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Major depression in family medicine:  
associated factors, recurrence and  
possible intervention

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## I. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numerals I–V.

- I Suija K, Kalda R, Maaros HI. Patients with depressive disorder, their co-morbidity, visiting rate and disability in relation to self-evaluation of physical and mental health: a cross-sectional study in family practice. *BMC Fam Pract* 2009;10:38.
- II Suija K, Kalda R, Maaros HI. Depression and musculoskeletal problems. *Br J Gen Pract* 2009;59:51.
- III Suija K, Kalda R, Maaros HI. Co-morbid condition as an important factor influencing depression treatment. *Eur J Gen Pract* 2008;14:136–7.
- IV Suija K, Aluoja A, Kalda R, Maaros HI. Factors associated with recurrent depression: a prospective study in family practice. *Fam Pract* (submitted 15 February 2010).
- V Suija K, Pechter Ü, Kalda R, Tähepõld H, Maaros J, Maaros HI. Physical activity of depressed patients and their motivation to exercise: Nordic Walking in family practice. *Int J Rehabil Res* 2009;32:132–8.

### **Author's contribution**

The author participated in the formulation of the research questions and methodology, in the designing of the study, data collection and analysis, and in the writing of the manuscripts during the whole study.

In detail:

- I–IV The author participated in the designing of the study, collected and analysed the data, and completed the manuscript.
- V The author contributed to the design of the study, carried out telephone interviews, performed measurement of physical activity, analysed the data, and wrote the manuscript.

## 2.ABBREVIATIONS

AHCPR	Agency for Health Care Policy and Research
APA	American Psychiatric Association
BMI	body mass index
CI	confidence intervals
CIDI	Composite Diagnostic Interview
DEPRES	study “Depression Research in European Society”
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EHIS	Estonian Health Interview Survey
EST-Q	Emotional State Questionnaire
HR	heart rate
ICD-10	International Classification of Diseases, tenth version
MDD	major depressive disorder
MDE	major depressive episode
MCS 12	mental component summary scale assessed by the Short-Form 12 Health Survey
MINI	Mini-International Neuropsychiatric Interview
NCS	National Comorbidity Survey
NCS-R	National Comorbidity Survey Replication
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NW	Nordic Walking
OR	odds ratio
PCS 12	physical component summary scale assessed by the Short-Form 12 Health Survey
PGHC	WHO study “Psychological Problems in General Health Care”
PredictD	study “Prediction of Future Episodes of Depression in Primary Medical Care: Evaluation of Risk Factor Profile”
SPSS	Statistical Package for the Social Sciences for Windows
UKK 2 km	outdoor 2-kilometre walking test
UK	United Kingdom
US	United States
WHO	World Health Organization

### 3. INTRODUCTION

A family doctor has multiple roles. During every consultation, it is necessary to prioritize acute and chronic health problems, psychosocial aspects, prevention, counselling, and administrative aspects of care. Above all, the spectrum of diseases seen in family practice is wide. One of the most common mental health problems in family practice is depression.

In Estonia, a transition to more personal, comprehensive, and continuous care on the primary care level started in the 1990s (Lember, 1996; Maaros, 1998). Currently, all primary health care physicians in Estonia are trained family doctors, who are able to provide a wide range of medical services and to take care of patients with different health problems (Maaros and Lember, 2007).

The role of family doctors as the first contact in psychosocial problems in Estonia has increased (Lember et al., 1998; Ööpik et al., 2007). According to the study conducted in Estonia, about a quarter of the patients visiting family practice had depression. Furthermore, most of these patients had a moderate or severe episode of depression (Aluoja et al., 2005). Besides depression, family practice attendees often have other health problems. Studies have shown that co-morbidity is a typical pattern for family practice (Schellevis et al., 1993; van Weel and Schellevis, 2006). Therefore, the workload and responsibility of family doctors are significant (Kalda et al., 2004).

In recent years, the majority of depressed people are treated in family practice (Gask, 2003; Ööpik et al., 2005). New strategies for diagnosing and treating depression have improved the lives of millions of people; still, there is little evidence that the overall burden of depression has decreased (Callahan and Berrios, 2005). On the contrary, there is evidence that depression will be the second leading cause of disability in the developed world by 2020 (Murray and Lopez, 1997). Recent studies have emphasised that depression should be managed in most cases as a chronic long-term and relapsing disease (Andrews, 2001; Tylee 2007). Thus, finding factors associated with depression, as well as new possibilities to influence the course of depression and to develop self-help strategies, which people can adopt by themselves or by the assistance of others, e.g. physical activity, are under research.

In Estonia, depression has been the subject of research in the Department of Polyclinic and Family Medicine, the University of Tartu, also earlier (Ööpik et al., 2007). Based on previously conducted studies, family doctors were ready and felt motivated to manage patients with depression (Ööpik et al., 2007). However, the course of depression, the role of factors associated with recurrence of depression, as well as the association of depression with co-morbidity and physical activity remained unclear. Therefore, we focused our research on these topics.

## 4. REVIEW OF THE LITERATURE

### 4.1. Diagnosis of depression

The essential features of depression are lowering of mood, loss of interest and pleasure in normal activities, and reduction of energy. However, there are a variety of words and expressions that patients use to describe this condition. Therefore, it is important to distinguish clinical depression from normal mood reactivity; depression is not just the loss of pleasure in one situation but a pervasive anhedonia (Sadock and Sadock, 2007). Depression is not related to only emotions but it affects also thinking (Kuyken and Brewin, 1995). A depressed person is usually negative about his/her past, present and future and feels hopeless that things will ever be different. Depressed people are often self-critical and feel themselves worthless or guilty, up to thoughts of death and suicide, the latter being the most serious outcome of mental disorders (Harris and Barraclough, 1997). Depression has also physical effects, such as altered circadian rhythm, and loss of appetite and sexual interest. According to the literature, physical symptoms of depression are especially common in depressed patients in primary care (Greco et al., 2004; Simon et al., 1999). All these symptoms together can lead depressed patient to withdrawal from social activities.

Depression can be diagnosed on the basis of the history and mental state examination. As there are no specific tests to guide the diagnosis, the diagnostic interview, such as the Composite International Diagnostic Interview (CIDI) remains as the “gold standard” (Kessler and Üstün, 2004). CIDI can be used to diagnose depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 1994) or according to the International Statistical Classification of Diseases and Related Health Problems (ICD) (WHO, 1993).

In DSM-IV unipolar forms of primary mood disorders are divided into three groups: major depressive disorder (MDD), dysthymic disorder, and depression not otherwise specified.

In ICD-10 mood disorders are divided into: manic episode, bipolar affective disorder, depressive episode (MDE), recurrent depressive disorder, persistent mood disorder, other mood disorders, and unspecified mood disorder.

In Table 1 the general characteristics of the diagnosis of major depression according to the DSM-IV and ICD-10 are presented. The both classifications categorize three separate levels of severity for depression: mild, moderate, and severe. Severity is based on the effect that depression has on the patients' social role, the number and type of symptoms present in depressed patients, and the presence of psychotic symptoms (APA, 1994; WHO, 1993).

Although the ICD-10 requires one symptom less for the diagnosis and includes fatigue or loss of energy in the core symptoms, both classifications are compatible and major depression is basically similar in both classifications. In Estonia we use the ICD-10 classification in clinical practice but in research both classifications are used.

**Table 1.** Diagnosis of major depression by DSM-IV and ICD-10

<b>DSM-IV criteria for diagnosis of MDD</b>	<b>ICD-10 criteria for diagnosis of MDE</b>
Duration of symptoms $\geq$ 2 weeks	
At least <b>one</b> of the following symptoms: – depressed mood – loss of interest or pleasure	At least <b>two</b> of the following symptoms: – depressed mood – loss of interest or pleasure – decreased energy or increased fatiguability
<b>Four</b> or more of the following symptoms: – weight loss or change in appetite – insomnia or hypersomnia – psychomotor agitation or retardation – fatigue or loss of energy – feeling of worthlessness or guilt – diminished ability to think or concentrate – recurrent thoughts of death	<b>Two</b> or more of the following symptoms: – diminished ability to think or concentrate – reduced self-esteem and self-confidence – feeling of worthlessness or guilt – recurrent thoughts of death or suicide – sleep disturbance – change in appetite – change in psychomotor activity
The symptoms cause clinically significant distress in social, occupational, or in other areas of functioning	
– <i>mild</i> (5 symptoms and minor social impairment) – <i>moderate</i> (5 or more symptoms and variable social impairment) – <i>severe</i> (5 or more symptoms and major social impairment) – with melancholic features – with psychotic features	– <i>mild</i> (4 symptoms) – <i>moderate</i> (6 symptoms) – <i>severe</i> (8 symptoms) – with somatic symptoms – with psychotic symptoms
– single episode – recurrent	– depressive episode – recurrent depressive disorder

## 4.2. Prevalence of depression

Prevalence of depression has been estimated in numerous studies. Variations in time frames (current or point prevalence, 1-month, 6-month, 12-month, or lifetime prevalence), age ranges, diagnostic criteria, and interview schedules complicate the synthesis of findings of prevalence of depression (Table 2). Nevertheless, all studies generally indicate that depression is a highly prevalent condition and thus an important area for research.

In population samples, the lifetime risk for major depression appears to be about 15% in the majority of large population surveys such as the National Comorbidity Survey (NCS) (Kessler et al., 1994), the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Bijl et al., 1998), and the National Comorbidity Survey Replication (NCS-R) (Kessler et al., 2003).

In Estonia, the cross-sectional Estonian Health Interview Survey conducted in 1996 found that 11.1% of the general population had depressive symptoms (Aluoja et al., 2004); by 2006 the 1-month prevalence of depressive symptoms in Estonia had decreased to 8.7% while the point prevalence of MDD was 4.9% (Kleinberg et al., 2008).

The widest epidemiological clinical study on depressive disorders in primary care in the mid-1990s was the World Health Organization (WHO) Collaborative Study on “Psychological Problems in General Health Care” (PGHC) that comprised 14 countries and 26 000 primary care patients around the world (Sartorius et al., 1993). In the PGHC study an average of 10% of patients in primary care appeared to suffer from current major depression. The prevalence of current depressive disorders revealed variations across countries: the point prevalence of depression in different countries ranged from 1.5 to 27.3, being the lowest in Japan (1.5%) and the highest in Chile (27.3%) (Simon et al., 1999).

According to the PredictD study, a prospective study in which consecutive general practice attendees in six European and one Latin-America country were recruited and followed up after 6 and 12 months, the 6-month prevalence of major depression in different countries was between 10.9 and 29.6% (King et al., 2008). The 6-month prevalence of depression among consecutive family practice patients in Estonia was 24.1% (King et al., 2008).

**Table 2.** Prevalence of depression

Name and location of the study		Type of the study and sample	Instrument and criteria	Prevalence of depression	Reference
NCS	USA	Cross-sectional General population	CIDI DSM-III-R	14.9% <sup>4</sup>	Kessler et al., 1994
NCS-R	USA	Cross-sectional General population	CIDI DSM-IV	16.2% <sup>4</sup>	Kessler et al., 2003
NEMESIS	Netherlands	Prospective General population	CIDI DSM-III-R	2.7% <sup>1</sup> 15.4% <sup>4</sup>	Bijl et al., 1998
EHIS	Estonia	Cross-sectional General population	EST-Q	11.1% <sup>2</sup>	Aluoja et al., 2004
EHIS	Estonia	Cross-sectional General population	EST-Q <sup>2</sup> MINI <sup>1</sup> DSM-IV	8.7% <sup>2</sup> 4.9% <sup>1</sup>	Kleinberg et al., 2008

**Table 2.** Continued

Name and location of the study		Type of the study and sample	Instrument and criteria	Prevalence of depression	Reference
PGHC	Brazil Chile China Germany Greece France India Italy Japan Netherlands Nigeria Turkey UK USA	Cross-sectional Primary care	CIDI DSM-IV	18.3% <sup>1</sup> 27.3% <sup>1</sup> 2.4% <sup>1</sup> 5.3% <sup>1</sup> 7.1% <sup>1</sup> 13.6% <sup>1</sup> 8.5% <sup>1</sup> 4.6% <sup>1</sup> 1.5% <sup>1</sup> 14.4% <sup>1</sup> 4.1% <sup>1</sup> 10.8% <sup>1</sup> 17.1% <sup>1</sup> 6.4% <sup>1</sup>	Simon et al., 1999
PredictD	Estonia Netherlands Portugal Slovenia Spain UK	Cross-sectional General practice	CIDI DSM-IV	24.1% <sup>3</sup> 18.4% <sup>3</sup> 24.3% <sup>3</sup> 10.9% <sup>3</sup> 29.6% <sup>3</sup> 25.9% <sup>3</sup>	King et al., 2008

<sup>1</sup> current depression

<sup>2</sup> 1-month depression

<sup>3</sup> 6-month depression

<sup>4</sup> lifetime depression

### 4.3. Risk factors for depression

Depression is considered a complex multifactorial disorder, where the risk factors are related and interacting with each other (Kendler et al., 2002; Melartin and Isometsä. 2009). Amount of research has made to study the risk factors for depression. Recurrent depression may differ from the first episode (Lewinsohn et al., 1999), leading researchers to try and identify also the risk factors associated with recurrent depression.

In Table 3 the findings from the available studies about the risk factors for the single and for the recurrent episode of depression are presented.

However, the exact pathogenesis of major depression remains unknown and little is known about the factors influencing the recurrence of depression in primary care.

