

Suvi-Päivikki Sinikumpu

SKIN DISEASES AND THEIR
ASSOCIATION WITH
SYSTEMIC DISEASES IN THE
NORTHERN FINLAND BIRTH
COHORT 1966

UNIVERSITY OF OULU GRADUATE SCHOOL;
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SUVI-PÄIVIKKI SINIKUMPU

**SKIN DISEASES AND THEIR
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FINLAND BIRTH COHORT 1966**

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Abstract

Skin diseases are common: one in every three of all general practice patients have at least one dermatological problem. However, epidemiological studies addressing the overall prevalence of skin diseases are sparse. The skin is the largest organ in the body and it has several vital and immunological functions. Cutaneous signs are often the first manifestation of many systemic diseases.

The aim of this study was to determine the overall prevalence, and the distribution according to sex and socioeconomic status, of skin diseases in an adult population. The study particularly focused on multiple melanocytic naevi and their risk factors because multiple melanocytic naevi are the strongest risk factor for melanoma. A further aim was to analyse the association between cutaneous disorders and systemic conditions; specifically to determine whether abnormal skin findings in toe webs have an association with abnormal glucose metabolism and whether skin diseases have a relationship with systemic low-grade inflammation.

For these purposes a comprehensive dermatological evaluation was performed as a part of the 46-year follow-up survey of the Northern Finland Birth Cohort 1966. Data on this cohort have been collected since birth. Numerous laboratory tests were also performed cross-sectionally during the 46-year follow-up survey, including an oral glucose tolerance test and the measurement of fasting plasma glucose and glycated haemoglobin fraction. High sensitivity C-reactive protein was measured as a marker of low-grade inflammation.

Over half (60%) of the 1 932 individuals examined had at least one skin disorder requiring further treatment. The need for treatment was more common in males and those with lower socioeconomic status. Multiple melanocytic naevi were found in 12% of individuals; high educational level, male sex and fair skin type increased the risk. Abnormal skin findings in toe web spaces was associated with undiagnosed type 2 diabetes. Atopic eczema, rosacea and onychomycosis were associated with low-grade inflammation.

This unique study with nearly 2 000 subjects reports for the first time the overall prevalence of skin diseases in an unselected Finnish population. Its findings support the previous postulate that skin diseases are common in adults and suggest that skin evaluation should be an essential part of routine medical examinations in clinical practice.

Keywords: birth cohort, epidemiology, low-grade inflammation, multiple melanocytic naevi, skin diseases, socioeconomic status, toe web spaces, undiagnosed diabetes

Sinikumpu, Suvi-Päivikki, Ihotaudit ja niiden yhteys yleissairauksiin Pohjois-Suomen syntymäkohortti 1966:ssa.

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Tiivistelmä

Ihotaudit ovat yleisiä, ja jopa 30 %:lla yleislääkärin potilaista on jokin ihoon liittyvä ongelma. Väestötason tutkimuksia ihotaudeista on kuitenkin niukasti. Iho on ihmisen suuri elin, ja sillä on useita tärkeitä tehtäviä, kuten osallistuminen immunologiseen puolustukseen. Monet yleissairaudet voivat näkyä iholla jo ennen taudin puhkeamista ja ihoilmentymät voivat olla varhaisia merkkejä piilevästä sairaudesta.

Tämän tutkimuksen tarkoituksena oli määrittää ihotautilien esiintyvyys aikuisväestössä sekä ihotautilien jakautuminen sukupuolen ja sosiaalisen aseman suhteen. Lisäksi tarkoituksena oli selvittää runsasluomisuuden (yli 50 pigmenttiluomea) esiintyvyyttä ja sen riskitekijöitä, sillä runsasluomisuus on melanooman merkittävin riskitekijä. Tutkimuksen tavoitteena oli myös selvittää ihotautilien yhteyttä yleissairauksiin, kuten poikkeavien varvasvälilöydösten yhteyttä häiriintyneeseen sokeriaineenvaihduntaan sekä matala-asteisen tulehduksen ja ihotautilien välistä yhteyttä.

Osana Pohjois-Suomen syntymäkohortti 1966:n 46-vuotistarkastusta tehtiin kokonaisvaltainen ihon tutkiminen yhteensä 1 932:lle tutkimushenkilölle vuosina 2012–13. Samassa yhteydessä tutkittavilta määritettiin paastoverensokeri ja pitkäaikainen verensokeri sekä tehtiin sokerirasitustesti sokeriaineenvaihdunnan häiriön toteamiseksi. Matala-asteisen tulehduksen arvioimiseksi määritettiin herkkä C-reaktiivinen proteiini. Tutkimusjoukon pitkäaikaiset taustatiedot perustuivat syntymäkohortin aiempiin aineistoihin.

Tutkittavista 60 %:lla todettiin jokin hoitoa vaativa ihotauti. Hoidon tarve oli suurempaa miehillä ja matalammissa sosiaaliluokissa. Runsasluomisuutta esiintyi 12 %:lla, ja korkea koulutustaso, miessukupuoli ja vaalea ihotyyppi lisäsivät riskiä. Varvasväleissä esiintyvät muutokset liittyivät diagnosoimattomaan diabetekseen. Atooppinen ihottuma, ruusufinni ja kynsien sieninfektioon sopivat muutokset olivat yhteydessä matala-asteiseen tulehdukseen.

Tämä lähes 2 000 henkilön koko ihon kliiniseen tutkimukseen perustuva työ raportoi ensimmäistä kertaa ihotautilien yleistä esiintyvyyttä suomalaisessa, valikoitumattomassa väestössä. Tutkimus tukee aiempaa oletusta, jonka mukaan ihotaudit ovat aikuisväestössä yleisiä; ihon tutkiminen tulisi olla oleellinen osa potilaan kliinistä perustutkimusta.

Asiasanat: diagnosoimaton diabetes, epidemiologia, ihosairaus, matala-asteinen tulehdus, runsasluomisuus, sosioekonominen asema, syntymäkohortti, varvasvälit

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“If you want to change the world, go home and love your family.”

Mother Theresa

Suvi-Päivikki Sinikumpu

November, 2017

Oulu

Abbreviations

| | |
|-------------------|--|
| ADA | American Diabetes Association |
| AGEs | advanced glycation end-products |
| BMI | body mass index |
| CI | confidence interval |
| CRP | C-reactive protein |
| HbA _{1c} | glycated haemoglobin fraction |
| hs-CRP | high sensitive C-reactive protein |
| EASI | eczema area and severity index |
| FINDRISC | Finnish Diabetes Risk Score |
| FPG | fasting plasma glucose |
| IARC | International Agency for Research on Cancer |
| IRQ | interquartile range |
| IFG | impaired fasting glucose |
| IGT | impaired glucose tolerance |
| IL | interleukin |
| NFBC | Northern Finland Birth Cohort |
| NHANES | National Health and Nutrition Examination Survey |
| NGT | normal glucose tolerance |
| OGTT | oral glucose tolerance test |
| OR | odds ratio |
| PASI | psoriasis area and severity index |
| PCO | polycystic ovary syndrome |
| RR | relative risk |
| SD | standard deviation |
| SDM | screen detected diabetes |
| SES | socioeconomic status |
| STATA | Data Analysis and Statistical Software |
| TNF- α | tumour necrosis factor alpha |
| UK | the United Kingdom |
| USA | the United States of America |
| UV | ultraviolet |
| WHO | World Health Organization |

Original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

- I Sinikumpu S-P, Huilaja L, Jokelainen J, Koironen M, Auvinen J, Hägg PM, Wikstöm E, Timonen M, Tasanen K (2014) High prevalence of skin diseases and need for treatment in a middle-aged population. A Northern Finland Birth Cohort 1966 Study. *Plos One* 9:e99533
- II Sinikumpu S-P, Huilaja L, Jokelainen J, Auvinen J, Timonen M, Tasanen K (2017) Association of Multiple Melanocytic naevi with education, sex and skin type: A Northern Finland Birth Cohort 1966 Study with 46 years' follow-up. *Acta Derm Venereol* 97(2): 219-224.
- III Sinikumpu S-P, Auvinen J, Jokelainen J, Huilaja L, Puukka K, Ruokonen A, Keinänen-Kiukaanniemi S, Tasanen K, Timonen M (2017) Abnormal skin in toe webs is a marker for abnormal glucose metabolism. A cross-sectional survey among 1, 849 adults in Finland. *Sci Rep* 7(1):9125.
- IV Sinikumpu S-P, Huilaja L, Auvinen J, Jokelainen J, Puukka K, Ruokonen A, Timonen M, Tasanen K (2017) The association between systemic low grade inflammation and skin diseases. A cross-sectional survey in the Northern Finland Birth Cohort 1966 Study. *Acta Derm Venereol* doi:10.2340/00015555-2795.

In addition, some previously unpublished data is also presented.

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1 Introduction

The skin is the largest organ in the body and is involved in several vital functions. More than simply a barrier for the underlying tissues, the skin is an active immunological organ, possibly associated with certain systemic diseases. The skin may also show secondary signs of other conditions, such as endocrinological or malignant diseases. Skin health affects the individual's self-esteem.

Skin diseases are common in all age groups (Sari *et al.* 2005). For example, it is known that up to 20% of children suffer from atopic eczema and nearly everyone has some form of acne during their adolescence (Williams *et al.* 1999, Williams *et al.* 2012). The prevalence of sun-induced skin malignancies increases with age (Rogers *et al.* 2015). Nevertheless, our knowledge of the overall prevalence of skin disorders and their associative factors is incomplete.

