been validated repeatedly with other questionnaires on depressive symptoms, such as the CESD (r=0.69),[25] the GDS (r=0.59)[26] and the Hamilton Depression scale (r=0.80).[27] The questionnaire contains 20 either positively or negatively formulated items, based on clinical diagnostic criteria commonly used to diagnose depressive disorders. The answers on those items are coded on a four-point Likert-type scale varying from 'none or sometimes' to 'most or always'. Positive items on the absence of depressive symptoms were recoded, so that a higher score indicated more depressive symptoms. An index for the SDS was derived by dividing the sum of the answers by 80 times 100 (range 25-100), with a higher score indicating more depressive symptoms. For the analyses a continuous measure was used per standard deviation (SD) (Finland SD=10.8, Italy SD=11.3 and the Netherlands SD=9.5) and the SDS was categorized into country-specific tertiles. The cut-off values for the middle and high tertile were 42 and 51 for Finland, 45 and 54 for Italy, and 39 and 46 for the Netherlands.

Autonomic dysfunction

Standard resting 12-lead electrocardiographic (ECG) recordings were performed according to the protocol of the SCS.[20] The duration of recording ranged from 15-30 seconds. Readings were made according to the 1968 edition of the Minnesota Code.[28] In the Netherlands and Italy resting heart rate was derived from the ECG. In Finland resting heart rate was measured from the radial artery with the men in supine position and counted for 30 seconds. Resting heart rate was expressed as beats per minute and used in the analyses as a continuous measure (per SD; Finland SD=11.7, Italy SD=12.4, Netherlands SD=13.5).

In addition, for the Dutch cohort HRV and QTc-intervals were determined. Intervals between all sinus beats were measured, using a digitizing table (Calcomp) and a personal computer. The resolution of the tables is 100 lines/ mm and the reproducibility is 0.25 mm (corresponding to 10 msec). HRV (msec) was defined as the SD of the duration of all normal RR-intervals.[7] QT-intervals were read from three leads: V2, V6 and lead I, II, or III of which the lead with the longest QT was chosen.[8] QT-intervals were adjusted for heart rate according to Bazett's formula resulting in QTc-intervals.[29]

Cardiovascular endpoints

Mortality data were collected during ten years of follow-up. In Finland, information on causes of death was obtained from the Finnish death register; in Italy and the Netherlands information was obtained from hospital registries and/or general practitioners. One person from Finland, one from Italy and one from the Netherlands were lost to follow-up. They were included in the analyses, but censored at the date of the examination round after which they were lost to follow-up. Coding of causes of death was done by one clinical epidemiologist who was blinded for the risk factor status of the subject. Mortality from CVD was coded according to the International Classification of Diseases, ninth Revision (ICD-9: 390-459). In the analyses, primary (n=199) and secondary (n=107) causes of cardiovascular death were combined and 233 men died from CVD. Men who died from other causes then CVD (n=209) were censored at date of death. Men who were still alive at the end of the study were censored at the last examination date.

Other variables

The self-administered questionnaire contained questions on demographic characteristics, educational level and lifestyle habits. Marital status was classified as living alone (unmarried, separated or widow) or together. In the Netherlands usual alcohol consumption was assessed in the dietary survey and in Finland and Italy with a self-administered questionnaire, and classified as alcohol consumption and non-consumption. Participants were classified as current and non- smokers. Body mass index (BMI) was calculated from

weight and height (kg/m^2), which were measured while the participant was standing in light clothing without shoes. Physical activity was assessed with a self-administered validated questionnaire designed for retired men.[30] All types of activity with an intensity of more than two kilocalories energy expended per kilogram of body weight during one hour, were summed and expressed as minutes of total physical activity per week (min/wk).

Arterial blood pressure was measured twice on the right arm after five minutes of rest, with the man in a supine position. In Finland and Italy standard sphygmomanometers were used, while in the Netherlands a random zero sphygmomanometer was used. The average of two readings of both systolic and diastolic blood pressure (fifth Korotkoff phase) was calculated. Non-fasting venous blood samples were taken and total- and high density lipoprotein (HDL) cholesterol (mmol/L) were determined using standardized procedures according to the criteria of the World Health Organization's Lipid Reference Laboratories in Prague, Czech Republic, or Atlanta, Georgia, United States of America.[31] History of myocardial infarction was obtained using the London School of Hygiene and Tropical Medicine questionnaire,[28] verified by information from general practitioners or hospital registries. Information was obtained on the use of antihypertensive drugs. A clinical history of stroke, heart failure, diabetes, and COPD was based on a doctor's conclusion using questionnaire information and the results of the physical examination.

Study samples

Depressive symptoms were measured for the first time during the second round of the FINE study, between October 1989 and November 1991, when in total 1416 men (82%) participated of the 1734 men still alive. Of these, 909 (64%) were free of CVD and diabetes. From these, 39 with atrial fibrillation based on the Minnesota code were excluded. Thus, a study sample of 870 men remained for analysis, 253 men from Finland, 362 men from the Netherlands and 255 men from Italy. For the analyses of HRV and QTc-interval, data for 362 men of the Dutch cohort were available.

Data analysis

To retain power and to prevent bias from missing values in a selective group of respondents a single imputation procedure in SPSS version 12.0.1 was used. We imputed missing values on the items of the SDS (on average 7%), HRV (2%), and the other covariates (on average 2%). All information of the baseline examination in 1990 and follow-up examinations was used to fill in missing values.

Frequency distributions are given for categorical variables for each country. Means and SD were computed for continuous baseline variables, and medians and 10-90 percen-

tiles for continuous variables with a skewed distribution. Differences between countries were tested with ANOVA, Kruskal-Wallis (in case of skewed distribution) or X^2-test.

Multiple linear regression analysis was used to calculate differences in resting heart rate across country specific tertiles of depressive symptoms, and HRV and QTc-intervals, respectively, in the Dutch cohort. The HRV distribution was skewed and therefore log-transformed. The transformed values were then used to compute geometric means. In the first model, we adjusted for age (years). In the second model, we also adjusted for the following potential confounders or intermediate factors: country (Finland vs the Netherlands and Italy vs the Netherlands), years of education, living alone (yes vs no), current smoking (no vs yes), alcohol consumption (yes vs no), physical activity (min/wk), systolic blood pressure (SBP) (mmHg), BMI (kg/m^2), total and HDL cholesterol levels (mmol/L), COPD (no vs yes) and use of anti-hypertensive drugs (no vs yes).

The prospective associations of resting heart rates per SD (in the FINE cohort), and HRV and QTc-interval (in the Dutch cohort) with cardiovascular mortality were estimated using Cox proportional hazard models. In the first model, we adjusted for age (as the time scale), and in the second model we also adjusted for cardiovascular risk factors. With a log minus log plot the assumptions of proportional hazards were checked. The assumptions of proportionality were not violated.

Finally, we investigated whether the relationship between depressive symptoms and cardiovascular mortality could be explained by autonomic dysfunction, by adding resting heart rate, HRV or QTc-interval to the adjusted model.

All analyses were repeated after stratification by country and performed with the SAS statistical software package, version 9.1.2[32] Point estimates are given with corresponding 95% confidence intervals (CI).

Results

Table 1 presents the baseline characteristics of the study sample per country. The average depression score was highest in Italy (49.4 ± 11) and lowest in the Netherlands (43.2 ± 10). The average depression scores were low in comparison with the clinical cut-off value for mild depression (≥ 50). Average resting heart rate was higher in the Netherlands (75.2 ± 14) compared to Finland (68.2 ± 12) and Italy (69.3 ± 12). In addition, men in Italy were older, more physically active, and had higher HDL-cholesterol levels than men in Finland and the Netherlands, while men in the Netherlands had higher levels of education, were more likely to smoke, had a lower systolic and diastolic blood pressure, and higher total cholesterol levels compared to those in Finland and Italy ($p < 0.05$).

Multiple linear regression analyses showed a dose-response relationship between depressive symptoms and resting heart rate (*P* for trend 0.01) **(Figure 1)**. Men in the high tertile of depressive symptoms had an increased mean resting heart rate adjusted for age

Table 1: Baseline characteristics for each country (n=870)

Characteristic	Finland n=253	Italy n=255	The Netherlands n=362
Age, mean (SD), years	76.5 (4.9)	77.5 (3.9)	75.5 (4.5)
Depressive symptoms, mean (SD)	46.6 (10.8)	49.4 (11.3)	43.2 (9.5)
Education, mean (SD), years	4.2 (3.1)	4.7 (2.6)	10.4 (4.2)
Living alone (%)	31	25	21
Physical activity,	520	580	483
median (P10-P90), min/wk	(60-1965)	(15-2100)	(75-1160)
Alcohol consumption (%)	80	82	75
Current smoking (%)	13	17	24
BMI, mean (SD), kg/m^2	26.0 (3.8)	26.1 (3.8)	25.5 (3.1)
SBP, mean (SD), mmHg	156 (22)	162 (20)	151 (21)
DBP, mean (SD), mmHg	84 (11)	86 (9)	82 (12)
Use of anti-hypertensive drugs (%)	25	46	12
Total cholesterol, mean (SD), mmol/L	5.6 (1.1)	5.5 (1.1)	6.1 (1.1)
HDL cholesterol, mean (SD), mmol/L	1.2 (0.3)	1.3 (0.3)	1.2 (0.3)
COPD (%)	22	78	28
Heart rate, mean (SD), beats/min	68.2 (11.7)	69.3 (12.4)	75.2 (13.5)
Heart rate variability, median (P10-P90), msec			18.1 (8.2-49.0)
QTc-interval, mean (SD), msec			412 (29)

Abbreviations: SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; COPD, chronic obstructive pulmonary disease

(73.1 beats/min; 95% CI 71.6-74.6) compared to men in the low tertile of depressive symptoms (69.6 beats/min; 95% CI 68.1-71.1). In the second model, after additionally adjusting for country, education, SBP, use of anti-hypertensive drugs, COPD and physical activity these estimates became 72.0 (95% CI 70.5-73.5) and 69.4 (95% CI 68.0-70.9), respectively for men in the high and low tertile of depressive symptoms. After additional adjustments for living alone, current smoking, alcohol consumption and total and HDL cholesterol levels these estimates did not change.