**Table 3.** Risk factors for single episode of depression and for recurrent depression

<b>Risk factor</b>	<b>Single episode of depression</b>	<b>Recurrent depression</b>
Genetic factors	Based on family and twin studies the heritability of depression is about 37% (Sullivan et al., 2000). Now, most of the genetic studies focus on finding out specific susceptibility genes.	The genetic determinants of recurrent depression are under investigation (Zubenko et al., 2002).
Socio-demographic factors (gender, age, living place, education, marital status)	There is about 2-times higher risk among women than among men for depression but there is no consensus on the association between depression and age (Aluoja et al., 2004; Kessler et al., 2003; Lepine et al., 1997; Weissman et al., 1996). Studies of urban-rural differences have given varying results: some authors report no differences (Aluoja et al., 2004; Kleinberg et al., 2008) while others show that urban residence is associated with depression (Lindeman et al., 2000). Lower educational level has been associated with depression (Aluoja et al., 2004; Kleinberg et al., 2008; Lindeman et al., 2000). About 2- to 4- fold increase in risk for major depression among divorced persons compared to married persons (Aluoja et al., 2004; Kessler et al., 2003; Weissman et al., 1996).	Sociodemographic factors, such as gender, age, living place, and marital status do not seem to be associated with recurrence of depression (Belsher and Costello, 1988; Burcusa and Iacono, 2007; Gonzales et al., 1985; van Weel-Baumgarten et al., 1998; Wilhelm et al., 1999).
Economic factors	Depression is more common among unemployed persons (Aluoja et al., 2004; Kleinberg et al., 2008). Also low income is associated with depression (Kessler et al., 2003).	Socioeconomic status does not seem to be associated with recurrence of depression (Belsher and Costello, 1988; Burcusa and Iacono, 2007; Gonzales et al., 1985).
Psychosocial factors	No single personality type predisposes a person to depression (Melartin and Isometsä, 2009). Stressful life events are often associated with development of depression (Aluoja et al., 2004; Melartin and Isometsä, 2009). Subjects with no relationships or with relationships only outside the family are at higher risk for depression than persons with relationships both in- and outside the family (Aluoja et al., 2004).	Lack of social support (Lewinsohn et al., 1988) and recent negative life events (Paykel and Tanner, 1976) have been proposed as risk factors for recurrent depression.

**Table 3.** Continued

<b>Risk factor</b>	<b>Single episode of depression</b>	<b>Recurrent depression</b>
<p>Negative experiences in childhood</p>	<p>The risk for depression is increased if a person has experienced negative life events in childhood, such as sexual abuse (Heim et al., 2000), parental loss or separation, and depression of parents (Lieb et al., 2002; Tennant, 1988).</p>	<p>Stressful life events in childhood (Wainwright and Surtees, 2002) have been proposed as risk factors for recurrent depression.</p>
<p>Co-morbidity</p>	<p>Individuals with one psychiatric disorder have an increased risk of having more disorders, the most frequent co-morbid disorders of depression are anxiety disorder, substance use disorder, and personality disorder (Kessler et al., 2003; Vuorilehto et al., 2005; Weissman et al., 1996). Co-morbidity between depression and somatic illness is also frequent (Al-Windi, 2005; Katon, 2003; Patten, 2001; Vuorilehto et al., 2005).</p>	<p>Psychiatric co-morbidity has been linked with recurrence of depression (Barkow et al., 2003; Gaynes et al., 1999; Wilhelm et al., 1999). Every episode of depression increases the possibility to have the next episode of depression (Gonzales et al., 1985; Keller and Shapiro, 1981). Vuorilehto et al. (2009) showed that chronic somatic illness also predicted recurrent depression.</p>

## **4.4. Co-morbidity of depression**

### **4.4.1. Definition of co-morbidity**

Co-morbidity is defined as “the existence or occurrence of any distinct additional entity during the clinical course of a patient who has the index disease under study” (Feinstein, 1967).

An increasingly used term is also multi-morbidity, which refers to the co-occurrence of two or more diseases within one person without a reference to an index condition (van den Akker et al., 1998).

Two or more diseases in the same person can occur by chance or selection bias, or there can be causal association: one disorder is a risk factor for another; both illnesses have a common cause; one disease is the cause of another (Katon, 2003; Valderas et al., 2009).

### **4.4.2. Prevalence of co-morbidity**

The occurrence of two or more psychiatric diagnoses in one person is frequent. Population based studies have reported that persons with major depression are at increased risk of having co-morbid mental disorder, most often alcohol abuse, panic disorder, or obsessive-compulsive disorder (Kessler et al., 2003; Weissman et al., 1996). Similarly, studies conducted in primary care have reported about high rate of co-morbidity between depression and other psychiatric disorders. About 40% of family practice patients with MDD had lifetime histories of substance abuse or anxiety disorder and 16% met criteria for current anxiety disorder which was significantly higher than for non-depressed patients (Coyne et al., 1994). On the other hand, co-morbidity of two or more psychiatric disorders has been criticized for being an artefact produced by categorical diagnoses, which are unable to differentiate between disorders according to their pathogenesis or etiology (Maj, 2005).

Prevalence of co-morbidity between depression and somatic disease is also frequent. Having a long-term medical condition (e.g. migraine, sinusitis, back problems) almost doubled the risk of MDD in Canadian National Population Health Survey (Patten, 2001). Similarly, studies involving patients with specific illnesses such as cancer, diabetes mellitus, Parkinson’s disease, and dementia have shown higher rates of depression in comparison with patients without these disorders (Anderson et al., 2001; Massie, 2004; Nuyen et al., 2006). Also chronic pain seems to increase the risk of associating depression, the rate of which has been reported to be 30% to 54% (Baune et al., 2008). Moreover, based on Bair et al. (2003) the prevalence of pain in depressed cohorts and depression in pain cohorts were higher than when these conditions were examined individually.

Co-morbidity and multi-morbidity are especially common in patients seen in family practice. According to a study conducted among consecutive primary

care patients in Finland, 88% of depressed patients had some co-morbid disorder: psychiatric co-morbidity was present in 59%, personality disorder in 52%, and general medical disorder in 47% of depressed patients (Vuorilehto et al., 2005). Some studies report that having a co-morbid somatic condition is even more common among depressed than non-depressed primary care patients (Al-Windi, 2005; Maier and Falkai, 1999).

However, the exact mechanism of the association of major depression with co-morbid condition is not clear. Several explanations involving biological and psychological mechanisms, such as inflammatory cytokines, psychosocial factors, and vulnerability theory have been proposed (Bair et al., 2003; Katon, 2003; Pincus and Williams, 1999). Moreover, because of heterogeneity in research, e.g. variations in assessment methods (screening and diagnostic instruments), study group (general population, primary care, and hospitalised patients; random versus consecutive sampling), and other factors analysed, it is still difficult to explain the link between depression and co-morbid illness.

#### **4.4.3. Impact of co-morbidity**

Most clinical specialities focus on one or more organ systems, however, the family doctor encounters a much broader spectrum of medical conditions. That is why co-morbidity is especially relevant in family practice. According to van Weel and Schellevis (2006), “co-morbidity is a regular feature of general practice and dealing with co-morbidity needs a patient-centred rather than a disease-oriented approach”. Studies have reported that co-morbidity is one of the major factors associating with poor outcome of depression: by increasing the risk of relapse and recurrence (Burcusa and Iacono, 2007; Vuorilehto et al 2009), chronicity (Keller et al., 1984), and suicide (Fawcett, 1997). Moreover depression may promote adverse health behaviours such as smoking, harmful alcohol consumption, unhealthy diet, sedentary lifestyle, and poor adherence to medical regimens, which may serve as risk factors for medical illnesses (Katon, 2003). Co-morbid depression increases the functional impairment in patients with somatic illnesses (Simon, 2003), is a predictor of shorter survival among cancer patients (Mainio et al., 2005); and influences presentation and recognition of depression in primary care (Simon et al., 1999). Co-morbidity should also be taken into account in treating depression (AHCPR, 2000; Schulberg et al., 1998). High prevalence of multi-morbidity in family practice makes the process of diagnosing more complicated (Noel et al., 2004). In other words, it is difficult to know whether a particular symptom is caused by depression, by a coexisting somatic illness, or by both. Co-morbidity may also complicate treatment of depression. Based on Smolders et al. (2008), co-morbid somatic condition led to higher prescription level of psychotropic drugs in general practice.

The prevalence and impact of co-morbidity in depressed patients in Estonia has not been assessed before.

## **4.5. Depression and functioning**

### **4.5.1. Depression and health-care utilization**

Psychiatric problems, including depression, are more prevalent among frequent attendees than among usual attendees in primary care (Karlsson et al., 1995). According to the DEPRES (Depression Research in European Society) study, sufferers from depression made about three times as many visits to their family doctor as non-sufferers (Lepine et al., 1997). A similar finding that depressed patients consulted the general practitioner more often than non-depressed patients was obtained in the PredictD study (King et al., 2008). Correlation has been established between severity of depression and use of healthcare facilities (Lepine et al., 1997). Overall, medical costs for patients with depression are higher compared with patients without depression (Callahan et al., 1994; Katon et al., 2003).

### **4.5.2. Depression and disability**

The rate of depression-related disability is increasing and there is evidence that it will be the second leading cause of disability in the developed world by 2020 (Murray and Lopez, 1997). The most important factor influencing disability is severity of depression (Judd et al., 2000).

A relatively objective measure of disability is work loss days (Lecrubier, 2001). Problems of mental health are among the most common groups of illnesses associated with high rate of days lost of work, e.g. sickness absence (Hensing et al., 2006; Savikko et al., 2001; Tellnes et al., 1989). Moreover, depression is associated with a larger number of days lost of work and poorer role functioning compared with several common general diseases, including arthritis, hypertension, and diabetes (Wells et al., 1989). Similarly, it has been established that depression is associated with disability pension (Isometsä et al., 2000; Vaez et al., 2007). According to Karpansalo et al. (2005), depressed subjects received disability pension on average 1.5 years earlier than those without depression.

### **4.5.3. Depression and well-being**

Well-being is defined as the subjective assessment of quality of life and health; functional status is the capacity to perform tasks and activities (Wells et al., 1989).

Depression is associated with poorer self-perceived health (Brenes, 2007; Callahan et al., 1994). Moreover, patients with depressive symptoms had a significantly worse health-related quality of life than patients with chronic somatic medical conditions (Wells and Sherbourne, 1999).

However, methodological as well as cultural and organizational differences may influence the use of healthcare resources and disability. Thus, we find important to study these factors in Estonia.

#### **4.6. Recurrence of depression**

Depression has a tendency to recurrence. Earlier studies often equated recurrence and relapse. Now the definitions have been standardised (Frank et al. 1991). According to Frank et al. (1991), relapse is a return of symptoms satisfying the full syndrome criteria for an episode that occurs during the period of remission but before recovery, e.g. an interval of more than two weeks but less than two months; and recurrence of depression is defined as the appearance of a new episode of depression after a period of recovery, with an interval of at least two months.

A US study indicated that nearly three quarters of people aged 15–54 years who had ever fulfilled the criteria for major depression had suffered more than one episode (Kessler et al., 1997). Based on the data from a survey conducted in the Netherlands (NEMESIS), Dutch adults meeting the criteria for major depression will experience on average about seven depressive episodes during their lifetime (Kruijshaar et al., 2005). However, most of these studies were conducted among general population or among psychiatric patients. Only a few studies have reported the course and outcome of depression in primary health care. A retrospective study conducted in Australia among primary care patients reported that during the study period (5 years) about 77% of the patients had more than one episode of depression: in about 25% of the cases within one year, in 25% of the cases within two years, and in half cases after two years (Wilson et al., 2003). A prospective study conducted among primary care patients found that in 40% of cases recurrence occurred within 3.5 years (Oldehinkel et al., 2000) and a cohort study with a study period of up to 10 years similarly reported that 40% of patients had more than one episode of depression during that time (van Weel-Baumgarten et al., 1998). Overall, there are wide variations in the recurrence of depression in primary care. No studies have assessed recurrence of depression in Estonia.

#### **4.7. Management of depression**

Family doctor is the first point of contact for depressive symptoms for more than half of the patients (Vuorilehto et al., 2007). Furthermore, most cases of depression are treated by primary care physicians (Gask, 2003; Gelenberg and Hopkins, 2007). The primary care centre is also the key point in referral of patients to special mental health care. Referral rate to secondary care is about 20% (Meeuwissen et al., 2008). However, there may be different obstacles to treatment of depression in family practice. For example, more than one third of

primary care patients with depression seem to be reluctant to accept the diagnosis (Williams et al., 1999). Similarly, high percentage of patients with depression report only physical symptoms (Simon et al., 1999). This may be related to the fact that patients tend to evaluate biomedical aspects more important than psychosocial aspects (Tähepõld et al., 2006). However, the consultation, which focuses on physical symptoms and on eliminating serious physical illness could be satisfying for the patient but may fail to get to the root of the problem. Detecting depression in connection with somatisation is related with professional skills of doctor (Timonen and Liukkonen, 2008). Also patients' adherence to antidepressant treatment may be poor (Johnson, 1973; Peveler et al., 1999). To sum up, studies have showed that up to half of all depressive disorders are unrecognised and undertreated in general practice (Freeling et al., 1985; Lecrubier, 2007). Therefore knowledge about effective management of depression in primary care is important for a family doctor. Based on Ööpik et al. (2006), family doctors in Estonia consider management of depression as their task and they feel ready to treat patients with depression. However, most of them reported that they need additional training (Ööpik et al., 2006).

There are different strategies to treat depression: pharmacotherapy, psychotherapy, phototherapy, electroconvulsive therapy, etc. or their combinations. Most studies on treatment of depression concentrate on pharmacotherapy and psychotherapy. There is evidence that treatment of depression with antidepressants (Arroll et al., 2009; Melander et al., 2008) and psychotherapy (DeRubeis et al., 2005) is effective.

Recently, new treatment modalities as exercising for treatment of depression have been proposed (Babyak et al., 2000; Blumenthal et al., 2007; Lawlor and Hopker, 2001). Moreover, there is some evidence that encouraging participation in exercising can also improve patient adherence to treatment (Trivedi et al., 2007). Literature is generally supportive of the beneficial effects of exercising on depression but there is still a need for a larger amount of well-designed research in this field (Lawlor and Hopker, 2001). However, recent research indicates that pharmacological and other treatment modalities are more similar to each other than previously thought: antidepressant therapy renews the neural network in the brain and combined effects of different forms of therapy will ensure higher efficacy (Castren, 2009).