Therefore, in addition to high-standard clinical and pre-clinical research of skin diseases, there is unmet need for dermatoepidemiological studies.

The main objectives of such research are to measure the occurrence of an event (prevalence), the rate of new diagnoses in a specific time-frame (incidence density) and to study the possible factors associated with events. Epidemiological studies can be broadly categorised as experimental and non-experimental (observational). The cohort study is widely appreciated type of observational study, having longitudinal follow-up as its strength (Nijsten & Stern 2012).

The present study was designed to add information to what is known of the epidemiology of skin diseases in an adult population by means of the comprehensive Northern Finland Birth Cohort 1966 Study. In addition to dermatological status, a great deal of data regarding the overall health of the cohort members was required to evaluate the potential associations between skin findings and diabetes and low-grade inflammation. In contrast to previous research, this study aimed to determine the overall skin status in a wide, unselected population.

2 Review of the literature

2.1 The epidemiology of skin diseases

2.1.1 The overall prevalence of skin diseases

With over half of adults having at least one, skin diseases are common (Rea *et al.* 1976) and are the fourth leading cause of nonfatal disease burden worldwide (Hay *et al.* 2014). Approximately one in every three general practice patients have a dermatological problem (Julian 1999, Lowell *et al.* 2001) and in more than half of these, the skin problem is the primary reason for medical consultation (Julian 1999, Sari *et al.* 2005). Skin diseases are rarely fatal but often chronic in nature causing disability and decreasing daily quality of life (Balieva *et al.* 2017, Hay *et al.* 2014, Julian 1999, Krueger *et al.* 2001).

With only a few important studies having been published since the 1970s, (Rea *et al.* 1976, Johnson & Roberts 1978, Plunkett *et al.* 1999, Augustin *et al.* 2011) the literature concerning the overall epidemiology of skin disorders is sparse. In a pioneering work performed in the United States in 1971-1974, (National Health and Nutrition Examination Survey, NHANES) approximately one-third of a population aged 1–74 years (N=20 749) had at least one skin finding requiring a treatment by a physician. In another diverse dermatoepidemiological study from UK, in 1976, skin conditions were found in more than half of all adults aged 15–74 years (N=614)(Rea *et al.* 1976). A more recent and larger population-based study reported a high prevalence of benign skin tumours (>50%) and psoriasis (6.6%) but the overall prevalence of skin disorders was not determined (Plunkett *et al.* 1999). The research comprised an unselected population, aged 20 years or older (N=1457). The largest epidemiological cross-sectional study so far was performed among 90 800 German workers. It revealed a 27% prevalence of skin disorders needing treatment (Augustin *et al.* 2011). (Table 1).

Aside from the population-based studies, there are few more epidemiological studies limited to populations of primary care patients (Table 1) (Julian 1999, Lowell *et al.* 2001, Sari *et al.* 2005, Kerr *et al.* 2009, Schofield *et al.* 2011). According to a retrospective chart review study carried out in Miami, United State of America (USA) between 1995 and 1997, 36.5% of patients seen in primary care (N=570) had at least one dermatological symptom (Lowell *et al.* 2001). That was a retrospective study based on chart reviews. A study of 11 191 general practice

patients in Cornwall, UK found that 21% demonstrated skin disease (Julian 1999). (Table 1)

In conclusion, incomparable age groups, differing definitions of skin diseases and divergent study methods make comparisons between findings difficult and the precise overall prevalence of skin disease at the population level remains uncertain (Table 1).

Table 1. The prevalence of skin diseases in previous epidemiological and primary care patient population studies.

| Author, year, country | Database/ population | n, age | Clinical diagnose method | Main findings |
|------------------------------|---|----------------------|---|--|
| Rea, 1976, United Kingdom | Population-based study, A community survey in Lambeth, London ('the Lambeth Study') | 614, 15–74 years | Exposed skin areas were examined by doctors or nurses | 22.5% had skin finding or disease that required further care |
| Johnson, 1978, United States | Population-based study, National Health and Nutrition Examination Survey | 20 749, 1-74 years | Clinical whole-body examination by dermatologists | 31.2% with skin finding or disease that required further care |
| Plunkett, 1999, Australia | Population-based study, randomly selected adults from Maryborough | 1 457, over 20 years | Clinical whole-body examination by dermatologists | Prevalence of skin diseases varied with age. Nonmalignant skin conditions were common. |
| Julian, 1999, United Kingdom | General practice database | 11 191, all ages | Clinical examination by general practitioners | 21.3% of patients had a dermatological diagnosis |
| Lowell, 2001, United States | A retrospective chart review, general medicine clinic | 570, 18-90 years | Clinical examination by general practitioners | 36.5% had at least one skin problem |
| Sari, 2005, United States | Family medicine database | 239, all ages | Clinical examination by general practitioners | 21.0% of patients had at least one skin condition |

| Author, year, country | Database/ population | n, age | Clinical diagnose method | Main findings |
|---------------------------------|--|---------------------|---|--|
| Kerr, 2009, United Kingdom | General practice database | 93 343, all ages | Clinical examination by general practitioners | 8.4% of patients had dermatological problem |
| Augustin, 2011, Germany | Population-based study, Cohort of working adults | 90 880, 16–70 years | Clinical whole-body examination by dermatologists | 26.8% had skin finding or disease that required further care |
| Schofield, 2011, United Kingdom | General practice database | 422 346, all ages | Clinical examination by general practitioners | 24.0% of the population had a skin problem |

2.1.2 The most common skin findings or diseases

Benign skin tumours such as dermal naevi or seborrhoeic keratosis are the most common abnormal skin findings (Rea *et al.* 1976, Johnson & Roberts 1978, Plunkett *et al.* 1999, Augustin *et al.* 2011). Their prevalences vary between 20.5% for benign skin tumours (Rea *et al.* 1976) and 58.2% for seborrhoeic keratosis (Plunkett *et al.* 1999). In a German cohort study, 25.1% of the participants had dermal naevi and 25.0% had seborrhoeic keratosis (Augustin *et al.* 2011).

The most frequently seen skin diseases are eczemas, with a prevalence of 9.1%–31.6% (Plunkett *et al.* 1999, Rea *et al.* 1976). Sebaceous gland diseases are also common: the prevalence of acne is between 3.9% and 12.8% (Augustin *et al.* 2011, Plunkett *et al.* 1999). Another common dermatological disease group is fungal skin infections; estimates of the prevalence of tinea have varied between 5.1 % and 12.0% (Augustin *et al.* 2011, Johnson & Roberts 1978, Plunkett *et al.* 1999).

Benign skin tumours, eczemas, acne and skin infections are the most common dermatologic diagnoses in studies utilizing selected general practice populations (Julian 1999, Lowell *et al.* 2001, Sari *et al.* 2005, Kerr *et al.* 2009, Schofield *et al.* 2011). In a highly selected population covering 190 dermatologic clinics in Japan (N= 67 448), the most common skin diseases were miscellaneous eczema (18.7%), atopic eczema (10.0%), tinea pedis (6.5%) and urticaria (5.0%) (Furue *et al.* 2011).

2.1.3 Sex differences in the prevalence of skin diseases

There are contradictory results as to whether skin diseases are more common in males or females. Female predominance (57–67%) was found in three recent studies at primary practices in the U.K. (Julian 1999, Lowell *et al.* 2001, Schofield *et al.* 2011). However, male predominance was found in two larger population-based studies (Johnson & Roberts 1978, Augustin *et al.* 2011). It has also been reported that a greater proportion of male patients than female require dermatological treatment (Augustin *et al.* 2011).

Some skin diseases are more likely to affect a particular sex. Fungal skin infections are more common in males (Johnson & Roberts 1978, Rea *et al.* 1976). More precisely, tinea has been found in 17.9% of males and 6.4% of females; psoriasis in 8.9% of males and 4.5% of females (Plunkett *et al.* 1999). In one study rosacea was more frequent in males (2.4% vs 2.1% in females) and acne (4.0%) predominated in males vs. females (3.5% in females) (Augustin *et al.* 2011). In contrast, there is predominance of female patients over males in allergic sensitization (48.4 vs 34.8%) (Augustin *et al.* 2011), eczemas (32.3 vs 30.8%) and benign skin tumours (58.4 vs. 50.2%) (Plunkett *et al.* 1999).

2.1.4 Skin diseases and socioeconomic status

Socioeconomic status (SES) describes an individual's economic and sociological position in society and is usually measured by determining the educational level, income and occupation (Adler *et al.* 1993). Education is thought to be the most specific indicator of socioeconomic status and is therefore the recommended measure in epidemiological studies (Winkleby *et al.* 1992). People with lower level of education have a higher risk of morbidity in general (Adler *et al.* 1993). However, there is not a unified consensus as to whether skin diseases disproportionately affect people with higher or lower SES. It is known that atopic eczema, allergy and skin cancers are most common in people with higher SES (Bergmann *et al.* 2000, Dalstra *et al.* 2005, Shack *et al.* 2008). In contrast, other eczemas such as hand eczema, contact eczema or seborrhoeic eczema are more common in people in lower educational groups (Dalgard *et al.* 2004, Rea *et al.* 1976). Among children skin diseases are more common in families with low SES classes when compared with families with higher SES (Mohammedamin *et al.* 2006). However, in a large epidemiological study of eight European countries (N=108 472) no association was found between SES and skin disorders (Dalstra *et al.* 2005).

