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With Reference to Awareness of Hypertension, Self-Rated Health, Cardiovascular Morbidity, and All-Cause Mortality

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To the memory of Eeva, Kauko, Raili, and Uolevi

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ABSTRACT

Depressive symptoms are psychological risk factors for cardiovascular disease. They seem to independently predict cardiovascular disease incidence and all-cause mortality, but it is not yet determined whether a specific subtype of depressive symptoms is especially accountable for the risk increase.

This study aimed to investigate depressive symptoms – combined and divided into melancholic and non-melancholic subtypes – in a middle-aged cardiovascular risk population; specifically, their association with hypertension awareness, self-rated health, cardiovascular morbidity, and all-cause mortality.

A population-based sample of middle-aged cardiovascular risk persons (n = 2676) was drawn from the Harjavalta Risk Monitoring for Cardiovascular Disease Project. At baseline, the health and lifestyle habits of the subjects were comprehensively assessed, including depressive symptoms with Beck's Depression Inventory. Data on cardiovascular morbidity and all-cause mortality were register-based.

At baseline, the prevalence of increased melancholic and non-melancholic depressive symptoms was 5 % and 15 %, respectively. Predictors of depressive symptoms were female gender, obesity, harmful alcohol use, smoking, low leisure-time physical activity, awareness of hypertension, and poor self-rated health. Among those with poor self-rated health, increased depressive symptoms modified their perception of physical health. Increased non-melancholic depressive symptoms increased risk for cardiovascular morbidity and all-cause mortality compared to not having increased depressive symptoms even in adjusted models.

In conclusion, increased depressive symptoms are prevalent among middle-aged cardiovascular risk subjects. They are associated with many traditional cardiovascular risk factors and poor self-rated health. Thus, assessing self-rated health might be a practical tool in cardiovascular risk management. Specifically, non-melancholic depressive symptoms influence risk persons' prognosis, and recognition of these symptoms should be emphasised.

KEYWORDS: Beck's Depression Inventory, cardiovascular disease, depressive symptoms, melancholic, non-melancholic

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Yleislääketiede
ANSA RANTANEN: Depressiiviset oireet sydän- ja verisuonitautiriskiväestössä käsitellen tietoisuutta verenpainetaudista, itse koettua terveyttä, sydän- ja verisuonitautisairastuvuutta ja kokonaiskuolleisuutta
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TIIVISTELMÄ

Depressiiviset oireet ovat sydän- ja verisuonitautien psyykkisiä riskitekijöitä. Ne näyttävät ennustavan itsenäisesti sydän- ja verisuonitautien ilmaantuvuutta ja kokonaiskuolleisuutta, mutta ei ole selvää, aiheuttaako riskin lisääntymisen erityisesti tietty depressiivisten oireiden alatyyppi.

Tämän tutkimuksen tavoitteena oli selvittää depressiivisten oireiden – kokonaisuutena ja jaettuna melankoliseen ja ei-melankoliseen alatyyppiin – yhteyttä tietoisuuteen verenpainetaudista, itse koettuun terveyteen, sydän- ja verisuonitautien ilmaantuvuuteen ja kokonaiskuolleisuuteen sydän- ja verisuonitautiriskiväestössä.

Väestöpohjainen otos keski-ikäisiä riskihenkilöitä (n = 2676) kerättiin Harjavallan valtimotautien ehkäisyprojektista. Lähtötilanteessa tutkittavien terveyttä ja elintapoja selvitettiin kattavasti. Depressiiviset oireet kartoitettiin Beckin depressioseulalla. Sydän- ja verisuonitautisairastuvuus- ja kokonaiskuolleisuustiedot kerättiin rekistereistä.

Lähtötilanteessa 5 %:lla tutkituista oli lisääntyneitä melankolisia ja 15 %:lla ei-melankolisia depressiivisiä oireita. Depressiivisiä oireita ennustavia tekijöitä olivat naissukupuoli, lihavuus, haitallinen alkoholin käyttö, tupakointi, vähäinen vapaa-ajan fyysinen aktiivisuus, tietoisuus verenpainetaudista ja huono itse koettu terveys. Depressiiviset oireet muovasivat terveytensä huonoksi kokevien käsitystä heidän fyysisestä terveydestään. Lisääntyneet ei-melankoliset depressiiviset oireet lisäsivät sydän- ja verisuonitautisairastuvuutta ja kokonaiskuolleisuutta ei-depressiivisyyteen verrattuna myös vakioiduissa malleissa.

Lisääntyneet depressiiviset oireet ovat yleisiä keski-ikäisillä sydän- ja verisuonitautiriskihenkilöillä. Ne ovat yhteydessä moniin perinteisiin sydän- ja verisuonitautien riskitekijöihin ja huonoon itse koettuun terveyteen, joten itsekoetun terveyden määrittäminen voisi olla käytännöllinen työkalu sydän- ja verisuonitautiriskien hoidossa. Erityisesti ei-melankoliset depressiiviset oireet vaikuttavat riskihenkilöiden ennusteeseen, ja niiden tunnistamiseen tulisi kiinnittää huomiota.

AVAINSANAT: Beckin depressioseula, depressiiviset oireet, ei-melankolinen, melankolinen, sydän- ja verisuonisairaudet

Table of Contents

Abbreviations

AUDIT	Alcohol Use Disorders Identification Test
BDI	Beck's Depression Inventory
BMI	Body mass index
BP	Blood pressure
CeVD	Cerebrovascular disease
CI	Confidence interval
CVD	Cardiovascular disease
DSM	Diagnostic and Statistical Manual for Mental Disorders
FINDRISC	Finnish Diabetes Risk Score
HDL-C	High-density lipoprotein cholesterol
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHD	Ischemic heart disease
IRR	Incidence rate ratio
LDL-C	Low-density lipoprotein cholesterol
LTPA	Leisure-time physical activity
MDD	Major depressive disorder
MeD	Melancholic depressive symptoms
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NESDA	Netherlands Study of Depression and Anxiety
NMeD	Non-melancholic depressive symptoms
OR	Odds ratio
PA	Physical activity
PAD	Peripheral artery disease
PAR	Population attributable risk
RR	Risk ratio
SBP	Systolic blood pressure

SCORE	Systematic Coronary Risk Evaluation
SD	Standard deviation
SF-36	Short-Form Health Survey
SMR	Standardized mortality rate
SRH	Self-rated health
T2D	Type 2 diabetes
UK	United Kingdom
US	United States

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Rantanen, A. T., Korkeila, J. J. A., Löyttyniemi, E. S., Saxén, U. K. M., & Korhonen, P. E. (2018). Awareness of hypertension and depressive symptoms: A cross-sectional study in a primary care population. *Scandinavian Journal of Primary Health Care*, *36*(3), 323–328. https://doi.org/10.1080/ 02813432.2018.1499588

II Rantanen, A. T., Korkeila, J. J. A., Kautiainen, H., & Korhonen, P. E. (2019). Poor or fair self-rated health is associated with depressive symptoms and impaired perceived physical health: A cross-sectional study in a primary care population at risk for type 2 diabetes and cardiovascular disease. *European Journal of General Practice*, *25*(3), 143–148. https://doi.org/10.1080/ 13814788.2019.1635114

III Rantanen, A. T., Korkeila, J. J. A., Kautiainen, H., & Korhonen, P. E. (2020). Non-melancholic depressive symptoms increase risk for incident cardiovascular disease: A prospective study in a primary care population at risk for cardiovascular disease and type 2 diabetes. *Journal of Psychosomatic Research*, *129*, 109887. https://doi.org/10.1016/j.jpsychores.2019.109887

IV Rantanen, A. T., Kallio, M. M., Korkeila, J. J. A., Kautiainen, H., & Korhonen P. E. (2020). Relationship of non-melancholic and melancholic depressive symptoms with all-cause mortality: A prospective study in a primary care population. *Submitted.*

1 Introduction

Major depressive disorder (MDD) and cardiovascular disease (CVD) are major health issues, being the global leading causes of lost health (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; World Health Organization, 2018b, 2018a). Furthermore, these diseases are interconnected: not only are depressive symptoms and MDD associated with many traditional CVD risk factors (Boden & Fergusson, 2011; Luger et al., 2014; Mannan et al., 2016; Meng et al., 2012; Schuch et al., 2017; Yu et al., 2015), but also depressive symptoms and CVD are suggested to be independent risk factors for one another (Wium-Andersen et al., 2019), while depressive symptoms and MDD are also associated with poorer prognosis in established CVD (Meijer et al., 2011; Nicholson et al., 2006). Another psychological risk factor for CVD is poor perception of one's general health, self-rated health (SRH). This easily administered measure has been associated with increased CVD morbidity (van der Linde et al., 2013; Waller et al., 2015) and CVD mortality (Bamia et al., 2017; Mavaddat et al., 2014). Moreover, SRH may be associated with depressive symptoms (Chang-Quan et al., 2010). In addition, both depressive symptoms and poor SRH have been associated with excess all-cause mortality risk (Bamia et al., 2017; DeSalvo et al., 2005; Walker et al., 2015).

However, evidence on these associations is not consistent. Specifically, it is unclear whether the major CVD risk factor elevated blood pressure *per se* associates with depressive symptoms. In addition, both mental and physical health can contribute to SRH, and their interaction among CVD risk persons is unclear. Furthermore, it is still uncertain whether there is a specific subtype of depressive symptoms that especially associates with CVD and mortality, as subtyping of depressive symptoms has rarely occurred when studying these associations despite of recommendations to do so (Baumeister & Parker, 2012; Baune et al., 2012; Penninx, 2017).

A straightforward classification of depressive symptoms is their division into melancholic and atypical subtypes (Penninx et al., 2013). These subtypes may be attributed to different biological mechanisms, and thus relate differently to somatic diseases. They differ especially in terms of neurovegetative symptoms and mood reactivity. Melancholic depressive symptoms include insomnia, loss of weight and

appetite, and diminished reactivity to affect and mood, whereas hypersomnia, increased appetite and weight gain, and mood reactivity are atypical depressive symptoms (American Psychiatric Association, 2013; Parker et al., 2010).

This thesis was conducted to clarify the abovementioned unanswered questions. The aim was to investigate depressive symptoms among CVD risk subjects in a primary care population: specifically, the association of these symptoms with hypertension awareness and SRH; and the association of melancholic and non-melancholic (including atypical) depressive symptoms with CVD morbidity, and finally, all-cause mortality.

2 Review of the Literature

2.1 Overview of Depressive Symptoms

Depressive symptoms refer to a wide range of affective, cognitive, and even somatic symptoms. They include, for example, depressed mood, loss of interest or pleasure, diminished ability to think or concentrate, ideas of worthlessness or excessive guilt, reduced self-esteem and self-confidence, fatigue or loss of energy, psychomotor changes, and changes in appetite, weight, and sleeping (American Psychiatric Association, 2013; World Health Organization, 2016). These symptoms constitute the base for a clinical diagnosis of major depressive disorder (MDD), for which a combination of these symptoms has to be present for at least a two-week period. At least four symptoms including a minimum of two of the core symptoms (depressed mood, loss of interest or pleasure, loss of energy) are required when diagnosing MDD according to the International Statistical Classification of Diseases and Related Health Problems (ICD) (World Health Organization, 2016). The Diagnostic and Statistical Manual for Mental Disorders (DSM) (American Psychiatric Association, 2013) suggests that at least five symptoms including a core symptom (either depressed mood or anhedonia) have to be present. Defining MDD according to the DSM, Fifth Edition (DSM-5) is illustrated in Figure 1 (Malhi & Mann, 2018).

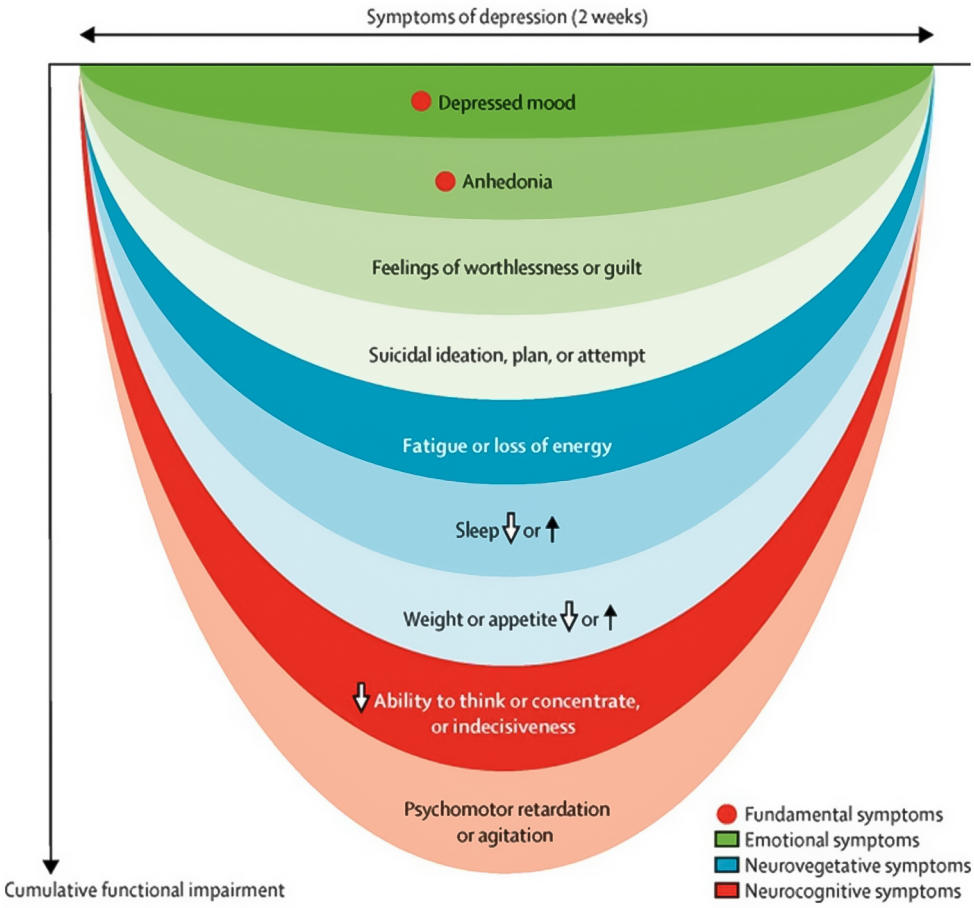

Figure 1. Defining major depressive disorder. Reprinted from Malhi & Mann (2018) with permission from Elsevier. Copyright © 2018 Elsevier Ltd.

However, MDD is a heterogeneous syndrome regarding, for example, its characteristic symptoms, onset, severity, and course of illness (Rush, 2007). An analysis of data from the Sequenced Treatment Alternatives to Relieve Depression study revealed over one thousand unique symptom profiles among 3700 depressed subjects (Fried & Nesse, 2015). In addition, not only MDD, but also presence of fewer depressive symptoms might have an impact on quality of life and cause a decrement in health status (Rodríguez et al., 2012). Accordingly, it has been proposed to consider depression as a spectrum of symptoms with different levels of severity, intensity, and activity; ranging from a subthreshold stage to major depression (Juruena, 2012; Rodríguez et al., 2012). These subthreshold stages of depression (referring to depressive states where criteria for MDD are not met) are also acknowledged in diagnostic classifications; including, for example, diagnosis

of minor depression in the DSM (two to four depressive symptoms including at least one core symptom) (American Psychiatric Association, 2013), and dysthymia and other mood disorders in the ICD (World Health Organization, 2016).

Moreover, in a World Health Study, subthreshold depressive symptoms have been found to have a similar effect on health status as major depression, at least when one of the core symptoms of depression is present (Ayuso-Mateos et al., 2010) (Figure 2).

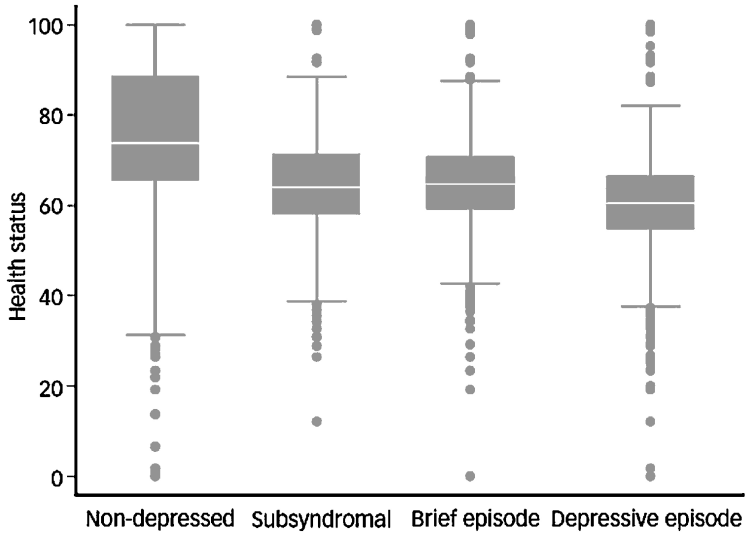

Figure 2. Mean health score estimates of respondents according to group. The measure of health status is based on 16 questions pertaining to difficulties in functioning in eight health domains (vision, mobility, self-care, cognition, interpersonal activities, pain and discomfort, sleep and energy affect), and it ranges from 0 (worse) to 100 (best health). Non-depressed: not fulfilling symptomatic, duration, or persistence criteria for depressive disorders; subsyndromal: at least one core depressive symptom (depressed mood, loss of interest, fatigability); brief episode: duration criteria of depressive disorder not met; depressive episode: at least four depressive symptoms lasting 2 weeks at least most of the day, at least two of the three core symptoms present. Reproduced from Ayuso-Mateos et al. (2010) with permission from Cambridge University Press. Copyright © 2010 Royal College of Psychiatrists.

2.1.1 Subtypes of Depressive Symptoms

Due to the heterogeneity of MDD, it has been proposed that subtyping depression would be useful (Baumeister & Parker, 2012; Malhi & Mann, 2018). Four symptom-based subtypes of MDD have often been acknowledged: melancholic, atypical, psychotic, and anxious (Baumeister & Parker, 2012; Rush, 2007). However, it has been suggested that the latter does not have sufficient specificity (Baumeister &

Parker, 2012). These subtypes are also acknowledged in the DSM-5 as specifiers for a major depressive episode (American Psychiatric Association, 2013). The characteristics of melancholic and atypical depressive subtypes are presented in Table 1.

Table 1. Features of melancholic and atypical major depressive disorder according to the DSM-5 (American Psychiatric Association, 2013).

WITH MELANCHOLIC FEATURES*	WITH ATYPICAL FEATURES**
anhedonia	mood reactivity
diminished reactivity to affect and mood	interpersonal rejection sensitivity
a pervasive and distinct quality of depressed mood that is worse in the morning	hypersomnia
guilt	fatigue
psychomotor disturbance	increased appetite
insomnia	weight gain
loss of weight	
loss of appetite	

*Anhedonia and/or diminished reactivity to affect and mood, and at least three of the following symptoms have to be present for a clinical diagnosis of melancholic depression.
**Mood reactivity and at least two of the following symptoms have to be present for a clinical diagnosis of atypical depression.

It has been proposed that MDD can be dichotomized into melancholic and non-melancholic depression (Leventhal & Rehm, 2005; Thase, 2007), or even into melancholic and atypical depression (Penninx et al., 2013). Latent class analyses conducted in samples from the general population in the United States (US) and in the Netherlands Study of Depression and Anxiety (NESDA) cohort have found support for a distinct melancholic (or typical) class and an atypical class (Lamers, Burstein, et al., 2012; Lamers et al., 2010). In addition, a class of moderate severity has been found in these studies. However, it has to be emphasised that in the dichotomized categorization into melancholic and non-melancholic subgroups, the non-melancholic subtype does not uniquely represent the atypical depressive subtype.

2.2 Epidemiology of Depressive Symptoms

2.2.1 Burden of Disease, Incidence, and Prevalence

Depressive disorders (MDD and dysthymia) are globally one of the leading causes of lost health. It has been estimated that in 2017, they globally contributed to over 40 million years lived with disability (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). The incidence of MDD has increased almost 50 % during the past three decades (Q. Liu et al., 2019). In 2017, there were over 250 million incident cases of depressive disorders (94 % MDD) worldwide (Q. Liu et al., 2019).

A recent meta-analysis stated that at least one in ten people has MDD in their lifetime but there was substantial variation in the prevalence estimates across studies determined by response rate, percentage of women in the population, and year of the publication (Lim et al., 2018). Data from the World Mental Health surveys suggest a significantly higher lifetime prevalence of a major depressive episode in high-income countries than in low- to middle-income countries (15 % and 11 %, respectively) (Bromet et al., 2011). In contrast, the one-year prevalence has been found to be equal (6 %) cross-nationally, probably reflecting differences in recall or persistence of depression (Bromet et al., 2011). Reasons for the differences in the prevalence have yet to be solved but they are suggested to be partly explained by differences in how standard tools measure depression across countries (Scorza et al., 2018).

Women have a significantly higher risk of lifetime MDD across countries than men (Seedat et al., 2009). In the Finnish Health 2011 Study, the one-year prevalence of depressive disorders was 9.6 %, 12.2 % in women and 6.7 % in men sampled from the general population, and the one-year prevalence of MDD was 7.4 %; 10.0 % in women and 4.4 % in men (Markkula et al., 2015). The prevalence has remained rather stable: in 2017, the prevalence of MDD was 8 % and 6 % in women and men, respectively (P. Koponen et al., 2018). In the same study, the prevalence of increased depressive symptoms was 13 % in women and 9 % in men (P. Koponen et al., 2018).

More specifically, in population-based cohorts of middle-aged or older subjects, the prevalence of increased depressive symptoms has been found to be even higher, as presented in Table 2.

Table 2. Prevalence of increased depressive symptoms in population-based cohorts of middle-aged or older subjects.

STUDY	COUNTRY	NUMBER OF SUBJECTS	PREVALENCE	
Alshehri et al., 2019	Netherlands	6459 (mean age 56 years, 56 % women)	All Women Men	23.4 % 30.2 % 16.6 %
Hamieh et al., 2019	France	10 541 (mean age 48 years, 57 % women)	All	22.5 %
Kozela et al., 2019	Poland	8833 (mean age 57 years, 54 % women)	All Women Men	25.3 % 32.1 % 18.7 %
Moise et al., 2018	US	29 491 (mean age 56 years, 55 % women)	All Women Men	11.0 % 13.9 % 7.5 %
Seppälä, Vanhala, et al., 2012	Finland	2820 (mean age 59* / 60** years, 53 % women)	All Women Men	15.3 % 17.7 % 14.5 %

*Subjects without increased depressive symptoms. **Subjects with increased depressive symptoms.

2.2.2 Sociodemographic Determinants of Depressive Symptoms

There is a comprehensively documented gender difference in depression risk. Women have a twofold risk for MDD (odds ratio (OR) 1.95, 95 % confidence interval (CI) 1.88–2.03) and an over 1.5-fold risk for increased depressive symptoms (OR 1.64 which is equivalent to a Cohen's *d* of 0.27, 95 % CI 0.26–0.29) (Salk et al., 2017). This risk difference is suggested to be caused by distinct biological and psychological susceptibility of women and men, and by environmental factors (Kuehner, 2017). However, there is some controversy as to whether the gender difference is age-related. Data from the World Mental Health surveys suggest that the difference in the lifetime prevalence of MDD is narrower among younger cohorts (Seedat et al., 2009), whereas in other studies, the association with gender has been found to become weaker with age (Patten et al., 2016).

The onset of MDD most often occurs during the second to fourth decade of life, and in high-income countries, the prevalence of depression decreases with age (Kessler & Bromet, 2013). Interestingly, the association between MDD and chronic physical conditions generally seems to weaken with age (Kessler et al., 2010).

Not being married and living alone are associated with MDD in high-income countries, as is also low income, but not low education (Bromet et al., 2011).