## **4.8. Depression and physical activity**

Epidemiological research suggests that physical inactivity may be associated with depressive symptoms (Camacho et al., 1991; Hassmen et al., 2000; Lampinen et al., 2000). The exact mechanism of how exercising reduces the risk of depression is not clear (Craft and Perna, 2004). To clarify it different hypotheses have been proposed, such as the thermogenic hypothesis (deVries, 1981), the endorphins hypothesis (Morgan, 1985), the monoamine hypothesis

(Tang et al., 1981), and the neuroprotective effect of exercising (Russo-Neustadt et al., 2000). Exercise in reducing depression can also be seen in the cognitive-behavioural perspective: avoidance, withdrawal, and other symptoms of depression will lead to physical inactivity; and behavioural activation strategies, on the other hand, are effective in dealing with depression (Martinsen, 2008). Important factors are also positive feedback from other persons, social contacts owing to physical activity, and exercising as a new skill that improves the person's well-being (Lepore, 1997; Sonstroem 1984). Several authors have suggested that physical exercising can be used as an alternative to more traditional drug therapy or cognitive psychotherapy for treating depression (Babyak et al., 2000; Blumenthal et al., 2007; Klein et al., 1985). Based on the meta-analysis made by Lawlor and Hopker (2001), exercise may be efficacious in reducing symptoms of depression but for this more well designed studies are needed. Hence, most studies of the effect of exercise on depression are of poor quality and have used a short follow-up period. Problems also arise with motivation of the patients to start regular physical activity, particularly if they have been depressed for a long time. Therefore, the use of physical activity in the rehabilitation of depressed patients, the type of physical activity and its frequency and duration are not clear.

Among new types of exercising that have gained popularity is Nordic Walking (NW). NW is walking by using poles in the same way as is done in Nordic style skiing (Morso et al., 2006). During NW the muscles of the upper body are activated and cardiovascular metabolism increases (Porcari et al., 1997). The popularity of NW can be explained by the fact that it is low-cost, low-risk, does not require much skill and can be performed by almost everybody who is able to walk.

## **5. AIMS OF THE STUDY**

The general aim of this study was to find out factors that are associated with or influence depression in family practice attendees.

The specific aims of this study were:

1. To analyse how depression influences the patients' consultation rate in family practice and what kind of impact depression exerts on the patients' ability to work (Paper I).
2. To study whether co-morbidity is more prevalent in depressed than in non-depressed patients and how co-morbidity influences management of depression (Papers I–III).
3. To find out how patients with depression compared with patients with non-depression self-evaluate their health (Paper I).
4. To determine the risk for recurrent depression and factors associated with it (Paper IV).
5. To assess the physical activity of depressed patients and their motivation to exercise regularly, to measure their physical fitness, and to find out how regular physical activity affects their mood (Paper V).

## 6. SUBJECTS AND METHODS

This study forms part of a collaborative depression research project, the PredictD (Prediction of Future Episodes of Depression in Primary Medical Care: Evaluation of Risk Factor Profile), conducted in seven countries: United Kingdom (UK), Spain, Slovenia, the Netherlands, Portugal, Estonia, and Chile. In this thesis, relevant Estonian data is reported.

### 6.1. Study design

Overview of the aims of the study, design, methods, and subjects are presented in Table 4.

**Table 4.** Aims, design, subjects, and methods of the study

Aims of the study	Study design and methods	Subjects	Papers
1. To analyse how depression influences the patients' consultation rate in family practice and what kind of impact depression exerts on the patients' ability to work. 2. To study whether co-morbidity is more prevalent in depressed than in non-depressed patients and how co-morbidity influences management of depression. 3. To find out how patients with depression compared with non-depression self-evaluate their health.	Cross-sectional study	Consecutive patients (N=1094) from 23 family practices across Estonia	I II III
	CIDI, SF-12 Health Survey, medical records		
4. To determine the risk for recurrent depression and factors associated with it.	Prospective study	Patients (N=123) with non-recurrent and recurrent MDD during the PredictD study	IV
	CIDI, questionnaires for assessment of risk factors, medical records		
5. To assess physical activity and motivation to exercise regularly of depressed patients, to measure their physical fitness, and to find out how regular physical activity affects their mood.	Intervention study	Patients (N=178) who had had at least two MDE during the PredictD study.	V
	Telephone calls, questionnaires; CIDI, UKK 2 km		

## 6.2. Subjects

The recruitment of the patients and the design of the study were carried out according to the PredictD study (King et al., 2006). The sample was recruited from April to June 2003 by 23 family doctors (15 from urban and 8 from rural areas). They were the family doctors who had shown interest in participating in research project according to the earlier study (Ööpik et al., 2006). All patients who visited the family doctors were asked to participate in the study, irrespective of their reasons for consulting the family doctors. The family doctors were specially instructed to recruit patients proceeding from the project criteria.

The inclusion criteria were: consecutive attendees of family doctors' consultations; patients from urban and rural areas; patients aged 18 to 75 years.

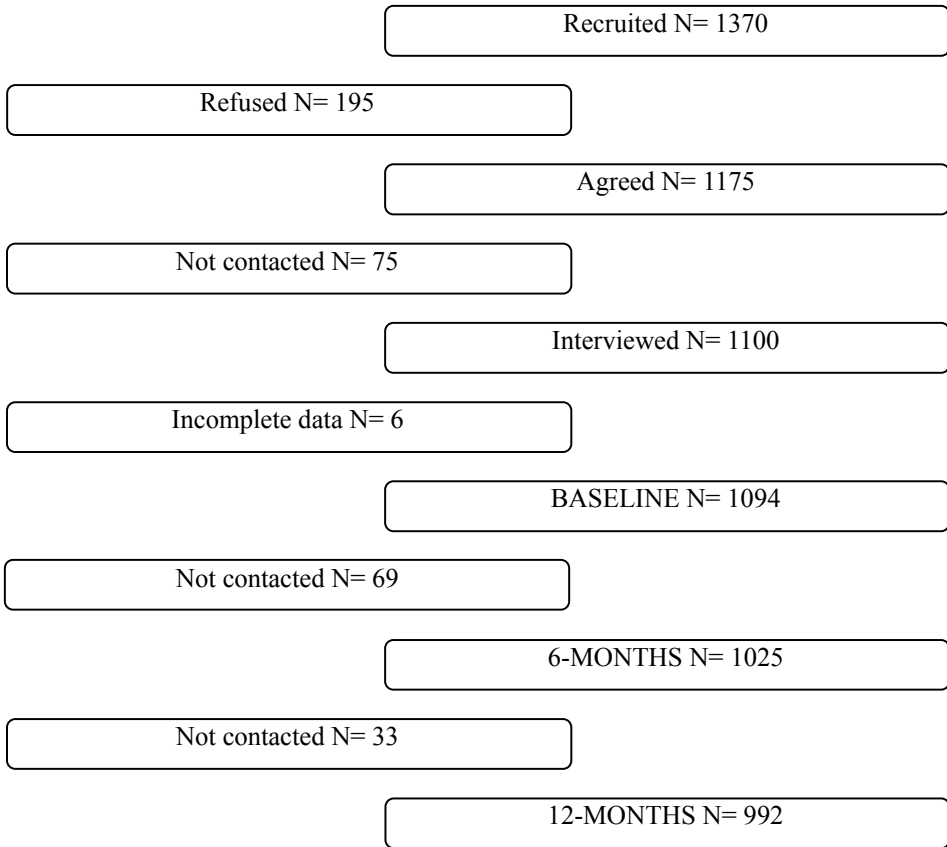
The exclusion criteria were: non-Estonian speakers; presence of a severe organic mental illness; presence of a terminal illness; mental retardation.

Figure 1 presents the flowchart of the study population.

The family doctors recruited altogether 1370 patients but 195 of them refused to take part in the study. Thus, 1175 of the patients agreed to participate in the study. After the participants had given their informed consent, we were not able to contact 75 of the patients. Therefore, an interview was carried out with 1100 patients. The detailed interview was carried out either at the patient's home or at the family practice centre by specially trained interviewers within two weeks of informed consent. The interview consisted of the Depression Section of the Composite International Diagnostic Interview (CIDI) version 2.1 and the questionnaire for assessment of demographic, health-related, and psychological risk factors of depression. All patients were interviewed three times during the PredictD study: at baseline, at 6 months, and at 12 months. Additionally, patients who participated in the NW programme were interviewed also before starting regular physical activity and after exercising.

Because of incomplete data we had to exclude 6 patients. The final study group at baseline consisted of 1094 patients. After 6 months we lost contact with 69 of the patients. Thus, 1025 of the patients were interviewed at 6 months.

For the interview at 12 months we failed to contact 33 of the patients and thus 992 patients participated in the interview at 12 months.



**Figure 1.** Flowchart of the study population.

### **6.2.1. Patients with depression**

To study co-morbidity and healthcare utilization, we analysed the data of patients with depression or non-depression according to ICD-10 at baseline (N= 1094).

### **6.2.2. Patients with recurrent depression**

To determine the factors associated with recurrent depression, we analysed the data of 123 patients: 89 of them had non-recurrent depression (major depression by DSM-IV at baseline, absence of depression at the 6-month interview, and absence of depression at the 12-month interview) and 34 of them had recurrent depression (major depression by DSM-IV at baseline, absence of depression at the 6-month interview, and recurrent depression at the 12-month interview) (Paper IV, Figure 1).

### **6.2.3. Patients participating in the NW programme**

The study group was formed of 178 patients who had had at least two depression episodes according to the ICD-10 during the PredictD study. We made phone calls to the patients but failed to contact 45 of the patients because of wrong contact numbers; 27 of the patients declined participating in the study. Thus, 106 patients were interviewed and invited to participate in NW exercising (Paper V, Figure 1).

## **6.3. Methods**

### **6.3.1. Composite International Diagnostic Interview**

The Composite International Diagnostic Interview (CIDI) is a fully structured and standardized psychiatric interview developed by the World Health Organization (WHO) in 1990 (WHO, 1997). The interview was designed to assess major mental disorders including unipolar depression and provides current psychiatric diagnoses according to the ICD-10 or DSM-IV (WHO, 1997).

In this thesis the occurrence of major depression during six months was estimated using the Depression Section of the CIDI version 2.1 according to the criteria of ICD-10 in Papers I–III and V and according to the DSM-IV in Paper IV.

We used ICD-10 in Papers I–III and V because the data of co-morbid diagnoses were provided by the family doctors, who use ICD-10 in their clinical practice. In Paper IV we assessed depression according to DSM-IV, which was used more often in the PredictD study.

### **6.3.2. Questionnaires for assessment of risk factors**

At baseline every patient filled in the questionnaires to assess demographic, health-related, and psychological factors associated with depression. The selection of the questionnaires was based on the PredictD study (King et al., 2006). Standardized questionnaires were evaluated for test-retest reliability before the study began (King et al., 2006).

Table 5 presents the questionnaires used for assessment of risk factors analysed in the current study.

**Table 5.** Questionnaires used for assessment of factors associated with depression

Socio-demographic and personal factors: age; sex; educational level; marital status; employment status; living alone or together with other person(s); experienced difficulties with unpaid and paid job; difficulties in getting along with people and maintaining close relationships (King et al., 2006).
Physical and mental well-being was assessed by the Short-Form 12 Health Survey (Version 1.0): the physical component summary scale (PCS 12) and the mental component summary scale (MCS 12) were calculated for each patient (Ware et al., 1995).
Alcohol misuse was assessed according to the WHO's AUDIT (Alcohol Use Disorders Identification Test) questionnaire (Barbor et al., 2001).
Use of any illicit drugs (cannabis, amphetamine, heroin, cocaine, LSD, anxiolytics, hypnotics) in order to relax or to improve mood (King et al., 2006).
Quality of sexual and emotional relationships with partner was assessed by the Brief Sexual Questionnaire (Reynolds et al., 1988).
Childhood experience of physical and/or emotional, and/or sexual abuse was based on the Childhood Trauma Interview (Fink et al., 1995).
Experience of discrimination on the grounds of sex, age, ethnicity, appearance, disability, or sexual orientation was based on a report by Janssen et al. (2003).
Panic attacks in history were assessed by the Patient Health Questionnaire (Spitzer et al., 1999).
Recent major life events were assessed using the List of Threatening Life Experiences (Brugha et al., 1985).
Family psychiatric history: suicide among first-degree relatives; serious physical, psychological or substance misuse problems with close relatives or friends (King et al., 2006).

### **6.3.3. Co-morbidity and health care utilization**

To study co-morbidity and healthcare utilization we asked relevant information from the family doctors. We sent registration forms to the family doctors inquiring about the patients' co-morbid diseases by the ICD-10, number of visits to the family doctor, number of days on sick-leave due to all causes, and prescribed medications (antidepressants, anxiolytics, hypnotics) for treatment of depression between January 2003 and December 2005, and disability. The doctors were asked to fill in the registration forms using information from the patients' medical records. All registration forms distributed among the family doctors were returned.

Disability was defined if the patient had a somatic or mental disease that limited his/her ability to work and if he/she received social benefits (disability pension) from the social system.

Days on sick-leave were defined as days absent from work due to illness.

### **6.3.4. Depression and physical activity**

Phone calls were made to patients (N=178) who had been diagnosed with MDE according to the ICD-10 at least twice during the PredictD study. Of the patients 106 gave their informed consent and were interviewed by using the CIDI. Three trained interviewers carried out the interview. The occurrence of depression was assessed three times, at the beginning of the study (Week 0), after 24-week exercising (Week 24), and after one year.

#### **6.3.4.1. Assessment of physical activity and motivation to exercise**

All patients were invited to participate in the NW programme. Before starting regular NW the patients were asked to assess their previous physical activity during the past two years. We used the following categories: at least 30 minutes on two or more days of a week; at least 30 minutes at least one day of a week; no regular physical activity during the past two years. After one year we inquired whether they exercise now more, less or as much as before entering to the programme. Feedback on the NW programme was assessed after 24-week exercising by three questions: what motivated them to take part of the study (to reduce depression, to improve health, to have poles, to exercise, or to reduce weight); what has changed in their lifestyle (nothing, mood improved, physical activity improved, health improved); and what was the attitude of their family and friends to the NW (positive, no information, negative).