2.1.5 Skin diseases and age

Skin diseases are common in all age groups (Johnson & Roberts 1978, Julian 1999, Plunkett *et al.* 1999, Rea *et al.* 1976). Atopic eczema is the most prevalent cause of skin illness among infants and pre-school children but the number of skin infections such as virus warts, impetigo and contact eczemas increases with age (Johnson & Roberts 1978, Tamer *et al.* 2008). The prevalence of sebaceous gland diseases increases towards adolescence and acne vulgaris is most common in people between 12 and 17 years of age (Johnson & Roberts 1978, Tamer *et al.* 2008) whereas inflammatory skin diseases such as rosacea, eczemas and psoriasis are most commonly found in people aged 30–50 years (Johnson & Roberts 1978). Among elderly, skin infections, pruritus, autoimmune skin diseases and malignant skin tumors are the most common cutaneous disorders (Yalçın *et al.* 2006). Altogether, the prevalence of skin diseases increases with age (Johnson & Roberts 1978).

2.1.6 Trends in prevalence and incidence of skin diseases

There is not a general agreement whether the overall prevalence of skin diseases has changed (Mohammedamin *et al.* 2006, Schofield *et al.* 2011, Hansen *et al.* 2013, Vena *et al.* 2012, Marks 1995). However, the prevalence of atopic eczema has increased over recent decades and continues to increase, particularly among young children and in developing countries (Flohr & Mann 2014, Hansen *et al.* 2013, McNeill *et al.* 2009). The annual incidence of psoriasis has doubled over a 30-years period (Icen *et al.* 2009, Tollefson *et al.* 2010) and the prevalence of adolescent acne is increasing (Lynn *et al.* 2016). In addition, the incidence of nonmelanoma skin cancers has increased on average 8% yearly since the 1960s and the incidence rate of cutaneous melanoma has increased threefold in USA and in Central Europe in three decades (Marks 1995, Rogers *et al.* 2015, Trakatelli *et al.* 2007, Garbe & Leiter 2009). In recent years the incidence rate of atopic eczema has been shown to be stable in Scandinavia (Henriksen *et al.* 2015). Similarly, the prevalence rate of hand eczema has not changed remarkably in Scandinavia in recent years (Thyssen *et al.* 2010).

2.2 Multiple melanocytic naevi

2.2.1 Melanocytic naevi and their prevalence

Melanocytic naevi are benign proliferations of melanocytes, which are epidermal cells producing melanin, the brown-black skin pigment (Hauschild *et al.* 2011) (Fig 1). Cutaneous melanocytes arise from the embryologic neural tube achieving the skin and hair follicle in about the third fetal month (Tonniier 2009). Melanocytes can also arise via sun-induced mutations (Bishop *et al.* 1994). Therefore, melanocytic naevi, can be classified as congenital (present at birth) or acquired (absent at birth).

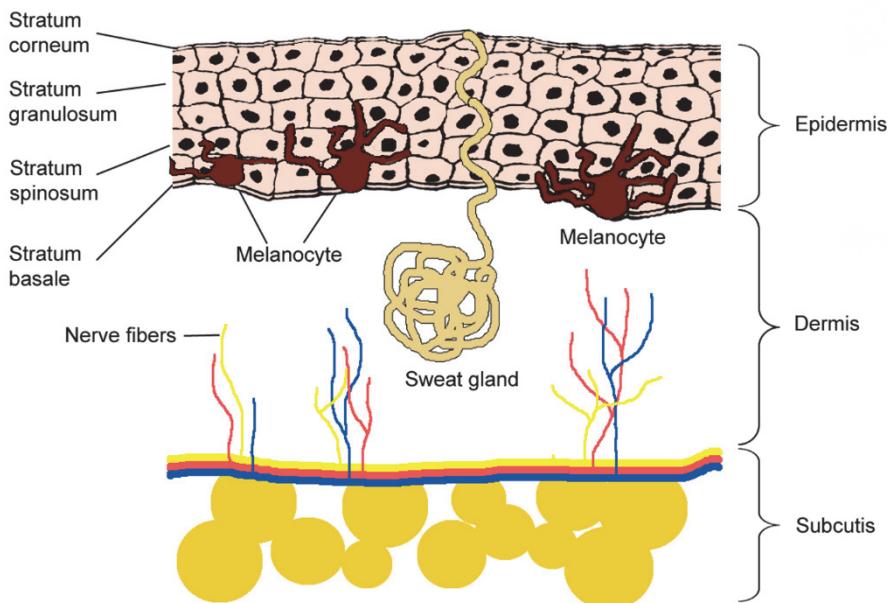
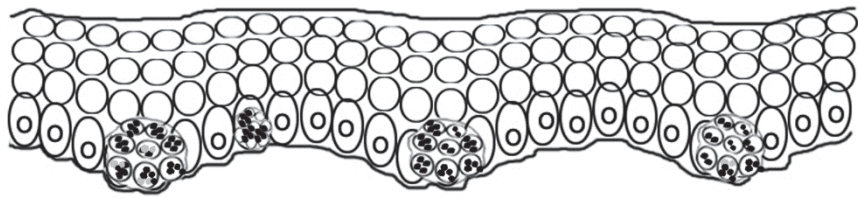


Fig. 1. Skin layers and melanocytes.

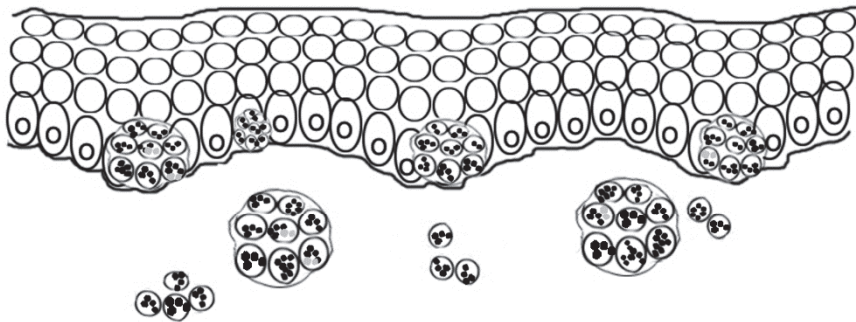
Melanocytic naevi undergo different developmental stages, each with different clinical and histological features. Lentigo simplex is an initial developmental stage of melanocytic naevi. Its histology is characterized by basal melanocyte hyperplasia and elongation of the rete ridges. Its clinical picture is a middle to dark brown macule. In junctional type melanocytic naevi, melanocytic cells form groups or nests which are localized at the dermo-epidermal border zone at the tips of the

rete ridges or (less commonly) between the rete ridges. A junctional type naevus looks like a flat, regular, oval or round brown area of pigmentation. A compound naevus has nests of nevus cells at the epidermal-dermal junction and in the dermis. Its clinical picture is a light to dark brown flat papule. The dermal melanocytic naevus has cell nests that reach the dermis. It is characterized as a skin-coloured nodule with a smooth surface. (Hauschild *et al.* 2011) (Fig 2)

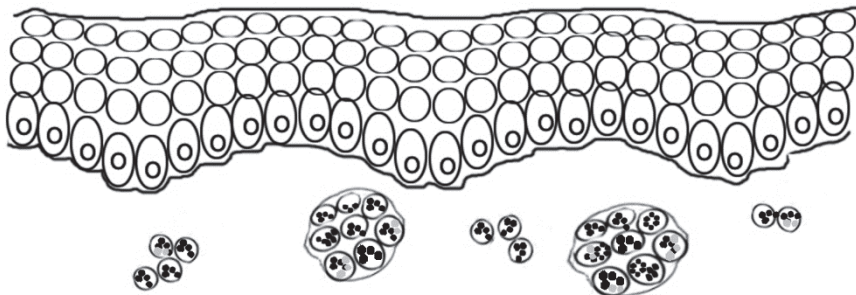
The International Agency for Research on Cancer (IARC) has set guidelines to standardize the methodologies of epidemiological studies that relate to naevi. According to the IARC, a countable melanocytic lesion must fulfil the following criteria: “brown to black pigmented macules or papules which are reasonably well defined and are darker in colour than the surrounding skin. Countable lesions do not have the features of freckles, solar lentigines, seborrhoeic keratosis, café-au-lait spots, or non-melanocytic lesions” (Gandini *et al.* 2005a). A countable melanocytic naevus should also have a diameter of at least 2 mm (Hauschild *et al.* 2011).



Junctional nevus



Compound nevus



Intradermal nevus

Fig. 2. Different types of melanocytic naevi.

Melanocytic naevi are the most common benign skin finding in white populations (Augustin *et al.* 2011, Hauschild *et al.* 2011). The average number of melanocytic naevi per individual increases with age from childhood and early adulthood (Öztaş *et al.* 2007). The average number per individual is highest in middle age after which the number starts to decrease (Öztaş *et al.* 2007). Children aged under seven years

have on average three to five naevi (Gefeller *et al.* 2007, Öztas *et al.* 2007). Among young adolescent (12–14 years) the number of naevi per person varies between 10 and 19, being markedly higher in Australia than in the European region (Green *et al.* 1989, Harrison *et al.* 1999, Moreno *et al.* 2016, Öztas *et al.* 2007).

In adults, the mean number of melanocytic naevi per person reported in Central and Northern Europe varies greatly between 15 and 50 (Bataille *et al.* 2000, Hauschild *et al.* 2011, Karlsson *et al.* 2000).