In the longitudinal Finnish Health 2011 Study, new-onset depressive disorders among middle-aged subjects were found to be predicted by younger age and female gender whereas education and income did not affect the incidence of these disorders (Markkula et al., 2017).

2.2.3 Course of Depressive Symptoms

The course of having increased depressive symptoms and MDD varies: recovery is frequent but so are relapse and recurrence (Richards, 2011). In recent population-based studies, the recurrence of MDD has been high, the recurrence rate increasing with the passing years: 4.3–13 % at 5 years, 13–23 % at 10 years, and 27–42 % at 20 years (Hardeveld et al., 2013; ten Have et al., 2018). However, the trajectories of depressive symptoms have been found to be heterogeneous in the general population (Musliner et al., 2016). A poor depressive symptoms trajectory has been found to be predicted by female gender, low income, low education, past history of psychopathology, and stressful life events (Musliner et al., 2016). Markkula et al. reported that in the Finnish general population, one in four subjects with a depressive disorder at baseline still had a depressive disorder after an 11-year follow-up (Markkula et al., 2016). Being single and disorder severity were associated with persistence.

Quite logically, having increased levels of depressive symptoms but not yet meeting the criteria for MDD has been found to predict incidence of MDD (Cuijpers & Smit, 2004; Y. Y. Lee et al., 2019). The risk is estimated to be doubled in community and primary care settings (Y. Y. Lee et al., 2019). In Finland, baseline subclinical depressive symptoms increased the risk for MDD from 1.5- to 3-fold depending on the severity of these symptoms during over 10 years of follow-up (Markkula et al., 2017).

Some persons with subthreshold depression may be more vulnerable to develop clinical depression than others. A recent analysis of the NESDA cohort revealed that from a set of sociodemographic factors, only body mass index (BMI), childhood trauma, and education level were predictors of subsequent MDD among those with subthreshold symptoms (S. Y. S. Han et al., 2019). Interestingly, the three depressive symptoms most predictive of MDD were fatigue and leaden paralysis, along with sadness (S. Y. S. Han et al., 2019).

2.2.4 Epidemiology According to Subtypes of Depressive Symptoms

To the best of our knowledge, there are no up-to-date estimates on the cross-national prevalence of specific subtypes of depressive symptoms. It has previously been estimated that 20–30 % of patients with major depression have pure melancholic features (Gold & Chrousos, 2002). The prevalence rates of atypical depression have varied in epidemiological studies for methodological reasons such as definition of atypicality and study settings (Łojko & Rybakowski, 2017). Suggested prevalence of melancholic and atypical or non-melancholic subtypes of depressive episodes or depressive symptoms in some general population samples are presented in Table 3.

Table 3. Prevalence of melancholic and atypical or non-melancholic subtypes of major depression or increased depressive symptoms in depressed samples from general populations.

STUDY	ASSESSMENT OF DEPRESSIVE SUBTYPES	PREVALENCE	
Blanco et al., 2012 US, NESARC cohort n = 7124	Diagnostic interview; DSM-IV-defined criteria for a lifetime MDE with or without atypical features (increased appetite and/or hypersomnia)	Non-atypical Atypical	38.0 % 62.0 %
Brailean et al., 2019 UK n = 37 434	Online-administered diagnostic interview based on DSM-5 criteria for probable lifetime MDD with and without atypical features (weight gain and hypersomnia)	Non-atypical Atypical	93.8 % 6.2 %
Seppälä, Vanhala, et al., 2012 Finland n = 434	BDI A summary score of melancholic symptoms	Melancholic Non-melancholic	32.2 % 67.8 %
Rodgers et al., 2016 Switzerland n = 1624	Diagnostic interview; DSM-5-defined criteria for melancholic and atypical MDD with minor alternations	Melancholic Atypical Combined Unspecified	26.0 % 15.8 % 12.1 % 46.1%
Lamers, Burstein, et al., 2012, US n = 805	Diagnostic interview; Latent class analysis	Typical Atypical Moderate	69.7 % 15.6 % 14.6 %
Lamers et al., 2010 Netherlands, NESDA cohort n = 818	Diagnostic interview; Latent class analysis	Melancholic Atypical Moderate	46.3 % 24.6 % 29.1 %
Melartin et al., 2004 Finland n = 269	Diagnostic interview; DSM-IV-defined melancholic MDD and non-melancholic MDD	Melancholic Non-melancholic	36.1 % 63.9 %

BDI, Beck's Depression Inventory; DSM, Diagnostic and Statistical Manual; MDD, major depressive disorder; MDE, major depressive episode; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NESDA Netherlands Study of Depression and Anxiety; UK, United Kingdom; US, United States.

There is some evidence for female predominance in atypical or non-melancholic MDD (Blanco et al., 2012; Bogren et al., 2018; Brailean et al., 2019) but not all studies have reported gender differences across melancholic and atypical subtypes (Musil et al., 2018; Rudaz et al., 2017).

Similarly, evidence of the course of different depressive subtypes is inconsistent. Analysis of data from the NESDA cohort has suggested that severe melancholic and severe atypical subtype groups have rather similar course trajectories (Lamers, Beekman, et al., 2016). However, in a Spanish study, melancholically depressed subjects had, for example, more depressive episodes with higher severity and lower rates of remission than subjects with atypical and non-melancholic depressive

symptoms (Gili et al., 2012). Likewise, a study in Germany reported that melancholic MDD was more severe and associated with shorter duration of current depressive episodes than atypical MDD (Musil et al., 2018). A history of subthreshold depression has been found to be predictive of both subtypes (Rudaz et al., 2017).

2.3 Pathophysiology of Depressive Symptoms

The pathophysiology of depressive symptoms is complex and not fully understood. Considering the heterogeneity of depressive symptoms and depressive disorders, it is plausible that also the mechanisms contributing to their development vary from one depressive subtype to another. These mechanisms include, for example, genetic and psychological vulnerability, and dysregulations of inflammatory, neuroendocrine, and autonomic systems. In addition, metabolic disturbances can induce depressive symptoms.

2.3.1 Genetic, Environmental, and Psychological Aspects

The risk of MDD is threefold among those with a first-degree relative with MDD, the heritability being 30–40 % (Sullivan et al., 2000). The genetics of MDD are, however, anything but clear (Flint & Kendler, 2014). Furthermore, there is probably a significant interplay between genes and environment (Otte et al., 2016).

The effect of major life events on the development of depressive symptoms and MDD is well-established (Kessler, 1997). In addition, not only recent events, but also adverse events in childhood predispose to depressive disorders later in life (Carr et al., 2013).

Furthermore, some individuals have cognitive vulnerability to being depressed. It has been associated for example with negative attributional style, negative memory bias, and rumination (Mathews & MacLeod, 2005).

2.3.2 Biological Dysregulations

There is substantial evidence of dysfunction of the immune system in the pathogenesis of MDD (Kiecolt-Glaser et al., 2015; Raison & Miller, 2011). In depressive subjects, the levels of proinflammatory cytokines have been found to be higher compared to those in the non-depressed (Dowlati et al., 2010; Haapakoski et al., 2015). More specifically, inflammation markers have been suggested to be especially associated with sleeping disturbances, energy level, appetite and weight changes, pain, and irritability (Fried et al., 2019).

MDD has also been consistently associated with hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Pariante & Lightman, 2008), although to a varying degree (Stetler & Miller, 2011). Dysfunction of the autonomic nervous system might also be involved in the pathogenesis of depressive symptoms (Kidwell & Ellenbroek, 2018; Sgoifo et al., 2015). In addition, leptin resistance or insufficiency may contribute to depressive symptoms (Lu, 2007), connecting them with obesity-related metabolic dysregulations. However, discussion of these highly complex and interacting mechanisms in more detail is beyond the scope of this literature review.

2.3.3 Pathophysiology According to Subtypes of Depressive Symptoms

Different subtypes of depressive symptoms might be attributable to different genetic factors (Kendler et al., 2013). Moreover, features of atypical MDD in probands have been associated with features of atypical MDD in relatives, whereas such associations have not been found concerning features of melancholic MDD (Lamers, Cui, et al., 2016).

There is some evidence that in melancholic and non-melancholic MDD, different biological mechanisms may play a crucial role. Disturbed HPA axis functions seem to be present particularly in melancholic subtypes of MDD and depressive symptoms (Juruena et al., 2018). Woelfer et al. (2019) recently reviewed the literature on neuroinflammation in different subtypes of MDD and suggested that inflammation played a greater role in atypical MDD. However, peripheral inflammation markers are proposed to have only a limited value in distinguishing between melancholic and non-melancholic MDD (Yang et al., 2018). Inflammation is also linked to metabolic dysregulations (K. L. Chan et al., 2019), and there is an established bidirectional association between metabolic syndrome and depressive symptoms (A. Pan et al., 2012). These metabolic dysregulations have been found to be more prevalent in non-melancholic or atypical than melancholic subtypes of MDD and depressive symptoms (Lamers et al., 2010; Seppälä, Vanhala, et al., 2012; Takeuchi et al., 2013).

2.4 Detection of Depressive Symptoms in Primary Care

Although subthreshold and clinical MDD are highly prevalent in primary care, and general practitioners deliver most care for these conditions, it is suggested that general practitioners are poorly equipped to recognize major depression (Mitchell et al., 2009). A meta-analysis from ten years ago revealed that primary care physicians

correctly identify MDD in under half of the cases (Mitchell et al., 2009). Non-recognition, and also recognition, may depend on the health care system, the care provider, or the patient (Ferenchick et al., 2019; Leff et al., 2017; Piek et al., 2012). Specifically, if a patient presents with somatic symptoms (Leff et al., 2017) or without typical features of major depression (Piek et al., 2012), depressive symptoms may remain unrecognized.

One means to enhance the detection of depression is screening. However, there is no general consensus on screening for depression in primary care (Ferenchick et al., 2019). In the US, screening is recommended in the general adult population (Siu & The US Preventive Services Task Force (USPSTF), 2016), whereas in the UK, screening for depression is suggested especially among subjects with a history of depression or a chronic physical health problem with functional impairment (National Institute for Health and Care Excellence (NICE), 2009). Similarly, in the Finnish Current Care Guideline for Depression (Depression: Current Care Guidelines, 2020), screening is suggested to be probably useful only among subjects at specific risk for depression (Table 4).

Table 4. Characteristics of patients who might benefit from screening for depression according to the Finnish Current Care Guidelines for depression (Depression: Current Care Guidelines, 2020) and Ferenchick et al., 2019.

Previous episode of depression, or history of other mental illness or suicide
History of substance use
Family history of depression or suicide
Chronic medical illness
Unexplained somatic symptoms
Recent childbirth
Unemployment, or work-related burnout or stress
Recent stressful life event that includes loss
Intimate partner's violence
Poor social support systems, social deprivation
Frequent use of health care services

When deciding to screen for depression, the primary care physician has a variety of instruments to choose from. There are at least 55 psychometrically tested tools or their adaptions for depression screening of an adult population in primary care (El-Den et al., 2018). With these instruments, also subthreshold depression can be detected, but the clinical diagnosis of depression warrants further diagnostic assessment.

2.4.1 Beck's Depression Inventory

One of the screening instruments is Beck's Depression Inventory (BDI) (Beck et al., 1961). The BDI was first introduced by Beck and his colleagues in 1961 as "an instrument designed to measure the behavioural manifestations of depression" (Beck et al., 1961). It is a 21-item inventory where every item represents a specific symptom or attitude observed to be present in depressive subjects (Beck et al., 1961). The symptom-attitude categories described by Beck et al. are mood, pessimism, sense of failure, lack of satisfaction, guilty feeling, sense of punishment, self-hate, self-accusations, self-punitive wishes, crying spells, irritability, social withdrawal, indecisiveness, body image, work inhibition, sleep disturbance, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido (Beck et al., 1961). Every item has four statements indicating the severity of the specific symptom (scored from 0 = no symptoms to 3 = severe symptoms), from which the subject is asked to choose the one best describing her/his situation during the previous week or two. The scores of the 21 items are added together to obtain a total score (range from 0 to 63) indicating the severity of the depressive symptomatology.

The psychometric properties of the BDI are considered good. It has high internal consistency, high concurrent validity with respect to other measures of depression, and strong construct validity (Beck et al., 1988). It has been suggested to reliably differentiate depression and non-depression (Richter et al., 1998). Thus, it is suitable for screening for depression, and it is a validated instrument to do so also specifically in the Finnish general population (Aalto et al., 2012).

However, there is not a constant cut-off score to be used. Instead, it has been proposed that the cut-off score should vary depending on the sample and the purpose for using the inventory (Beck et al., 1988). Beck has proposed a cut-off point of 9/10 among medical patients, and 12/13 among psychiatric patients (Beck & Beamesderfer, 1974). The cut-off point of 9/10 has been encouraged to be used for comparability of the results in population-based studies (Aalto et al., 2012). In a set of Finnish population-based studies among middle-aged subjects, a BDI score ≥ 10 has been used to indicate increased depressive symptoms (Joutsenniemi et al., 2013; H. Koponen et al., 2010; Mäntyselkä et al., 2011; Seppälä, Vanhala, et al., 2012; Tusa et al., 2019).

2.5 Cardiovascular Disease

In addition to MDD, cardiovascular disease (CVD) is another major global health issue. CVD refers to a set of diseases affecting heart and blood vessels. Of these, ischemic heart disease (IHD) and stroke (or cerebrovascular disease, CeVD) are attributable to most of the disease burden. They are the global leading causes of death (World Health Organization, 2018a), and they also cause a substantial amount of healthy life lost due to disability. Over 330 million healthy life years are lost annually

because of IHD and stroke (World Health Organization, 2018b). Moreover, it has been estimated that nearly four million healthy life years lost due to IHD are attributable to MDD (Charlson et al., 2013). In high-income countries, another atherosclerotic CVD, peripheral artery disease (PAD), is a significant contributor to the disease burden. The global age-standardized prevalence of different CVD cases and deaths are presented in Figures 3 and 4 (Roth et al., 2017), respectively.

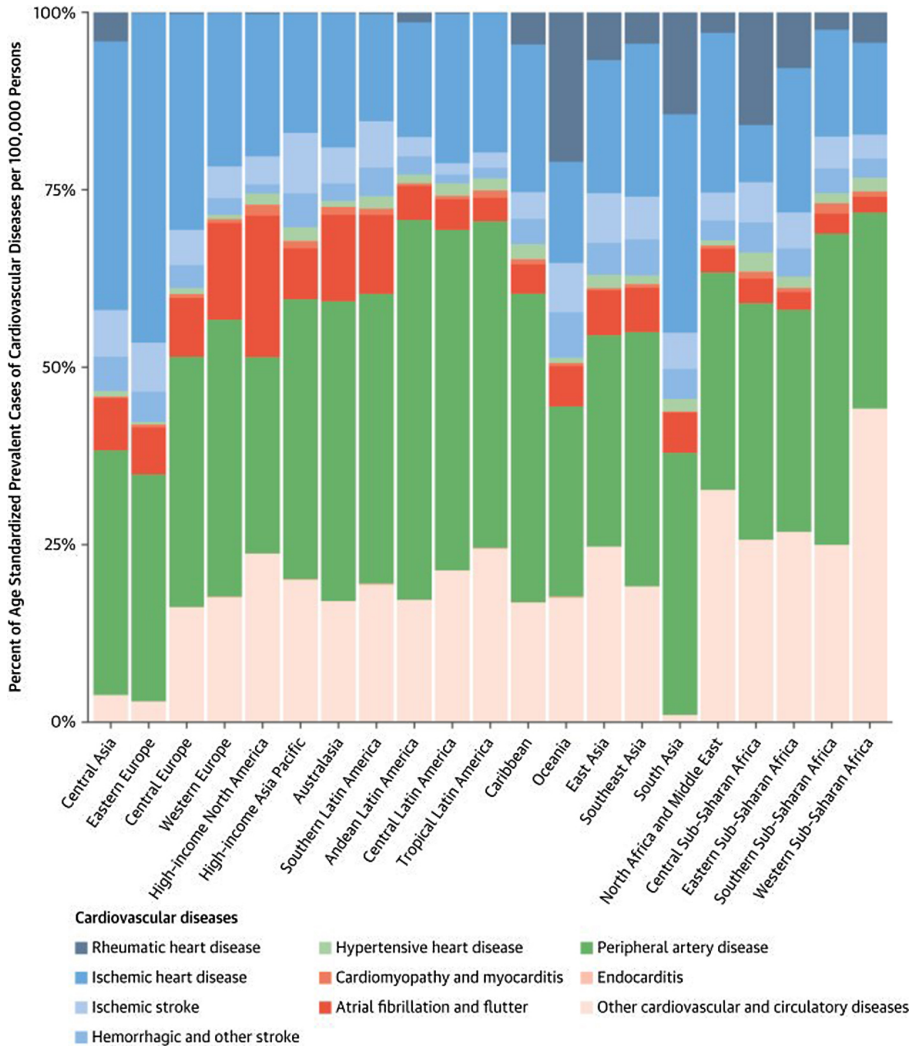

Figure 3. Percent of age-standardized prevalent cases per 100,000 for CVD causes, 2015. This figure displays the relative distribution of age-standardized prevalence by CVD cause for 21 Global Burden of Disease world regions. CVD, cardiovascular disease. Reprinted from Roth et al. (2017). Copyright © 2017 The Authors. Published by Elsevier. Distributed under the terms of the Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/).

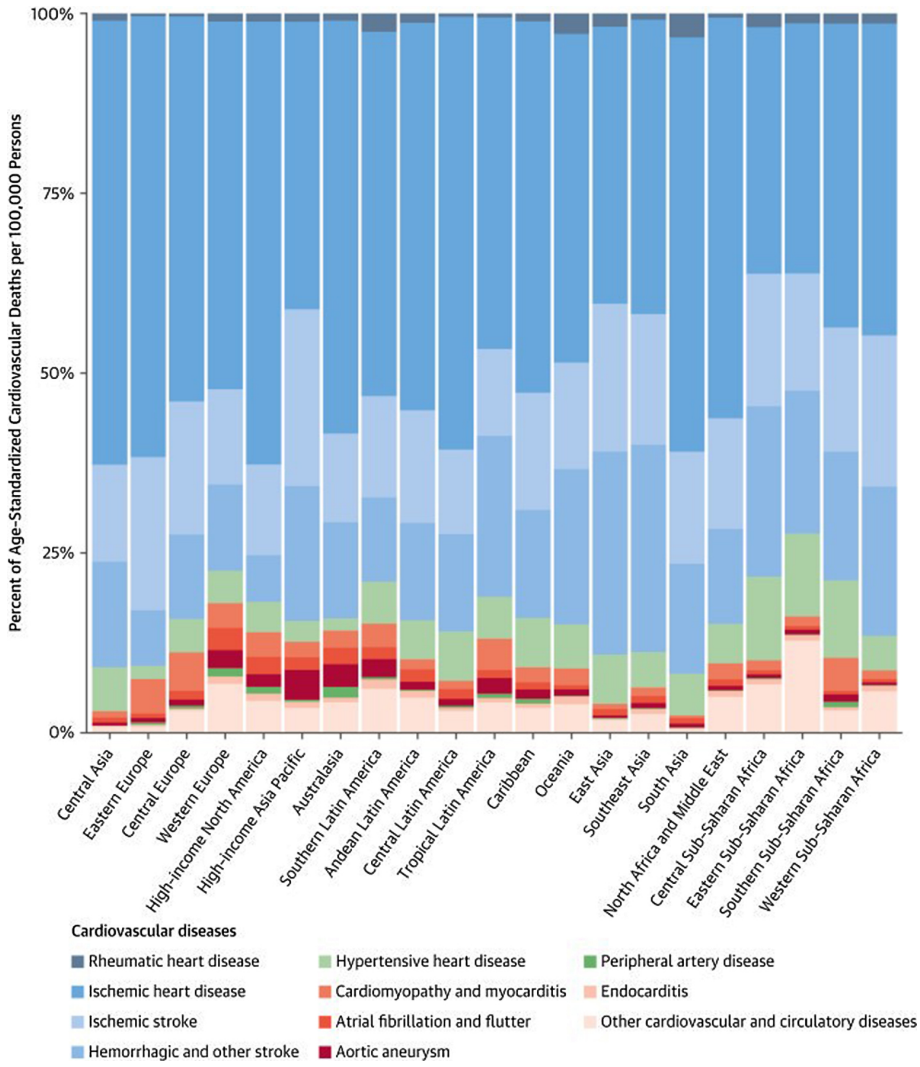

Figure 4. Percent of age-standardized deaths per 100,000 for CVD causes, 2015. This figure displays the relative distribution of age-standardized prevalence by CVD cause for 21 Global Burden of Disease world regions. CVD, cardiovascular disease. Reprinted from Roth et al. (2017) with permission from Elsevier. Copyright © 2017 The Authors. Published by Elsevier. Distributed under the terms of the Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/).

Considering the high burden of CVDs, efforts to prevent them are a core concern in healthcare. In high-income countries, there has been a decline in CVD mortality during past decades (Roth et al., 2017), but this might be challenged by populations growing older, more obese, and more diabetic (Ezzati et al., 2015; NCD Risk Factor Collaboration (NCD-RisC), 2016a, 2016b).

In the following sections, the suggested magnitude of risk increase, and the population attributable risk (PAR) of major CVD risk factors are first presented. Then, some aspects of CVD risk assessment and prevention at individual level are briefly discussed. The burden of primary modifiable CVD risk factors and their association with depressive symptoms are reviewed in section 2.7.

2.5.1 Predominant Risk Factors for Cardiovascular Disease

PAR presents the proportion of the incidence of a disease in a population that is due to exposure to a certain risk factor. If the risk factor were eliminated, the disease incidence would decline by this proportion. Evidence from two large multinational case-control studies suggest that dyslipidaemia, smoking, and psychosocial factors are the most important risk factors for myocardial infarction, whereas stroke is most attributable to hypertension (O'Donnell et al., 2016; Yusuf et al., 2004) (Table 5). Engaging to healthy diet (PAR 23.2 %) and regular physical activity (PAR 35.8 %) would prevent many stroke cases (O'Donnell et al., 2016). In addition, diabetes and regular alcohol consumption are among the predominant risk factors for CVD. By elimination of these risk factors, 90 % of IHD and stroke cases could probably be prevented (O'Donnell et al., 2016; Yusuf et al., 2004).

Table 5. Population attributable risk of major risk factors for myocardial infarction and stroke based on the INTERHEART (Yusuf et al., 2004) and INTERSTROKE (O'Donnell et al., 2016) studies.

RISK FACTOR	POPULATION ATTRIBUTABLE RISK (PAR)	
	Myocardial infarction	Stroke
Hypertension	17.9 %	47.9 %
Abdominal obesity	20.1 %	18.6 %
Dyslipidaemia	49.2 %	26.8 %
Smoking	35.7 %	12.4 %
Psychosocial factors	32.5 %	17.4 %

2.5.2 Cardiovascular Risk Assessment and Prevention of Cardiovascular Disease

An approach for assessment of an individual's CVD risk is illustrated in Figure 5. As those with the highest risk burden benefit most from preventive activities, and subjects with low risk might even suffer from them, it is essential to make a comprehensive, individual assessment of a subject's risk (Piepoli et al., 2016). However, at population level, even small risk reductions appear to be effective because of the higher number of individuals at low risk (Piepoli et al., 2016; Rose, 1992).