In the Netherlands, data on heart rate variability and QTc-interval were also assessed. Men with high depressive symptoms had a non-significantly lower heart rate variability (17.8 msec; 95% CI 15.6-20.2) compared to men with low depressive symptoms (19.7 msec; 95% CI 17.2-22.4), adjusted for age, country, education, SBP, use of anti-hypertensive drugs, COPD and physical activity. In addition, men with high depressive symptoms had a non-significantly longer QTc-interval (415 msec; 95% CI 410-420), compared to men with low depressive symptoms (411 msec; 95% CI 406-415).

After ten years of follow-up, 442 of the 870 men (51%) had died. Two-hundred and thirty-three men (27%) had died from CVD. The total number of person years was 6321

and the mean follow-up duration was 7.3 years (SD=3.1). Prospectively, an increase in resting heart rate per SD, adjusted for age was associated with a 26% (95% CI 1.12-1.42) increased risk of cardiovascular mortality. After additional adjustment this risk became 22% (95% 1.08-1.38). In addition, in the Dutch sample a longer QTc-interval (hazard ratio (HR) 1.28; 95% CI 1.06-1.53) was associated with an increased risk of cardiovascular mortality, while increased HRV (HR 0.78; 95% CI 0.61-1.01) was non-significantly associated with a lower risk of cardiovascular mortality **(Table 2)**. These indicators of autonomic dysfunction were also associated with total mortality, but less strongly (results not shown).

Finally, an increase in depressive symptoms per SD on the SDS, adjusted for age, country, living alone and physical activity, was associated with a 38% (95% CI 1.21-1.58) increased risk of cardiovascular mortality. Adjustment for current smoking, alcohol consumption, BMI, SBP, total and HDL cholesterol, COPD and use of anti-hypertensive drugs did not change this risk. After additional adjustment for separate measures of autonomic dysfunction **(Table 3)** this risk did not materially change. There were no differences between countries (results not shown).

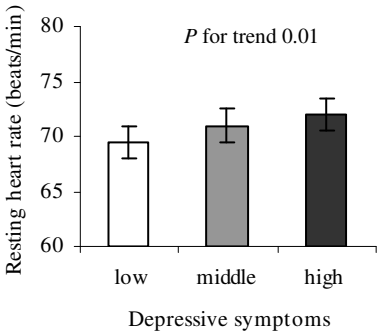

Figure 1: Autonomic function expressed as resting heart rate by tertiles of depressive symptoms for elderly men from Finland, Italy and the Netherlands, adjusted for age (years), country (Finland, Italy, the Netherlands (reference)), years of education, systolic blood pressure (mmHg), anti-hypertensive drugs (no vs yes), COPD (no vs yes) and physical activity (min/wk)

Discussion

This study examined whether depressive symptoms in old men were associated with autonomic dysfunction, and whether autonomic dysfunction could explain an increased risk of depressive symptoms on cardiovascular mortality. We observed that depressive symptoms were associated with increased resting heart rate, but not significantly with lower

Table 2: Adjusted hazard ratios of 10-year cardiovascular mortality for autonomic dysfunction per standard deviation (n=870)

	Model 1*	Model 2†
	HR (95% CI)	HR (95% CI)
Resting heart rate		
per SD beats/min increase	1.26 (1.12-1.42)	1.22 (1.08-1.38)
Dutch cohort (n=362)		
Heart rate variability		
per SD msec increase	0.80 (0.61-1.04)	0.78 (0.61-1.01)
QTc-interval		
per SD msec increase	1.32 (1.11-1.57)	1.28 (1.06-1.53)

Abbreviations: HR, hazard ratios; CI, confidence interval; SD, standard deviation

*Model 1: adjusted for age

†Model 2: additionally adjusted for country (Finland, Italy, The Netherlands (reference)), living alone (yes vs no), systolic blood pressure (mmHg), physical activity (min/wk), total and HDL cholesterol levels (mmol/L), COPD (no vs yes) and use of antihypertensive drugs (no vs yes)

HRV or prolonged QTc-intervals. Increased resting heart rate, however, did not explain the increased risk of cardiovascular mortality associated with depressive symptoms observed in the present study.

Strengths of this study are its prospective design with a long follow-up period, in a study sample of elderly men free of CVD and diabetes at baseline. This made it possible to examine the causal direction between depressive symptoms, autonomic dysfunction and cardiovascular mortality. Second, the mortality follow-up was virtually complete, and the findings will thus not be influenced by selective loss to follow-up. Third, we were able to adjust for a large number of potential confounding factors.

There are some methodological limitations of the current study that also need to be considered. First, selective participation of healthier respondents[33] may have diluted the associations. Second, although we adjusted for a range of known classical cardiovascular risk factors, the possibility of residual confounding cannot be excluded. Third, HRV was based on one short-term ECG-recording during daytime. It is known that HRV changes during the day and the reliability of short-term measurements seems to be lower in sick people.[34] However, short-term HRV measurements during day-time are correlated with 24-hour HRV measures and[9] for the present study population, we excluded men with CVD or atrial fibrillation to lower the risk of measurement errors. If misclassification may occurred, however, it was likely to be random, which may have diluted the observed associations.

Our finding of an increased resting heart rate with increase in depressive symptoms is concordant with several other studies, although not all, showing an association between depression and several indicators of autonomic dysfunction in patients with myocardial

Table 3: Hazard ratios of 10–year cardiovascular mortality for depressive symptoms (n=870)

	HR (95% CI)
Depressive symptoms (per SD)	
model 1*	1.38 (1.21-1.58)
Additional adjustment:	
resting heart rate	1.39 (1.22-1.59)
Dutch cohort (n=362)	
model 1*	1.37 (1.14-1.65)
Additional adjustment:	
heart rate variability	1.39 (1.13-1.70)
QTc-interval	1.35 (1.10-1.65)

Abbreviations: HR, hazard ratios; CI, confidence interval; SD, standard deviation

*Model 1: adjusted for age (as time scale), country (Finland, Italy, the Netherlands (reference)), years of education, living alone (yes vs no) and physical activity (min/wk)

infarction.[5,14,35-39] In subjects without myocardial infarction, associations between depression and indicators of autonomic dysfunction have also been observed.[15-17] We did not find a significant association of low HRV and QTc-prolongation with depressive symptoms. The mean depression score in the present study population was low compared to the clinical cut-off values of depression, this may have decreased the power to detect an association. It is notable therefore that these mild depressive symptoms were associated with resting heart rate and cardiovascular mortality. Autonomic dysfunction was associated with cardiovascular mortality, which is in concordance with results from the literature.[6,8-10,40-42]

The exact mechanisms how depression may affect the autonomic nervous system are not well understood, but are thought to involve deactivation of the right hemisphere, promoting predominance of the left hemisphere associated with cardiac arrhythmia.[43] Alternatively, autonomic dysfunction may also predispose to depression, because recent studies indicated that vagal nerve stimulation in patients with major depression may improve remission.[44]

To our knowledge, this is the first study that investigated whether indicators of autonomic dysfunction could explain the increased risk of depressive symptoms for cardiovascular mortality in subjects without CVD. One previous study showed that decreased HRV partly explained the relationship between depression and mortality in patients after acute myocardial infarction.[18] In our study, autonomic dysfunction could not explain the increased risk between depression and cardiovascular mortality. An explanation for these

seemingly discordant findings may be that autonomic dysfunction is stronger associated with mortality in patients after acute myocardial infarction,[18] than in subjects without CVD.

If autonomic dysfunction cannot explain the increased risk of depression on cardiovascular mortality in old men without prevalent CVD, what other mechanism may explain this relationship? Alternative hypotheses are, first, that dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, with its elevated cortisol levels and often present in depression, promotes atherosclerosis through injury of vascular cells, hypertension, hypercholesterolemia and inflammation.[3] Second, inflammation and platelet reactivity may explain the relationship between depression and CVD[3] and genetic vulnerability may play a role in these mechanisms.[45] In addition, in the elderly atherosclerosis and cerebral white-matter lesions may increase the risk of depression as well as cerebrovascular disease.[46]

In conclusion, this population-based study in old men shows that mild depressive symptoms are associated with a higher resting heart rate. However, this indicator of autonomic dysfunction did not explain the increased risk of 10-year cardiovascular mortality associated with depressive symptoms that we observed in our study. Further studies are needed to examine what other mechanisms may explain the frequently observed relation between depression and cardiovascular disease.

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Chapter 4.2

Health

The association of depressive symptoms with cardiovascular mortality is partly explained by subjective health status.

Abstract

Background: Depression is associated with an increased risk of cardiovascular diseases (CVD) and cardiovascular mortality. We investigated to what extent subjective health status explained the apparent association between depressive symptoms and cardiovascular mortality in older European men.

Methods: Data were used from the population-based prospective Finland, Italy and the Netherlands Elderly (FINE) Study. Depressive symptoms were measured with the Zung Self-rating Depression Scale in 909 men, aged 70-90 years, free of CVD and diabetes in 1990. Subjective health status was estimated with a single question on self-rated health and with a standardized questionnaire about activities of daily living. Cardiovascular mortality was determined during ten years of follow-up.