2.2.2 Risk factors for melanocytic naevi

Sun exposure and sunscreens

Sun exposure is the main known environmental risk factor for melanocytic naevi (Bataille *et al.* 2000, Dogan 2007, Gefeller *et al.* 2007). Intermittent and intensive ultraviolet (UV) radiation is especially harmful for those who are not accustomed to intensive sun exposure (Karlsson *et al.* 2000, Rodvall *et al.* 2007). A study of 2189 children showed that those who had been on vacations in sunny areas had a higher number of naevi than those who had not travelled in sunny areas (Gefeller *et al.* 2007). Sunburns, especially those occurring before the age of 20, increase the number of naevi (Garbe *et al.* 1994, Kennedy *et al.* 2003b). People living in lower latitudes have higher mean numbers of naevi (Rodvall *et al.* 2007). For example, the average number of naevi per person is higher in white people living in Australia than those living in the United Kingdom (UK) despite that the two countries' white populations are thought to share a relatively homogenous genetic background (Bataille *et al.* 1998). Melanocytic naevi are most commonly present in sun-exposed body areas such as the trunk, legs, arms and face, which demonstrates the role of sun exposure in naevus development (Moreno *et al.* 2016).

The role of sunscreens in naevus development is controversial. Children using sunscreens regularly have lower numbers of naevi whereas adults who use sun lotions have a heightened risk of melanocytic naevi (Autier *et al.* 1999, Moreno *et al.* 2016).

Genetic factors and skin type

Twin studies and epidemiological studies of the relatives of melanoma cases have confirmed that genetic factors are important in naevus expression (Bataille *et al.*

2000, Bishop *et al.* 1994, Easton *et al.* 1991). It has also been reported that the number of naevi in parents predict the number of naevi in their children (Wiecker *et al.* 2003). Similarly, skin type is a genetic trait and affects the number of naevi. By using the Fitzpatrick's classification people can be classified into subgroups according to their skin type and their ability to tolerate sun: Group I – skin always burns and never tans; Group II – skin often burns and seldom tans; Group III – skin seldom burns and often tans; Group IV – skin never burns and tans always and rapidly (Fitzpatrick 1988). A higher risk of melanocytic naevi has been associated with fair skin types which burn easily (Groups I and II) and with certain other phenotypic traits such as fair hair, blue eyes and the presence of freckles (Valiukeviciene *et al.* 2005, Wiecker *et al.* 2003).

Gender

Males are more prone than females to melanocytic naevi (Dogan 2007, English & Armstrong 1994, Green *et al.* 1989). This difference results mainly from clothing and behavioural factors – for example, boys may spend more time than girls exercising outdoors or use less protective clothes (Dogan 2007) but the difference may also be based on hormonal factors (Carli *et al.* 2002, Ginarte *et al.* 2000). Male predominance has been found both in children and adults (Augustin *et al.* 2011, Gallagher & McLean 1995).

Inflammatory skin diseases and immune status

Adults with chronic atopic eczema have fewer melanocytic naevi than those without (Broberg & Augustsson 2000). This association has not been found in children (Uter *et al.* 2005) but children who have immunosuppressive treatment have higher naevus counts than healthy children (Naldi *et al.* 1996).

Socioeconomic status

Previous publications have not found an association between the presence of a high number of melanocytic naevi and socioeconomic status (Coombs *et al.* 1992, Dennis *et al.* 1996).

2.2.3 The prevalence of multiple melanocytic naevi

The presence of either 50 or 100 naevi over the entire body area has typically been used as the threshold for classification of an individual as having ‘multiple melanocytic naevi’ (Augustsson *et al.* 1991, Bataille *et al.* 2000, Garbe *et al.* 1994, Karlsson *et al.* 2000, Youl *et al.* 2002). Figure 3 shows an individual with multiple melanocytic naevi. The prevalence of multiple melanocytic naevi in adolescents or adults varies between geographical areas. It is highest in Australia (31% had >50 naevi, N=63/205) (Youl *et al.* 2002) and lowest in Asian countries (1.4% had over 20 naevi, N= 5/140) (Rokuhara *et al.* 2004). The prevalence is 18% in Germany (>50 naevi), and, 23% in the UK (>100 naevi) (Bataille *et al.* 2000, Garbe *et al.* 1994). In Sweden, estimates of the prevalence rates of multiple naevi have varied between 6% and 22% (>100 naevi) and the rate is markedly higher in the southern part of the country (Augustsson *et al.* 1991, Karlsson *et al.* 2000). In Australia the prevalence of multiple melanocytic naevi varies within the continent, being higher in areas closer to the equator (Kelly *et al.* 1994).

As well as geographical location, ethnic background, phenotypic traits and cultural factors can all affect an individual’s naevus count. People of European origin living in Australia have higher naevus counts than those of other ethnic origins (English & Armstrong 1994). Naevus counts are lower in people living in Turkey compared with those living in Melbourne, Australia, which lies on the same latitude (Dogan 2007). This is probably due to cultural or religious reasons such as the use of more clothing in Turkey (Dogan 2007).



Fig. 3. Multiple melanocytic naevi (Department of Dermatology, Oulu University Hospital).

2.2.4 Multiple melanocytic naevi and the risk of malignant melanoma

The presence of multiple melanocytic naevi is the strongest risk factor for cutaneous melanoma (Green *et al.* 1985, Grob *et al.* 1990, Grulich *et al.* 1996). The risk for melanoma increases almost linearly with every additional melanocytic naevus (Bauer & Garbe 2003, Grob *et al.* 1990); the risk has been estimated to be approximately 3- to 5-fold greater in people with multiple naevi (>50) compared with those with only few naevi (Bauer & Garbe 2003, Youl *et al.* 2002). There can even be a 7- to 50-fold difference in risk in cases where over 100 naevi are present (Bauer & Garbe 2003, Gandini *et al.* 2005b, Youl *et al.* 2002).

2.3 Skin findings as a signs of other diseases

The skin is the largest organ in the human body. It forms a physical barrier to the external environment and defends the body from microbial, chemical and mechanical threats. The skin has many other functions too. It contributes to the body's temperature regulation system. The skin also protects the body from UV radiation and participates in the synthesis of vitamins and hormones. (Wolff 2009)

Given that the skin has many vital functional and immunological functions, it is perhaps unsurprising that several internal diseases have been reported to be associated with abnormal dermatological findings (Artantaş *et al.* 2009, Parker 1985). Abnormal skin findings may precede the clinical manifestation of an occult systemic disease, or - in turn - skin signs may progress slowly long after the outbreak of the disease (Murphy-Chutorian *et al.* 2013). For example, eruptive xanthomas, waxy yellow nodules on the skin of the legs or arms, can indicate dyslipidemia and high triglyceride levels (Parker 1985). An abnormal darkening of the skin, can be a sign of an adrenal disease, such as Addison's disease (Nieman & Turner 2006). Disrupted glucose metabolism is known to be associated with many dermatologic complications and findings (Murphy-Chutorian *et al.* 2013). However, until now, skin findings have not been utilized to enhance the early detection of diabetes.

2.3.1 Diabetes and the skin

2.3.2 Epidemiological aspects of diabetes

Diabetes is a heterogeneous group of conditions which are characterized by a long lasting, increased blood glucose (hyperglycaemia). Hyperglycaemia is caused by impaired insulin secretion and/or an insufficient effect of insulin in tissues (National Diabetes Data Group 1979). Diabetes can be classified in four etiopathogenetic categories: type 1 diabetes, type 2 diabetes, specific types of diabetes (such as genetic defects of β -cells, or drug or chemical induced diabetes), and gestational diabetes (American Diabetes Association 2010). The majority of the cases with diabetes are of types 1 (5–10%) and 2 (90–95%) (American Diabetes Association 2010). Type 1 is caused by β -cell destruction that can result in full insulin deficiency, whereas type 2 diabetes results from insulin resistance with relative insulin deficiency (American Diabetes Association 2010).

Diabetes is one of the most common chronic diseases and it is independent of socioeconomic status. The global prevalence of diabetes is 8.3% (Guariguata *et al.* 2014). Most patients with diabetes live in low- and middle-income countries. The highest prevalence rates (approximately 10%) are in the Pacific island region, the Middle East and Northern Africa (Guariguata *et al.* 2014). There are up to 98 million patients in China alone (Guariguata *et al.* 2014). About 380 million people worldwide had diabetes in the year 2013, and the number of patients is estimated to grow to 600 million by the year 2035 (Guariguata *et al.* 2014). Approximately 500 000 people have diabetes in Finland (Working group set up by the Finnish Medical Society Duodecim, the Society of Internal Medicine and the Council of Finnish Diabetes Association 2016). This projected increase is based on prolonged life expectancy worldwide, and a rise in unhealthy living habits (Björk 2001). The prevalence of diabetes increases with age. The highest age-specific prevalence is in people aged 60–70 years, although most patients are aged 40–59 years (Guariguata *et al.* 2014).

Diabetes is the fifth most important cause of mortality globally: 6–27% of all deaths in people aged 35–64 years are associated with diabetes (American Diabetes Association 2010). The annual economic cost of diagnosed diabetes in the USA is approximately \$245 billion, comprising hospital inpatient care (43%) and cost of medication (American Diabetes Association 2013). Diabetes causes 15% of all public health costs in Finland (Working group set up by the Finnish Medical

Society Duodecim, the Society of Internal Medicine and the Council of Finnish Diabetes Association 2016).

