DEPRESSIVE SYMPTOMS IN RELATION TO ORAL HEALTH AND RELATED FACTORS IN A MIDDLE-AGED POPULATION

Analytical approach

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Abstract

The most common mental disorder, depression, is internationally acknowledged as a considerable public health problem, major depression being one of the leading causes of premature mortality and disability in the world (Murray & Lopez 1996).

Besides its associations with disturbances in psychological and social functioning, depression is also associated with various biological alterations. Accordingly, extensive research has been conducted to link depression with several somatic diseases. The relationship between depression and oral health is still obscure, however.

This study was carried out to investigate the relationship of depressive symptoms with oral health and related factors in 55-year-old inhabitants of Oulu, 780 of whom participated. Depressive symptoms were measured with the Zung Self-Rating Depression Scale (ZSDS). A high rate of depressive symptoms was associated with symptoms of temporomandibular disorders (TMD), the subjective sensation of dry mouth, and high counts of salivary lactobacilli. An uncertain association was demonstrated between depressive symptoms and abundant growth of salivary mutans streptococci and the presence of yeasts in saliva. Depressive symptoms were associated with edentulousness in a subgroup of men who had never smoked. The dentate women with high rates of depressive symptoms did not consider it equally important to preserve their natural teeth as did the dentate women with fewer depressive symptoms. They also consumed sweets, snacks, and soft drinks more often, and a longer time had elapsed since their last visit to a dentist. No associations between depressive symptoms and periodontal pocketing or dental caries could be demonstrated in this cross-sectional study.

It is suggested that depression should be considered as a possible underlying factor when treating patients with TMD symptoms and complaints of oral dryness. Furthermore, considering the discovered association between depressive symptoms and microbial growth, the possibility of an increased risk for impaired oral health among depressed persons is emphasized.

Keywords: dental caries, depression, edentulousness, lactobacillus, oral health, oral health behavior, periodontal diseases, saliva, temporomandibular joint disorders, xerostomia

To Juho

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Oulu, April 2003 Sirpa Anttila

Abbreviations

APA	American Psychiatric Association
BDI	Beck's Depression Inventory
BSI	Brief Symptom Inventory
CES-D	Center for Epidemiological Studies Depression Scale
CFU	colony-forming unit
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CVD	cardiovascular diseases
Di	Helkimo's Clinical Dysfunction index
DIS	Diagnostic Interview Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
HAD	Hospital Anxiety and Depression Scale
HPA	hypothalamic-pituitary-adrenal
HRSD	Hamilton Rating Scale for Depression
5-HT	serotonin
ICD-10	International Classification of Diseases, 10^{th} revision
MDI	Major Depression Inventory
MG1	high-molecular-weight mucin
MG2	low-molecular-weight mucin
MMPI	Minnesota Multiphasic Personality Inventory
MUC5B	gene encoding high-molecular-weight mucin
MUC7	gene encoding low-molecular-weight mucin
OR	odds ratio
PDS	temporomandibular joint pain and dysfunction syndrome
PSE	Present State Examination
RR	relative risk
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SCL-90	Symptom Checklist-90

SCL-90-R	Symptom Checklist-90-Revised
SCL-25	Symptom Checklist-25
s-IgA	secretory immunoglobulin A
TMD	temporomandibular disorder
WHO	World Health Organization
ZSDS	Zung Self-Rating Depression Scale

List of original papers

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Vimpari SS, Knuuttila MLE, Sakki TK & Kivelä S-L (1995) Depressive symptoms associated with symptoms of the temporomandibular joint pain and dysfunction syndrome. Psychosom Med 57: 439–444.

II Anttila SS, Knuuttila MLE & Sakki TK (1998) Depressive symptoms as an underlying factor of the sensation of dry mouth. Psychosom Med 60: 215–218.

III Anttila SS, Knuuttila MLE & Sakki TK (1999) Depressive symptoms favor abundant growth of salivary lactobacilli. Psychosom Med 61: 508–512.

IV Anttila SS, Knuuttila MLE & Sakki TK (2001) Relationship of depressive symptoms to edentulousness, dental health, and dental health behavior. Acta Odontol Scand 59: 406–412.

In addition, some previously unpublished results are presented.

Contents

1 Introduction

Depressive disorders represent a major public health problem internationally. The prevalence rates of depression in representative Finnish and international population surveys reviewed by Lehtinen and Joukamaa (1994) varied from 2.6% to 5.5% in men and from 6.0% to 11.8% in women. Depressive symptoms were much more common, their prevalences varying from 10% to 19% and from 18% to 34% in men and women, respectively. A cross-national comparison of the results of large-scale epidemiological surveys throughout the world (WHO International Consortium in Psychiatric Epidemiology 2000) suggests an increase in the lifetime prevalences of mood disorders across successive generations.

The basic emotional and symbolic importance of the mouth in mental development and some characteristics connected with depression and depressive symptoms support the hypothesis that there is an association between "mood and mouth". Comorbidity of somatic illnesses and depression is a largely reported phenomenon. For example, there exists cogent evidence of the association between depression or depressive symptoms and cardiovascular diseases (Aromaa *et al.* 1994, Pratt *et al.* 1996), with many studies supporting depression as a risk factor for these diseases (reviewed by Musselman *et al.* 1998). The comorbidity of depression and diabetes has also been reported in several studies (Andersson *et al.* 2001, meta-analysis). The question of whether there exists comorbidity of oral diseases and depression is still unclear.

Psychoneuroimmunological studies have thrown light on the associations between psychological factors and immunity and immune-mediated diseases. Convincing evidence of links between negative affect and depression and infectious diseases (reviewed by Cohen & Herbert 1996) supports the possibility that these conditions may also be associated with oral infections. There is, in fact, some evidence to support the association between periodontal disease and depression (Monteiro da Silva *et al.* 1996, Genco *et al.* 1999).

Chronic pains and various physical conditions are strongly associated with depression (Ohayon & Schatzberg 2003), which was also found to be a common diagnosis among chronic facial pain patients (Korszun *et al.* 1996). One explanation of this comorbidity is somatization, *i.e.* the tendency to express emotional distress in the form of physical complaints (reviewed by Clarke & Smith 2000).

In addition to some biological alterations seen in depression, which possibly predispose to dental diseases, depression may be accompanied by a loss of motivation (Beck 1967), dietary changes, and smoking (Kivelä *et al.* 1986, Wallin & Rissanen 1994, Jorm *et al.* 1999), which can either directly or indirectly predispose a subject to deterioration of oral health. On the other hand, the consequences of dental diseases may interfere with enjoyment of life and the maintenance of a positive self-image, thus having a negative effect on psychological well-being (Sheiham *et al.* 1997). This assumption was supported by Locker *et al.* (2000), who showed in their prospective study that self-perceived oral health predicted subjects' psychological well-being and life satisfaction.

The holistic approach to health is currently widely advocated as a prerequisite for successful outcomes in patient care. Consequently, an integrated approach covering biological, psychological, and social factors is also essential in oral health research. As a whole, there are relatively few studies concerning the association of depression or depressive symptoms with oral health. This study was conducted to increase our knowledge about the relationship between these disease entities with multifactorial etiologies and thus to improve the facility for identifying depression and depressive symptoms as underlying or contributory factors of orofacial diseases and symptoms and *vice versa*.

2 Review of the literature

2.1 Definition of depression

The definition of the term 'depression' is complicated because of the inherent ambiguity involved. In the psychiatric sense, depression can be seen as a state of mood, as a special symptom manifesting itself in many different mental disorders, as a syndrome measured by depression rating scales, and as a clinical diagnosis operationalized in diagnostic classifications (reviewed by Lehtinen & Joukamaa 1994). Being depressive is not necessarily equal to having a mental illness. Occasional depressive mood experienced as low spirits, dejection, and sadness can be a normal reaction to disappointments, adversities, and losses and should be differentiated from depressive disorders, which represent actual psychological illness and are often accompanied by distinct impairment of psychological, somatic, and social functioning (Akiskal 2000).

DSM-III (The Diagnostic and Statistical Manual of Mental Disorders (3rd ed.), the American Psychiatric Association 1980) and its revised version DSM-III-R (APA 1987), DSM-IV (APA 1994), DSM-IV-TR (APA 2000) and ICD-10 (the International Classification of Diseases (10th revision), World Health Organization 1992), are widely used international classifications of diseases, which include the diagnostic criteria of depressive disorders defined by the presence of certain symptoms.

The two depressive disorders common to all DSM classifications are major depression and dysthymia, the definition of major depression being virtually identical in all the four versions of DSM classifications. It is defined as a depressive episode that lasts for at least two weeks and includes at least five of the following symptoms: depressed mood, loss of interest or pleasure in all or almost all activities, significant weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, diminished ability to think or concentrate and recurrent thoughts of death. To meet the criteria for major depression, either depressed mood or loss of interest or pleasure must be included in the symptoms. (American Psychiatric Association 1980, 1987, 1994, 2000.) In the ICD-10, major depression was replaced by the term 'depressive episode', which is diagnosed based on the presence of four instead

of five of the above-mentioned symptoms and is, furthermore, classified as mild, moderate, or severe, depending upon the number and severity of symptoms (WHO 1992).

Dysthymia or dysthymic disorder is defined as a chronic disturbance of mood involving depressed mood for at least two years, during which the condition has not met the criteria for major depression. At least two of the following symptoms must be present: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty in making decisions, and feelings of hopelessness. (APA 1987, APA 1994, APA 2000.)

Apart from major depressive disorder and dysthymic disorder, DSM-IV has a category titled "depressive disorder not otherwise specified", which includes, for example, premenstrual dysphoric disorder and minor depressive disorder, defined as at least two but fewer than five of the symptoms of a major depressive episode during a given 2-week period with the presence of either depressed mood or loss of interest or pleasure in activities and significant impairment of functional status (APA 1994). All nomenclatures include several subclassifications of depressions, and depressive episodes can further be present in various other mental disorders, such as the bipolar disorder (formerly known as manic-depressive illness). It has been suggested that the spectrum of depression is much wider than that reflected in the current diagnostic nomenclature (Angst & Merikangas 1997), and there is substantial research going on concerning the concept and meaning of subsyndromal depressive symptoms (Judd *et al.* 1994, Angst & Merikangas 1997, Judd *et al.* 1997, Judd *et al.* 1998, Lewinsohn *et al.* 2000, Ormel *et al.* 2001) not meeting the criteria for minor or major depression or dysthymia and to find out whether major depression, minor depression and subsyndromal symptoms alternate over time in the same patients as a symptomatic continuum of a single clinical disease (Judd *et al.* 1997, Judd *et al.* 1998, Lewinsohn *et al.* 2000, Ormel *et al.* 2001).

2.1.1 Diagnosis and measurement of depression and depressive symptoms

In Finland, the officially used diagnoses of depressive disorders are those presented in the ICD-10 (Tamminen 1998). In addition to the traditional interview, various methods have been developed for assessing and measuring depression and depressive symptoms, such as structured interviews, checklists, interview-based rating scales, and self-assessed rating scales. Some of these are specific for depression and depressive symptoms, while others are multidimensional. Examples of the most widely used multidimensional structured interviews are the Diagnostic Interview Schedule (DIS) (Robins *et al.* 1981), the Composite International Diagnostic Interview (CIDI) (WHO, 1990), the Present State Examination (PSE) (Wing *et al.* 1974), and the SCAN (The Schedules for Clinical Assessment in Neuropsychiatry) (WHO 1994), which is based on the PSE.

Among the interviewer-rated scales, the HRSD (the Hamilton Rating Scale for Depression), which was originally developed for measuring the severity of depression for clinical and experimental purposes (Hamilton 1960, 1967), is the most commonly used

(reviewed by Kivelä 1992). It has been extensively used especially in clinical trials of antidepressant drugs and for other purposes in clinical research (Hamilton 1980).

The Zung Self-Rating Depression Scale (ZSDS) (Zung 1965), the Beck Depression Inventory (BDI) (Beck *et al.* 1961), and the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977) are among the most frequently used self-rating scales measuring depressive symptoms. The ZSDS was primarily developed for screening depressive symptoms among middle-aged populations. It consists of 20 items, formulated either positively or negatively, each of which must be rated by the respondent on a 4-point scale as to how well the item pertains to him- or herself at the time of testing. The four alternative answers are: a little of the time, some of the time, a good part of the time, most of the time. The raw sum score of the points varies from 20 to 80, with less depressed subjects scoring low on the scale and more depressed subjects having a higher scores. The items of ZSDS include the clinical diagnostic criteria generally used to characterize depressive disorders. (Zung 1965.)

The reliability, validity and psychometric properties of ZSDS were studied in 40 depressed patients (29.65 ± 9.38 years) and 120 controls (27.23 ± 10.62 years) against a clinical diagnosis of depression (Fountoulakis *et al.* 2001). At a cutoff point of 43/44, the sensitivity and specificity values were 92.5% and 89.2%, respectively (Fountoulakis *et al.* 2001). At a cutoff point of 39/40, the corresponding values were 95% and 83.33% (Fountoulakis 2002, personal communication). Pearson's correlation coefficient (test-retest reliability) for the total ZSDS score was 0.92 and the five factors revealed in factor analysis were anxiety-depression, cognitive, gastro-enterological symptoms, cognitive and irritability, social and interpersonal functioning (Fountoulakis *et al.* 2001).

ZSDS turned out to discriminate well between nondepressed subjects and those suffering from a depressive disorder in a sample of depressed patients and a sample of normal subjects from the Czech population (Kožený 1987). Three factors of the ZSDS interpretable as cognitive, affective, and somatic symptoms with good cross-validity of the factor structures were found by Sakamoto and coworkers in a large sample of Japanese undergraduates (1998). Turner & Romano (1984) tested the validity of the ZSDS, BDI, and MMPI (Minnesota Multiphasic Personality Inventory) against the diagnosis of major depression on the basis of the DSM-III criteria in chronic pain patients. ZSDS and BDI showed good sensitivity and specificity and were comparable in detecting major depression in this sample. The results of Biggs and coworkers (1978) showed ZSDS to be a valid and sensitive measure of clinical severity in depressed patients.

There are no published studies on the validation of the ZSDS compared to clinically diagnosed depression among unselected middle-aged populations. However, according to the unpublished results of a population study of elderly Finnish men and women, the sensitivity and specificity values with the ZSDS cutoff at 43/44 raw sum points compared with the clinical diagnosis of depression were 73.7% and 83.5%, respectively, in the age-group of 65- to 74-year-olds. The corresponding values with the cutoff at 39/40 were 88.2% and 68.2%. (Kivelä, personal communication.)

The BDI, originally designed for the measurement of the intensity of depression in patients with psychiatric diagnoses, includes 21 items, which are rated on a four-point severity scale from zero to three (Beck *et al.* 1961). Extensive research supports the discriminant validity of the BDI between psychiatric and nonpsychiatric samples (Beck *et*

al. 1988), and it has been widely used in clinical research but less widely in population studies (reviewed by Kivelä 1992).

CES-D is a 20-item self-rating scale designed for epidemiological use to detect depressive symptomatology in general populations (Radloff 1977). Its reliability, validity, and factor structure have been found to be similar in different age groups and in general U.S. population samples (Radloff 1977), and it is widely used in community research.

The HAD scale (Hospital Anxiety and Depression scale) was designed to detect mood disorders in nonpsychiatric populations treated at medical clinics. It is a self-rating scale divided into two subscales relating to anxiety and depression, each subscale containing seven items which can be scored from zero to three. The items exclude symptoms of somatic reference, symptoms that may have arisen from either somatic or mental diseases, and symptoms relating to severe mental disorders. (Zigmond & Snaith 1983.)

Brief Symptom Inventory (BSI) (Derogatis & Melisaratos 1983) is a shortened version of the original 90-item SCL-90 questionnaire designed by Derogatis and coworkers (1973). It is a 53-item multidimensional self-report psychometric instrument, which provides an assessment of psychological symptoms in nine areas, including depression. Another shortened version of SCL-90 is SCL-25 (Derogatis *et al.* 1974), a 25-item self-report questionnaire about the presence and intensity of anxiety and depression symptoms over the preceding week.

The MMPI (Hathaway & McKinley 1951) is the most widely used and studied self-report measure of psychopathology and personality. The 556-item MMPI contains four validity scales and 10 clinical scales, one of which is a depression scale. The MMPI and its successor, the MMPI-2, are widely used in the assessment of patients with chronic pain. (Reviewed by Vendrig 2000.)

The recently developed MDI (Major Depression Inventory) is a unidimensional self-rating inventory for depression, based on the symptoms of DSM-IV major depression and ICD-10 moderate to severe depression. It consists of 12 items, using the past two weeks as the time frame, and it can be used as a measuring or diagnostic instrument. (Bech 1997, Bech & Wermuth 1998.)

Another new scale, DEPS (Depression Scale) (Salokangas *et al.* 1995), was developed to improve the recognition of depression in primary care. It consists of 10 items, which measure the psychological and social symptoms of depression. In addition to utility in primary care, it may be suitable for screening depression in the general population and for identifying high-risk groups. (Salokangas *et al.* 1995.)

Numerous shortened versions of the older rating scales have been developed, and some of them have been modified to cover the new psychiatric classifications, such as the HRSD (Bech 1996, Bech *et al.* 1997) and the BDI (Beck *et al.* 1996).

2.2 Descriptive and analytical epidemiology of depression

In the Mini-Finland Health Survey, which comprised a total of 8,000 persons representing the whole adult population of Finland (aged 30 years or more), the prevalence of neurotic depression was 3.6% in men and 5.5% in women (Lehtinen *et al.* 1990a). The original

sample of the Uusikaupunki-Kemijärvi follow-up study (UKKI) consisted of 500 subjects from southern Finland (Uusikaupunki) and 500 subjects from northern Finland (Kemijärvi) aged 15 to 64 years. At the 16-year follow-up, the prevalence of depressions was 2.4% in men and 6.5% in women (Lehtinen *et al.* 1990b).

