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The prevalence and risk factors of rosacea. Subjective disease perception of rosacea patients

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III Abram K, Silm H, Maaroos HI, Oona M. Subjective disease perception and symptoms of depression in relation to healthcare-seeking behaviour in patients with rosacea. Acta Derm Venereol 2009; 89: 488–491.

Contribution of Kristi Abram to original publications:

Paper I: participation in the study design, compiling the questionnaire, data collection, participation in data analysis, writing the the first draft of the manuscript to which other authors contributed

Paper II: participation in the study design, compiling the questionnaire, data collection, collection of blood samples, participation in performing *H. pylori* serological analysis, data analysis, writing the the first draft of the manuscript to which other authors contributed

Paper III: participation in the study design, compiling the questionnaire and visual analogue scale (VAS), data collection, data analysis, writing the the first draft of the manuscript to which other authors contributed

2. ABBREVIATIONS

CagA	cytotoxin-associated gene A
CI	confidence interval
CLO	*Campylobacter*-like organisms
EMS	Estonian Mood Scale (Enesehinnanguline meeleolu skaala)
EST-Q	Emotional State Questionnaire
ETR	erythematotelangiectatic rosacea
GST	glutathione-S-transferases
Hp	*Helicobacter pylori, H. pylori*
Ig	immunoglobulin
MMP	matrix metalloproteases
NRSEC	National Rosacea Society Expert Committee
NS	nonsignificant
OR	odds ratio
PhR	phymatous rosacea
PPR	papulopustular rosacea
ROS	reactive oxygen species
SD	standard deviation
UV	ultraviolet
VAS	visual analogue scale
VEGF	vascular endothelial growth factor

3. INTRODUCTION

Rosacea is a chronic skin condition with an unknown aetiology, that usually starts between the ages 30 and 50 (Jansen and Plewig 1997). Rosacea is a very common dermatosis, but data about its prevalence are scarce. There exist only a few previous population-based epidemiological studies (Berg and Lidén 1989; Schaefer *et al*., 2008) and these studies were initiated before the adoption of the standard classification system established by American National Rosacea Society Expert Committee (NRSEC) in 2002 (Wilkin *et al*., 2002).

Rosacea is characterized by symptoms of facial flushing and a spectrum of clinical signs, including erythema, telangiectasia, coarseness of skin, and an inflammatory papulopustular eruption resembling acne (Wilkin *et al*., 2002). Rosacea typically affects the face, which is an emotionally charged area and has therefore an impact on the patient's psychosocial life. It was previously found that patients with rosacea have higher odds for comorbidity with depression (Gupta *et al*., 2005). However, previous population-based studies report higher prevalence rate of rosacea than is estimated on the basis of referrals to various dermatology centres. This suggests that many patients with rosacea never seek medical care for their rosacea and the opinion that rosacea has a psychosocial impact has mainly evolved from observations of clinic-based patients, while relevant data for rosacea patients who have not sought medical care are scarce.

Although rosacea is a common disease, the cause of it is still a unknown. Endocrinological, pharmacological, immunological, infectious, climatic, thermal, and alimentary factors are implicated as triggers of rosacea (Mini *et al*., 2005). For prevention of rosacea and for applying better causal treatment, it is important to have better knowledge about the etiopathogenesis. A common opinion is that rosacea affects mostly fair-skinned people of Celtic and northern European heritage (Jansen and Plewig 1997), its inheritance is unclear. Previously, GSTM 1 and GSTT 1 null genotypes were found to be associated with an increased risk of rosacea (Yazici *et al*., 2006). Only a few cases exist that report rosacea in twins (Ee *et al*., 2005; Palleschi and Torchia 2007). Common opinion is that sun exposure is an aggravating factor for rosacea. However, little evidence supports this opinion (Jaworek *et al*., 2008; Lazaridou *et al*., 2010). The relationship between rosacea and *Helicobacter pylori* infection has previously been investigated by a number of researchers. Nevertheless, such attempts to establish a link between *H. pylori* infection and rosacea are at present controversial, mainly based on case reports or small-scale studies. Some authors reckon that *H. pylori* probably constitutes a risk factor (Rebora *et al*., 1995; Bonamigo *et al*., 2000; Szlachic 2002; Argenziano *et al*., 2003; Zandi *et al*., 2003; Diaz *et al*., 2003), at least in certain groups of individuals (Bonamigo *et al*., 2000; Argenziano *et al*., 2003). Other investigators contradict any associations between rosacea and *H. pylori* infection (Sharma *et al*., 1998; Jones *et al*., 1998; Bamford *et al*., 1999; Herr and You 2000; Gedik *et al*., 2005). Although alcohol is recognized as a trigger of flushing episodes and rhinophyma is known as "drinker's nose", no relationship has been proved

between alcohol consumption and rosacea (Parish and Fine 1985; Higgins and Vivier 1999; Curnier and Choudhary 2004). The association between rosacea and caffeine intake has not been proved either (Wilkin 1981), although most doctors recommend to avoid hot beverages. In addition, rosacea is predominantly known as a disease of non-smokers rather than active smokers (Mills and Marks 1996). However, most of the previous researches in the field of etiopathogenesis of rosacea have concentrated on some limited issues and have not followed up on combined risk factors.

For a better comprehension of rosacea-associated health problems and clarification of triggering factors, it was important to determine its prevalence according to valid diagnostic criteria and to find out also cases that otherwise never reach the focus of researchers.

4. REVIEW OF THE LITERATURE

4.1. Clinical symptoms and diagnostic criteria of rosacea

Rosacea is a chronic skin disorder affecting the facial convexities (Jansen and Plewig 1997), but it can also have extrafacial manifestations observed in the retroauricular areas, and on the chest, the neck, the back, the scalp, and the extremities (Jansen and Plewig 1997; Wong 2004; Marks 2007; Pereira *et al*., 2008). The course of the disease is typically chronic, with remissions and relapses (Powell 2005).

The diagnostic criteria of rosacea were not well established until 2002. There are no histological or serologic markers of rosacea; therefore, the American National Rosacea Society Expert Committee (NRSEC) introduced a standard classification system of rosacea based on existing scientific knowledge and morphologic characteristics, to serve as a diagnostic instrument to investigate the manifestations and relationships of several subtypes and potential variants of rosacea (Wilkin *et al*., 2002). The NRSEC classification system describes the primary features of rosacea and defines 4 subtypes and 1 variant. The presence of one or more of the following signs on the convexities of the central face is indicative of rosacea:

1) transient erythema *seu* flushing;
2) nontransient erythema;
3) red papules with or without accompanying pustules, nodules may also occur;
4) visible blood vessels *seu* telangiectasia.

Comedones are unrelated to rosacea and should be considered as part of acne process. Besides one or more of the primary features of rosacea, a variety of secondary features can occur: burning or stinging sensations, plaques, dry appearance, oedema, ocular manifestations, peripheral localisation and/or phymatous changes (Wilkin *et al*., 2002).

The 4 subtypes of rosacea by the NRSEC classification are following:

- Subtype 1: Erythematotelangiectatic rosacea (ETR) is the most common subtype accounting for 72% to 81% of all cases of rosacea (Berg and Lidén 1989; Kyriakis *et al*., 2005). Erythematotelangiectatic rosacea is characterised by flushing and persistent central facial erythema with or without telangiectasia. Secondary features, as oedema, stinging and burning sensations, roughness or scaling may also occur (Wilkin *et al*., 2002).
- Subtype 2: Papulopustular rosacea (PPR) is the second most frequent subtype of rosacea accounting for 19% to 28% of all cases of rosacea (Berg and Lidén 1989*;* Kyriakis *et al*., 2005). Papulopustular rosacea is characterised by persistent facial erythema with transient, central facial papules or pustules, or both. Papules and pustules may also occur periorificially. Burning or stinging sensations may occur (Wilkin *et al*., 2002).

- Subtype 3: Phymatous rosacea (PhR) is a rare subtype of rosacea (Berg and Lidén 1989*;* Kyriakis *et al*., 2005), predominantly associated with the male gender (Curnier and Choudhary 2004; Kyriakis *et al*., 2005; Bittencourt *et al*., 2006). It usually starts between 40 and 60 years of age (Bittencourt *et al*., 2006). Phyma , a Greek term importing a tuber, tubercle or small swelling, from *φύω*, "produco, erumpo", was used among the Greek and Roman physicians with great latitude and no small want of precision (Good 1825), hence phymatous rosacea is characterised by thickening skin, irregular surface nodularities and enlargement. Phymas may occur on the nose (rhinophyma), the chin (gnatophyma *seu* mentophyma), the forehead (frontophyma *seu* metophyma), the cheeks (zygophyma), the ears (otophyma), or the eyes (blepharophyma), but rhinophyma is the most common presentation (Jansen and Plewig 1998; Wilkin *et al*., 2002).
- Subtype 4: Ocular rosacea – ocular signs may accompany in 6% up to 50% (Berg and Lidén 1989; Michel and Cabibel 2003; Powell 2005; Lazaridou *et al*., 2010) of rosacea patients with skin signs and symptoms, but ocular signs and symptoms may precede skin symptoms in up to 20% of patients with ocular rosacea (Akpek *et al*., 1997; Wilkin *et al*., 2002). Ocular rosacea should be considered if one or more of the following sings and symptoms are present: interpalpebral conjunctival hyperaemia, foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periocular erythema. As might be expected, eye signs and symptoms are more commonly noted in the eye clinic than in the dermatology clinic (Ghanem *et al*., 2003) and ocular rosacea in its most developed form still remains the domain of the ophthalmologist (Michel and Cabibel 2003).

To date, the NRSE Committee has recognized one variant of rosacea which does not represent morphologic patterns or combinations as seen in rosacea subtypes – granulomatous rosacea. This variant is characterised by noninflammatory, hard, brown, yellow, or red cutaneous papules or nodules of uniform size, that may be severe and lead to scarring. They are monomorphic in each individual patient, and typically appear on the cheeks and in the periorifical areas (Wilkin *et al*., 2002).

In 2004, to enhance the utility of the system for both clinicians and researches, the NRSEC has devised a standard method for assessing gradations of the severity of rosacea (Wilkin *et al*., 2004). For assessing, primary signs and symptoms may be graded as absent, mild, moderate, or severe (grades 0–3), and most secondary features may be graded simply as absent or present.

The histopathology of rosacea varies with the stage and type of the disease (Jansen and Plewig 1997). Erythematotelangiectatic rosacea is characterized mainly by irregularly dilated ectatic venules and lymphatics in the upper dermis, perivascular and perifollicular infiltration, moderate elastic tissue hyperplasia, slight oedema and actinic elastosis (Jansen and Plewig 1997; Marks 2007; Lazaridou *et al*., 2010). In papulopustular rosacea, there is evidence of intrafollicular collections of neutrophils, increased perifollicular and perivas-

cular infiltration, diffuse expansion of connective tissue and distorted follicular canals, accompanied by hyperplasia of sebaceous follicles (Jansen and Plewig 1997; Marks 2007; Lazaridou *et al*., 2010).

Phymatous lesions reveal diffuse expansion of the connective tissue, accompanied by sebaceous hyperplasia, dilated follicular infundibula, telangiectases, perifollicular infiltrates of plasma cells, lymphocytes and histiocytes, suppuration and severe elastosis. Demodex folliculorum mites are often found within the follicular infundibula and sebaceous ducts as commensals (Jansen and Plewig 1997; Lazaridou *et al*., 2010).

4.2. Epidemiology of rosacea

Although rosacea is apparently a common skin disease, data about its true prevalence are scarce. Several studies on patients of dermatology clinics have established the prevalence rate of rosacea to be 0.5% to 3% on the basis of referrals to various dermatology centres in Europe and the US: 1.2% in Greece (Kyriakis *et al*., 2005), 0.5–1.8% in UK (Powell 1998; Doe *et al*., 2001), 2.3% in the US (Gupta *et al*., 2005), and 3.0% in Ireland (Powell 1998), while no referrals due rosacea were found among 2254 consecutive new patients attending a dermatology clinic in Ghana (West-Africa) (Doe *et al*., 2001). However, the diagnostic criteria of rosacea used in those studies were poorly defined.

Two previous population-based studies have found the prevalence rate of rosacea to be 10% in Sweden (Berg and Lidén 1989) and 2% in Germany (Schaefer *et al*., 2008). Both of these studies were carried out among employee populations during working hours at their offices. The first study, which found rosacea prevalence to be 10%, was carried out among 809 working persons in Sweden by one investigator. In that study, rosacea was diagnosed in subjects with papules and/or pustules, erythema, telangiectases and swelling, or with an anamnesis of rosacea within the last 2 years, but individuals with telangiectases alone were classified as subjects without rosacea. In another study, where 50673 persons of an employee population of Germany were examined by 111 investigators, rosacea prevalence was found to be 2%. As the study was mainly focused on skin cancer screening, it did not present a detailed methodology according to which diagnostic criteria were used for diagnosis of rosacea; however, the standardized examination procedure of the study was applied in 2001, thus before the establishment of NRSEC criteria in 2002.

In a study conducted among general population, the majority of subjects with cutaneous forms of rosacea had a mild disease, markedly fewer had a moderate disease and only a few persons had a severe disease (Berg and Lidén 1989); severity of ocular damage was not correlated with stage of cutaneous involvement (Michel and Cabibel 2003).

Thus, previous prevalence studies were initiated before the establishment of the NRSEC classification in 2002 (Wilkin *et al*., 2002), and were based on the diagnosis relying on self-report or poorly-defined signs and symptoms.