#### **6.3.4.2. Measurement of physical fitness**

To measure physical fitness, we used the outdoor 2-kilometre walking test (UKK 2 km), which is developed in the Urho Kaleva Kekkonen Institute in Tampere. The test is simple, safe, and its validity has been proven (Laukkanen et al., 1992; Oja et al., 1991; Rance et al., 2005). Every patient walked two kilometres as fast as possible. The polar FS2c heart rate monitor was employed to measure heart rate (HR). Physical fitness was calculated by taking the time for walking the 2-kilometre distance in minutes and seconds, heart rate was measured at the end of the distance, age in years was recorded, and body mass index (BMI) was calculated. The calculations of physical fitness for males and females were different.

Aerobic fitness or physical fitness in males was calculated using the formula  $420 - (11.6 \times \text{minutes} + 0.2 \times \text{seconds} + 0.56 \times \text{HR} + 2.6 \times \text{BMI} - 0.2 \times \text{age})$  and in females using the formula  $304 - (8.5 \times \text{minutes} + 0.14 \times \text{seconds} + 0.32 \times \text{HR} + 1.1 \times \text{BMI} - 0.4 \times \text{age})$ .

Fitness index below 70 indicated very poor physical fitness, 70–90 indicated poor, 90–110 moderate, 110–130 good, and above 130 indicated excellent physical fitness (Oja and Tuxworth, 1995).

### **6.3.4.3. NW programme**

All participants received poles free of charge (from Pole About Original poles, Finland) and were instructed by a trained supervisor. The study physician established that the patient had no medical contraindications for physical exercise (significant orthopaedic problems or cardiopulmonary disease that would prevent regular aerobic exercise). According to the protocol, the participants attended the unsupervised home-based exercise programme, NW, at least three times a week at least 30 minutes at a time.

Altogether 21 volunteers completed first UKK 2 km and started exercising. After 12-week regular training they were invited for the second UKK 2 km. After testing they continued training according to the same protocol. At week 24 the participants passed the third UKK 2 km and completed the same questionnaires as at the beginning of the study. After exercising for one year the participants had the possibility to pass the fourth UKK 2 km test.

All participants had to fill out the exercise diary during the study. They were asked to record the time spent on walking per week. Also they were asked to assess their mood at the beginning of exercising and after it. For assessment of mood, we used a 10-point scale where 1–2 was very bad mood, 3–4 bad, 5–6 moderate, 7–8 good and 9–10 the best possible mood. The diaries were returned to the researchers after 12-week and 24-week exercising.

All participants were free to call the study physician if they had any questions or health-related problems during exercising.

## **6.4. Statistical methods**

The Statistical Package for the Social Sciences (SPSS) for Windows was used for data analysis: Release 10.0.1 in Papers I–III and V; Release 17.0.0 was used in Paper IV.

Standard methods (mean, standard deviation, percentages) were used for descriptive statistics (Papers I–V). Differences in variables between depressed and the non-depressed patients were analysed with the Chi-Square Test and the t-test (Papers I–II and V).

To find out factors independently associated with depression, we used logistic regression analysis and computed the odds ratios (OR) with the 95% confidence intervals (95% CI) (Paper I).

To find out factors associated with recurrent depression, we also used logistic regression analysis and computed the OR with 95% confidence intervals (95% CI) (Paper IV). First, in univariate models we entered each variable

one at a time. Second, we constructed a multivariate model by combining the variables that were associated with recurrent depression in the univariate model to find out factors that were independently associated with recurrent depression (Paper IV).

Logistic regression analysis was also used in Paper III to find out how comorbidity is associated with treatment of depression.

All tests were two-sided and statistical significance was assumed when  $p < 0.05$ .

## **6.5. Ethics**

The Committee of Ethics of the University of Tartu approved the study protocol and the form of informed consent of the study.

## 7. RESULTS

### 7.1. Study group

Main characteristics of the study group are presented in Table 6.

**Table 6.** Main characteristics of the study group (N= 1094)

Characteristic		Number (n)	Percentage (%)
Gender	Female	803	73
	Male	291	27
Age groups	18–29	337	31
	30–59	573	52
	60–75	184	17
Living place	Urban area	813	76
	Rural area	263	24
Education	Higher	287	26
	Secondary	673	62
	Primary	134	12

### 7.2. Depression and the patients' consultation rate and days absent from work

There was no difference in the consultation rate between patients with depression and patients with non-depression. The mean number of consultations for patients with depression was 14.3 and for patients with non-depression 13.0 ( $p=0.156$ ) within three years (Paper I, Figure 2).

Depressed patients were significantly longer on sick-leave compared with non-depressed patients (26.5 and 16.3 days, respectively) ( $p=0.002$ ) (Paper I, Figure 2).

### 7.3. Depression and co-morbidity

The three most prevalent illnesses necessitating to consult the family doctor for all patients were diseases of the musculoskeletal, respiratory, and cardiovascular systems. Mental and behavioural disorders occupied the ninth place among the causes to consult the family doctor (Paper I).

Of the depressed patients 90% and of the non-depressed patients 87% had at least one co-morbid diagnosis ( $p=0.368$ ) (Paper I).

There were no significant differences between the mean number of different co-morbid diagnoses for depressed and non-depressed patients (3.3 and 3.2 different co-morbid diagnoses, respectively) ( $p=0.546$ ) (Paper I, Figure 2).

Patients with depression had significantly more co-morbid psychiatric disorders (F00-F99) ( $p=0.042$ ) and less endocrine, nutritional and metabolic disorders (E00-E90) ( $p=0.040$ ) than patients with non-depression (Paper I, Table 3). However, in logistic regression analysis having a co-morbid illness was not associated with depression (Paper I).

A total of 202 participants aged  $\geq 50$  years presented with musculoskeletal pain. Of them 48 (23.8%) were depressed and 154 (76.2%) were non-depressed (Paper II).

Antidepressants were prescribed for 33%, anxiolytics for 24%, and hypnotics for 11% of the depressed patients. More antidepressants, anxiolytics, and hypnotics were prescribed to patients with co-morbid mental disorder (odds ratio [95% CI] 5.49 [3.61–8.40], 8.38 [5.33–13.18], and 4.02 [2.30–7.02], respectively) compared to patients who did not have such disorder (Paper III, Table 1).

#### **7.4. Depression and patients' self-evaluation of their health**

We found that 22% of the depressed patients and 12% of the non-depressed patients evaluated their health in general as poor ( $p<0.001$ ). Compared with non-depressed patients depressed patients reported much more limitations in their work, significantly less accomplishment owing to problems with physical and mental health, more limitations in everyday life, and that their social activities were interfered with by their health ( $p<0.05$ ). 81% of the patients with depression and 19% of the patients with non-depression reported that their work was interfered with by pain ( $p<0.001$ ) (Paper I, Table 2).

#### **7.5. Recurrent depression**

Of the depressed patients 28% had a recurrent episode of major depression by the DSM-IV criteria 12 months later (Paper IV).

The factors that were significantly associated with recurrent depression in univariate analysis were: lower educational level; non-working status; age 40–59 years; disability; difficulties with paying bills; not having enough money for food and clothes; history of drug abuse; history of panic attacks; level of satisfaction with emotional relationship with partner; co-morbid respiratory illness; prescribed antidepressants; experience of discrimination on the grounds of sex, age, ethnicity, appearance, disability, or sexual orientation; and childhood experience of physical, emotional, or sexual abuse (Paper IV, Table 2).

For assessing association between different risk factors and recurrence of depression, we used multivariate logistic regression analysis. According to the multivariate model, the odds of having recurrence of depression were significantly higher for those who had misused drugs in their history, OR 7.48

(95%CI=1.42–39.43); for those who had experienced discrimination, 2.92 (95%CI=1.05–8.11); and for those with a history of childhood abuse, OR 1.58 (95%CI=1.05–2.38) (Paper IV, Table 3).

The most prevalent misused drugs were anxiolytics and hypnotics: 68% of the patients with recurrent depression and 32% of the patients with non-recurrent depression reported about using these drugs ( $p=0.005$ ) to improve their mood or relax.

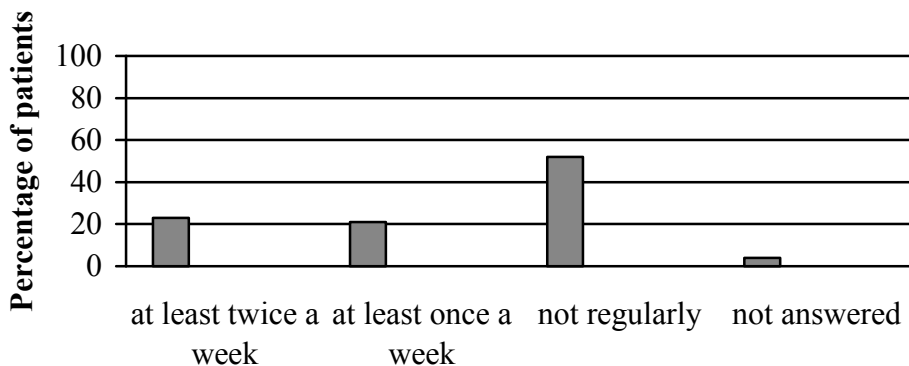
## 7.6. Depression and physical activity

### 7.6.1. Physical activity and patients' motivation to exercise

Previous physical activity of the study group was low, 52% of them reported that they had not had any regular physical activity during the previous two years (Figure 2).

About 20% of the studied patients were motivated to start regular physical activity. The most common reasons for starting it were the hope that physical activity could reduce their depression or improve their health. Other reasons, such as to exercise or to reduce weight were reported more seldom (Paper V, Table 4).

The attitude of the participants' families and friends to the NW programme was positive. One-quarter of the patients also completed the whole programme. The main reason for withdrawal was lack of time (Paper V).



**Figure 2.** Previous physical activity of the study group during the past two years (N=106)

### 7.6.2. Physical fitness of the study group

The mean fitness index for depressed patients was  $21.99 \pm 20.38$  at the beginning of the study (week 0) and  $38.72 \pm 26.12$  at week 24 ( $p=0.179$ ) (Paper V, Table 3).

According to the diaries, a depressed patient exercised  $23.70 \pm 11.81$  times and a non-depressed patient exercised  $28.60 \pm 8.38$  times during the 12 weeks (Paper V).

After one year we were able to contact 18 of the patients: 13 of them reported that they exercised more than before entering the programme, 5 of the patients reported that they exercised as much as before.

### 7.6.3. Physical activity and mood

At the beginning of the study (week 0) 16 of the patients were depressed: seven had mild, five had moderate, and four had severe depression (Table 7).

At week 24, of the patients 12 were non-depressed and 7 had still depression. The patients who were depressed at the end of the study were the same patients who had been depressed at the beginning of the study. None of the patients had worse depression; neither had any patient of the non-depressed group developed depression after 24-week exercising (Table 7).

After exercising NW for one year 3 of the depressed patients were still depressed according to the CIDI (Table 7).

Eleven of the participants evaluated their mood as bad or very bad at the beginning of the study and eight participants evaluated their mood as good or very good. After 24-week exercising, 11 of the participants evaluated their mood as good or very good and five participants evaluated their mood as bad (Paper V, Table 2).

**Table 7.** Assessment of depression at week 0, week 24, and after one year by the CIDI

Characteristics	Number of patients (N= 21)		
	Week 0	Week 24	One year
Depression by the CIDI			
No depression	5	12	15
Mild	7	5	3
Moderate	5	0	0
Severe	4	2	0
Missing data	0	2	3

## **8. DISCUSSION**

This thesis addresses some identified gaps in the knowledge of consultation rate, sickness absence, co-morbidity, physical activity, and factors associated with recurrent depression in patients seen in family practice in Estonia. Consecutive patients were recruited and followed up after 6 and 12 months. Consequently, our study provides a good knowledge of the problems of consecutive family practice attendees, which is important for family doctors' readiness to have necessary skills for management of patients with different problems. A reliable instrument, CIDI was used to diagnose depression; additional information was inquired from the patients and from their family doctors. Selection of questionnaires for assessment of demographic, health-related, and psychological risk factors for depression was based on a systematic review of the literature by the members of the work group of PredictD (King et al., 2006). Data about the number of visits, co-morbidity, and sickness absence was based on medical records and was therefore obtained from the family doctors. To study physical activity, we chose Nordic Walking, which is a mode of training available to everyone, its only prerequisite being the ability to walk. As walking is the most natural physical activity of all (Oja and Tuxworth, 1995), we used the two kilometre walking test to measure physical fitness. We consider that the use of diaries and the possibility for the patients to contact the study physician throughout the NW study were evidently important motivating and mood-improving factors.

### **8.1. Depression and the patients' consultation rate and days absent from work**

We found that depressed patients did not visit the family doctor more often than non-depressed patients. Earlier studies have shown that depressed patients consult the doctor more frequently than non-depressed patients (Karlsson et al., 1995; King et al., 2008; Lepine et al., 1997). This can be related to differences in the methodology used in those studies and in our study. For example, the sources of information about consultation rate were different. To prevent any recall bias we inquired information from the family doctor and not from the patient. Discrepancies can also be related to the length of the study period. We registered the number of visits to the family doctor during three years while in other studies this period was six months (King et al., 2008, Lepine et al., 1997). Indeed, patients with depression consult the doctor more often during an illness episode the duration of which is usually about six months, and further, after recovery, the consultation rate will decrease. Cultural and organizational differences may also influence the consultation rate. For example, in Estonia, it is possible to consult the psychiatrist without referral. However, according to an earlier study 65% of the antidepressants in Estonia are prescribed by family

doctors (Õöpik et al., 2005). According to the study made among random sample of Estonian residents (N=1446), the average number of visits during the last 12 months to the family doctor was 2.8 but for the chronically ill people 4.5 (Põlluste et al., 2007). Thus, our results are comparable with previously conducted studies in Estonia.