In 1994, Isometsä *et al.* (1997) interviewed by telephone 2,293 out of 3,250 individuals randomly drawn from the population registry and representing the adult population of Finland in the age group of 25–79 years. The interview included a short form of the University of Michigan version of the Composite International Diagnostic Interview (UM-CIDI). The age-adjusted 6-month prevalence was 4.1% for major depressive episode and 1.7% for current dysthymia, while depressive mood during the preceding month was reported in 17% of cases. Major depressive episodes and depressive mood were significantly more prevalent among females than males. Lindeman and coworkers (2000) also used the UM-CIDI to study the 12-month prevalence of major depressive episode and its risk factors in a representative nationwide sample of noninstitutionalized Finnish individuals aged 15–75 years (n = 5,993) in 1996. The prevalence of major depressive episode was 9.3% among the whole study population, and the age-adjusted prevalence rates for females and males were 10.9% and 7.2%, respectively. It turned out that the factors associated with major depressive episode after adjustment for age were urban residency, smoking, alcohol intoxication, and chronic medical conditions. Furthermore, being single and obese were found to be risk factors for males.

In the Health 2000 health examination survey, the 12-month prevalence rates of major depression in the age group of 45–54 years were 4.7 and 7.2 in men and women, respectively. In the age group of 55–64 years, the respective figures were 2.9 and 5.9. (Aromaa & Koskinen 2002.)

The EURODEP Programme assessed the prevalence of depression among randomized samples aged ≥ 65 years in nine European centres and found that considerable variation occurs in the levels of depression across Europe. According to meta-analysis (n = 13,808) an overall prevalence of depression was 12.3%, the rates being 14.1% for women and 8.6% for men. (Copeland *et al.* 1999.) Another large European study (the ODIN study) of the general population in five European countries reported an overall prevalence of depressive disorders of 8.56%, the rate being 10.05% for women and 6.61% for men. The prevalence figures were highest in urban Ireland and urban United Kingdom and lowest in urban Spain. (Ayuso-Mateos *et al.* 2001.) In a randomized telephone survey of 18,980 subjects aged 15 years and older among the general populations of the United Kingdom, Germany, Italy, Portugal, and Spain, the point prevalence of major depression was 4% (3.1% in men and 4.9% in women) (Ohayon & Schatzberg 2003).

In the Epidemiologic Catchment Area Study (ECA) of over 18,000 adults from five United States communities, the one-year and lifetime prevalences of major depression were 2.6% and 4.4%, respectively, while the lifetime prevalence for dysthymia was 3.1% (Weissman *et al.* 1988). In the National Comorbidity Survey (Blazer *et al.* 1994) of 8,098 persons aged 15–54 years, the estimated prevalence of current major depression was 4.9%, with a relatively higher prevalence in females, young adults, and persons with less than college education, while the prevalence for lifetime major depression was estimated to be 17.1%.

In a cross-sectional national survey of the elderly population of Saudi Arabia with nearly 8,000 participants (mean age 68.8 years ± 7.7), depressive symptoms were reported in 39% of the subjects, while 8.4% were in the severe depressive symptoms score group (Al-Shammari & Al-Subaie 1999).

To investigate the effect of aging on rates of depression prospectively, Roberts and coworkers (1997) examined data on symptoms compatible with the DSM-IV diagnostic criteria for major depressive episode in the 1994 and 1995 cohorts of the Alameda County Study. The reported analyses were based on a subsample of 2,219 respondents aged 50 years or older in 1994, the mean age of the subjects being 64.7 years. In 1994 the point prevalence of major depressive episodes was 8.7%, while it was 9.0% in 1995. Among the subjects aged 60 years and older, there was a tendency toward a higher prevalence in 1995. Multivariate analyses demonstrated, however, that the initial age effects were mainly due to chronic health problems and functional impairment, and the authors concluded that healthy, normally functioning older adults are at no greater risk for depression than younger adults. (Roberts *et al.* 1997.)

One of the most consistent findings in research on depression is its higher prevalence among women (Aneshensel *et al.* 1981, Boyd & Weissman 1981, Klerman & Weissman 1988, Kivelä *et al.* 1988, Cho *et al.* 1998, Barry *et al.* 1998, Ohayon & Schatzberg 2003). It has been suggested that it is the social factors rather than the biological differences that are of key relevance for the female preponderance in depression (Harris *et al.* 1991, Maier *et al.* 1999). Bebbington and coworkers (1998) found a clear reversal of the sex difference in the prevalence of depression among subjects aged over 55, which could not be explained by social variables, however.

Depression has been found to be associated with poor social support (Oxman *et al.* 1992, Paykel 1994), an increased number of recent life events (Paykel 1994), being separated or divorced or unhappily married (Weissman 1987), and widowhood (Pahkala *et al.* 1995, Cho *et al.* 1998). The personal characteristics that correlated strongly with depression among the Saudi Arabian elderly were poor education, unemployment, divorced or widowed status, old age, female sex, lower income, loss of a close relative, living alone, and limited participation in recreational activities (Al-Shammari & Al-Subaie 1999). In a Canadian sample of 2,542 household residents, the prevalence of major depression was associated with stress and recent life events, social support and marital status, income and level of education, alcohol consumption and use of drugs, and family history of major depression (Patten 2001). Klerman & Weissman (1989) suggest that there is a persistent family effect in major depression, the risk of depression being about two- to threefold in first-degree relatives compared with controls. In their meta-analytical review of five family studies and five twin studies meeting the inclusion criteria, Sullivan and coworkers (2000) conclude that major depression is a familial disorder, and that its familiality mostly or entirely results from genetic influences, although the environmental influences specific to an individual are also etiologically significant.

A longitudinal study of 1,747 Chinese Americans confirmed the previous evidence that aspects of psychosocial vulnerability, including a higher degree of acculturation, greater stress exposure, and reduced social support are important predictors of risk for first-onset depressive episodes (Hwang *et al.* 2000). In the Alameda County Study, female gender, chronic health conditions, problems with activities of daily living,

cognitive problems, neighborhood problems, social isolation, and depression in 1994 were significant predictors of depression in 1995 (Roberts *et al.* 1997).

2.3 Biological aspects of depression

There have been a variety of theories concerning the neurobiologic etiology of depression. The classic biogenic amine theory of depression suggests that a shortage of noradrenalin (NA) and serotonin (5-HT) in the synaptic clefts is the neurobiological basis of depression (Schildkraut 1965, Bunney & Davis 1965, Coppen 1967). Although the serotonin system is still the most widely studied system, there is evidence suggesting that other neurotransmitter systems also play important roles (Barros *et al.* 2002). It is suggested that instead of being a consequence of a simple decrease in some crucial cerebral transmitter concentrations depression may be the result of a disturbed balance between different regulatory systems and consequent transmitter overactivity in some brain regions (Syvälahti 1994). According to a hypothesis by Harro & Oreland (1996) the neurobiological starting-point of depression lies in the malfunction of the noradrenergic innervation from the locus coeruleus, which, in turn, leads to dysregulation of serotonergic and dopaminergic neurotransmission. A molecular and cellular theory of depression posits that stress-induced vulnerability and the therapeutic action of antidepressant treatments occur via intracellular mechanisms that decrease or increase, respectively, the neurotrophic factors necessary for the survival and function of particular neurons (Duman *et al.* 1997).

As reviewed by Sheline (2000), there is increasing evidence for structural brain changes associated with major depression. Brain changes associated with early-onset major depression have been reported in the hippocampus, amygdala, caudate nucleus, putamen, and frontal cortex, which structures are extensively interconnected. Furthermore, several studies utilizing the magnetic resonance imaging (MRI) technology have reported losses of left and right hippocampal volumes in subjects with a history of severe recurrent depression. (Sheline 2000.) Moreover, functional neuroimaging studies have identified abnormal blood flow in the medial prefrontal cortex in patients with depression. The medial prefrontal cortex is a region where activity is crucially modulated by the neurotransmitters believed to be implicated in depression. (For a review, see Elliott 1998.)

There are several neuroendocrine changes that may be associated with major depression, *e.g.* reduced secretion of thyrotrophin (TSH), somatotrophin, and luteinizing hormone as well as increased prolactin and cortisol secretion (Syvälahti 1994). Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in patients with major depression, resulting in elevated cortisol levels, is one of the most consistent findings in biological psychiatry as reviewed by Pariante & Miller (2001). Fine-tuned homeostasis of the HPA system is important because no other molecule is secreted in a such a wide concentration range into the circulation as cortisol (Holsboer 2001). Reduced sensitivity to the inhibitory effects of glucocorticoid dexamethasone on the production of adrenocorticotropic hormone (ACTH) and cortisol during the dexamethasone suppression

test is one of the features of HPA axis hyperactivity (Pariante & Miller 2001). Subsequently, a much more sensitive dexamethasone-corticotropin-releasing hormone test (Dex/CRH test) was presented for detecting HPA system alterations (Heuser *et al.* 1994). Blood samples can be displaced by samples of saliva in this test procedure, which makes it a suitable tool for monitoring the course of depressive illness (Baghai *et al.* 2002). As stated by Holsboer (2001), the parameter that is actually measured with these tests is the capacity of the glucocorticoid receptors to exert a negative regulatory effect on the release of ACTH and, consequently, cortisol. Subsequently, there exist plenty of data demonstrating the association between reduced corticosteroid receptor function and depression (for reviews, see Holsboer 2001 and Pariante & Miller 2001).

Depression is often accompanied by certain biological alterations, which may well explain the comorbidity of depression and various diseases. The corticosteroid overdrive and noradrenergic hyperactivity present in depression may impair the normal functions of the immune system (Syvälahti 1994). The reports on immune alterations in the context of depression are contradictory, however. According to the meta-analysis of Herbert & Cohen (1993), it seems that such alterations mainly occur in cellular immunity. The association between depression and coronary heart disease, rheumatoid arthritis, and stroke as well as the higher incidence of depression among females have been explained with the macrophage theory of depression, suggesting that excessive secretion of macrophage monokines is the cause of depression (Smith 1991). Many aspects of cellular immunity are activated in depression, including the increased release of proinflammatory cytokines from activated macrophages in the periphery and brain, the excessive synthesis of prostaglandin E_2 (PGE_2) and nitric oxide (NO), and the increased release of acute-phase proteins from the liver, while there is also evidence of the suppression of natural killer (NK) cell activity, T-lymphocytes, and neutrophils. It is also suggested, that many of these unfavorable changes in immune function involving depression can be normalized with antidepressant treatment. (For a review, see Leonard 2001.)

2.4 Depression and health behavior

The results of an Australian community survey of 2,725 participants aged 18–79 years showed that smokers had more depression and anxiety symptoms, more stressors, and lower socioeconomic status compared with nonsmokers (Jorm *et al.* 1999). A number of other studies have also found an association between smoking and depression or depressive symptoms (Hall *et al.* 1993, Escobedo *et al.* 1998, Simantov *et al.* 2000, Green & Pope 2000, Allgower *et al.* 2001). Hämäläinen and coworkers (2001) investigated the associations of cigarette smoking and alcohol intoxication with major depressive episode in a random sample of 599 noninstitutionalized Finnish people aged 15–75 years. Their results showed that major depressive episode in the past 12 months was associated with smoking 10 or more cigarettes daily (OR=2.26, 95% CI 1.68-3.04) and alcohol intoxication at least once a week (OR=2.99, 95% CI 1.70-5.25), which remained significant after adjustment for other major risk factors. (Hämäläinen *et al.* 2001.) Considering the favorable effects of nicotine on mood, sleep, and the serotonergic

system, it has been suggested that smoking represents a form of self-medication for patients with depression (Mihailescu & Drucker-Colín 2000).

Depressive symptoms were significantly associated with an increased risk for regular drinking among adolescents in a nationally representative study in USA (Simantov *et al.* 2000). Individuals with histories of depressive symptoms were more likely to drink more alcohol in a survey of randomly sampled members of a large health maintenance organization (n = 5,841) (Green & Pope 2000). Lynch *et al.* (1996) found drinking to be a significant predictor of depressive symptoms in men and women. The results of a study on a Swedish population-based sample of 316 women also supported the association between depressive disorders and alcohol dependence/abuse (Spak *et al.* 2000). In a review of alcohol and depression, Schuckit (1994) presented that the likelihood of individuals with major depressive disorder to develop alcohol dependence is similar to that of the general population. On the other hand, alcoholics are much more likely to demonstrate severe episodes of major depression, the majority of which are temporary and occur in the context of repeated heavy intoxication with alcohol (Schuckit 1994).

Common symptoms of the depressive syndrome, such as fatigue and psychomotor retardation, may impair the ability to do physical exercise (Martinsen 1994). In a large international study of university students, it was found that after controlling age, social support, and clustering by country, depressive symptoms were significantly associated with a lack of physical activity (Allgower *et al.* 2001). An association was found between depression and a lack of regular physical exercise in elderly Finnish men and women ($\geq$ 60 years) (Kivelä & Pahkala 1991). In a study of 32 women with major depressive disorder and 32 healthy female controls, depression was associated with greater tobacco and caffeine consumption, poorer sleep quality, and less physical activity (Miller *et al.* 1999).

By increasing the uptake of tryptophan (TRP) into the brain, carbohydrate intake increases the brain serotonin concentration, which is known to be involved in mood and appetite (reviewed by Wallin & Rissanen 1994). The positive effects of carbohydrate-rich meals on mood have been observed among obese carbohydrate cravers (Lieberman *et al.* 1986). A carbohydrate-rich and protein-poor diet lowered the stress-induced cortisol responses and depressive mood in subjects highly prone to stress in the study of Markus and coworkers (2000). Subjects with premenstrual syndrome (PMS) (*i.e.* an increase of depressive symptoms during the luteal phase) consumed significantly more calories and demonstrated a specific preference for carbohydrate-rich meals and snacks during the premenstrual phase, suggesting that persons suffering from PMS may eat carbohydrates as self-medication because of their antidepressant effects (Wurtman *et al.* 1989). Increased carbohydrate consumption among depressed persons has also been reported by Christensen & Somers (1996).

Cooper-Patrick and coworkers (1999) assessed the relationship between psychiatric disorders and lack of regular medical care in individuals with chronic medical diseases. In prospective analyses, depression predicted discontinuation of regular medical care one year later (RR 2.4, $p < 0.04$). Depressive symptom severity was associated with a poorer diet and poorer adherence to prescribed medication in primary care diabetic patients (Ciechanowski *et al.* 2000).

The oral hygiene of psychiatric inpatients has been shown to be poor (Lewis *et al.* 2001, Hede 1995a, Angelillo *et al.* 1995, Velasco & Bullon 1999), but the patients in

these studies have mainly been schizophrenics. Poor oral hygiene and accumulations of supra- and subgingival calculus were common findings in 40 patients with bipolar disorder on long-term lithium maintenance therapy (Friedlander & Birch 1990). Stiefel and coworkers (1990) found more plaque and calculus and more frequent consumption of carbonated beverages among noninstitutionalized adults with chronic mental illness compared with control subjects without mental illness. Hede & Petersen (1992) found lower rates of use of dental services and a lower frequency of tooth brushing among Danish noninstitutionalized psychiatric patients compared with the general Danish population.

The mean depression scores, as assessed on the HAD scale, were associated with plaque in a study addressing the relationship between psychological mood, stress, and oral hygiene behavior in a group of 51 regular dental attenders (Kurer *et al.* 1995), while another study investigating whether depression and some other psychosocial factors could predict dental plaque levels in adult periodontitis patients before treatment found no evidence of such association (Monteiro da Silva *et al.* 1998). Personality differences and stressful life events were compared between treated periodontal patients with and without maintenance therapy (Becker *et al.* 1988). The maintained group had a more positive image of themselves and higher achievement, endurance, and affiliation scores than the patients without maintenance. The unmaintained group, on the other hand, had higher negative aggression scores, a higher incidence of stressful life events, and less stable personal relationships in their lives.

2.5 Pain and depression

The results of epidemiological studies have shown that pain is associated with depressive disorders, as reviewed by Von Korff & Simon 1996. In a cross-sectional postal survey of 2,034 adults in the north of England, Croft *et al.* (1993) found that subjects with chronic widespread pain were more likely to report depressive symptoms. Magni *et al.* (1994) showed in their prospective study of 2,324 subjects that depressive symptoms at baseline predicted the development of chronic musculo-skeletal pain at year 8 (OR = 2.14). The high comorbidity of musculoskeletal pain, especially fibromyalgia, and depressive symptoms in Finnish preadolescents was shown by Mikkelsson *et al.* (1997). The association between musculoskeletal pains and high rates of depressive symptoms measured with ZSDS was also verified among 55-year-old Finnish subjects by Rajala *et al.* (1995).

In a study of 4,175 Hispanic Americans, chronic abdominal pain was shown to be associated with depression (Magni *et al.* 1992). Wang and coworkers (1999) investigated the relationship between headache and depression in 1,421 Chinese subjects aged ≥ 65 years. High comorbidity of depression was found in the elderly with migraine or chronic tension-type headaches. The headache frequency ≥ 7 days/month in the past year and the presence of any reported lifetime headache were important in predicting current depression in the elderly. (Wang *et al.* 1999.)

Ohayon & Schatzberg (2003) explored the relationship of five different types of chronic painful physical condition (CPPC) with depression in a cross-sectional telephone survey of a random sample of 18,980 subjects (aged 15 years and older) representative of the general populations of five European countries. The results showed that CPPC was strongly associated with major depressive disorder (unadjusted OR = 4.0, 95% CI 3.5–4.7). After adjustment for sociodemographic factors, alcohol intake, smoking, stress, and body mass index, the OR for having major depressive disorder was still 3.6 (95% CI 2.9–4.4) for subjects with CPPC. (Ohayon & Schatzberg 2003.)

2.5.1 Depression and orofacial pain

Temporomandibular disorders share many features with other common chronic pain conditions (Dworkin & Massoth 1994). Most of the growing pool of evidence supports the view, that for a successful outcome, treatment of chronic temporomandibular disorders requires a multidisciplinary approach with a strong focus on psychological factors (Foreman 1998). This, however, does not eliminate the possible role of occlusal factors as risk factors for TMD, which was supported by the results of Kirveskari *et al.* (1992, 1998).

TMD patients scored higher than healthy controls on the depression, hypochondriasis, and hysteria scales of MMPI in the study of Meldolesi *et al.* (2000). The presence of depressive disorders was examined among 72 chronic facial pain patients presenting at a facial pain clinic (Korszun *et al.* 1996). Of the patients, 28% met the criteria for major depression, while 25% met the criteria for minor depression and 22% reported subsyndromal depressive symptoms. Temporomandibular disorders were demonstrable in 71% of these patients, but the remaining 29% had no objective physical findings. These groups did not differ in the comorbidity of depressive disorders. (Korszun *et al.* 1996.)