Recently, McAleer *et al*., carried out a study among 500 indoor and 500 outdoor workers from fair-skinned Irish population. Papulopustular rosacea was established, if the patient had at least 5 inflammatory, erythematous papules and/or pustules present in a centrofacial distribution on a background of erythema. Authors found the prevalence rate of papulopustular rosacea to be 2.7%. However, the prevalence rates of other subtypes of rosacea were not reported in that study (McAleer *et al*, 2010).

4.3. Risk factors of rosacea

Although rosacea is a common dermatosis, its etiopathogenesis is still unclear. Rosacea may occur at any age; typically the onset begins after age 30 (Wilkin *et al*., 2002). The prevalence rate of rosacea increases consistently with age, being the highest between 40 and 50 years, and decreases slightly after that (Berg and Lidén 1989). Rarely, rosacea occurs also in pediatric patients (Kroshinsky and Glick 2006).

Rosacea occurs both in men and women (Wilkin *et al*., 2002). Although there is the common opinion that rosacea affects more often women than men (Berg and Lidén 1989; Jansen and Plewig 1997; Bonamigo *et al*., 2000; Powell 2005), some studies have shown that both genders are affected equally (Kyriakis *et al*., 2005; Schaefer *et al*., 2008).

Rosacea has been mostly observed in patients with fair skin (Berg and Lidén 1989), especially in people of Celtic and northern European heritage (Jansen and Plewig 1997); the prevalence of rosacea decreases with the darkening of the skin type (Berg and Lidén 1989; Lazaridou *et al*., 2010). According to an epidemiological study, the prevalence rates of rosacea among Fitzpatrick I–IV skin phototypes (Braun-Falco 2000) were 7%, 10%, 11%, and 3% respectively (Berg and Lidén 1989). In another clinical study 63% of the patients were classified into phototype II, and 30%, 4%, and 3% of the patients were classified into phototype III, I, and IV, respectively (Lazaridou *et al*., 2010). However, rosacea has rarely also been diagnosed in Asians and even in people with the black skin (Khoo and Saad 1980; Rosen and Stone 1987; Jansen and Plewig 1997; Wilkin *et al*., 2002; Koffi-Aka *et al*., 2002; Gupta *et al*., 2005; Allah *et al*., 2009). Although the skin phototype is a genetically determined characteristic, data about the inheritance of rosacea are scarce. In some studies a positive family history of rosacea was established in 15–30% of cases by patients self-reports (Powell 1998; Powell 2005; Lazaridou *et al*., 2010). Recently, GSTM 1 and GSTT 1 null genotypes were found to be associated with an increased risk of rosacea (Yazici *et al*., 2006). There exist a few case reports that describe the occurrence of rosacea in twins (Ee *et al*., 2005; Palleschi and Torchia 2007;). Ee *et al*., described the presence of rosacea in two

non-identical twin brothers and in their mother (Ee *et al*., 2005). On the contrary, Palleschi reported a case of a monozygotic female twin pair in which only one of the twins suffered from rosacea. The author argued that environmental factors may play a major role in the pathogenesis of rosacea (Palleschi and Torchia 2007).

Several factors, *e.g.* infections, climatic circumstances (*e.g.* UV radiation), ingested agents, or detrimental habits are implicated as triggers in the rosacea process (Mini *et al*., 2005), throughout an altered innate immune response (Yamasaki and Gallo 2009). In two small-scale studies patients with rosacea were inquired about the factors triggering their skin changes. One study was conducted among 69 outpatients of a dermatology clinic in Poland and the results are published in Polish (Jaworek *et al*., 2008); another study was carried out among 100 rosacea patients in a dermatology department in Greece (Lazaridou *et al*., 2010). The patients' self-reported triggering or aggravating factors for rosacea in these two studies were the following: sun exposure 56.5–73%, alcochol intake 24–33%, exercise 29%, hot beverages 5–21.7%, hot meals 20.3%, heat 10%, spicy food 1%, smoking 1%, and abrupt changes in temperature 1% (Jaworek *et al*., 2008; Lazaridou *et al*., 2010). Stress was mentioned as an aggravating factor by 58% of the subjects of first study (Jaworek *et al*., 2008), but only by 8% subjects of the other study (Lazaridou *et al*., 2010). However, these studies based on patients self-reports, were small-scaled and uncontrolled.

Sun exposure has been implicated in exacerbation of rosacea in the majority of patients' self-report cases (Jaworek *et al*., 2008; Lazaridou *et al*., 2010). Ultraviolet (UV) irradiation could influence rosacea *via* different pathways. It has been shown convincingly that UV irradiation increases reactive oxygen species (ROS) production and lipid peroxidation in fibroblasts (Bossi *et al*., 2008), while cellular antioxidative protective mechanisms in patients with severe rosacea are incapable of preventing the toxic effects of ROS (Öztas *et al*., 2003; Tisma *et al*., 2009). *In vitro* UV irradiation induces expression of vascular endothelial growth factor (VEGF) in human keratinocytes and fibroblasts by multiple mechanisms, which is a potent multifunctional cytokine responsible for cutaneous microvascular permeability and angiogenesis (Brauchle *et al*., 1996; Trompezinski*et al*., 2001; Kosmadaki *et al*., 2003). Also UV radiation enhances release of matrix metalloproteases (MMP), which degrade collagen and other extracellular matrix proteins that comprise the dermal connective tissue, leading to abnormal matrix degradation and accumulation of non-functional matrix components (Dong *et al*., 2008). However, this knowledge is based mainly *in vitro* studies, and there is also controversial evidence. An epidemiological study of rosacea found that more individuals with rosacea (26%) noted improvement in skin condition compared with worsening (17%) after sun exposure, especially in the case of papulopustular rosacea (Berg and Lidén 1989); two studies have also shown that it is more common for rosacea to worsen in the winter than in the summer (Berg and Lidén 1989; Kyriakis *et al*., 2005). This is likely due to cold-induced vasodilatation, especially in the acral

regions (*e.g.* nose, cheeks, forehead) of the face, in response to wind and low temperature (Brajkovic and Ducharme 2006; Tikuisis *et al*., 2007).

Besides cold, both exo- and endogenic heat have been described as provoking factors for cutaneous vasodilatation and increase in blood flow, especially in older patients (Hellon and Lind 1958). As previously mentioned, some rosacea patients note exacerbation of symptoms after consumption of hot beverages or meals (Jaworek *et al*., 2008; Lazaridou *et al*., 2010). Therefore, consumption of hot beverages and coffee has been found to be slightly lower among individuals with rosacea (Berg and Lidén 1989). It has been concluded that the active agent causing flushing after consuming coffee at 60°C is heat but not caffeine (Wilkin 1981).

Alcohol is recognized to trigger flushing in rosacea (Higgins and Vivier 1999) and at least one-fourth of patients with rosacea experience exacerbation of their symptoms after alcohol intake (Jaworek *et al*., 2008; Lazaridou *et al*., 2010). Patients with high alcohol consumption have been found to have increased levels of collagen III pro-peptide, which is a marker of increased collagen metabolism. Increased dermal collagen has also been noted in histological skin samples from alcoholics; hence this could provide a clue to the mechanism of tissue hyperplasia seen in phymatous rosacea (Higgins and Vivier 1999). Although patients recognized alcohol as a trigger of flushing episodes and exacerbation of rosacea symptoms (Jaworek *et al*., 2008; Lazaridou *et al*., 2010) and although rhinophyma is historically known as "drinker's nose" (Higgins and Vivier 1999), no relationship has been proved between alcohol consumption and rosacea (Parish and Fine 1985; Higgins and Vivier 1999; Curnier and Choudhary 2004). Smoking and alcohol consumption are closely linked (Nuttens *et al*., 1992; Willard and Schoenborn 1995). Cigarette smoke causes, *via* its oxidative effects, premature skin aging (Egawa *et al*., 1999; Morita 2007) and is considered to be a triggering or at least aggravating factor of various skin diseases, *e.g.* acne inverse (König *et al*., 1999), psoriasis (Gerdes *et al*., 2010), palmoplantar pustulosis (O'Doherty and MacIntyre 1985), and hand eczema (Thyssen *et al*., 2010). Relatively few data are available about the relationship between tobacco use and rosacea. Only 1% of patients with rosacea associated the exacerbation of their symptoms with smoking in a self-report questionnaire (Lazaridou *et al*., 2010). Berg and Lidén found, in their epidemiological study of rosacea, no differences between subjects with rosacea and controls in the use of tobacco (Berg and Lidén 1989). At the same time Mills and Marks found relatively few smokers among rosacea patients compared with age and sex matched controls (Mills and Marks 1996).

It has been hypothesized that focal infections could trigger or at least be aggravating factors for chronic skin diseases. Infestations can trigger innate immune responses, such as the release of cathelicidin antimicrobial peptides, which can promote leukocyte chemotaxis, angiogenesis and the expression of extracellular matrix components. It has been demonstrated that individuals with rosacea express abnormally high levels of cathelicidin in their facial skin and the proteolytically processed forms of cathelicidin peptides found in rosacea are

different from those present in normal individuals (Yamasaki *et al*., 2007; Yamasaki and Gallo 2009). In the 1990s researchers from Italy found that in patients with rosacea the prevalence of *Helicobacter pylori* according to histology and serology was higher (84% of 31 patients) than expected in the reference population (50%) (Rebora *et al*., 1995). Since that time the relationship between rosacea and *H. pylori* infection have been discussed and investigated by a number of researchers. *H. pylori* is a gram-negative, flagellate, microaerophilic, spiral or curved bacillum that infects the gastric mucosa (Marshall and Warren 1984). *H. pylori* infection is one of the most common bacterial infections in the world (Parsonnet 1998). It is known as a major cause of chronic gastritis, peptic ulcer, gastric carcinoma and gastric lymphoma (Mégraud *et al*., 2007). It is argued that toxic substances released by *H. pylori* could invade the circulatory system and may play a role also in the pathogenesis of extragastrointestinal diseases, such as skin diseases, *e.g.* rosacea (Argenziano *et al*., 2003; Hernando-Harder *et al*., 2009), chronic urticaria (Di Campli *et al*., 1998; Shiotani *et al*., 2001; Hernando-Harder *et al*., 2009;), psoriasis (Qayoom and Ahmad 2003; Hernando-Harder *et al*., 2009), blepharitis (Sacca *et al*., 2006), Schönlein-Henoch purpura, alopecia areata, atopic dermatitis, cutaneous pruritus, and many other skin conditions (Shiotani *et al*., 2001; Wedi and Kapp 2002; Hernando-Harder *et al*., 2009). Yet the results of attempts to establish a link between *H. pylori* infection and rosacea are at present controversial, mainly based on case reports or small-scale studies.

Some authors believe that *H. pylori* may consitute a risk factor (Rebora *et al*., 1995; Bonamigo *et al*., 2000; Szlachic 2002; Argenziano *et al*., 2003; Zandi *et al*., 2003; Diaz *et al*., 2003; Mini *et al*., 2005;), at least in certain groups of individuals (Bonamigo *et al*., 2000; Argenziano *et al*., 2003). Szlachic *et al*., investigated *H. pylori* prevalence in 60 rosacea patients and in 60 age- and sex-matched controls using the ^{13}C-urea breath test, CLO-test, *H. pylori* culture and serology. The author found significantly higher *H. pylori* prevalence in rosacea patients (88%) compared with controls (65%) (Szlachic 2002). Bonamigo, *et al*. investigated *H. pylori* serology in 62 rosacea patients and in 124 patients without rosacea, but they found strong association between bacteria and dermatosis only after stratified analysis taking account of previous antibiotic use (Bonamigo *et al*., 2000). Argeniziano *et al*., found that anti-*Hp* IgG, IgA and anti-CagA IgG antibodies were more prevalent in patients with papulopustular rosacea than erythematotelangiectatic rosacea, but their study involved only 48 roscea patients without any skin-healthy controls at all (Argenziano *et al*., 2003).

Some other investigators have not found association between rosacea and *H. pylori* infection (Sharma *et al*., 1998; Jones *et al*., 1998; Bamford *et al*., 1999; Herr and You 2000; Gedik *et al*., 2005). Sharma *et al*., found no significant difference in the seroprevalence of *H. pylori* infection between 45 rosacea patients (n=45) and 43 healthy controls (26.7% vs 34.9%; p=NS) (Sharma *et al*., 1998*)*. Lazaridou *et al*., compared the prevalence of immunoglobulin G antibodies against *H. pylori* in 100 rosacea patients and in 100 age- and gender-

matched healthy indviduals; the statistical difference between these groups was insignificant, while a strong association was found between *H. pylori* and rosacea in patients who had not taken any antibiotics (Lazaridou *et al*., 2010). Bamford, *et al*. showed in their study that less than half of the patients with rosacea had a serological evidence of *H. pylori* infection. Moreover, there were no significant differences in the cure of rosacea (patients n=44) between the *H. pylori* eradication active treatment group compared with the placebo group (Bamford *et al*., 1999). Gedik *et al*., reported that there were no significant differences after *H. pylori* infection eradication treatment between the patients who had *H. pylori* at the end (n=4) of treatment and those in whom *H. pylori* was eradicated (n=20). However, the small study population and lack of the control group were the limitations of that study (Gedik *et al*., 2005).