2.3.3 Undiagnosed type 2 diabetes

Almost half of all adult patients with type 2 diabetes are still not diagnosed (Beagley *et al.* 2014). There is a particularly large proportion of undiagnosed cases of diabetes in developing countries (Beagley *et al.* 2014). As long as the disease remains undiagnosed, its attendant complications develop undetected. Hyperglycaemia results in irreversible micro- and macrovascular complications in several internal organs (Beagley *et al.* 2014).

Notably, the first signs of the type 2 diabetes can be present as early as 12 years before a diagnosis is made (Bennett *et al.* 2007, Harris 1993). Up to one in every five patients have retinopathy at the time of diagnosis, 7–13% have neuropathy, 20% have peripheral arterial disease and 59% have coronary heart disease (Harris & Eastman 2000). Undiagnosed diabetes carries a mortality risk 1.5-fold greater than that of normoglycaemic subjects (Wild *et al.* 2005). In order to find people with a high risk of type 2 diabetes practical screening scores have been developed (Griffin *et al.* 2000, Lindstrom & Tuomilehto 2003, Schulze *et al.* 2007). One of the most widely used instruments among Caucasian population is the Finnish Diabetes Risk Score (FINDRISC) questionnaire (Lindstrom & Tuomilehto 2003).

2.3.4 Diagnostic criteria of type 2 diabetes

The World Health Organization (WHO) and the American Diabetes Association (ADA) have established criteria to diagnose type 2 diabetes (American Diabetes Association 2014, World Health Organization 1999). (Table 2)

Table 2. Diagnostic criteria of type 2 diabetes (American Diabetes Association 2014, World Health Organization 1999).

| Screening test | Diagnostic threshold | Description |
|--|----------------------|---|
| Fasting plasma glucose | ≥ 7.0 mmol/l | Measured after an 8-hour overnight fasting period |
| Oral glucose tolerance test, the glucose level which is taken 2 hours after the oral load (a 2-hour glucose) | ≥ 11.0 mmol/l | Measured after an 8-hour overnight fasting period after a 75 g glucose load |
| Glycated haemoglobin fraction | ≥ 6.5% | No prior fasting required |

Screening tests for type 2 diabetes

Fasting plasma glucose (FPG) and oral glucose tolerance tests (OGTT) are the most widely used screening tests for type 2 diabetes (Bennett *et al.* 2007) but there is no consensus on which test (FPG, OGTT or glycated haemolytic fraction, HbA_{1c}) is the most accurate. The advantage of FPG is its low cost. However, nearly one-third of individuals with diabetes remain undetected when only FPG is used for screening (Barrett-Connor & Ferrara 1998). FPG should be repeated at least twice because of its common day-to-day variation. HbA_{1c} is considered equally effective as FPG for the purposes of identifying early diabetes. The use of HbA_{1c} has some limitations in the clinical setting: as well as diabetes, its level is influenced by diseases such as renal failure or haemolytic anemia and by medications like acetylsalicylic acid (Bennett *et al.* 2007). However, HbA_{1c} is still a widely used marker of glycemic control and satisfactory marker of an individual response to treatment. OGTTs are sensitive enough to detect prediabetic conditions but are time-consuming and more expensive than other methods. (Bennett *et al.* 2007).

2.3.5 Prediabetes

Prediabetes is the term used for the condition wherein an individual is at high risk for developing diabetes (Tabák *et al.* 2012). It is characterized by an elevation of plasma glucose above the normal value but below the threshold required for a diabetes diagnosis (Tabák *et al.* 2012, Bennett *et al.* 2007). (Table 3). Prediabetes can be screened for by testing for impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). IGT can be detected by OGTT.

Table 3. Diagnostic criteria of prediabetes (American Diabetes Association 2014, World Health Organization 1999).

| Screening test | Diagnostic threshold |
|-------------------------------|---|
| WHO | |
| Impaired fasting glucose | FPG ≥ 6.1 mmol/l and < 7.0 mmol/l and no presence of IGT |
| Impaired glucose tolerance | FPG < 7.0 mmol/l and 2-hour glucose in OGTT ≥ 7.8 mmol/l and < 11.1 mmol/l |
| ADA | |
| Impaired fasting glucose | FPG ≥ 5.6 and ≤ 6.9 mmol/l |
| Impaired glucose tolerance | FPG < 7.0 mmol/l and a 2 hour glucose in OGTT ≥ 7.8 mmol/l and < 11.1 mmol/l |
| Glycated haemoglobin fraction | $\geq 5.7\%$ and $\leq 6.4\%$ |

ADA, American Diabetes Association; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization

The prevalence of prediabetes is increasing worldwide and it has been estimated that nearly 500 million people will have prediabetes by 2030 (Tabák *et al.* 2012). Every year 5–10% of people with prediabetes develop diabetes and 70% get the disease finally (Forouhi *et al.* 2007, Tabák *et al.* 2012). However, it is possible to recover from prediabetes and reach normoglycemic blood glucose concentration (Forouhi *et al.* 2007) through lifestyle adjustments such as increasing physical activity, losing weight and maintaining a healthy diet (Diabetes Prevention Program Research Group 2009, Tuomilehto *et al.* 2001).

2.3.6 The effect of glucose and insulin on the skin

Diabetes affects the skin by several mechanisms. Insulin controls the proliferation and differentiation of keratinocytes, which are the main cell types in the epidermis. When the function of keratinocytes is impaired in diabetes, the epidermal barrier doesn't work normally and the skin becomes more fragile and susceptible to pathogens (Behm *et al.* 2012, Spravchikov *et al.* 2001, Wertheimer *et al.* 2000). Hyperglycaemia results in advanced glycation end-products (AGEs) which are protein, lipids or nucleic acids. These end-products can induce the formation of reactive oxygen species (ROS), affect protein function, and influence the production of proinflammatory cytokines (Behm *et al.* 2012, de Macedo *et al.* 2016). AGEs participate in the development of fibrosis, alter collagen properties and decrease skin flexibility (Avery & Bailey 2006). Hyperglycaemia raises the concentration of cutaneous glucose and increases the pH of the skin's surface

(Behm *et al.* 2012). This creates an optimal environment for dermatophytes, yeasts and other microbes to colonize to the skin. Furthermore, hyperglycemia reduces the activity of sebaceous glands, causing a lower level of hydration, resulting in dryness of the skin. (Sakai *et al.* 2005)

2.3.7 Skin manifestations in diabetes

Diabetes can have clinical manifestations in every organ system in the body, including the skin (Murphy-Chutorian *et al.* 2013). Between 30 and 90% of patients with diabetes have at least one skin condition at some point during the course of the disease (Murphy-Chutorian *et al.* 2013). Skin diseases are common in both type 1 and type 2 diabetes but are more commonly seen in type 2 (Chatterjee *et al.* 2014). Skin manifestations of diabetes can be classified into four groups: 1) skin diseases directly linked with diabetes, 2) skin reactions to diabetic treatment, 3) skin infections, and 4) skin manifestations of diabetic complications (diabetic foot problems) (Perez & Kohn 1994).

The most common skin manifestation in diabetes is diabetic dermopathy which is caused by microangiopathy. It is seen more often in type 2 diabetes than type 1, usually after the patient has had diabetes for a long time. Its clinical picture is round or oval hyperpigmented lesions, typically localized on the shins. Acanthosis nigricans is another very common skin sign in diabetes. It is characterized by hyperpigmented, hyperkeratotic and warty like areas in the axillae or on the neck and is associated with type 2 diabetes, obesity and other endocrinology disorders such as polycystic ovary syndrome (PCO). Other typical skin findings in patients with diabetes are necrobiosis lipoidica, bullosis diabeticorum, diabetic thick skin and eruptive xanthomas (de Macedo *et al.* 2016, Murphy-Chutorian *et al.* 2013). Granuloma annulare, vitiligo, psoriasis and lichen planus are also frequently seen in diabetes populations (Murphy-Chutorian *et al.* 2013).

Insulin injections can cause local allergic reactions such as erythema, pruritus and lipoatrophy at the injection site, and, rarely, type I IgE-mediated hypersensitivity reactions (Behm *et al.* 2012). Oral antidiabetic agents can induce skin diseases like leukocytoclastic vasculitis, erythema multiforme and bullous pemphigoid (Ben Salem *et al.* 2006, Béné *et al.* 2016, Burger & Goyal 2004).

Skin infections and diabetes

Patients with diabetes are prone to skin infections, which are found in approximately half of all patients (Mahajan *et al.* 2003). The most common bacterial skin infections in diabetes are erythrasma, impetigo and folliculitis but the risks of fulminant skin infections like erysipelas and necrotising fasciitis are also increased (Bartholomeeussen *et al.* 2007, Peleg *et al.* 2007). The clinical manifestations of bacterial skin infections are more severe in people with diabetes than in healthy individuals and the risk of hospitalisation due to bacterial skin infection is 6–7 fold higher in those with the diabetes (Jorup-Rönström 1986, Peleg *et al.* 2007, Perez & Kohn 1994).