The results of the clinical trial of Holzberg *et al.* (1996) indicated that depression is directly related to both the physical and the psychosocial functioning of facial pain patients, while the self-reported level of pain is not. Von Korff *et al.* (1993) carried out a three-year follow-up to find out whether depressive symptoms at baseline were associated with the onset risks of 5 common pain conditions (back pain, severe headache, chest pain, abdominal pain, and temporomandibular disorder (TMD) pain). There were no significant differences in the onset rates of back pain, abdominal pain, or TMD pain by the severity or chronicity of depressive symptoms. However, compared to non-depressed subjects, persons with moderate-to-severe depressive symptoms were more likely to develop headache and chest pain. (Von Korff *et al.* 1993.)

TMD symptoms and depressive symptoms were studied with questionnaires in a subsample of 5,696 subjects in the 31-year follow-up study of the Northern Finland Birth Cohort (Sipilä *et al.* 2001). In both genders, the proportion of depression measured with the SCL-25 depression subscale was significantly higher in subjects with symptoms of TMD compared with asymptomatic subjects, with crude odds ratios varying between 1.4–2.3 and OR adjusted for marital status, education, and self-rated general health

between 1.3–2.3 in different symptoms. Of the TMD symptoms, those related to pain had the most significant relations to the depression score. (Sipilä *et al.* 2001.)

Two subgroups of patients with TMD were compared (patients with temporomandibular joint (TMJ) disease vs. patients whose pain was of muscular origin) with respect to depressive symptoms measured with BDI, pain disability, and exposure to stressful life events (Auerbach *et al.* 2001). The patients whose pain was of muscular origin had significantly higher mean BDI scores than the TMJ patients, and they also had higher levels of stressful life events and pain disability. The lowest BDI scores were obtained by male TMJ disease patients and the highest by female patients whose pain was of muscular origin. (Auerbach *et al.* 2001.)

Riley at al. (1999) investigated compliance with the recommended therapy modalities among facial pain patients and found that depressive symptoms were negatively associated with compliance with medication changes, therapeutic injections, and splint therapy, but not with psychological counseling or physiotherapy. They further suggested that psychological distress can be a barrier for positive patient outcomes through reduced treatment compliance.

In a study of 56 glossodynia patients, the psychopathologic profiles of the subjects were evaluated with a SCL-90 questionnaire (Eli *et al.* 1994). In this data, glossodynia patients showed relatively high psychopathologic profiles, especially on the scales of somatization and depression, which also correlated significantly with the intensity of pain experienced by the patients (Eli *et al.* 1994).

The burning mouth syndrome (BMS) is a condition with unknown aetiology, *i.e.* no underlying dental or medical causes have been identified and no oral signs found. The prominent feature of this syndrome is burning pain in the tongue and/or the lips or some part or the whole of the oral cavity, and the reported prevalence rates in general populations vary from 0.7% to 15%. Many of these patients show evidence of anxiety, depression, and personality disorders. (Zakrzewska *et al.* 2001.) Depression, anxiety, subjective oral dryness, age, medication, taste disturbances, intake of L-thyroxines, illness, and stimulated salivary flow rate associated with BMS in the study of Bergdahl & Bergdahl (1999).

2.5.2 Characteristics of pain-depression comorbidity

The characteristics that most strongly predict depression are the diffuseness of pain and the extent to which pain interferes with activities (reviewed by Von Korff & Simon 1996). Blumer & Heilbronn (1982) viewed chronic pain of uncertain origin as a manifestation of muted depression, and termed this form of masked depression the pain-prone disorder. Pain-depression comorbidity has been explained by susceptibility to both dysphoric physical symptoms (including pain) and psychological symptoms (including depression) and a state of somatosensory amplification, in which psychological distress amplifies dysphoric physical sensations (Von Korff & Simon 1996). Psychological illness and behavioral dysfunction may be a maladaptive response to pain. On the other hand,

pain constitutes a significant physical and psychological stressor that may induce or exacerbate psychological distress. (Von Korff & Simon 1996.)

In their review, Gallagher & Verma (1999) show evidence that patients with depression occurring after the onset of chronic pain have similar rates of affective disorders in family members as the general population and significantly lower rates than the families of patients with major depression alone, suggesting that it is the stress of living with chronic pain, rather than a personal or family predisposition, that causes the depression in these patients. Even though most chronic pain patients seem to maintain adaptive levels of psychosocial function, part of them appear unable to cope as well and demonstrate high rates of depression, somatization, and health care use (Dworkin & Massoth 1994).

The results of a causal analysis of chronic pain and depression strongly supported the view that pain predicts depression (Brown 1990). In their review of 83 selected studies, Fishbain *et al.* (1997) concluded that depression is more common in chronic pain patients than in healthy controls as a consequence rather than the antecedent of chronic pain. A report by von Knorring & Ekselius (1994) summarized the research concerning the hypothesis that idiopathic chronic pain syndrome and depressive disorders share certain pathogenetic mechanisms. The factors common to both syndromes include, for example, common personality traits, hypercortisolaemia, and disturbances in the serotoninergic system. It has been suggested that a decreased brain serotonin level may play a pathophysiologic role in fibromyalgia (Russell *et al.* 1989, Yunus *et al.* 1992, Russell *et al.* 1992). The algesic effect of serotonin (5-HT) has been shown in both animal and human studies (Taiwo & Levine 1992, Babenko *et al.* 1999, Babenko *et al.* 2000). Ernberg and coworkers (1999) found the level of serotonin in the masseter muscle in relation to the serum serotonin level to be higher in patients with pain and tenderness of the masseter muscle than in healthy individuals.

Furthermore, antidepressant medications seem to have favorable effects on the treatment of some chronic pain disorders, including fibromyalgia, migraine, and atypical facial pain. Plesh and coworkers (2000) investigated the 6-week and 1-year effectiveness of low-dose amitriptyline (10–30 mg) (a tricyclic antidepressant agent) in the treatment of patients with chronic temporomandibular disorder pain. The results showed a significant reduction of pain after 6 weeks and 1 year post-treatment. The depression scores changed in the depressed but not in the non-depressed patients. The analgesic effect of amitriptylin on chronic facial pain was also shown by Sharav and coworkers (1987). Among antidepressants, tricyclics are most widely investigated and used in the management of chronic pain. Selective serotonin reuptake inhibitors (SSRIs) and some new antidepressants also appear to be effective in treating specific types of pain, the existing data concerning their use as analgesics being quite limited, however. (Reviewed by O'Malley *et al.* 2000 and Mattia *et al.* 2002.)

2.6 Somatization and depression

Somatization, *i.e.* the expression of distress in the form of physical symptoms, is usually accompanied by depression and anxiety and results in unexplained physical complaints (for reviews, see Clarke & Smith 2000, Servan-Schreiber *et al.* 2000). According to Katon *et al.* (1982), somatizing patients often selectively complain about the somatic manifestations of depression, minimize the affective and cognitive components, and are treated symptomatically. Estimates of the prevalence of people who are depressed but seek treatment for physical disorders in the primary care setting range from 12% to 55% out of all patients (Betrus *et al.* 1995). A large multicenter study with 25,916 patients screened at 15 primary care centers in 14 countries on 5 continents investigated the relation between somatic symptoms and depression (Simon *et al.* 1999). The weighted prevalence for major depression was 10.1%, and the overall prevalence of patients with depression who reported somatic symptoms was 69%. Notably, somatic presentation was found to be more common at centers where patients lacked an ongoing relationship with a primary care physician. Moreover, half of the depressed patients reported multiple unexplained somatic symptoms, and 11% denied having psychological symptoms of depression on direct questioning. (Simon *et al.* 1999.)

Somatoform disorder is defined as a condition in which the patient reports somatic complaints in the absence of any evidence of organic disease (American Psychiatric Association 1994). The World Health Organization International Study of Somatoform disorders (Isaac *et al.* 1995) showed that various aches and pains in different parts of the body represented cross-culturally the most frequent symptoms for which there was no medical explanation. It is suggested that major depression may be associated with most of the somatization seen in medical clinics (Katon & Russo 1989). In a study by Silverstein (1999), subjects with major depression were divided into ones who exhibited fatigue, appetite disorders, and sleep disturbance ("somatic depression") and ones who did not exhibit these somatic criteria ("pure depression"). Female subjects were shown to exhibite a higher prevalence of somatic depression than male subjects, but not a higher prevalence of pure depression. Somatic depression was associated with a high prevalence of anxiety disorder and, among female subjects, with body aches and onset of depression during early adolescence. (Isaac *et al.* 1995.) The diagnosis of masked depression was formerly used about depressive conditions in which physical symptoms predominate while depressive symptoms are concealed (Bschor 2002). According to Bschor (2002), the present diagnoses of comparable conditions include somatization disorder, somatoform disorder, psychosomatic disorder, conversion disorder, neurasthenia, and hypochondriasis.

Wilson and coworkers (1994) investigated the relationship between somatic and psychological symptoms and pain among 220 patients with chronic temporomandibular disorder pain. A high level of somatization (measured with the SCL-90-R somatization subscale) and high-intensity pain were strong predictors of widely dispersed pain on muscle palpation during the clinical examination. Furthermore, high-somatization patients were 3 times more likely than low-somatization subjects to report having a painful placebo site. Moreover, pain dispersion was more closely linked to the report of a number of somatic symptoms than to the report of affective and cognitive symptoms of

psychological distress (assessed with the non-somatic items of the Anxiety and Depression subscales of SCL-90-R). (Wilson *et al.* 1994.) There were significantly more high-somatization subjects among chronic orofacial pain patients than among control subjects in the study of McGregor *et al.* (1996).

Portegijs and coworkers (1996) studied somatization in frequent attenders of general practice in a group of 80 general practice patients with a history of back, neck, or abdominal complaints and at least 12 consultations in the previous 3 years. Somatization, the prevalence of which was 45% in this group, was related to depressive complaints, female sex, more frequent visits to general practitioner, and a higher number of health problems (Portegijs *et al.* 1996).

2.7 Comorbidity of depression and somatic diseases

Several pharmacological factors as well as physical diseases, including malignant diseases and diseases of the thyroid gland and the central nervous system, have been associated with the onset of depression (Akiskal 2000). Cohen and coworkers (1998) examined the prospective associations between somatic illness and mental illness from childhood to adulthood in a cohort of over 700 randomly selected children in New York from ages of 1–10 years in 1975 to young adulthood in 1992. The results showed, that ill health increased the risk of new-onset major depressive disorder at all ages. Moreover, MDD also predicted subsequent ill health, independently of prior health problems. These relations were not attributable to familial socioeconomic status. (Cohen *et al.* 1998.)

Meeks and coworkers (2000) examined the relationships between health and depression in a prospective study of 1,479 community-resident middle-aged and older adults. Their findings suggested that different durations of depressive symptoms are differently related to health. Health had an impact on the short-term increase of depressive symptoms, whereas short-term depressive symptoms had only a minor impact on health. Longer-term depressive symptoms had a clear impact on health, however. (Meeks *et al.* 2000.)

A cohort of 6,247 subjects ($\geq$ 65 years) in the USA, initially free of disability, were followed up for 6 years to examine the effect of depression on the incidence of physical disability and the role of confounding and explanatory variables in this relationship (Penninx *et al.* 1999). It was found that depression increased the risk for disability in mobility and disability in the activities of daily living. Decreased physical activity and social interaction partly explained this excess risk**.** Various chronic medical conditions were associated with an increased prevalence of major depression in a sample of 17,626 Canadians (Patten 1999). However, comorbidity of major depression with chronic medical conditions was not associated with increased health care service use.

Depressive symptoms were associated with three-year mortality in older persons hospitalized with medical illnesses (Covinsky *et al.* 1999). Depressed mood was an independent predictor of mortality from all causes at one year in general medical inpatients (Herrmann-Lingen *et al.* 2001). In a 6-year follow-up of 4,051 community-living older persons, the mortality risk of neurotic and psychotic depression was

calculated after adjustment for demographic variables, physical illness, cognitive decline, and functional disabilities (Schoevers *et al.* 2000). The results showed, that psychotic depression was associated with significant excess mortality in both men and women, whereas neurotic depression was associated with a 1.67-fold mortality risk in men only. The global burden of disease (GBD) study, based on the collaboration of over 100 scientists from more than 20 countries, predicts major depression to become the second leading cause of disability and premature mortality worldwide by 2020 (Murray & Lopez 1996).

The association between depressiveness and subsequent incidence of lung cancer was studied with 14-year follow-up in the nationally representative Mini-Finland Health Survey, where the study population comprised 7,018 adult men and women free from cancer at baseline (Knekt *et al.* 1996). The relative risk of lung cancer in depressive persons compared to individuals with normal depressiveness scores was 3.32 (95% CI 1.53–7.20). Neither adjustment for the potential confounding factors nor exclusion of the cancer cases occurring during the first 4 years of follow-up notably altered the results. The relative risks of lung cancer in smokers compared to nonsmokers was 3.38 at the normal depressiveness levels and 19.67 at strongly elevated levels, respectively. (Knekt *et al.* 1996.)

The relationship between cerebrovascular changes and depressive symptoms was supported by the results of a multicenter community-based population study from the USA (Steffens *et al.* 1999). Furthermore, evidence showing that depressive symptomatology precedes the onset of acute coronary syndromes and influences the course of the disease is accumulating (Appels 1997). Pratt and coworkers (1996), using prospective data from the Baltimore ECA follow-up study, examined whether a history of a major depressive episode or dysphoria (two weeks of sadness) increases the risk of myocardial infarction. The role of psychotropic medication use in this relationship was also evaluated. The odds ratio for myocardial infarction associated with a history of major depressive episode was 4.54 (95% CI 1.65–12.44), while that with a history of dysphoria was 2.07 (95% CI 1.16–3.71), independent of the coronary risk factors. Nor did comorbid psychiatric disorders or psychotropic medication use explain these relationships. (Pratt *et al.* 1996.) Depression was found to be an independent risk factor for heart failure among elderly women but not among elderly men in a prospective 14-year follow-up study in a community sample of 2,501 persons aged ≥ 65 years (Williams *et al.* 2002).

The association between depression and cardiovascular diseases (CVDs) was examined in the Mini-Finland Health Survey. Cross-sectionally, cardiovascular diseases and neurotic depression were associated both before and after adjustment for covariates. Consistently, during the follow-up, the risk of CVD death and coronary death was elevated in depressed persons both with and without CVDs at entry. (Aromaa *et al.* 1994.)

A meta-analysis by Anderson *et al.* (2001) showed significant comorbidity of diabetes and depression in adults. Furthermore, another meta-analysis demonstrated a significant and consistent association between diabetes complications and depressive symptoms (de Groot *et al.* 2001). According to Rajala *et al.* (1997) depression, while being more common among previously diagnosed diabetic patients, was not associated with elevated

glucose levels or a more severe metabolic disease, suggesting a psychosocial instead of a biological association between these disorders.

Numerous clinical observations and several retrospective studies suggest that psychological factors play a role in the onset and exacerbation of autoimmune diseases, as reviewed by Cohen & Herbert 1996. Increased prevalence rates of depression and depressive symptoms have been reported in patients with primary Sjögren's syndrome (Vitali *et al.* 1989, Dohrenbusch *et al.* 1996), rheumatoid arthritis (for a review, see Dickens *et al.* 2002), and Parkinson's disease (Robins 1976, Caap-Ahlgren & Dehlin 2001).

An association between depression and gastrointestinal symptoms (Walker *et al.* 1992) as well as the irritable bowel syndrome (Masand *et al.* 1995, Trikas *et al.* 1999) has been suggested. Antidepressant therapy has been found to be effective in the treatment of functional gastrointestinal disorders (Jackson *et al.* 2000, meta-analysis). In the case of upper respiratory tract infections, there exists convincing evidence of links between stress and negative affect and disease onset and progression. Studies concerning herpes infections generally support a relation between negative emotional states and disease recurrence. (Reviewed by Cohen & Herbert 1996.)

2.7.1 Depression and oral health

The studies on the oral health and dental treatment needs of hospitalized psychiatric patients mainly show that the oral health of these patients is relatively poor, and that there is a major need for dental treatment, depending on the length of institutionalization (Hede 1995b, Angelillo *et al.* 1995, Velasco *et al.* 1997, Velasco & Bullon 1999). Lewis and coworkers (2001) studied over 300 psychiatric inpatients in South Wales, of whom 47% had dementia, 23% had schizophrenia, and 19% had depressive illness. Comparison with the general population showed a similar level of decay, but fewer filled teeth and more missing teeth in the study population. No significant differences were found within the population by their age, psychiatric diagnosis, psychotropic medication use, or length of hospitalization. (Lewis *et al.* 2001.) More edentulous persons and denture wearers were found among the non-institutionalized psychiatric patients compared with the general Danish population in a study by Hede & Petersen 1992. Stiefel *et al.* (1990) found a higher incidence of self-reported dry mouth, mucosal, lip, and tongue lesions, and coronal smooth surface caries among noninstitutionalized adults with chronic mental illness compared with control subjects without mental illness. In the above-mentioned studies, however, depressed subjects were a minority, and all study subjects received psychotropic medications, which interferes with the interpretation of the results.

Several human and animal studies suggest an association between stress and periodontal disease (Green *et al.* 1986, Axtelius *et al.* 1998, Genco *et al.* 1999, Breivik *et al.* 2000, Hildebrand *et al.* 2000, Fedi 1958, Gupta *et al.* 1960, Cohen *et al.* 1969), but there exist relatively few studies on the relationship between depression and periodontal conditions. However, the concepts of stress and depression are biologically related, and there is substantial evidence that alterations of the stress hormone system play a major

causal role in the development of depression (reviewed by Holsboer 2001). In a large population study of 1,426 subjects aged 25 to 74 years, Genco and coworkers (1999) evaluated the associations of stress, distress, and coping behaviors with periodontal disease. The results of multivariate analysis showed that depression measured with BSI was associated with a higher level of clinical attachment loss after adjustment for the known risk factors for periodontal disease (OR = 1.5, 95% CI 1.02–2.22). Likewise, a statistically significant association was found between financial strain and clinical attachment loss as well as bone loss. Stratification of the subjects according to their coping behavior showed that the risk for clinical attachment loss among the subjects with financial strain was modifiable by coping style in such a way that highly emotion-focused coping (poor coping), which is suggested to correlate with depression (Whatley *et al.* 1998), increased the risk, while problem-focused coping (good coping) decreased it. (Genco *et al.* 1999.) In a cross-sectional study of an adult Swedish population aged 50 to 80 years, individuals with external locus of control, which is characterized by poorly developed strategies to cope with stressful life events, had significantly more severe periodontal disease than those with an internal and well-developed coping style (age adjusted OR = 1.13, 95% CI 1.05–1.22, $p < 0.01$) (Hugoson *et al.* 2002). Patients with chronic periodontitis (n = 89) differed significantly from controls with regard to their strategies of coping with stress in the study of Wimmer and coworkers (2002). Moreover, the patients with severe clinical attachment loss ($\geq$ 5mm) used defensive coping strategies to a significantly greater extent than the patients with moderate or mild clinical attachment loss. No direct association was found between psychosocial stress and remaining periodontal support in a study of 681 Lithuanian adults (Aleksejūnienė *et al.* 2002).