There has also been found some beneficial effect of *H. pylori* eradication on rosacea (Son *et al*., 1999; Utaş *et al*., 1999; Mayr-Kanhäuser *et al*., 2001; Boixeda de Miquel *et al*., 2006). Szlachcic reported the disappearance or improvement of rosacea after *H. pylori* eradication in 51 of 53 patients, but there was no placebo group in that study (Szlachic 2002). Son *et al*., found lower disease severity scores after *H. pylori* eradication treatment among patients who were *H. pylori*-positive at baseline compared with those who were *H. pylori*-negative before treatment. At the same time, they found no statistically difference in the prevalence of *H. pylori* infection in rosacea patients compared with the adult population of the study area (Son *et al*., 1999). Utaş *et al*., did not find any difference in *H. pylori* prevalence between 25 rosacea patients and 87 controls, but they observed a significant decrease in severity of the disease at the end of treatment compared with the initial scores in patients positive for *H. pylori*. However, the small study group and lack of the placebo-controlled treatment group are also the limititions of that study (Utaş *et al*., 1999*)*.

There are more studies that support the hypothesis about the relationship between rosacea and *H. pylori* infection compared with those that do not confirm this theory. This could be explained also with a publication bias, as studies with positive results, even when based on small-scale and/or uncontrolled studies (Son *et al*., 1999; Utaş *et al*., 1999; Gürer *et al*., 2002; Argenziano *et al*., 2003; Diaz *et al*., 2003; Zandi *et al*., 2003; Boixeda de Miquel *et al*., 2006) or on case reports (Mayr-Kanhäuser *et al*., 2001), are more favoured.

4.4. Rosacea and emotional status

Although quite few skin diseases have a fatal outcome, their psychosocial aspects have to be taken into account. It is recognised that disfiguring skin diseases affecting patients' self-image, could influence their socio-economic life (Jowett and Ryan 1985; Balkrishnan *et al*., 2006; Chodkiewicz *et al*., 2007;), lead to depression (Gupta and Gupta 1998; Gupta *et al*., 2005), social disturbance (Blairvacq *et al*., 2008) and recluse (Sharma *et al*., 2005), or even to suicidal ideation (Cohen *et al*., 1991; Cotterill and Cunliffe 1997; Gupta and

Gupta 1998), irrespective of severity of disfigurement (Gupta and Gupta 1998; Balkrishnan *et al*., 2006). In an uncontrolled study in an outpatient clinic it was found that 25.2% out of 2379 dermatologic patients had significant psychiatric morbidity (Picardi *et al*., 2000). In controlled studies there has been found higher psychiatric comorbidity in patients with hand eczema (Schmitt *et al*., 2009), psoriasis, and chronic idiopathic urticaria (Conrad *et al*., 2008). A great number of psychiatric patients have skin problems (Mookhoek *et al*., 2010), and pychic stress is also associated with exacerbation of a skin disease (Harvima *et al*., 1993; Kissling and Wüthrich 1993; Harvima *et al*., 1996; Kodama *et al*., 1999; Raychaudhuri and Gross 2000; Toyoda and Morohashi 2001; Sowińska-Gługiewicz *et al*., 2005; Manolache and Benea 2007). According to patients' self-reports, stress and psychogenic factors have also been implicated in exacerbation of rosacea in 8–58% of cases (Bonamigo *et al*., 2000; Lazaridou *et al*., 2010; Jaworek *et al*., 2008) but there is little solid evidence that the condition is associated with the personality type or is precipitated by emotional disturbance (Jansen and Plewig 1997).

The common misconception that both facial redness and rhinophyma associated with rosacea are due to excessive alcohol consumption makes rosacea a socially stigmatizing condition for many patients (Powell 2005). It has been shown previously that patients with rosacea have higher odds for co-morbidity with depression (Gupta *et al*., 2005). It has also been noted that psychological assessment of patients with rosacea revealed high incidence of anxiety and high frequency of the feelings of guilt and shame (Higgins and Vivier 1999).

In fact, the theory that rosacea has a psychosocial impact has evolved mainly from observations of clinic-based patients. As mentioned above, population-based studies have found the prevalence rate of rosacea to be in the range 2–10% (Berg and Lidén 1989; Schaefer *et al*., 2008), while studies with patients of dermatology clinics have established the prevalence rate of rosacea to be 0.5–3% on the basis of referrals to various dermatology centres (Powell 1998; Doe *et al*., 2001; Kyriakis *et al*., 2005; Gupta *et al*., 2005). As it was previously noted, many patients mainly with mild rosacea had not consulted a physician about it, and a number of patients with rosacea were not aware of having any skin problems at all (Berg and Lidén 1989). This suggests that rosacea is a far more common disease than is estimated by referrals of dermatology clinics, and many patients with rosacea never seek medical care for their rosacea. Relevant data for rosacea patients who have not sought medical care are scarce.

5. AIMS OF THE STUDY

The general aim of this study was to obtain additional knowledge of rosacea-associated problems.

The specific aims of the study were:

1. to determine the prevalence rate of rosacea in Estonia among ≥30-year-old population using the standard classification (NRSEC, 2002);
2. to explore the association between rosacea and supposed risk factors (age, gender, familial predisposition, *H. pylori* infection, skin phototype, working conditions, smoking status, alcohol consumption, and coffee intake) concurrently;
3. to observe the subjective disease perception of subjects with primary features of rosacea in relation to severity of the disease;
4. to compare presence of depressive symptoms between subjects with and without primary features of rosacea;
5. to find predictors of healthcare-seeking behaviour among rosacea patients and assess the factors (*incl.* symptoms of depression, subjective disease perception) associated with the healthcare-seeking behaviour.

6. SUBJECTS AND METHODS

6.1. General information

The two studies for data collection were carried out from May 2005 to December 2007: (1) among employees of randomly selected institutions of Tartu; and (2) among patients attending the Clinic of Dermatology of Tartu University Hospital due to rosacea during the same period.

Tartu is the second largest city in Estonia with about 101 000 inhabitants, and the largest city in Southern Estonia with the following ethnic composition in 2000: Estonians, approximately 80%, Russians, 16%, and others, 4% (Statistical Office of Estonia). The Clinic of Dermatology of Tartu University Hospital is the main provider of the primary dermatological care to the population of Tartu with an average of 30 500 outpatient visits yearly.

The study was approved by the Ethics Commitee of the University of Tartu. Every subject gave his or her informed written consent prior to the enrolment in the study.

6.2. Study subjects (sampling and recruitement)

Two stage sampling was implemented to recruit study subjects. A list of organizations and institutions from the Tartu was complied based on the telephone directory. A random sample of 140 was selected for further recruitement on individual study subjects. Prior to the study data collection, written detailed information specifying the aim and design of the study was sent to selected institutions (n=140); after a few days a call was made to the head of the institution and in the case of agreement an appointment was made. In 26 (19%) cases we failed to establish contact. Of the 114 contacted institutions 23 (20%) were excluded because of employing less than 3 persons aged ≥30 years. Thirty-one (27%) contacted institutions did not participate for different reasons: unsuitable organization of work (n=18), distrust in or ambivalence toward research (n=5), unclear reason (n=8). Sixty (53%) institution leaders approved the study and the institutions were visited within a few days. Of the 60 complying institutions 4 were providing health care services, 5 were research or education institutions, and the rest were active in transportation (n=1), entertainment (n=1), manufacturing (n=4), sales or services provision (n=21) and the rest (n=24) were offices.

The individual data collection was conducted during working hours and all employees aged at least 30 years, who were present on the day of the study, were invited to participate. Of the 524 eligible study subjects 348 (66%) participated (completed a questionnaire). Altogether 176 subjects did not participate in study because they were either too busy or out of the office during the visit, 102 (58%) were teachers from one and same educational institution.

All the subjects in the employees' group (n=348) were included in the analysis aimed to determine the prevalence rate of rosacea (Study I; Paper I).

Further categorisation of the study subjects was as follows: (1) subjects from the employees group with defined symptoms of rosacea were classified rosacea patients; (2) subjects with self-reported frequent flushing episodes were classified as flushers; and (3) subjects without any rosacea signs were classified as skin-healthy controls in the analysis aimed to determine the risk factors of rosacea (Study II; Paper II). Further, subjects with defined symptoms of rosacea from the employees group who had not sought medical care due to their rosacea were classified according to their healthcare seeking behaviour as nonseekers in Study III (Paper III), which focused on evaluation of the emotional status of rosacea patients (Table 1).

The consecutive patients with rosacea accessing for the medical care (n=92) were recruited by the study researcher at the Clinic of Dermatovenereology of the University of Tartu. As they had rosacea, these patients were classified as rosacea patients in Study II (Paper II) which aimed to determine the risk factors of rosacea. According to their healthcare seeking behaviour, these patients were classified as seekers in Study III (Paper III), the aim of was evaluation of the emotional status of rosacea patients (Table 1).

Table 1. Participation of study subjects, recruited from the randomly selected employee population and from Clinic of Dermatology of the University of Tartu, in Studies I–III, in Tartu 2005–2007.

	Employees	Clinic-based patients	Total
Study I*	348	None	348
Study II**	348	92	440
Study III***	227	66	293

* Prevalence of rosacea

** Risk factors of rosacea

*** Emotional status, disease perception and predictors for healthcare-seeking behaviour

6.3. Methods

6.3.1. Skin examination and disease status classification

The skin status of all study subjects was examined by one and same dermatologist among all study subjects. Erythema, telangiectasia, and phymatous changes were graded according to the NRSEC Standard Grading System (Wilkin *et al*., 2004) as mild, moderate and severe; papules and pustules were counted on one side of the face.

According to the condition of the facial skin, the subjects were classified into the following subgroups:

I subjects without any signs or symptoms of rosacea were defined as the group of non-rosacea, or controls;

II subjects who reported suffering transitory erythema episodes several times day were defined as the group of flushers;
III subjects with persistent erythema and/or visible blood vessels (telangiectases) without any other disease of facial skin were defined as the group of erythematotelangiectatic rosacea (ETR);
IV subjects with papulopustular facial rash without comedones were defined as the group of papulopustular rosacea (PPR);
V subjects with a predominantly thickening skin, irregular surface nodularities and enlargement of the nose were defined as the group of phymatous rosacea (PhR).

6.3.2. Socio-behavioural data collection

A standardised self-administered questionnaire was used to collect data on socio-behaviour life-style characteristics and medical history. The questionnaire was developed based on considering of potential risk factors of rosacea and possible confounding factors. The following data were obtained from each study subject:

- Gender
- Age
- Educational status was categorized as elementary education, vocational education, high school education, acquiring of university degree, university degree.
- Presence of flushing episodes: never, sometimes, frequently
- Family history: for collecting data on family history, photos of different subtypes of rosacea (Schmutz, *et al*. 2001) were shown to the study subjects who recorded the presence of rosacea-like skin conditions or frequent flushing episodes among the first- or second-degree relatives. Presence of frequent flushing episodes or primary symptoms of rosacea in at least one of the first- or second-degree adult relatives was defined as positive family history.
- The subjects described their skin reaction to 30 minutes of midday sunlight for the first time in summer. Sun-reactive skin types were categorized into subgroups on the basis of skin reaction as follows: Fitzpatrick I – always burn, never tan; Fitzpatrick II – usually burn, sometimes tan; Fitzpatrick III – sometimes burn, usually tan, and Fitzpatrick IV – never burn, always tan (Braun-Falco *et al*., 2000).
- Personal detrimental habits:
  - smoking status status was recorded in three categories: I – never smoked (lifelong non-smokers); II – previous smoking period with at least 1 cigarette per day but not any more (ex-smokers), and III – current smoking of at least 1 cigarette per day (active smokers).
  - alcohol consumption was recorded as an intake of at least one ‘unit’ of alcoholic beverage (*e.g.* one glass of wine, half a pint of beer or 40 mL of

spirits) in the following frequency categories: I – never or rarely, less than 1 time per month; II – occasional use, 1–3 times every month; III – week-end use, 1–2 times every week, and IV – frequent use, three or more times per week.
    - caffeine intake was recorded as follows: I – less than one cup every day; II – 1–2 cups per day; III – 3–5 cups per day, and IV – more than five cups per day.
- Occupational characteristics were recorded in two categories: I – indoor working conditions; II – both outdoor and indoor working conditions; III – outdoor working conditions.
- Medical history:
    - Duration of rosacea symptoms.
    - Use of medications for current skin condition: peroral medications (tetracycline, doxycyclin, minocycline, metronidazole, isotretinoin, or something else), prescription topical preparations (metronidazole, azelaic acid, ketoconazole, clotrimazole, or something else), physiotherapy (laser, cryotherapy), or over-the counter topical products.
    - Previous general medical history (*incl.* gastrointestinal, cardiovascular and endocrinological disorders), use of medications for other medical reasons.

6.3.3. Detection of *Helicobacter pylori*

For *H. pylori* antibodies detection venous blood samples were collected from every subject complying with venipuncture. Blood samples were transported in test tubes to the laboratory within 2 h of collection and centrifuged. Sera were stored at –20°C until assays were performed. *H. pylori* serostatus was evaluated using a commercial ELISA for anti-*H. pylori* IgG (Pyloriset EIA-G, III; Orion Diagnostica, Espoo, Finland) according to the manufacturer's instructions. Positive results were defined as a marker of *H. pylori* infection.