According to our results, depressed patients were more days on sick-leave than non-depressed patients. Yet it is difficult to make definite conclusions about this finding because we did not register the causes of sick-leave or the number of days of sick-leave that were due to depression. On the other hand, psychiatric disorders are among the most common diagnostic groups accounting for high sickness absence (Hensing et al., 2006) and mental health problems have been associated with high rate of sickness absence irrespective of other factors (Savikko et al., 2001).

## **8.2. Depression and co-morbidity**

Almost all of the patients had some co-morbid diagnosis but there were no differences between the number of co-morbid diagnoses of depressed and non-depressed patients. In other words, we cannot claim that patients with several co-morbid illnesses are more likely to have depression. To our knowledge, this is a new finding. Earlier studies have reported that co-morbidity is more common among depressed than non-depressed patients (Al-Windi, 2005; Maier and Falkai, 1999). This can be related to differences in the methodology used in those studies and in our study. We inquired information from the family doctor and consider that the use of patients' medical database is the most reliable source to collect data about co-morbidity.

Based on our findings, depression should be considered an independent serious disorder that requires also an independent approach. Moreover, the impact of depression should not be underestimated when it occurs as a co-morbid disease. From the clinical point of view, it is important to point out that as almost all patients have some co-morbid diagnosis, management of these patients is often a challenge for the doctor. Therefore, patient-centred rather than disease-oriented approach is essential (van Weel and Schellevis, 2006).

We also found that co-morbidity influenced treatment of depression in family practice. As expected, antidepressants, anxiolytics, and hypnotics were prescribed more often to patients with some co-morbid mental disorder than to patients without it. Similar finding that co-morbidity, especially psychiatric co-morbidity, leads to higher prescription level of psychotropic medications in depressed patients was reported by Smolders et al. (2008).

### **8.3. Depression and patients' self-evaluation of their health**

The result that patients with depression compared with patients with non-depression were more days on sick-leave can be related to the finding that patients with depression in our study also evaluated their health as poor. Moreover, the depressed patients reported that they accomplished less and were less careful as a result of emotional problems. These are typical emotional symptoms of depression. Additionally, depressed patients reported more pain than non-depressed patients. There is evidence that pain and depression are often associated (Bair et al., 2003). Thus, from the practical point of view, it is important to emphasise that, besides information about specific emotional symptoms, also information about non-specific symptoms such as pain should be obtained from depressed patients. According to the literature, a high number of depressed patients in primary care even report only physical symptoms (Greco et al., 2004; Simon et al., 1999). On the other hand, based on our analyses among patients aged  $\geq 50$  years whose problem was musculoskeletal pain, about a quarter had co-morbid depression. This means that most people with musculoskeletal pain were non-depressed. This result is contrary to the finding by Mallen and Peat (2008) that most old people with musculoskeletal pain are also depressed. The difference can be related to the study instrument: Mallen and Peat (2008) used screening instruments while we employed the diagnostic instrument, which is more specific.

### **8.4. Recurrent depression**

According to our analysis, about one third of the patients who presented with depression also experienced recurrent depression 12 months later. This means that most patients stayed in remission and did not have a recurrent episode of depression. Previously conducted studies in primary care have reported similar rates of recurrence (van Weel-Baumgarten et al., 1998; Vuorilehto et al., 2009). Recurrent depression may differ from the first episode (Lewinsohn et al., 1999), encouraging researchers to try identify risk factors associated with recurrent depression.

The factors associated with recurrence in this study were: lower educational level; non-working status; age 40–59 years; disability; difficulties with paying bills; having not enough money for food or clothes; misuse of drugs; history of panic attacks; co-morbid respiratory disease; not prescribed antidepressants; experience of discrimination and childhood abuse. However, when we analysed all these factors in the same model only drug abuse, experience of discrimination, and childhood abuse remained significantly associated with recurrence of depression during one year. Other studies have also suggested that these

factors play a role in development of recurrent depression (Barkow et al. 2003; Molnar et al., 2001; Vuorilehto et al., 2009; Wainwright and Surtees, 2002).

The misused drugs revealing the most significant difference in the frequency of use between patients with recurrent depression and patients with non-recurrent depression were anxiolytics and hypnotics. It is possible that patients who have residual symptomatology after recovery from a depressive episode resort to self-medication to alleviate distress. At the same time, our results suggest that the use of anxiolytics and hypnotics does not prevent further development of depression.

Coulehan and Zettler-Segal (1987) estimated the prevalence of substance abuse among primary care patients at 7.8%, presenting as the third most common mental health diagnosis after depression and alcohol abuse. Prescription drug abuse is also a rising problem forming the second most prevalent category of drug abuse after marijuana in the USA (Manchikanti, 2006). On the other hand, drug abuse is often unrecognised in family practice (Molnar et al., 2001). This can be explained by several reasons. Patients whose main problem is drug abuse are typically reluctant to present because of legal consequences; or they present indirectly with symptoms that are not specific to substance abuse. Drug use has a huge impact on the users' medical, social and economic lives, inevitably creating a cluster of problems that affect not only the user but also their families. Consequently, it is important for the family doctor to identify drug abuse. Physicians recognize drug abuse well if the patient has also a concurrent antisocial personality disorder, but it is often missed if the patient has concomitant depression (Coulehan and Zettler-Segal, 1987). More attention should be paid to the identification of patients who abuse drugs.

The prevalence of childhood abuse is reported to range from 2.5 to 44% (Gould et al., 1994; Molnar et al., 2001). The relationship between childhood abuse and adulthood psychiatric disorder is well documented (Gould et al., 1994; Molnar et al., 2001; Paykel and Tanner, 1976). Similarly, discrimination is suggested to be related with poorer mental health, although it is difficult to separate the causality between discrimination and diagnosis (Pascoe and Smart Richman, 2009). Further studies are needed in this field, especially among primary care patients. Like drug abuse, experience of discrimination and abuse can easily remain unrecognised in family practice. This could be related to the context surrounding these events as well as to moral and legal issues (Gould et al., 1994). Evidently, more attention should be paid to the topic of how family doctors could detect problems such as discrimination and abuse.

We failed to find association between recurrence of depression and socio-demographic factors such as gender, marital status, and educational level. Similarly, recent major life events did not predict recurrence of depression. This is in line with other studies showing that sociodemographic factors do not represent significant risk factors for recurrence (Burcuse and Iacono, 2007; Gonzales et al., 1985).

From the practical point of view, if we can identify individuals at risk for recurrent depression, we are able to monitor them more carefully and consider

tailored interventions, such as psychotherapy that has been shown to be effective in the treatment of recurrent depression (Bockting et al., 2009), or we are able to develop self-help strategies, such as regular exercising to reduce the overall burden of depression.

## **8.5. Depression and physical activity**

Studies have shown that physical inactivity is related with poor self-rated health (Molarius et al., 2006; Oja, 2008; Svedberg et al., 2006; Tekkel and Veideman, 2008). Thus, poor self-reported health of the depressed patients in our study could be influenced by their low physical activity. According to our results, half of the patients reported that they had not had any regular physical activity during the previous two years. In comparison, about 70% of the respondents were engaged in moderate physical activity during the past four weeks according to the Estonian Health Interview Survey 2006 (Oja, 2008). Low level of physical activity of the depressed patients could be associated with major depression that has been linked with low physical activity in epidemiological studies (Hassmen et al., 2000; Tolmunen et al., 2006). Also, the baseline physical fitness index of the depressed patients was very low but it improved with exercising. This is a quite expected change (Haskell et al., 2007).

Physical activity is one of the most effective and non-costly possibilities to improve the patient's health (US Department of Health and Human Services, 2000). However, promotion of physical activity among population and especially among patients with health problems is an important yet often a complicated issue.

About one-fifth of the studied patients were motivated to start regular physical activity. Only one quarter of them completed the whole programme. This could be explained by depression that reduces adherence to exercise (Flegal et al., 2007), or by the fact that a home-based programme requires more activity from the individual. On the other hand, most people know that exercising is beneficial but this knowledge does not guarantee starting and following up regular exercising. Patients with depression present a special challenge for exercise compliance, however, the best method for improving exercise compliance has yet to be identified (Martinsen, 2008).

Most of the depressed patients reported their motivation to start with the training programme because they hoped that physical activity could reduce their depression and improve their health. This is a very positive finding, which indicates that even when being depressed the patients were motivated to seek help.

About half the depressed patients were non-depressed after 24-week exercising and there was none whose depression had worsened after exercising. All patients evaluated their mood as much better after exercising, including even those who were still depressed according to the CIDI. Thus, we can conclude that physical activity has a good influence on mood, which has been shown also in earlier studies (Babyak et al., 2000; Blumenthal et al., 2007).

## **8.6. Summary**

Our findings illustrate that patients with major depression in family practice report pain and low functioning related to emotional problems. Also their ability to work and motivation to exercise regularly may be decreased. However, depressed patients consult the family doctor as often as do patients without depression and the patients of both groups have an equal number of co-morbid diagnoses. It should be emphasised that about one third of depressed patients have a recurrent episode of depression during one year. The factors that play an important role in development of recurrent depression are drug abuse, discrimination, and childhood abuse. These factors should be taken into consideration by family doctors when managing patients with depression. Moreover, although the depressed patients' motivation to exercise regularly is low, regular physical activity increases their fitness and improves their mood. Therefore, physical activity could be used as possible intervention for depressed patients in family practice.

## 9. CONCLUSIONS

1. Depressed patients consulted their family doctor almost as often as non-depressed patients but their working ability was decreased: depressed patients were more days on sick-leave than non-depressed patients.
2. Co-morbidity was prevalent among depressed patients, 90% of the depressed patients had at least one co-morbid diagnosis. However, we did not find any differences in the number and pattern of co-morbid diagnoses between depressed and non-depressed patients. Treatment of patients with high rate of co-morbidity is often a challenge for the family doctor.
3. Depressed patients evaluated their health general as poorer than non-depressed patients: they reported significantly more limitations in their work, and social and physical activities, especially due to emotional problems; also they reported about pain that extremely interfered with their normal work. Hence, besides information about emotional symptoms, also data about non-specific symptoms such as pain should be obtained from depressed patients.
4. About one-third of the depressed patients had a recurrent episode of major depression 12 months later. The factors predicting recurrence included drug abuse, discrimination, and childhood abuse. These factors should be taken into account by family doctors when managing patients with depression.
5. Although, the level of physical activity of depressed patients as, well as their motivation to exercise regularly were low, regular physical activity increased their physical fitness and improved mood. The feedback from exercising was positive. Thus, regular physical activity could be used as possible intervention for depressed patients in family medicine.

## 10. REFERENCES

- AHCPR (Agency for Health Care Policy and Research) Depression Guideline Panel. Depression in Primary Care: Detection, Diagnosis, and Treatment. In: Technical Report Number 5. US Department of Health and Human Services, Public Health Service: Rockville, MD; 2000.
- Aluoja A, Leinsalu M, Shlik J, Vasar V, Luuk K. Symptoms of depression in the Estonian population: prevalence, sociodemographic correlates and social adjustment. *J Affect Disord* 2004;78:27–35.
- Aluoja A, Kalda R, Ööpik P, Maaros HI. Depressioon esmatasandi meditsiinis: PREDICT uuringu esimese etapi tulemused. *Eesti Arst* 2005;84:443–9.
- Al-Windi A. Depression in general practice. *Nord J Psychiatry* 2005;59:272–7.
- American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). Washington, DC: American Psychiatric Association; 1994.
- Andrews G. Should depression be managed as a chronic disease? *BMJ* 2001;322:419–21.
- Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of co morbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24:1069–78.
- Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, Kerse N, MacGillivray S. Antidepressants versus placebo for depression in primary care. *Cochrane Database Syst Rev* 2009; Issue 3.
- Babyak M, Blumenthal JA, Herman S, Khatri P, Doraiswamy M, Moore K, Craighead WE, Baldewicz TT, Krishnan KR. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom Med* 2000;62:633–8.
- Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and Pain Comorbidity. *Arch Intern Med* 2003;163:2433–45.
- Barbor TF, de la Fuente JR, Saunders J, Grant M. The alcohol use disorders identification test: guidelines for use in primary care. 2<sup>nd</sup> ed. World Health Organization; 2001.
- Barkow K, Maier W, Üstün TB, Gänssicke M, Wittchen HU, Heun R. Risk factors for depression at 12-month follow-up in adults primary care patients with major depression: an international prospective study. *J Affect Disord* 2003;76:157–69.
- Baune BT, Caniato RN, Garcia-Alcaraz MA, Berger K. Combined effects of major depression, pain and somatic disorders on general functioning in the general adult population. *Pain* 2008;138:301–7.
- Belsher G, Costello CG. Relapse After Recovery From Unipolar Depression: A Critical Review. *Psychol Bull* 1988;104:84–96.
- Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: Results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Soc Psychiatry Psychiatr Epidemiol* 1998;33:587–95.
- Blumenthal JA, Babyak MA, Doraiswamy PM, Watkins L, Hoffman BM, Barbour KA, Herman S, Craighead WE, Brosse AL, Waugh R, Hinderliter A, Sherwood A. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med* 2007;69:587–96.
- Bockting CLH, Spinhoven P, Wouters LF, Koeter MWJ, Schene AH. Long-Term Effects of Preventive Cognitive Therapy in Recurrent Depression: A 5.5-Year Follow-Up Study. *J Clin Psychiatry* 2009;70:1621–8.