Baker and coworkers (1961) investigated the relationships between periodontal disease and personality factors measured with MMPI in a study of 62 psychiatric patients and 40 controls. A significant correlation was found between somatization and periodontal disease, while the depressive personality pattern and periodontal status were not significantly associated. Mobley & Smith (1967) used the MMPI and Russell's Periodontal Index to measure personality variables and periodontal status in a study of 897 black high school students aged 13 to 19 years old. Those with the greatest degree of periodontal disease had significantly higher mean scores on the schizophrenia scale of the MMPI than those with the lowest degree of periodontal disease. Other personality traits found to be slightly related to periodontal status were depression, hypomania, psychasthenia and social introversion. (Smith 1967.)

Brown and coworkers (1994) investigated the incidence of attachment loss of 3 mm or more and associated factors in an 18-month follow-up study of over 1,000 community-dwelling older adults in North Carolina. The etiologic model for whites indicated that people who felt themselves depressed were at a higher risk for periodontal disease progression (OR = 2.6, 95% CI 1.25–5.56). Monteiro da Silva and coworkers (1996) investigated the associations between psychosocial factors and periodontal disease by comparing 50 patients with rapidly progressing periodontitis (RPP), 50 patients with routine chronic adult periodontitis (RCAP), and 50 patients without significant periodontal destruction. Depression, measured on a HAD scale, was significantly increased in the group of RPP patients compared to the RCAP and control groups.

The results of a case-control study of psychosocial factors and adult periodontitis in 71 cases and 77 controls showed the IgG antibody level to *Bacteroides forsythus* to be associated with periodontal disease among individuals scoring high on depression (OR = 6.75, 95% CI 1.25–36.5) (Moss *et al.* 1996). Likewise, this group with elevated levels of antibody and high depression scores at baseline were more likely to experience extensive disease activity during the 1-year follow-up period.

Depression, determined by the presence of any diagnostic code indicative of depression on the patient record, was significantly associated with poor periodontal treatment outcome (adjusted OR = 2.16, 95% CI 1.12–4.16) in a study based on data of 697 adult health maintenance organization patients having a periodontal examination at baseline and one year after treatment (Elter *et al.* 2002).

A positive association was found between gingival bleeding and HAD scores by Borkowska and coworkers (1998). Existing evidence strongly supports the view that emotional stress is one of the predisposing factors of acute necrotizing ulcerative gingivitis (ANUG) (Monteiro da Silva *et al.* 1995), and higher scores on the MMPI depression scale among ANUG patients compared to controls have also been found (Cohen-Cole *et al.* 1983).

It has been suggested that patients with oral lichenoid reactions have a tendency to be depressed (Bergdahl *et al.* 1995). A psychometric evaluation of 100 patients with oral lichen planus (OLP) and 50 control subjects showed that the OLP patients exhibited greater anxiety and depression than the controls. Furthermore, patients with erosive lichen planus had higher depression scores than patients with non-erosive lichen planus (Rojo-Moreno *et al.* 1998). However, the study of McCartan (1995) revealed no association between OLP and depression measured on a HAD scale.

Reduced saliva secretion as a consequence of antidepressant medication has been widely reported (Bahn *et al.* 1972, Hunter & Wilson 1995, Sreebny & Schwartz 1997), dry mouth being a common adverse effect of tricyclic antidepressants as well as selective serotonin reuptake inhibitors (SSRIs) (Trindade *et al.* 1998). Accordingly, increased caries activity has been found in depressed patients receiving antidepressants (Bassuk & Schoonover 1978, Rundegren *et al.* 1985, von Knorring & Wahlin 1986, Thomson *et al.* 1995, Peeters *et al.* 1998). The question of whether there is an association between dental caries and depression itself, however, cannot be answered on the basis of these studies. Severe stress, on the other hand, has been suggested to predispose to the development of acute dental caries (Sutton 1965, Borysenko *et al.* 1980, Honkala *et al.* 1992).

Apart from antidepressants, depression itself is related to increased anticholinergic activity (Friedlander & Norman 2002). There are, in fact, several studies concerning depression and decreased salivary flow. Strongin & Hinsie (1938) compared parotid gland flow rates in 6 manic-depressive patients with flow rates in normal control subjects. In the manic group the flow rates fell within the normal range, whereas the flow rates in the depressed subjects were below the lowest rate of the normal group.

The technique of collecting whole-mouth saliva on dry preweighed cotton rolls was used by Peck (1959), who found consistent and good correlations between clinical depression and lowered rates of salivary secretion. Both resting and stimulated salivary secretions of the depressed subjects were lower than the normal secretion levels in a study of 30 depressed females (Davies & Gurland 1961). In a longitudinal study of 18 depressive patients, the salivary secretion rates remained low while the MMPI measures

of anxiety and depression declined upon clinical recovery (Gottlieb & Paulson 1961). The authors suggested that a low salivary flow rate is characteristic of persons prone to depression.

In a study of 22 depressive female patients, Davies & Palmai (1964) found significant differences in salivary secretion rates related to the degree of depression. Furthermore, the secretion rates normalized upon recovery. A clear reduction in salivary flow and reversal of the normal diurnal rhythm in 20 female inpatients with early morning wakening and a diurnal variation in mood was demonstrated by Palmai & Blackwell (1965). Palmai *et al.* (1967) also measured salivary flow in 20 female inpatients with depression without early morning wakening or marked diurnal fluctuation in mood. Before treatment, the depressed subjects' mean 24-hour salivary flow rate was significantly below that of the controls. Their diurnal rhythm was normal, however. During the treatment, the patients treated with electroconvulsive therapy (ECT) showed a steady return to normal salivary flow, while the patients treated with imipramine showed a less complete restoration of normal salivary flow. (Palmai *et al.* 1967.) Lowered salivary flow in depressed patients has also been reported by Busfield & Wechsler (1961). The results of Toone & Lader (1979), on the contrary, did not support these earlier findings.

An association between the subjective complaint of oral dryness and depression has been suggested in a few studies (Cohen *et al.* 1990, Bergdahl *et al.* 1997, Bergdahl & Bergdahl 2000), but no association was found between subjectively felt dry mouth and depressive symptoms measured with BDI by Mathew *et al.* (1979).

Kressin and coworkers (2002) examined the association between depressive symptoms and oral quality of life among community-dwelling individuals aged 65 years or older in Los Angeles (n = 1,653) and metropolitan Boston (n = 212). Oral quality of life, *i.e.* the extent to which oral conditions affect one's functioning and well-being, was measured with the Geriatric Oral Health Assessment Instrument (GOHAI) (Atchison & Dolan 1990) and the Oral Health-related Quality of Life measure (OHQOL) (Kressin *et al.* 1996, Kressin 1997). Depressive symptoms were determined with the CES-D scale. Subjects with more depressive symptoms were shown to report worse oral quality of life even after controlling for self-reported oral health, age, education, income, and marital status. This result was found in men and women and with both measures of oral quality of life. The use of antidepressant medications was not included in the analyses, however. (Kressin *et al.* 2002.)

3 Aims of the study

3.1 Working hypotheses

Based on the complex biological, psychological, and social disturbances involved in depression and the associations between depression and unfavorable health behavior and regarding the comorbidity of depression and a wide variety of somatic illnesses, it was hypothesized that high rates of depressive symptoms might be associated with impaired oral health and poor oral health behavior. Furthermore, depressive symptoms were thought to have associations with saliva-related factors and symptoms and signs of temporomandibular disorders.

3.2 Aims

The specific aims of the study were to investigate

1. the relationship of depressive symptoms with edentulousness, number of teeth, dental caries, and periodontal disease,
2. whether depressive symptoms are associated with various aspects of oral health behavior,
3. the relationship between depressive symptoms and symptoms and signs of TMD,
4. whether depressive symptoms are associated with salivary flow rate, the sensation of dry mouth, and salivary microbial growth.

4 Subjects and methods

4.1 Study population and study design

The population comprised all of the 1012 inhabitants born in 1935 and living on October 1, 1990 in Oulu, a city of 100,000 inhabitants in northern Finland. There were 458 (45%) men and 554 (55%) women in the original study population, of whom 780 persons (77%) (345 men and 435 women) participated. Two men and two women died before the examination could be performed. A separate postal questionnaire was sent to those who failed to participate in the examination, and 121 (53%) returned it. Of the non-participants, 51% were women compared to 56% of the subjects examined. 39% of the non-participants were edentulous and 56% were workers compared to 32% and 47% of the subjects examined, respectively.

This study was part of a more extensive epidemiological research project on the 55-year-old population of the city of Oulu, including examinations of general and oral health. The clinical examinations and interviews took place at the Institute of Dentistry, University of Oulu, between October 15, 1990 and October 1, 1991.The data collection was performed by two dentists (Sirpa Anttila née Vimpari, and Tero Sakki), one dental nurse (Pirkko Koski), two physicians (Ulla Rajala and Aira Uusimäki), and one nurse (Marja-Riitta Honkanen).

4.2 Methods

4.2.1 Measurement of depressive symptoms

Depressive symptoms were determined using the Zung Self-Rating Depression Scale (ZSDS), which was filled in at the meeting with the nurse. The ZSDS includes 20 items, each with four specified alternative answers (Zung 1965). The items measure common

psychic and somatic symptoms, including the criteria generally used in diagnosing depression. The points were calculated as total raw sum points on a scale from 20 to 80, using the method described by Zung (Zung 1965). The cutoff points of 43/44 and 39/40 were used in the substudies, and the participants who scored 44 raw sum points or more (Paper I) or 40 raw sum points or more (Papers II, III and IV) were regarded as having high rates of depressive symptoms.

4.2.2 Postal questionnaire and interview

The postal questionnaires were sent to the participants two weeks before the clinical examinations, where they were checked. The background data gathered with the postal questionnaires and the classification of responding variables into categories are presented in Table 1. The questions were based on Finnish national surveys (Pohjolainen 1987, Niemensivu *et al.* 1988, Vehkalahti *et al.* 1991, Hartikainen 1994). Occupational status was classified according to the Central Statistical Office of Finland (1981). The data on alcohol consumption (none, 1–6 drinks *per* two weeks, more than 6 drinks *per* two weeks) and smoking habits (nonsmoker, ex-smoker, occasional smoker, regular smoker) were gathered through an interview. In the case of smoking, the classification into categories was made on the basis of the studied issue, and it is therefore different in the Papers II, III and IV, in which the first three, the first two, and the last three catogories were pooled together in the analyses, respectively.

Table 1. The study variables based on the postal questionnaire and their classification into categories.

Variable: categories (grouping of categories expressed with *vs.*)	
1.	Gender: male *vs*.female
2.	Marital status: married/cohabiting *vs.* unmarried/divorced/widowed
3.	Occupational status: upper white collar worker/lower white collar worker *vs.* blue collar worker
4.	Vocational education: none/vocational or other courses *vs.* vocational school/college/university
5.	Family net income per month: < 6,000 FIM/6,000–9,000 FIM/ > 9,000 FIM
6.	Frequency of dental visits: at least once in 2 years *vs*. rarely/never
7.	Time elapsed since the last dental visit: < 3 years *vs*. 3 years or more
8.	Tooth brushing frequency: twice a day *vs*. once a day/rarely
9.	Regular use of tooth picks, dental floss, interdental brush, or solo brush: yes *vs.* no
10.	Attitude towards the preservation of one's natural teeth: very important *vs.* fairly important/unimportant
11.	Use of sugar in coffee or tea: no *vs*. yes
12.	Consumption of sweets, snacks, or soft drinks: never/occasionally *vs.* once or twice a week/daily
13.	Consumption of vegetables, fruit, and root crops: daily *vs.* once or twice a week/rarely
14.	Self-perceived health: very good/fairly good *vs.* moderate/fairly poor/very poor
15.	Self-perceived physical condition: very good/fairly good *vs.* moderate/fairly poor/very poor
16.	Life satisfaction: very satisfied/satisfied *vs.* moderately satisfied/dissatisfied/most dissatisfied
17.	Work satisfaction: very satisfied/satisfied/moderately satisfied *vs.* dissatisfied/most dissatisfied (Paper I); very satisfied/satisfied *vs.* moderately satisfied/dissatisfied/ most dissatisfied (Paper IV)
18.	Level of work-related physical stress: very high/high *vs.* fairly low/low/very low
19.	Level of work-related mental stress: very high/high *vs.* fairly low/low/very low
20.	Physical activity: the persons who walked or biked for less than 15 minutes on their way to work and whose frequency of exercise periods exceeding 30 minutes during leisure time was once a week or less were classified as having a low physical activity. In the other cases, physical activity was rated as high.

4.2.3 Dental examination

The presence of subjective symptoms of temporomandibular disorders (TMD) was recorded during an interview at the beginning of the clinical examination using the criteria recommended by Helkimo (1974). The presence and severity of the clinical signs and symptoms of TMD were recorded using Helkimo's Clinical Dysfunction index (Di) (Helkimo 1974), which has four categories: Di0 (clinically symptom-free), Di I (mild dysfunction), Di II (moderate dysfunction), and Di III (severe dysfunction). In the analyses, Di0 and DiI as well as DiII and DiIII were combined to give a dichotomous scale.

The subjective sensation of oral dryness was recorded during an interview at the dental examination. The subjects were asked if they felt their mouth to be dry never or rarely, sometimes, or often. The subjects who answered 'sometimes' or 'often' were placed into the sensation of dry mouth category.

The occurrence of dental decay (primary and secondary dentin caries and root caries) was recorded separately for each tooth surface using the diagnostic criteria of the World Health Organization (1987). Panoramic tomography was used to supplement the clinical diagnosis. The presence of periodontal pockets (≥ 4mm) was recorded with a periodontal probe at four surfaces of each tooth and expressed as a percentage of the risk surfaces.

The level of oral hygiene (poor/moderate/good) was estimated clinically, using plaque accumulation on teeth or dentures as the main criterion in accordance with the principles presented by Silness and Löe (1964) and Ambjørnsen (1982).

The dentists were trained carefully and the measurements were calibrated before the examinations. Inter- and intraexaminer agreement was analyzed with regard to dental caries and periodontal pocketing with duplicate examinations of 19 and 10 subjects, respectively. The interexaminer agreement was 99.1% in the diagnosis of decayed surfaces (*kappa* statistic 0.77) and 92.9% in the diagnosis of probing depth deeper than 3mm (*kappa* statistic 0.72). The intraexaminer agreement in caries diagnosis was 99.5% and the *kappa* statistic 0.80 for S. Anttila (née Vimpari), the corresponding figures for T. Sakki being 99.7% and 0.77. The intraexaminer agreement in the diagnosis of periodontal pocketing was 95.3% and the *kappa* statistic 0.78 for S. Anttila, being 96.7% and 0.80 for T. Sakki. In the case of Helkimo's Clinical Dysfunction Index (Di), the interexaminer variation was measured with 13 subjects, Spearman's correlation coefficient for the examiners being 0.912.

4.2.4 Salivary and microbial analyses

For measurement of unstimulated saliva secretion, the subjects spat the freely secreted saliva into a test tube via a funnel. After the collection of unstimulated saliva, paraffin wax-stimulated salivary flow rate was measured after 1 minute of prestimulation. Collection time was 5 minutes for both measurements, and flow rates were calculated as milliliters per minute. Unstimulated salivary flow rates of ≤ 0.1ml/min and stimulated flow rates of ≤ 0.7ml/min represented low flow rates (Sreebny & Valdini 1988, Fure & Zickert 1990, Navazesh *et al.* 1992, Närhi *et al.* 1993).

Buffering capacity was measured from unstimulated and stimulated saliva immediately after collection with the Dentobuff strip® method (Orion Diagnostica, Espoo, Finland) and classified as high (final saliva pH ≥ 6.0) or low (final saliva pH of ≤ 5.5). The pH of saliva was measured with indicator paper immediately after collection and classified as ≤ 7 or ≥ 8.

Salivary lactobacilli counts were measured with the Dentocult-LB® test (Orion Diagnostica, Espoo, Finland), as described by Larmas (1975). The lactobacilli count was considered high if the number of microorganisms was ≥ 10^5 CFU/ml (Parvinen 1984a, Klock *et al.* 1990). Mutans streptococci counts of saliva were measured with the Dentocult-SM® strip (Orion Diagnostica), and counts ≥ 10^6 CFU/ml were considered as high (Klock *et al.* 1990, Alaluusua *et al.* 1990).

The occurrence of yeasts in saliva was measured with the Oricult-N® test (Orion Diagnostica) and the growth of yeasts in the media was categorized as either positive or negative. All the tests were made according to the manufacturer's instructions.

4.2.5 Determination of illnesses, use of drugs and measurement of symptoms and life events

Diagnosed diseases and the use of medication were determined in the interviews performed by physicians. The classification of diseases potentially associated with dry mouth was accordant with the classification used by Mandel (1990). Xerogenic medications included all the drugs which, according to the list published by the Finnish Association of Pharmaceutical Chemists (1992), may have xerogenic side effects and were available in Finland in 1990. Symptoms relating to the neck, cervical spine, or back of the head during the preceding 12 months were recorded by the nurse during an interview, as were the symptoms in the shoulders or upper arms during the past 12 months. These symptoms were recorded on a structured questionnaire developed by Kuorinka *et al.* (1987). The alternative answers were: no, occasionally, often, or almost continuously. In the analyses, the categories "no" and "occasionally" were pooled together, as were the categories "often" and "almost continuously".