6.3.4. Screening of depressive symptoms

For screening for presence of depressive symptoms, all subjects completed an Estonian Mood Scale (EMS) questionnaire (also known as EST-Qnew2) (Aluoja *et al*., 1999; Ööpik *et al*., 2006). The EMS has proved to be an applicable screening instrument for identifying depressive symptoms in primary care attendees, with a sensitivity of 0.81 and specificity of 0.81 (Ööpik *et al*., 2006). The subjects evaluated, on a 5-point scale (0 = not at all; 1 = seldom; 2 = sometimes, 3 = frequently, 4 = continuously), such symptoms as feeling of sadness, lack of interest, worthlessness, no enjoyment, excessive worrying and rest does not restore strength during the past 4 weeks. Subjects with an EMS score > 11 were defined as EMS-positive and those with a score of 0–11 were defined as EMS-negative.

6.3.5. Measuring of subjective disease perception

For evaluating subjective disease perception, the participants were asked to mark on a 10-cm continuous visual-analogue-scale (VAS) how disturbing their rosacea had been during the past 4 weeks. The location of each mark on VAS was scored from 0 to 10 (0 = not at all disturbing; 10 = maximally disturbing) and was measured to 1 mm. To avoid any evaluation bias, the study subjects while completing the EMS questionnaire and VAS, were unaware of the dermatologist's opinion about the severity of their skin changes.

6.4. Statistical analysis

Continuous variables are presented as mean values (with SD), and categorical variables are presented as absolute and relative frequencies with 95% confidence intervals. To compare variables for the groups, the Chi-square test or Fisher's exact test (when the expected values were <5%) was used. The unpaired t-test was employed to compare the mean of continuous variables. Kolmogorov-Smirnov criterion was used for the assessment of normality.

Multivariate logistic analysis was performed and age-adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated for the association between different skin statuses and the study variables. Differences with a *P*-value < 0.05 were considered to be statistically significant. Multiple logistic regression analysis was used to assess the relationship between dependent and independent variables (to asess for confounding). Age, gender, and education level were entered in multiple logistic regression models as confounding factors, while rest of the other covariates were entered as observed risk factors. For multivariate analysis, the following variables were further dichotomised as follows:

- educational status was categorized into the subgroups with a below-university degree and with an university degree;
- skin phototypes were categorized into the subgroups of photosensitive (Fitzpatrick I and II) and non-photosensitive skin (Fitzpatrick III and IV);
- smoking status was categorized into the subgroups of stable smoking habits (current smokers and life-long non-smokers) and changed smoking habits (previous smoking status);
- working conditions were categorized into the subgroups of indoor working conditions and outdoor working conditions (*incl.* both indoor and outdoor working conditions).

The data of study I were analysed using the SAS 9.1 program. The data of studies II and III were analysed using the SPSS 11.0 program.

7. RESULTS

7.1. Main characteristics of the subjects

Altogether 92 clinic-based patients and 348 subjects from the employee population were enrolled in the study. The main characteristics of all study subjects are presented comparatively in Table 2.

There were no statistically significant differences in gender, education level and *H. pylori* seropositivity between the clinic-based population and the random employee population.

The study subjects recruited from the clinic were older (mean age 49 *vs* 44 years, $P<0.0001$), had more pronounced disease-rosacea status, and higher proportion of photosensitive skin type (61% vs 42%, $P<0.01$).

Table 2. Data of clinic-based patients and the randomly selected employee population, in Tartu (2005–2007)

Parameter	Clinic-based patients n (%)	Employees n (%)	*P* value
Gender			
Male	31 (34)	128 (37)	
Female	61 (66)	220 (63)	NS
Age (years)*			
30–39	27 (29)	143 (41)	
40–49	27 (29)	109 (31)	
50–59	20 (22)	66 (19)	
60+	18 (20)	30 (9)	<0.05
Mean age (±SD)	48.6±12.8	43.7±10.2	<0.0001
Median age	47	42.5	
Age range	30–81	30–77	
Education			
Below university degree	60 (70)	180 (56)	
University degree	25 (30)	139 (44)	NS
Unknown	7	29	
Fitzpatrick skin types			
I	4 (4)	9 (3)	
II	52 (57)	136 (39)	
III	32 (35)	178 (51)	
IV	4 (4)	25 (7)	<0.05
Rosacea			
Non-rosacea	0 (0)	217 (62)	
Flushing	1 (1)	52 (15)	
ETR	19 (21)	60 (17)	
PPR	63 (68)	18 (5)	
PhR	9 (10)	1 (<1)	<0.0001

Parameter	Clinic-based patients n (%)	Employees n (%)	*P* value
Severity of rosacea			
None	1 (1)	269 (77)	
Mild	22 (24)	64 (18)	
Moderate	45 (49)	14 (4)	
Severe	24 (26)	1 (<1)	<0.0001
H. pylori serostatus†			
Positive	66 (78)	174 (75)	
Negative	19 (22)	58 (25)	NS
Positive family history			
Yes	44 (48)	91 (26)	
No	47 (51)	249 (72)	
Unknown	1 (1)	8 (2)	<0.0001
Smoking status			
Never smoked	50 (54)	185 (53)	
Ex-smoker	30 (33)	74 (21)	
Active smoker	12 (13)	87 (25)	
Unknown	0	2 (1)	<0.05
Caffeine intake cups per day			
≤1	23 (25)	50 (14)	
1–2	53 (58)	169 (49)	
3–5	14 (15)	112 (32)	
>5	2 (2)	17 (5)	<0.005
Alcohol intake			
< 1 times per month	31 (34)	111 (32)	
1–3 times per month	35 (38)	127 (37)	
1–2 times per week	16 (17)	77 (22)	
≥3 times per week	10 (11)	33 (9)	NS
Occupational environment			
Indoors	68 (74)	293 (84)	
Both outdoor and indoor	18 (20)	55 (12)	
Outdoors	6 (6)	42 (4)	NS

* The ages 50–59 and 60+ are considered under one subgroup ≥50 years in Fig. 2.

† Blood samples were collected from 85 clinic-based patients and from 232 employees

7.2. Prevalence of rosacea

Altogether 348 subjects from the employee population were enrolled in the study. The data about the study population are shown in Table 1.

Seventy-eight of the 348 study subjects (22%; 95% CI 18–27%) had one or more primary features of rosacea. The most common features were erythema with 74 cases (21%; 95% CI 17–26%) and telangiectasia with 64 cases (18%; 95% CI 15–23%). The profile of the observed skin changes among the study subjects is presented in Table 2. The most commonly affected facial areas were the cheeks. The distribution of skin changes in different facial areas is shown in Fig. 1.

Sixty-one of the 78 rosacea patients (78%; 95% CI 67–87%) had ETR and 17 (22%; 95% CI 13–33%) had PPR, only one person had, besides moderate ETR, also mild rhinophyma. The majority of subjects with rosacea had mild erythema and/or telangiectasia and 0–5 papules/pustules on one side of the face (Table 3). Fifty-two out of the 348 study subjects (15%; 95% CI 11–19%) suffered frequent flushing episodes without permanent rosacea features and these subjects were classified as the flushers.

The prevalence rate of rosacea in the age group 30–39 years was 16% (95% CI 11–23%), and in the older groups, 27.5% (95% CI 19–37%; 40–49 years) and 26% (95% CI 18–36%; ≥50 years) ($P < 0.05$). Flushing episodes without permanent symptoms of rosacea were more prevalent in the age group 30–39 years compared with the older age groups. There were no age-specific differences among persons without rosacea and without frequent flushing episodes. The age distribution of subjects without rosacea, flushers and subjects with different rosacea subtypes is presented in Fig. 2. and in Paper I, Fig. 2.

There were no statistically significant differences in skin changes between the genders. Subjects with photosensitive skin types suffered flushing episodes and ETR more frequently compared with sbjects with non-photosensitive skin types (Fitzpatrick I and II), while in the non-rosacea group the dominated skin types were III and IV. There were no differences in terms of skin type according to Fitzpatrick among the patients of the papulopustular rosacea group (Fig. 3).

Table 3. Profile of observed skin changes among the study subjects (n=348) recruited from the randomly selected employee population, in Tartu (2005–2007).

Type of skin changes	No of subjects (%)
Erythema	
None	274 (79)
Mild	63 (18)
Moderate	10 (3)
Severe	1 (<1)
Telangiectasia	
None	284 (82)
Mild	54 (15)
Moderate	9 (3)
Severe	1 (<1)
No of papules on one side of the face	
None	329 (95)
1–5	11 (3)
6–10	6 (2)
11–15	2 (<1)
No of pustules on one side of the face	
None	341 (98)
1–5	7 (2)
>5	0 (0)

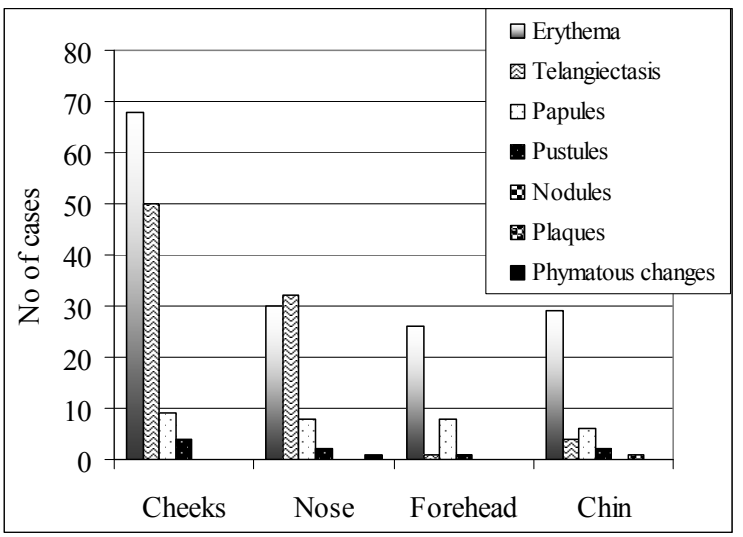

Figure 1. Distribution of skin changes in different facial areas among subjects with persistent symptoms of rosacea (n=78), recruited from the randomly selected employee population, in Tartu (2005–2007).

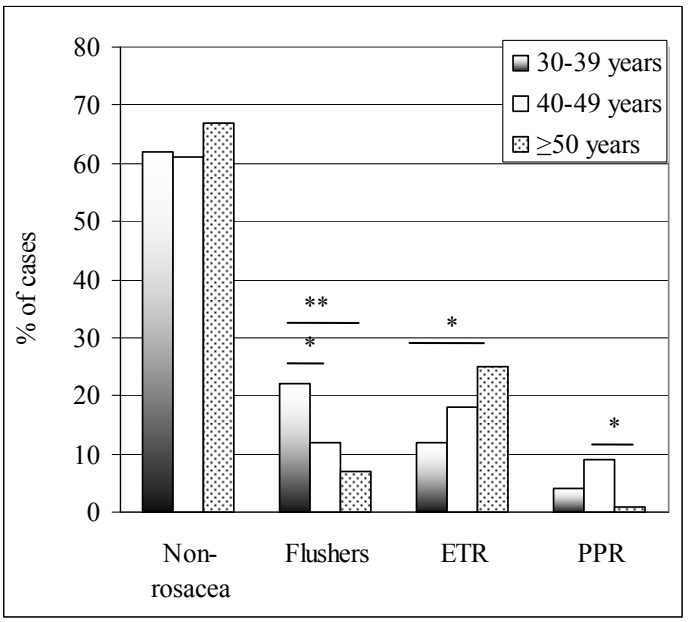

Figure 2. Age distribution of subjects with a different skin status (n=348), recruited from the randomly selected employee population, in Tartu (2005–2007).
* $P < 0.05$; ** $P < 0.005$

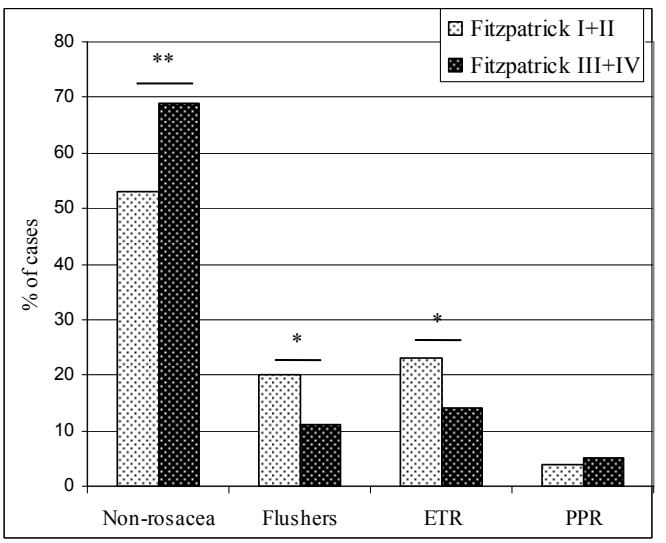

Figure 3. Skin type distribution of subjects without rosacea and those with different rosacea subtypes (n=348), recruited from the randomly selected employee population in Tartu (2005–2007).
* $P < 0.05$; ** $P < 0.005$

7.3. Risk factors for rosacea

For analysis of risk factors, 92 clinic-based patients and 348 subjects from the random employee population (Table 2) were divided into subgroups according to skin changes (Table 4; Paper II).

Flushers showed a significantly lower mean age (39.3 ± 8.4 years) compared to the other study groups (Table 3) and presented also the lowest rate of *H. pylori* seropositivity (57%; 95% CI 40–73%) (Fig. 4; Table 4). The rate of *H. pylori* seropositivity increased with age in the whole study population and was significantly higher in the age group of 50+ years compared with that in the age group of 30–39 years (Fig. 5.). There were significantly more ex-smokers than active smokers in the papulopustular rosacea group compared with controls, flushers or the erythematotelangiectatic rosacea group (Table 4).