- Brenes GA. Anxiety, Depression, and Quality of Life in Primary Care Patients. *Prim Care Companion J Clin Psychiatry* 2007;9:437–43.
- Brugha TS, Bebbington PE, Tennant C, Hurry J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol Med* 1985;15:189–94.
- Burcusa SL, Iacono WG. Risk for Recurrence in Depression. *Clin Psychol Rev* 2007;27:959–85.
- Callahan CM, Hui SL, Nienaber NA, Musick BS, Tierney WM. Longitudinal study of depression and health services use among elderly primary care patients. *J Am Geriatr Soc* 1994;42:833–8.
- Callahan CM, Berrios GE. Reinventing depression: a history of the treatment of depression in primary care, 1940–2004. United States of America: Oxford University Press, Inc.; 2005.
- Camacho TC, Roberts RE, Lazarus NB, Kaplan GA, Cohen RD. Physical activity and depression: evidence from the Alameda County Study. *Am J Epidemiol* 1991;134:220–31.
- Castren E. Hermoston muovautuvuus ja masennuksesta toipuminen. *Duodecim* 2009;125:1781–6.
- Coyne JC, Fechner-Bates S, Schwenk TL. Prevalence, nature, and comorbidity of depressive disorders in primary care. *Gen Hosp Psychiatry* 1994;16:267–76.
- Coulehan JL, Zettler-Segal M. Recognition of alcoholism and substance abuse in primary care patients. *Arch Intern Med* 1987;147:349–52.
- Craft LL, Perna FM. The Benefits of Exercise for the Clinically Depressed. *Prim Care Companion J Clin Psychiatry* 2004;6:104–11.
- DeRubeis RJ, Hollon SD, Amsterdam JD, Shelton RC, Young PR, Salomon RM, O'Reardon JP, Lovett ML, Gladis MM, Brown LL, Gallop R. Cognitive Therapy vs Medications in the Treatment of Moderate to Severe Depression. *Arch Gen Psychiatry* 2005;62:409–12.
- deVries HA. Tranquilizer effects of exercise: a critical review. *Phys Sportsmed* 1981;9:46–55.
- Fawcett J. The detection and consequences of anxiety in clinical depression. *J Clin Psychiatry* 1997;58:35–40.
- Feinstein A. *Clinical judgement*. New York: The Willaims&Wilkins Company; 1967.
- Fink LA, Bernstein D, Handelsman L, Foote J, Lovejoy M. Initial reliability and validity of the childhood trauma interview: a new multidimensional measure of childhood interpersonal trauma. *Am J Psychiatry* 1995;152:1329–35.
- Flegal KE, Kishiyama S, Zajdel D, Haas M, Oken BS. Adherence to yoga and exercise interventions in a 6-month clinical trial. *BMC Complement Altern Med* 2007;7:37.
- Frank E, Prien RF, Jarret RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry* 1991;48:851–5.
- Freeling P, Rao BM, Paykel ES, Sireling LI, Burton RH. Unrecognised depression in general practice. *Br Med J* 1985;290:1880–3.
- Gaynes BN, Magruder KM, Burns BJ, Wagner HR, Yarnall KSH, Broadhead WE. Does a coexisting anxiety disorder predict persistence of depressive illness in primary care patients with major depression? *Gen Hosp Psychiatry* 1999;21:158–67.
- Gask L. The burden of depression in primary care. *World Psychiatry* 2003;2:161–2.
- Gelenberg AJ, Hopkins HS. Assessing and treating depression in primary care medicine. *Am J Med* 2007;120:105–8.

- Gonzales LR, Lewinsohn PM, Clarke GN. Longitudinal follow-up of unipolar depressives: An investigation of predictors of relapse. *J Consult Clin Psychol* 1985; 53:461–9.
- Gould DA, Stevens NG, Ward NG, Ward NG, Carlin AS, Sowell HE, Gustafson B. Self-reported childhood abuse in an adult population in a primary care setting: prevalence, correlates, and associated suicide attempts. *Arch Fam Med* 1994;3:252–6.
- Greco T, Eckert G, Kroenke K. The outcome of physical symptoms with treatment of depression. *J Gen Intern Med* 2004;19:813–8.
- Harris EC, Barraclough B. Suicide as an outcome for mental disorders: A meta-analysis. *Br J Psychiatry* 1997;170:205–28.
- Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical Activity and Public Health: Updated Recommendation for Adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc* 2007;39:1435–45.
- Hassmen P, Koivula N, Uutela A. Physical exercise and psychological well-being: a population study in Finland. *Prev Med* 2000;30:17–25.
- Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, Miller AH, Nemeroff CB. Pituitary-Adrenal and Autonomic Responses to Stress in Women After Sexual and Physical Abuse in Childhood. *JAMA* 2000;284:592–7.
- Hensing G, Andersson L, Brage S. Increase in sickness absence with psychiatric diagnosis in Norway: a general population-based epidemiologic study of age, gender and regional distribution. *BMC Medicine* 2006;4:19.
- Isometsä ET, Katila H, Aro T. Disability Pension for Major Depression in Finland. *Am J Psychiatry* 2000;157:1869–72.
- Janssen I, Hanssen M, Bak M, Bijl RV, de Graaf R, Vollebergh W, McKenzie K, van Os J. Discrimination and delusional ideation. *Br J Psychiatry* 2003;182:71–6.
- Johnson DAW. Treatment of depression in general practice. *BMJ* 1973;266:18–20.
- Judd LL, Akiskal HS, Zeller PJ, Paulus M, Leon AC, Maser JD, Endicott J, Corvell W, Kunovac JL, Mueller TI, Rice JP, Keller MB. Psychosocial disability during the long-term course of unipolar major depressive disorder. *Arch Gen Psychiatry* 2000; 57:375–80.
- Kalda R, Põlluste K, Maaroos HI, Lember M. Patients' opinion on family doctor accessibility in Estonia. *CMJ* 2004;45:578–81.
- Karlsson H, Lehtinen V, Joukamaa M. Psychiatric Morbidity Among Frequent Attender Patients in Primary Care. *Gen Hosp Psych* 1995;17:19–25.
- Karpansalo M, Kauhanen J, Lakka TA, Manninen P, Kaplan GA, Salonen JT. Depression and early retirement: prospective population based study in middle aged men. *J Epidemiol Community Health* 2005;59:70–4.
- Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry* 2003;54:216–26.
- Keller MB, Shapiro RW. Major depressive disorder: Initial results from a one-year prospective naturalistic follow-up study. *J Nerv Ment Dis* 1981;169:761–8.
- Keller MB, Klerman GL, Lavori PW, Coryell W, Endicott J, Taylor J. Long-term outcome of episodes of major depression. Clinical and public health significance. *JAMA* 1984;252:788–92.
- Kendler KS, Gardner CO, Prescott CA. Towards a Comprehensive Developmental Model for Major Depression in Women. *Am J Psychiatry* 2002;159:1133–45.
- Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric

- disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8–19.
- Kessler RC, Zhao S, Blazer DG, Swartz M. Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. *J Affect Disord* 1997;45:19–30.
- Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder: results from the national comorbidity survey replication (NCS-R). *JAMA* 2003;289:3095–105.
- Kessler RC, Üstün TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res* 2004;13:93–121.
- King M, Weich S, Torres-González F, Svab I, Maarros HI, Neeleman J, Xavier M, Morris R, Walker C, Bellón-Saameño JA, Moreno-Küstner B, Rotar D, Rifel J, Aluoja A, Kalda R, Geerlings MI, Carraça I, de Almeida MC, Vicente B, Saldivia S, Rioseco P, Nazareth I. Prediction of depression in European general practice attendees: the PREDICT study. *BMC Public Health* 2006;6:6.
- King M, Nazareth I, Levy G, Walker C, Morris R, Weich S, Bellon-Saameno JA, Moreno B, Svab I, Rotar C, Rifel J, Maarros HI, Aluoja A, Kalda R, Neeleman J, Geerling MI, Xavier M, de Almeida MC, Correa B, Torres-Gonzalez F. Prevalence of common mental disorders in general practice attendees across Europe. *Br J Psychiatry* 2008;192:362–7.
- Klein MH, Greist JH, Gurman RA, Neimeyer RA, Lesser DP, Bushnell NJ, Smith RE. A comparative outcome study of group psychotherapy vs. exercise treatments for depression. *Int J Ment Health* 1985;13:148–77.
- Kleinberg A, Aluoja A, Vasar V. Depressiooni ja ärevuse esinemine Eesti inimestel: depressiivse häire hetkelevimus, depressiivsuse ja ärevuse levimuse muutus kümne aasta jooksul. *Eesti Arst* 2008;88 (Lisa 2):80–6.
- Kruijshaar ME, Barendregt J, Vos T, de Graaf R, Spijker J, Andrews G. Lifetime prevalence estimates of major depression: an indirect estimation method and a quantification of recall bias. *Eur J Epidemiol* 2005;20:103–11.
- Kuyken W, Brewin R. Autobiographical memory functioning in depression and reports of early abuse. *J Abnorm Psychol* 1995;104:585–91.
- Lampinen P, Heikkinen RL, Ruoppila I. Changes in intensity of physical exercise as predictors of depressive symptoms among older adults. *Prev Med* 2000;30:371–80.
- Laukkanen RMT, Oja P, Oja KH, Pasanen ME, Vuori IM. Feasibility of a 2-km walking test for fitness assessment in a population study. *Scand J Soc Med* 1992;20:119–26.
- Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: a systematic review and meta-regression analysis of randomised controlled trials. *BMJ* 2001;322:763–7.
- Lecrubier Y. The Burden of Depression and Anxiety in General Medicine. *J Clin Psychiatry* 2001;62 (Suppl 8):4–9.
- Lecrubier Y. Widespread underrecognition and undertreatment of anxiety and mood disorders: results from 3 European studies. *J Clin Psychiatry* 2007;68 (Suppl 2):36–41.
- Lember M. Family practice training in Estonia. *Fam Med* 1996;28:282–6.
- Lepine JP, Gastpar M, Mendlewicz J, Tylee A. Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). *Int Clin Psychopharmacol* 1997;12:19–29.
- Lepore SJ. Expressive writing moderates the relation between intrusive thoughts and depressive symptoms. *J Pers Soc Psychol* 1997;73:1030–7.

- Lewinsohn PM, Hoberman HM, Rosenbaum M. A prospective study of risk factors for unipolar depression. *J Abnorm Psychol* 1988;97:251–64.
- Lewinsohn PM, Allen NB, Seeley JR, Gotlib IH. First onset versus recurrence of depression: differential processes of psychosocial risk. *J Abnorm Psychol* 1999;108:483–9.
- Lieb R, Isensee B, Hofler M, Wittchen HU. Parental depression and depression in offspring: evidence for familial characteristics and subtypes? *J Psychiatr Res* 2002;36:237–46.
- Lindeman S, Hämäläinen J, Isometsä E, Kaprio J, Poikolainen K, Heikkinen M, Aro H. The 12-month prevalence and risk factors for major depressive episode in Finland: representative sample of 5993 adults. *Acta Psychiatr Scand* 2000;102:178–84.
- Maaroos HI. Family medicine as academic speciality. In: Maaroos HI, Lember M, editors. *Family medicine*. Tartu: Elmatar; 1998. p. 11–21.
- Maaroos HI, Lember M. Specialist training of family physicians in non-UEMO countries: An Estonian experience. *Eur J Gen Pract* 2007;13:246–7.
- Maier W, Falkai P. The epidemiology of comorbidity between depression, anxiety disorders and somatic diseases. *Int Clin Psychopharmacol* 1999;14 (Suppl 2):S1–6.
- Mainio A, Hakko H, Timonen M, Niemelä A, Koivukangas J, Räsänen P. Depression in relation to survival among neurosurgical patients with a primary brain tumor: a 5-year follow-up study. *Neurosurgery* 2005;56:1234–42.
- Maj M. “Psychiatric comorbidity”: an artefact of current diagnostic systems? *Br J Psychiatry* 2005;186:182–4.
- Mallen CD, Peat G. Screening older people with musculoskeletal pain for depressive symptoms in primary care. *Br J Gen Pract* 2008;58:688–93.
- Manchikanti L. Prescription drug abuse: what is being done to address this new drug epidemic? Testimony before the subcommittee on Criminal Justice, Drug Policy and Human resources. *Pain Physician* 2006;9:287–321.
- Martinsen EW. Physical activity in the prevention and treatment of anxiety and depression. *Nord J Psychiatry* 2008;62 (Suppl 47):25–9.
- Massie M J. Prevalence of depression in patients with cancer. *J Nat Cancer Institute Monographs* 2004;32:57–71.
- Meeuwissen JAC, van der Feltz-Cornelis CM, van Marwijk HWJ, Rijnders PBM, Donker MCH. A stepped care programme for depression management: an uncontrolled pre-post study in primary and secondary care in The Netherlands. *Int J Integr Care* 2008;8:e05.
- Melander H, Salmonson T, Abadie E, van Zwieten-Boot B. A regulatory Apologia- a review of placebo-controlled studies in regulatory submissions of new generation antidepressants. *Eur Neuropsychopharmacol* 2008;18:623–7.
- Melartin TK, Isometsä ET. Miksi ihminen masentuu? *Duodecim* 2009;125:1771–9.
- Molarius A, Berglund K, Eriksson C, Lambe M, Nordström E, Eriksson HG, Feldman I. Socioeconomic conditions, lifestyle factors, and self-rated health among men and women in Sweden. *Eur J Public Health* 2006;17:125–35.
- Molnar BE, Buka SL, Kessler RC. Child sexual abuse and subsequent psychopathology: results from the National Comorbidity Survey. *Am J Public Health* 2001;91:753–60.
- Morgan WP. Affective beneficence of vigorous physical activity. *Med Sci Sports Exerc* 1985;17:94–100.
- Morso L, Hartvigsen J, Puggaard L, Manniche C. Nordic Walking and chronic low back pain: design of a randomized clinical trial. *BMC Musculoskelet Disord* 2006;7:77.
- Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997;349:1498–504.