The extent of symptoms was measured by the nurse with a questionnaire modified from the symptom scale used in the 25-year follow-up survey of the East-West study (Kivelä *et al.* 1986). The questionnaire included 39 somatic, psychosomatic, or psychic symptoms, and the subjects were asked if they had had any of these symptoms during the preceding two weeks. The alternative answers were: no, occasionally, often, almost continuously. A sum index was calculated, and the range of the sum scores was 39–156.

Life events during the preceding 5 years were assessed by the nurse with a structured inquiry consisting of twelve questions modified from the fifteen questions in the life event scale developed by Holmes & Rahe (1967). The range of the sum scores was 0–12.

4.2.6 Statistical analyses

Cross-tabulation was used to analyze the variation in the distributions of the variables, and the statistical testing included the *chi*-square-test, Fisher's exact test, and estimates of the common relative risk (odds ratio and 95% confidence limits). When analyzing the associations between depressive symptoms and the continuous variables (dental caries, fillings, periodontal pockets, number of teeth), the non-parametric Wilcoxon two-sample test was used. When the Zung scale was used as a continuous variable, the correlations were calculated with Spearman's rank correlation coefficient. When the occurrence of depressive symptoms and smoking status were cross-tabulated with dental status (Paper IV), statistical testing of the difference of proportions was used (Robert 1998).

The variables associated with the occurrence of subjective and moderate or severe clinical symptoms of TMD were analyzed using stepwise logistic regression analysis with forward and backward selection of factors, in which the significance of the added variables was tested at each stage, omitting the non-significant ones (Paper I). When analyzing the determinants of the subjective sensation of dry mouth (Paper II), salivary microbes (Paper III and previously unpublished results in chapter 5.5), and depressive symptoms (Paper IV), a logistic regression analysis fitted in a forward manner by adding one variable or variable group in turn was used. The improvement of the goodness of fit of the model was measured by a change of the log likelihood and by the difference of deviance at each step when a new term was included in the model. The PLR program of the BMDP statistical software was used in fitting the logistic models.

5 Results

5.1 Distribution of the sum scores of the Zung Self-Rating Depression Scale (ZSDS)

The median of the ZSDS sum score was 35 for women and 33 for men, and the 25% and 75% quartiles were 30 and 40 for women and 28 and 39 for men, respectively. The mean was 35.5 for women and 33.8 for men.

Of women, 26.1% (n = 112) scored 40 raw sum points or more and 15.6% (n = 67) 44 raw sum points or more on the ZSDS. The respective figures for men were 20.7% (n = 70) and 8.0% (n = 27). The difference between the sexes was statistically significant when the cutoff point of 43/44 was used (p = 0.001, OR = 2.1 and 95% CI 1.3–3.4).

5.2 Depressive symptoms in relation to socio-economic status

The prevalences of high rates of depressive symptoms in relation to marital status, vocational education, occupational status, and family income are presented in Table 2.

Depressive symptoms were significantly associated with marital status, vocational education, and family income among women. Among men, there were no statistically significant associations between depressive symptoms and the above socio-economic variables, but men with low family income tended to have high rates of depressive symptoms more often than men with higher family income (p = 0.065).

Table 2. Prevalences of high rates of depressive symptoms in relation to marital status and socioeconomic factors.

Variable	Men			Women		
		ZSDS ≥ 40	ZSDS≥44		ZSDS ≥ 40	ZSDS ≥ 44
	n	%	%	n	%	%
Marital status					*	**
married/cohabiting	285	20.0	7.7	285	22.5	12.3
unmarried/divorced/widowed	52	25.0	9.6	145	33.1	22.1
Vocational education						*
university, college or vocational school	133	20.3	6.8	123	24.4	12.2
vocational or other courses	103	26.2	10.7	162	21.6	11.7
no vocational education	96	13.5	7.3	138	31.9	22.5
Occupational status						
white collar worker	150	22.0	10.0	240	22.9	13.4
blue collar worker	186	19.4	6.5	181	30.4	18.2
Family income					**	**
< 6000 FIM	77	29.9	13.0	149	34.2	22.8
6000–9000 FIM	91	17.6	5.5	113	24.8	14.2
> 9000 FIM	154	17.5	6.5	141	17.0	7.1

n = size of the denominator group, * $p < 0.05$, ** $p < 0.01$

5.3 Relationship of depressive symptoms with edentulousness, dental health, and dental health behavior

There was no statistically significant association between depressive symptoms and edentulousness either in men or in women. However, after controlling for smoking, it turned out that, among men, there was a statistically significant difference between smokers and those who had never smoked in the occurrence of depressive symptoms related to dental status (Table 3). Consequently, a logistic regression analysis fitted for nonsmoker men was made with depressive symptoms as an outcome variable. It turned out that, in this subgroup, edentulousness was associated with a high rate of depressive symptoms (OR = 6.4, 95% CI 1.4–29.2) after controlling for self-perceived health, life satisfaction, work satisfaction, and occupational status (Table 4). No such association was found among smoking men (Paper IV, Table 3) or women (data not presented).

Table 3. Prevalence of a high rate of depressive symptoms (ZSDS ≥ 40) in relation to dental status and smoking among men and women.

Smoking status	Men					Women				
	Dentate		Edentulous		p-value	Dentate		Edentulous		p-value
	n	(%)	n	(%)		n	(%)	n	(%)	
Nonsmoker	93	(16)	12	(50)	0.014	184	(23)	95	(32)	NS
Smoker	169	(22)	64	(17)		73	(25)	78	(28)	
Total	262	(20)	76	(22)	NS	257	(23)	173	(30)	NS

ZSDS = Zung Self-Rating Depression Scale, n = size of the denominator group, NS = not significant

Table 4. Logistic regression analysis among nonsmoker men with depressive symptoms (ZSDS ≥ 40 vs. ZSDS ≤ 39) as the outcome variable (n = 104).

Variable	Level	Odds ratio	95% Confidence Interval	p-value
Self-perceived health	Good	1.0		
	moderate or poor	5.7	(1.1, 29.8)	0.027
Life satisfaction	Good	1.0		
	Impaired	2.8	(0.8, 9.9)	0.082
Work satisfaction	Good	1.0		
	Impaired	1.8	(0.5, 6.2)	0.332
Occupational status	white collar worker	1.0		
	blue collar worker	0.4	(0.1, 1.5)	0.153
Dental status	Dentate	1.0		
	edentulous	6.4	(1.4, 29.2)	0.011

ZSDS = Zung Self-Rating Depression Scale

Depressive symptoms were not associated with the number of decayed tooth surfaces (Table 5a), periodontal pocketing (Table 5c), or the number of teeth (Table 5d) among men or women. Likewise, no association emerged between these variables when smoking status was controlled (data not presented). Women with a high rate of depressive symptoms tended to have a lower percentage of filled tooth surfaces than women with fewer depressive symptoms (p = 0.063) (Table 5b).

Dentate women with high rates of depressive symptoms did not consider it so important to preserve their own teeth as did dentate women with fewer depressive symptoms. They also consumed sweets, snacks, and soft drinks more often, and a longer time had elapsed since their last visit to a dentist (Paper IV, Table 5). Depressive symptoms were not associated with the tooth brushing frequency, the frequency of dental visits, the use of sugar in coffee or tea, the use of extra cleaning methods, or the dentist's view of the subject's oral hygiene either in men or in women (Paper IV, Table 5).

Using of the ZSDS as a continuous variable in bivariate analyses did not change the results.

Table 5a. Decayed surfaces[a] in relation to depressive symptoms among dentate subjects (n = 519).

Gender	n	X	min	Q_1	med	Q_3	max	p-val
Men								
ZSDS ≤ 39	209	4.2	0	0	0.8	4.2	52.5	
ZSDS ≥ 40	53	7.5	0	0	0	4.4	100	NS
Women								
ZSDS ≤ 39	197	2.5	0	0	0	2.3	35.0	
ZSDS ≥ 40	60	4.2	0	0	0	3.2	60.0	NS

Table 5b. Filled tooth surfaces[a] in relation to depressive symptoms among dentate subjects.

Gender	n	X	min	Q_1	med	Q_3	max	p-val
Men								
ZSDS ≤ 39	209	25.4	0	12.5	24.0	38.2	100	
ZSDS ≥ 40	53	21.9	0	10.0	18.4	30.5	60.0	NS
Women								
ZSDS ≤ 39	197	31.8	0	20.0	33.6	43.3	74.2	
ZSDS ≥ 40	60	28.7	0	17.6	25.9	38.1	100	0.063

Table 5c. Periodontal pockets ≥ 4mm[a] in relation to depressive symptoms among dentate subjects.

Gender	n	X	min	Q_1	med	Q_3	max	p-val
Men								
ZSDS ≤ 39	209	14.3	0	0.9	7.5	18.5	100	
ZSDS ≥ 40	53	15.0	0	0	9.5	22.1	70.0	NS
Women								
ZSDS ≤ 39	197	8.7	0	0	3.4	12.5	76.0	
ZSDS ≥40	60	8.4	0	0	1.8	9.4	52.3	NS

Table 5d. Number of teeth in relation to depressive symptoms among dentate subjects.

Gender	n	X	min	Q_1	med	Q_3	max	p-val
Men								
ZSDS ≤ 39	209	17.0	2	9	18	24	32	
ZSDS ≥ 40	53	16.5	2	9	17	24	29	NS
Women								
ZSDS ≤ 39	197	16.9	1	8	19	24	29	
ZSDS ≥ 40	60	15.6	2	7	15.5	24.5	28	NS

Tables 5a-5d:

[a] as percentages of risk surfaces; ZSDS = Zung Self-Rating Depression Scale; X = mean; min = minimum; Q_1 = 25% quartile; med = median; Q_3 = 75% quartile; max = maximum; NS = not significant.

5.4 Association of depressive symptoms with the sensation of dry mouth

The prevalence of subjective sensations of dry mouth (often or sometimes) was 25.8% among men and 33.3% among women (Table 6). Altogether 8.8% of men and 12.7% of women often had a sensation of dry mouth.

Table 6 shows the bivariate associations between the subjective sensations of dry mouth and the studied variables. Subjects with a high rate of depressive symptoms (ZSDS ≥ 40) had a sensation of oral dryness more often than subjects with ZSDS≤39 ($p < 0.001$, unadjusted OR = 2.2, 95% CI 1.6–3.1). There was no association between depressive symptoms and unstimulated salivary flow rate or stimulated salivary flow rate.

Table 6. Prevalence of subjective sensations of dry mouth in relation to study variables in the total population.

Variable	n	%	p-value
Gender			
men	341	25.8	
women	433	33.3	0.025
Smoking habits			
regular smoker	163	38.6	
occasional, ex-, or nonsmoker	611	27.7	0.007
Unstimulated salivary flow rate			
≤ 0.1 ml/min	123	39.8	
> 0.1 ml/min	649	27.9	0.008
Stimulated salivary flow rate			
≤ 0.7 ml/min	312	31.7	
> 0.7 ml/min	462	28.8	NS
Diseases known to be xerogenic			
yes	191	39.8	
no	583	26.8	0.001
Xerogenic medication			
yes	204	43.1	
no	570	25.3	0.001
Self-perceived physical condition			
good	167	22.7	
moderate	432	26.6	< 0.001
poor	171	46.2	
Self-perceived health			
good	203	19.2	
moderate	428	29.9	< 0.001
poor	134	45.5	
Depressive symptoms			
ZSDS ≤ 39	582	25.8	
ZSDS ≥ 40	180	43.3	< 0.001

To confirm the relation between the sensation of oral dryness and depressive symptoms, a logistic regression model was made with subjective sensation of oral dryness as an outcome variable. Depressive symptoms were added to the model after the addition of gender, smoking, unstimulated salivary flow rate, stimulated salivary flow rate, diseases which may associate with dry mouth (Table 7), xerogenic medication (Table 8), and self-perceived physical condition and health. After controlling for the effects of the other variables, depressive symptoms still turned out to be significantly associated with the sensation of dry mouth (OR = 1.54, 95% CI 1.04–2.26) (Table 9). When self-perceived physical condition and health were excluded from the model, the significance of depressive symptoms increased (OR = 1.79, 95% CI 1.24–2.59) (data not shown).

Table 7. Systemic diseases which may reduce salivary flow rate [a] and their occurrence in the study population (n = 774).

Disease	n
Sjögren's syndrome	1
Rheumatoid diseases	19
Sarcoidosis	3
Hypertension	144
Hyperlipidemia	26
Diabetes mellitus	34
Anxiety disorder	2

[a] Only the diseases occurring in this study population are included.

Table 8. Number of subjects using xerogenic medication[a] (included in the respective drug group) in the study population.

Drug group		n
1.	Drugs affecting the alimentary tract	21
2.	Serum lipid-reducing agents	6
3.	Cardiovascular and antihypertensive agents	12
4.	Diuretics	76
5.	Drugs for disorders of the musculo-skeletal system	10
6.	Analgesics and antipyretics	9
7.	Antiepileptics and anti-parkinson drugs	6
8.	Antipsychotics	21
9.	Anxiolytics	46
10.	Hypnotics and sedatives	20
11.	Antidepressants	6
12.	Antiasthmatics	8
13.	Antihistamines for systemic use	3
14.	Combination of a psychopharmacological drug and a drug from group 1, 3, 5, 6, 11, or 13	26

[a] Determined by means of the list published by the Finnish Association of Pharmaceutical Chemists (Kostiainen 1992).

Table 9. Improvement of the goodness of fit of the logistic regression model related to subjective sensation of dry mouth by adding variables or variable groups in a stepwise manner in the total population (n = 749).

Variables in model[a]	Difference of deviance	Degree of freedom	p-value
only constant (0)			
0 + 1	4.578	1	0.032
0 + 1 + 2	9.296	1	0.002
0 + 1 + 2 + 3	6.542	1	0.010
0 + 1 + 2 + 3 + 4	0.068	1	0.794
0 + 1 + 2 + 3 + 4 + 5	9.638	1	0.002
0 + 1 + 2 + 3 + 4 + 5 + 6	10.088	1	0.001
0 + 1 + 2 + 3 + 4 + 5 + 6 + 7	20.536	4	< 0.001
0 + 1 + 2 + 3 + 4 + 5 + 6 + 7 + 8[b]	4.676	1	0.031

[a] 1 = gender; 2 = smoking; 3 = unstimulated salivary flow rate; 4 = stimulated salivary flow rate; 5 = diseases which may associate with dry mouth; 6 = xerogenic medication; 7 = self-perceived physical condition and health; 8 = depressive symptoms.

[b] Adjusted OR = 1.54 (95% CI 1.04–2.26) for depressive symptoms.

Depressive symptoms were associated with the sensation of dry mouth in subjects with normal or high unstimulated salivary flow rates. The group with low unstimulated flow rates showed a slight, though not statistically significant, association between depressive symptoms and the sensation of dry mouth (Table 10).

Table 10. Prevalence of subjective sensations of dry mouth in relation to unstimulated salivary flow rate and depressive symptoms.

Depressive symptoms	Subjects with low[a] unstimulated salivary flow rate			Subjects with normal or high[b] unstimulated salivary flow rate		
	n	%	p-value	n	%	p-value
ZSDS ≤ 39	93	35.5		489	23.9	
ZSDS ≥ 40	29	55.2	0.059	149	40.3	< 0.001

[a] ≤ 0.1 ml/min

[b] > 0.1 ml/min

5.5 Depressive symptoms and the growth of salivary lactobacilli, mutans streptococci and yeasts

The prevalence of high salivary lactobacilli counts (≥ 100 000 CFU/ml) was 31% in dentate men and 22% in dentate women. Thirty-seven percent of dentate subjects with a high rate of depressive symptoms (ZSDS ≥ 40) and 23% of those with lower ZSDS scores had high counts of lactobacilli (p = 0.003) (Table 11).

Table 11 shows the bivariate associations between salivary lactobacilli counts and the study variables in a dentate population. The use of at least three daily medications and the use of a combination of psychopharmacological and other drugs were the only variables associated with both abundant lactobacilli growth and a high rate of depressive symptoms (Paper III, Table 1).

Table 11. Prevalences of high salivary lactobacilli counts in relation to the study variables in the dentate population (n = size of the denominator group).

		Lactobacilli ≥ 10^5 CFU/ml	
Variable	n	%	p-value
Gender			
female	259	22	
male	265	31	0.020
Unstimulated salivary flow rate			
≤ 0.1ml/min	77	35	
> 0.1ml/min	447	25	0.054
pH of unstimulated whole saliva			
5–7	131	40	
8–9	393	22	0.001
Stimulated salivary flow rate			
≤ 0.7ml/min	201	28	
> 0.7ml/min	323	25	NS
Buffering capacity final pH of stimulated saliva			
≤ 5.5	136	36	
≥ 6.0	386	23	0.003
Subjective sensation of dry mouth			
never/rarely	375	25	
occasionally	89	28	NS
often	55	29	
Combination of psychopharmacological and other drugs			
yes	16	50	
no	508	25	0.027
Number of concomitant drugs			
0–2 drugs	390	24	
≥ 3 drugs	134	34	0.023

Table 11. Continued.

Xerogenic medication			
yes	121	30	
no	403	25	NS
Depressive symptoms			
ZSDS ≤ 39	403	23	
ZSDS ≥ 40	113	37	0.003
Diseases known to be xerogenic			
yes	124	25	
no	400	26	NS
Oral hygiene			
good	135	13	
moderate	251	26	0.001
poor	136	40	
Smoking			
no	428	20	
regularly or occasionally	96	54	0.001
Use of sugar in coffee or tea			
yes	224	30	
no	298	23	0.052
Consumption of sweets, snacks, or soft drinks			
never/occasionally	312	24	
1–2 times a week or daily	209	29	NS
Consumption of vegetables, fruit, and root crops			
daily	366	23	
1–2 times a week or rarely	155	32	0.026
Removable dentures			
yes	274	35	
no	250	16	0.001
Decayed surfaces			
0–2	412	22	
3 or more	112	42	0.001

ZSDS = Zung Self-Rating Depression Scale

NS = not significant

The logistic regression model with salivary lactobacilli count as an outcome variable further confirmed the association between depressive symptoms and abundant growth of salivary lactobacilli in dentate subjects (Table 12). After controlling for the confounding variables, the odds ratio (with 95% confidence interval) for depressive symptoms was 2.0 (1.2–3.3), while the unadjusted odds ratio (and 95% CI) for depressive symptoms was 2.0 (1.3–3.1) (Paper III, Table 3).