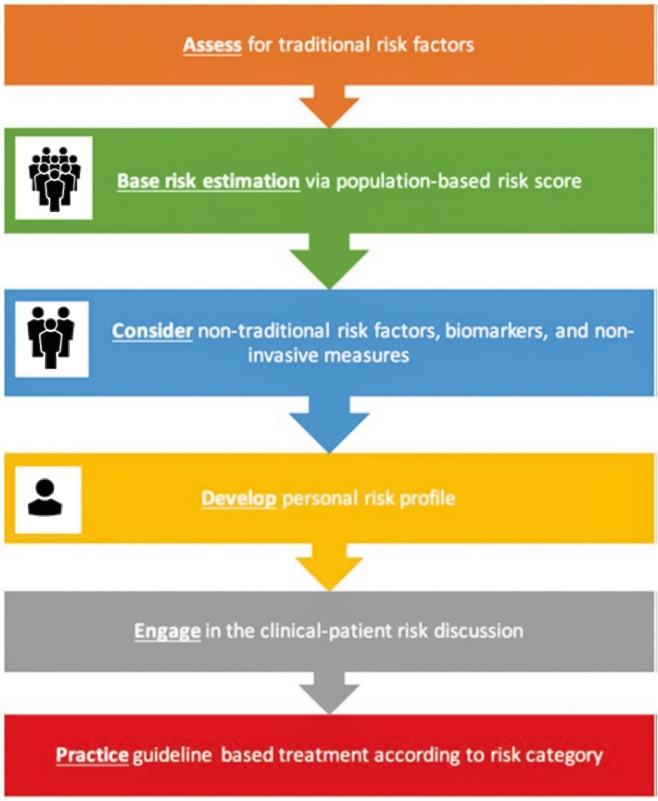

Figure 5. Approach to CV risk assessment. "ABCDE: Assess, Base Risk Estimation, Consider, Develop, Engage" is the recommended approach to initiate risk assessment from a population perspective and, subsequently, individualize CV risk. CV, cardiovascular. Reprinted from Khambhati et al. (2018) with permission from Wiley and Sons. Copyright © 2018 Wiley Periodicals, Inc.

Assessment of total CVD risk refers to consideration of multiple CVD risk factors at the same time to determine the absolute risk for experiencing a CVD event in a given time period (Collins et al., 2017). According to European Guidelines on CVD risk prevention (Piepoli et al., 2016), systematic assessment of total CVD risk is recommended repeatedly in subjects who have family history of premature CVD or major CVD risk factors such as smoking, high blood pressure (BP), diabetes or dyslipidaemia. There are several tools for this risk prediction to choose from, although only some of them are properly validated (Damen et al., 2016) such as the Framingham Risk score (D'Agostino et al., 2008) and the Systematic Coronary Risk Evaluation tool (SCORE) (Conroy et al., 2003). Most of these models include the following predictors: age, smoking, BP, blood cholesterol, diabetes, and BMI (Damen et al., 2016). In clinical practice, these risk factors are easy to assess, and all but age are even modifiable. Family history of CVD is another unmodifiable risk

factor that is important to consider when assessing total CVD risk. Both paternal and maternal history of CVD has been associated with doubled odds for CVD events, and the risk is even higher if parents have had CVD under the age of 65 (Weijmans et al., 2015). However, this risk increase might be mostly mediated by traditional risk factors (Yusuf et al., 2004).

In addition to these so-called traditional risk factors, there are several factors that might modify the CVD risk. These include for example psychosocial risk factors and certain diseases. The psychological risk modifiers include increased depressive symptoms and a subject's perception of her/his health, both of which are discussed in detail in the following sections. They also comprehend, for instance, low socioeconomic status and work stress. In a recent meta-analysis, low education (compared to high) was estimated to increase the risk for stroke by 17 %, for IHD by 36 %, for CVD events by 50 %, and for CVD deaths by 39 %; low income (compared to high) increased especially risk for IHD (49 %) and CVD death (80 %) (Khaing et al., 2017). Job strain has also been associated with an estimated 23 % IHD risk increase (Kivimäki et al., 2012).

In primary care, prevalent diseases contributing to CVD risk include chronic kidney disease, obstructive sleep apnoea, and rheumatologic autoimmune disease. Chronic kidney disease is an established CVD risk factor (Sarnak et al., 2003), and estimated glomerulus filtration rate and albuminuria have been suggested to be taken into consideration even among healthy subjects when assessing CVD risk (Matsushita et al., 2015). Obstructive sleep apnoea has been associated with a 2.5-fold risk for CVD (Dong et al., 2013). Rheumatoid arthritis and systemic lupus erythematosus are associated with significantly increased CVD mortality risk, the meta-standardized mortality rate being 1.5 and 2.3 compared to the general population, respectively (Aviña-Zubieta et al., 2008; Y. H. Lee et al., 2015). Furthermore, gestational hypertension and diabetes increase the risk for future CVD (Goueslard et al., 2016; Tooher et al., 2017).

In addition, growing interest has arisen in biomarkers such as high-sensitivity C-reactive protein and signs of subclinical atherosclerosis in assessment of CVD risk (Khambhati et al., 2018; Pletcher & Moran, 2017). However, consideration of these factors (apart from ankle-brachial index) is today not applicable in primary care, and thus, they are not further discussed here.

Engaging in a healthy lifestyle including non-smoking, physical activity, and healthy diet is at the core of CVD risk prevention (Rippe, 2019). In addition, reducing the magnitude of the modifiable risk factors, especially elevated BP and dyslipidaemia, is essential. Goals and target levels of CVD risk factors according to European Guidelines on CVD risk prevention are presented in Table 6 (Piepoli et al., 2016).

Table 6. Risk factor goals and target levels for important cardiovascular risk factors according to European Guidelines on cardiovascular disease risk prevention in clinical practice (Piepoli et al., 2016).

No smoking or other exposure to tobacco
Healthy diet low in saturated fat, including wholegrain products, vegetables, fruit, and fish
At least 150 minutes moderate or 75 minutes vigorous aerobic PA at weekly basis
Normal weight (BMI 20-25 kg/m^2) and waist circumference < 94 cm (men) or < 80 cm (women)
Blood pressure < 140/90 mmHg
LDL-cholesterol < 3.0 mmol/l (if low to moderate risk) < 2.6 mmol/l (if high risk) < 1.8 mmol/l (if very high risk)
HbA1c < 53 mmol/mol

BMI, body mass-index; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; PA, physical activity.

2.6 Depressive Symptoms and Cardiovascular Risk

There are many possible mechanisms that may link depressive symptoms to increased CVD risk, listed in Table 7 (Penninx, 2017). However, evidence on these mechanisms is still inconsistent (Cohen et al., 2015; Penninx, 2017). Many traditional CVD risk factors are more prevalent among depressed individuals (reviewed in section 2.7) than among the non-depressed, which is a plausible mediator of increased depressive symptoms increasing CVD risk. It has especially been suggested that the relationship between depressive symptoms and CVD is driven by behavioural mechanisms such as physical inactivity, smoking, and poor medication adherence (Whooley et al., 2008).

However, substantial evidence also supports increased depressive symptoms and depression being CVD risk factors independently of other risk factors (reviewed in section 2.8). Considering pathological pathways, many of the dysregulations associated with depressive symptoms (section 2.3) are also associated with CVD. Inflammation is a core factor in atherosclerosis (Libby et al., 2002), and inflammatory markers such as C-reactive protein have been found to be predictive of CVD events (The Emerging Risk Factors Collaboration, 2010a). Dysregulation of the neuroendocrine system has also been associated with both depression and depressive symptoms and CVD although the evidence for this is mixed (Penninx, 2017). However, elevated plasma morning cortisol has been associated with an increased risk of incident CVD in a recent comprehensive study (Crawford et al., 2019). In addition, autonomic dysfunction may be a link connecting depression and CVD. Low heart rate variability is a marker of disturbed regulation of autonomic nervous system, and it has been associated with 40 % increased risk of CVD in

populations without known CVD (Hillebrand et al., 2013). Finally, metabolic disturbances are a plausible pathway connecting depressive symptoms and CVD. There is growing evidence that different biological dysregulations might be responsible for the depression–CVD association in different subtypes of depressive symptoms and depression (Baune et al., 2012).

Table 7. Summary of potential mechanisms linking depression to increased cardiovascular risk.

CAUSAL MEDIATING MECHANISMS	
Unhealthy lifestyle	smoking
	excessive alcohol use
	physical inactivity
	unhealthy diet
	lower treatment compliance and worse medical care
Pathophysiology	metabolic dysregulations
	immuno-inflammatory dysregulations
	autonomic dysregulations
	HPA-axis dysregulations
ALTERNATIVE MECHANISMS	
Residual confounding	depression picks up or is a prodrome of not yet discovered or not measured (sub)clinical conditions
Iatrogenic effects	pharmacological impact of antidepressants increases cardiovascular risk
"Third underlying factors" *	childhood stressors
	personality
	genetic pleiotropy

*Factors that influence in parallel both cardiovascular risk and depression risk, but potentially independently from each other. HPA, hypothalamic-pituitary-adrenal. Reprinted from Penninx (2017) with permission from Elsevier. Copyright © 2016 Elsevier Ltd.

The connection between depressive symptoms and CVD can be illustrated as a mutually reinforcing cycle worsening both physical and mental health (Figure 6) (Whooley & Wong, 2013). Indeed, it is important to notice that the association of depressive symptoms and CVD is bidirectional (Wium-Andersen et al., 2019). IHD and stroke have been associated with increased risk for incident and prevalent major depression and depressive symptoms (Kendler et al., 2009; Osler et al., 2016; Thombs et al., 2006), while MDD and depressive symptoms in established CVD have consistently been associated with poorer outcomes (Meijer et al., 2011; Nicholson et al., 2006). However, depressive symptoms as a prognostic factor in established CVD or CVD as a risk factor for depressive symptoms are beyond the scope of this literature review.

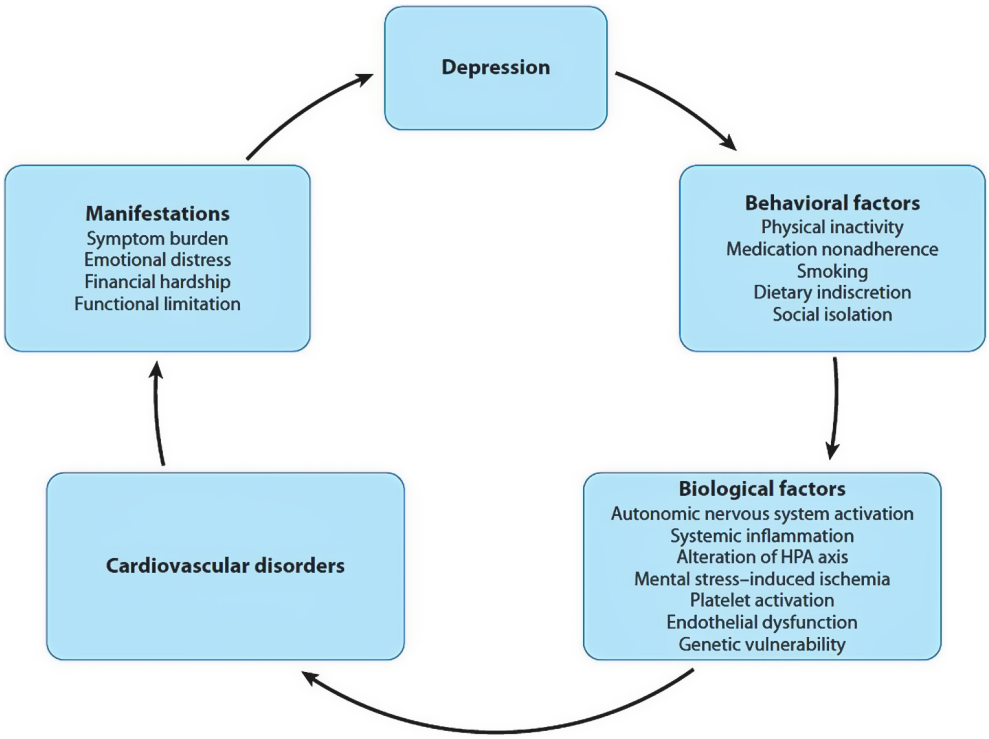

Figure 6. Conceptual model of the relationship between depression and cardiovascular disease. HPA, hypothalamic-pituitary-adrenal. Republished from Whooley & Wong (2013) with permission of Annual Reviews, Inc. Permission conveyed through Copyright Clearance Center, Inc. Copyright © 2013 by Annual Reviews, Inc.

2.7 Depressive Symptoms and Other Cardiovascular Risk Factors

In the following section, the burden of the primary modifiable CVD risk factors, evidence of their contribution to CVD risk, and their association with depressive symptoms are discussed. Furthermore, the meaning of assessment of self-rated health (SRH) when at CVD risk and its relation to depressive symptoms is described.

2.7.1 Depressive Symptoms and Hypertension

High systolic blood pressure (SBP), defined in reference to the minimum risk exposure level of SBP 110–115 mmHg, is globally the leading risk factor for healthy life years lost (GBD 2017 Risk Factor Collaborators, 2018). In 2017, it accounted for over 10 million deaths and 200 million disability-adjusted life years

(GBD 2017 Risk Factor Collaborators, 2018). Globally, over 3.5 billion adults have high SBP, and nearly 900 million adults have hypertension (SBP ≥ 140 mmHg) (Forouzanfar et al., 2017). In Finland, the prevalence of elevated blood pressure (SBP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, or antihypertensive medication) among men and women ≥ 30 years old is 58 % and 48 %, respectively (P. Koponen et al., 2018).

Hypertension is a well-established risk factor for CVD (Stamler et al., 1993), with a graded and continuous association, without a threshold for risk (Oparil et al., 2018). Most of the lost health related to SBP is caused by IHD and stroke (Forouzanfar et al., 2017). Hypertension at the age of 30 years has been associated with a 20 % higher life-time risk for developing CVD, and even five years earlier than normotensives (Rapsomaniki et al., 2014). In middle-aged subjects, the risk for CVD death has been found to increase twofold for every 20 mmHg increase in SBP and 10 mmHg increase in DBP (Prospective Studies Collaboration, 2002). On the other hand, every 10 mmHg reduction of SBP has been found to reduce the risk for major CVD events by 20 % (Ettehad et al., 2016). However, a risk decrease with primary preventive BP lowering has more recently been suggested to exist only if baseline SPB ≥ 140 mmHg (Brunström & Carlberg, 2018).

Evidence on the association of depressive symptoms or major depression and hypertension is mixed. However, a meta-analysis of these data suggests that increased depressive symptoms and MDD are probable independent risk factors for incident hypertension (adjusted risk ratio (RR) 1.42, 95 % CI 1.09–1.86) (Meng et al., 2012). The effect of hypertension on incident depressive symptoms has been studied especially among older subjects, and a recent meta-analysis did not find support for hypertension being a risk factor for increased depressive symptoms (Long et al., 2015).

More recently, a positive association between increased depressive symptoms or MDD and hypertension has been found in some large cross-sectional and prospective population studies. Cross-sectional analysis from a population-based cohort study among late middle-aged and older German adults (aged 57 to 84 years) showed clinically significant depressive symptoms to be associated with an increased risk of hypertension even after adjustment for several possible confounding factors (OR 1.76, 95 % CI 1.14–2.74) (Maatouk et al., 2016).

In Sweden, the association has been found to be stronger among men than women. In a large (n = 2 058 408) population-based registry study, men with hypertension had a 23 % increased risk for depression (adjusted OR 1.23, 95 % CI 1.19–1.27) compared to normotensives, but among women adjustments for some sociodemographic variables made the association non-significant (OR 1.02, 95 % CI 0.99–1.04) (Sandström et al., 2016).

In an Australian population-based study among 9182 middle-aged women, Jackson et al. (2016) found depression to be associated with a 30 % increased risk for hypertension (unadjusted OR 1.30, 95 % CI 1.19–1.43) during 15 years of follow-up. However, adjustment for various sociodemographic, lifestyle associated and biological factors attenuated the association to non-significance (OR 1.02, 95 % CI 0.91–1.18) (Jackson et al., 2016). Similar results were reported by Zambrana et al. among 2680 middle-aged Hispanic women after three years of follow-up: the association of baseline increased depressive symptoms with incident hypertension was significant when adjusted for age, education, insurance and even behavioural variables (OR 1.74, 95 % CI 1.10–2.74), but became non-significant (OR 1.53, 95 % CI 0.95–2.46) when clinical variables such as BMI were taken into account (Zambrana et al., 2016).

Moreover, a cross-sectional analysis from the NESDA cohort suggested remitted and current MDD to be associated with lower SBP and decreased risk of isolated systolic hypertension compared to subjects without MDD (OR 0.60, 95 % CI 0.44–0.82, and OR 0.72, 95 % CI 0.53–0.98, respectively) (Licht et al., 2009).

In terms of hypertension increasing the risk for depressive symptoms, supportive evidence was found in a long follow-up study of 1190 male medical students: hypertension before the age of 65 was associated with an almost threefold risk of increased depressive symptoms after the age of 65 years (Armstrong et al., 2017).

Whether having increased depressive symptoms is an independent risk factor for hypertension or not, and vice versa, their co-existence is suggested to be a toxic combination. In the National Health and Nutrition Epidemiologic Follow-up Study (n = 10 025, mean age 57 years at the baseline, 63 % women, average follow-up 8 years), subjects with hypertension and increased depressive symptoms had a 15 % higher adjusted relative hazard for all-cause mortality (hazard ratio (HR) 1.59, 95 % CI 1.08–2.34) than those with hypertension but without depressive symptoms (HR 1.38, 95 % CI 1.04–1.84) (Axon et al., 2010).

In addition, having a diagnosis of hypertension, not hypertension *per se*, has been suggested to partly explain the increase in psychological distress among patients treated for hypertension. Hamer et al. studied the association of hypertension awareness and psychological distress among 33 105 subjects (mean age 52 years, 54 % women) sampled from the general population in the UK (Hamer et al., 2010). They found that precisely the awareness of elevated BP was associated with the increased mental distress (adjusted OR 1.57, 95 % CI 1.41–1.71). In another population-based study (n = 5000, age 35 to 74 years, 46 % women) conducted in Germany, unawareness of hypertension was inversely associated with prevalent depression (OR 0.60, 95 % CI 0.38–0.95) (Michal et al., 2013).

2.7.1.1 Hypertension According to Subtypes of Depressive Symptoms

In studies assessing hypertension among subjects with melancholic and non-melancholic or atypical MDD or depressive symptoms, no differences in BP values or changes in them between the groups have been reported (Lamers et al., 2013; Lasserre et al., 2017; Seppälä, Vanhala, et al., 2012). In one study, hypertension has been found to be protective for particularly incident atypical MDD (Patel et al., 2018) but in another study, hypertension was protective of melancholic MDD (Rudaz et al., 2017).

2.7.2 Depressive Symptoms and Metabolic Risk Factors

2.7.2.1 Overweight and Obesity

The burden of disease caused by overweight (BMI 25.0–29.9 kg/m^2) and obesity (BMI ≥ 30.0 kg/m^2) is remarkable. In 2015, over 600 million adults were obese (GBD 2015 Obesity Collaborators, 2017), and in 2017, high BMI caused almost 150 million healthy life years lost (GBD 2017 Risk Factor Collaborators, 2018). In Finland, 60 % of women and 75 % of men (aged ≥ 30 years) are overweight (P. Koponen et al., 2018).

Both overweight and obesity are risk factors for incident CVD (Khan et al., 2018). Nearly 70 % of the deaths related to high BMI are due to CVD (GBD 2015 Obesity Collaborators, 2017). Among middle-aged subjects, the risk for an incident CVD event increases with increasing BMI (25.0–29.9 kg/m^2, 30.0–39.9 kg/m^2, and ≥ 40.0 kg/m^2, respectively) compared to normal BMI (18.5–24.9 kg/m^2): HR 1.32 (95 % CI 1.24–1.40), HR 1.85 (95 % CI 1.72–1.99), and HR 2.53 (95 % CI 2.20–2.91) among women and HR 1.21 (95 % CI 1.14–1.28), HR 1.67 (95 % CI 1.55–1.79), and HR 3.14 (95% CI 2.48–3.97) among men (Khan et al., 2018). However, other metabolic risk factors (BP, cholesterol and glucose) have been found to mediate almost half of the excess risk for IHD and over 75 % of the excess risk for stroke (The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), 2014).

Obesity is suggested to be bidirectionally associated with depression and depressive symptoms (Luppino et al., 2010; Mannan et al., 2016). A pooled analysis of 15 studies investigating this association revealed that obese persons had a 55 % increased risk (OR 1.55, 95 % CI 1.22–1.98) for developing increased levels of depressive symptoms or MDD, and persons with those had a 58 % increased risk (OR 1.58, 95 % CI 1.33–1.87) for obesity (Luppino et al., 2010). A weaker, but still significant association was suggested more recently in a pooled analysis of 19 studies (226 063 participants): obese persons had an 18 % increased risk (RR 1.18, 95 % CI

1.04–1.35) for increased depressive symptoms or MDD and persons with those had a 37 % increased risk (RR 1.37, 95 % CI 1.17–1.48) for obesity (Mannan et al., 2016). In 2017, a meta-analysis of six cohort studies and 26 cross-sectional studies (1.8 million participants) on the association between obesity and depressive symptoms or MDD was conducted (Jung et al., 2017). In cohort studies, the association between obesity and increased depressive symptoms or MDD was statistically significant only in subgroup analyses: among women (OR 1.26, 95 % CI 1.15–1.38), when using a self-reported depression definition (OR 1.23, 95 % CI 1.13–1.33), and in European studies (OR 1.23, 95 % CI 1.13–1.33). In studies with cross-sectional design, obesity was significantly associated with increased depressive symptoms and MDD (OR 1.18, 95 % 1.11–1.26).

More recently, a large register-based study in the UK among 363 037 obese patients showed that increasing BMI is independently associated with a linear increase in the risk of depression (Moussa et al., 2019). A cross-sectional study assessing Dutch middle-aged subjects (n = 6459, mean age 56 years, 56 % women) suggested that not only BMI, but also excess total and abdominal body fat, and elevated waist circumference were associated with depressive symptoms (Alshehri et al., 2019). The associations remained unchanged when subjects with type 2 diabetes (T2D), CVD, and hypertension were excluded. Moreover, Jokela et al. analysed the data from eight cohorts (n = 39 377, mean age 46 years), and found that even metabolically healthy obesity (referring to obesity with at most one metabolic risk factor) is associated with an increased risk for depressive symptoms (Jokela et al., 2014). In addition, increased depressive symptoms have been associated with engaging in unhealthy and ineffective weight loss behaviours (Vrany et al., 2018).

2.7.2.2 Glucose Disorders

High fasting plasma glucose (≥ 5.5 mmol/l) is the fourth largest risk factor contributing to healthy life years lost (GBD 2017 Risk Factor Collaborators, 2018). In 2016, diabetes was the 8th contributor to lost health (World Health Organization, 2018b). Globally, over 430 million people have diabetes (International Diabetes Federation, 2019). In Finland approximately 430 000 adults are diabetic (P. Koponen et al., 2018).

Diabetes doubles the risk for CVD (The Emerging Risk Factors Collaboration, 2010b). T2D in subjects without prior myocardial infarction has even been found to be as strong a risk factor for IHD death as prior myocardial infarction among non-diabetic subjects (Juutilainen et al., 2005).

In recent meta-analyses of the published literature, increased depressive symptoms and MDD have been associated with prevalent and incident diabetes

(Wang et al., 2019; Yu et al., 2015). Wang et al. (2019) suggested an OR of 1.73 (95 % CI 1.38–2.16) for MDD in diabetic subjects compared to the general population. Depressed subjects have been found to have a 32 % increased risk (RR 1.32, 95 % 1.18–1.47) for incident T2D (Yu et al., 2015), and diabetes is suggested to increase the risk for depressive symptoms by 34 % (OR 1.34, 95 % CI 1.14–1.57) (Chireh et al., 2019). Furthermore, globally over 9.5 million cases of increased depressive symptoms might be attributable to diabetes (Chireh et al., 2019).

Nevertheless, studies where no association between depressive symptoms or MDD and glucose disorders have also been published (Chireh et al., 2019; Wang et al., 2019; Yu et al., 2015). For example, in a population-based Finnish study among 2700 middle-aged subjects, the risk for increased depressive symptoms (defined as BDI score ≥ 10) was not increased among those with impaired glucose regulation (adjusted OR 0.91, 95 % CI 0.69–1.20), screen-detected (OR 0.70, 95 % CI 0.45–1.08) and previously known (OR 1.35 (95 % CI 0.84–2.15) T2D, compared to subjects with normal glucose regulation (Mäntyselkä et al., 2011).