For analysing supposed risk factors for rosacea simultaneously, several logistic regression models were constructed; in multivariate logistic analysis, the following risk factors were considered: age, gender, *H. pylori* seropositivity, skin phototype, family history, occupational environment, smoking status, caffeine intake, alcohol consumption and education (Table 5). When comparing skin-healthy controls with rosacea patients and flushers in multivariate analysis, the significant risk factors were photosensitive skin types and positive family history (Table 5). When comparing skin-healthy controls with only rosacea patients in multivariate logistic analysis, the significant risk factors were age, photosensitive skin types, positive family history and ex-smoking status (Table 5). Significant risk factors after the exclusion of mild forms of rosacea were age, photosensitive skin types, positive family history for rosacea, outdoor working conditions and ex-smoking status (Table 5). When comparing flushers (n = 35) with rosacea patients (n = 122) in multivariate logistic analysis, the only difference between these groups was age: subjects with advanced age had higher odds of developing rosacea (OR = 1.13; 95% CI 1.06–1.20; $P < 0.0001$).

Table 4. Distribution of baseline characteristics between the study subjects (n=440), recruited from the randomly selected employee population and from Clinic of Dermatology of Tartu University Hospital, in Tartu (2005–2007)*.

	Controls n (%)	Flushers n (%)	ETR n (%)	PPR n (%)	PhR n (%)	*P* value
Gender						
Male	83 (38)	13 (25)	26 (33)	29 (36)	8 (80)	
Female	134 (62)	40 (75)	53 (67)	52 (64)	2 (20)	NS
Age						
30–39 years	88 (41)	33 (62)	23 (29)	25 (31)	1 (10)	
40–49 years	65 (30)	13 (25)	25 (32)	30 (37)	3 (30)	
50+ years	64 (29)	7 (13)	31 (39)	26 (32)	6 (60)	<0.005
Mean age (±SD)	44.2±10.8	39.3±8.4	46.4±9.6	46.7±11.6	57.6±15.8	

	Controls n (%)	Flushers n (%)	ETR n (%)	PPR n (%)	PhR n (%)	*P* value
Education						
Below university degree	110 (55)	28 (56)	44 (63)	51 (67)	7 (87)	
University degree	90 (45)	22 (44)	26 (37)	25 (33)	1 (13)	NS
Unknown	17	3	9	5	2	
H. pylori serostatus						
Negative	32 (22)	16 (43)	15 (27)	12 (17)	2 (29)	
Positive	113 (78)	21 (57)	41 (73)	60 (83)	5 (71)	<0.05
Positive family history						
Yes	36 (17)	22 (43)	40 (52)	33 (42)	4 (40)	
No	178 (83)	29 (57)	37 (48)	46 (58)	6 (60)	<0.0001
Unknown	3	2	2	2		
Photosensitive skin types by Fitzpatrick						
I	4 (2)	0 (0)	5 (6)	3 (4)	1 (10)	
II	73 (34)	30 (57)	42 (53)	37 (46)	6 (60)	
III	123 (57)	22 (42)	27 (34)	36 (44)	2 (20)	
IV	17 (8)	1 (2)	5 (6)	5 (6)	1 (10)	<0.005
Smoking status						
Never smoked	118 (55)	30 (57)	42 (53)	41 (51)	4 (40)	
Ex-smoker	42 (19)	11 (21)	17 (22)	30 (37)	4 (40)	
Active smoker	55 (26)	12 (23)	20 (25)	10 (12)	2 (20)	<0.05
Unknown	2	0	0	0	0	
Caffeine intake cups per day						
≤1	33 (15)	7 (13)	15 (19)	16 (22)	2 (20)	
1–2	107 (49)	24 (45)	37 (47)	48 (59)	6 (60)	
3–5	68 (31)	22 (42)	22 (28)	12 (15)	2 (20)	
>5	9 (4)	0	5 (6)	5 (6)	0	NS
Alcohol intake						
< 1 times per month	59 (27)	25 (47)	33 (42)	24 (30)	1 (10)	
1–3 times per month	88 (41)	16 (30)	21 (26)	34 (42)	3 (30)	
1–2 times per week	45 (21)	11 (21)	18 (23)	16 (20)	3 (30)	
≥3 times per week	25 (11)	1 (2)	7 (9)	7 (9)	3 (30)	NS
Occupational environment						
Indoors	183 (84)	48 (91)	61 (77)	64 (79)	5 (50)	
Both in- and outdoors	34 (16)	5 (9)	18 (23)	17 (21)	5 (50)	NS

* phymatous rosacea and cases with unknown characteristics are not included in calculation of proportions and of *P*-values

Table 5. Multivariate logistic analysis of risk factors for rosacea among the study subjects, recruited from the randomly selected employee population and from Clinic of Dermatology of Tartu University Hospital, in Tartu (2005–2007).

	OR	95% CI	*P* value*
Rosacea patients (n = 122)			
Age (for one-year age difference)	1.04	1.01–1.07	.007
I + II skin phototype	1.75	1.01–3.04	.047
Positive family history	4.31	2.34–7.92	<0.0001
Ex-smoking status	2.01	1.07–3.80	.031
Patients with moderate and severe rosacea (n = 66)			
Age (for one-year age difference)	1.06	1.03–1.10	<0.0001
I +II skin phototypes	2.76	1.34–5.72	0.006
Positive family history	4.77	2.21–10.32	<0.0001
Outdoor working conditions	3.37	1.24–9.14	0.017
Ex-smoking status	2.25	1.001–5.05	0.05

* The reference group for each logistic regression model is controls (n=132); cases with unknown characteristics are excluded

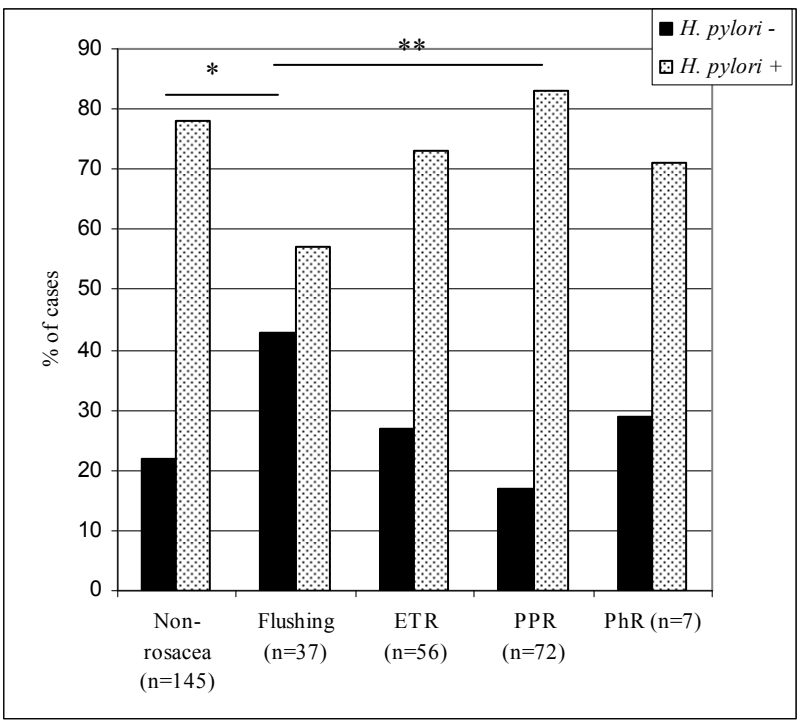

Figure 4. *H. pylori* seropositivity in relation to the subtypes of rosacea among the study population (n=317), recruited from the randomly selected employee population and from Clinic of Dermatology of Tartu University Hospital, in Tartu (2005–2007).
*$P < 0.05$; **$P < 0.005$

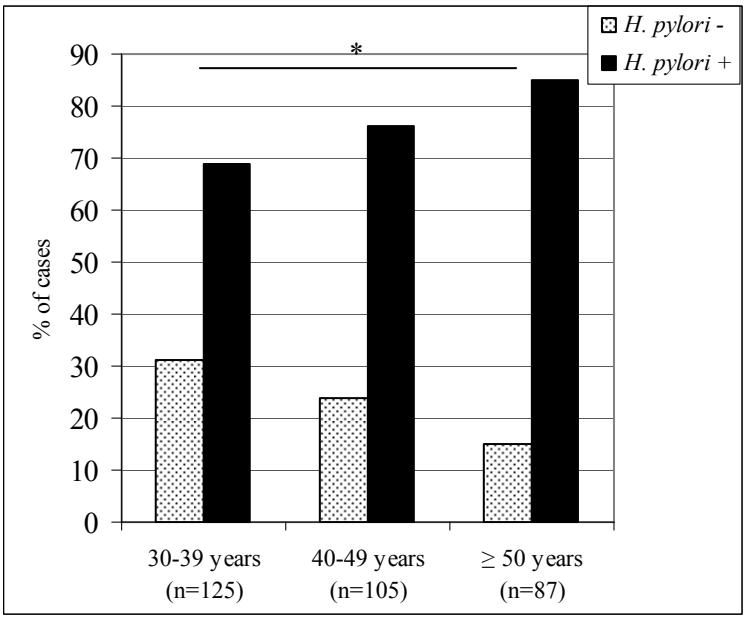

Figure 5. *H. pylori* seropositivity in relation to age among the study population (n=317), recruited from the randomly selected employee population and from Clinic of Dermatology of Tartu University Hospital, in Tartu (2005–2007).
*$p<0.01$

7.4. Emotional status, disease perception and predictors for healthcare-seeking behaviour

Altogether 126 rosacea patients (70 seekers and 56 nonseekers) were included in the screening of depressive symptoms and in the study on subjective disease perception. Besides seekers and nonseekers, 167 skin healthy controls from the employee population were included in the screening of depressive symptoms.

There were no statistically significant differences in gender, age, education level, or EMS scores between seekers and non-seekers, but seekers had more frequently moderate or severe forms of rosacea, and had more frequently either papulopustular or phymatous rosacea compared with non-seekers (Table 6). Seekers presented significantly higher VAS scores (6.2 ± 3.1) compared with non-seekers (3.1 ± 2.7) ($P < 0.0001$). Nineteen of the 56 nonseekers (34%; 95% CI 22–48%) had not noticed their skin changes at all. However, mean VAS scores were not related to severity of rosacea: among seekers the mean VAS scores were > 6 in all severity groups, while among non-seekers mean VAS scores remained around 3 in all severity groups (Fig. 6.). Female subjects with rosacea had significantly higher mean ± SD VAS scores (5.9 ± 3.2) compared with male subjects (3.2 ± 2.6) ($P < 0.0001$) (Fig. 7.).

Table 6. Comparison of subjects with rosacea (n=126), recruited from the randomly selected employee population and from Clinic of Dermatology of Tartu University Hospital, in Tartu (2005–2007), in relation to health care-seeking behaviour.

Variable	Seekers (n=70)	Nonseekers (n=56)	*P* value
Gender, n (%)			
Male	26 (37)	22 (39)	
Female	44 (63)	34 (61)	NS
Mean age (± SD) years	48 (±13)	45 (±9)	NS
Education, n (%)			
Elementary or high school	51 (73)	36 (64)	
University degree	19 (27)	20 (36)	NS
Severity of rosacea, n (%)			
Mild	24 (34)	45 (80)	
Moderate	33 (47)	10 (18)	
Severe	13 (19)	1 (2)	<0.0001
Subtypes of rosacea, n (%)			
Erythematotelangiectatic	16 (23)	42 (75)	
Papulopustular	46 (66)	14 (25)	
Phymatous	8 (11)	0	<0.0001
EMS score, n (%)			
<11	55 (79)	47 (84)	
>11	15 (21)	9 (16)	NS
VAS score, n (%)			
0–5	25 (36)	44 (79)	
>5	45 (64)	12 (21)	<0.0001
Mean VAS score (± SD)	6.2 (±3.1)	3.1 (±2.7)	<0.0001

The prevalence rate of depressive symptoms according to the EMS was 21% (15 out of 70; 95% CI 12.5–33%) for seekers, 16% (9 out of 56; 95% CI 8–28%) for non-seekers (Table 6), and 11% (18 out of 167; 95% CI 6.5–16.5%) for skin healthy controls. There were no statistically significant differences, either in co-morbidities, which might add to depressive symptoms (*e.g.* thyroid disease or previous history of malignancies), or in the use of medication for any other medical purposes. EMS-positive seekers had significantly higher mean ± SD VAS scores (7.9 ± 2.1) compared with EMS-negative seekers (5.8 ± 3.1) ($P < 0.05$); this difference was non-significant for non-seekers (Fig. 8.).

Multivariate analysis showed that the independent predictors for healthcare-seeking behaviour among seekers were higher subjective disease perception (VAS scores > 5) (OR=12.0; 95% CI 3.51–40.74; $P < 0.0001$), presence of papulopustular rosacea (OR=6.9; 95% CI 2.41–19.49; $P < 0.0001$) and presence of moderate or severe forms of rosacea (OR=6.8; 95% CI 2.23–20.55; $P = 0.001$) compared with nonseekers. Healthcare-seeking behaviour was not dependent on age, gender, education or EMS-positivity. Separate multivariate logistic regression models were constructed for seekers and nonseekers compared with controls; the following risk factors were considered: age, gender,

education level, and presence of depressive symptoms. Multivariate logistic analysis showed that seekers were more likely to be depressive (OR=2.7; 95% CI 1.19–5.98; $P < 0.05$), older (OR=1.026 for one-year age difference; 95% CI 1.001–1.051; $P < 0.05$), and with education level below university degree (OR=2.0; 95% CI 1.06–3.77; $P < 0.05$) compared with skin-healthy controls. There were no significant differences between nonseekers and skin-healthy controls.