Results: At baseline, poor self-rated health and more disability in activities of daily living were both associated with more depressive symptoms using multiple linear regression analysis. Prospectively men who reported to be unhealthy or with moderate to severe disability had an approximately two and a half times higher risk of cardiovascular mortality using Cox regression analysis. An increase in depressive symptoms by one standard deviation was associated with an increased risk of cardiovascular mortality (HR 1.37; 95% CI 1.21-1.56). A substantial part of this association was explained by poor self-rated health and more disability in activities of daily living (proportion explained 0.32; 95% CI 0.09-0.55). However, a significant risk of depressive symptoms on cardiovascular mortality remained (HR 1.25; 95% CI 1.09-1.43) after adjustment for subjective health status.

Conclusions: In older men, subjective health status explains a considerable part of the association between depression and risk of cardiovascular mortality.

Introduction

Depression is associated with an increased risk of non-fatal and fatal cardiovascular disease (CVD) in patients with CVD as well as in middle-aged and elderly persons without CVD.[1,2] Several mechanisms have been proposed to explain this. Indirectly, an unhealthy diet or lifestyle in depressed persons and medication non-adherence in cardiac patients may increase their risk of CVD. In addition, more direct mechanisms that may explain the association include induction of the hypothalamic-pituitary-adrenocortical (HPA) axis, autonomic dysfunction, inflammation, and increased platelet reactivity.[3] Studies are ongoing to gain more insight in the proposed mechanisms.

An alternative explanation for the increased risk of depression on CVD may be that depression reflects a general poor health, in particular if the depression is mild or present at a subthreshold level. This is suggested by a study of a middle-aged population where the relationship between depression and all-cause mortality was attenuated when health status was taken into account.[4] In addition, a recent review showed that in patients with myocardial infarction, the relationship of depression with cardiovascular mortality could partly be explained by severity of the infarction.[5] While some studies adjusted for disability in their analyses together with history of CVD and cardiovascular risk factors,[6-9] it is unclear to what extent the association between depressive symptoms and cardiovascular mortality is explained by subjective health status in elderly subjects without symptomatic CVD.

We investigated to what extent subjective health status, estimated as self-rated health and disability in activities of daily living, explained the relationship of depressive symptoms and subsequent cardiovascular mortality in older European men.

Methods

The FINE study

The FINE (acronym for Finland, Italy and the Netherlands Elderly) Study is a prospective population-based cohort study on risk factors and health in elderly men. The study design and measurements have been described in detail elsewhere.[10] In brief, the FINE study started in 1984 as a continuation of the Seven Countries Study (SCS), which was originally initiated in 1958 by Keys as a cardiovascular risk factor survey among 12,763 middle-aged men.[11] In total, 2,285 men from Finland (n=716), Italy (n=682) and the Netherlands (n=887) participated in the baseline examination of the study in 1984-1985. Informed consent was obtained from all study participants. Data collection followed the international protocol used in previous surveys of the SCS,[11] extended with gerontologic variables. In 1989-1991 the second round of the FINE Study took place. In this round, measures on de-

pression, functional status, self-rated health and activities of daily living were added. Mortality data were collected until the year 2000.

Depressive symptoms

Depressive symptoms were measured using the Self-rating Depression Scale (SDS), developed by Zung.[12] This scale was developed to assess depression among patients admitted to a psychiatric hospital, but also for non-institutionalized elderly,[13] and was found to be comparable among different countries.[14] The reliability of the SDS is good in elderly men (Cronbach alpha 0.75)[15] and has been validated repeatedly with other questionnaires on depressive symptoms, such as the CESD (r=0.69),[16] the GDS (r=0.59)[17] and the Hamilton Depression Scale (r=0.80).[18] The questionnaire contains 20 either positively or negatively formulated items, based on clinical diagnostic criteria commonly used to diagnose depressive disorders. The answers on those items are coded on a four-point Likert-type scale varying from 'none or sometimes' to 'most or always'. Positive items on the absence of depressive symptoms were recoded, so that a higher score indicated more depressive symptoms. An index for the SDS was derived by dividing the sum of the answers by 80 times 100 (range 25-100), with a higher score indicating more depressive symptoms. For the analyses a continuous measure of the SDS was used per standard deviation (SD) (Finland SD=10.6, Italy SD=11.3 and the Netherlands SD=9.6).

Self-rated health

Self-rated health was assessed with a single-item question: "How do you rate your health?" Participants could choose between four answer categories: 1) healthy, 2) rather healthy, 3) moderately healthy, 4) not healthy. In the analyses, self-rated health was categorized into three groups indicating healthy; rather healthy; and moderately healthy to not healthy.

Disability

Disability was measured using a standardized questionnaire about routine activities of daily living and has been described in detail elsewhere.[19] In brief, three domains were assessed, instrumental activities, mobility, and basic activities. The participants were classified as being disabled on a certain item if they reported a need for help or were not able to perform that activity. Subjects were classified as having no, mild, moderate or severe disabilities following a hierarchical disability coding scheme.[20] In the analyses, disability was categorized into three groups indicating no disability; mild disability; and moderate to severe disability.

Cardiovascular endpoints

Mortality data were collected during ten years of follow-up. In Finland, information on causes of death was obtained from the Finnish death register, while in Italy and the Netherlands information was obtained from hospital registries and/or general practitioners. One person from Finland, one from Italy and one from the Netherlands were lost to follow-up. They were included in the analyses, but censored at the date of the examination round after which they were lost to follow-up. Coding of causes of death for all countries was done by one clinical epidemiologist who was blinded to the risk factor status of the subject. Mortality from CVD was coded according to the International Classification of Diseases, ninth Revision (ICD-9: 390-459). In the analyses, primary (n=214) and secondary (n=120) causes of death were combined and 256 men died from CVD. Men who died from other causes than CVD (n=215) were censored at date of death. Men who were still alive at the end of the study were censored at the last examination date.

Other variables

The self-administered questionnaire contained questions on marital status, educational level, alcohol consumption, smoking habits, physical activity and past and current morbidity. Marital status was classified as living alone (unmarried, separated or widowed) or together. Educational level was expressed as years of education. In Finland and Italy habitual alcohol consumption was assessed with a self-administered questionnaire, while in the Netherlands it was assessed in the dietary survey, and men were classified as alcohol consumers or non-consumers. Participants were classified as non-smokers or current smokers. Physical activity was assessed with a self-administered validated questionnaire designed for retired men.[21] All types of activity with an intensity of more than two kilocalories energy expended per kilogram of body weight during one hour, were summed and expressed as minutes of total physical activity per week (min/wk). Body mass index (BMI) was calculated from weight and height (kg/m^2), which were measured while the participant was standing in light clothing without shoes. Arterial blood pressure was measured twice on the right arm after five minutes of rest, with the man in a supine position. In Finland and Italy standard sphygmomanometers were used, while in the Netherlands a random zero sphygmomanometer was used. The average of two readings of both systolic and diastolic blood pressure (fifth Korotkoff phase) was calculated. Non-fasting venous blood samples were taken and total- and high density lipoprotein (HDL) cholesterol (mmol/L) were determined using standardized procedures according to the criteria of the World Health Organization's Lipid Reference Laboratories in Prague, Czech Republic, or Atlanta, Georgia, United States of America.[22]

Study sample

Depressive symptoms were measured during the second round of the FINE study, between October 1989 and November 1991, when in total 1416 men (82%) participated of the 1734 men still alive. Of these, 909 (64%) were free of CVD and diabetes. Thus a study sample of 909 men remained for analysis, 268 men from Finland, 380 men from the Netherlands and 261 men from Italy.

Data analysis

To retain power and to prevent bias from missing values in a selective group of respondents a single imputation procedure in SPSS version 12.0.1 was used. We imputed missing values on the items of the SDS (on average 7%), self-rated health (10%), disability (6%), and the other covariates (on average 2%). All information of the baseline examination in 1990 and follow-up examinations was used to fill in missing values.

Frequency distributions are given for categorical variables for each country. Means and SD were computed for continuous baseline variables, and medians and 10-90 percentiles for continuous variables with a skewed distribution. Differences between countries were tested with ANOVA, Kruskal-Wallis (in case of skewed distribution) or X^2-test.

Multiple linear regression analyses were performed to estimate the association of subjective health status with depressive symptoms at baseline. Categories of self-rated health and disability in activities of daily living were entered as the independent variables and depressive symptoms (continuously) as the dependent variable. Adjustments were made for age (years), country (Finland vs the Netherlands and Italy vs the Netherlands), living alone (yes vs no), years of education, physical activity (min/wk).

Cox proportional hazard analyses were performed to estimate the prospective associations between self-rated health and disability in activities of daily living, respectively, with cardiovascular mortality. With a log minus log plot the assumptions of proportional hazards were checked and the assumptions were met. In the first model we adjusted for potential confounders: age (as the time scale), country (Finland vs the Netherlands and Italy vs the Netherlands), living alone (yes vs no) and years of education. In the second model, we also adjusted for physical activity (min/wk), current smoking (no vs yes), alcohol consumption (yes vs no), BMI (kg/m^2), systolic blood pressure (SBP) (mmHg), total- and HDL cholesterol levels (mmol/L) which could be confounders or intermediate factors. In the third model, we also adjusted for disability (in the model with self-rated health as determinant) or self-rated health (in the model with disability as determinant).

Finally, we investigated to what extent the association between depressive symptoms and cardiovascular mortality could be explained by subjective health status, by adding categories of self-rated health and disability in activities of daily living to the model adjusted

for cardiovascular risk factors, and calculating the percentage reduction in the coefficient of depressive symptoms after adjustment for these health status parameters. The percentage reduction was calculated by one minus the estimate of depressive symptoms in the model with subjective health status divided by the estimate of depressive symptoms in the model without subjective health status. Accompanying confidence limits were also calculated.[23]

All analyses were performed with the SAS statistical software package, version 9.1.2.[24] Point estimates are given with corresponding 95% confidence intervals (CI).