2.7.2.3 Dyslipidaemia

A high low-density lipoprotein cholesterol (LDL-C) plasma level was one of the ten leading risk factors for healthy life lost in 2017 (GBD 2017 Risk Factor Collaborators, 2018). In Finland, 60 % of women and 54 % of men have dyslipidaemia (total cholesterol ≥ 5.0 mmol/l) (P. Koponen et al., 2018). Half of the adult (≥ 30 years old) population has elevated (≥ 3.0 mmol/l) LDL-C values, and one in ten has low (≤ 1.00 mmol/l) high-density lipoprotein cholesterol (HDL-C) level (P. Koponen et al., 2018).

There is consistent, strong evidence that LDL-C causes atherosclerotic CVD (Ference et al., 2017). The association of LDL-C to CVD is log-linearly dose-dependent, increasing with increasing duration of exposure (Ference et al., 2017). Lowering LDL-C by 1.0 mmol/l has been found to reduce major vascular events by 20 % without any threshold value (Cholesterol Treatment Trialists' (CTT) Collaboration, 2010). It was recently shown that low HDL-C increases CVD risk in association with LDL-C and triglyceride levels: when low HDL-C is accompanied with either high LDL-C or high triglyceride level, the risk is increased by 30 % (OR 1.3, 95 % CI 1.0–1.6 and OR 1.3, 95 % CI 1.1–1.5, respectively) and when both are present, the risk is increased by 60 % (OR 1.6, 95 % CI 1.2–2.2) (Bartlett et al., 2016). In addition, high triglyceride levels have been suggested to be independently associated with CVD risk (Toth, 2016).

In 2008, a meta-analysis of 30 studies showed that total cholesterol has an inverse association with increased depressive symptoms and MDD (Shin et al., 2008). The investigators did not find significant association of depressive symptoms or MDD

with LDL-C, but a positive association of HDL-C with depressive symptoms or MDD among women was found (Shin et al., 2008). A more recent meta-analysis on the association of increased depressive symptoms or MDD and LDL-C has reported both low and high LDL-C in subjects with these conditions (Persons & Fiedorowicz, 2016). However, a pooled analysis of nine Dutch cohorts (10 145 controls and 5285 persons with MDD or increased depressive symptoms) aiming to investigate metabolomic profile in depression suggested that there is a shift towards less HDL, and more very-low-density lipoprotein and triglyceride particles in depressive states (Bot et al., 2020). Moreover, patients with newly diagnosed dyslipidaemia and pre-existing depression were found to have a 24 % higher risk (HR 1.24, 95 % CI 1.09–1.41) for CVD compared to patients without depression among 72 235 Koreans (Kim et al., 2019).

2.7.2.4 Metabolic Risk Factors According to Subtypes of Depressive Symptoms

Considering depressive subtypes, metabolic risk factors have been found to accumulate among those with non-melancholic or atypical MDD and depressive symptoms (Brailean et al., 2019; Glaus et al., 2013; Lamers et al., 2013; Lasserre et al., 2014, 2017; Seppälä, Vanhala, et al., 2012).

In a Finnish population-based study among 4500 middle-aged subjects, those with increased non-melancholic depressive symptoms had a twofold risk of metabolic syndrome compared to subjects without depressive symptoms: the age- and gender-adjusted OR was 2.10 (95 % CI 1.62–2.73) (Seppälä, Vanhala, et al., 2012). Further adjustments for lifestyle attenuated the association slightly (OR 1.68, 95 % CI 1.16–2.22). Persons with increased non-melancholic depressive symptoms had higher risk for metabolic syndrome also when compared to melancholically depressive subjects (age- and gender-adjusted OR 1.84, 95 % CI 1.20–2.80; age-, gender-, and lifestyle-adjusted OR 1.87, 95 % CI 1.19–2.93) (Seppälä, Vanhala, et al., 2012).

Similarly, data analysis of 157 366 UK adults showed that metabolic syndrome (OR 2.39, 95 % CI 2.04–2.80), overweight (OR 2.79, 95 % CI 2.44–3.17), and obesity (OR 6.47, 95 % CI 5.71–7.35) associated with atypical MDD (Brailean et al., 2019). Atypical depression was associated with overweight (OR 1.5, 95 % CI 1.1–2.0), diabetes (OR 2.0, 95 % CI 1.1–3.5), and metabolic syndrome (OR 1.6, 95 % CI 1.0–2.4) also among 3716 middle-aged Swiss subjects (Glaus et al., 2013). These findings are consistent with a study of Lamers et al. (2013) who reported atypical depression being associated with higher mean BMI, larger waist circumference, higher triglycerides, and lower HDL-C levels compared to melancholic depression.

In a prospective setting, Lasserre et al. have found atypical MDD to predict a higher increase of adiposity (in regards to BMI, waist circumference, and obesity) (Lasserre et al., 2014), and incidence of metabolic syndrome (Lasserre et al., 2017). Data from the same Swiss cohort of middle-aged subjects also revealed that elevated BMI was associated with incidence of particularly atypical depression (Rudaz et al., 2017). In the NESDA cohort, a severe atypical subtype was associated with continuously high BMI and rate of metabolic syndrome during a six-year follow-up (Lamers, Beekman, et al., 2016). However, during the follow-up, those in the severe melancholic subgroup seemed to have a steeper increase in BMI and metabolic syndrome (Lamers, Beekman, et al., 2016).

2.7.3 Depressive Symptoms and Unhealthy Lifestyle

2.7.3.1 Smoking

Smoking is the second leading risk factor for healthy life lost globally (GBD 2017 Risk Factor Collaborators, 2018). In 2015, 25 % of men and 5 % of women worldwide were daily smokers, and 12 % of global deaths were attributable to smoking (GBD 2015 Tobacco Collaborators, 2017). In Finland, 16 % of men and 11 % of women (≥ 30 years) are current smokers (P. Koponen et al., 2018).

Smoking is an established risk factor for CVD, having an effect on all phases of atherosclerosis (Ambrose & Barua, 2004). Compared to never smoking, current smoking is associated with an almost threefold risk (OR 2.95, 95 % CI 2.77–3.14) of non-fatal myocardial infarction (Teo et al., 2006), a twofold risk (OR 1.92, 95 % CI 1.49–2.48) of stroke (B. Pan et al., 2019), and a threefold risk (RR 3.06, 95 % CI 2.46–3.82) of sudden cardiac death (Aune et al., 2018). In a Finnish study, current smoking significantly increased the risk for CVD death among middle-aged subjects (n = 9694, age 45–64 years): CVD risk factor-adjusted HRs were 4.28 (95 % CI 2.29–7.99), and 2.67 (95 % CI 1.92–2.67) in women and men, respectively (Barengo et al., 2019).

According to a meta-analysis on the association of smoking and depressive symptoms or MDD, current smokers have a 50 % increased risk (OR 1.50, 95 % CI 1.39–1.60) for being depressed than subjects who have never smoked, and subjects with increased depressive symptoms or MDD are 40 % more likely (OR 1.40, 95 % CI 1.17–1-68) current smokers than subjects without those (Luger et al., 2014). However, in prospective settings, the evidence of causality is still inconsistent. The majority of studies have however found significant associations from increased depressive symptoms to smoking, and vice versa (Fluharty et al., 2017). Moreover, subjects with IHD and depressive symptoms are less likely to quit smoking than nondepressed subjects (Doyle et al., 2014).

2.7.3.2 Alcohol Use

Alcohol use is one of the ten leading risk factors for death and disability-adjusted life years globally (GBD 2016 Alcohol Collaborators, 2018). In Finland, 25 % of women and 20 % of men are abstinent. Approximately 10 % of men and 3 % of women use alcohol at least four times a week or at least six alcohol units per occasion on a weekly basis (P. Koponen et al., 2018).

Low to moderate alcohol consumption has been associated with a reduced risk for CVD outcomes (Ronksley et al., 2011). Not surprisingly, heavy drinking (≥ 60 g of ethanol/day) is not protective for IHD events (Roerecke & Rehm, 2014). In addition, the protective effect of low or moderate alcohol use on stroke risk has been questioned (O'Donnell et al., 2016). Approximately one fourth of alcohol-attributable deaths are caused by CVD (Rehm et al., 2016).

Alcohol use disorders and depressive disorders are bidirectionally associated, one disorder doubling the risk for the other disorder (Boden & Fergusson, 2011). The causal pathway is suggested to proceed from alcohol use to depression (Boden & Fergusson, 2011).

2.7.3.3 Physical Activity

The recommended level of physical activity (PA) is at least 150 minutes of moderate-intensity, or 75 minutes of vigorous-intensity PA per week, or any equivalent combination of the two (World Health Organization, 2010). Physical inactivity, i.e. not meeting this recommendation contributes to 9 % of the premature mortality worldwide (I.-M. Lee et al., 2012). It has been estimated that in the high-income western countries, only 60 % of the adult population (Guthold et al., 2018), and in Finland, half of the over 30-year-old population meets the recommendation for aerobic PA (P. Koponen et al., 2018).

Meeting the recommended levels of PA has repeatedly been associated with a dose-dependent reduced risk of incident major CVD events (Lear et al., 2017; J. Li & Siegrist, 2012; Wahid et al., 2016). The magnitude of risk reduction is approximately 20 %.

Subjects with MDD rarely meet the recommended levels of PA: only one third meet these recommendations (Schuch et al., 2017). In addition, the longitudinal association of PA and depressive symptoms has been suggested to be bidirectional. In the Whitehall II study (n = 9309), baseline increased depressive symptoms were associated with a higher odds for not meeting the recommended levels of PA (OR 1.79, 95 % CI 1.17–2.74), and regular PA during the eight-year follow-up was associated with a reduced risk for depressive symptoms (OR 0.71, 95 % CI 0.54–0.99) (Azevedo Da Silva et al., 2012). Even

low levels of PA may prevent depressive symptoms (Mammen & Faulkner, 2013; Teychenne et al., 2008).

2.7.3.4 Lifestyle According to Subtypes of Depressive Symptoms

There are few studies investigating lifestyle and different subtypes of depressive symptoms, and their findings have been inconsistent. Smoking has been found to be more prevalent among the melancholically than the non-melancholically depressed in some studies (Lamers et al., 2010; Seppälä, Vanhala, et al., 2012), but also contrary suggestions have been made (Brailean et al., 2019). In addition, former but not current smoking has been suggested to increase odds for incident atypical MDD (Patel et al., 2018). Those with melancholic features seem to be more active physically (Brailean et al., 2019; Seppälä, Vanhala, et al., 2012), although in some studies there have been no differences in PA between the subtypes (Lamers et al., 2010; Lasserre et al., 2017). Alcohol dependence disorder has been found to be more prevalent in non-melancholic depression than in melancholic depression (Brailean et al., 2019). However, in some studies, those with melancholic MDD have been found to use more alcohol (Lasserre et al., 2017), while in some studies there has been no difference in the alcohol use between the subtypes (Seppälä, Vanhala, et al., 2012).

2.7.4 Depressive Symptoms and Self-Rated Health

According to a statement from the American Heart Association, patient-reported health status should be incorporated as a key measurement in clinical practice and in research when CVD health is considered (Rumsfeld et al., 2013). The subject's own view of her/his health, SRH, has been suggested to be a useful indicator of one's health (Gallagher et al., 2016) and to reflect objective health (Jylhä, 2009; Wu et al., 2013). The answer to the seemingly simple question "In general, how would you rate your health?" has been suggested to be a product of a complex process of subjective and contextual self-evaluation (Figure 7) (Jylhä, 2009).

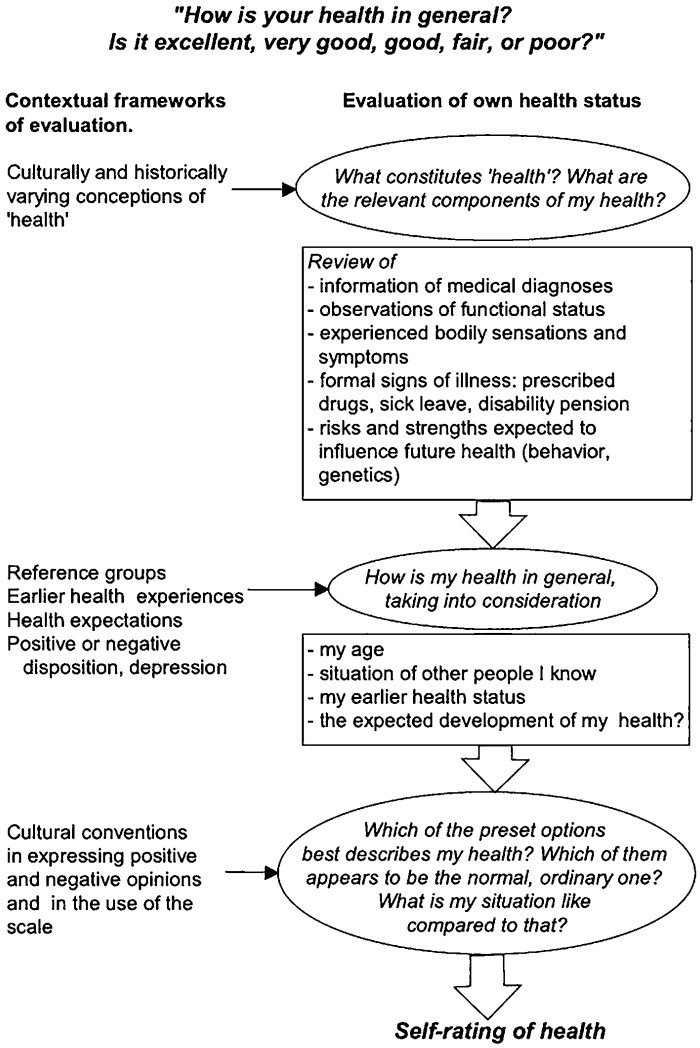

Figure 7. The process of individual health evaluation. Reprinted from Jylhä (2009) with permission from Elsevier. Copyright © 2009 Elsevier Ltd.

Certainly, when rating their health, individuals consider different aspects: for some health equals to lack of physical diseases or disability, whereas others may emphasise mental or even social facets. All of these may influence SRH (Mavaddat et al., 2011) (Figure 8).

At population level, SRH has been found to be determined by a variety of factors such as age, gender, socioeconomic conditions, morbidity and disability, and lifestyle (Y. Y. Chan et al., 2015; Darviri et al., 2011; Gallagher et al., 2016; Girón, 2012; Molarius et al., 2007; Ul-Haq et al., 2014; Yamada et al., 2012). In middle-

aged populations, similar determinants have been suggested. For example, in a population-based cohort from the UK (n = 20 941) those with poor SRH were more often women than men, less educated, smoked more often and had higher alcohol consumption levels compared to those with better self-ratings of health (van der Linde et al., 2013). In Sweden, poor SRH has been found to be associated with a variety of chronic diseases and symptoms among 6061 middle-aged subjects (Molarius & Janson, 2002). Among a small sample of Finnish middle-aged men (n = 665, mean age 41 years), PA was linearly associated with SRH (Engberg et al., 2015).

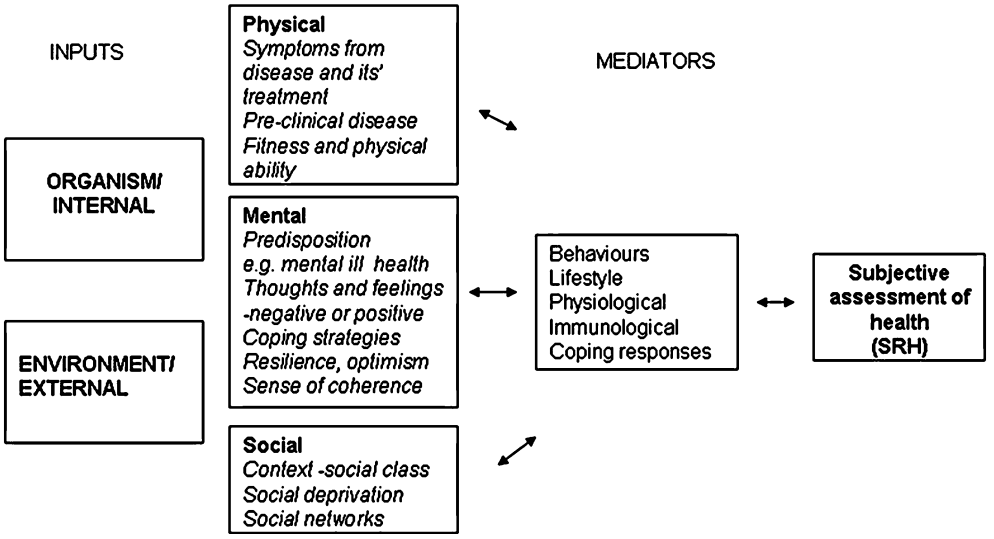

Figure 8. Model of influences on self-rated health. Reproduced from Mavaddat et al. (2011) with permission from BMJ Publishing Group Ltd. Copyright © 2011 BMJ Publishing Group Ltd.

Poor SRH has been shown to increase the risk for all-cause mortality (Bamia et al., 2017; DeSalvo et al., 2005) and CVD mortality (Bamia et al., 2017; Mavaddat et al., 2014). In the UK, middle-aged subjects with poor SRH have been found to have a threefold risk (HR 3.3, 95 % CI 2.4–4.4) of non-fatal and fatal CVD events after adjustment for various sociodemographic, behavioural and clinical risk factors (van der Linde et al., 2013). Consistent although not so strong results have been reported from a Swedish population-based cohort: when adjusted for standard CVD risk factors, poor SRH health increased the risk for myocardial infarction by 61 % (HR 1.61, 95 % CI 1.13-2.31) (Waller et al., 2015).

Recently, analysis of prospective data from the US National survey suggested that poor SRH increases the risk for CVD mortality nearly twofold (HR 1.84, 95 %

CI 1.45–2.35) after approximately ten years of follow-up, when adjusted for CVD risk score (Barger et al., 2016). Among middle-aged subjects without established CVD at baseline, the association was slightly attenuated, but still strong (HR 1.67, 95 % CI 1.27–2.18, adjusted for CVD risk score and non-traditional biomarkers). In another large population-based study in the US (The Multi-Ethnic Study for Atherosclerosis) (n = 6764, mean age 62 years, 53 % women), excellent SRH was associated with a 45 % lower risk (HR 0.55, 95 % CI 0.39–0.77) of CVD events compared to those with poor or fair health (Orimoloye et al., 2019).

In addition to being an independent predictor of CVD, poor SRH is also associated with many traditional CVD risk factors (Emmelin et al., 2006; Orimoloye et al., 2019; van der Linde et al., 2013; Waller et al., 2015). Moreover, poor SRH has previously also been associated with increased risk for undetected hypertension and diabetes (Korhonen et al., 2014).

It is reasonable to presume that depressive symptoms affect SRH. This association has been previously studied especially among middle-aged and older (≥ 55 years) populations, where poor SRH has been found to be strongly associated with increased depressive symptoms (OR 4.08, 95 % CI 3.25–5.12 for prevalent depressive symptoms among those with poor SRH; RR 2.40, 95 % CI 1.94–2.97 for incident depressive symptoms among those with poor SRH) (Chang-Quan et al., 2010). Having depressive symptoms has been suggested to increase the risk for poorer SRH at all levels of functional impairment and physical illness burden (Mulsant et al., 1997), and it has also been found to negatively affect changes in SRH (B. Han, 2002). However, also opposing results have been published: in their longitudinal analysis, Kosloski et al. (2005) found that depressive symptoms had very little effect on SRH; on the other hand, SRH had a consistent, modest effect on depressive symptoms.

In the Finnish Health 2000 study, SRH was lower in subjects with recent or current depressive disorder, compared to those without depression (Pirkola et al., 2009). In a Swedish population-based study among middle-aged subjects (n = 6061, 35–79 years old) self-reported depression was most strongly associated with poor SRH compared to a variety of somatic diseases (Molarius & Janson, 2002). Odds for poor SRH among the depressed was 8.1 (95 % CI 5.8–11.2) while it was 2.5 (95 % CI 1.9–3.3) among those with CVD, for example. Likewise, an analysis of data from the Health and Retirement Study (n = 17 930, age 50–104 years) found depressive symptoms to be the strongest predictor of SRH (Wagner & Short, 2014).

However, a meta-analysis has suggested that physical functioning is more important than mental health when assessing SRH (Smith et al., 1999). In concordance, in a more recent study among middle-aged UK adults (n = 20 853), physical functioning was more strongly associated with poor SRH than mental health

(OR 3.7, 95 % CI 3.3–41 and OR 1.4, 95 % CI 1.6–2.0, respectively) (Mavaddat et al., 2011). On the other hand, it has been suggested that physical health is a slightly stronger determinant of general health in subjects who feel generally unhealthy, whereas mental health is more important when general health is good (Au & Johnston, 2014).

In addition, among subjects with a history of depressive symptomatology, poor or fair SRH has been associated with a twofold risk for MDD (Ambresin et al., 2014). A comprehensive literature search yielded no studies on the association of melancholic and non-melancholic or atypical depressive symptoms and SRH.

2.8 Depressive Symptoms as Independent Cardiovascular Risk Factors

There is rather strong evidence of depressive symptoms being risk factors for CVD, independent of the traditional risk factors reviewed in the preceding section. Moreover, the risk is suggested to be similar in new-onset and previous depression, and for a variety of CVD without evidence of disease specificity (Daskalopoulou et al., 2016). A meta-analysis of 13 longitudinal studies recently reported an almost doubled risk for CVD among depressed subjects compared to the non-depressed (Correll et al., 2017).

At least five meta-analyses on the association between MDD or increased depressive symptoms and incident IHD have been published (Gan et al., 2014; Nicholson et al., 2006; Rugulies, 2002; Van der Kooy et al., 2007; Wulsin & Singal, 2003). One of the most recent meta-analyses suggested a 30 % increased risk (RR 1.30, 95 % CI 1.22–1.40 and RR 1.30, 95 % CI 1.18–1.44) for incident IHD and myocardial infarction, respectively, among subjects with increased depressive symptoms compared to non-depressive persons (Gan et al., 2014). The associations of depressive symptomatology and IHD remained significant, and of the same magnitude also in the subgroup analyses where various variables, including sociodemographic, lifestyle, and other CVD risk factors were adjusted for (Gan et al., 2014). Moreover, the risk increase has been suggested to be similar among women and men (Smaardijk et al., 2019).

Depressive symptoms have also been associated with increased risk for incident stroke in a set of meta-analyses (Barlinn et al., 2014; Dong et al., 2012; M. Li et al., 2015; A. Pan et al., 2011). In subjects without baseline CVD, the risk for incident stroke has been suggested to be over 40 % higher among those with increased depressive symptoms or MDD than among the non-depressed (Barlinn et al., 2014; M. Li et al., 2015). Pooled risk estimates for CVD in depressive subjects without baseline IHD/stroke drawn from recent meta-analyses are summarized in Table 8.

Table 8. Increased depressive symptoms or major depression as risk factors for incident cardiovascular disease in subjects without baseline cardiovascular disease.

META-ANALYSIS	NUMBER OF STUDIES	NUMBER OF PARTICIPANTS	ODDS RATIO OR RELATIVE RISK (95 % CI) FOR CVD
Ischemic heart disease			
Rugulies, 2002	11	36 279	1.64 (1.29–2.08)
Wulsin & Singal, 2003	10	28 737	1.64 (1.41–1.90)
Nicholson et al., 2006	21	124 509	1.81 (1.53–2.15)
Van der Koyy et al., 2007	16	656 991	1.57 (1.36–1.81)
Gan et al., 2014	30	893 850	1.30 (1.22–1.40)
Stroke			
A. Pan et al., 2011	21	206 978	1.44 (1.26–1.65)
Dong et al., 2012	17	206 641	1.34 (1.17–1.54)
Barlinn et al., 2014	15	186 794	1.43 (1.19–1.72)
M. Li et al., 2015	27	248 380	1.48 (1.30–1.67)

CI, confidence interval; CVD, cardiovascular disease.