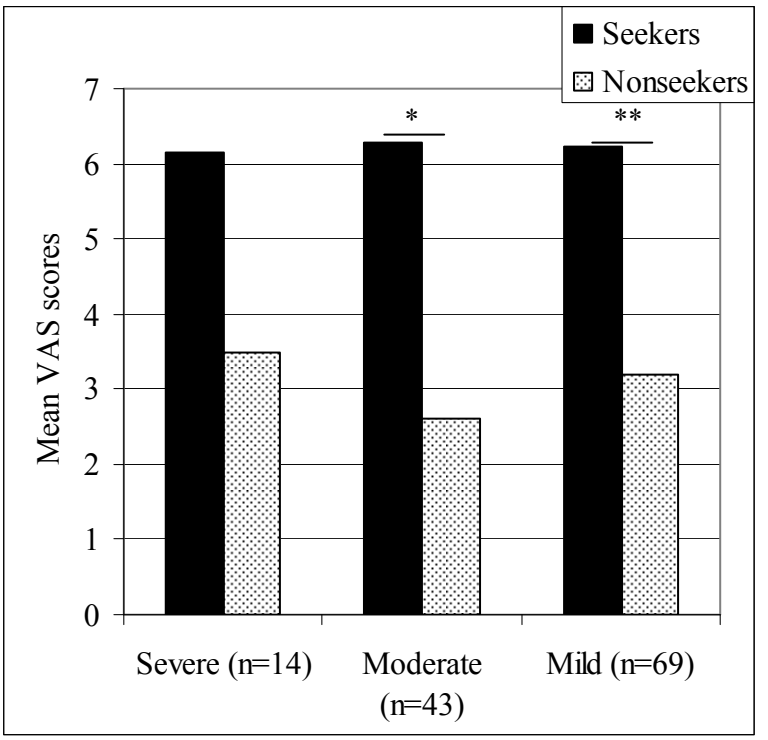

Figure 6. Scores of the mean visual analogue scale (VAS) for seekers (n=70) and non-seekers (n=56), recruited from the randomly selected employee population and from Clinic of Dermatology of Tartu University Hospital, in Tartu (2005–2007), in relation to severity of rosacea. *$P = 0.001$, **$P < 0.0001$.

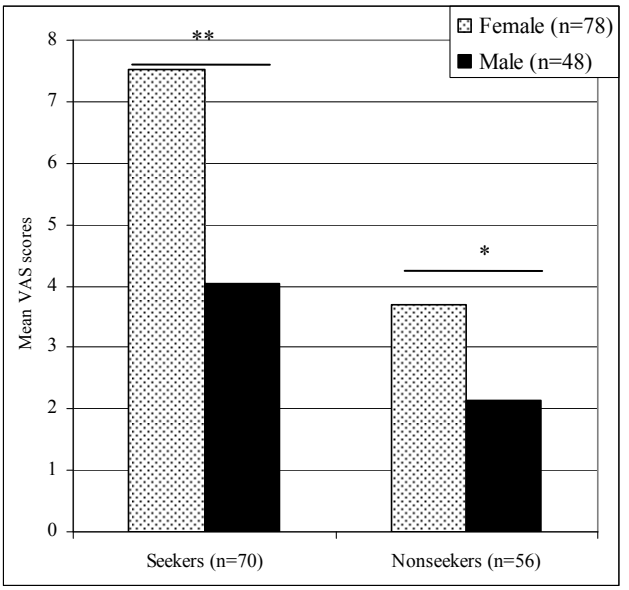

Figure 7. Scores of the mean visual analogue scale (VAS) for male and female study subjects (n=126), recruited from the randomly selected employee population and from Clinic of Dermatology of Tartu University Hospital, in Tartu (2005–2007). **P* = 0.012, ***P* < 0.0001.

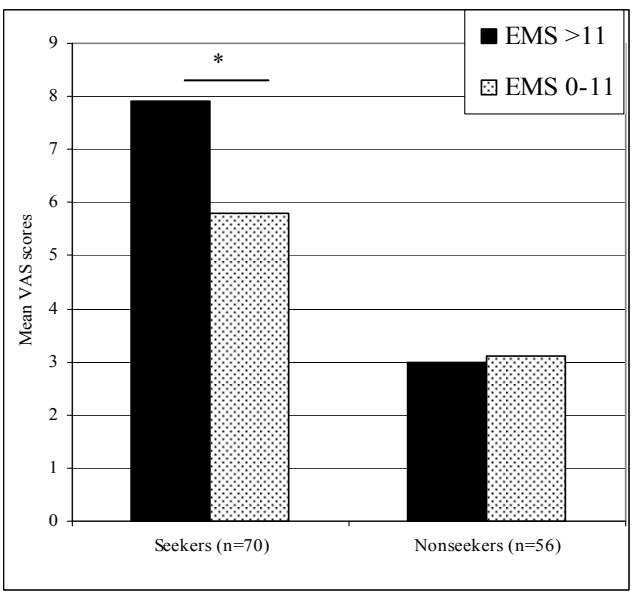

Figure 8. Scores of the mean visual analogue scale (VAS) for seekers (n=70) and nonseekers (n=56), recruited from the randomly selected employee population and from Clinic of Dermatology of Tartu University Hospital, in Tartu (2005–2007), in relation to the scores of the Estonian Mood Scale (EMS). **P* < 0.05

8. DISCUSSION

The prevalence of rosacea was investigated in a randomly selected working population, aged ≥30 years, by following directly the NRSEC criteria (Wilkin *et al*., 2002). The overall prevalence rate of rosacea symptoms was found to be 22% (95% CI 18–27%). In similar studies conducted in Sweden (Berg and Lidén 1989) and in Germany (Schaefer *et al*., 2008) the prevalence rate of rosacea in the general working population was 10% and 2%, respectively. In 1989, Berg *et al*., defined the "rosacea group" as individuals having papules and/or pustules, erythema, telangiectasia and swelling, or an anamnesis of rosacea within the past two years; they reported that, besides the rosacea group, also 55% of the rest of the study population had telangiectasia (Berg and Lidén 1989), which is one of the primary signs of rosacea and should be classified as erythematotelangiectatic rosacea according to the NRSEC classification (Wilkin *et al*., 2002). Schaefer *et al*., did not specify the criteria used for diagnosing rosacea, but that study was started before the establishment of the NRSEC classification in 2002 (Wilkin *et al*., 2002). It has been noted that the prevalence rate depends on the classification used by the researcher (Berg and Lidén 1989). Use of different diagnostic criteria of rosacea might explain discrepancies in the results of different studies. Results may also vary among different investigators, as some examiners could detect mild skin changes more carefully comparing with others.

Most of the skin changes observed in the current study were rather mild. According to the NRSEC classification, the clinical scorecard of rosacea depends on severity of primary and secondary features. For scoring PPR, the NRSEC suggests counting of papules and pustules as being few, several or many. Like some other authors (Gessert and Bamford 2003), we are of the opinion that for a better understanding, the exact number of lesions should be taken into account. For the sake of clarity, the issue of classification of papules and pustules requires further discussion among experts.

The prevalence rate of ETR was three times higher than that of PPR and phymatous changes were very rare. Similar proportions of rosacea subtypes have also been reported previously (Berg and Lidén 1989; Kyriakis *et al*., 2005). Fifteen percent of the study subjects suffered frequent flushing episodes without permanent rosacea features. As the data were mainly based on the subjects' reports and as, besides rosacea, there are many other causes of flushing, *e.g.* fever, medications, climacterium, malignancies, anaphylaxis, *etc.* (Izikson *et al*., 2006), those persons were included in a separate group but not in the rosacea group.

There is common opinion that the prevalence of rosacea peaks between 40 and 60 years of age (Braun-Falco *et al*., 2000). In the current study it was also found that the prevalence rate of rosacea was significantly higher after age 40 years. The prevalence of PPR was higher in the fourth decade of life and remained lower in the later life decades (Fig. 2. and in Paper I, Fig. 2.).

Both genders were equally affected with rosacea. Rosacea has been previously thought to be a disease with female predominance (Jansen and Plewig 1997; Berg and Lidén 1989), however some other epidemiological studies found that both genders were equally affected (Kyriakis *et al*., 2005; Schaefer *et al*., 2008;). A possible explanation for the opinion about the female predominance of this disease is the fact that women seek care for rosacea more often compared with men (Feldman *et al*., 2001).

In the current study it was found that subjects with light photosensitive skin types suffered both flushing episodes and ETR more frequently, which confirms the results of previous reports that rosacea is predominately a disease of the fair skin (Berg and Lidén 1989; Lazaridou *et al*., 2010; Abram *et al*., 2010b). The prevalence of flushing episodes without permanent rosacea signs decreased in the older age groups giving way to ETR whose prevalence increased with age, contrary to flushing. This suggests that transition from flushing episodes to erythematotelangiectatic rosacea is presumably related to the (photo)ageing process.

Although the proportions of the subtypes and genders were similar to those in earlier studies, the prevalence rate of rosacea according to our study was markedly higher than that found in other studies on rosacea prevalence (Berg and Lidén 1989; Schaefer *et al*., 2008). Yet approximately one-third of the subjects from general population had not even noticed their skin changes. Also Berg *et al*., reported that many rosacea patients, mainly men, had not consulted a physician due to rosacea and 10 out of 81 subjects with typical rosacea lesions were not aware of having any skin problems at all (Berg and Lidén 1989). This raises the question whether rosacea is more common than previously expected, or whether its diagnostic criteria are too slack. It has been suggested that the NRSEC classification is too permissive and presence of papules and pustules at minimum are required for the diagnosis of rosacea; and in absence of papules and pustules, actinic erythema and/or actinic telangiectasia would be better referring diagnoses (Danby 2005). On the other hand, our study suggested that subjective disease perception was an independent reason for healthcare seeking among rosacea patients and was not always related to severity of the disease (Paper III); some patients may react with subjective skin symptoms even without having any visible skin signs (Lonne-Rahm *et al*., 1999).

Several possible risk factors for rosacea were investigated coincidently. The major focus of interest was association between rosacea and *H. pylori* infection. The current study found no association between rosacea and *H. pylori* infection. We found that flushers had significantly lower *H. pylori* seroprevalence compared with all other study groups, however, as the flushers were significantly younger than the other study subjects, the difference in *H. pylori* serostatus disappeared in multivariant analysis after adjustment for age. This phenomenon is explicable by the birth cohort effect, which means that younger generations have lower prevalence rate of *H. pylori* infection due to different environmental exposures and society changes (Banatvala *et al*., 1993). Also in the current

study the rate of *H. pylori* seropositivity among the study subjects was significantly lower in the fourth decade of life than in the sixth decade or later.

Multivariate logistic analysis also revealed that the only difference in the risk factors between flushers and rosacea patients was the age. This finding supports the theory that frequent flushing episodes, irrespective of their triggering factors, would be the stage of pre-rosacea, and development of persistent rosacea signs in future among these subjects is likely. It has been shown that in aging cells the potential of endogenous antioxidants decreases and response to harmful factors (e.g. UV irradiation) delays (Bossi *et al*., 2008); this explains why rosacea typically begins after age 30 (Wilkin *et al*., 2002), increasing consistently with years (Berg and Lidén 1989; Paper I), and only rarely occurs in pediatric patients (Kroshinsky and Glick 2006). There were no statistically significant differences in the age distribution between controls, subjects with ETR, and subjects with PPR; mean age was significantly higher in the phymatous rosacea group – this finding confirms previous observation that phymatous rosacea starts in later decades compared with other subtypes (Azhary *et al*., 1991).

There were no marked gender related differences between study groups, except for the phymatous rosacea group with significant male predominance (Paper II). As already mentioned above, rosacea affects both genders equally (Kyriakis *et al*., 2005; Schaefer *et al*., 2008; Paper I), although phymatous rosacea occurs almost exclusively in men (Curnier and Choudhary 2004; Kyriakis *et al*., 2005; Bittencourt *et al*., 2006). Yet although phymatous rosacea is a so rare subtype (Berg and Lidén 1989; Paper I), this it does not affect the prevalence rates of rosacea for the genders in general.

There was a significantly higher proportion of ex-smokers in the papulopustular rosacea group compared with the other study groups. In multivariate analysis there the risk of developing rosacea was approximately two-fold higher among ex-smokers than among other subjects who had not changed their smoking habit. In a previous study (Mills and Marks 1996) it was found that rosacea is predominantly a disease of non-smokers; the authors explained that the possible reason for the lower prevalence of the disease in the smokers' group could be the result of decreased inflammatory response in smokers. However, the authors did not analyse the risks of the disease separately for ex-smokers and lifelong non-smokers. Despite the enormous burden of tobacco related diseases, smoking seems to prevent development of several immune-mediated granulomatous diseases. The incidence of sarcoidosis is significantly lower in smokers than in non-smokers (Hance *et al*., 1986), and ulcerative colitis is more prevalent in ex-smokers than in current smokers (Calcins 1989) or in lifelong non-smokers. The authors argue that the withdrawal of the immunosuppressive effect of smoking acts as a trigger for the disease onset (Abraham *et al*., 2003), or induces an increase in disease activity (Beaugerie *et al*., 2001). It has also been found that smoking may have a protective role in development of inflammatory facial acne in girls (Rombouts *et al*., 2007); it is

possible that discontinuation of the immunosuppressive effect of smoking might also have a effect in inflammatory rosacea.