Results

At baseline, the average depression score was highest in Italy (49.6; SD=11) and lowest in the Netherlands (43.2; SD=10). In Finland, very few men rated their health status as healthy (4%), while this percentage was much higher in the Netherlands (57%) and Italy (26%). Men in Italy were older, more physically active, and had higher HDL-cholesterol levels than men in Finland and the Netherlands, while men in the Netherlands had higher levels of education, were more likely to smoke, had a lower systolic and diastolic blood pressure, and higher total cholesterol levels compared to those in Finland and Italy ($p < 0.05$) **(Table 1)**.

Cross-sectionally, men who reported to be rather healthy or moderately-not healthy had more depressive symptoms (46.3; 95% CI 45.2-47.4 and 52.2; 95% CI 50.9-53.5, respectively) compared to men who reported to be healthy (43.9; 95% CI 42.5-45.3), independent of age, country, living alone, education, physical activity and disability (*P* for trend < 0.0001) **(Figure 1A)**. In addition, men with mild or moderate to severe disability in activities of daily living were more depressed (47.3; 95% CI 46.2-48.4 and 50.9; 95% CI 49.2-52.6, respectively) compared to men with no disability (44.1; 95% CI 43.2-45.0) (*P* for trend < 0.0001) **(Figure 1B).**

After ten years of follow-up 471 of the 909 men (52%) had died. Two-hundred and fifty-six men (28%) had died from CVD. The total number of person years was 6550 and the mean follow-up duration was 7.2 years (SD=3.1). Prospectively, there was a dose-response relation between self-rated health and cardiovascular mortality. Men who rated themselves as rather healthy had an 43% (95% CI 1.01-2.01) higher risk of cardiovascular mortality compared to men who rated themselves as healthy; men who rated themselves as moderately to not healthy had a 2.59 (95% CI 1.70-3.95) times higher risk on cardiovascular mortality (*P* for trend <0.0001) **(Table 2)**. This relation was independent of age, country, living alone and education. After additional adjustment for physical activity and disability the dose-response relation weakened, but a worse self-rated health was still significantly associated with cardiovascular mortality (*P* for trend 0.01) **(Table 2)**. Other classical cardivascular risk factors such as current smoking, alcohol consumption, BMI, SBP, total- and HDL cholesterol levels did not change the risk estimates. In addition, with

Table 1: Baseline characteristics for each country (n=909)

	Finland	Italy	The Netherlands
Characteristic	n=268	n=261	n=380
Age, mean (SD), years	76.7 (5.0)	77.4 (3.9)	75.6 (4.5)
Depressive symptoms, mean (SD)	46.6 (10.6)	49.6 (11.3)	43.2 (9.6)
Education, mean (SD), years	4.2 (3.0)	4.7 (2.6)	10.4 (4.2)
Living alone (%)	30	26	21
Physical activity,	492	580	480
median (P10-P90), min/wk	(60-1890)	(20-2100)	(63-1165)
Alcohol consumption (%)	80	80	74
Current smoking (%)	13	17	24
BMI, kg/m^2, mean (SD)	26.0 (3.8)	26.1 (3.8)	25.5 (3.1)
SBP, mean (SD), mmHg	156 (22)	162 (19)	150 (21)
DBP, mean (SD), mmHg	84 (11)	86 (9)	82 (12)
Total cholesterol, mean (SD), mmol/l	5.6 (1.1)	5.5 (1.1)	6.1 (1.1)
HDL cholesterol, mean (SD), mmol/l	1.2 (0.3)	1.3 (0.3)	1.2 (0.3)
Disability severity			
no (%)	56	47	55
mild (%)	28	36	32
moderate-severe (%)	16	17	13
Self-rated health			
healthy (%)	4	26	57
rather healthy (%)	20	59	35
moderately-not healthy (%)	76	15	8

Abbreviations: SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein

an increase of disability in activities of daily living the risk of cardiovascular mortality increased (*P* for trend < 0.0001) **(Table 2)**.

Depressive symptoms also increased the risk of cardiovascular mortality (HR per SD increase 1.37; 95% 1.21-1.56), independent of age, education, country, living alone and physical activity. Additional adjustment for current smoking, alcohol consumption, BMI, SBP, total- and HDL cholesterol levels did not change this risk **(Table 3)**. The proportion explained by self-rated health and disability in activities of daily living was 0.16 (95% CI 0.01-0.32) and 0.23 (95% CI 0.06-0.41), respectively. The proportion explained by self-rated health and disability together was 0.32 (95% CI 0.09-0.55). Still, a significant risk of depressive symptoms on cardiovascular mortality remained (HR 1.25; 95% 1.09-1.43) after adjustment for these subjective health status indicators. We repeated the analyses for separate countries and no significant differences in results were observed between countries.

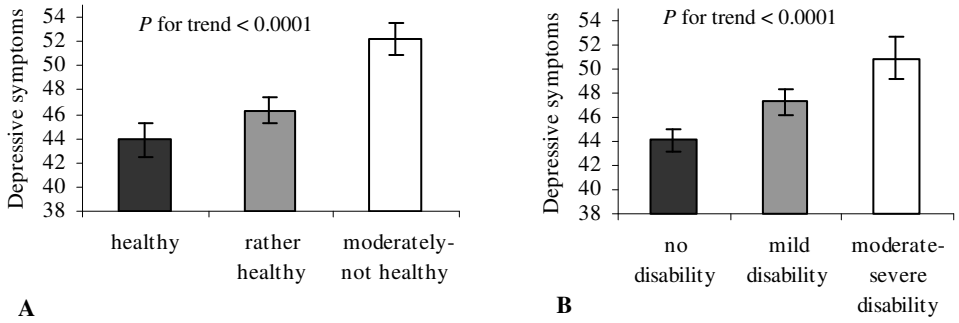

Figure 1: Depressive symptoms are provided for categories of (A) self-rated health and (B) categories of disability in activities of daily living, adjusted for age (years), country (Finland, Italy, the Netherlands (reference)), living alone, years of education, physical activity (min/wk)

Discussion

The results of the present study in older men free from cardiovascular disease and diabetes show that a worse subjective health status is associated with more depressive symptoms as well as with a higher risk of cardiovascular mortality. Moreover, the higher risk of depressive symptoms on cardiovascular mortality can partly be explained by subjective health status. Therefore, even in subjects without manifest CVD or diabetes depressive symptoms may reflect underlying disease. This questions the causal role of depression in cardiovascular disease. Depressive symptoms remained related to cardiovascular mortality, however, even when subjective health status was taken into account.

To appreciate these findings some aspects of our study need to be addressed. Strengths of this study are its prospective design with a long follow-up period, in a study sample of elderly men free of CVD and diabetes at baseline. This made it possible to examine the temporal sequency between depressive symptoms, subjective health status and CVD. Second, the mortality follow-up was virtually complete and the findings were thus not influenced by selective loss to follow-up. Third, we had information on the specific causes of death in addition to all-cause mortality.

A potential limitation of the study is that we had to rely on subjective health and self-reported disability in activities of daily living. Subjects with depressive symptoms may rate their health poorer than subjects without these symptoms, and the proportion of the risk of depressive symptoms explained by subjective health status may be an overestimation. However, it has been shown that men who rated their health as bad, had more atherosclerosis than men who rated their health as good,[25] suggesting that self-rated health is associated

Table 2: Hazard ratios of 10-year cardiovascular mortality for categories of self-rated health and disability (n=909)

		Model 1	Model 2	Model 3
	Cases/ PY	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Self-rated health				
healthy	68/ 2318	1	1	1[*]
rather healthy	87/ 2429	1.43 (1.01-2.01)	1.40 (0.99-1.96)	1.25 (0.88-1.77)
moderately-not healthy	101/ 1803	2.59 (1.70-3.95)	2.32 (1.52-3.54)	1.76 (1.13-2.74)
P for trend		< 0.0001	0.0001	0.01
Self-reported disability				
no	106/ 3776	1	1	1[†]
mild	87/ 2073	1.37 (1.02-1.82)	1.30 (0.97-1.74)	1.26 (0.94-1.69)
moderate-severe	63/ 701	2.92 (2.12-4.03)	2.59 (1.84-3.63)	2.26 (1.59-3.22)
P for trend		< 0.0001	< 0.0001	< 0.0001

Abbreviations: PY; person years, HR; hazard ratio, CI; confidence interval

Model 1: adjusted for age (as time-scale), country (Finland, Italy, the Netherlands (reference)), living alone (yes vs no), years of education

Model 2: additionally adjusted physical activity (min/wk)

Model 3: additionally adjusted for [*]self-reported disability or [†]self-rated health

with subclinical disease. Still, the measure may not have detected more subtle manifestations of poor health which may have made the adjustments incomplete.

This study showed that at baseline a worse-self-rated health and more disability in activities of daily living were both associated with more depressive symptoms, which is in concordance with other studies showing that poor health status and more disability are associated with a higher risk of developing depression[26-28] In addition, a worse self-rated health and more disability in activities of daily living were both associated with an increased risk of cardiovascular mortality. This agrees with results from previous studies that showed an increased risk of all-cause mortality [29] and cardiovascular mortality[25,30-32] for subjects who reported to be unhealthy. Previous research has also shown subjects with more severe disability in activities of daily living to be at an increased risk of all-cause mortality.[33] However, no studies reported on disability in relation to cardiovascular mortality.