More recent prospective, population-based studies have suggested similar results. For example, longitudinal data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) survey among 32 345 US adults (mean age 45 years; 58 % women), free of IHD at baseline were recently analysed (H. Liu et al., 2019). After three years of follow-up, and adjustment for sociodemographic and CVD risk factors, incident (RR 2.07, 95 % CI 1.69–2.54), persistent (RR 1.78, 95 % CI 1.30–2.44), and remitted (RR 1.38, 95 % CI 1.11–1.73) MDD were shown to increase the risk for incident IHD (H. Liu et al., 2019).

In France, an analysis of the Gazel cohort added to the evidence suggesting that depressive symptoms are independent CVD risk factors (Hamieh et al., 2019). Among 10 541 middle-aged subjects (mean age 48 years; 26 % women), and after 20 years of follow-up, time-varying increased depressive symptoms were significantly associated with incident cardiac events even after adjustment for gender, age, hypertension, diabetes, dyslipidaemia, occupational grade, parental IHD history, obesity, smoking status, and physical activity. The fully-adjusted HR for incident cardiac events was 1.55 (95 % CI 1.17–2.05) among those with increased depressive symptoms compared to those without (Hamieh et al., 2019). Moreover, the investigators found no evidence of major CVD risk factors (hypertension, diabetes, and dyslipidaemia) affecting this association (Hamieh et al., 2019).

In a NESDA cohort study among 2541 subjects (mean age 41 years, 68 % women) without CVD at baseline, current but not remitted depression was associated with incident IHD and stroke (HR 2.33, 95 % CI 1.36–4.00) after adjustment for sociodemographic and CVD risk factors, during six years of follow-up (Seldenrijk et al., 2015).

Among 481 355 middle-aged and older Koreans, depression was associated with a 41 % increased risk (HR 1.41, 95 % CI 1.34–1.48) for incident CVD among men, and a 48 % increased risk (HR 1.48, 95 % CI 1.42–1.54) among women after adjustment for several CVD risk factors (Jee et al., 2019).

In Denmark, ten population-based cohorts (n = 93 076, mean age 54 years, 53 % women) were analysed to assess the bidirectional relationship of increased depressive symptoms or depression with CVD. They were found to be associated with an increased risk for IHD (adjusted HR 1.63, 95 % CI 1.36–1.95) and stroke (adjusted HR 1.94, 95 % CI 1.63-2.30) (Wium-Andersen et al., 2019). Moreover, the associations were similar in a subpopulation with self-reported depressive symptoms.

When taking the severity of depression into account, all levels of major depression have been associated with CVD risk among a Swedish sample of 10 443 adults (mean age 41 years, 56 % women) (Almas et al., 2015). However, in adjusted models, only depression with moderate severity significantly increased the risk for CVD (OR 2.1, 95 % CI 1.3–3.5), compared to no depression.

In Greece (n = 853, mean age 43 years, 49 % women), after ten years of follow-up, increased depressive symptoms were found to increase the risk for incident CVD almost fourfold (OR 3.6, 95% CI 1.3–11) after adjustment for multiple CVD risk factors (Kyrou et al., 2017).

Among subjects ≥ 65 years old, high levels of depressive symptoms have been associated with a 15 % cumulative increase (HR 1.15, 95 % CI 1.06–1.25) of incident IHD and stroke risk per 2–3 years (Péquignot et al., 2016). In this study, baseline depressive symptoms predicted only fatal CVD events. A sample of a similar older population from the US (n = 4319, mean age 72, 58 % women) showed namely stable high levels of depressive symptoms to be associated with increased risk for stroke (adjusted HR 1.65, 95 % CI 1.06–2.56) whereas new or remitted symptoms did not seem to increase the stroke risk (Gilsanz et al., 2017). In addition, Stewart et al. (2016) did not find depression screens to be associated with an elevated risk for hard CVD events among 2041 subjects aged 60 years or older.

2.8.1 Subtypes of Depressive Symptoms and Incident Cardiovascular Disease

Studies on the association of different depressive subtypes and incident CVD among subjects without established CVD are very scarce. Case et al. (2018) analysed data from the NESARC cohort. In their study among 28 726 US adults, both atypical and typical MDD predicted incident CVD even after adjustment for CVD risk factors (OR 1.78, 95% CI 1.37–2.30 and OR 1.42, 95% CI 1.23–1.65, respectively), but comparisons between these groups were not significant (Case et al., 2018).

2.9 Depressive Symptoms and All-Cause Mortality

Depression and depressive symptoms have been suggested to be associated with excess mortality (Baxter et al., 2011; Walker et al., 2015; Wei et al., 2019). It has been proposed that the increased mortality risk is similar in major and subthreshold depression (Cuijpers et al., 2013), in specific patient groups and in the general population (Cuijpers et al., 2014a), and in both genders, although higher in men (Cuijpers et al., 2014b).

2.9.1 Linking Mechanisms

Many possible explanations for the excess mortality risk among depressed subjects have been proposed. As the increased mortality risk has been found to be similar in community and clinical samples, it has been suggested that this association is driven by generic mechanisms (Cuijpers et al., 2014a). These might include lifestyle and biological mechanisms.

Depression and increased depressive symptoms are associated with unhealthy lifestyle (section 2.7), and poorer adherence to medical treatment (DiMatteo et al., 2000; Grenard et al., 2011). Specifically, depressive symptoms have been associated with non-adherence to antihypertensive therapy (Lemstra & Alsabbagh, 2014), lower adherence to diabetes self-care (Sumlin et al., 2014), and non-adherence to medication after acute coronary syndrome (Crawshaw et al., 2016). These factors inevitably contribute to mortality risk due to these somatic diseases.

Likewise, dysregulations of metabolic, immuno-inflammatory, autonomic, and HPA axis that have been associated with depressive symptoms (Penninx et al., 2013) (section 2.3) plausibly mediate the association of depressive symptoms with all-cause mortality. In addition, depressive symptoms are major risk factors for self-harm (Ribeiro et al., 2018). In Table 9, possible causes of increased mortality in depressive states are summarized (Cuijpers & Schoevers, 2004).

Table 9. Possible causes of increased mortality in depression.

Increased suicide rates in depressed patients
More hazardous health behaviours
tobacco use
unhealthy eating habits
alcohol use
less physical activity
hazardous behaviour such as dangerous driving
Depression is a psychological reaction to medical illness*
Biological dysregulations
hyperactivity of the HPA-axis
neuro-immune dysregulation
sympatho-adrenergic dysregulation
"vascular" depression in the elderly
Less compliance with treatment in depressed patients

*Excess mortality is not caused by depression, but the illness. HPA, hypothalamic-pituitary-adrenal. Reprinted from Cuijpers & Schoevers (2004) by permission from Springer Nature. Copyright © 2004 by Current Science Inc.

2.9.2 Evidence of the Relationship of Depressive Symptoms and All-Cause Mortality

In recent meta-analyses of studies conducted in general population cohorts, increased depressive symptoms have been found to increase the risk for all-cause mortality by 34–70 % (Baxter et al., 2011; Cuijpers et al., 2014a; Walker et al., 2015; Wei et al., 2019).

Recent studies among middle-aged subjects have reported similar results. For example, in a Finnish population-based study among 30–70 -year old subjects (n = 6372) risk for all-cause mortality was doubled after an eight-year follow-up among those with depressive disorders compared to non-depressed subjects (HR 1.97, 95 % CI 1.15–3.39, adjusted for socioeconomic factors, health status and smoking) (Markkula et al., 2012). In this study, depression increased the risk for death as much as cardiovascular disorders (adjusted HR 1.82, 95 % CI 1.34–2.47). In addition, depressive symptomatology measured by the BDI was also associated with mortality after controlling for confounders (HR 1.53, 95 % CI 1.11–2.11 for BDI summary score 10–18, HR 1.77, 95 % CI 1.09–2.85 for BDI summary score ≥ 19) (Markkula et al., 2012).

In Denmark, middle-aged men (n = 10 517, born in 1953) with register-based hospital diagnosis of depression had an almost threefold mortality risk (HR 2.80, 95 % CI 1.65–4.76) compared to those with no depression when adjusted for social

class, comorbidity, BMI, and lifestyle (Christensen et al., 2017). A similar risk increase was detected with self-reported depression.

In a large population-based longitudinal study in the US among 29 491 adults (≥ 45 years, mean age 65 years, 55 % women), risk for all-cause mortality was increased by 24 % (adjusted HR 1.24, 95 % CI 1.14-1.39) and non-CVD mortality by 29 % (adjusted HR 1.29, 95 % CI 1.16–1.44) with increased depressive symptoms (Moise et al., 2018). Interestingly, the association of depressive symptoms and all-cause mortality was found to be stronger with better SRH (HR 1.48, 95 % CI 1.27–1.78 in excellent/very good SRH and HR 1.17, 95 % CI 1.06–1.30 in poor/fair/good SRH). In their study, depressive symptoms were not associated with increased CVD mortality, whereas in a study of 24 542 middle-aged subjects in Central and Eastern Europe, depressive symptoms associated as well with all-cause as with CVD mortality (Kozela et al., 2016). In this study, the risk for all-cause and CVD mortality increased by 17 % (HR 1.17, 95 % CI 1.10–1.25) and 23 % (HR 1.23, 95 % CI 1.12–1.35) in women, and by 13 % (HR 1.13, 95 % CI 1.09–1.18) and 20 % (HR 1.20, 95 % CI 1.16–1.24) in men with one SD increase in severity of depressive symptoms (Kozela et al., 2016).

In addition, even a single-item measure of increased depressive symptoms (”I felt depressed”) has been suggested to be associated with a 15 % increased risk (HR 1.15, 95 % CI 1.05–1.27) for mortality after adjustment for various covariates in the Gazel cohort (Lefèvre et al., 2012).

However, also conflicting results have been published. For example, depression did not appear to have an influence on mortality during 25 years of follow-up among the subjects (n = 15 449) from the Epidemiologic Catchment Area Study in the US (Eaton et al., 2013). In a study among 11 104 UK adults (≥ 50 years old) even low levels of depressive symptoms seemed to be associated with mortality, but adjustment for PA, physical illnesses, and impairments in physical and cognitive functioning fully attenuated the association (White et al., 2015).

Accordingly, a causal effect of depression on all-cause mortality has recently been questioned (Machado et al., 2018). When reviewing systematic reviews and meta-analyses, Machado et al. suggest that this association remains unproven. However, in mixed-sample populations the association is supported by highly suggestive evidence (Machado et al., 2018). In another recent review, among the reasons for poor quality of evidence were proposed to be inadequate adjustment for possible confounding variables and publication bias (Miloyan & Fried, 2017).

2.9.2.1 Subtypes of Depressive Symptoms and All-Cause Mortality

Given the possible differences in pathophysiology of the subtypes of depressive symptoms (section 2.3) their association with mortality risk might be different. However, studies assessing the effect of depressive symptoms on all-cause mortality have rarely considered different subtypes. Lasserre et al. (2016) reported that subjects with current depressive disorder had a threefold risk (HR 3.2, 95 % CI 1.1–10.0) for all-cause mortality, but depression with atypical features was not associated with mortality in a middle-aged population in Switzerland (n = 3668, mean age 51 years, 53 % women) (Lasserre et al., 2016).

In specific patient groups, cognitive/affective and somatic depressive symptoms have been suggested to differently predict all-cause mortality. Among patients with chronic heart failure, namely increased somatic/affective depressive symptoms predicted all-cause mortality (Schiffer et al., 2009). A similar but not statistically significant association has been proposed among patients with IHD (Herbison et al., 2015). Fatigue, one of the non-melancholic depressive symptoms, has been associated with a 26 % increased (HR 1.26, 95 % CI 1.10–1.45) risk for all-cause mortality in the UK EPIC-Norfolk study among 18 101 middle-aged persons (Basu et al., 2016).

3 Aims

This thesis aimed to investigate increased depressive symptoms in a middle-aged CVD risk population, and their association with hypertension awareness, SRH, CVD morbidity, and all-cause mortality. The specific aims were:

1. To assess the relationship of increased depressive symptoms with hypertension awareness (Study I).
2. To assess the relationship of SRH and increased depressive symptoms, traditional CVD risk factors, and perceived physical health (Study II).
3. To assess increased melancholic and non-melancholic depressive symptoms and their relationship with CVD morbidity (Study III).
4. To assess increased melancholic and non-melancholic depressive symptoms and their relationship with all-cause mortality (Study IV).

4 Materials and Methods

4.1 Study Population

The study population was a subsample of subjects who attended the Harmonica Project (Harjavalta Risk Monitoring for Cardiovascular Disease), a population survey carried out in the semirural towns of Harjavalta and Kokemäki (7646 and 8217 inhabitants on 31.12.2007, respectively) from August 2005 to September 2007. The formulation of the Harmonica Project is illustrated in Figure 9.

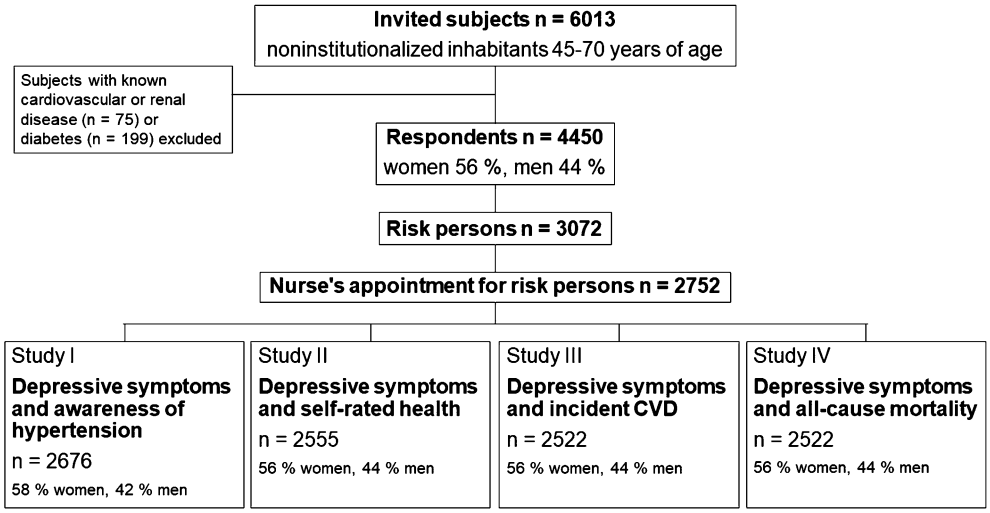

Figure 9. Formulation of the study population. CVD, cardiovascular disease.

All home-dwelling inhabitants aged 45 to 70 years (n = 6013) were invited, and mailed a CVD risk factor survey (Table 10), a tape for waist circumference measurement, and a T2D risk assessment form (FINDRISC, Finnish Diabetes Risk Score (Lindström & Tuomilehto, 2003), Table 11). The subjects were asked to return the risk factor survey if they were able to participate. The participation rate was 74 % (4 450/6 013). Subjects who had at least one of the considered CVD risk factors (n = 3072) but did not have known CVD or renal disease (n = 75) or diabetes (n =

199) were invited for an enrolment examination performed by a trained study nurse. Of those, 2752 were willing to participate. The number of the subjects included in the different studies of this thesis slightly varied due to missing of important variables needed for specific analyses. The number of the study subjects was 2676, 2555, and 2522 in Studies I, II and III-IV, respectively.

Table 10. Risk factor survey: Factors considered and definition of cardiovascular risk.

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

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

Table 11. Factors considered in the Finnish Diabetes Risk Score (FINDRISC) (Lindström & Tuomilehto, 2003).

Age
Body mass index
Waist circumference
Physical activity level
Consumption of vegetables, fruit, and berries
Use of antihypertensive medication
Previously detected elevated blood glucose
Family history of diabetes (type 1 or 2)

4.2 Methods

4.2.1 Questionnaires

Before the physical enrolment examination, the subjects completed self-administered questionnaires concerning their health and lifestyle habits, and sociodemographic factors.

4.2.1.1 Depressive Symptoms

Depressive symptoms were assessed by the self-administered BDI, version BDI-1A (Beck et al., 1979) which is a revised version of the original BDI. A total summary score ranging from 0 to 63 was calculated based on the scores (range from 0 to 3) on the 21 items rated. In this thesis, a cut-off point ≥ 13 (Lasa et al., 2000) of the summary score was used in Study I, and a cut-off point ≥ 10 (Aalto et al., 2012; H. Koponen et al., 2010; Mäntyselkä et al., 2011; Seppälä, Vanhala, et al., 2012) in the other studies (II-IV) to indicate increased depressive symptoms.

Subjects were divided into melancholic and non-melancholic depressive subgroups by comparing means of summary scores of melancholic and non-melancholic items in the BDI (Studies III, IV) (Ovaskainen et al., 2009; Seppälä, Vanhala, et al., 2012; Steer et al., 1999; Vanhala et al., 2009). Items considered melancholic based on DSM-5-defined criteria were sadness, past failure, loss of pleasure, guilty feelings, punishment feelings, irritability, loss of interest, change in sleeping, and change in appetite. Other items were considered non-melancholic. A subject was classified into the melancholic subtype if the mean of the summary score of the melancholic items was higher than that of the non-melancholic items, and vice versa. If the means were equal, the subtype was considered melancholic.

4.2.1.2 Sociodemographic Factors

The sociodemographic factors considered in this thesis were age, gender, education, and cohabiting. The study subjects were asked to report their level of education and marital status. Education was dichotomized to upper secondary school completed/not (Studies I, II), and handled as a continuous variable (mean education years) (Studies III, IV). Based on the marital status, a dichotomized variable "cohabiting" was created.

4.2.1.3 Lifestyle Associated Factors

Lifestyle associated factors considered were smoking, alcohol use, and level of leisure-time physical activity (LTPA). In the questionnaire, subjects were asked to provide information on smoking (never, ever, and current smoking) and current frequency of LTPA for at least 30 minutes at a time. Smoking status was dichotomized to current/not current smoking. Alcohol use was assessed by the Alcohol Use Disorders Identification Test, AUDIT (Babor et al., 1989). A cut-off score of ≥ 8 points was used to divide the subjects into those without and those with harmful alcohol use (Babor et al., 1989) (Studies I, II), or the score was handled as a continuous variable (mean AUDIT score) (Studies III, IV). The level of LTPA was classified into three categories: high (LTPA for at least 30 min at a time for six or

more times a week), moderate (LTPA for at least 30 min at a time for four to five times a week), and low (LTPA for at least 30 min at a time for a maximum of three times a week).

4.2.1.4 Self-Rated Health and Perceived Physical Health

SRH and perceived physical health were assessed by the Short-Form Health Survey (SF-36), version 1.0 (Hays & Morales, 2001). The SF-36 is a widely used 36-item survey instrument for assessing health-related quality of life. It comprises eight health concepts: physical functioning, role limitations caused by physical health problems, and pain (these three measures reflects primarily physical health); role limitations caused by emotional problems and emotional well-being (reflecting primarily mental health); and social functioning, energy/fatigue, and general health perceptions reflecting both physical and mental dimensions of health (Hays & Morales, 2001). For the scoring, every item is most commonly transformed linearly to a scale of 0–100, and then all items are averaged in the same scale together (Hays & Morales, 2001). The SF-36 is available and validated in multiple languages (Hays & Morales, 2001), and it has been found to have reliability and construct validity to measure health-related quality of life also specifically in the Finnish general population (Aalto et al., 1999).

The first question of the SF-36, "In general, how would you rate your health?" assesses SRH on a 5-point Likert scale: 1 = poor, 2 = fair, 3 = good, 4 = very good, and 5 = excellent. In this thesis, SRH was categorized into three levels as follows: level I: poor or fair; level II: good; level III: very good or excellent.

The study subjects´ perception of their physical health was assessed by the SF-36 physical component summary score. The eight health domains were aggregated into the physical component summary by using the US reference population (1990) for standardization of the domains and for factor score coefficients. The physical component score was standardized using a mean of fifty and a SD of ten (Ware & Kosinski, 2001).

4.2.2 Physical Examination

After completing the abovementioned questionnaires, the study subjects attended an enrolment examination performed by a trained study nurse.

4.2.2.1 Blood Pressure

BP was measured by a trained nurse with a mercury sphygmomanometer with subjects in a sitting posture, after resting for at least five minutes with the cuff placed

on the arm. The mean of two readings taken at an interval of at least two minutes was used to determine BP level. However, if the mean of two readings of systolic BP was ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, and the subjects had no antihypertensive medication, they were instructed to perform home BP monitoring with an automatic validated blood pressure monitor (Omron®M4-1) to confirm the BP level. The participants whose arm circumference was ≥ 32 cm used a larger cuff. The subjects were advised to perform duplicate BP measurements in a seated position after five minutes of rest in the morning and evening for one week. The recorded measurements except those from the first day were used to calculate the mean home BP.

In Study I, the subjects were classified according to their hypertension status into three categories: aware hypertensives (subjects with antihypertensive medication), unaware hypertensives (no antihypertensive medication, the mean of home BP monitoring ≥ 135 mmHg for systolic or ≥ 85 mmHg for diastolic BP), and normotensives.

4.2.2.2 Weight, Height, Body Mass Index, and Waist Circumference

Weight and height were measured with subjects in a standing position without shoes and outer garments, and waist circumference at the level midway between the lower rib margin and iliac crest. BMI was calculated as weight (kg) divided by the square of height (m^2). BMI was handled as a continuous variable, and in Study I, it was classified as follows: normal weight BMI < 25.0 kg/m^2, overweight BMI 25.0–29.9 kg/m^2, obese BMI 30.0–34.9 kg/m^2, very obese BMI ≥ 35.0 kg/m^2.

4.2.3 Laboratory Measurements

Before the enrolment examination, laboratory tests were determined in blood samples obtained after at least 12 hours of fasting. An oral glucose tolerance test was also performed. Glucose values were measured from capillary whole blood with the HemoCue Glucose 201+ system (Angelholm, Sweden) which converts the result into plasma glucose values.

Glucose metabolism disorders were categorized into T2D (fasting glucose ≥ 7.0 mmol/l or 2-hour postload plasma glucose ≥ 12.2 mmol/l), impaired glucose tolerance (IGT, 2-hour postload plasma glucose 8.9–12.1 mmol/l), and impaired fasting glucose (IFG, fasting glucose 6.1–6.9 mmol/l) (World Health Organization & International Diabetes Federation, 2006). Those with both IGT and IFG were classified as IGT (Studies III, IV). In Study II, IGT and IFG were combined into intermediate hyperglycaemia.

Plasma total cholesterol, HDL-C, and triglycerides were measured from venous plasma enzymatically (Olympus® AU640, Japan). LDL-C was calculated according to Friedewald's formula.

4.2.4 Baseline Medication

Data on regularly used medication were gathered from the questionnaire and medical records. Medications considered in this thesis were antihypertensive medication, and medication for lipid disorders and depression/anxiety.

4.2.5 Intervention on Cardiovascular Risk Factors

The study nurse gave lifestyle counselling to all subjects attending the enrolment examination. Subjects (n = 1928) were further invited to a physician's appointment, if at least one of the following was detected at the nurse's appointment: hypertension, diabetes, IGT, metabolic syndrome according to the International Diabetes Federation criteria (Alberti et al., 2005), obesity (BMI ≥ 30.0 kg/m^2), or ≥ 5 % ten-year risk for CVD death estimated by the SCORE (Conroy et al., 2003). Preventive medication (an antihypertensive drug, a lipid lowering agent, or low dose aspirin) was started if the SCORE indicated ≥ 5 % ten-year risk for developing a fatal CVD event. Antihypertensive medication was prescribed according to the national care guidelines if systolic BP was ≥ 160 mmHg or diastolic BP ≥ 100 mmHg, or target organ damage was diagnosed (The working group of the Finnish Hypertension Society, 2002). Ongoing antihypertensive medication was intensified if SBP was ≥ 140 mmHg or diastolic BP ≥ 85 mmHg (≥ 80 mmHg in patients with diabetes).