Table 12. Improvement of the goodness of fit of the logistic regression model related to a high count of salivary lactobacilli ($\geq 10^5$ CFU/ml) in dentate subjects by adding variables or variable groups in a stepwise manner (n = 508).

Variables in model[a]	Difference of deviance	Degree of freedom	p-value
Only constant (0)			
0 + 1	4.294	1	0.038
0 + 1 + 2	19.514	3	< 0.001
0 + 1 + 2 + 3	19.22	1	< 0.001
0 + 1 + 2 + 3 + 4	9.252	1	0.002
0 + 1 + 2 + 3 + 4 + 5	10.488	2	0.005
0 + 1 + 2 + 3 + 4 + 5 + 6	20.734	1	< 0.001
0 + 1 + 2 + 3 + 4 + 5 + 6 + 7	0.198	2	0.905
0 + 1 + 2 + 3 + 4 + 5 + 6 + 7 + 8	2.686	1	0.101
0 + 1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9	3.422	1	0.064
0 + 1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9 + 10[b]	6.508	1	0.011

[a] 1 = gender; 2 = unstimulated salivary flow rate, pH of unstimulated whole saliva, buffering capacity final pH of stimulated saliva; 3 = removable dentures; 4 = decayed surfaces; 5 = oral hygiene; 6 = smoking; 7 = use of sugar in coffee or tea, consumption of vegetables, fruit, and root crops; 8 = combination of psychopharmacological and other drugs; 9 = number of drugs; 10 = depressive symptoms.

[b] Adjusted OR = 2.0 (95% CI 1.2–3.3) for depressive symptoms

The prevalences of high counts of salivary mutans streptococci ($\geq 10^6$ CFU/ml) and salivary yeast growth for dentate men were 24% and 60%, respectively, the corresponding figures for dentate women being 28% and 61%. In bivariate analysis, a high salivary mutans streptococci count was associated with a high rate of depressive symptoms among dentate subjects (unadjusted OR = 1.61, 95% CI 1.02–2.53) (Table 13). After controlling for gender, the flow rate and buffering capacity of stimulated saliva, dental caries, tooth brushing frequency, consumption of sweets, snacks, or soft drinks, and smoking in a logistic regression model in the dentate population with salivary mutans streptococci count as an outcome variable, the odds ratio for depressive symptoms was 1.6 (95% CI 0.998– 2.57). (Additional data not included in the original papers.)

Yeast growth was significantly more common among dentate women with high rates of depressive symptoms than among dentate women with fewer depressive symptoms (unadjusted OR = 1.98, 95% CI 1.04–3.75) (Table 13). The logistic regression model for dentate women with yeast growth as an outcome variable and the following confounding variables: flow rate and pH of unstimulated saliva, flow rate and buffering capacity of stimulated saliva, removable dentures, dental caries, smoking, use of sugar in coffee or

tea, consumption of sweets, snacks, or soft drinks, consumption of vegetables, fruits, and root crops, and number of daily medications, produced an adjusted OR of 2.06 (95% CI 0.98–4.32) for depressive symptoms. (Additional data not included in the original papers.)

Table 13. Prevalences of high salivary mutans streptococci counts ($\geq 10^6$ CFU/ml) and yeast growth in relation to depressive symptoms and gender among the dentate population.

	Gender	ZSDS ≤ 39		ZSDS ≥ 40		p-value
		n	%	n	%	
Mutans streptococci	male	209	22.5	53	30.2	0.24
	female	196	25.5	60	36.7	0.09
	all[a]	405	24.0	113	33.6	0.04
Yeast growth	male	209	61.2	53	56.6	0.54
	female[b]	196	58.2	60	73.3	0.03
	all	405	59.8	113	65.5	0.27

n = number of the denominator group

[a] OR = 1.61, 95% CI 1.02–2.53

[b] OR = 1.98, 95% CI 1.04–3.75

Edentulous subjects showed no statistically significant associations between depressive symptoms and the numbers of salivary lactobacilli or mutans streptococci or the growth of salivary yeasts.

5.6 Association of depressive symptoms with subjective symptoms and clinical findings of TMD

The prevalence of subjective symptoms of temporomandibular disorders was 6.7% among dentate men and 14.5% among dentate women. Among edentulous men and women, the corresponding prevalences were 10.7% and 17.4%. Moderate or severe clinical findings of TMD (categories DiII and DiIII of Helkimo's Clinical Dysfunction Index) were present in 4.8% of dentate men and 2.7% of dentate women, and the corresponding figures for edentulous men and women were 2.7% and 9.3%. (Paper I.)

Subjective symptoms of TMD were more common among subjects with high rates of depressive symptoms (ZSDS ≥ 44) than among those with fewer depressive symptoms (Table 14). The association was revealed among the total population in stepwise logistic regression analysis controlling for the variables shown in Table 15 and the three continuous variables (extent of symptoms during the past 2 weeks (the questionnaire of symptoms), number of tooth pairs in occlusion, and life events during the preceding 5 years). The other selected variables in the final fitted model were the occurrence of symptoms in the shoulders or upper arms during the past 12 months and the extent of symptoms during the past 2 weeks (Table 16).

Table 14. Prevalence of subjective symptoms of TMD in relation to depressive symptoms, dental status, and gender.

Dental status	Gender	ZSDS ≤ 43		ZSDS ≥ 44		OR (95% CI)	p-value
		n	%	n	%		
Dentate	male	244	5.7	22	18.2	3.6 (1.1, 12.3)	0.05
	female	225	12.4	34	26.5	2.5 (1.1, 6.0)	0.03
	all	469	9.0	56	23.2	3.1 (1.5, 6.2)	0.001
Edentulous	male	67	9.0	5	20.0	2.5 (0.2, 26.6)	NS
	female	138	13.0	33	33.3	3.3 (1.4, 8.0)	0.005
	all	205	11.7	38	31.6	3.5 (1.6, 7.8)	0.002
Total		674	9.8	94	26.6	3.3 (2.0, 5.6)	0.001

n = number of the denominator group

NS = not significant

Table 15. Distribution of subjective symptoms of TMD in relation to background variables in the total population (n =number of the denominator group).

Variable	n	%	p-value
Gender			
male	345	7.5	
female	435	15.6	0.001
Depressive symptoms			
ZSDS ≤ 43	674	9.8	
ZSDS ≥ 44	94	26.6	0.001
Marital status			
married/cohabiting	577	11.6	
unmarried/divorced/widowed	202	13.4	0.5
Level of work-related physical stress			
very low, low or fairly low	391	9.2	
high or very high	383	14.9	0.02
Level of work-related mental stress			
very low, low or fairly low	404	11.1	
high or very high	369	13.0	0.4
Satisfaction with work			
very satisfied, satisfied or moderately satisfied	762	11.9	
dissatisfied or most dissatisfied	16	18.8	0.4
Self-perceived health			
very good or fairly good	204	8.8	
moderate, fairly poor or very poor	567	13.2	0.1
Satisfaction with personal life			
very satisfied or satisfied	503	11.3	
moderately satisfied, dissatisfied, most dissatisfied	271	12.9	0.5
Symptoms relating to neck, cervical spine, or back of the head during the past 12 months			
not more than occasionally	446	7.9	
often or almost continuously	333	17.7	0.001
Symptoms in the shoulders or upper arms			
not more than occasionally	381	6.6	
often or almost continuously	398	17.3	0.001
Physical activity			
high	574	11.9	
low	192	12.5	0.8
Alcohol consumption			
0/two weeks	413	13.8	
1–6 drinks/two weeks	226	12.8	
> 6 drinks/two weeks	141	5.7	0.03

Table 16. Relationship between subjective symptoms of TMD and the most essential background variables in the final model given by logistic regression analysis in the total population (n = 720).

Variable	Adjusted Odds Ratio	95% CI	p-value
Depressive symptoms[a]	2.40	(1.33, 4.34)	0.004
Symptoms in the shoulders or upper arms during the past 12 months[b]	2.06	(1.17, 3.64)	0.013
Extent of symptoms during the past 2 weeks (the questionnaire of symptoms)	1.03	(1.00, 1.07)	0.04

[a] Total raw sum score on ZSDS ≤ 43 as reference

[b] Not more than occasionally as reference

Moderate or severe clinical findings of TMD (DiII + DiIII) were significantly more common in dentate subjects with high rates of depressive symptoms than in dentate subjects with ZSDS≤43 (Table 17). This association was confirmed after controlling the variables shown in Table 18 and the three continuous variables (extent of symptoms, number of tooth pairs in occlusion, and life events) by stepwise logistic regression analysis with the occurrence of clinical findings of TMD (Di) as an outcome variable (Table 19). The other variables in the final fitted model were the occurrence of symptoms in the neck, cervical spine, or back of the head during the past 12 months, male sex, and a high or very high level of work-related physical stress (Table 19).

Table 17. Prevalence of moderate or severe clinical findings of TMD ($D_iII + D_iIII$) in relation to depressive symptoms, dental status, and gender.

Dental status	Gender	ZSDS ≤ 43		ZSDS ≥ 44		OR (95% CI)	p-value
		n	%	n	%		
Dentate	male	244	4.1	22	13.6	3.7 (0.9, 14.6)	0.082
	female	225	1.8	34	8.8	5.3 (1.1, 25.0)	0.05
	all	469	3.0	56	10.7	3.9 (1.4, 10.6)	0.004
Edentulous	male	67	1.5	5	0	4.0 (0.2, 111.1)	0.8
	female	138	10.1	33	6.1	0.6 (0.1, 2.7)	0.4
	all	205	7.3	38	5.3	0.7 (0.2, 3.2)	0.6
total		674	4.3	94	8.5	2.1 (0.9, 4.7)	0.074

n = number of the denominator group

Table 18. Distribution of moderate and severe clinical findings ($D_iII + D_iIII$) of TMD in relation to background variables in the dentate population (n = number of the denominator group).

Variable	n	%	p-value
Gender			
male	270	4.8	
female	263	2.7	0.2
Depressive symptoms			
ZSDS ≤ 43	469	3.0	
ZSDS ≥ 44	56	10.7	0.004
Marital status			
married/cohabiting	412	3.6	
unmarried/divorced/widowed	120	4.2	0.8
Level of work-related physical stress			
very low, low or fairly low	297	2.0	
high or very high	233	6.0	0.02
Level of work-related mental stress			
very low, low or fairly low	275	3.6	
high or very high	253	4.0	0.8
Satisfaction with work			
very satisfied, satisfied or moderately satisfied	522	3.6	
dissatisfied or most dissatisfied	10	10.0	0.3
Self-perceived health			
very good or fairly good	156	3.2	
moderate, fairly poor or very poor	371	4.0	0.6
Satisfaction with personal life			
very satisfied or satisfied	348	2.9	
moderately satisfied, dissatisfied, most dissatisfied	182	5.5	0.1
Symptoms relating to neck, cervical spine, or back of the head during the past 12 months			
not more than occasionally	333	1.2	
often or almost continuously	200	8.0	0.001
Symptoms in the shoulders or upper arms			
not more than occasionally	278	1.1	
often or almost continuously	255	6.7	0.001
Physical activity			
high	384	3.7	
low	137	3.7	1.0
Alcohol consumption			
0/two weeks	259	3.5	
1–6 drinks/two weeks	167	3.0	0.5
> 6 drinks/two weeks	107	5.6	

Table 19. Relationship between moderate or severe clinical findings of TMD (D_i II + D_i III) and the most essential background variables in the final model given by logistic regression analysis in the dentate population (n = 491).

Variable	Adjusted Odds Ratio	95% CI	p-value
Occurrence of symptoms relating to the neck, cervical spine, or back of the head during the past 12 months[a]	5.09	(1.56, 16.60)	0.006
Depressive symptoms[b]	4.25	(1.38, 13.10)	0.01
Sex[c]	4.19	(1.38, 12.80)	0.01
Level of work-related physical stress[d]	2.91	(0.96, 8.84)	0.056

[a] Not more than occasionally, [b] sum score on ZSDS ≤ 43, [c] female sex, and [d] low as reference.

6 Discussion

6.1 Methodological considerations

6.1.1 Subjects

The study population consisted of the 55-year-old residents of Oulu. The chosen age group provided certain advantages in view of the nature of the phenomena examined. As reviewed by Lehtinen & Joukamaa (1994), the prevalence of depression is relatively high in this age group. In this study, the number of subjects with high rates of depressive symptoms was 182 with the lower cutoff point and 94 with the higher cutoff. In subjects of this age, the prevalence of dental diseases is also adequate for studying the association between these diseases and depressive symptoms. As to the confounding factors, however, systemic diseases at this age are less frequent than in older subjects. In a study of this type, consequently, extension of the age range would hardly have thrown any further light on this topic.

As already pointed out, when studying such phenomena as oral health and depressive symptoms, controlling for the multiple confounding factors is essential for producing reliable results. A population-based study design is therefore preferable to a study of hospitalized inpatients or institutionalized subjects, who would not only have more severe depressive symptoms but presumably also multiple problems and medications difficult to control. Furthermore, the associations found in general populations may be more applicable and the results more comparable than those obtained in selected samples.

The participation rate was 77%, which can be considered high. A shortened version of the postal questionnaire was sent to the nonparticipants, and 53% of them returned it. There were slightly more blue collar workers among the nonparticipants compared with the participants, but no major differences in employment status were found between these groups. It is thus unlikely that the prevalences of high rates of depressive symptoms would have been under- or overestimated. Secondly, observation of the prevalences was not an issue, which further reduced the risk of bias.

6.1.2 Measurement of depressive symptoms

A self-rated scale has certain benefits over interviewer-rated scales and clinical interviews in a large population study of this kind, where the examinations and data collection took about three hours per subject. A self-rated scale takes less time and does not require trained personnel. The administration and scoring process is also more standardized for self-rated scales (Biggs *et al.* 1978).

The major advantage of interviewer-rated scales and clinical interviews is the experience of the interviewer, which allows the symptoms detected in an individual subject to be evaluated relative to those observed and studied previously (Biggs *et al.* 1978). In fact, Faravelli and coworkers (1986) compared the distributions of three doctor-rated scales and three self-rated scales in a series of 100 depressed patients and noted that doctor-rated scales tend to be asymmetric toward the left, while self-rated scales tend to be asymmetric toward the right. This may result from the tendency of patients to judge their own condition as severe, while the doctor's evaluation is based on a comparison of different patients with symptoms of varying degrees of severity (Faravelli *et al.* 1986). However, the use of clinical diagnosis would have excluded the milder forms of depression, which may quite well be significant from the subjective point of view.

The Zung Self-Rating Depression Scale has primarily been designed for screening depressive symptoms among middle-aged populations, and it is widely used in epidemiological studies. Its psychometric properties have been thoroughly tested and found to be acceptable.

Zung demonstrated that depressive symptomatology as measured by the ZSDS is age-related, and that the baseline values on the ZSDS for normal younger (≤ 19 years) and older subjects (≥ 65 years) are higher than those in the middle age groups, where an ZSDS index of 50 (corresponding to a raw sum score cutoff of 39/40 (Zung 1965)) was recommended as the morbidity cutoff score (Zung 1973). This cutoff was also used in this study in the Papers II, III, and IV. However, several studies have suggested that pain patients' reports of psychological distress primarily load on somatic signs, reflecting pain-related somatic effects rather than affective disturbance (Buckelew *et al.* 1986, Wesley *et al.* 1991, Williams & Richardson 1993, Wilson *et al.* 1994, Chibnall & Tait 1994, Estlander *et al.* 1995). Considering the substantial number of somatic symptoms in ZSDS and to avoid an overestimation of depressive symptoms, a slightly higher cutoff (a raw sum score cutoff of 43/44) was used when the relationship between depressive symptoms and symptoms and clinical findings of TMD was studied. According to Fountoulakis *et al.* (2001), the sensitivity and specificity values of the cutoff 43/44 were high (92.5% and 89.17%, respectively), as were the corresponding values for the cutoff 39/40 (95% and 83.3%, respectively) (Fountoulakis 2002, personal communication) when tested against a clinical diagnosis of depression. However, because of certain inclusion criteria, their subjects did not represent the general population, and their results are thus not directly applicable to our study.

Combining the results of cross-cultural studies using ZSDS, Zung showed that patients with global ratings of mild to moderate depressions had ZSDS indices between 50 to 59 (raw sum scores 40 – 47), while patients with moderate to severe depressions had indices of 60 to 69 (raw sum scores 48 − 55) and patients globally rated as severely depressed

had indices of 70 and over (raw sum scores 56 and over) (Zung 1973). In this study, however, a high score of ZSDS was not regarded as a clinical diagnosis of depression but rather as a level of depressive symptoms of potential clinical significance.

6.1.3 Study variables

The heterogeneous nature of depression with psychological, biological, behavioral, and social aspects made us hypothesize that depression may have multidimensional effects on the oral environment. As it was shown in the review of the literature, there are various possible mechanisms that may link depression with oral health. Consequently, an extensive approach was chosen, including the risk factors of dental diseases and related phenomena, and the selected study variables thus represent a comprehensive view of oral and dental health.

In order to get an adequate picture of masticatory function in relation to depressive symptoms, both subjective and objective symptoms and signs of temporomandibular disorders (TMD) were studied using the criteria recommended by Helkimo (1974). Helkimo's Clinical Dysfunction index (Di), which was used in clinical examination of TMD, was developed mainly for epidemiological purposes in the diagnosis of TMD (Helkimo 1974) and is widely used (Carlsson & LeResche 1995).

Definitions of the cutoffs between low and normal unstimulated and stimulated salivary flow rates were based on earlier research (Sreebny & Valdini 1988, Fure & Zickert 1990, Navazesh *et al.* 1992, Närhi *et al.* 1993). Salivary flow rates were measured between 8.00 *a.m.* and 14.30 *p.m.*, and the diurnal variation might hence have caused some interindividual differences in secretion rates (Dawes 1974, Rantonen & Meurman 1998). However, it is very unlikely that this variation could have influenced the relationship between depressive symptoms and flow rate.