Despite the traditionally widespread opinion that the red face, particularly with rhinophyma, is associated with excessive use of alcohol, we found no statistically significant differences between the study groups in relation to the frequency of alcohol consumption. It is known that alcohol causes, due to elevation of acetaldehyde level, facial reddening among subjects who are predisposed to flush (Eriksson 2001); therefore some of them find this flushing reaction sufficiently disabling so that they are more likely to voluntarily abstain from alcohol (Higgins and Vivier 1999). We did not find associations between skin changes and caffeine intake, either. Only a few data are available on the effect of caffeine and coffee on rosacea; these data show that the active agent causing flushing at 60°C is heat but not caffeine (Wilkin 1981). Thus, to prevent flushing, all kinds of hot beverages should be avoided.

In the current study, one of the risk factors for rosacea was the photosensitive skin type, which is also in accordance with previous observations (Berg and Lidén 1989; Lazaridou *et al*., 2010). As the photosensitive skin types are more likely predisposed to UV harmful effects, it suggests that rosacea is related to the photoaging process. This theory is also supported by the finding that working in outdoor conditions was the risk factor for moderate and severe rosacea, as these patients had evidently experienced longer exposure to sun. However, it is worthwhile to remember that also wind, cold, or temperature changes have a negative influence on the skin, which should not be underestimated, especially at higher latitudes as in Estonia and other nothern countries.

Owning a certain skin phototype is largely genetically determined. A positive family history of rosacea was constantly the strongest risk factor for rosacea throughout different models of multivariate analysis in the current study. Although a positive family history of rosacea was also reported in some previous studies (Powell 1998; Lazaridou *et al*., 2010; Powell 2005), the mode of inheritance is not yet clear and only a few studies have addressed the genetic background of rosacea (Yazici *et al*., 2006; Jansen *et al*., 2004). The current study did not answer the question whether familial predisposition is associated more with the genetic background or with shared environmental factors, and this area needs further research.

The current study compared subjective disease perception and presence of depressive symptoms among rosacea patients, in relation to their healtcare-seeking behaviour. In the current study VAS was used as a self-assessment tool for evaluating subjective disease perception. Seekers presented significantly higher subjective disease perception compared with non-seekers but this measure was not related to severity of rosacea (Fig. 6). It has also been found, in the case of other dermatological diseases, that the clinical severity of a skin disease measured by the dermatologist does not correlate with the patients' subjective health measures (Reimus *et al*., 2007; Jemec and Serup 1992). This is especially the case if the disease affects an "emotionally charged" body region, such as the face (Balkrishnan *et al*., 2006; Gupta and Gupta 2003), particularly

in female patients (Jemec and Serup 1992; Holm *et al*., 2004), as was also found in the current study. It should be noted that women have higher disease perception compared with men in general (Apostolidis *et al*., 2009; Ghezeljeh *et al*., 2010). Subjective disease perception and social factors are thought to have a greater impact on health-related quality of life than the clinical issue (Lee *et al*., 2007); illness perception also significantly influences treatment behaviour (Buck *et al*., 2007), and it is suggested that more attention should be paid to mental well-being, at least in the case of patients seeking actively medical care (Harvima *et al*., 1996). In a previous study conducted among atopic eczema patients a simple VAS score of the patients' assessment of disease severity showed significant correlation with most methods for assessment of health-related quality of life (HRQoL) (Holm *et al*., 2006). Although VAS described well the relevant differences between the subjects in the current study, this instrument has rarely been used for evaluation of subjective disease perception among dermatological patients.

In this study an EMS questionnaire was used as the tool for comparing depressive symptoms in seekers, non-seekers, and skin-healthy controls. The prevalence rate of depressive symptoms among skin-healthy controls was comparable with that in a previous study from Estonia, which found depressive symptoms in 11% of the general population during the past month by using EST-Q (Aluoja *et al*., 2004). The prevalence rate of depressive symptoms was significantly higher among seekers compared with controls, while there were no statistically significant differences between nonseekers and controls in this respect. This finding contradicts the opinion that rosacea patients are depressive due to their skin disease, but subjects who seek healthcare have more often depressive symptoms than subjects from the general population. Previous studies also suggest that depressive symptoms are associated with higher health service consumption (Kurdyak *et al*., 2008) and with an increase in the time spent for treatment (Jemec *et al*., 2006).

The current study also evaluated indicators that predict healthcare-seeking behaviour in rosacea patients. Independent predictor for healthcare-seeking behaviour was severity of disease, although about 20% of the non-seekers with either moderate or severe rosacea had not sought dermatological care. Similar results were also found in another study conducted among dermatological patients with hand eczema (Hald *et al*., 2008). Besides the advanced forms of rosacea, subjective disease perception was a strong independent predictor for healthcare-seeking behaviour irrespective of disease severity. Although EMS-positivity was not an independent predictor for healthcare-seeking behaviour, higher subjective disease perception among seekers was associated with presence of depressive symptoms, even in mild cases. This suggests that healthcare-seeking behaviour, combined with high subjective disease perception, might be a sign of disguised depression. However, the issue whether higher disease perception affects depression, or whether higher disease perception is caused by depression remains still unclear.

The strengths of the current study is that to the best of our knowledge it is the first study on the prevalence rate of rosacea that directly and strictly follows the NRSEC criteria, in which all study subjects represent a randomly selected working population. In the current study all investigations were made by the same dermatologist, and the results did not vary among different investigators. It is the first study that observes both clinic-based patients and subjects with rosacea who have never sought medical care due to rosacea.

There are also some limitations to the study. First, there was an over-representation of female subjects. As the study subjects of the employees' group were mainly recruited from working offices, we suppose that there is a relatively higher proportion of women than men among office employees, while there are more men than women among outdoor workers. Due to the study design, non-working people were not included to rosacea prevalence study. However, the rate of registered unemployment in the study period (2005–2007) was very low (4.3%, 2.4%, and 2.1%, respectively) (http://www.tootukassa.ee/public/RegU_2009_11.xls). It was impossible to analyse the influence of duration of rosacea on disease perception, because the majority of non-seekers could not detect the onset of their rosacea and one third of non-seekers had not even noticed their skin changes.

9. CONCLUSIONS

1. According to the current classification, the prevalence of rosacea is approximately 22% among ≥30 year-old population, which is significantly higher than previously estimated on the basis of earlier epidemiological studies or by referrals to dermatology centres. The prevalence of rosacea increases with age. Rosacea affects both genders equally.
2. Risk factors for rosacea are familial predisposition, photosensitive skin types, and advanced age. Outdoor working conditions and previous smoking status are the risk factors for advanced forms of rosacea. No evidence is found that rosacea is associated with exposition to *Helicobacter pylori* infection.
3. Subjective disease perception is not associated with the objectively measured severity of the rosacea.
4. Rosacea patients who have sought medical care due to the condition have two-fold odds to have depressive symptoms compared with skin-healthy controls from the general population. There is no significant difference in depressive symptoms between skin-healthy controls and subjects with rosacea symptoms who have not sought medical care. The opinion that rosacea causes higher comorbitidy with depression has been formed on the basis of observations of patients from healthcare centers. The presence of depressive symptoms is related to the patients' subjective disease perception but not to the severity of the rosacea recorded by the doctor.
5. Independent predictors for healthcare-seeking behaviour in rosacea patients are presence of severe forms of rosacea and higher subjective disease perception. Subjective disease perception is higher among women. The more frequent attendance of female patients due to rosacea is associated with higher subjective disease perception among women rather than with gender-related predisposition to rosacea.

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11. SUMMARY IN ESTONIAN

Rosaatsea levimus ja riskitegurid. Rosaatseahaigete subjektiivne haigustunnetus

Rosaatsea on näo kumeraid alasid hõlmav krooniline dermatoos, mis kulgeb ägenemiste ja remissioonidega. Rosaatsea diagnoosimiseks puuduvad laboratoorsed markerid ja kuni 2002. aastani polnud ka diagnostilised kriteeriumid täpselt defineeritud. Alates 2002. aastast on kasutusel NRSEC (National Rosacea Society Expert Committee) poolt välja töötatud standardklassifikatsioon, mille kohaselt on rosaatsea diagnoosiks vajalik ühe või mitme primaarse sümptomi olemasolu näo tüüpilistes piirkondades. Nendeks sümptomiteks on õhetushoogude esinemine, püsiv punetus, punetavad paapulid, millele võivad kaasneda pustulid ja nähtavad veresooned ehk telangiektaasiad. Lisaks primaarsetele tunnustele võib esineda põletus- või torkimistunnet, naaste, kuivust, turset, silmamanifestatsioone ja fümatoosseid muutusi. Vastavalt standardklassifikatsioonile eristatakse 4 alatüüpi:

- Alatüüp 1: Erütematotelangiektaatiline rosaatsea (ETR) on kõige sagedam vorm ja sellele on iseloomulik õhetushoogude esinemine, püsiv punetus ja telangiektaasiad.
- Alatüüp 2: Paapulopustulaarne rosaatsea (PPR) on sageduselt järgmine alatüüp. Sellele on iseloomulik püsiv punetus koos paapulite ja pustulitega.
- Alatüüp 3: Fümatoosne rosaatsea (PhR) on harvaesinev alatüüp ja esineb peamiselt meestel alates 40.–60. eluaastast. Sellele vormile on iseloomulik naha paksenemine ja ebakorrapärane sõlmeline pind. Fümatoossed muutused esinevad kõige sagedamini ninal.
- Alatüüp 4: Okulaarne rosaatsea – silmamuutused võivad esineda 6–50% rosaatseahaigetest ning võivad 20% juhtudest eelneda nahamuutustele. Tunnusteks on konjunktiivide hüpereemia, võõrkehatunne silmas, põletus- või torkimistunne, kuivus, sügelemine, valguskartus, nägemise halvenemine, telangiektaasiad silmas ja punetus silmade ümber.

Rosaatsea raskusastme määramisel võetakse arvesse primaarsete tunnuste raskusastet skaalal 0-st 3-ni (puudub, kerge, mõõdukas, raske) ning sekundaarsete tunnuste esinemist. Rosaatsea histoloogilised muutused sõltuvad haiguse tüübist ja staadiumist. ETR korral esinevad peamiselt üladermas dilateerunud veenulid ja lümfisooned, perivaskulaarne ja -follikulaarne infiltraat, mõõdukas elastse koe hüperplaasia, kerge turse ja aktiiniline elastoos. PPR korral esineb intrafollikulaarseid neutrofiilide kogumikke, perifollikulaarse ja –vaskulaarse infiltraadi rohkenemist, sidekoe diffuusset ekspansiooni ja follikulaarkanalite keerdumist, millele kaasneb rasufolliiklite hüperplaasia. PhR korral esineb sidekoe ja rasunäärmete hüperplaasia, folliiklite avauste laienemine, telangiektaasiad, perifollikulaarsed plasmarakkude, lümfotsüütide ja histiotsüütide infiltraadid, supuratsioon ja väljendunud elastoos.

Kuigi rosaatsea on sage haigus, puuduvad täpsed andmed selle levimuse kohta. Euroopas ja USAs läbi viidud erinevate uuringute andmetel moodustavad rosaatseahaiged dermatoloogi juurde pöördunud patsientidest 0,5–3%. Kahes varasemas rahvastikupõhises uuringus leiti rosaatsea levimuseks 10% Rootsis ja 2% Saksamaal. Enamikul rosaatseahaigetest esines nendes uuringutes kerge või mõõdukas haigusvorm, rasket rosaatseat esines harva. Siiski olid mõlemad uuringud alustatud enne praeguse diagnoosimissüsteemi kasutusele võtmist.

Rosaatsea tekkepõhjused on tänini ebaselged. Rosaatsea võib alata igas eas, kuid tüüpiliselt algab siiski peale 30. eluaastat. Rosaatseat esineb nii meestel kui naistel; mõnedes uuringutes on naistel leitud kõrgem levimus kui meestel, teistes mitte. Rosaatseat esineb rohkem heledanahalistel keldi ja Põhja-Euroopa päritoluga inimestel, tumedanahalistel esineb seda väga harva. Haiguse perekondlikku esinemist on kinnitanud 15–30% patsientidest, kuid andmeid pärilikusse kohta on siiski vähe. Arvatakse, et rosaatsea patogeneesis mängivad olulist rolli keskkonnategurid. *In vitro* uuringutes on näidatud, et ultraviolettkiirgus soodustab hapniku reaktiivsete osakeste teket, angiogeneesi ja aktiveerib sidekoe degeneratsiooni. Samas märkavad paljud patsiendid haiguse ägenemist hoopis talvel, mille põhjuseks võib olla külmast ja tuulest tingitud vasodilatatsioon. Vasodilatatsiooni võib põhjustada nii ekso- kui ka endogeenne soojus, sh. kuumade toiduainete (nt. kohvi) tarbimine. Ühes katses on veenvalt tõestatud, et kohvi puhul pole õhetust esile kutsuvaks teguriks mitte kofeiin, vaid joogi temperatuur >60 °C. Vähemalt neljandik patsientidest märkavad sümptomite ägenemist seoses alkoholi tarbimisega, kuid uuringutes pole leitud tõendeid, et rosaatseahaigete hulgas esineks sagedamini alkoholismi. Rosaatseahaigete hulgas on leitud üllatavalt vähe suitsetajaid, kuid patsiendid ise ei pea suitsetamist rosaatseat ägestavaks teguriks.