4.2.6 Incident Cardiovascular Disease (Study III)

Data on incident CVD were obtained from the Care Register for Health Care of the National Institute of Health and Welfare. Endpoints of interest were incident CVD diagnosed according to the ICD, 10th Revision (ICD-10, Finnish language), specifically: I20 angina pectoris, I21 acute myocardial infarction, I25 chronic ischemic heart disease, I60 subarachnoid haemorrhage, I61 intracerebral haemorrhage, I62 other nontraumatic intracranial haemorrhage, I63 cerebral infarction, I65 occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction, I66 occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction, I70 atherosclerosis, I71 aortic aneurysm and dissection, and I74 arterial embolism and thrombosis. We categorised CVD diagnoses into IHD (ICD-10 codes I20, I21, I25), CeVD (ICD-10 codes I60, I61, I62, I63, I65, I66), and PAD (ICD-10 codes I70, I71, I74).

Follow-up time started at the time of the enrolment examination, and ended on 31st December 2013, or on the date of the first occurrence of incident CVD, or death.

4.2.7 Mortality (Study IV)

Data on mortality were obtained from The Official Statistics of Finland provided by Statistics Finland. Causes of death were classified according to the ICD-10 as follows: malignant neoplasms (C00–C97), diseases of the nervous system (G00–G99), diseases of the circulatory system (I00–I99), diseases of the digestive system (K00–K93), external causes of death (V01–X84 accidents and intentional self-harm), and other causes of death (diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50–89), endocrine, nutritional and metabolic diseases (E00–E90), mental and behavioural disorders (F00–F99), diseases of the respiratory system (J00–J99), diseases of the musculoskeletal system and connective tissue (M00–M99), diseases of the genitourinary system (N00–N99), symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)).

Follow-up time started at the time of the enrolment examination, and ended on December 31st, 2017, or on the date of death.

4.2.8 Statistical Analyses

Descriptive statistics are shown as the number of subjects, as proportions with percentages for categorical variables, and as means with SDs for normally distributed continuous variables. In Study I, a median with interquartile range is otherwise shown. In all analyses, a significance level was set at 0.05, and the 95 % CIs are shown.

Statistical comparisons between groups were made by using analysis of variance, Kruskal–Wallis test, chi-square test, or Cochran–Armitage test. Normality of the variables was evaluated graphically and/or using Shapiro–Wilk W-test. The bootstrap method was used when the theoretical distribution of the test statistics was unknown, or in the case of violation of the assumptions (e.g. non-normality) (Studies III-IV). Hommel's adjustment was applied to correct levels of significance for multiple testing, if appropriate.

In Study I, the predictors of increased depressive symptoms were modelled with logistic regression with the following independent variables: hypertension status, age, gender, education, cohabiting, smoking, alcohol use, LTPA, BMI as categorised. In addition, a similar model was executed for subjects using antihypertensive medication including medication (beta-blocker, calcium antagonist,

angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, diuretic). ORs and their 95 % CIs were calculated from the logistic regression model.

In Study II, the adjusted hypothesis of linearity of SRH and depressive symptoms was evaluated using generalized linear statistical models (e.g. analysis of covariance and logistic models) with appropriate distribution and link function. Models included age, cohabiting status, smoking, LTPA, BMI, years of education, plasma glucose level, SBP level, and medication as covariates.

In Study III, unadjusted cumulative CVD morbidity rates were based on the Kaplan–Meier failure function. Age- and gender-adjusted Kaplan–Meier cumulative CVD morbidity rates were estimated using two propensity score-based techniques, stratification and weighting (marginal mean weighting through stratification) (Linden, 2014). Adjusted incidence rate and incidence rate ratio (IRR) were calculated using Poisson regression models, including age, gender, education, smoking, alcohol use, LTPA, hypertension, and dyslipidaemia as covariates.

In Study IV, the Kaplan–Meier method was used to estimate the cumulative mortality. Adjusted survival curves were based on a stratified Cox model using gender and baseline age, smoking, and education years as covariates. The possible non-linear relationship between BDI and all-cause mortality was modelled using restricted cubic splines with three knots at the 10^{th}, 50^{th}, and 90^{th} percentiles. Spline functions were estimated using multivariable Cox proportional hazard regression models, including gender and baseline age, smoking, and education years as covariates. The proportional hazards assumption was tested graphically and by use of a statistical test based on the distribution of Schoenfeld residuals. The standardized mortality rate (SMR) for all-cause deaths was calculated using the subject-years method with 95 % CIs, assuming a Poisson distribution. Probabilities of survival in an age- and gender-matched sample of the general population were calculated from data of The Official Statistics of Finland.

In Study I, the analyses were performed using SAS® System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) and SPSS Statistics (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). In other Studies, statistical analyses were carried out with Stata, version 15.1 or 16.0 (StataCorp LP, College Station, TX, USA).

4.2.9 Ethical Issues

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

5 Results

5.1 Prevalence of Increased Depressive Symptoms

The mean of the BDI summary score was 6.0 (SD 5.6) in the whole study population (n = 2676), 3.8 (SD 2.8) among those without, and 14.9 (SD 5.5) among those with increased depressive symptoms when the BDI summary score ≥ 10 was set as the cut-off value for increased depressive symptoms. Figure 10 illustrates the distribution of the BDI summary score in subjects (n = 2522) without and those with increased depressive symptoms (BDI ≥ 10), dichotomized into melancholic and non-melancholic subgroups. In this subsample, the mean of the BDI summary score was 14.8 (SD 5.5) in melancholically and 15.1 (SD 5.5) in non-melancholically depressive subjects.

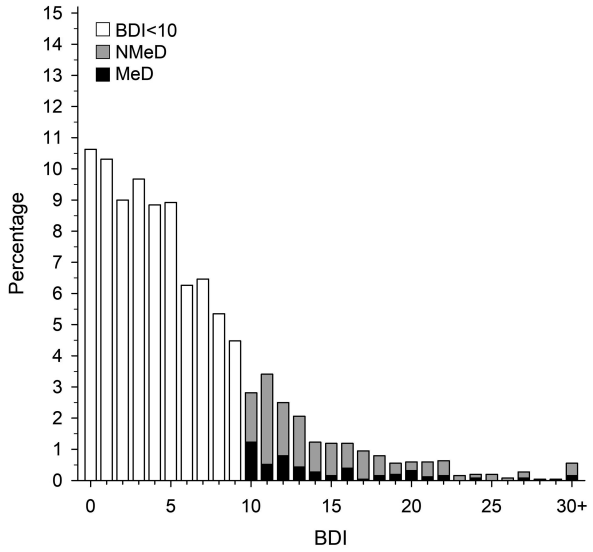

Figure 10. The distribution of the Beck's Depression Inventory score in subjects without depressive symptoms (BDI <10), with melancholic and non-melancholic depressive symptoms (BDI ≥ 10). BDI, Beck's Depression Inventory; MeD, melancholic depressive symptoms; NMeD, non-melancholic depressive symptoms. Reprinted from Study III (Rantanen et al., 2020) with permission from Elsevier. Copyright © 2019 Elsevier Inc.

In the studies of this thesis, the prevalence of increased depressive symptoms varied from 10.7 % to 21.1 % according to the used cut-off point of the BDI summary score, and the subsample of the study population. In the whole study population (n = 2676), the prevalence of increased depressive symptoms defined by the BDI summary score ≥ 10 and ≥ 13 was 19.5 % and 10.7 %, respectively. Women had more often increased depressive symptoms than men (BDI ≥ 10: 23.4 % vs. 15.0 %, $p < 0.001$; BDI ≥ 13: 13.4 % vs. 7.3 %, $p < 0.001$). The prevalence of increased depressive symptoms (BDI ≥ 10) appeared slightly higher in Studies II (n = 2555) and III-IV (n = 2522): 20.0 % and 21.1 %, respectively.

The prevalence of increased melancholic and non-melancholic depressive symptoms (Studies III, IV) was 5.2 % and 14.9 %, respectively. Increased non-melancholic depressive symptoms were more prevalent in women (18.3 %) than in men (10.6 %) ($p < 0.001$), whereas the prevalence of increased melancholic depressive symptoms was similar in both genders (5.0 % and 5.5 % in women and men, respectively, $p = 0.59$) (Figure 11).

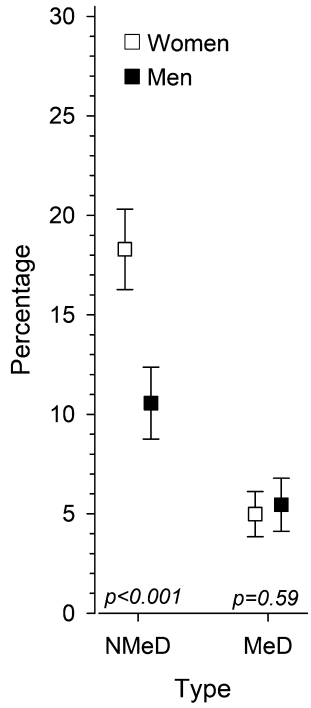

Figure 11. The prevalence of increased (BDI ≥ 10) melancholic and non-melancholic depressive symptoms according to gender. MeD, melancholic depressive symptoms; NMeD, non-melancholic depressive symptoms.

5.2 Sociodemographic and Lifestyle Associated Risk Factors for Increased Depressive Symptoms

The association of more severe levels of increased depressive symptoms (BDI ≥ 13) with assessed sociodemographic and lifestyle associated factors is presented in Table 12. The odds for increased depressive symptoms was increased with female gender (OR 3.08, 95 % CI 2.15–4.42, p < 0.001) and harmful alcohol use (OR 2.52, 95 % CI 1.73–3.75, p < 0.001), and it decreased with non-smoking (OR 0.63, 95 % CI 0.44–0.90, p = 0.011), and moderate LTPA compared to low LTPA (OR 0.62, 95 % CI 0.46–0.85, p = 0.013). Age, cohabiting, and education did not impact the risk of increased depressive symptoms.

Table 12. Sociodemographic and lifestyle associated factors predisposing to increased depressive symptoms (BDI ≥ 13).

VARIABLES	OR (95% CI)	P-VALUE
Age	1.02 (0.99–1.04)	0.21
Female gender	3.08 (2.15–4.42)	< 0.001
Upper secondary school	1.27 (0.86–1.89)	0.23
Cohabiting	0.89 (0.64–1.25)	0.51
Non-smoking	0.63 (0.44–0.90)	0.011
Harmful alcohol use	2.54 (1.73–3.75)	< 0.001
Leisure-time physical activity		0.013
low	1.00 (reference)	
moderate	0.62 (0.46–0.85)	
high	0.79 (0.49–1.25)	

CI, confidence interval; OR, odds ratio.

5.3 Sociodemographic, Lifestyle Associated, and Clinical Factors Associated with Subtypes of Increased Depressive Symptoms (Studies III, IV)

In Studies III and IV, subjects (n = 2522) were divided according to depressive subtype, and the baseline characteristics of these subjects are presented in Table 13.

Table 13. Baseline characteristics of the subjects (n = 2522) according to categories of depressive symptoms.

	I BDI < 10 N = 2016	II BDI ≥ 10 NMED N = 375	III BDI ≥ 10 MED N = 131	P-VALUE* [MULTIPLE COMPARISON]
Age, mean, years (SD)	58 (7)	59 (7)	58 (7)	< 0.001 [I/II]
Females, n (%)	1078 (53)	257 (69)	70 (53)	< 0.001 [I/II, II/III]
Education years, mean (SD)	10.4 (2.7)	10.1 (2.7)	10.8 (3.1)	0.013 [I/II, II/III]
Cohabiting, n (%)	1587 (79)	279 (74)	102 (78)	0.18
Body mass index, kg/m2, mean (SD)	28.6 (4.7)	30.0 (5.9)	28.9 (5.6)	< 0.001 [I/II, II/III]
Waist circumference, cm, mean (SD)				
women	91 (12)	96 (15)	92 (15)	< 0.001 [I/II, II/III]
men	101 (11)	104 (13)	101 (13)	0.046 [I/II]
Current smoking, n (%)	343 (17)	74 (20)	30 (23)	0.12
AUDIT-score, mean (SD)	4.5 (4.6)	4.8 (5.2)	6.9 (7.1)	< 0.001 [I/III, II/III]
Leisure-time physical activity level, n (%)				< 0.001 [I/II]
low	333 (17)	95 (25)	29 (22)	
moderate	1020 (51)	182 (49)	59 (46)	
high	653 (33)	97(26)	41(32)	
Blood pressure, mmHg, mean (SD)				
systolic	141(19)	140 (18)	139 (17)	0.57
diastolic	84 (10)	84 (10)	86 (10)	0.29
Plasma lipids, mmol/l, mean (SD)				
total cholesterol	5.4 (1.0)	5.5 (1.1)	5.5 (1.0)	0.068
HDL cholesterol	1.6 (0.4)	1.6 (0.5)	1.5 (0.4)	0.84
LDL cholesterol	3.2 (0.9)	3.3 (1.0)	3.3 (0.9)	0.30
triglycerides	1.4 (0.7)	1.6 (0.9)	1.5 (0.7)	< 0.001 [I/II]
Plasma glucose, mmol/l, mean (SD)				
fasting	5.6 (1.1)	5.7 (1.3)	5.6 (1.7)	0.14
2h glucose	7.3 (2.2)	7.7 (2.7)	7.5 (2.2)	0.040 [I/II]
Glucose disorder, n (%)				0.040 [I/II]
impaired fasting glucose	202 (10)	40 (11)	14 (11)	
impaired glucose tolerance	265 (13)	50 (13)	16 (12)	
type 2 diabetes	153 (8)	50 (13)	13 (10)	
Medication, n (%)				
hypertension	623(31)	165 (44)	47 (36)	< 0.001 [I/II]
lipid disorders	242 (12)	47 (13)	16 (12)	0.96
depression/anxiety	39 (2)	50 (13)	15 (11)	< 0.001 [I/II, I/III]

*Hommel's multiple comparison procedure was used to correct significance levels for post hoc testing ($p < 0.05$). AUDIT, Alcohol Use Disorders Identification Test; BDI, Beck's Depression Inventory; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MeD, melancholic depressive symptoms; NMeD, non-melancholic depressive symptoms. Reprinted from Study III (Rantanen et al., 2020) with permission from Elsevier.

Subjects with increased non-melancholic depressive symptoms were older than non-depressive subjects, and a little less educated than all the others. Women and men with increased non-melancholic depressive symptoms had higher BMI, and women also larger waist circumference compared to the other groups, and men compared to non-depressive subjects. Glucose disorders were more prevalent and triglyceride level higher among those with increased non-melancholic depressive symptoms compared to those without increased depressive symptoms. Compared to the two other groups, the mean of the AUDIT score was higher in those with increased melancholic depressive symptoms. Persons with increased non-melancholic depressive symptoms performed less LTPA than subjects without increased depressive symptoms. At baseline before the physician's appointment, persons with either type of increased depressive symptoms more often used medication for depression/anxiety compared to non-depressive subjects, whereas antihypertensive medication was more often used by subjects with increased non-melancholic depressive symptoms compared to non-depressive subjects. In addition, those with increased non-melancholic depressive symptoms had the poorest perception of their general health: 31 % of those without increased depressive symptoms, 62 % of those with increased melancholic depressive symptoms, and 74 % of those with increased non-melancholic depressive symptoms rated their health as poor ($p < 0.001$).

5.4 Increased Depressive Symptoms and Hypertension Status (Study I)

In Study I, we evaluated 2676 subjects with a mean age of 58 years (SD 7), 56 % women. Characteristics of the subjects according to the hypertension status are displayed in Table 14. Hypertension was diagnosed in 1282 (47.9 %) of the subjects, of whom 442 (34.5 %) had not previously been detected as having hypertension and were thus unaware of the disease. Hypertensive subjects were slightly older, more often men, less educated, and more frequently at-risk users of alcohol than the normotensive subjects. Of those unaware of their hypertension, 25.8 % reported harmful alcohol use (AUDIT score ≥ 8). The prevalence of obesity (BMI ≥ 30.0 kg/m^2) was 49.9 % among aware hypertensives, 29.9 % among unaware hypertensives, and 21.5 % among normotensive subjects ($p < 0.001$).

Table 14. Characteristics of the subjects (n = 2676) according to hypertension status.

	NORMO-TENSIVES N = 1394	UNAWARE HYPER-TENSIVES N = 442	AWARE HYPER-TENSIVES N = 840	P-VALUE
Age, mean, years (SD)	57 (7)	59 (7)	60 (7)	< 0.001
Females, n (%)	814 (58.4)	218 (49.3)	458 (54.5)	0.003
Upper secondary school, n (%)	239 (17.8)	54 (12.7)	91 (11.3)	< 0.001
Cohabiting, n (%)	1030 (76.6)	352 (82.6)	630 (77.7)	0.031
Depressive symptoms (BDI ≥ 13), n (%)	129 (9.3)	38 (8.7)	116 (14.1)	< 0.001
BDI-score, median (IQR)	4.0 (2.0–8.0)	4.0 (2.0–7.0)	5.0 (3.0–9.0)	< 0.001
Current smoking, n (%)	258 (18.5)	80 (18.1)	131 (15.6)	0.202
AUDIT-score ≥ 8, n (%)	251 (18.7)	111 (25.8)	162 (20.1)	0.006
LTPA, n (%)				0.219
low	445 (34.0)	162 (37.9)	312 (38.9)	
moderate	683 (51.1)	207 (48.4)	383 (47.7)	
high	199 (14.9)	59 (13.8)	108 (13.4)	
Systolic blood pressure, mmHg, mean (SD)	134 (17)	157 (16)	146 (17)	< 0.001
Diastolic blood pressure, mmHg, mean (SD)	81 (9)	91 (9)	86 (10)	< 0.001
Total cholesterol, mmol/l, mean (SD)	5.4 (1.0)	5.4 (0.9)	5.1 (1.0)	< 0.001
Fasting glucose, mmol/l, mean (SD)	5.5 (1.1)	5.6 (1.0)	5.8 (1.3)	< 0.001
Body mass index, kg/m^2, mean (SD)	28.2 (4.7)	28.5 (4.6)	30.7 (5.4)	< 0.001
Body mass index category, n (%)				< 0.001
< 25 kg/m^2	207 (20.7)	81 (19.5)	87 (10.6)	
25.0–29.9 kg/m^2	491 (49.2)	203 (48.8)	311 (38.1)	
30.0–34.9 kg/m^2	228 (22.8)	101 (24.3)	277 (33.9)	
≥ 35.0 kg/m^2	72 (7.2)	31 (7.5)	142 (17.4)	
Current medication, n (%)				
antidepressant	28 (2.0)	17 (3.8)	45 (5.4)	< 0.001
beta-blocker	0	0	433 (51.5)	< 0.001
calcium antagonist	0	0	233 (26.5)	< 0.001
ACE inhibitor or ATR antagonist	3 (0.2)	0	473 (56.3)	< 0.001
diuretic	2 (0.1)	0	231 (27.5)	< 0.001
statin	61 (4.4)	25 (5.7)	184 (21.9)	< 0.001

ACE, angiotensin-converting enzyme; ATR, angiotensin receptor; AUDIT, Alcohol Use Disorders Identification Test; BDI, Beck's Depression Inventory; IQR, interquartile range; LTPA, leisure-time physical activity. Reprinted from Study I (Rantanen et al., 2018).

Increased depressive symptoms (BDI ≥ 13) were most prevalent among those aware of their hypertension (14.1 %), whereas 8.7 % of those unaware and 9.3 % of the normotensives had increased depressive symptoms. Hypertension status was significantly associated with depressive symptoms ($p < 0.001$). Even after adjusting for common risk factors (age, gender, cohabiting, education, smoking, alcohol use, LTPA, and BMI), the difference in depressive symptoms between hypertension status categories remained significant ($p = 0.0030$) in the logistic regression analysis. A lower risk for increased depressive symptoms was found among the normotensive (OR 0.62, 95 % CI 0.45–0.86, $p = 0.0038$) and the unaware hypertensive subjects (OR 0.54, 95 % CI 0.35–0.84, $p = 0.0067$), compared to aware hypertensives.

5.4.1 Factors Predisposing Aware Hypertensives to Increased Depressive Symptoms

Similarly to the whole study population, the strongest predictor of increased depressive symptoms among the aware hypertensives was female gender (OR 3.61, 95 % CI 2.06–6.32). Likewise, harmful alcohol use (OR 2.55, 95 % CI 1.40–4.64), and obesity (OR 2.50, 95 % CI 1.01–6.21) substantially increased the risk. Non-smoking (OR 0.57, 95 % CI 0.33–0.99) and moderate LTPA compared to low LTPA (OR 0.53, 95 % CI 0.33–0.84) seemed to have a buffering effect against increased depressive symptoms, whereas education, cohabiting, and the medications assessed were not predictive of these symptoms.

5.5 Increased Depressive Symptoms and Self-Rated Health (Study II)

The association of increased depressive symptoms and SRH was investigated among 2555 subjects (mean age 58 (SD 7) years, 56 % women) (Study II). Characteristics of the subjects according to the categories of SRH are presented in Table 15. Poor or fair health was reported by 39.6 %, good health by 30.6 %, and very good or excellent health by 29.8 % of the subjects. Those with poor or fair SRH were a little older, less educated, and living alone more often than those with better ratings of their health. In addition, they smoked more often, performed less LTPA, were more often obese and had more often hypertension, glucose disorders, and medications for hypertension, lipid disorders, and depression/anxiety.

Table 15. Characteristics of the subjects (n = 2555) according to the categories of self-rated health.

	SELF-RATED HEALTH			P-VALUE*
	Level I n = 1013	Level II n = 781	Level III n = 761	
Age, mean (SD)	60 (7)	57 (7)	57 (7)	< 0.001
Females, n (%)	560 (55)	450 (58)	410 (54)	0.63
Education years, mean (SD)	9.7 (2.5)	10.7 (2.8)	11.0 (2.8)	< 0.001
Cohabiting, n (%)	770 (76)	606 (78)	618 (81)	0.01
Current smoking, n (%)	199 (20)	126 (16)	121 (16)	0.035
AUDIT score, mean (SD)	4.7 (5.4)	4.7 (4.7)	4.5 (4.2)	0.28
AUDIT-score ≥ 8, n (%)	4.7 (5.4)	4.7 (4.7)	4.5 (4.2)	0.28
LTPA, n (%)				< 0.001
low	230 (23)	133 (17)	97 (13)	
moderate	499 (49)	394 (51)	391 (51)	
high	281 (28)	252 (32)	272 (36)	
Blood pressure, mmHg, mean (SD)				
systolic	142 (18)	140 (19)	139 (18)	< 0.001
diastolic	84 (10)	84 (10)	84 (10)	0.77
Hypertension (BP ≥ 140/90), n (%)	571 (56)	405 (52)	376 (50)	0.004
Total cholesterol, mmol/l, mean (SD)	5.4 (1.0)	5.4 (1.0)	5.4 (0.9)	0.89
Total cholesterol ≥ 5.0, n (%)	656 (65)	519 (67)	506 (67)	0.41
Plasma glucose, mmol/l, mean (SD)				
Fasting glucose	5.7 (1.3)	5.6 (1.1)	5.5 (0.9)	< 0.001
2-hour postload	7.8 (2.5)	7.3 (2.1)	7.1 (2.1)	< 0.001
Glucose disorder, n (%)				
intermediate hyperglycaemia	290 (29)	171 (22)	144 (19)	< 0.001
new diagnosis of type 2 diabetes	81 (8)	43 (6)	28 (4)	< 0.001
Body mass index, kg/m^2, mean (SD)	29.9 (5.4)	28.4 (4.7)	27.7 (4.3)	< 0.001
Body mass index ≥ 30.0 kg/m^2, n (%)	428 (42)	216 (28)	188 (25)	< 0.001
BDI score, mean (SD)	8.7 (6.5)	5.0 (4.5)	3.5 (3.7)	< 0.001
BDI score ≥ 10, n (%)	363 (36)	102 (13)	46 (6)	< 0.001
Medication, n (%)				
blood pressure	569 (46)	226 (29)	569 (46)	< 0.001
lipid disorders	172 (17)	89 (11)	172 (17)	< 0.001
depression/anxiety	74 (7)	17 (2)	74 (7)	< 0.001

*P-value for linearity (linear trend) across categories of SRH level. Self-rated health level, level I: poor or fair; level II: good; level III: very good or excellent. AUDIT, Alcohol Use Disorders Identification test; BDI, Beck's Depression Inventory; BP, blood pressure; LTPA, leisure-time physical activity. Modified from Study II (Rantanen et al., 2019).