The hypothesis that health status could explain the association of depression with CVD, because depression reflects a general poor health, is supported by studies in patients with symptomatic cardiovascular disease. A recent review showed that a worse prognosis in depressed post-MI patients was partial due to severity of the infarction.[5] In addition, in post-MI patients the relation between depression and cardiac prognosis was partly explained by somatic health status, although an independent risk remained.[34]

Table 3: Hazard ratios of 10-year cardiovascular mortality according to depressive symptoms and proportion explained by subjective health status (n=909)

	HR (95 % CI)	% Explained of beta depressive symptoms
Depressive symptoms (per SD)		
model 1*	1.37 (1.21-1.56)	
Additional adjustment:		
self-rated health	1.31 (1.14-1.49)	0.16 (0.01-0.32)
disability in activities of daily living	1.28 (1.12-1.46)	0.23 (0.06-0.41)
self-rated health and disability	1.25 (1.09-1.43)	0.32 (0.09-0.55)

*Model 1: additional adjustments for age (as time scale), country (Finland, Italy, the Netherlands (reference)), years of education, living alone (yes vs no) and physical activity (min/wk)

There are also data to suggest that health status may explain the relation between depression and cardiovascular mortality in the general population. A previous study showed that the association between depression and all-cause mortality was confounded by health status in middle-aged persons.[4] Another report showed that in elderly woman the association between depressive symptoms and CHD was explained by functional impairment.[7]

In the present study an independent risk remained after adjustment of subjective health status, which agrees with previous studies showing an independent effect of depression on CVD, after adjustment for activities of daily living together with history of CVD and cardiovascular risk factors in the analyses.[6,8,9] However, the validity of these observations relies on the extent to which the effect of health status is fully removed by the adjustments. Given the necessarily crude measures of self reported health status the presence of a residual effect can not be excluded.

We assumed that depressive symptoms reflected a worse health status, and that therefore health status may confound an apparent direct association between depression and CVD. Alternatively, health status may also lie in the causal pathway and adjustment for health status may mask a true association, because a worse self-rated health may also reflect a depression related unhealthy lifestyle, which in turn elevates the risk of (cardiovascular) mortality.[29,35] One lifestyle factor that qualifies for this role is physical activity. However, in the present study physical activity only explained a small part of the association between depressive symptoms and cardiovascular mortality. In addition, studies also showed that depression may lead to more disability or a decline in physical performance as well as with a decline in self-rated health.[36-38]

In summary, the results of the present study show that the increased risk of depression on CVD in older men is partly, but not completely, explained by subjective health status.

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Chapter 5

General discussion

Depression and cardiovascular disease: cause, consequence, or innocent bystander?

Does depression cause cardiovascular diseases (CVD), is it a consequence, or just an innocent bystander? A large body of evidence from prospective observational studies supports the presence of a causal relation between depression and (CVD). Nevertheless, depression is not on the list of cardiac risk factors recognized by the American College of Cardiology.[1] One of the reasons may be that cardiologists are still not convinced of a true association between depression and CVD. This may be due to the heterogeneity in study designs, residual confounding, or the possibility of reversed causality.[1] The latter implies that depression is a consequence of subclinical or asymptomatic CVD and therefore associated with an increased risk of developing symptomatic CVD. In addition, the results of clinical trials of anti-depressive treatments on cardiovascular outcomes are thus far not convincing.[2] This increases the possibility that reversed causality or confounding may play a role. We will discuss the putative causal role of depression in CVD, in view of the evidence from the literature and the results presented in this thesis.

Depression causes CVD

The first evidence for a causal relation between depression and CVD **(Figure 1)** came from studies that showed that patients with coronary artery disease[3] or myocardial infarction (MI)[4] were more likely to be depressed. Moreover, these depressed patients had a worse prognosis and increased mortality compared to non-depressed patients, independent of left ventricular function.

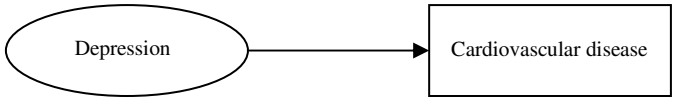

Figure 1

Since then discussion arose as to whether depression was not only a consequence of CVD, but could also be causally involved in the etiology and prognosis of CVD. A meta-analysis showed that in post-MI patients depression was associated with an increased risk of recurrence of cardiac events and cardiac mortality.[5] More recent studies showed that also in the general population, depression was associated with an increased risk of fatal and non-fatal CVD.[6,7] Two meta-analyses provided evidence that in middle-aged persons, major depressive disorder and depressive symptoms may be associated with an increased risk of incident fatal and non-fatal coronary heart disease, independent of CVD history or cardiovascular risk factors.[8,9] The combined risk was somewhat stronger for depressive

disorders (RR 2.69; 95% CI 1.63-4.43) than for depressive symptoms (RR 1.49; 95% CI 1.16-1.92). In addition, studies that excluded subjects with suspicious ECG findings or early cardiac events still showed a significant effect of depression on CVD risk (RR 1.51; 95% CI 1.03-2.20).[8] Depression was also associated with a higher risk of fatal and non-fatal stroke in middle-aged and elderly subjects.[10] In this thesis we were able to show a dose-response association between depressive symptoms and subsequent cardiovascular mortality in elderly men without symptomatic CVD or diabetes at baseline. Exclusion of subjects who died within the first five years of follow-up, and who were more likely to have had asymptomatic CVD, did not change the risk estimate of depressive symptoms for cardiovascular mortality.

Several mechanisms have been proposed to explain a causal relationship between depression and CVD. Indirectly, non-adherence to cardiac medication in depressed post-MI patients may worsen their prognosis.[11] In addition, an unfavourable lifestyle of depressed persons could increase their risk of CVD. For instance, depressed persons may become less physically active.[12] In patients with coronary artery disease the relation between depressive symptoms and mortality is to some extent explained by physical inactivity.[13] In this thesis we showed that depressive symptoms were inversely associated with physical activity in elderly men without symptomatic CVD or diabetes. However, in multivariable analyses the increased of depressive symptoms on cardiovascular mortality was not explained by variation in physical inactivity. Similarly, dietary factors were not likely to explain the relation between depression and cardiovascular mortality. We showed that a relatively high intake of the dietary n-3 fatty acids was associated with a lower risk of depressive symptoms, but this could not explain the association between depressive symptoms and cardiovascular mortality. Other lifestyle factors, such as smoking and alcohol consumption, also did not explain the association. These results agree with the literature where most studies showed that depression is associated with CVD, independent of social- and lifestyle factors.[9] Importantly, the results of this thesis do indicate that the combination of depressive symptoms and physical inactivity may lead to an excess risk of cardiovascular mortality. Although this finding should be confirmed by other studies, it suggests biological interaction between depressive symptoms and physical activity.

Direct mechanisms that have been proposed to explain the relationship between depression and CVD are dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis; inflammation; platelet reactivity; and autonomic dysfunction.[14] First, dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, with its elevated cortisol levels and often present in depression, promotes atherosclerosis through injury of vascular cells; hypertension; hypercholesterolemia; and inflammation.[14] So far, there is no evidence that dysregulation of the HPA-axis explains the assocation between depression and CVD. Recent cross-sectional studies showed that depression is associated with atherosclerosis in young men,[15] as well as in elderly persons.[16] However, this was not confirmed in a prospective study,[15] although in another study depression was associated with progression of

atherosclerosis.[17] In addition, it has been demonstrated that persons with recurrent major depressive disorder episodes have more atherosclerosis than persons with no or only one depressive episode.[18,19] A second mechanism that may explain the relation between depression and CVD is inflammation.[14] Inflammation is associated with depression as well as with CVD, but there is no evidence that inflammatory factors explain the relation between depression and CVD.[20] Third, increased platelet reactivity has been reported in depressed MI patients.[21] While trials on treatment of depression are inconclusive,[2] treatment with selective serotonin reuptake inhibitors (SSRIs) is associated with a slight reduction in cardiac mortality, possibly through inhibition of platelet reactivity.[22] A fourth mechanism that may link depression to CVD is autonomic dysfunction. In this thesis depression was associated with a higher resting heart rate, an indicator of autonomic dysfunction, which agrees with results from the literature.[23-26] One study in post-MI patients showed that heart rate variability explained part of the association between depression and mortality.[24] This was not confirmed by another study in post-MI patients, however.[26] Also, in our study among elderly men without prevalent CVD or diabetes, autonomic dysfunction, although crudely estimated, could not explain the relation between depressive symptoms and cardiovascular mortality.

CVD leads to depression

Depression was first recognized as a consequence of CVD **(Figure 2)** in the sixties of the last century, when a high prevalence of minor and major depression (20-30%) was observed in post- MI [27] and post-stroke[28] patients.

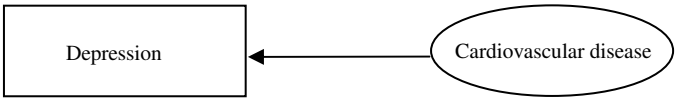

Figure 2

Not only was the prevalence of depression high in post-MI patients, depressed patients also had a worse prognosis compared to non-depressed patients, as described above. Thus far, trials have demonstrated that anti-depressive medication or cognitive therapy in post-MI patients may improve depressive symptoms, but it does not materially improve cardiovascular prognosis.[2] A slight reduction in mortality in depressed post-MI patients compared to placebo was only shown for SSRIs.[29] However, SSRIs may have direct

cardioprotective effects by inhibiting platelet activation, i.e. have beneficial effects beyond their antidepressant properties.[30]

It has been proposed that the increased prevalence of depression in post-MI patients is caused by hospitalization or occurs in response to the MI.[27] A recent study showed that the severity of depressive symptoms was associated with the severity of left ventricular dysfunction,[31] and a meta-analysis suggested that the effects of post-MI depression were at least partly related to the severity of the infarction.[5] Also, general health status explained part of the association between depression and CVD in patients with CAD.[32] Collectively, these findings suggest that depression is a consequence or marker of the severity of MI, and therefore predicts a poorer prognosis. Indeed, data from a population-based study in middle-aged subjects support the view that the association between depression and all-cause mortality may be explained by health status.[33] In another study that could not confirm an association between depression and the incidence of CHD in elderly men, the observed association in women could be explained by functional limitations.[34] Our results provide support to the view that, even in a population without prevalent CVD or diabetes, the relation between depressive symptoms and cardiovascular mortality may partly be explained by subjective health status. Still, although the magnitude attenuated after adjustment for health status, an independent risk of depressive symptoms for cardiovascular mortality remained.