Fungal skin infections, most usually tinea pedis and onychomycosis, are found in 30–80% of patients with diabetes (Currie *et al.* 1998, Foss *et al.* 2005, Galdeano *et al.* 2013, Gupta & Humke 2000, Legge *et al.* 2008, Perez & Kohn 1994, Yosipovitch *et al.* 1998). Onychomycosis is present in one in every three patients with diabetes; diabetes patients have 3-fold higher risk of fungal nail infections than healthy individuals (Gupta & Humke 2000). Onychomycosis is usually considered as a slight disease having mostly cosmetic disadvantages, while the nails are thickened, dystrophic and they have sharp edges (Elewski & Hay 1995). These characteristics, typical of a fungal infection, can damage the surrounding skin (Fard *et al.* 2007) and act as a portal for the entry of pathogens that cause cutaneous infections. The risk of concomitant cutaneous infection is especially high in patients who suffer from neuropathy (Eckhard *et al.* 2007). Onychomycosis increases the risk for cellulitis 2- to 3-fold (Bjornsdottir *et al.* 2005), and the risk may be higher still in patients with diabetes. Onychomycosis also predisposes for diabetic foot, gangrene (Gupta *et al.* 1998, Gupta & Humke 2000) and finally, to lower leg amputation (Nather *et al.* 2008).

Tinea pedis is the most common fungal skin infection in patients with diabetes and it is typically found in the toe web spaces: maceration, peeling and erythema are typical clinical manifestations (Moriarty *et al.* 2012) (Fig 4). Tinea pedis is found in more than one in every three patients (Galdeano *et al.* 2013, Wambier *et al.* 2014). Patients with diabetes are 2.5-fold more likely to have tinea pedis than healthy individuals (Gupta *et al.* 1998). This skin infection can result in fissures in the skin and it may progress to fulminant infections such as erysipelas, cellulitis, sepsis, osteomyelitis and even to diabetic ulcer (Singh *et al.* 2005). The risk of cellulitis is 3- to 15-fold greater in people with tinea pedis than in those with healthy toe webs (Bjornsdottir *et al.* 2005, Lewis *et al.* 2006).

Candida infections are also common in patients with diabetes. Galdeano and co-workers found candidiasis in 17% of their study population of 125 patients with diabetes (Galdeano *et al.* 2013). Skin surface pH in intertriginous regions is higher in people who have diabetes than in healthy subjects, and this may explain the tendency for candidiasis (Yosipovitch *et al.* 1993).



Fig. 4. Abnormal skin findings in toe webs (Department of Dermatology, Oulu University Hospital).

2.3.8 Diabetic foot problems

Foot ulcer, gangrene, infections and limb loss due to amputation are the most usual diabetic foot complications (Al-Rubeaan *et al.* 2015, Nather *et al.* 2008). They are the most common reasons for hospitalization of diabetes patients and together account for a large part of total health care expenditure on diabetes (Nather *et al.* 2008, Sargen *et al.* 2013, Tan *et al.* 2011). Foot ulcer is found in 2–5% of patients with diabetes every year and patients' lifetime risk is 15–25% (Al-Rubeaan *et al.*

2015, Tan *et al.* 2011). It is the major reason of non-traumatic limb amputation (Tan *et al.* 2011).

The main preceding risk factors for diabetic foot complications are peripheral vascular disease and peripheral neuropathy, local infections, Charcot joint and long time since diabetes onset (Al-Rubeaan *et al.* 2015). Tinea pedis and onychomycosis often precede diabetic foot complications and close foot care would therefore be an appropriate preventative measure for diabetic complications (Al-Rubeaan *et al.* 2015, Matricciani *et al.* 2011, Tan *et al.* 2011).

2.4 Skin diseases and low-grade inflammation

Many chronic cutaneous diseases, such as atopic eczema and psoriasis, are immunological in nature (Dowlatshahi *et al.* 2013, Silverberg & Greenland 2015, Williams *et al.* 2012). Increased number of lymphocytes, macrophages, cytokines and chemokines are found in inflamed skin (Peng & Novak 2015). Because the skin is an active immunological organ it is not surprising that certain skin diseases have extra-dermatological effects; for example, psoriasis is associated with cardiovascular diseases (Ahlehoff *et al.* 2011). Nevertheless, there is no wide understanding about the association between conventional skin diseases and systemic inflammation. No comprehensive research has yet used highly sensitive methods to investigate the potential association between systemic inflammation and skin diseases in general.

2.4.1 Immune system, inflammation and C-reactive protein

The immune system is composed of two components: the innate and the adaptive immune systems. The innate immune system is a non-specific, first-line host defense against environmental threats, such as microbial infection or physical injury. It is mediated by phagocytes including macrophages and dendritic cells. In addition to these cells the innate immune system initiates the release of cytokines and acute phase proteins. It responds instantly against the threat. The innate immune system does not have any memory response. By contrast, the adaptive immune system activates slowly and utilizes memory. (Parkin & Cohen 2001).

Signs that the innate immune system is activated include clinical symptoms like heat, pain, redness and swelling. The acute phase response also becomes activated. This is characterized by the presence of acute phase reactants such as C-reactive protein (CRP), fibrinogen and serum amyloid A. CRP is synthesized in the

liver and released into the blood after infection, trauma or tissue damage. The production of CRP is induced by proinflammatory cytokines, mostly by interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-17 (IL-17) and tumour necrosis factor alpha (TNF- α). These cytokines in turn are influenced by other cytokines, steroid hormones and bacterial components (Eklund 2009). CRP is very sensitive to inflammation and its concentration can increase rapidly up to 1000-fold. It is used in diagnostics for many diseases (Ford *et al.* 2003).

2.4.2 Factors influencing to CRP-levels

Increasing age is associated with higher CRP levels (Eklund 2009). People with a low socioeconomic position have higher CRP levels than those who have higher education status (Hurme *et al.* 2007, Yanbaeva *et al.* 2007). Those with lower SES may experience poverty, more challenges in everyday life and more stress which could increase CRP levels (Nazmi & Victora 2007). CRP is linked to ethnicity: people in Africa, or Latin and South Asia have higher CRP levels than those living in Europe (Nazmi & Victora 2007). There is also a gender difference; females have higher mean levels of CRP than males. This may result from native hormonal factors and additionally the use of hormonal contraception elevates CRP levels (Bermudez *et al.* 2002, Eklund 2009, Ford *et al.* 2003, Wener *et al.* 2000). A woman's CRP level varies according to the menstrual cycle and the highest levels are at midcycle (Jilma *et al.* 1997).

Body weight has a clear correlation with CRP levels (Bermudez *et al.* 2002, Eklund 2009, Ford *et al.* 2003, Waheed *et al.* 2016). CRP associates in particular with the mass of fat tissue (McLaughlin *et al.* 2002, Visser *et al.* 1999). Overweight people have more adipocytes than leaner people. Adipocytes produce IL-6, a cytokine that induces the release of CRP from hepatocytes (Heilbronn *et al.* 2001). Another possible mechanism clarifying the association between high body weight and high CRP is insulin resistance (subjects with both obesity and insulin resistance are particularly likely to have elevated CRP levels) (McLaughlin *et al.* 2002).

Behavioural and environmental factors, such as smoking and diet affect an individual's CRP level (Eklund 2009, Esposito *et al.* 2006, Estruch *et al.* 2006, Hurme *et al.* 2007, Yanbaeva *et al.* 2007). A Mediterranean-style diet (whole grain, vegetables, nuts, fruits and olive oil) is associated with lower CRP-levels (Esposito *et al.* 2006, Estruch *et al.* 2006).

2.4.3 Low-grade inflammation

A minor elevation of inflammatory markers in blood is called low-grade inflammation, which is a state of inflammation that usually has no visible symptoms (Eklund 2009). The most commonly used marker of low-grade inflammation is CRP level, which is a sensitive, stable, powerful but non-specific marker of inflammation (Dowlatshahi *et al.* 2013, Eklund 2009, Maachi *et al.* 2004). Low levels of CRP can be measured with a highly sensitive CRP (hs-CRP) method, which is more precise than standard CRP measurements. Hs-CRP can be used as a predictive marker of diseases and complications. For example, the detection of a minor rise in CRP level can predict an elevated risk of coronary heart disease (CHD) (Danesh *et al.* 2000, Pearson *et al.* 2003).

In recent years many noncommunicable diseases have been reported to be associated with low-grade inflammation. These include atherosclerosis (Ross 1999) (Ross 1999), metabolic syndrome (Sutherland *et al.* 2004), type 2 diabetes (Pradhan *et al.* 2001), obesity (Maachi *et al.* 2004), depression (Liukkonen *et al.* 2006), polycystic ovary syndrome (Kelly *et al.* 2001) and some malignancies (Heikkilä *et al.* 2009).

2.4.4 Low-grade inflammation and skin diseases

Previous literature suggests that there is an association between low-grade inflammation and skin diseases. The strongest evidence exists in the relationship between low-grade inflammation and psoriasis, which is a chronic inflammatory skin disease. Patients with psoriasis have higher IL-6, TNF- α and CRP levels than those with healthy skin (Dowlatshahi *et al.* 2013). CRP levels also correlate with the severity of psoriasis (Rocha-Pereira *et al.* 2004) and CRP can be used in estimating the activity of the disease (Serwin *et al.* 2006). The association between elevated CRP has also been reported with rosacea, chronic urticaria and lichen ruber planus (Ataş *et al.* 2016, Duman *et al.* 2014, Kasperska-Zajac *et al.* 2011). The same association has also been seen in atopic dermatological diseases. A Danish study of 411 children showed an association between allergic sensitization and increased hs-CRP-levels (Chawes *et al.* 2015). Elevated CRP markers have also been documented in children and young adolescents with atopic eczema (Hayes *et al.* 2016, Khandaker *et al.* 2014). Until now, no relationship between acne and low-grade inflammation has been found (Namazi *et al.* 2015).