The subjective sensation of oral dryness was evaluated with a single question on dry mouth, which has been shown to correlate strongly with the multi-item Xerostomia Inventory Scale score (Thomson *et al.* 1999). Salivary lactobacilli and mutans streptococci counts as well as the occurrence of yeasts (growth or no growth) were measured with the widely used Dentocult-LB®, Dentocult-SM®, and Oricult-N® methods, respectively. The limits for abundant growth of lactobacilli ($\geq 10^5$) and mutans streptococci ($\geq 10^6$) were those generally used in population studies (Parvinen 1984a, Klock *et al.* 1990, Fure 1998).

Clinical examinations followed the generally accepted practice, and the intra- and interexaminer agreements concerning periodontal pocketing and dental caries were good, as was the interexaminer correlation concerning the clinical examination of TMD. Due to the nature of the TMD findings, the practical arrangements for measurements of intraexaminer variation in Di would have been difficult and were therefore not made.

6.1.4 Study analysis

Logistic regression analysis was used to control the confounding factors and thus to evaluate the independent associations between the explanatory variables and the outcome. The selection of explanatory variables was guided by the results of bivariate analysis and prior knowledge. Although depressive symptoms were also used as a continuous variable in bivariate analyses (Paper IV), they were only processed as dichotomized in multivariate models, to facilitate interpretation of the associations. There is an axiom in the logistic model concerning the linear connection between the continuous variable and the logit function, which is not always the case. Consequently, the decision to treat the covariates as continuous variables may, in some cases, lead to biased interpretations. (Uhari & Nieminen 2001.) On the other hand, classification of depressive symptoms into three categories, which would have enabled evaluation of the dose-response effect, was not rational because of the insufficient number of subjects.

In Paper I, a stepwise logistic regression analysis with forward and backward selection of variables was used to reduce the discrepancies between the data and the model and to find a model with relatively few parameters. However, the ordering of the variables from stepwise regression is an artifact of the algorithm used in the regression program and need not reflect relationships of substantive interest (Weisberg 1980). To avoid this problem, we evaluated the estimated logistic regression models using the change in the goodness of fit statistic (the difference of deviance test) (Papers II, III, and IV). The method used encourages one to think in terms of sets of variables that together represent factors associated with the response. Secondly, addition of the variables to the models in different orders made it possible to evaluate the influence of each covariate on the association between the studied variable and the outcome (Paper III).

6.2 Results

6.2.1 Relationship of depressive symptoms with dental health behavior

The results of this study only partly supported the hypothesis that subjects with high rates of depressive symptoms would have less favorable dental health behavior than subjects with fewer depressive symptoms. A few minor associations, somewhat different in men and women, were found, however. Depressed dentate women consumed sweets, snacks, or soft drinks more frequently than non-depressed dentate women. Dentate men showed a parallel tendency without statistical significance (Paper IV, Table 5). This finding is in accordance with the reports of increased carbohydrate consumption by depressed persons (Wurtman *et al.* 1989, Christensen & Somers 1996).

The time elapsed since the last dental visit was longer and the preservation of natural teeth less important among depressed dentate women than among non-depressed dentate women. Dentate men showed opposite tendencies in this respect (Paper IV, Table 5). However, oral hygiene was slightly poorer among depressed dentate men compared to

non-depressed dentate men ($p = 0.065$). Kurer and coworkers (1995) also found more plaque in subjects with more depressive symptoms, while no such association was found by Monteiro da Silva *et al.* (1998). An analysis of the association between lactobacilli growth and depressive symptoms with logistic regression models showed that a high rate of depressive symptoms increased the liability to abundant growth of salivary lactobacilli both independently and partly through other factors, such as poor oral hygiene (Paper IV).

There were no associations between depressive symptoms and the frequency of dental visits, tooth brushing frequency, use of extra cleaning methods, or use of sugar in coffee or tea among either men or women. As it was pointed out in the review of the literature, depression and depressive symptoms have been shown to associate with unfavourable health behaviors, such as smoking, drinking, and lack of regular physical exercise. In the light of these results, one might have anticipated a stronger negative association between depressive symptoms and dental health behavior. It is possible that some of the dental health habits, such as tooth brushing, represent such fixed activities that they tend to remain unchanged even in the presence of mild depressive disorder. As indicated in the studies concerning the dental health behavior of psychiatric inpatients, however, it is likely that when the severity of depression increases its effects on dental health behavior also become emphasized. There are no previous studies on the association between depressive symptoms and various aspects of oral health behavior.

6.2.2 Depressive symptoms in relation to periodontal disease and dental caries

The results of this study did not support our hypothesis that there would be an association between depressive symptoms and periodontal disease as measured with periodontal pocketing. The earlier studies concerning depression or depressive symptoms and periodontitis are few, with small sample sizes in most cases. A variety of methods have been used in the measurement of depression in these studies, some of which deal with depressive personality patterns or the simple question of depressive emotions (Brown *et al.* 1994). However, a large population study by Genco *et al.* (1999) as well as the follow-up study of Elter and coworkers (2002), which used patient records to determine diagnosed depression, suggest an association between depressive symptoms and periodontal disease and between clinical depression and periodontal treatment outcome, respectively. Research on the relationship between periodontal disease and depression is complicated because of the multifactorial etiologies and the variety of factors associating with both depressive symptomatology and periodontal disease. Furthermore, the possible fluctuation of depressive symptom levels over time together with the slow progression of periodontal disease may set additional requirements for the study design and methods. In fact, the clinical attachment loss used as a measure of periodontal disease by Genco *et al.* (1999) reflects better long-term periodontal tissue destruction than periodontal pocketing, which was used in this study, which may explain the controversy in the results. It is also possible that a chronic pattern of depression is required to cause a measurable impact on

periodontal disease. A cross-sectional study design cannot give information of the chronicity of depressive symptoms, and longitudinal studies are thus still needed to further clarify the relationship between these disease entities.

Although the relationship between depressive symptoms and periodontal disease was not empirically supported in this study, the above reasons and the data available concerning biological alterations in depression and comorbidity of depression and physical illnesses suggest that such a link is, nevertheless, possible. There are many immunological changes in depression that could increase the risk of periodontal diseases in depressed subjects. For example, the increased release of proinflammatory cytokines from activated macrophages, excessive synthesis of PGE_2, and suppression of natural killer cell activity, T-lymphocytes, and neutrophils are all factors that can increase periodontal disease susceptibility (for a review, see Leonard 2001). Secondly, the hyperactivity of the hypothalamus-pituitary-adrenal axis consistently found in major depression (reviewed by Sheline 2000) has recently been suggested to associate with experimental periodontal disease susceptibility in rats (Breivik *et al.* 2000a, 2000b, 2001). The suggested mediating mechanism is the shift of T-helper 1 synthesis toward a T-helper 2 response as a result of elevated plasma levels of corticosterone (Breivik *et al.* 2000c). Activation of the HPA axis may also take place in chronic stress in connection with inadequate coping capacity (Olff 1999). There are various studies suggesting that psychosocial stress may contribute to an increased susceptibility to periodontal disease (Green *et al.* 1986, Marcenes & Sheiham 1992, Genco *et al.* 1998, 1999, LeResche & Dworkin 2002) and a few studies indicating that coping behaviors may have an influence on this stress-associated risk (Genco *et al.* 1999, Hugoson *et al.* 2002, Wimmer *et al.* 2002).

No strict associations were found between untreated dental caries and depressive symptoms in this study. The tendency of women with high rates of depressive symptoms to have a lower percentage of filled tooth surfaces compared to women with fewer depressive symptoms (Paper IV, Table 4) might reflect avoidance of dental services. This is supported by the finding that depressed women reported a longer time since their last visit to a dentist (Paper IV, Table 5). However, abundant growth of salivary lactobacilli was significantly more common in subjects with high rates of depressive symptoms, which was confirmed in multivariate analysis. In bivariate analysis, abundant growth of salivary mutans streptococci also associated with depressive symptoms in the dentate population. However, after standardization of the confounding variables, the association turned out to be of uncertain significance (OR = 1.6, 95% CI = 0.998–2.57). Mutans streptococci and lactobacilli are generally regarded as the most cariogenic bacteria (reviewed by van Houte 1994). Their associations with depressive symptoms will be discussed later in this chapter. Furthermore, a bivariate association was found between depressive symptoms and the consumption of sweets, snacks, or soft drinks, xerogenic medication, and diseases known to be xerogenic, all of which are factors that may increase the risk of dental decay.

Increased caries activity in the context of antidepressant use has been shown in many studies (Bassuk & Schoonover 1978, Rundegren *et al.* 1985, von Knorring & Wahlin 1986, Thomson *et al.* 1995, Peeters *et al.* 1998), but earlier findings of a possible independent association between depression or depressive symptoms and dental caries are lacking. There are studies, however, which suggest that severe stress is a predisposing

factor to the development of acute dental caries (Sutton 1965, Honkala *et al.* 1992, Borysenko *et al.* 1980).

Although some etiological factors predisposing to dental caries seem to be more prevalent in depressed people, depressive symptoms, such as measured in this cross-sectional study, do not seem to associate with the prevalence of dental caries. However, similarly to periodontal disease, dental caries has multifactorial etiology and takes a relatively long time to develop. Therefore, assessment of caries increment in longitudinal studies might be a preferable tool for studying the relationship between these diseases.

6.2.3 Depressive symptoms in relation to edentulousness

Edentulousness is a complex phenomenon, as it reflects not only the accumulation and susceptibility to dental diseases but also treatment choices. Naturally, these choices influence the progression of dental caries and periodontal disease, but are manifested more clearly in the number of lost teeth and edentulousness. Among women, dental diseases are not necessarily the most important reason for edentulousness. It is known that women formerly lost their teeth earlier than men (for a review, see Suominen-Taipale *et al.* 1999), which was seen in this study group, too. However, men generally have higher prevalences of dental caries and periodontal disease, as was also the case in this study. In addition to socioeconomic factors that may naturally have influenced the treatment choices, it has been suggested that women formerly chose edentulousness and full dentures for esthetic reasons (Suominen-Taipale *et al.* 1999). Because of the diverse and complicated background to edentulousness among especially women, the association between depressive symptoms and edentulousness is difficult to show. On the other hand, among those who have chosen full dentures for esthetic reasons, the psychological impact of edentulousness may have been lesser.

A statistically significant difference was seen between smokers and those who had never smoked in the occurrence of depressive symptoms related to dental status. Furthermore, in logistic regression analysis, the high rate of depressive symptoms among nonsmoker men was explained by edentulousness with an odds ratio of 6.4. Smoking can be seen as one of the most important confounding factors regarding dental diseases and edentulousness. According to previous studies, smokers do have poorer dental health than nonsmokers (Drake *et al.* 1997, Norderyd *et al.* 1999) and are at a greater risk of tooth loss (Slade *et al.* 1997, Worthington 1999). They brush and floss their teeth less frequently than nonsmokers (Andrews *et al.* 1998) and also make dental visits less frequently (Attwood *et al.* 1993). Assuming there is a difference in valuation and attitude towards oral health among smokers and nonsmokers, one might think that oral and dental health is less important for smokers than nonsmokers. Thus, the emotional impact of edentulousness and its effect on psychological well-being might also be of minor importance for them, which might explain the different relationship between depressive symptoms and edentulousness in these groups.

6.2.4 Depressive symptoms and factors related to saliva

6.2.4.1 Salivary flow rate and sensation of dry mouth

In our study, no association was found between depressive symptoms and unstimulated or stimulated saliva flow rates. This was not in accordance with the results of several earlier studies, which have reported decreased salivary flow rates among depressed patients (Peck 1959, Davies & Gurland 1961, Gottlieb & Paulson 1961, Davies & Palmai 1964, Palmai & Blackwell 1965, Palmai *et al.* 1967). In these earlier studies, the study groups consisted of clinically depressed patients, part of whom had severe symptoms. The degree or severity of symptoms, on the other hand, has been suggested to associate with flow rate (Davies & Palmai 1964). It is thus possible that the present series included only a few severely depressed subjects. On the other hand, Toone and Lader (1979), whose study group included 12 patients with a diagnosis of clinical depression did not find any associations between depression and salivary flow, either. In their study, however, a positive correlation was found between salivary secretion and appetite (Toone & Lader 1979), which has not been adequately considered in the studies of salivation and depression (Russ & Ackerman 1987). Accordingly, it has been suggested that the diminished salivary flow rate in depressive illness may be more closely related to the appetite disturbances commonly associated with depression than to the mood disorder or depressive illness itself (Russ & Ackerman 1987).

Our result on the association between subjectively felt dry mouth and depressive symptoms was in accordance with the results of Bergdahl *et al.* (1997) and Bergdahl & Bergdahl (2000). In our study, the subjective sensation of dry mouth was related to unstimulated but not to stimulated salivary flow rate. Subjectively felt dry mouth was also associated with female gender, regular smoking, diseases that may associate with dry mouth, xerogenic medication, poor self-perceived physical condition and health, and finally, after controlling for these factors, with a high rate of depressive symptoms. Although part of the association between depressive symptoms and subjectively felt dry mouth is probably mediated by the above-mentioned factors, including xerogenic medication, the results of the logistic regression analysis demonstrated that at least part of this association was independent of these confounding factors. The association between depressive symptoms and subjective sensation of dry mouth was statistically significant ($p < 0.001$) even in subjects with normal or high unstimulated salivary flow rates and nearly significant in subjects with low unstimulated flow rates ($p = 0.059$). Bergdahl & Bergdahl (2000) found in their study that both subjects with low unstimulated salivary flow rates concomitantly with subjective oral dryness and subjects with normal salivary flow rates connected with subjective oral dryness scored significantly higher in depression, anxiety, and stress compared with the group with low unstimulated salivary flow and no subjective oral dryness as well as with the control group with normal unstimulated flow and no subjective oral dryness. In view of the fact that subjective reports of oral dryness may not necessarily reflect actual salivary gland function (Busfield *et al.* 1961, Fox *et al.* 1985, Närhi 1994) and the above-mentioned results, it can be concluded that there are also some other factors apart from the quantity of saliva

that play a role in the genesis of subjective oral dryness and, consequently, in the existing relation between depressive symptoms and sensation of dry mouth.

There are several possible mechanisms that may connect these two phenomena, both of which are likely to have multifactorial etiology. One of these mechanisms is somatization, the expression of distress in the form of physical symptoms that cannot be explained biomedically, which is known to associate with depression (Katon 1984). Somatization has also been suggested to be the underlying factor of diverse salivary complaints with no known biological explanation (Votta & Mandel 2002).

Based on the discussion presented in the context of flow rate, it is also possible that appetite disturbances serve as a link between depressive symptoms and the sensation of dry mouth, which was found to associate with a recent loss of appetite by Dormenval and coworkers (1999).

After swallowing, a film of residual saliva covers the oral hard- and soft-tissue surfaces (Wolff & Kleinberg 1998) and functions as a moisture retainer and a protective barrier (Won *et al.* 2001). It has been shown that the thickness of this film, in other words mucosal wetness, is associated positively with the resting saliva flow rate (Wolff & Kleinberg 1998, Won *et al.* 2001) and negatively with symptoms of oral dryness (Wolff & Kleinberg 1998). Furthermore, the study of Won and coworkers (2001) showed that mucosal wetness on the soft palate correlated with the minor salivary gland secretion rate, which, on the other hand, has been suggested to associate with the perception of oral dryness (Niedermeier & Huber 1989). Almost 80% of the resting, *i.e.* unstimulated, saliva comes from submandibular, sublingual, and minor salivary glands (Izutsu 1987), which are together responsible for the production of mucins (Culp & Richardson 1996).

6.2.4.2 Growth of salivary microbes

Due to the limited ability of single-point measurements of disease to reveal the relationships between the studied parameters in a cross-sectional study, the risk indicators were assessed in addition to strict measurement of disease. High counts of lactobacilli and mutans streptococci as well as the presence of salivary yeasts have been found to associate with dental caries increment (Alaluusua *et al.* 1990, Kirstilä *et al.* 1998, Raitio *et al.* 1996). Milk containing probiotic *Lactobacillus rhamnosus GG* bacteria, on the other hand, was found to reduce the risk of dental caries in children aged 1-6 years (Näse *et al.* 2001). *Candida albicans* is suggested to play a role in denture stomatitis (Budtz-Jørgensen 1974), and its salivary level as well as the salivary levels of lactobacilli and mutans streptococci have been suggested as microbial indicators of dental caries (Loesche *et al.* 1995). Lactobacilli, mutans streptococci, and yeasts are acidophilic microorganisms, which have been associated with similar environmental factors. Low salivary flow rate and pH (Parvinen & Larmas 1981, Fure & Zickert 1990), low buffering capacity of saliva (Närhi *et al.* 1994), poor oral hygiene and smoking (Heintze 1984, Sakki & Knuuttila 1996, Parvinen 1984a), frequent intake of sugary products (Crossner 1984, Carlsson 1989), removable dentures (Parvinen 1984b, Närhi *et al.* 1993, Närhi *et al.* 1999), and open caries lesions (Klock & Krasse 1977) favor abundant growth of these

microbes. A genetic predisposition to oral accumulation of mutans streptococci and lactobacilli has also been suggested (Ozawa *et al.* 2001).

In this study, depressive symptoms increased the liability to abundant growth of salivary lactobacilli in the dentate population even after controlling for the above-mentioned confounding factors (adjusted OR = 2.0, 95% CI 1.2–3.3). The associations between depressive symptoms and mutans streptococci as well as yeast growth were uncertain (adjusted OR = 1.6, 95% CI 0.998–2.57 for mutans streptococci; adjusted OR = 2.06, 95% CI 0.982–4.32 for yeast growth). Nevertheless, in addition to the already known risk factors concerning abundant growth of salivary lactobacilli, mutans streptococci, and yeasts, there must exist a formerly unknown factor or factors accompanying the number of salivary microbes that are also associated with depression. The importance of salivary composition in the maintenance of oral microbial homeostasis on the one hand and the manifold biological alterations related to depression on the other raises the possibility of biologically mediated linkage between depression and oral microbial ecology.