Autonomic dysfunction could also be a marker of health status or subclinical disease. In this thesis depression was associated with an increased resting heart rate, which agrees with results from the literature.[23-26] Since these studies examined the association between depression and autonomic dysfunction cross-sectionally it is not clear whether autonomic dysfunction is a cause of depression, a consequence, or a marker of disease severity. In particular, in the elderly autonomic dysfunction is likely to be a marker of less favourable health.[35] Interestingly, preliminary results indicate that vagal nerve stimulation may reduce depressive symptoms in depressed patients, lending further support to the view that depression may be a consequence of autonomic dysfunction.[36]

Depression in stroke patients is quite common. Lesions in the left hemisphere, left frontal cortex and left basal ganglia have been associated with an increased risk of depression.[28] In addition, it has been shown that ischemic brain injury affects the content and metabolism of brain catecholamines.[28] The vascular depression hypothesis supports the view that depression is a consequence of cerebral vascular damage. Depression in later life could also be a marker of subclinical atherosclerosis and lesions in the brain.[37] The latter view is supported by cross-sectional studies on atherosclerosis, cerebral white matter lesion and depression.[16,38-41] Again, data are not fully consistent as one study did not find an association, either at baseline or during follow-up.[42] A case-control study could not disclose an association of depression with white-matter lesions although an association between depression and brain atrophy was observed.[43] In line with a role of cerebral ischemia in promoting the occurrence of depression, findings in patients with carotid artery disease suggest that carotid artery stent placement may reduce depressive symptoms.[44] In this thesis

we showed that depressive symptoms were more strongly associated with mortality from stroke than with mortality from coronary heart disease or other degenerative heart diseases in elderly men. While men with a history of stroke were excluded from these analyses, we were not able to exclude men with silent brain infarcts.[37] Depressive symptoms may have resulted from silent brain infarcts and therefore associated with an increased risk of mortality from stroke.

Depression as innocent bystander

Apart from a cause or a consequence of CVD, depression could also be an innocent bystander or epiphenomenon. **(Figure 3)** This is the case if a third factor causes both depression and CVD, and depression and CVD therefore coincide but do not result from a true association.

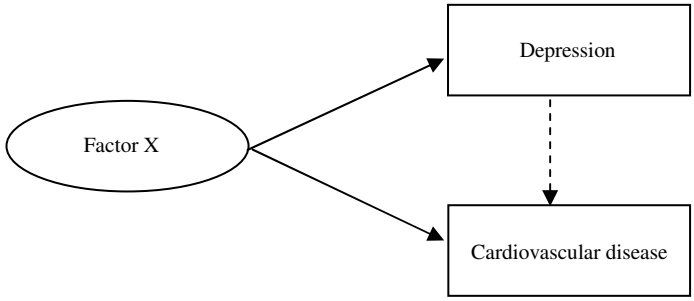

Figure 3

Physical inactivity may be such as third factor that causes both depression and CVD. Physical inactivity is thought to be involved in the development of CVD[45,46] and may also increase the risk of depression through separate mechanisms.[47] It has been shown that exercise may indeed decrease depressive symptoms in elderly women.[48] Moreover, a number of studies show that increase in physical activity reduces the risk of CVD.[49,50] However, in a number of studies, including ours, lack of physical activity could not explain the relation between depression and CVD.[13,51] As an alternative perspective, long chain n-3 fatty acids are thought to be involved in the etiology of depression as well as of CVD.[52,53] We could indeed demonstrate in our study that a relatively high intake of n-3 fatty acids was associated with a lower risk of depression as well as with a lower risk of CVD. Again, however, the intake of n-3 fatty acids could not explain the observed relation between depressive symptoms and cardiovascular mortality. In a more general sense, the increased

presence of classical cardiovascular risk factor such as high LDL cholesterol levels and high blood pressure in depressed persons may reflect similar underlying pathophysiology for depression and CVD.[54] In our research depression was not associated with total- and high density cholesterol levels and blood pressure and thus could not explain the increased cardiovascular risk.

Some of the biological mechanisms proposed to explain a causal relation between depression and CVD may also separately cause depression and CVD. While induction of the HPA-axis is shown in depressed persons as we described above, it is not clear whether dysregulation of the HPA-axis is a consequence or a cause of depression. If dysregulation of the HPA-axis is a consequence of depression, then it may link depression to CVD. However, if it is a cause of depression, then dysregulation of the HPA-axis caused by stress is a common cause of depression and CVD, and depression is the innocent bystander. Thus far animal studies have not been able to determine whether induction of the HPA-axis is a cause or a consequence of depression[55] and no results from prospective epidemiological studies have been reported. Inflammation is another mechanism that is associated with both depression and atherosclerosis. Although several cross-sectional studies showed an association between depression and inflammatory markers in patients with MI as well as in healthy subjects,[56-59] it is not clear whether depression is caused by inflammation or a whether it may promote inflammation.[60] Moreover, genetic vulnerability to inflammation may play a role in the etiology of depression as well as CVD.[61]

Conclusion

The available literature, combined with the results presented in this thesis, do not support the view that depression is a causal risk factor for CVD. Part of the association is due to health status, implying that depression may be a consequence of subclinical disease and the association thus reflects reversed causality. In our analyses, even after adjustment for health status, a significant association between depression and CVD remained. While the possibility remains that depression is a true risk factor for CVD, the remaining risk may also reflect residual confounding of health status, or result from a third underlying factor that causes both depression and CVD.

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Chapter 6

Summary
Samenvatting
Dankwoord
Curriculum-Vitae

Chapter 6

Summary
Samenvatting
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Curriculum-Vitae

In **chapter 1** we described the background and aim of the studies presented in this thesis. A Report from the World Health Organization showed that cardiovascular diseases (CVD) were the main causes of mortality world wide in 2002 and that they are also projected to stay the main causes of mortality till 2030. In addition, depression and CVD are both predicted to become main contributors of disability in 2030. Not only are depression and CVD highly prevalent and main contributors of disability, many studies have also shown that they are more closely related. The first evidence for a relation between depression and CVD came from studies that found an increased prevalence of depression in patients after myocardial infarction (MI) and stroke. In addition, these depressed patients had a worse prognosis compared to non-depressed patients. More recent studies suggested that depression may also increase the risk of CVD in subjects without prevalent CVD. This may indicate that depression is a causal risk factor of CVD. It is not clear which factors may explain the relation between depression and CVD. Indirectly an unhealthy diet or lifestyle in depressed persons may increase their risk of CVD. Also, biological mechanisms are proposed to explain the relation, such as dysregulation of the hypothalamic-pituitary-adrenocortical axis, autonomic dysfunction and inflammation.

The aim of this thesis was to investigate the relation between depression and CVD. We first investigated whether depressive symptoms were a risk factor of cardiovascular mortality in a sample of older European men. In addition, we investigated the role of diet, lifestyle, and health in the relationship between depressive symptoms and cardiovascular mortality. Finally, we discussed whether depression is a cause, consequence, or innocent bystander of CVD.

Data were used of the FINE (acronym for Finland, Italy and the Netherlands Elderly) Study, which is a prospective population-based cohort study on risk factors of CVD in elderly men. The FINE study started in 1984 among 2285 men born between 1900 and 1920. For this thesis we used data of the second round in 1989-1991, when depressive symptoms were measured for the first time. Fourteen- hundred and sixteen men with an average age of 77 participated in this second round. Depressive symptoms were measured with the Zung Self-rating Depression Scale (SDS). An index score was calculated (range of 25 to 100), with a higher score referring to more depressive symptoms. Mortality data were collected until the year 2000 and mortality from CVD was coded according to the International Classification of Diseases, ninth Revision (ICD-9: 390-459). For the studies described in this thesis we excluded men with prevalent CVD and diabetes at baseline.

In **chapter 2** we assessed the relation between depressive symptoms and 10-year cardiovascular mortality in 799 older European men. During ten years of follow-up 396 men died, of whom 224 died from CVD. The hazard ratio (HR) of cardiovascular mortality for a 5-point increase in depressive symptoms was 1.15 (95% CI 1.08-1.23), after adjusting for classical cardiovascular risk factors. This risk was stronger for mortality from stroke

(HR 1.35; 95% CI 1.19-1.53) and heart failure (HR 1.16; 95% CI 1.00-1.35) in comparison with mortality from coronary heart disease (HR 1.08; 95% CI 0.97-1.20) and other degenerative heart diseases (HR 1.06; 95% CI 0.91-1.23). Exclusion of men who died from cardiovascular diseases within five years after baseline did not change the strength of the associations. There were no significant differences in hazard ratios between Finland, Italy and the Netherlands. We concluded that these results provided further and more convincing prospective evidence for depressive symptoms as a risk factor for cardiovascular mortality in elderly men.

Chapter 3 described the role of dietary and lifestyle factors in the relationship between depression and CVD.

In **chapter 3.1** we investigated whether a low dietary intake of B-vitamins and high levels of serum homocysteine were associated with depressive symptoms in 332 men aged 70-90 years of the Dutch cohort of the FINE study (the Zutphen Elderly Study). Dietary intake of folate (-1.19; 95% CI -2.03 to -0.36) and vitamin B6 (-2.10; 95% CI -2.92 to -1.27) per standard deviation increase were inversely associated with levels of serum homocysteine, while vitamin B12 was not. Intake of folate, vitamin B6, vitamin B12 and levels of serum homocysteine were not associated with depressive symptoms. These results do not support the hypothesis that a low dietary intake of B-vitamins and high levels of serum homocysteine are related to depression in elderly men without CVD or diabetes. Therefore, a low dietary intake of B-vitamins and high levels of serum homocysteine cannot explain for the relation between depression and CVD.