3 Aims of the study

The purpose of the present study was to add the understanding of the epidemiology of skin diseases in general and of separate skin diseases among an adult, unselected population and to investigate factors associated with these diseases by using the unique Northern Finland Birth Cohort 1966 data.

The specific aims of this study were:

- I to determine the overall prevalence of skin disorders and the distribution of skin diseases according to sex and socioeconomic status.
- II to determine the overall prevalence of melanocytic naevi and multiple melanocytic naevi and to investigate the possible preceding and concurrent environmental and other factors that are associated with the presence of naevi at the age of 46 years.
- III to investigate a possible association between skin findings in the toe web spaces and previously undiagnosed diabetes or prediabetes at the age of 46 years.
- IV to investigate a possible cross-sectional association between skin diseases and low-grade inflammation in an unselected adult population at the age of 46 years.

4 Materials and methods

The present work is based on the data from the Northern Finland Birth Cohort 1966 Study (NFBC 1966) including a 46-year follow-up survey of NFBC 1966. Roman numbers (I-IV) refer to the original articles.

4.1 The Northern Finland Birth Cohort 1966 Study (I-IV)

The NFBC 1966 is an epidemiological and longitudinal research program in the two northernmost provinces in Finland (Oulu and Lapland). The study was initially launched in 1965 by Professor Paula Rantakallio, who examined the association between low birth weight and perinatal death (Rantakallio 1969). All mothers living in the specified geographic area and whose expected delivery date fell between 1st January and 31th December 1966 created the original source of material for the study. Altogether, 12 055 mothers with 12 058 live birth children (12 068 deliveries) formed the study population. These births included 96.3% of all births in that area during the year 1966. The children of NFBC 1966 have been followed regularly since their birth and their mothers have been followed since, on average, the 16th week of their pregnancy. The follow-up has been conducted via health questionnaires and clinical examinations from which diverse data have been collected regarding health, life-style factors and socioeconomic status. Until now, four main follow-up surveys have been made of the 1966 children: at birth, at the age of 14, at the age of 31 and at the age of 46. (Fig 6)

Flow chart of Northern Finland Birth Cohort 1966

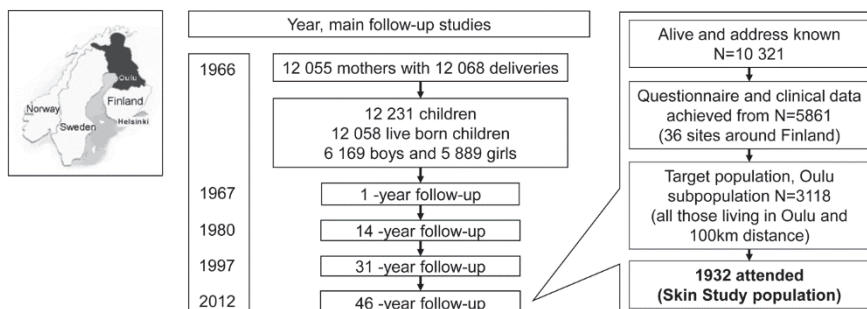


Fig. 5. Flow chart of Northern Finland Birth Cohort 1966 Study.

4.1.1 A 46-year follow-up survey (I-IV)

In 2012, at the age of 46 years all subjects, who participated in the NFBC 1966 study, were invited to a clinical examination at 36 sites around Finland. The most intensive investigations were performed in Oulu for subjects who lived within 100 km of Oulu (N=3118, target population). A total of 1932 subjects from this subpopulation attended (participation rate 62.0%) and these participants formed the basis of what is referred to in the present document as the Skin Study population. This 46-year follow-up survey included several clinical examinations such as a heart echo test, a dental examination, ophthalmological testing, a pulmonary breath test, a dermatological evaluation, laboratory tests and health questionnaires. The data were collected between April 2012 and May 2013 on the premises of the Faculty of medicine of Oulu University.

4.1.2 Dermatological evaluation (I-IV)

A whole body skin examination was performed for all study cases by three investigators; one was a specialist in dermatology and other two were experienced residents. All skin areas were observed including nails, hair and scalp. The evaluation included a detailed examination of the feet and toe web spaces and maceration, scales, vesicles or localized erythema were reported if present. Skin

tumours were further observed using a dermatoscope and their numbers were calculated. The locations and durations of all skin symptoms and their severity were recorded. Diagnoses based on the International Classification of Diseases (ICD-10) and widely known tools in dermatology; EASI (eczema area and severity index) and PASI (psoriasis area and severity index) were used to define the severity of these skin diseases (Hanifin *et al.* 2001, Schmitt & Wozel 2005). The International classification of disease characteristics system was utilized for rosacea and acne (Crawford *et al.* 2004, White 1998, Wilkin *et al.* 2002). Androgenetic alopecia was classified in three groups (mild, moderate and severe) using the modified Norwood's classification system (Norwood 1975).

Diagnoses of fungal, bacterial, and viral skin infections were based on the clinical picture; no skin samples were taken for further culture investigation. This group of diseases includes virus warts, folliculitis, onychomycosis and tinea pedis.

Registration of findings and the definition of need for treatment (I-IV)

All skin findings were documented in a pre-designed computerized database (Fig 6). In order to analyze the severity of skin diseases or skin findings the cohort members were further classified into four subgroups according to their need of further interventions: I) no further care needed, II) expected to recover with self-treatment, III) general practitioner visit recommended and IV) further treatment by a dermatologist required. The group "no further care needed" included subjects with benign tumours, erytematoteleangiectatic rosacea and androgenetic alopecia. If a study case showed any skin disease that required treatment (e.g. untreated eczema), further follow-up, an outpatient visit or more comprehensive diagnostic investigation by a dermatologist, the subject was referred to a primary health care unit or to an occupational health care provider. If a subject had any suspected skin malignancy (e.g. basal cell carcinoma) or premalignancy (e.g. actinic keratosis), they were referred to the Department of Dermatology, University Hospital of Oulu, for a skin biopsy or for other further examination and treatment.

| | Has study case this finding or disease? | Amount of findings? | Location of findings? | |
|--|---|---|---|--|
| Benign skin tumors | 1=No 2=Yes 3=Maybe | 1=<10 2=10-50 3=>50 ▶ | 1=head/neck 2=body 3=upper extremities 4=lower extremities 5= several areas | |
| Pigmented naevus Granuloma pyogenicum Blue naevus Halo naevus Dermatofibroma Cherry angioma Keloid Seborrheic keratosis Lentigo senilis Lipoma Congenital melanocytic naevus Naevus flammeus Cafe au lait -spot Something else, what: | | | | |
| | Has study case this finding? | Location? | Number of findings? | Size of finding? |
| Premalign skin tumors | 1=No 2=Yes 3=Maybe | 1=Head/neck 2=Body 3=Upper extremities 4=Lower extremities | | 0=can't be measured 1=1mm etc. |
| Solar keratosis Bowen's disease Paget's disease | | | | |
| | Has study case this finding? | Location? | Number of findings? | Size of finding? |
| Malign skin tumors | 1=No 2=Yes 3=Maybe | 1= Head/neck 2=Body 3=Upper extremities 4=Lower extremities | | 0=can't be measured 1=1mm etc. |
| Melanoma Bacal cell carcinoma Spinocellular carcinoma | | | | |
| | Has study case this disease? | Location? | Degree of severity? | Duration of symptoms? |
| Eczemas | 1=No 2=Yes 3=Maybe | 1= Head/neck 2=Body 3=Upper extremities 4=Lower extremities 5= Several body areas | 1=Mild 2=Moderate 3=Severe | 1= <1 years 2= 1-5 y 3= 5-10 y 4= >10 y |
| Atopic eczema Hand eczema Seborrheic eczema Eczema nummulare Eczema infectiosum Contact eczema Eczema staticum Neurodermatitis Something else, what: | | | | |
| EASI-value: | | | | |
| | Has study case this disease? | Location? | | Duration of symptoms? |
| Psoriasis | 1=No 2=Yes 3=Maybe | 1=Head/neck 2=Body 3=Upper extremities 4=Lower extremities 5= Several body areas | | 1= <1 years 2= 1-5 y 3= 5-10 y 4= >10 y |

Fig. 6. Part of the dermatological research protocol.

Interobserver reliability

The degree to which the results were consistent between different study investigators was examined. The findings of two of the three investigators (those who performed the majority of the dermatological evaluations) was compared. The findings in a random selection of thirty patients were tested for consistency between examinations performed on separate days by investigators. Each examiner had no knowledge of the skin findings by the other. The analysis of interobserver reliability was performed by using Kappa statistic for observed agreement between paired examiners and calculated for the diagnoses of all skin conditions. The level of reliability was high; it varied from good for the eczemas (0.87) to very good in skin infections (100.0).

4.1.3 Questionnaires (I-IV)

Socioeconomic status (SES) of study cases (I-IV)

The SES of cohort members was categorized based on their education level. This information was obtained from the National Education Register maintained by Statistics Finland in connections with the 31-year follow-up survey and was supplemented with a self-reported questionnaire (a 46-year follow-up survey) (Isohanni *et al.* 2001). The cohort members were classified in three subgroups according to their education level: 1) basic, 2) secondary and 3) tertiary education. The basic education group included those who had completed comprehensive schools (duration in total 9 years), secondary level those with upper secondary school or vocational school (10-12 years) and tertiary level (over 13 years) those who had completed university or polytechnic courses (Isohanni *et al.* 2001).