In addition to the salivary flow rate, there are many immune and nonimmune defense systems as well as a broad range of cytokine and growth factors in saliva which play a role in the elimination of microorganisms from the oral cavity (reviewed by Slomiany *et al.* 1996). Salivary glycoproteins account for an important part of these defensive actions of saliva, and it is generally agreed that salivary glycoproteins may contribute to the decreased adherence of microorganisms on teeth and oral mucosal surfaces by aggregating the bacteria, which are then removed by swallowing (Ericson & Arwin 1985). Large, highly glycosylated glycoproteins, *i.e.* mucins, secreted from the submandibular, sublingual, and minor salivary glands have the potential for binding to bacterial surfaces, inhibiting direct epithelial-bacterial binding and thereby limiting bacterial colonization of oral surfaces (reviewed by Tabak 1995). Furthermore, the structural heterogeneity of mucins has been suggested to modulate the bacterial clearance-adherence phenomena in the oral cavity (reviewed by Tabak *et al.* 1982). Also, the lubrication of oral, oropharyngeal, and esophageal mucosa is largely mediated by mucins (Pedersen *et al.* 2002), which are the principal organic constituents of the slimy viscoelastic mucus coating all mucosal surfaces and protecting them from desiccation and environmental insult (Tabak *et al.* 1982). Besides the above-mentioned functions, mucins also interact selectively with their environment, including epithelial and endothelial cells, thereby regulating a great number of biological processes (reviewed by Nieuw Amerongen *et al.* 1998). If there were some linkage between depression and the secretion and composition of mucins, which possibility will be discussed below, it might well explain the associations found between depressive symptoms and subjectively felt dry mouth as well as the high count of salivary microbes.

Salivary mucins fall into two major catogories referred to as high-molecular-weight mucin (MG1) and low-molecular-weight mucin (MG2) (for a review, see Schenkels *et al.* 1995). MGI consists primarily of the MUC5B gene product (Nielsen *et al.* 1997), whereas MG2 is encoded in the MUC7 gene (Bobek *et al.* 1993). MUC5B and MUC7 are both secreted soluble mucin gene products produced in all salivary glands except in the parotid gland (Liu *et al.* 2002). In addition to these mucin forms, the salivary glands, including the parotid gland, produce mucins called membrane-associated mucins with somewhat different and, so far, unclear functions (Liu *et al.* 2002).

There are alterations associated with depression that may influence the structure and amount of mucins and thereby the sensation of dry mouth and the growth of salivary microbes. It has been suggested that the biosynthesis of mucins is regulated by multiple extrinsic controls, and that the mucin structure is controlled by neurotransmitters (for a review, see Tabak *et al.* 1982). A regulatory role of serotonin (5-HT) has been defined in the salivary glands of some lower species (Baumann *et al.* 2002) as well as in mammalian salivary glands, involving the modification of the volume and protein content of saliva (Turner *et al.* 1996). Serotonin has been found to induce intestinal and colonic mucin secretion in animal models (Moore *et al.* 1996, Plaisancie *et al.* 1998). Furthermore, the tricyclic antidepressant desipramine was found to induce the secretion of high-molecular-weight mucin-type glycoproteins in rats (Koller *et al.* 2000).

In laboratory rodents, thyroid hormone and corticosteroids, both of which are known to have important roles in the endocrine regulatory systems involving depression, and hypercortisolism, which is a common finding in depression, participate the regulation of protein synthesis in the submandibular gland (Sabbadini & Berczi 1995). In rat submandibular gland, hypothyroidism significantly decreased the concentrations of soluble proteins, whereas the concentration of sialic acid was significantly elevated (Morgan *et al.* 1985). In rat gastric mucosa, a physiological concentration of glucocorticoid was necessary for mucin biosynthesis, but high doses of hydrocortisone directly suppressed the expression of mucin (Tanaka *et al.* 2001). Responsive results have been demonstrated in isolated human gastric mucosa with dexamethasone treatment decreasing mucin secretion and MUC1 levels (Okazaki *et al.* 1998).

Bosch and coworkers (2000) demonstrated a direct link between stress-mediated biochemical changes and altered bacterial adherence of saliva. Saliva from 17 male students was collected before, during, and after an experimental stress situation. The acute stressor induced a marked increase in the saliva-mediated adherence of *Helicobacter pylori* induced by MUC5B and an increase in the secretion of sulfo-Lewis carbohydrate structure, which was suggested to be due to increased release of MUC5B mucin. It was concluded that the stress-mediated release of MUC5B most likely, as a consequence of autonomic activation, might affect the microbial homeostasis of the mucosa by favoring the colonization of bacteria that preferentially bind to MUC5B. (Bosch *et al.* 2000.) In the longitudinal study of Bosch and coworkers (1996), 28 dental students provided unstimulated whole saliva before an academic examination and subsequently 2 weeks and 6 weeks later in non-stress situations. The results showed a statistically significant decrease in the aggregation of *Streptococcus gordonii* under stress compared with non-stress situations (13.1% *vs.* 23.3%, respectively). Furthermore, the decrease in bacterial aggregation was related to the increase in state-anxiety. The results also showed a significant stress-mediated increase of salivary total protein concentration, *alpha*-amylase activity and output as well as s-IgA concentration and output, whereas salivary flow rate remained unchanged. The bacterial aggregation did not, however, correlate with these factors. (Bosch *et al.* 1996.)

The possibility of genetic linkage between depression and salivary composition is worth considering, since the MUC5B mucin gene is known to be located at chromosome 11p15 (Velcich *et al.* 1997), while the locus 11p15 has been suggested as potential disease locus in affective illness (Ciaranello & Ciaranello 1991, Muglia *et al.* 2002).

Assuming that a change in mucin biosynthesis, secretion, or function is the mediating factor between depressive symptoms and subjective dry mouth on the one hand and abundant growth of salivary lactobacilli on the other hand, one could easily presume that the latter two variables would correlate. This was not the case, however. The explanation might be the different roles of the secreted mucins MUC5B and MUC7 in oral defense, the first having highly viscoelastic properties and thus functioning primarily in lubrication and as a protective barrier, while MUC7 has less viscoelastic but highly antimicrobial properties and is largely responsible for microbial clearance (for a review, see Nieuw Amerongen & Veerman 2002). In fact, Almståhl and coworkers (2001) reported decreased MUC5B concentrations in subjects with hyposalivation of different origins, while none of the microbial species analyzed (including *Streptococcus mutans*, *Lactobacillus*, *Fusobacterium nucleatum*, and *Candida albicans*) correlated with the concentration of MUC5B in saliva. The presence of an indigenous protease enzyme capable of degradation of the high-molecular-weight salivary mucin (MUC5B) to a low-molecular-weight mucin (MUC7) has been demonstrated in human submandibular saliva (Piotrowski *et al.* 1992). The activity of this protease toward the high-molecular-weight glycoprotein was found to be 3.8-fold in caries-resistant individuals compared to caries-susceptible subjects (Slomiany *et al.* 1993a). Furthermore, the conversion of the high-molecular-weight mucin to a low-molecular-weight mucin through the action of salivary protease enhanced the mucin's bacterial aggregating potential toward *Streptococcus mutans* and *Streptococcus sanguis* (Slomiany *et al.* 1993b). The same protease is inhibited by *alpha*-1-antitrypsin (Piotrowski *et al.* 1992), which has also been found to be elevated in dental caries (Sikorska *et al.* 2002) and depression (Maes *et al.* 1992, Song *et al.* 1994). According to Baughan *et al.* (2000), elevated *S. mutans* titers were significantly associated with diminished concentrations of MG2 in unstimulated whole saliva. A decreased output of salivary MG2 has also been demonstrated in subjects with *Actinobacillus actinomycetemcomitans*-associated periodontal disease compared to periodontally healthy subjects (Groenink *et al.* 1999). Furthermore, Hoffman & Haidaris (1993) showed human salivary low-molecular-weight mucin to be the constituent of saliva to which *Candida albicans* is capable of binding.

6.2.5 Depressive symptoms in relation to symptoms and signs of temporomandibular disorders (TMD)

Functional disturbances of the masticatory system have been identified by a wide variety of terms, including 'temporomandibular joint pain and dysfunction syndrome' (PDS), which was also used in Paper I. However, use of the term 'temporomandibular disorders' (TMD) (Bell 1982) has been recently recommended as an appropriate collective term to describe musculoskeletal disorders arising from the masticatory structures (Okeson 1997). Not only the terminology but also the definitions and diagnostic criteria of TMD have been diverse and, moreover, the distinction between disease and non-disease has not always been clearly defined (de Bont *et al.* 1997). Consequently, epidemiological studies concerning TMD have reported a wide variety of prevalences. In a large epidemiologic

study by Salonen *et al.* (1990), the age group of 50–59 years demonstrated 7% and 1% of moderate and severe dysfunction, respectively, while a comparable study of Dutch adults gave an overall prevalence of 2.8% for moderate or severe dysfunction (De Kanter *et al.* 1993). Both studies used Helkimo's clinical dysfunction index (Di), which was also used in the present study. The prevalence of moderate or severe dysfunction (DiII and DiIII) in our study was 4.9%, which means that it falls somewhere between the previously reported figures. Much higher prevalences have also been reported, however. A meta-analysis of 51 prevalence studies (De Kanter *et al.* 1993) registered extreme variations of 6% to 93% in anamnestic and 0% to 93% in clinically assessed dysfunction, the high prevalences being due to inclusion of mild signs and symptoms (Carlsson 1999). In this study, the prevalences of anamnestic symptoms and clinical symptoms and signs, including mild ones, were 12.1% and 54.2%, respectively.

The independent association between symptoms and signs of temporomandibular joint pain and dysfunction syndrome (PDS, *i.e.* TMD) and high rates of depressive symptoms found in this study was in accordance with the results of the large Northern Finnish population-based study of Sipilä and coworkers (2001), who found an association between depressive symptoms and TMD symptoms in 31-year-old subjects. Symptoms relating to pain had the most significant relations to depression. Korszun *et al.* (1996) also found high prevalences of clinically diagnosed major and minor depression (53%) as well as subsyndromal depressive symptoms (22%) in 72 chronic facial pain patients. No statistically significant difference was seen in comorbidity of depression in patients with objective findings of TMD compared with patients without TMD. Consistently, in this study, the subjects with a lower degree of depressive symptoms did not seem to differ from the subjects with high rates of depressive symptoms in relation to comorbidity of subjective and objective signs and symptoms of TMD in the sense that both non-depressed and depressed subjects had highly significant associations between these two variables. Furthermore, comorbidity of depression and TMD in patient samples has been shown in various other studies (Gallagher *et al.* 1991, Wright *et al.* 1991, Gatchel *et al.* 1996, Carlson *et al.* 1998, Meldolesi *et al.* 2000). Controversial results were presented by Moss & Adams (1984) as well as McGregor and coworkers (1996), who did not find any differences in the prevalences of depressive symptoms in facial pain patients *vs.* controls.

In our study, a distinction was made between subjective symptoms and clinically determined signs and symptoms of TMD, both of which were connected with high rates of depressive symptoms. Helkimo's clinical dysfunction index does not, however, differentiate between temporomandibular joint and masticatory muscle problems, which constitute the two main categories of the TMD subclassification (Okeson 1996). Some evidence exists to support the view that depression (Lundeen *et al.* 1987, Auerbach *et al.* 2001) and psychological factors (McCreary *et al.* 1991, Scholte *et al.* 1993, Lobbezoo-Scholte *et al.* 1995, Wexler & Steed 1998) have a more pronounced role in the myogenous form of TMD compared with the arthrogenous form. However, various studies fail to support this notion (Marbach & Lund 1981, Michelotti *et al.* 1998, Visscher *et al.* 2001). Moreover, it has been suggested that differences in pain intensity between these groups may explain the positive results (Visscher *et al.* 2001), which was actually the case in the studies of Lundeen *et al.* (1987) and McCreary *et al.* (1991).

The most frequent presenting symptom in temporomandibular disorders is pain originating from musculoskeletal structures (Okeson 1996). This was also the case in a

retrospective study of 425 TMD patients, 84% of whom had reported having facial muscular pain (Esposito *et al.* 2000). Furthermore, according to Sipilä *et al.* (2002), clinically assessed TMD defined as DiII and DiIII in Helkimo's clinical dysfunction classification significantly increased the liability to facial pain (OR = 6.1, 95% CI 2.6–14.2). It is suggested that temporomandibular disorders share many features with other common chronic pain conditions (Dworkin & Massoth 1994), which, on the other hand, have been found to associate with depression in a wide variety of studies (Magni *et al.* 1992, Croft *et al.* 1993, Magni *et al.* 1994, Rajala *et al.* 1995, Mikkelson *et al.* 1997, Wang *et al.* 1999). On the contrary, McGregor *et al.* (1996) did not find an association between depression and chronic orofacial muscle pain or pain severity.

Because of the cross-sectional design of the present study, no conclusions could be drawn concerning the causality of the associations found. In the existing literature, however, the nature of pain-depression comorbidity has been an object of many hypotheses, and causal explanations in both directions have been given. Depression has been found to predict the onset of chronic pain (Leino & Magni 1993, Von Korff *et al.* 1993, Magni *et al.* 1994) and *vice versa* (Brown 1990, Magni *et al.* 1994, Wang *et al.* 1999). In a review article of Fishbain and coworkers (1997), it was concluded that depression is rather a consequence than the antecedent of chronic pain. Dohrenwend *et al.* (1999) found the lifetime prevalence of major depressive disorder to be higher in 106 myofascial face pain patients in comparison with healthy controls. However, the lifetime rates of major depression and depressive spectrum disorders were not elevated in the first-degree relatives of myofascial face pain patients. Similar evidence was shown in a review by Gallagher & Verma (1999), who supported the view that it is the stress of living with chronic pain, rather than a personal or family predisposition, that contributes to the elevated rates of depression in these patients. It is suggested that part of the chronic pain patients with inadequate coping fail to maintain adaptive levels of psychosocial functioning, demonstrating higher rates of depression, somatization, and health care use (Dworkin & Massoth 1994).

Idiopathic chronic pain and depressive disorders seem to share certain pathogenetic mechanisms (Knorring & Ekselius 1994). It has been suggested that these disease states may be linked via chronic stress-induced HPA axis dysfunction (Blackburn-Munro & Blackburn-Munro 2001). In fact, TMD patients showed markedly increased daytime cortisol levels compared to controls in the study of Korszun and coworkers (2002). The most interesting postulation is the link through the neurotransmitter serotonin and certain subtypes of serotonin receptors, which are known to be involved in pain modulation by both central (Gyermek 1996) and peripheral mechanisms (Graven-Nielsen & Mense 2001). Serotonergic and noradrenergic neurons descend from the brainstem to the spinal cord, constituting a gating mechanism that controls impulse transmission and thus significantly contributes to the modulation of pain (Fürst 1999). Serotonin is one of the algesic substances shown to induce nociception in animals (Taiwo & Levine 1992) and muscle pain in humans (Jensen *et al.* 1990, Babenko *et al.* 1999, Babenko *et al.* 2000, Graven-Nielsen & Mense 2001). On the other hand, the low central serotonin levels also found in depression have been suggested to play a pathophysiologic role in fibromyalgia (Russell *et al.* 1989, Yunus *et al.* 1992, Russell *et al.* 1992, Russell 1998), and the possible involvement of the serotonin transporter gene polymorphism in TMD has been studied (Herken *et al.* 2001). Furthermore, a wide range of pain conditions, including

facial pain, have been shown to be responsive to antidepressant drug treatment (Sharav *et al.* 1987, Magni 1991, Gruber *et al.* 1996, Jung *et al.* 1997, O'Malley *et al.* 2000, Ferrari *et al.* 2001).

Our results support the already existing evidence concerning comorbidity of depression and TMD. The question of whether there is some causality between these phenomena, and/or if they share some common etiological factors cannot be answered based on this cross-sectional study. However, the associations between depressive symptoms and clinically defined TMD as well as self-perceived symptoms of TMD remained statistically significant after adjustment for confounding factors, including the scale of somatic and psychosomatic symptoms. This further suggests that, apart from somatization, there are other, possibly biological mechanisms connecting depression and TMD.

7 Conclusions

This study showed that there are connections between emotional state and oral health, and it consequently supports the holistic view of health, suggesting that neither oral nor mental health should be separated from the entity of general health.

These results yield population-based evidence for the earlier suggested associations between depressive symptoms and temporomandibular disorders as well as subjectively felt dry mouth. Furthermore, this study demonstrated an association between depressive symptoms and abundant growth of salivary lactobacilli. It is also suggested that the abundant growth of salivary mutans streptococci and the presence of yeasts in saliva might be associated with high rates of depressive symptoms. Although abundant growth rates of both lactobacilli and mutans streptococci can be considered indicators for an increased risk of dental caries, no association between depressive symptoms and dental decay was found in this cross-sectional study. Nor was the hypothesized association between depressive symptoms and periodontal disease supported. However, an association between depressive symptoms and edentulousness emerged in the subgroup of men who had never smoked. The finding that depressed women did not consider it equally important to preserve their natural teeth as did non-depressed women, as well as their tendency to have lower percentages of filled tooth surfaces might reflect somewhat different treatment choices among women with high rates of depressive symptoms compared with non-depressed women.

Although a high rate of depressive symptoms cannot be equalized with clinical depression, it seemed to have associations with TMD and saliva-related phenomena. It is therefore suggested that, when treating patients with such findings or complaints, the possibility of depression should be considered. It is further emphasized that, apart from somatization, in the case of comorbid depression and undefined orofacial complaints, the possibility of an underlying biological link between them should be taken into account. Eventually, this study highlights the emotional impact of edentulousness, which should be borne in mind in dental care and treatment planning.

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Appendix

Zung Self-Rating Depression Scale

	None or a little of time	Some of the time	Good part of the time	Most or all the time
1. I feel down-hearted and blue.	1	2	3	4
2. Morning is when I feel the best.	4	3	2	1
3. I have crying spells or feel like it.	1	2	3	4
4. I have trouble sleeping at night.	1	2	3	4
5. I eat as much as I used to do.	4	3	2	1
6. I still enjoy sex.	4	3	2	1
7. I notice that I am losing weight.	1	2	3	4
8. I have trouble with constipation.	1	2	3	4
9. My heart beats faster than usual.	1	2	3	4
10. I get tired for no reason.	1	2	3	4
11. My mind is as clear as it used to be.	4	3	2	1
12. I find it easy to do the things I used to do.	4	3	2	1
13. I am restless and can't keep still.	1	2	3	4
14. I feel hopeful about the future.	4	3	2	1
15. I am more irritable than usual.	1	2	3	4
16. I find it easy to make decisions.	4	3	2	1
17. I feel that I am useful and needed.	4	3	2	1
18. My life is pretty full.	4	3	2	1
19. I feel that others would be better off if I were dead.	1	2	3	4
20. I still enjoy the things I used to do.	4	3	2	1