Fokaalinfektsioone peetakse nahahaigusi ägestavateks teguriteks. Alates 1990-ndatest aastatest, kui ühes uuringus avastati rosaatseahaigete hulgas kõrgem *H. pylori* infektsiooni levimus võrreldes sama piirkonna üldrahvastikuga, on tegeletud rosaatsea ja *H. pylori* infektsiooni omavaheliste seoste uurimisega. Mõnedes uuringutes on näidatud ka *H. pylori* eradikatsioonravi soodsat mõju rosaatseale. Siiski on enamus töid väikesemahulised, paljudes puudub kontrollrühm või pole arvestatud kaasnevaid riskitegureid, samuti on nende uuringute tulemused vastuolulised.

Rosaatsea on haigus, mis haarab näopiirkonda ning võib seetõttu oluliselt mõjutada patsientide psühhosotsiaalset heaolu ning soodustada depressiooni. Samuti võib psühhogeenne stress patsientide arvates olla haigust ägestavaks teguriks. Siiski baseerub see arvamus üksnes arsti poole pöördunud patsientide hulgas läbi viidud uuringutel ning andmed arsti juurde mittepöördunud isikute kohta puuduvad.

Eesmärgid:

1. Hinnata rosaatsea levimust Eestis ≥30-aastaste isikute hulgas kasutades standardklassifikatsiooni (NRSEC, 2002).

2. Uurida seoseid rosaatsea ja arvatavate riskifaktorite vahel (vanus, sugu, perekondlik eelsoodumus, *H. pylori* infektsioon, naha fototüüp, töökeskkond, suitsetamine, kohvi- ja alkoholitarbimine) samaaegselt.
3. Hinnata rosaatseahaigete subjektiivset haigustunnetust sõltuvalt haiguse raskusastmest.
4. Võrrelda depresiivsete sümptoomide esinemist rosaatseaga ja ilma rosaatseata isikute vahel.
5. Leida rosaatseahaigete hulgas arsti juurde pöördumist ennustavad tegureid ja hinnata haiguskäitumisega seotud tegureid (k.a. depressiivsed sümptoomid ja subjektiivne haigustunnetus).

Uuritavad ja metoodika

Uuring viidi läbi aastatel 2005–2007 Tartus. Esimese uuritavate grupi moodustasid Tartu linna juhuslikult valitud asutuste ≥30-aastased töötajad (n=348), kes hõlmati rosaatsea levimust, riskifaktoreid ja rosaatseahaigete emotsionaalset seisundit hindavatesse analüüsidesse (publikatsioonid I–III). Teise uuritavate grupi moodustasid TÜ Nahahaiguste Kliinikusse rosaatsea tõttu pöördunud järjestikused patsiendid (n=92), kes hõlmati rosaatsea riskifaktoreid ja rosaatseahaigete emotsionaalset seisundit hindavatesse analüüsidesse (publikatsioonid II, III). Kõigi uuritavate nahaseisundit hindas sama dermatoloog vastavalt NRSEC standardkriteeriumitele. Kõik uuritavad täitsid küsimustiku vanuse, soo, haridustaseme, pereanamneesi, õhetushoogude sageduse, naha fototüübi, personaalste kahjulike harjumuste, töötingimuste, põetud haiguste ja kasutatud ravimite kohta. Rosaatseahaigetele olid lisaks eraldi küsimused sümptoomide kestvuse ja kasutatud ravimeetodite kohta. 317 uuritavat (85 kliiniku patsienti ja 232 üldpopulatsiooni uuritavat) olid nõus andma vereproovi, millest määrati ELISA testiga *H. pylori*-vastased IgG tüüpi antikehad. Depressiivsete sümptoomide esinemise hindamiseks kasutati enesehinnangulise meeleolu skaala (EMS) küsimustikku. Subjektiivse haigustunnetuse hindamiseks paluti rosaatseatunnustega isikutel visuaal-analoog-skaalal (VAS) hinnata (0-st 10-ni), kui palju viimase kuu jooksul on nahamuutused neid häirinud. Andmeid analüüsiti kasutades statistikaprogramme SAS 9.1 ja SPSS 11.0.

Tulemused

Haiglapatsientide ja üldrahvastikust pärit uuritavate vahel ei olnud statistiliselt olulisi erinevusi soolise jaotuse, haridustaseme ja *H. pylori* seropositiivsete osakaalu osas. Haiglapatsientide hulgas leidus rohkem fotosensitiivse nahatüübiga isikuid ja nende keskmine vanus oli 5 aastat kõrgem kui üldrahvastikust pärit uuritavate rühmas. Levimusuuringus leiti, et 348-st juhuslikult valitud isikust 78-l (22%; 95% CI 18–27%) esines üks või mitu persisteerivat primaarset rosaatsea tunnust; 30–39-aastaste hulgas oli rosaatsea levimus 16% (95% CI 10,5–23%), samal ajal kui vanemates eagruppides oli levimusmäär kõrgem, vastavalt 27,5% (95% CI 19–37%; 40–49 aastased) ja 26% (95% CI 18–36%; ≥50 aastased) (P<0.05). Sagedasi õhetushoogusid ilma püsivate nahamuutusteta esines 52-l (15%; 95% CI 11–19%) uuritaval. Sagedaseimateks nahamuutusteks

olid erüteem (21%; 95% CI 17–26%) ja telangiektaasiad (18%; 95% CI 15–23%). Kõige sagedamini esinev subtüüp oli ETR (61 juhtu), PPR esines 17 uuritaval, kerget fümatoosset rosaatseat esines ainult ühel uuritaval.

Rosaatsea arvatavate riskitegurite samaaegseks analüüsimiseks kasutati mitmest logistilist regressioonanalüüsi, võttes arvesse järgmisi riskitegureid: vanus, sugu, haridustase, perekondlik eelsoodumus, *H. pylori* seropositiivsus, naha fototüüp, töökeskkond, suitsetamine, kohvi- ja alkoholitarbimine. Kontrollrühma võrdlusel rosaatseahaigete ja õhetajatega osutusid olulisteks riskiteguriteks hele nahk ja positiivne pereanamnees. Kontrollirühma võrdlusel üksnes rosaatseahaigetega osutusid olulisteks riskiteguriteks kõrgem vanus, fotosensitiivne nahatüüp, positiivne pereanamnees ja varasem suitsetamine. Eemaldades samast mudelist kerge rosaatsea juhud, osutus oluliseks riskiteguriks ka töötamine välitingimustes. Õhetajate ja rosaatseahaigete omavahelises võrdluses osutus ainsaks riskiteguriks kõrgem vanus. Üheski mitmese logistilise regressioonanalüüsi mudelis ei esinenud rosaatsea ja *H. pylori* infektsiooni vahel statistiliselt olulisi seoseid.

EMS küsimustiku täitis ja oma subjektiivset haigustunnetust hindas 70 rosaatsea sümptomitega pöördujat ja 56 mittepöördujat. Kahe uuritavate grupi vahel ei esinenud erinevusi soo, vanuse, haridustaseme; pöördujate hulgas esines märkimisväärselt sagedamini raskeid haigusvorme võrreldes mittepöördujatega. Pöördujate subjektiivne haigustunnetus osutus oluliselt kõrgemaks võrreldes mittepöördujatega, kuid need väärtused polnud seotud objektiivselt haiguse raskusega: pöördujatel oli keskmised VAS-skoorid kõigi (sh. kergete) haigusvormide korral >6, samal ajal kui mittepöördujatel jäid keskmised VAS-skoorid 3 lähedale isegi raskete haigusvormide korral; 56-st mittepöördujast 19 isikut (34%; 95% CI 22–48%) polnud oma nahamuutusi isegi märganud. Depressiivseid sümptoome (EMS skoor >11) esines 21% (95% CI 12,5–33%) pöördujatest ja 16% (95% CI 8–28%) mittepöördujatest ja nende vahel statistiline erinevus puudus, samal ajal esines kontrollgrupis depressiivseid sümptoome 11% (18 isikul 167-st; 95% CI 6.5–16.5%). Mitmene logistiline reressioonanalüüs näitas, et pöördujate hulgas esines suurem šanss depressiivsete sümptomite esinemiseks (OR=2,0; 95% CI=1,06–3,77; P<0,05) kui kontrollrühmas, mittepöördujate ja kontrollrühma vahel erinevused puudusid. Depressiivsete sümptomitega pöördujate keskmised VAS-skoorid oluliselt kõrgemad võrreldes mittedepressiivsete pöördujatega; mittepöördujate hulgas selline erinevus puudus. Naiste keskmine subjektiivne haigustunnetus oli nii pöördujate kui mittepöördujate seas kõrgem kui vastava grupi meestel. Mitmene logistiline regressioonanalüüs analüüs näitas, et sõltumatuteks arsti juurde pöördumist määravateks teguriteks olid raskemate haigusvormide olemasolu ja keskmisest kõrgem subjektiivne haigustunnetus (VAS-skoorid >5).

Järeldused

1. Vastavalt NRSEC klassifikatsioonile on rosaatsea levimus ≥30-aastaste hulgas ligikaudu 22%, mis oluliselt kõrgem, kui senini arvatud varasemate epidemioloogiliste uuringute või dermatoloogiakeskustesse pöördumiste

põhjal. Rosaatsea levimus suureneb vanuse suurenedes. Rosaatsea esineb meestel ja naistel võrdsel määral.

2. Rosaatsea korral on riskiteguriteks perekondlik eelsoodumus, fotosensitiivne nahatüüp ja kõrgem vanus. Rosaatsea raskemate vormide kujunemist soodustavad töötamine välitingimustes ning endine suitsetajastaatus. Ei leitud kinnitust, et rosaatsea oleks seotud *Helicobacter pylori* infektsiooniga.
3. Patsientide subjektiivne haigustunnetus ei ole seotud haiguse objektiivse raskusastmega.
4. Arsti juurde pöördunud rosaatseahaigete hulgas esines kaks korda suurema tõenäosusega depresiivseid sümptomeid võrreldes rosaatseatunnusteta isikutega üldrahvastikust. Rosaatseatunnusteta isikute ja rosaatseatunnustega, kuid arsti juurde mittepöördunud isikute vahel puudub erinevus depressiivsete sümtomite esinemise osas. Arvamus, et rosaatsea võib põhjustada depressiooni, on kujunenud raviasutustesse pöördunud patsientide uurimistulemuste alusel. Depressiivsete sümptoomide esinemine on seotud patsiendi subjektiivse haigustunnetusega, kuid mitte arsti poolt hinnatud haiguse raskusastmega.
5. Sõltumatuteks arsti juurde pöördumise põhjusteks rosaatseahaigete hulgas on raskemate haigusvormide olemasolu ja patsiendi subjektiivselt kõrgem haigustunnetus. Subjektiivselt kõrgem haigustunnetus esineb naistel. Naiste sagedasem arsti poole pöördumine rosaatsea tõttu on seotud subjektiivselt kõrgema haigustunnetusega, mitte sooliselt suurema disponeeritusega rosaatseale.

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13. PUBLICATIONS

CURRICULUM VITAE

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Professional employment

2005–…	Clinic of Dermatology, University of Tartu, assistant
2008–…	Clinic of Dermatology, Clinics of University of Tartu, dermatovenereologist

Scientific work

Special interest has been rosacea.

Total nine scientific articles, 3 oral presentations at international conferences, and 7 poster presentations.

List of publications during last 5 years:

1. Abram K, Silm H, Oona M. Prevalence of Rosacea in an Estonian Working Population Using a Standard Classification. Acta Derm Venereol. 2010; 90:269–273.
2. Abram K, Silm H, Maaroos HI, Oona M. Risk factors associated with rosacea. J Eur Acad Dermatol Venereol. 2010;24:565–571.

3. Abram K, Silm H, Maaroos HI, Oona M. Subjective disease perception and symptoms of depression in relation to healthcare-seeking behaviour in patients with rosacea. Acta Derm Venereol 2009;89:488–491.
4. Abram K, Oona M, Silm H. Rosaatsea ja perioraalne dermatiit. Eesti Arst 2007;10:729–35.
5. Aus I, Abram K, Kull M. Peritonsillaarsed abstsessid TÜ Kliinikumi Kõrvakliinikus aastatel 1999–2005. Eest Arst. 2006;85:425–7.
6. Abram K, Oona, M, Silm, H. Smoking habits among patients with rosacea. Medimond International Proceedings, 2006, p.639–42, GX04C0007.

Membership of professional organizations

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2008–…	SA Tartu Ülikooli Kliinikum, Nahahaiguste Kliinik, dermatoveneroloog

Teadustöö

Peamiseks teadustöö valdkonnaks on olnud rosaatsea.

Ilmunud on 9 teadusartiklit, 3 suulist ettekannet rahvusvalistel konverentsidel ja 7 posterettekannet.

Viimase 5 aasta teaduslikud publikatsioonid:

1. Abram K, Silm H, Oona M. Prevalence of Rosacea in an Estonian Working Population Using a Standard Classification. Acta Derm Venereol. 2010; 90:269–273.
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