5.5.1 Increased Depressive Symptoms, Perception of Physical Health, and Self-Rated Health

Of those with poor/fair SRH, 35.8 % had increased depressive symptoms (BDI ≥ 10), when this prevalence was 13.1 % and 6.0 % among those with good and better

ratings of health, respectively. The association of BDI mean summary score (Panel A), prevalence of increased depressive symptoms (BDI ≥ 10) according to gender (Panel B), physical health summary score (Panel C), and categories of SRH are illustrated in Figure 12. In these adjusted (age, cohabiting, education, smoking, LTPA, BMI, SBP level, plasma glucose level, medication usage, and gender when appropriate) models, there was a linear decrease in the mean summary score of BDI and the prevalence of increased depressive symptoms with better SRH ($p < 0.001$). In all SRH categories, women had more increased depressive symptoms than men ($p < 0.001$). The physical health summary score was higher with increasing levels of SRH ($p < 0.001$). There was no significant interaction between the presence of depressive symptoms and SRH ($p = 0.98$), whereas there was a significant interaction between the presence of depressive symptoms and perceived physical health on SRH ($p = 0.009$). Presence of increased depressive symptoms modified perception of physical health among those with poor or fair SRH ($p < 0.001$).

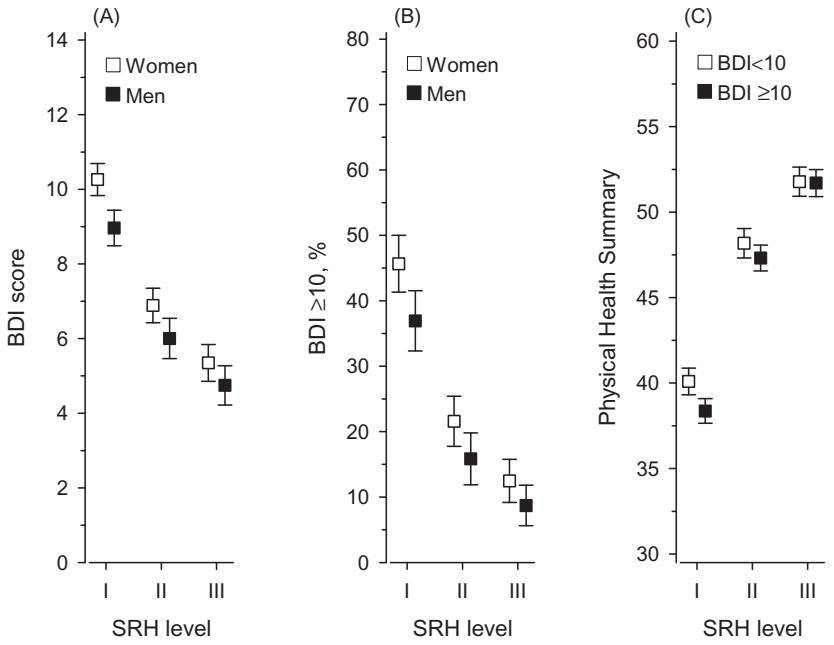

Figure 12. Association of BDI mean score (Panel A), increased depressive symptoms (BDI ≥ 10) (Panel B), physical health summary score (Panel C) and self-rated health, adjusted for age, cohabiting status, smoking, leisure-time physical activity, body mass index, education, systolic blood pressure level, plasma glucose level, and medication usage; Panel C also adjusted for gender. Whiskers show 95 % confidence intervals. BDI, Beck´s Depression Inventory; SRH, self-rated health level, level I: poor or fair; level II: good; level III: very good or excellent. Reprinted from Study II (Rantanen et al., 2019).

5.6 Increased Depressive Symptoms and Incident Cardiovascular Disease (Study III)

The incidence of CVD was studied among 2522 subjects (mean age 58 (SD 7) years, 56 % women) (Study III). Table 13 in section 5.3 presents baseline characteristics of these subjects according to categories of depressive symptoms. A total of 18 413 person-years was followed up; 14 790 in non-depressive, 961 in melancholically depressive, and 2262 in non-melancholically depressive subjects. In total, 263 subjects (10.4 %) were diagnosed with incident CVD. A diagnosis of CVD was made for 193 (9.6 %) of those without depressive symptoms, for 17 (13.0 %) of those with increased melancholic depressive symptoms, and for 53 (14.1 %) of those with increased non-melancholic depressive symptoms (p = 0.018).

Unadjusted cumulative CVD morbidity rates in non-depressive, melancholically depressive and non-melancholically depressive subjects (p = 0.004), respectively were 5.3 % (95 % CI 4.4–6.4), 5.4 % (95 % CI 0.7–6.9), and 9.0 % (95 % CI 6.4–12.4) over 5 years, and 8.7 % (95 % CI 7.5–10.1), 13.9 % (95 % CI 3.4–22.2), and 13.1 % (95 % CI 9.8–17.3) over 8 years. Age- and gender-adjusted cumulative CVD morbidity rates (p = 0.003) are presented in Figure 13.

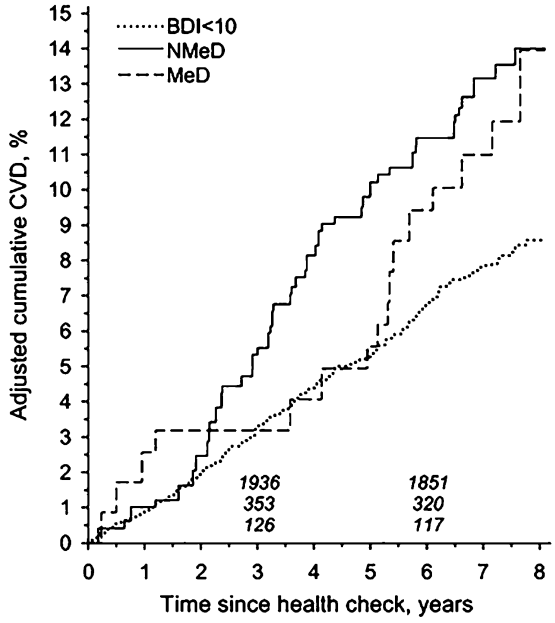

Figure 13. Age-and gender-adjusted cumulative cardiovascular morbidity rates according to depressive symptoms. The numbers of individuals at 3 and 6 years still at risk (BDI < 10, NMeD, MeD). BDI, Beck's Depression Inventory; CVD, cardiovascular disease; MeD, increased (BDI ≥ 10) melancholic depressive symptoms; NMeD, increased non-melancholic depressive symptoms. Reprinted from Study III (Rantanen et al., 2020) with permission from Elsevier. Copyright © 2019 Elsevier Inc.

The CVD incidence rate per 1000 person-years increased linearly ($p < 0.001$) across BDI scores, when adjusted for age, gender, education, smoking, alcohol use, and LTPA (Figure 14).

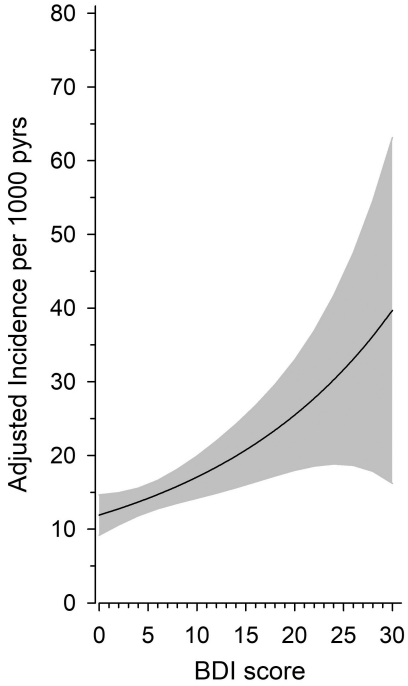

Figure 14. Adjusted* cardiovascular disease incidence rate per 1000 person-years according to Beck's Depression Inventory summary score. * Adjusted for age, gender, education, smoking, alcohol use, leisure time physical activity. BDI, Beck's Depression Inventory; pyrs, person-years.

The IRRs, adjusted for sociodemographic factors and lifestyle, for all and different subtypes of CVD are illustrated in Figure 15. Compared to non-depressive subjects, those with non-melancholic depressive symptoms had an increased risk for all and different subtypes of CVD. Increased melancholic depressive symptoms did not significantly increase the risk for CVD incidence, although a trend for a positive association was seen especially for all CVD, and for IHD and CeVD.

When further adjustments with major CVD risk factors hypertension and dyslipidaemia were made, almost all the associations found became stronger (Table 16). However, the association of increased melancholic depressive symptoms and incident CVD remained non-significant.

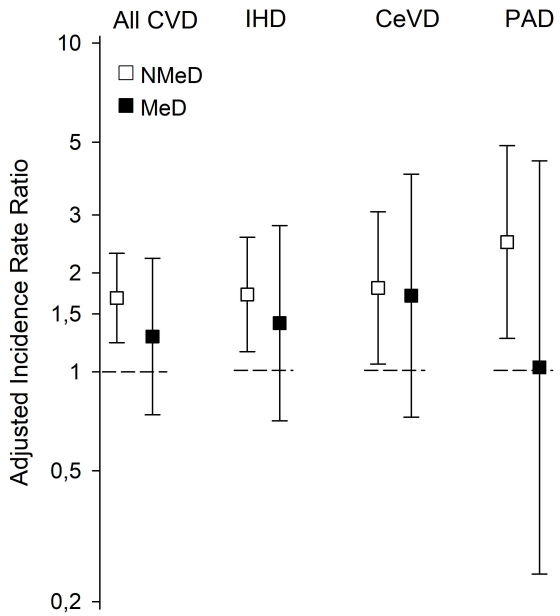

Figure 15. Adjusted* incidence rate ratios for cardiovascular disease according to depressive subtypes compared to not having increased depressive symptoms. *Adjusted for age, gender, education, smoking, alcohol use, leisure time physical activity. CeVD, cerebrovascular disease; CVD, cardiovascular disease; IHD, ischemic heart disease; MeD, increased (BDI ≥10) melancholic depressive symptoms; NMeD, increased non-melancholic depressive symptoms; PAD, peripheral artery disease.

Table 16. Number of* and adjusted** incidence rate ratios (IRR) for cardiovascular disease according to depressive subtypes compared to not having increased depressive symptoms.

	All CVD		**IHD**		**CeVD**		**PAD**	
	N	IRR (95% CI)	N	IRR (95% CI)	N	IRR (95% CI)	N	IRR (95% CI)
BDI < 10	193	1.00	121	1.00	60	1.00	30	1.00
NMeD	53	1.69 (1.23 to 2.31)	32	1.71 (1.14 to 2.55)	19	1.78 (1.04 to 3.04)	13	2.39 (1.21 to 4.70)
MeD	17	1.31 (0.75 to 2.26)	10	1.40 (0.71 to 2.78)	9	1.74 (0.74 to 4.08)	4	1.11 (0.26 to 4.73)

*The sum of the events in the three categories exceeds the number of all CVD events because some of the subjects were diagnosed with more than one CVD at the same time. **Adjusted for age, gender, education, smoking, alcohol use, leisure time physical activity, hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, or antihypertensive medication), dyslipidaemia (total cholesterol ≥ 5.0 mmol/l or medication for lipid disorders). CeVD, cerebrovascular disease; CVD, cardiovascular disease; IHD, ischemic heart disease; MeD increased (BDI ≥10) melancholic depressive symptoms; NMeD, increased non-melancholic depressive symptoms; PAD, peripheral artery disease. Reprinted from Study III (Rantanen et al., 2020) with permission from Elsevier.

5.7 Increased Depressive Symptoms and All-Cause Mortality (Study IV)

The relationship of increased melancholic and non-melancholic depressive symptoms with all-cause mortality (Study IV) was investigated among 2522 subjects (mean age 58 (SD 7), 56 % females), the baseline characteristics of whom are presented in Table 13 in section 5.3.

5.7.1 Cumulative All-Cause Mortality

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

Adjusted (age, gender, education, smoking) HRs for all-cause mortality rose with higher and declined with lower BDI summary score levels when BDI summary score 10 was set as the reference level (Figure 16).

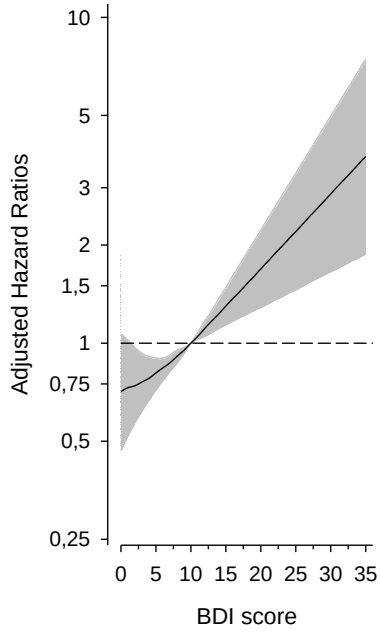

Figure 16. Adjusted (age, gender, education, and smoking) hazard ratios for all-cause mortality according to BDI. Hazard ratios were derived from a 3-knot restricted cubic flexible parametric survival models, with BDI score 10 as the reference value. The 95 % confidence intervals are denoted by the grey area. BDI, Beck's Depression Inventory. From Study IV (submitted).

Finally, the adjusted cumulative all-cause mortality according to increased depressive symptoms is presented in Figure 17. Compared to non-depressive subjects, the HR for all-cause mortality was 1.12 (95 % CI 0.63–2.02, p = 0.69) in melancholically depressive and 1.82 (95 % CI 1.33–2.50, p < 0.001) in non-melancholically depressive subjects.

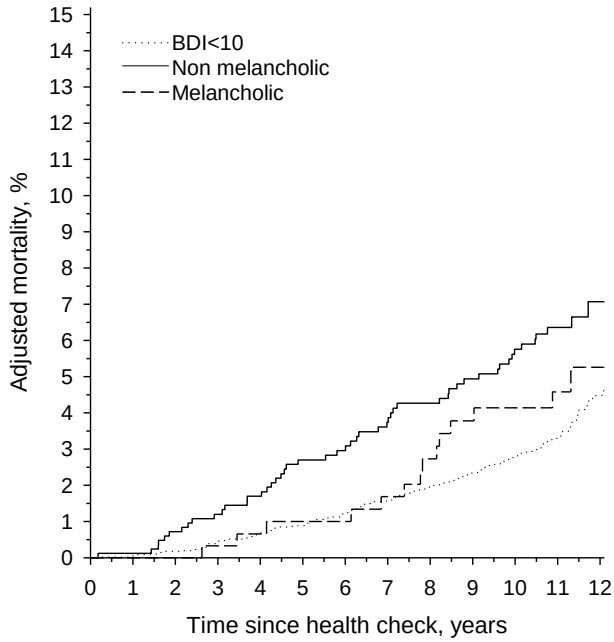

Figure 17. Cumulative all-cause mortality rate according to depressive symptoms. Adjusted for age, gender, smoking, and education years. BDI, Beck's Depression Inventory. From Study IV (submitted).

5.7.2 Causes of Death

In total, 27 681 person-years (mean 11.0) were followed up, and 230 deaths occurred: 164 (8.1 %) among those without increased depressive symptoms, 14 (10.7 %) among those with increased melancholic depressive symptoms, and 52 (13.9 %) among those with increased non-melancholic depressive symptoms. The most prevalent cause of death was cancer (42 % of all deaths), followed by CVD (28 % of all deaths). The causes of death according to depressive symptoms are presented in Table 17.

Table 17. Causes of death according to depressive symptoms.

CAUSE OF DEATH, N (%)	ALL N = 230	BDI < 10 N = 164	MED N = 14	NMED N = 52
Malignant neoplasms	97 (42)	63 (38)	8 (57)	26 (50)
Nervous system	16 (7)	12 (7)	0 (0)	4 (7)
Circulatory system	64 (28)	48 (29)	4 (29)	12 (23)
IHD	31 (13)	23	0	8
CeVD	17 (7)	15	2	0
other	16 (7)	10	2	4
Digestive system	13 (6)	7 (4)	1 (7)	5 (10)
External cause	23 (10)	20 (12)	0 (0)	3 (4)
Other	17 (7)	14 (9)	1 (7)	2 (4)

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

5.7.3 Standardized Mortality Rate

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

6 Discussion

In this thesis, a representative sample of middle-aged subjects with at least one traditional CVD risk factor was assessed. The main findings of the study indicate that in particular increased non-melancholic depressive symptoms are prevalent among CVD risk persons and related to increased risk for CVD morbidity and all-cause mortality. Female gender, harmful alcohol use, obesity, and hypertension awareness seem to predispose CVD risk subjects to having increased depressive symptoms. In addition, poor SRH is a risk factor for increased depressive symptoms, and when both are present, depressive symptoms even modify a subject's perception of her/his physical health.

6.1 Study Population

The study population (n = 2676) was drawn from a population-based survey conducted in two semirural Finnish towns in 2005–2007, and it consisted of subjects who were middle-aged (45–70 years of age) at the time of the enrolment. Of the invited subjects (n = 6013), three out of four were willing to participate; thus, the sample can be considered as representative of the Finnish general middle-aged population. However, our study population consisted of CVD risk persons with at least one traditional CVD risk factor and thus is not a pure sample of the general population. In addition, women were slightly over-represented (56 % of the subjects) compared to the gender distribution among the middle-aged population in Finland at that time (51 % women and 49 % men) (Statistics Finland, 2007).

Subjects with known CVD, diabetes or renal disease were excluded, and hence, the study sample consisted of apparently healthy subjects at CVD risk which attenuated the possibility of confounding by comorbidities. Of the CVD risk factors, specifically obesity has increased, and the prevalence of the other modifiable risk factors have remained quite stable in Finland since the baseline (P. Koponen et al., 2018). This indicates that our study sample presumably is comparable to middle-aged apparently healthy subjects in Finland also today.

There was a little variation in the number of subjects included in the different studies of this thesis due to the different variables studied, but it is unlikely that this significantly affects the comparability of the results.

6.2 Methods

6.2.1 Assessment of Depressive Symptoms

Depressive symptoms were assessed by self-administered BDI, version BDI-1A (Beck et al., 1979). This is a questionnaire with good psychometric properties, and it is widely used in screening for depressive symptoms and depression. In this thesis, two different cut-off values to indicate increased depressive symptoms were used: BDI score ≥ 10 as suggested by Beck himself (Beck & Beamesderfer, 1974), and as used in other population-based studies among middle-aged Finnish subjects (H. Koponen et al., 2010; Mäntyselkä et al., 2011; Seppälä, Vanhala, et al., 2012); and BDI score ≥ 13 indicating more severe increased depressive symptoms. In this thesis, the use of the lower cut-off point in most of the studies was justified: we did not aim to screen for MDD but to find subjects with even low levels of depressive symptoms. As even this subthreshold depression can diminish the quality of life and affect health (Rodríguez et al., 2012), its consideration is relevant in population-based studies. Nevertheless, the assessment of depressive symptoms by a questionnaire has to be considered as a limitation, affecting the robustness of our results. Consideration of a definite diagnosis of depression would have reduced subjectivity in the assessment of the depressive status, and comparability of the results with other studies would have been enhanced. In addition, depressive symptoms were assessed only at baseline, and changes in depressive status could not be controlled for. However, the subtypes of at least MDD have been found to be quite stable (Lamers, Rhebergen, et al., 2012).

The division of increased depressive symptoms into melancholic and non-melancholic subgroups was made by using a summary score of melancholic symptoms in the BDI. This particular method has previously been used in some Finnish studies (Järvimäki et al., 2016; Ovaskainen et al., 2009; Seppälä et al., 2013; Seppälä, Koponen, et al., 2012; Seppälä, Vanhala, et al., 2012). It captures the features of melancholic depression, and in the subgroup of those with increased non-melancholic depressive symptoms, many of the characteristics of atypical depression are presented. However, increased levels of non-melancholic depressive symptoms and MDD with atypical features cannot be considered as exactly the same entity.

6.2.2 Other Questionnaires

A large variety of important sociodemographic and lifestyle factors were assessed by self-administered questionnaires. These factors could have confounded the associations studied and it was relevant to control for them. However, they were assessed only at baseline, and in the prospective settings, their variation over time

could not be considered. In addition, self-reports of smoking, alcohol use, and LTPA can be unreliable (Del Boca & Darkes, 2003; Gorber et al., 2009; Tucker et al., 2011). In this thesis, the classification of LTPA was strict compared to the recommended levels of PA today. Low LTPA was defined as LTPA for at least 30 min at a time for a maximum of three times a week, and today the recommended level of PA is at least 150 minutes of moderate-intensity, or 75 minutes of vigorous-intensity PA per week, or any equivalent combination of the two (World Health Organization, 2010). Moreover, data on household income or occupational status were not available. These factors have previously been found to affect the association of depressive symptoms and CVD (Cho et al., 2019; Lemogne et al., 2017; Wiernik et al., 2018).

SRH and perceived physical health were assessed by the SF-36 which is a widely used and validated instrument for assessing health-related quality of life (Hays & Morales, 2001).

6.2.3 Clinical and Laboratory Measurements

Clinical measurements were performed by trained study nurses which is clearly a more accurate method than self-report. Especially among those who are overweight or obese, self-reports on weight and BMI have been found to be biased (Maukonen et al., 2018). Likewise, self-reports on BP, dyslipidaemia, and glucose disorders can under- or overestimate the prevalence of these risk factors (Peterson et al., 2016). In addition, confirmation of hypertension status (aware/unaware hypertensives and normotensives) was based on home BP measurements which prevented confounding by white coat hypertension.

6.2.4 Incident Cardiovascular Disease and All-Cause Mortality

Data on incident CVD were obtained from the Care Register for Health Care of the National Institute of Health and Welfare and data on mortality from The Official Statistics of Finland provided by Statistics Finland. These registries are well-known for their quality. The correctness and completeness of the hospital discharge register has been proposed to be from satisfactory to very good (Sund, 2012), and the coverage of death statistics is virtually 100 % (Statistics Finland, 2018).

Possible confounding factors that could not be controlled for in the prospective analyses include the time a participant has had a certain risk factor, the time-dependent variation in the variables assessed at baseline, and treatment of depression. It must also be noted that the study subjects had interventions on CVD risk factors at baseline: lifestyle counselling and initiation of preventive medication

(an antihypertensive drug, a lipid lowering agent, or low dose aspirin) according to the guidelines on CVD prevention. On the other hand, data on adherence to this medication, the baseline medication, or other treatment during the follow-up were not available.

6.3 Results

6.3.1 Prevalence of Increased Depressive Symptoms

The mean BDI summary score in the whole study population was 6.0 indicating low levels of depressive symptoms. In melancholically and non-melancholically depressive subjects the mean BDI summary score was and 14.8 and 15.1, respectively; thus, there was no substantial difference in the severity of depressive symptoms between the subgroups. The prevalence of increased depressive symptoms combined varied according to the used cut-off point of the BDI score and the subsample of the study population. When the definition of increased depressive symptoms was a BDI score ≥ 10, the prevalence of increased depressive symptoms was 20 % among the whole study population of this thesis. Increased depressive symptoms were more prevalent among women (23 %) than men (15 %) which is a robust finding in previous research (Salk et al., 2017). Indeed, we found female gender to be associated with a threefold risk for increased depressive symptoms.