In **chapter 3.2** the role of omega (n)-3 fatty acids (FAs) in the relationship of depressive symptoms with cardiovascular mortality was investigated in 332 elderly men from Zutphen. During ten years of follow-up 170 men died, of whom 92 died from CVD. Compared to a low intake (mean: 21 mg/d), a high intake (mean: 407 mg/d) of n-3 FAs was associated with fewer depressive symptoms (OR 0.46; 95% CI 0.22-0.95) at baseline, and with a non-significant reduced risk of 10-year cardiovascular mortality (HR 0.88; 95% CI 0.51-1.50). The adjusted HR for cardiovascular mortality associated with an increase in depressive symptoms with one standard deviation (10 points) was 1.28 (95% CI 1.03-1.57). This risk did not change after additional adjustment for the intake of n-3 FAs. We concluded that an average intake of about 400 mg n-3 FAs per day may be associated with a lower risk of depression. These results, however, do not support the hypothesis that the intake of n-3 FAs explains the relationship between depression and CVD.

In **chapter 3.3** we analyzed the relation between depressive symptoms, physical inactivity and cardiovascular mortality in 909 elderly men from Europe. At baseline men with more depressive symptoms were less physically active (722 min/wk; 95% CI 642-802) than men with fewer depressive symptoms (919 min/wk; 95% CI 823-1015). A decrease in physical activity with 30 minutes per day was associated with a 9% higher cardiovascular

mortality risk (HR 1.09; 95% CI 1.04-1.14). An increase in depressive symptoms with one standard deviation was associated with a 42% higher cardiovascular mortality risk (HR 1.42; 95% CI 1.26-1.60). After additional adjustment for physical inactivity the risk decreased with 9%, but an independent risk remained (HR 1.37; 95% CI 1.21-1.56). The excess risk on cardiovascular mortality attributable to the combined effect of depressive symptoms with inactivity was 47% (1.47; 95% CI -0.17 to 3.11). We concluded that the increased risk of depressive symptoms on cardiovascular mortality could not be explained by physical inactivity. However, the results indicate that depressive symptoms and physical inactivity may interact to increase the risk of cardiovascular mortality.

Chapter 4 described the role of health status in the relationship between depression and CVD.

In **chapter 4.1** we investigated whether indicators of autonomic dysfunction could explain the relationship between depressive symptoms and cardiovascular mortality in 870 elderly men without CVD, diabetes, or atrial fibrillation from Europe. At baseline, men in the high tertile of depressive symptoms had an increased mean resting heart rate (72.0 beats/min; 95% CI 70.5-73.5) compared to men in the low tertile of depressive symptoms (69.4 beats/min; 95% CI 68.0-70.9), but depressive symptoms were not significantly associated with heart rate variability or prolonged QTc-interval. Prospectively, an increase in resting heart rate with one standard deviation was associated with an increased risk of cardiovascular mortality (HR 1.22; 95% CI 1.08-1.38). In addition, low heart rate variability (HR 0.78; 95% CI 0.61-1.01) and prolonged QTc-interval (HR 1.28; 95% CI 1.06-1.53) were associated with cardiovascular mortality. The increased risk of depressive symptoms for cardiovascular mortality (HR 1.38; 95% CI 1.121-1.58) could, however, not be explained by indicators of autonomic dysfunction.

In **chapter 4.2** we investigated to what extent subjective health status explained the association between depressive symptoms and cardiovascular mortality in 909 elderly men from Europe. Subjective health status was determined as self-rated health and as self-reported disability in activities of daily living. At baseline, poor self-rated health and more disability in activities of daily living were associated with more depressive symptoms using multiple linear regression analysis. Prospectively, men who reported to be unhealthy and men with more disabilities had an approximately 2.5 times higher risk of cardiovascular mortality using Cox regression analysis. An increase in depressive symptoms by one standard deviation was associated with an increased risk of cardiovascular mortality (HR 1.37; 95% CI 1.21-1.56). A substantial part of this association was explained by poor self-rated health and disability (proportion explained 0.32; 95% CI 0.09-0.55). However, a significant risk of depressive symptoms on cardiovascular mortality remained (HR 1.25; 95% CI 1.09-1.43) after adjustment for subjective health status.

In **chapter 5** we discussed whether depression is a cause, consequence, or innocent bystander of CVD. We concluded that the available literature combined with the results presented in this thesis do not support the view that depression is a causal risk factor for CVD. Part of the association is due to health status, implying that depression may be a consequence of subclinical disease and the association thus reflects reversed causality. In our analyses, even after adjustment for health status, a significant association between depression and CVD remained. While the possibility remains that depression is a true risk factor for CVD, the remaining risk may also reflect residual confounding of health status, or result from a third underlying factor that causes both depression and CVD.

Chapter 6

Summary
Samenvatting
Dankwoord
Curriculum-Vitae

In **hoofdstuk 1** hebben we het belang en het doel van het onderzoek in dit proefschrift beschreven. Wereldwijd vormen hart- en vaatziekten (HVZ) de belangrijkste oorzaak van sterfte. Volgens berekeningen van de Wereldgezondheidsorganisatie zullen HVZ in 2030 nog steeds de belangrijkste oorzaak van sterfte zijn en zullen zij ook een belangrijke oorzaak zijn van beperkingen in het dagelijks functioneren. Tevens heeft de Wereldgezondheidsorganisatie berekend dat depressie wereldwijd, na HIV/ AIDS, de belangrijkste oorzaak zal zijn van beperkingen in het dagelijks functioneren.

Uit wetenschappelijk onderzoek blijkt dat depressie en HVZ niet alleen vaak voorkomen en ernstige aandoeningen zijn, maar ook dat ze aan elkaar gerelateerd zijn. Het eerste bewijs voor een directe relatie tussen depressie en HVZ kwam van onderzoek dat aantoonde dat patiënten die een hartinfarct of een beroerte hadden doorgemaakt, vaker depressief waren in vergelijking met de algemene bevolking. Daarnaast bleken deze depressieve patiënten een hogere kans op herhaling van een hartinfarct of beroerte te hebben en eerder te overlijden, in vergelijking met patiënten die niet depressief waren na een hartinfarct of beroerte. Recent onderzoek laat zien dat ook bij gezonde personen zonder HVZ, depressie geassocieerd is met een verhoogd risico op het ontwikkelen van HVZ. Dit duidt er op dat depressie mogelijk een oorzaak zou kunnen zijn voor het ontstaan van HVZ. Het is echter nog onduidelijk via welke mechanismen depressie zou kunnen leiden tot HVZ. Indirect kan ongezonde leefstijl en voeding in depressieve personen het risico op HVZ verhogen, maar ook biologische factoren zoals, disfunctie van het autonome zenuwstelsel en activatie van ontstekingseiwitten zouden de relatie tussen depressie en HVZ kunnen verklaren.

Het doel van dit proefschrift was om de relatie tussen depressie en HVZ te bestuderen. In dit proefschrift hebben we eerst onderzocht of depressieve symptomen verband hielden met sterfte aan HVZ bij gezonde oudere mannen in Europa. Daarnaast onderzochten we wat de rol van leefstijl, voedingsfactoren en gezondheidstoestand was in de relatie tussen depressie en HVZ. Tot slot hebben we bediscussieerd in hoeverre depressie een oorzaak, een gevolg, of een epifenomeen (bijverschijnsel) is van HVZ.

Voor dit onderzoek hebben we gebruik gemaakt van gegevens uit de ‘Finland, Italy, and the Netherlands Elderly (FINE) Study’. Dit is een internationaal prospectief cohortonderzoek gestart in 1984, bij 2285 mannen die geboren waren tussen 1900 en 1920 en afkomstig zijn uit Finland, Italië en Nederland. Voor dit proefschrift hebben we gebruik gemaakt van gegevens die verzameld zijn tijdens de tweede onderzoeksronde van de FINE Studie tussen 1989 en 1991, omdat tijdens deze ronde voor de eerste keer gegevens over depressie zijn verzameld met behulp van de Zung depressie vragenlijst. Aan de hand van deze vragenlijst werd een depressie schaal berekend met een score van 25 tot 100 punten, waarbij een hogere score duidt op meer depressieve symptomen. Aan deze tweede ronde deden 1416 mannen mee met een gemiddelde leeftijd van 77 jaar. Zij zijn gevolgd tot en met het jaar 2000 en er is bijgehouden wie er in die periode overleed aan HVZ. Voor het onderzoek beschreven in dit proefschrift hebben we alleen gebruik gemaakt van de

gegevens van de mannen die aan het begin van het onderzoek nog geen HVZ en geen diabetes hadden.

In **hoofdstuk 2** hebben we gekeken naar de relatie tussen depressieve symptomen en de kans op sterfte aan HVZ bij 799 oudere mannen uit Europa. Na 10 jaar waren 396 mannen overleden, van wie 224 aan HVZ. Per 5 punten op de depressie schaal nam het risico om te overlijden aan HVZ met 15% toe, onafhankelijk van klassieke risicofactoren van HVZ zoals roken, serum cholesterol en hoge bloeddruk. Dit risico was hoger voor sterfte aan een beroerte (35% hoger risico) en hartfalen (16% hoger risico) in vergelijking met sterfte aan hartinfarcten (8% hoger risico) en overige hartziekten (6% hoger risico). Om de mogelijkheid uit te sluiten dat de mannen met depressieve symptomen aan het begin van het onderzoek minder gezond waren, hebben we de analyses herhaald zonder de mannen die gedurende de eerst vijf jaar na het begin van het onderzoek zijn overleden aan HVZ. Dit veranderde echter niets aan de risico's. Er waren eveneens geen statistisch significante verschillen in sterftekans op HVZ door depressieve symptomen tussen Finland, Italië en Nederland. Deze resultaten ondersteunen de hypothese dat depressie een oorzaak kan zijn van HVZ.