- Noel HP, Williams JW Jr, Unützer J, Worchel J, Lee S, Cornell J, Katon W, Harpole LH, Hunkeler E. Depression and comorbid illness in elderly primary care patients: impact on multiple domains of health status and well-being. *Ann Fam Med* 2004; 2:555–62.
- Nuyen J, Schellevis FG, Satariano WA, Spreeuwenberg PM, Birkner MD, van den Bos GA, Groenewegen PP. Comorbidity was associated with neurologic and psychiatric disease: A general practice-based controlled study. *J Clin Epidemiol* 2006;59:1274–84.
- Oja P, Laukkanen R, Pasanen M, Tyry T, Vuori I. A 2-km walking test for assessing the cardiorespiratory fitness of healthy adults. *Int J Sports Med* 1991;12:356–62.
- Oja P, Tuxworth B. Eurofit for adults. Assessment of health-related fitness. Council of Europe, Committee for the Development of Sport and UKK Institute for Health Promotion Research; 1995.
- Oja L. Kehaline aktiivsus ja enesehinnanguline tervis. *Eesti Arst* 2008;88 (Lisa 2):50–6.
- Oldehinkel AJ, Neeleman J, Ormel J. Predictors of time to remission from depression in primary care patients: do some people benefit more from positive life change than others? *J Abnorm Psychol* 2000;109:299–307.
- Paykel ES, Tanner J. Life events, depressive relapse and maintenance treatment. *Psychol Med* 1976;6:481–5.
- Pascoe EA, Smart Richman L. Perceived discrimination and health: a meta-analytic review. *Psychol Bull* 2009;135:531–54.
- Patten SB. Long-term medical conditions and major depression in a Canadian population study at waves 1 and 2. *J Affect Disord* 2001;63:35–41.
- Peveler R, George C, Kinmonth AL, Campbell M, Thompson C. Effect of antidepressant drug counselling and information leaflets on adherence to drug treatment in primary care: randomised controlled trial. *BMJ* 1999;319:612–5.
- Pincus T, Williams A. Models and measurements of depression in chronic pain. *J Psychosom Res* 1999;47:211–9.
- Porcari JP, Hendrickson TL, Walter PR, Terry L, Walsko G. The physiological responses to walking with and without Power Poles on treadmill exercise. *Res Q Exerc Sport* 1997;68:161–6.
- Rance M, Boussuge PY, Lazaar N, Bedu M, van Praagh E, Dabonneville M, Duche P. Validity of a V.O<sub>2</sub> max prediction equation of the 2-km walk test in female seniors. *Int J Sports Med* 2005;26:453–6.
- Reynolds CF 3<sup>rd</sup>, Frank E, Thase ME, Houck PR, Jennings JR, Howell JR, Lilienfeld SO, Kupfer DJ. Assessment of sexual function in depressed, impotent, and healthy men: factor analysis of a Brief Sexual Function Questionnaire for men. *Psychiatry Res* 1988;24:231–50.
- Russo-Neustadt AA, Beard RC, Huang YM, Cotman CW. Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. *Neuroscience* 2000;101:305–12.
- Sadock BJ, Sadock VA. *Kaplan&Sadock's Synopsis of Psychiatry: behavioural sciences/clinical psychiatry*. 10<sup>th</sup> ed. Philadelphia: Lippincott Williams&Wilkins, a Wolters Kluwer Business; 2007. p.527–62.
- Sartorius N, Üstün B, Costa e Silva JA, Goldberg D, Lecrubier Y, Ormel J, von Korff M, Wittchen HU. An International Study of Psychological Problems in Primary Care. Preliminary Report From the World Health Organization Collaborative project on 'Psychological Problems in General Health care'. *Arch Gen Psychiatry*. 1993;50: 819–24.

- Savikko A, Alexanderson K, Hensing G. Do mental health problems increase sickness absence due to other diseases? *Soc Psychiatr Epidemiol* 2001;36:310–6.
- Schellevis FG, van der Velden J, van de Lisdonk E, van Eijk JthM, van Weel C. Comorbidity of chronic diseases in general practice. *J Clin Epidemiol* 1993;46:469–73.
- Schulberg HC, Katon W, Simon GE, Rush J. Treating major Depression in primary Care Practice. An Update of the Agency for Health Care Policy and Research Practice Guidelines. *Arch Gen Psychiatry* 1998;55:1121–7.
- Simon GE, VonKorff M, Piccinelli M, Fullerton C, Ormel J. An International Study of the Relation between Somatic Symptoms and Depression. *NEJM* 1999;341:1329–35.
- Simon GE. Social and economic burden of mood disorders. *Biol Psychiatry* 2003; 54:208–15.
- Smolders M, Laurant M, van Rijswijk E, Mulder J, Braspenning J, Verhaak P, Wensing M, Grol R. Depressed and co-morbid condition: More psychotropics prescribed! *Eur J Gen Pract* 2008;14:10–8.
- Sonstroem RJ. Exercise and self-esteem. *Exerc Sport Sci Rev* 1984;12:123–55.
- Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME\_MD: the PHQ primary care study. Primary care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999;282:1737–44.
- Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry* 2000;157:1552–62.
- Svedberg P, Bardage C, Sandin S, Pedersen NL. A prospective study of health, life-style and psychosocial predictors of self-rated health. *Eur J Epidemiol* 2006;21:767–76.
- Zubenko GS, Hughes HB III, Stiffler JS, Zubenko WN, Kaplan BB. D2S2944 identifies a likely susceptibility locus for recurrent, early-onset, major depression in women. *Mol Psychiatry* 2002;7:460–7.
- Tang SW, Stancer HC, Takahashi S, Shephard RJ, Warsh JJ. Controlled exercise elevates plasma but not urinary MHPG and VMA. *Psychiatry Res* 1981;4:13–20.
- Tekkel M, Veideman T. Tervise enesehinnangu seos tervisekäitumisega: Eesti terviseuuring 2006. *Eesti Arst* 2008;88 (Lisa 2):37–42.
- Tellnes G, Svendsen KOB, Bruusgaard D, Bjerkedal T. Incidence of sickness certification. Proposal for use as a health status indicator. *Scand J Prim Health Care* 1989;7:111–7.
- Tennant C. Parental loss in childhood. Its effect in adult life. *Arch Gen Psychiatry* 1988;45:1045–50.
- Timonen M, Liukkonen T. Management of depression in adults. *BMJ* 2008;336:435–9.
- Tolmunen T, Laukkanen JA, Hintikka J, Kurl S, Viinamäki H, Salonen R, Kauhanen J, Kaplan GA, Salonen JT. Low maximal oxygen uptake is associated with elevated depressive symptoms in middle-aged men. *Eur J Epidemiol* 2006;21:701–6.
- Trivedi MH, Lin EH, Katon WJ. Consensus recommendations for improving adherence, self-management, and outcome in patients with depression. *CNS Spectr* 2007;12 (Suppl 13):1–27.
- Tähepõld H, van den Brink-Muinen A, Maaroos HI. Patient expectations from consultation with family physician. *Croat Med J* 2006;47:148–54.
- Tylee A. We need a chronic disease management model for depression in primary care. *Br J Gen Pract* 2007;57:348–50.
- U.S. Department of Health and Human Services. *Healthy People 2010: understanding and Improving Health*. 2nd ed. Washington, DC: U.S. Government Printing Office; 2000. URL: <http://www.healthypeople.gov/Publications>.

- Vaez M, Rylander G, Nygren Å, Åsberg M, Alexanderson K. Sickness absence and disability pension in a cohort of employees initially on long-term sick leave due to psychiatric disorders in Sweden. *Soc Psychiatry Psychiatr Epidemiol* 2007;42:381–8.
- Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining Comorbidity: Implications for Understanding Health and Health Services. *Ann Fam Med* 2009; 7:357–63.
- van den Akker M, Buntinx F, Metsemakers JFM, Roos S, Knottnerus A. Multimorbidity in General Practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol* 1998;51:367–75.
- van Weel C, Schellevis FG. Comorbidity and guidelines: conflicting interests. *Lancet* 2006;367:550–1.
- van Weel-Baumgarten E, van den Bosch W, van den Hoogen H, Zitman FG. Ten year follow-up of depression after diagnosis in general practice. *Br J Gen Pract* 1998; 48:1643–6.
- Vuorilehto MS, Melartin TK, Isometsä ET. Depressive disorders in primary care: recurrent, chronic, and co-morbid. *Psychol Med* 2005;35:673–82.
- Vuorilehto MS, Melartin TK, Ryttsälä HJ, Isometsä ET. Do characteristics of patients with major depressive disorder differ between primary and psychiatric care? *Psychol Med* 2007;37:893–904.
- Vuorilehto MS, Melartin TK, Isometsä ET. Course and outcome of depressive disorders in primary care: a prospective 18-month study. *Psychol Med* 2009;39:1697–707.
- Wainwright NWJ, Surtees PG. Childhood adversity, gender and depression over the life-course. *J Affect Disord* 2002;72:33–4.
- Ware JE, Kosinski M, Keller SD. How to score the SF-12 Physical and mental Health Summary Scales. 2<sup>nd</sup> ed. Boston MA: The Health Institute, New England Medical Center; 1995.
- Wells KB, Stewart A, Hays RD, Burnam A, Rogers W, Daniles M, Berry S, Greenfield S, Ware J. The Functioning and Well-being of Depressed Patients: results from the Medical Outcomes Study. *JAMA* 1989;262:914–9.
- Wells KB, Sherbourne CD. Functioning and utility for current health of patients with depression or chronic medical conditions in managed, primary care practices. *Arch Gen Psychiatry* 1999;56:897–904.
- Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lellouch J, Lepine JP, Newman SC, Rubio-Stipec M, Wells E, Wickramaratne PJ, Wittchen HU, Yeh EK. Cross-national Epidemiology of Major Depression and Bipolar Disorder. *JAMA*. 1996;276:293–9.
- Wilhelm K, Parker G, Dewhurst-Savellis J, Asghari A. Psychological predictors of single and recurrent major depressive episodes. *J Affect Disord* 1999;54:139–47.
- Williams JW Jr, Rost K, Dietrich AJ, Ciotti MC, Zyzanski SJ, Cornell J. Primary care physicians' approach to depressive disorders. Effects of physician speciality and practice structure. *Arch Fam Med* 1999;8:58–67.
- Wilson I, Duszynski K, Mant A. A 5-year follow-up of general practice patients experiencing depression. *Fam Pract* 2003;20:685–9.
- World Health Organization. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: WHO; 1993.
- World Health Organization. Composite International Diagnostic Interview (CIDI). Version 2.1. Geneva: WHO; 1997.
- Ööpik P, Aluoja A, Kalda R, Maaros HI. Depressiooni ravimine esmatasandil. *Eesti Arst* 2005;84:481–7.

Ööpik P, Aluoja A, Kalda R, Maaroos HI. Family doctors' problems and motivating factors in management of depression. *BMC Fam Pract* 2006;7:64.

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## **I I. SUMMARY IN ESTONIAN**

### **Depressiooniga patsient peremeditsiinis: seonduvad tegurid, kordumine ja mõjutamise võimalused**

Depressioon on esmatasandi meditsiini patsientide hulgas sage probleem ning järjest sagedamini ka töövõimetuse põhjustaja. Igapäevases töös puutub perearst aina enam kokku lisaks somaatilistele haigustele ka psüühikahäiretega patsientidega, veelgi sagedasem on nende koosinemine. Eestis läbiviidud uuringu alusel esines Rahvusvahelise Haiguste Klassifikatsiooni 10.versiooni (RHK-10) diagnostilistele kriteeriumitele vastav depressiivne episood viimase 6 kuu jooksul igal neljandal perearsti külastanud patsiendil (Aluoja et al., 2005). Uuringud on näidanud, et perearstid on valmis tegelema depressiooni diagnoosiga patsientidega ja rohkem kui pool depressiooni ravis kasutatavatest antidepressantidest Eestis on perearstide määratud (Ööpik et al., 2005).

Vaatamata diagnostika ja ravivõimaluste paranemisele viimastel aastakümnetel on depressioon siiski üha sagedasemaks töövõimetuse põhjustajaks ning prognoositakse isegi depressioonist tingitud töövõimetuse tõusu (Murray and Lopez, 1997). Samuti on uuringud näidanud, et depressiooniga patsiendid külastavad arsti oluliselt sagedamini kui mitte-depressiivsed ning hindavad oma tervist halvemaks kui depressioonita patsiendid (Lepine et al., 1997; Callahan et al., 1994).

Kui enamik meditsiinierialasid keskendub konkreetsele haiguste grupile, siis peremeditsiinis on käsitletavate haiguste spekter oluliselt laiem. Seetõttu ongi mitme haiguse koosinemine ehk komorbiidus peremeditsiinis pigem reegel kui erand (van Weel and Schellevis, 2006). Uuringud on viidanud, et komorbiidsus on depressioonihaigete hulgas sagedasem kui mitte-depressiooniga haigetel (Al-Windi, 2005; Maier and Falkai, 1999). Täpne seos depressiooni ja kaasuvate haiguste vahel ei ole teada. On näidatud, et depressioon võib soodustada tervisele kahjulikke harjumusi, nagu suitsetamine, alkoholi tarvitamine, vähene liikumine ning raviga mittesoostumus (Katon, 2003). Niisamuti on viiteid, et kaasuva somaatilise haiguse olemasolu võib raskendada depressiooni diagnoosimist ja muuta ravi keerukamaks (AHCPR, 2000; Noel et al., 2004; Schulberg et al., 1998).

Depressioonile iseloomulik tunnus on haiguse kordumine. Uuringud on näidanud, et 30–70% haigetest esineb elu jooksul mitu depressiooni episoodi (Oldehinkel et al., 2006; Wilson et al., 2003). Seejuures on viiteid, et korduva depressiooni riskitegurid võivad olla erinevad esmase episoodi riskiteguritest. Nii näiteks seostatakse ühekordse depressiivse episoodiga mitmeid sotsiodemograafilisi tegureid, nagu naissugu, vähene haridus ja mitte abielus olemine (Aluoja et al., 2004; Kessler et al., 2003). Samas aga korduva depressiooni ja nimetatud tegurite vaheline seos ei ole nii kindel (Belsher and Costello, 1988; Burcusa and Iacono, 2007). Praktilisest aspektist on korduva depressiooni riskitegurite tundmine perearstile oluline, see võimaldaks depressiooni diagnoosiga

patsiente jälgides ja spetsiaalseid interventsioone kasutades ennetada järgnevat depressiooni episoodi.