In European population-based cohort studies among middle-aged subjects, the prevalence of increased depressive symptoms has been found to be even slightly higher, varying from 20–25 % in total study populations, and being even near 30 % among women, and over 15 % in men (Alshehri et al., 2019; Hamieh et al., 2019; Kozela et al., 2019). Previous studies among Finnish middle-aged subjects drawn from the general population have reported the prevalence of increased depressive symptoms (defined as BDI score ≥ 10) to be 15 % (Mäntyselkä et al., 2011; Seppälä, Vanhala, et al., 2012). Differences in the prevalence are probably due to methodological reasons such as definition of "being depressed" and characteristics of study populations.

Increased non-melancholic depressive symptoms were more prevalent (15 %) than melancholic depressive symptoms (5 %) in our study sample. This finding is in line with previous studies in Finland where both non-melancholic MDD and non-melancholic depressive symptoms have been found to be twice more prevalent as their melancholic counterparts (Melartin et al., 2004; Seppälä, Vanhala, et al., 2012). Moreover, the prevalence of increased melancholic depressive symptoms was similar in both genders whereas non-melancholic depressive symptoms were more prevalent among women than men (18 % vs. 11 %, respectively). Melancholic

depression has also earlier been found to be as prevalent among women as men (Bogren et al., 2018) although not always (Musil et al., 2018; Rudaz et al., 2017)

6.3.2 Sociodemographic and Lifestyle Associated Risk Factors for Increased Depressive Symptoms

Considering the sociodemographic characteristics assessed, only female gender was associated with an increased risk for increased depressive symptoms among our study subjects, consistent with sound evidence (Salk et al., 2017). Our study subjects were all middle-aged and within a narrow age range which probably contributes to the non-significant impact of age on the increased depressive symptoms. Lowering socioeconomic status has been associated with increasing risk of depression previously but not always in Finland (Freeman et al., 2016; Markkula et al., 2017). We had data on education but not on income, of which the latter can have a more profound effect on a person's socioeconomic status. On contrary to evidence from larger samples (Bromet et al., 2011), we did not find that those living alone had increased levels of depressive symptoms more likely than their cohabiting counterparts.

Considering lifestyle, our results suggest that harmful alcohol use independently predisposes to increased depressive symptoms, whereas non-smoking and moderate (compared to low) LTPA seem to buffer against them. These findings are in concordance with those reported in recent meta-analyses (Boden & Fergusson, 2011; Luger et al., 2014; Schuch et al., 2017), and emphasise the meaning of promoting healthy lifestyle in prevention of depression and CVD.

In our study population, subjects with increased non-melancholic depressive symptoms more often had traditional CVD risk factors such as obesity, glucose disorders, and physical inactivity than non-depressed subjects. Thus, our results are supportive for increased non-melancholic depressive symptoms being associated with metabolic CVD risk factor clustering, as suggested previously (Brailean et al., 2019; Glaus et al., 2013; Lamers et al., 2013; Lasserre et al., 2014, 2017; Seppälä, Vanhala, et al., 2012). Increased melancholic depressive symptoms were, on the other hand, associated with higher AUDIT scores. This may be due to the proportionally higher number of men in this subgroup than in the non-melancholic subgroup as harmful alcohol use is more prevalent among men than women.

However, these associations are based on cross-sectional analyses, and we cannot draw any definite conclusions on the direction of the associations among our study population. It is plausible, and also supported by previous research (Azevedo Da Silva et al., 2012; Chireh et al., 2019; Lasserre et al., 2017; Luger et al., 2014; Mannan et al., 2016; Rudaz et al., 2017; Yu et al., 2015), that many of these

associations are directional. For example, it may be that a person has first been depressed and then gained weight or started to feel depressed due to obesity.

6.3.3 Increased Depressive Symptoms and Hypertension Status (Study I)

Hypertension was highly prevalent (48 %) in this middle-aged CVD risk population at baseline. This is no surprise considering hypertension was one of the inclusion criteria of the study, and the overall prevalence of hypertension in the general population. In 2007, the prevalence of hypertension in the Finnish general adult population was 43 % among men and 23 % among women (Laatikainen et al., 2012). In this thesis, one third of the hypertensive subjects were unaware of their elevated BP which is in line with findings from the general Finnish population in 2007 (Vartiainen, 2008), and population-based studies conducted for example in Germany (Michal et al., 2013) and Spain (Mena-Martin et al., 2003). Awareness of hypertension has since increased in Finland, but unfortunately, although every three in four hypertensives are today aware of their disease, only half of the hypertensives receive treatment and one third has controlled hypertension (NCD Risk Factor Collaboration (NCD-RisC), 2019). The prevalence of obesity (50 %) among the aware hypertensives sadly represents the overwhelming issue of excess weight among middle-aged subjects with another major CVD risk factor. Interestingly, unaware hypertensives were not so often obese (30 %), but one in four was an at-risk user of alcohol.

Among the hypertensive subjects, the prevalence of increased depressive symptoms was 23 %. This is a little less than reported in a meta-analysis of over 10 000 hypertensive subjects: the summarised meta-analytical prevalence of increased depressive symptoms was 30 % in 27 studies using self-rating scales (Z. Li et al., 2015). This difference is likely due to methodological heterogeneity among the studies, including ours (Z. Li et al., 2015). Only 5 % of the previously diagnosed hypertensives in our study population used antidepressant medication, suggesting a low level of clinically significant depression or underdiagnosed depression among medicated hypertensives. Antidepressant medication was even more infrequently used among the others.

The key finding of Study I was that not hypertension itself, but the awareness of this risk factor was associated with an increased risk for increased depressive symptoms. Compared to aware hypertensives, normotensive and unaware subjects had a 40 % and a 50 % decreased risk for increased depressive symptoms, respectively. In keeping with this result, Hamer et al. (2010) observed an elevated risk of psychological distress in patients treated for hypertension, but not in unaware hypertensives compared to normotensive subjects in a large population-based study

conducted in the UK. Similarly, Michal et al. (2013) found controlled treated hypertension to be associated with increased risk for increased depressive symptoms compared to normotension. Moreover, in their study of German middle-aged subjects, unawareness of hypertension seemed to buffer against depressive symptoms (Michal et al., 2013). One possible reason for these somewhat mixed results can be the misclassification of the hypertension status and confounding by comorbidity, as in the abovementioned studies hypertension status was determined by a single measurement and the study subjects had somatic diseases.

One explanation for increased psychological distress among aware hypertensives is the labelling effect of having a diagnosis of hypertension (Ogedegbe, 2010; Pickering, 2006). This underlines the importance of discussing a new chronic condition in a delicate, supporting manner. In addition, it is possible that depressive subjects use more healthcare services than non-depressive subjects and are thus more likely to be diagnosed with hypertension, as suggested also by Michal et al. (2013). In a recent study among Finnish primary care patients those with depressive symptoms (even when not fulfilling diagnostic criteria for clinical depression) really visited their general practitioner more often than those without (Tusa et al., 2019).

On the other hand, having hypertension diagnosed and treated could provide possibilities to be diagnosed with depression more easily as well, as subjects with hypertension are usually followed up. The recognition of increased depressive symptoms among hypertensive subjects is important, as depressive symptoms in hypertensive subjects might have deleterious effects. For example, it has been suggested that this co-existence is associated with a 15 % increased risk for all-cause mortality (Axon et al., 2010).

We found female gender, harmful alcohol use, obesity, smoking, and low level of LTPA to predispose hypertensive subjects to increased depressive symptoms. All of these factors have also before been associated with depression or depressive symptoms (Boden & Fergusson, 2011; Luger et al., 2014; Mannan et al., 2016; Salk et al., 2017; Schuch et al., 2017). In addition, the lifestyle associated factors are also risk factors for elevated BP. Hence, contributing to these modifiable risk factors may effectively attenuate the effect of the toxic combination of depressive symptoms and hypertension.

6.3.4 Increased Depressive Symptoms and Self-Rated Health (Study II)

Poor perception of one's health was prevalent among the subjects of this study: 40 % of them considered their health as poor or fair. This is however comparable to the Finnish validation study of the SF-36 (Aalto et al., 1999). Subjects with poor or fair

SRH had more often an adverse lifestyle and CVD risk factors (specifically obesity, hypertension, and glucose disorders) compared to those with better ratings of health. This is also consistent with previous research (Emmelin et al., 2006; Engberg et al., 2015; Orimoloye et al., 2019; van der Linde et al., 2013; Waller et al., 2015), and suggests that poor perception of one's health might also indicate a poorer capacity to engage in a healthy lifestyle.

Among those with poor or fair SRH, 45 % of women and 35 % men had increased depressive symptoms, and there was an inverse relationship between SRH and depressive symptoms. Our results thus indicate that a subject's self-rating of poor or fair health is associated with increased depressive symptoms which is in line with some previous studies conducted especially in older populations (Chang-Quan et al., 2010), and in middle-aged population-based samples in Finland (Pirkola et al., 2009) and Sweden (Molarius & Janson, 2002). The recognition of depression by general practitioners has been found to be poor (Mitchell et al., 2009) and often delayed (Leff et al., 2017), but our results suggest that by using a few seconds asking the patient's own perception of his or her overall health, primary care practitioners may enhance the detection of depressive symptoms. Thus, assessment of SRH might be a practical tool in consideration of psychological risk factors in CVD risk management.

The importance of assessing SRH is emphasised considering that poor SRH itself is a risk factor for having traditional CVD risk factors (Emmelin et al., 2006; Orimoloye et al., 2019; van der Linde et al., 2013; Waller et al., 2015), and for incident CVD and its mortality (Bamia et al., 2017; Barger et al., 2016; Mavaddat et al., 2014; Orimoloye et al., 2019). SRH has been suggested to represent an integration of social determinants of health (including increased depressive symptoms) and traditional CVD risk factors, and thus could be a useful complement in CVD risk prediction, especially among those at borderline or intermediate "traditional" CVD risk (Orimoloye et al., 2019). Writing down the patient's own view of her/his health in the medical records seems beneficial, and worsening ratings might act as a red flag for health hazards. Among those with poor or fair SRH, namely depressive symptoms may act as a barrier to the adoption of healthy lifestyle. Treatment of depression would be worth prioritizing before attempting to make changes in lifestyle.

In our study, the perception of physical health was enhanced by better ratings of SRH. The novel finding of our study is that among subjects considering their health at most fair, the perception of physical health was lower in depressive than in non-depressive subjects. On the contrary, if a subject rated her/his health as at least good, increased depressive symptoms had no impact on the perception of physical health. This might mean that the question "How would you rate your general health?" may prompt apparently healthy CVD risk persons to compare their physical performance

with others of the same age and gender. In previous studies on the association of perceived general health status and different functional domains, physical functioning has been found to be more important when assessing SRH than mental health (Mavaddat et al., 2011; Smith et al., 1999) which seems to be in concordance with our results. However, it has also been suggested that physical health would play a bigger role in determining SRH if it is generally poor, and that mental health would be more important if health is generally good (Au & Johnston, 2014).

6.3.5 Increased Depressive Symptoms and Incident Cardiovascular Disease (Study III)

One in ten of our study population developed incident CVD during the follow-up of eight years. At the beginning, it must be noted that our study population was drawn from a population survey targeted to diminishing CVD risk: the study subjects received lifestyle counselling, and preventive medication was even initiated if CVD risk was high. These actions should have affected the morbidity risk; and we at least do hope that was the case.

The main finding of this study was that specifically increased non-melancholic depressive symptoms seem to be associated with excess CVD morbidity risk. Already after two years of follow-up, the age- and gender-adjusted cumulative morbidity rate started to rise more sharply among those with increased non-melancholic depressive symptoms compared to the non-depressed subjects, and the rise continued steadily thereafter. Even after adjustment for major CVD risk factors (age, gender, education, smoking, alcohol use, LTPA, hypertension, and hyperlipidaemia), increased non-melancholic depressive symptoms were associated with a 70 % higher risk for all CVD morbidity, compared to not having increased levels of depressive symptoms. Although increased non-melancholic depressive symptoms were associated with traditional CVD risk factors in our study population, our results suggest that these do not completely mediate the association of depressive symptoms with incident CVD. We did not adjust for BMI. Overweight and obesity are risk factors for CVD, but a large amount of the excess risk associated with them are suggested to be mediated by hypertension, dyslipidaemia, and glucose disorders (The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), 2014).

On the contrary, increased melancholic depressive symptoms did not significantly increase the morbidity risk. However, there was a lack of statistical power to confirm this non-significant association due to the small number of incident CVD cases among the melancholically depressed. Consistent with previous research (Daskalopoulou et al., 2016), we found no significant difference in the risk increase according to the subtype of CVD.

The probable risk difference between the subtypes of increased depressive symptoms might be due to different biological dysregulations more strongly associated with a certain subtype. In specific, atypical depressive symptoms or MDD might be associated with greater inflammation (Lamers et al., 2013; Woelfer et al., 2019; Yang et al., 2018). Inflammation is a core factor in atherosclerosis (Libby et al., 2002), and strongly associated with fat-mass associated metabolic dysregulations (Penninx et al., 2013). Thus, the increased morbidity risk among non-melancholically depressive subjects may partially be inflammation driven.

Our findings are in line with a recent study by Case et al. (2018) who reported that atypical MDD significantly predicts incident CVD after adjustment for CVD risk factors. Despite the methodological differences (assessment of depression with a fully structured diagnostic interview, self-report of incident CVD, and three years of follow-up), the strength of this association was comparable to our results (OR 1.8). However, in their study also nonatypical MDD increased the risk for incident CVD by a significant 20 %. Comparisons between depression groups were not significant (Case et al., 2018).

In addition, we found a linear increase in the adjusted CVD incidence rate with increased BDI summary score, indicating that the more severe the depressive symptoms, the higher the incidence rate of CVD. This finding is in concordance with previous research where a dose-response relationship with severity of depressive symptoms and incident CVD has been found (Rowan et al., 2005; Seldenrijk et al., 2015). However, in a large Swedish population-based study, the morbidity risk was highest among those with moderate depression (Almas et al., 2015). It is plausible that increasing levels of depressive symptoms cause increasing challenges to CVD prevention which is especially mediated by unhealthy lifestyle. As a matter of fact, it has been shown that increasing severity of depression is associated with increased odds for worse lifestyle (Rahe et al., 2016). However, we had adjusted for age, gender, education, smoking, alcohol use, and LTPA; thus, the association we found seemed not to be only lifestyle mediated. It is possible that more severe depressive symptoms are associated with more severe disturbances in biological pathways connecting depressive symptoms and CVD, contributing to more incident CVD. However, it is noteworthy that even low levels of depressive symptoms (as indicated by the BDI mean summary score 15 among depressive subjects) increased the risk for CVD in our study population. On the other hand, we cannot rule out the possibility that the increased levels of depressive symptoms at baseline were partly caused by premorbid symptoms of CVD. Similarly, as many of the traditional CVD risk factors may increase depressive symptoms (Armstrong et al., 2017; Azevedo Da Silva et al., 2012; Chireh et al., 2019; Luger et al., 2014; Mannan et al., 2016; Patel et al., 2018; Rudaz et al., 2017), it may be that those with most baseline depressive symptoms had the highest load of other CVD risk factors.

Our findings add to evidence of depressive symptomatology being an independent risk factor for CVD among middle-aged persons. Moreover, this risk increase seems to be especially associated with non-melancholic depressive symptoms. Our results thus suggest that consideration of subtypes of depressive symptoms is relevant when studying the association of depressive symptoms and CVD. In clinical practise, namely non-melancholic depressive symptoms such as increased appetite, fatigue, and mood reactivity should be noted. It has previously been suggested that physicians might not recognize atypical depressive symptoms (Piek et al., 2012), and they might thus underestimate a subject's CVD risk, and obstacles to engage in preventive lifestyle activities. In addition, our results emphasise the importance of drawing attention to CVD risk factors and metabolic side effects of antidepressants when treating non-melancholically depressed subjects.

6.3.6 Increased Depressive Symptoms and All-Cause Mortality (Study IV)

In this prospective study with a mean follow-up time of 11 years, we found that not having increased depressive symptoms was associated with a decreased SMR compared to the mortality rate throughout Finland over the same period. There was a linear relationship between BDI summary score and adjusted (age, gender, education, smoking) HR for all-cause mortality: the higher the BDI score, the higher the risk. Moreover, specifically increased non-melancholic depressive symptoms were associated with an increased risk for all-cause mortality. The risk was almost doubled when adjusted for age, gender, smoking, and education years. Increased melancholic depressive symptoms did not seem to be associated with excess mortality, but there were only few deaths among those with increased melancholic depressive symptoms which can weaken this association.

There is a substantial lack of research on subtypes of depressive symptoms and their relationship with all-cause mortality, although the need for subtyping depressive symptoms and depression in research has been acknowledged already for some time (Baumeister & Parker, 2012). One published study on this association among a general population did find that current depression was associated with a threefold risk for all-cause mortality compared to non-depressed subjects, but in contrast to our results, atypicality of depression was not associated with increased all-cause mortality risk (Lasserre et al., 2016). However, there is a profound difference between this study and ours: Lasserre et al. (2016) based their depression diagnosis on a semi-structured interview and assessed the atypicality of depression based on DSM-5 criteria (not requiring mood reactivity thought), whereas we assessed depressive symptoms and divided them into melancholic and non-

melancholic subgroups. Nevertheless, the means of assessment of depression have not been found to substantially affect the found association of depressive symptomatology and all-cause mortality (Cuijpers et al., 2014a). Our findings do support the evidence of increased depressive symptoms being associated with excess mortality, and are in line with a set of recent studies assessing depressive symptoms and mortality in general middle-aged populations (Kozela et al., 2016; Markkula et al., 2012; Moise et al., 2018). In these studies, depression or increased depressive symptoms have been associated with at most doubled all-cause mortality risk.

As reviewed in section 2.9, several possible mechanisms may connect increased depressive symptoms to increased mortality. Our results suggest that this association is not entirely driven by sociodemographic factors such as age, gender, and education, nor smoking. It is possible that the excess mortality risk among those with increased non-melancholic depressive symptoms is due to specific pathophysiological mechanisms behind this subtype. Inflammation might play a bigger role in non-melancholic than in melancholic depression (Lamers et al., 2013; Woelfer et al., 2019; Yang et al., 2018). In addition to being essential in the pathogenesis of CVD (Libby et al., 2002), inflammation is a crucial factor in the pathogenesis of malignant neoplasms, possibly connecting them to depression (Currier & Nemeroff, 2014). Furthermore, those with non-melancholic depressive symptoms in our study population had the poorest perception of their general health. Poor SRH is associated with excess mortality risk (Bamia et al., 2017; DeSalvo et al., 2005), and this can partly explain our findings. However, it has also been suggested that the increased mortality risk caused by increased depressive symptoms grows with better ratings of self-assessed health (Moise et al., 2018).

Among the assessed 2522 apparently healthy middle-aged CVD risk subjects, 230 deaths occurred during the follow-up, and the most prevalent causes of death were cancer (42 %) and CVD (28 %). In 2017, these two causes contributed to 24 % and 36 % of deaths in Finland, respectively (Statistics Finland, 2019). The mean age of the study population at the start of follow-up was 58 years which inevitably affected the number of deaths and the prevalence of causes of death. In addition, the study subjects were drawn from a population survey targeted at diminishing CVD risk, and subjects with established CVD were excluded at baseline. These factors presumably contributed to the severity of the manifested CVD, and thus the CVD mortality found; they probably also explain why not having increased depressive symptoms was associated with decreased SMR. Although depression is a major risk factor for self-harm (Ribeiro et al., 2018), the excess mortality among non-melancholically depressive subjects seemed not to be explained by suicide. There were even fewer deaths from external causes among those with increased depressive symptoms than among those without. Unfortunately, the sample size was insufficient to investigate the association of depressive subtypes with specific causes of death.

Our findings are a start to filling a gap in our knowledge of the relationship between different subtypes of depressive symptoms and all-cause mortality. Based on our results, subtyping depressive symptoms in these studies seems important. In primary care, recognition and consideration of specifically non-melancholic depressive symptoms are essential as they might negatively affect prevention and treatment of somatic diseases such as CVD.

6.4 Strengths and Limitations

The main strengths of this study are a representative study population, comprehensive evaluation of the subjects, and register-based data on morbidity and mortality. The study sample was population-based, and the response rate was high (74 %). The CVD risk factors of which having at least one was the inclusion criterion are highly prevalent in primary care. On the other hand, the exclusion of subjects with established CVD and diabetes reduced the effect of confounding by comorbidities and created a cohort in a primary prevention setting. All in all, the generalizability of our results to primary care patients at CVD risk is good. All clinical measurements were performed by trained study nurses, and questionnaires considering the subject's health and lifestyle habits were administered before the enrolment examination, enhancing the reliability of these measurements. In addition, we took into consideration several possible confounding variables including gender, age, education, and lifestyle. The registers from which data on CVD morbidity and all-cause mortality were gathered are reliable and comprehensive.

However, limitations are also acknowledged. First, depressive symptoms were assessed with a self-administered questionnaire and only at baseline. The division of increased depressive symptoms into melancholic and non-melancholic subgroups does not strictly represent melancholic and atypical depression. In prospective settings, we could not consider time-dependent variation in depressive symptoms and other variables. On the other hand, cross-sectional design in the assessment of all baseline characteristics, and in Studies I and II prevented us from drawing conclusions on the direction of the association of increased depressive symptoms with the variables studied. However, by excluding subjects with established CVD, we could diminish the possibility of reverse causality. Nevertheless, remaining possibility of confounding is always present. Bias could have been caused especially by unreliability of self-report in assessing lifestyle associated factors, undetermined socioeconomic position, the time a participant had been at CVD risk, and treatment of depression and CVD risk factors. Finally, the baseline data were gathered over ten years ago.

6.5 Implications for Future Research

This study offers several implications for future research. First, as studies on the association of different subtypes of depressive symptoms and CVD morbidity and all-cause mortality are very scarce, replication of these results in the future is important. More specifically, in order to increase the robustness of the results, it could be beneficial to base the classification of depressive subtypes on structured interviews and course of illness. A larger sample and longer follow-up time would probably provide enough statistical power to verify whether melancholic depressive symptoms are non-significantly associated with CVD morbidity and mortality and allow consideration of specific causes of death. Importantly, future research should clarify whether consideration and treatment of depressive symptoms could prevent CVD morbidity, and even reduce the excess mortality risk. In addition, longitudinal studies on incorporating SRH assessment into CVD risk management are needed to determine whether assessing SRH promotes detection and treatment of depressive symptoms. Likewise, a need for clarification on whether treatment of depressive symptoms would lower blood pressure levels in hypertensive subjects is implicated by our results.

7 Conclusions

Increased depressive symptoms are prevalent among middle-aged subjects at CVD risk; one in five experiences such symptoms. These symptoms are more prevalent among women than men and are associated with many traditional CVD risk factors such as obesity, smoking, and low LTPA. In addition, awareness of hypertension and poor SRH associate with increased depressive symptoms. Among those with poor SRH, these symptoms even negatively affect their perception of their physical health. Especially increased non-melancholic depressive symptoms including increased appetite, fatigue, and mood reactivity increase risk for CVD morbidity and even all-cause mortality.

In regard to these findings, the following conclusions can be drawn:

- Not elevated blood pressure *per se* but the awareness of it is associated with increased depressive symptoms. Thus, a diagnosis of a new chronic condition such as hypertension should be discussed in a supportive manner.
- Assessment of SRH might be a practical tool in consideration of psychological risk factors in CVD risk management.
- Recognition of non-melancholic depressive symptoms among CVD risk subjects should be emphasised.

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