Hoofdstuk 3 beschrijft de rol van voedings- en leefstijlfactoren in de relatie tussen depressie en HVZ.

In **hoofstuk 3.1** hebben we onderzocht of lage inname van verschillende B-vitamines in de voeding en hoge niveaus van homocysteïne (een metaboliet van het essentiele aminozuur methionine in het bloed) gerelateerd waren aan depressieve symptomen bij 332 mannen van 70-90 jaar uit het Nederlandse cohort (Zutphen) van de FINE Studie. De inname van B-vitamines is berekend uit het voedingspatroon. Groene groenten en fruit zijn belangrijke bronnen van vitamine B11 (folaat), vitamine B6 en B12 zitten vooral in vlees en vis. Een hogere inname van vitamine B11 en B6 waren beide gerelateerd aan lagere niveaus van homocysteïne in het bloed. Er was geen samenhang tussen de inname van vitamine B12 en het niveau van homocysteïne. De inname van vitamine B11, B6 en B12 alsmede het niveau van homocysteïne in het bloed hielden geen verband met het hebben van depressieve symptomen. Deze resultaten ondersteunen niet de hypothese dat een lage inname van B vitamines in de voeding en een hoog niveau van homocysteïne in het bloed, de kans op depressie kunnen verhogen. Het is dan ook niet waarschijnlijk dat B vitamines en homocysteïne de relatie tussen depressie en HVZ verklaren.

Hoofdstuk 3.2 beschrijft de rol van omega(n)-3 vetzuren, die met name afkomstig zijn uit vette vis zoals zalm en haring, in de relatie tussen depressieve symptomen en sterfte aan HVZ, eveneens bij 332 oudere mannen uit Zutphen. Na 10 jaar waren 170 mannen overleden, van wie 92 aan HVZ. Aan het begin van het onderzoek hadden mannen met een

hoge inname van n-3 vetzuren (gemiddeld 407 milligram per dag) een 54% lagere kans op het hebben van depressieve symptomen in vergelijking met mannen die een lage inname van n-3 vetzuren hadden (gemiddeld 21 milligram per dag). Daarnaast hadden mannen met een hoge inname van n-3 vetzuren aan het begin van het onderzoek een 12% lager risico om te overlijden aan HVZ in vergelijking met mannen met een lage inname. Per 10 punten op de depressie schaal nam het risico om te overlijden aan HVZ met 28% toe. Dit risico kon niet verklaard worden door inname van n-3 vetzuren in de voeding. Uit deze resultaten concludeerden we dat een inname van gemiddeld 400 mg n-3 vetzuren per dag mogelijk de kans op depressieve symptomen kan verlagen. Het verhoogde risico om te overlijden aan HVZ bij mannen met meer depressieve symptomen kon echter niet worden verklaard door een lagere inname van n-3 vetzuren.

In **hoofdstuk 3.3** hebben we gekeken naar depressieve symptomen, lichamelijke inactiviteit, en de kans op sterfte aan HVZ bij 909 oudere mannen uit Europa. Aan het begin van het onderzoek waren mannen met veel depressieve symptomen minder lichamelijk actief (gemiddeld 722 minuten per week) dan mannen met weinig depressieve symptomen (gemiddeld 919 minuten per week). Voor een verminderde lichamelijke activiteit met 30 minuten per dag nam het risico om te overlijden aan HVZ met 9% toe. Per 10 punten op de depressie schaal nam het risico om te overlijden aan HVZ met 42% toe. Dit risico kon niet verklaard worden door lichamelijke inactiviteit (overgebleven risico 38%). De combinatie van veel depressieve symptomen en weinig lichamelijke activiteit resulteerde in een extra hoge kans op sterfte aan HVZ. Hieruit concludeerden we dat de verhoogde kans om te overlijden aan HVZ bij mannen met meer depressieve symptomen kon niet worden verklaard, doordat deze mannen minder lichamelijk actief waren. Echter, de combinatie van beide factoren kan wel leiden tot een extra hoge kans op sterfte aan HVZ.

Hoofdstuk 4 beschrijft de invloed van gezondheidstoestand in de relatie tussen depressie en HVZ.

In **hoofdstuk 4.1** hebben we bij 870 oudere mannen uit Europa onderzocht of indicatoren van disfunctie van het autonome zenuwstelsel (dat deel van het zenuwstelsel dat buiten de wil om organen verzorgt) de relatie tussen depressieve symptomen en sterfte aan HVZ konden verklaren. Indicatoren van disfunctie van het autonome zenuwstelsel zijn een hoge hartslag, een lage hartritmevariabiliteit en een lang QTc-interval (afgeleid uit een hartfilm). Mannen met depressieve symptomen hadden een hogere hartslag, een (niet statistisch significant) lagere hartritmevariabiliteit en een (niet statistisch significant) langer QTc-interval aan het begin van het onderzoek. Daarnaast hadden mannen met een hogere hartslag, een lagere hartritme variabiliteit of een langer QTc-interval een grotere kans om te overlijden aan HVZ. Echter, het hoge risico om te overlijden aan HVZ bij mannen met

meer depressieve symptomen (38% hoger) kon niet worden verklaard, doordat zij een slechtere functie van het autonome zenuwstelsel hadden.

In **hoofdstuk 4.2** is voor 909 oudere mannen uit Europa beschreven of subjectieve gezondheid de relatie tussen depressieve symptomen en sterfte aan HVZ kon verklaren. Subjectieve gezondheid werd bepaald door middel van één vraag over zelfgerapporteerde gezondheid (Hoe beoordeelt u uw eigen gezondheid?), en door middel van zelfgerapporteerde beperkingen tijdens dagelijkse activiteiten. Mannen die hun eigen gezondheid als matig of slecht rapporteerden en mannen met milde of ernstige beperkingen tijdens hun dagelijks activiteiten hadden meer depressieve symptomen aan het begin van het onderzoek in vergelijking met mannen die hun gezondheid als goed beoordeelden of geen beperkingen hadden. Tevens hadden deze mannen een 2.5 keer hoger risico om aan HVZ te overlijden. Het verhoogde risico om aan HVZ te overlijden bij depressieve mannen kon voor één derde deel verklaard worden door een slechtere zelfgerapporteerde gezondheid en beperkingen tijdens dagelijkse activiteiten, maar er bleef een onafhankelijk risico om te overlijden aan HVZ bij mannen met depressieve symptomen bestaan (25% hoger risico). Deze resultaten gaven aan dat het hogere risico om te overlijden aan HVZ bij mannen met depressieve symptomen voor een deel verklaard kon worden door subjectieve gezondheidstoestand. Er resteerde echter een verhoogd risico van depressieve symptomen op HVZ, onafhankelijk van subjectieve gezondheidstoestand.

In **hoofdstuk 5** hebben we aan de hand van onze onderzoeksresultaten en de beschikbare literatuur bediscussieerd in hoeverre depressie een oorzaak, een gevolg, of een epifenomeen is van HVZ. We concluderen dat het niet waarschijnlijk is dat depressie een oorzaak is van HVZ. Het verhoogde risico kan gedeeltelijk worden verklaard door een slechtere subjectieve gezondheidstoestand. Hoewel het overgebleven risico op HVZ nog zou kunnen duiden op een oorzakelijk verband, is het ook mogelijk dat dit alsnog een slechtere (ongemeten) gezondheidstoestand weerspiegelt, of dat een derde (onbekende) factor zowel tot depressie als HVZ leidt, wat zou betekenen dat depressie een epifenomeen is van HVZ.

Chapter 6

Summary
Samenvatting
Dankwoord
Curriculum-Vitae

Tja, en dan is het zover, het proefschrift is (bijna) af, maar dat was zeker niet gelukt zonder de hulp van een aantal personen, daarom maak ik graag gebruik van deze gelegenheid om degene te bedanken, aan wie dit proefschrift mede is te danken.

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Chapter 6

Summary
Samenvatting
Dankwoord
Curriculum-Vitae

Marjolein Hendrikje Kamphuis was born on June 4th, 1981 in Hengelo (O), the Netherlands. In 1999, after graduating secondary school at the Thijcollege in Oldenzaal, she started her training in Biomedical Health Sciences at the Catholic University of Nijmegen, the Netherlands. As part of this traineeship two research projects were conducted. Her first project for a major in toxicology was conducted at the department of Experimental Urology of the University Medical Center Nijmegen (supervisor: dr.ir. GW Verhaegh), on modulation of cell adhesion complexes in the progression of cancer. The second project for her major in epidemiology was performed at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (supervisor: dr.ir. YT van der Schouw), concerning the relation between elevated body iron levels and cardiovascular diseases. In August 2003 she obtained her Master of Science degree in Biomedical Health Sciences and in September 2003 she started the work described in this thesis at the Julius Center for Health Sciences and Primary Care (supervisors dr. S Kalmijn, dr. MI Geerlings and prof.dr. DE Grobbee), which was conducted in cooperation with the National Institute of Public Health and Environment, the RIVM in Bilthoven and the division of Human Nutrition, Wageningen University (supervisors dr. MAR Tijhuis and prof.dr.ir. D Kromhout). She attended the World Heart Federation 37th Ten Day Teaching Seminar in Cardiovascular Disease Epidemiology and Prevention, Beijing, China August 29 - September 10 2004 and obtained her Master of Science in Epidemiology at the Netherlands Institute of Health Sciences, Erasmus University Rotterdam in June 2005. As of in September 2006 she started with the Selective Utrecht Medical Master (SUMMA) in Utrecht and continued to work as a researcher at the Julius Center for Health Sciences and Primary Care.