Mitmete populatsiooniuuringute põhjal on vähest liikumist seostatud suurenenud depressiooniriskiga (Hassmen et al., 2000; Camacho et al., 1991). Täpne toimemehhanism on teadmata, arvatakse, et see tuleneb liikumise neuroprotektiivsest toimest. Mitte vähem oluline on liikumisega kaasnev positiivne tagasiside teistelt inimestelt, sotsiaalsed kontaktid ja uue oskuse omandamine, mis kõik tõstavad isiku enesehinnangut ja enesega rahulolekut. Liikumise kui ravi-meetodi võimalused depressiooni ravis on huviorbiiti tõusnud uudne teema. Mitmed mõjutusuuringud märgivad, et liikumisravi tulemused on samaväärsed antidepressantravi tulemustega (Blumenthal et al., 2007; Babyak et al., 2000). Uuem, enam motiveeriv ja populaarsust koguv kehalise aktiivsuse vorm on kepikõnd. Kepikõnni eelisteks on suurem töötavate lihasgruppide hulk ja sellest tulenevalt on hapnikutarbimine suurem võrreldes keppideta tavalise kõnniga (Porcari et al., 1997). Jõukohasuse ja käepärasuse tõttu võiks kepikõnnist kujuneda tõhus meetod ka depressiooni preventsis ja ravis.

### **Uurimistöö eesmärgid**

1. Analüüsida, kuidas depressioon mõjutab perearsti patsientide konsultatsioonide sagedust ja töövõimelisust.
2. Uurida, kas depressiooniga patsientidel esineb sagedamini kaasuvaid haigusi kui depressioonita patsientidel ning kuidas see mõjutab depressiooni käsitlust perearstiabis.
3. Leida, kuidas depressiooniga patsiendid võrreldes depressioonita patsientidega ise hindavad oma tervist.
4. Leida korduva depressiooni tekkimise risk ja depressiooni kordumisega seotud tegurid.
5. Uurida depressiooniga patsientide kehalist aktiivsust, nende motiveeritust tegeleda regulaarse kehalise aktiivsusega, hinnata patsientide kehalise võimekuse taset ning regulaarse kehalise aktiivsuse mõju meeleolule.

### **Uuritavad ja meetodid**

Uurimisgrupi moodustasid aastatel 2003–2005 Eestis toimunud PredictD uuringu patsiendid. PredictD uuringus intervjueriti 1100 järjestikust perearsti vastuvõtule pöördunud patsienti vanuses 18–75 eluaastat. Uuring viidi läbi kolme-etapilisena: baasuuring, 6 kuu ja 12 kuu möödudes ning depressiooni olemasolu kindlaks tegemiseks kasutati Rahvusvahelise Diagnostilise Liitintervjuu (Composite International Diagnostic Interview, CIDI) depressiooni alaosa (King et al., 2006). Lisaks täitis patsient ise riskiküsimustiku, mis oli koostatud depressiooniga seotud sotsiaalmajanduslike ja tervisetegurite mõõtmiseks. Küsimustikus hinnati järgmisi näitajaid: demograafilised tegurid, tööprobleemid, majan-

duslikud pinged, enesehinnang tervisele, varasemad isiklikud ja perekondlikud vaimse tervise probleemid, negatiivsed elusündmused, sotsiaalne toetus ning turvalisus (King et al., 2006). Depressiooni ja töövõimetuslehe ning kaasuvate haiguste ja puude vahelise seose uurimiseks palusime informatsiooni uuringus osalenud patsientide perearstidelt. Tervisekaartidest saadud info alusel kaardistasime uuritavate kaasuvad haigused, töövõimetuslehel oldud päevade arvu, patsientidele määratud depressiooni ravi ning puude olemasolu ajavahemikul 2003–2005. Võrdlesime omavahel depressiooni põdevate patsientide ja samas uuringus osalenud depressioonita patsientide andmeid.

Depressiooni kordumisega seotud tegurite leidmiseks uurisime 123 patsienti, kellel baasuuringul oli depressioon, 6 kuu pärast olid paranenud ning 12 kuu pärast tekkis uuesti (korduv depressioon) või ei tekkinud (mittekorduv depressioon).

Depressiooni ja kehalise aktiivsuse seose hindamiseks pöördusime 178 PredictD uuringu patsiendi poole, kellel oli depressioon CIDI alusel diagnoositud vähemalt kahel korral. Teostasime CIDI intervjuud ja 21 patsienti soovisid alustada kepikõnniga vähemalt 3 korda nädalas vähemalt 30 minutit korraga 24 nädala jooksul. Iga uuritav andis uuringu alguses hinnangu oma senise kehalise aktiivsuse tasemele viimase 2 aasta jooksul. Aeroobse kehalise võimekuse hindamiseks kasutasime 2 km kõndimise testi. Aeroobse võimekuse indeksi leidsime distantsi läbimise aja (min. sek.) ja südame löögisageduse (HR) alusel finišeerimise hetkel, arvestasime ka testitava kehamassi indeksi (BMI) ja vanust (Oja and Tuxworth, 1995). Peale testimist tegid uuritavad kaasa kepikõnni meetodika ja soojendus-venitusharjutuste instrueerimise, said individuaalselt tellitud sobiva pikkusega kõnnikepid (PoleAbout Original, Soome) ning liikumisravi päeviku.

Andmetöötluseks kasutasime programmi SPSS 10.0 ja 17.0.0 for Windows.

## Uurimistöö peamised tulemused

1. Depressiooniga haiged pöördusid terviseprobleemide tõttu kolme aasta jooksul oma perearsti poole keskmiselt 14.3 korda ja ilma depressioonita haiged keskmiselt 13.0 korda ( $p=0.156$ ). Depressiooniga patsiendid võrreldes depressioonita patsientidega olid oluliselt kauem töövõimetuslehel (vastavalt 26.5 ja 16.3 päeva) ( $p=0.002$ ).
2. Kolm kõige sagedasemat perearstiga konsulteerimise põhjust oli tugiliikumissüsteemi, hingamisteede ja südame-veresoonkonna haigused. Psüühikahäired olid sageduselt üheksandal kohal. 90%-l depressiooniga patsientidest ja 87%-l depressioonita patsientidest oli veel vähemalt üks kaasuv haigus ( $p=0.368$ ). Me ei leidnud statistiliselt olulist erinevust kaasuvate haiguste arvus depressiooni diagnoosiga ja depressioonita patsientide vahel ( $p=0.546$ ).
3. Leidsime, et 22% depressiooniga patsientidest ja 12% depressioonita patsientidest hindas oma tervist viletsaks ( $p=0.001$ ). Depressiooniga patsientidel oli võrreldes depressioonita patsientidega oluliselt rohkem piiranguid

töös, sotsiaalsetes ja füüsilistes tegevustes, mis olid eelkõige seotud emotsionaalsete probleemidega, lisaks nimetasid nad, et nende igapäevast tööd segas valu ( $p < 0.05$ ).

4. 28% depressiooniga haigetest esines DSM-IV kriteeriumitele vastav korduva depressiooni episood viimase 12 kuu jooksul. Korduva depressiooni tekke risk oli oluliselt kõrgem neil, kes olid kasutanud narkootilisi ravimeid OR 7.48 (95%CI=1.42–39.43); neil, kes olid kogunud diskrimineerimist OR 2.92 (95%CI=1.05–8.11); ning neil, keda oli lapseas väärkoheldud OR 1.58 (95%CI=1.05–2.38).
5. Uuritavate varasem kehaline aktiivsus oli madal, 52% neist väitis, et nad polnud tegelenud regulaarse kehalise koormusega viimase kahe aasta jooksul. 20% uuritavatest oli motiveeritud alustama regulaarse kehalise aktiivsusega. Kõige sagedasem põhjus oli lootus, et regulaarne kehaline koormus parandab meeleolu ja tervist. Osavõtnute ja nende perede ning sõprade suhtumine kepikõndi oli positiivne. Keskmise aeroobse võimekuse indeks oli depressiooniga haigetel keskmiselt  $21.99 \pm 20.38$  uuringu alguses ja  $38.72 \pm 26.12$  peale 24 nädalast regulaarset kepikõndi ( $p=0.179$ ). 12 kuud pärast uuringut vastas 13 uuritavat 18-st, et nad on nüüd kehaliselt aktiivsemad kui enne uuringut. Uuringu alguses oli depressioon 16 patsiendil, pärast 24-nädalast regulaarset kehalist aktiivsust 7 uuritaval ja pärast 12 kuud 3 uuritaval. Mitte ühegi uuritava depressioon ei süvenenud ja mitte ükski uuringu alguses depressioonita olnud uuritav ei saanud depressiooni uuringuperioodi jooksul.

## Järeldused

1. Depressiooniga patsiendid külastasid oma perearsti sama sagedusega kui depressioonita haiged, kuid olid oluliselt kauem töövõimetuselhel.
2. Enamikul depressiooniga patsientidest esines lisaks depressioonile veel vähemalt üks kaasuv haigus. Kuid võrreldes omavahel depressiooniga ja depressioonita patsientide kaasuvate haiguste arvu ja haiguste gruppe RHK-10 alusel, olulisi erinevusi me ei leidnud.
3. Depressiooniga patsiendid hindasid oma tervist halvemaks kui depressioonita patsiendid ja lisaks emotsionaalsetele probleemidele segas nende igapäevast elu ka valu.
4. Umbes kolmandikul depressiooniga haigetest esines korduva depressiooni episood 12 kuu jooksul. Tegurid, mis seostusid depressiooni kordumisega olid narkootiliste ravimite kasutamine, diskrimineerimine ja väärkohtlemine lapseas. Enam tähelepanu peaks pöörama patsientidele, kellel esinevad eelpool nimetatud tegurid.
5. Vaatamata sellele, et depressiooniga patsientide kehalise aktiivsuse tase ja nende motivatsioon alustada regulaarse kehalise tegevusega oli madal, parandas regulaarne kehaline aktiivsus uuritavate kehalise võimekuse taset ja meeleolu. Seetõttu võib regulaarset kehalist aktiivsust kasutada depressiooni mõjutamiseks perearsti patsientidel.

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## **13. PUBLICATIONS**

# CURRICULUM VITAE

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2008– University of Tartu, Faculty of Medicine, Department of Family  
Medicine, teaching assistant (part time)  
2008– Ülikool Family Practice Centre, family doctor (part time)  
2006–2007 Primary Health Care Centre (Turku, Finland), general  
practitioner  
2005–2008 South-West Cancer Society (Turku, Finland), home care doctor  
2005–2005 Ropka Family Practice Centre, family doctor

## II. Research activity

The main area of scientific work has been depression in family practice. Four publications are published in international peer-reviewed journals and three publications in the journal of Eesti Arst. Thesis presented in 6 international conferences.

## III. Teaching activity

Since 2007 I have been involved in teaching family medicine to second and sixth year medical students, also teaching pharmacy students and residents of family medicine.

#### **IV. Administrative work**

Society of Family Doctors of Estonia  
European Academy of Teachers in General Practice  
South-Estonian Cancer Society  
Finnish Palliative Care Association

#### **V. Training**

2009 Intensive course of primary care, Network of Primary Care, University of Radboud, Nijmegen, the Netherlands,  
2006–2009 Nordic Specialist Course of Palliative Medicine  
2003–2005 Course of cognitive-behavioural psychotherapy

# ELULOOKIRJELDUS

## I. Üldandmed

1. Ees- ja perekonnanimi: Kadri Suija
2. Sünniaeg ja koht: 21.07.1977, Võru, Eesti
3. Kodakondsus: Eesti
4. Aadress, telefon, *e-mail*: Puusepa 1a–2120, 50406 Tartu  
+372 731 9215, +372 517 2857  
kadri.suija@ut.ee
5. Praegune töökoht: TÜ peremeditsiini õppetool,  
OÜ Ülikooli Perearstikeskus
6. Haridus:  
2006– Tartu Ülikool, arstiteaduskond, doktoriõpe  
2002–2005 Tartu Ülikool, arstiteaduskond, peremeditsiini residentuur  
2001–2002 Tartu Ülikool, arstiteaduskond, üldinternatuur  
1995–2001 Tartu Ülikool, arstiteaduskond  
1984–1995 Tartu Tamme Gümnaasium
7. Keelteoskus: eesti, inglise, soome ja vene keel
8. Teenistuskäik  
2008– OÜ Ülikooli Perearstikeskus, perearst (osalise koormusega)  
2008– Tartu Ülikool, arstiteaduskond, peremeditsiini õppetool,  
assistent (0,3)  
2006–2007 Turu linna tervisekeskus (Turku, Soome), tervisekeskuse arst  
2005–2008 Edela-Soome Vähiühing (Turku, Soome), koduraviarst  
2005–2005 Ropka Perearstikeskus, perearst

## II. Teaduslik ja arendustegevus

Peamiseks teadustöö valdkonnaks on olnud depressioon peremeditsiinis. Ilmunud on 4 artiklit rahvusvahelistes eelretsenseeritavates ajakirjades, lisaks 3 artiklit ajakirjas Eesti Arst. Olen esinenud ettekandega 6 rahvusvahelisel konverentsil.

## III. Õppetöö

Alates 2007. aastast õppetöö arstiteaduskonna arstiteaduse eriala II ja VI aasta üliõpilastele perearstiteaduse kursuse raames. Lisaks õppetöö proviisoriõppe üliõpilastele, valikkursused ja teoreetiline koolitus peremeditsiini residentidele.

#### **IV. Administratiivtöö ja muud kohustused**

Eesti Perearstide Selts  
European Academy of Teachers in General Practice  
Lõuna-Eesti Vähiühing  
Suomen Palliatiivisen Hoidon Yhdistys

#### **V. Erialane enesetäiendus**

2009 Intensive course of primary care, Network of Primary Care, University of Radboud, Nijmegen, Holland  
2006–2009 Nordic Specialist Course of Palliative Medicine  
2003–2005 Eesti Kognitiivse ja Käitumisteraapia Assotsiatsiooni kognitiiv-käitumisteraapia põhiväljaõppe koolitus

## DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maarros.** The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
2. **Mihkel Zilmer.** Na-pump in normal and tumorous brain tissues: Structural, functional and tumorigenesis aspects. Tartu, 1991.
3. **Eero Vasar.** Role of cholecystokinin receptors in the regulation of behaviour and in the action of haloperidol and diazepam. Tartu, 1992.
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