Socioeconomic status of subject's childhood family and childhood living area (II)

The SES of a subject's childhood family was determined by their father's occupation and prestige, which were assessed in 1966 and 1980 (Rantakallio 1988, Rantakallio 1969). In the present study only the data from 1980 were used (supplemented with a 14-year follow up-study questionnaire). When the father's occupational status was not known, the mother's was used. Childhood SES was classified into five groups: 1) father had an academic education 2) father was a

professional with lower esteem and less education than those in the first group, 3) father was a skilled worker, 4) father was an unskilled worker or on a disability pension, and 5) father was a farmer.

The information of subjects' childhood living area (living in a town, a village or the countryside) was obtained from the records of maternity care visits in the 1960s (Rantakallio 1988).

Longitudinal risk of sun exposure, skin type, smoking and leisure time activity (II-IV)

At the age of 46 years study cases were asked about the number of sun burns in their history (>10 times, ≤ 10 times), the frequency of holidays in sunny places during the previous ten years (at least every other year, fewer than every other year, never) and how they used sunscreens (regularly, sometimes, never or do not spend time in the sun). Skin type was self-reported and was classified using the modified Fitzpatrick's criteria as follows: skin type I "skin always burns", type II "skin burns often", type III "skin burns occasionally" and type IV "skin never burns" (Fitzpatrick 1988).

Information on smoking status and leisure time activity was gathered via the 46-year follow-up questionnaire.

Previously diagnosed type 2 diabetes and systemic diseases (III, IV)

Previously diagnosed type 2 diabetes and the use of regular medications for diabetes were self-reported in the 46-year follow-up questionnaire. The information was supplemented by hospital outpatient and inpatient registers (from year 1973-74 to 2014) and medication registers from the Social Insurance Institution of Finland (from the year 1997). Other systemic diseases such as cardiovascular diseases, thyroid gland diseases, depression, rheumatic diseases, inflammatory bowel diseases were self-reported.

Use of oral contraceptive pills or other hormonal replacement therapy (IV)

The use of the following products was self-reported in the 46-year follow-up questionnaire: contraceptive pills/similar products, minipills, intrauterine contraceptives, contraceptive implants, condoms, hormone replacement therapy.

4.1.4 Anthropometric measurements and laboratory tests (I-IV)

Body mass index (I-IV)

The clinical examination of the 46-year follow-up survey included body weight in light clothing, which was measured with a digital scale. Height was measured twice using a standard and calibrated stadiometer and the mean of the two measurements was used. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2). Study participants were classified into five groups, based on their BMI, according to WHO criteria: Underweight (<18.5); normal ($18.5\text{--}25$); overweight ($25\text{--}30$); obese ($30\text{--}35$) and severely obese (>35) (World Health Organization 2000).

Glucose metabolism (III)

FPG and HbA_{1c} were taken at the cohort laboratory between 7.00 and 11.00 after an overnight fasting period as a part of the 46-year follow-up survey. An OGTT was performed few days later, again after overnight fasting. Study cases with previously diagnosed diabetes and those whose pre-test FPG was >8.0 mmol/l were excluded from the test. Glucose samples were analysed using an enzymatic hexokinase/glucose-6-phosphate dehydrogenase method in NordLab Oulu, a testing laboratory (T113) accredited by the Finnish Accreditation Service (FINAS) (EN ISO 15189), (both method: Advia 1800; Siemens Healthcare Diagnostics Inc., Tarrytown, Ny, USA). The classification of glucose status followed the criteria of the WHO and ADA in the further analyses.

Hs-CRP (IV)

Blood samples for measuring the low-grade inflammation by hs-CRP testing were taken in connection with the 46-year follow-up survey after an overnight fast and stored at -70C . The samples were further analysed using an immune nephelometric assay (BN, Siemens Healthcare Diagnostics Inc., Newark, DE, USA). The hs-CRP was sensitive enough to detect CRP values of 0.2 mg/l and greater. (IV)

4.2 Statistical methods (I-IV)

The overall point prevalence of skin disorders and the prevalence of each skin disease or finding was calculated. In order to estimate the crude and adjusted prevalence ratios (relative risk, RR) and their 95% confidence intervals (CI), the modified Poisson regression model was used. The adjusted model included sex and educational level variables and interactions between these variables were also tested. Tests were adjusted for sex and education level.(I)

The cross-sectional point prevalence of melanocytic naevi (< 10 naevi, 10–50 naevi and >50 naevi) was calculated. The number of naevi was defined as the main outcome and sun-related risk factors as explanatory variables. Education, parents' education, childhood living area, inflammatory skin diseases, obesity, the use of sunscreens, the number of sunburns, the number of holidays in sunny places and sex were analysed as risk factors for naevus number. Multivariate multinomial regression analyses were performed and a multinomial logistic regression analyses (stepwise backward selection) was used to determine the strongest risk factors for multiple naevi and to see gradually increasing risk factors between different groups based on naevus number (<10, 10–50 and >50). Adjustments were made for sex, education, inflammatory skin diseases, skin type and the use of sunscreens. (II)

FPG and HbA_{1c} levels and the OGTT status (normal glucose tolerance [NGT], IFG, IGT, screen detected diabetes, [SDM]) of study cases were calculated. Multivariate, multinomial logistic regression was used to evaluate the association between abnormal skin findings in toe webs and glucose metabolism, in which the glucose status were the outcome variables and the skin findings the explanatory variable. Study cases with previously diagnosed diabetes were excluded from the analysis. The predictive power of toe web findings was tested by comparing it to the FINDRISC score by using the logistic regression analysis. Toe web findings was added to a modified FINDRISC model as an additional variable and statistical analyses followed the methodology by original publication of Lindström and Tuomilehto (Lindstrom & Tuomilehto 2003). Adjustments were made for smoking, physical activity, education, sex and BMI. (III)

The associations between skin diseases and low-grade inflammation were analysed by performing logistic regression. The analyses were conducted in three subgroups based on CRP levels: hs-CRP < 1mg/l, hs-CRP 1–3 mg/l and hs-CRP >3 mg/l to identify any possible gradient effect between increasing CRP level and skin diseases. Study cases with hs-CRP ≥10 mg/l were not excluded from the study. The main outcome was CRP level and skin diseases were taken as explanatory variables.

Adjustments were made for tobacco smoking, sex, the use of oral contraceptives, education level and physical activity. Additional adjustments were performed for BMI and systemic diseases. (IV)

To test the difference in categorical variable, the Pearson's Chi-Square test or Fisher's Exact test (when appropriate) was used. One-way analysis of variance (ANOVA) or Mann-Whitney U-Test was used for continuous variables and their distributions were expressed as mean and standard deviation (SD) or median and interquartile ranges (IRQ). Odds ratios (OR) (crude and adjusted) with related 95% CI were reported as measures of association. Statistical analyses were performed using SAS 9.3. or 9.4 for Windows (The SAS Institute, Cary, NC, USA) or the STATA (Data Analysis and Statistical Software, MP 13, StataCorp LP, College Station, TX 77845, USA) and the SAS software package (version 9.4, SAS Institute, Inc). P-values < 0.05 were recognized to be statistically significant.(I-IV)

4.3 Ethical approval (I-IV)

The study was approved by Ethical Committee of the Northern Ostrobothnia Hospital District and it was performed according to the principles of the 1983 Declaration of Helsinki. The subjects took part in the examinations on a voluntary basis and all gave signed and informed written consent form on their own behalf. In that form study participants were informed about their option to discontinue the study whenever they wanted. Participants were aware that the data would be handled on a group level. Personal information was replaced by identification codes during the statistical analyses.

5 Results

5.1 Characteristics of the study population (I-IV)

The Skin Study population comprised 1932 study cases; there were 1036 females (53.7%) and 896 males (46.3%). All subjects were 45–47 years of age at the time of the follow-up visit. The majority (58.6%) of participants had completed secondary level education, over one in every three (38.7%) tertiary level and 2.8% basic level.

5.2 The prevalence of skin diseases and skin findings (I)

At the age of 46 years most cases (N=1281, 66.3%) presented a skin disease. While more than half of these (N=688, 53.7%) had one skin disease, one quarter (N=327, 25.5%) were diagnosed with two diseases and 17.3% (N=221) showed three or more diseases.

Skin infections were the most common dermatological diseases, found in 840 of all subjects (43.5%): tinea pedis was seen in 517 (26.8%) and onychomycosis in 181 (9.4%). Virus warts were found on the feet of 179 (9.3%) subjects and on the hands of 51 (2.6%). The most frequent bacterial skin infection was folliculitis, which was found in 116 (6.0%) subjects. Other skin infections, such as pityriasis versicolor, tinea corporis and pyoderma were rare, each occurring in 0.1–2% of all subjects.

The overall prevalence of eczemas was 27.4%; hand eczema (N=171, 8.9%) was more common than seborrhoeic eczema (N=141, 7.3%) and atopic eczema (N=93, 4.8%). Sebaceous gland diseases affected 26.7% of study cases; rosacea was the most common type (N=292, 15.1%) and 242 (82.9%) of rosacea cases were erythematoteleangiectatic. The prevalence of acne vulgaris was 7.9% (N=152). Acne scars were visible in 9.8% of the cohort. The prevalence of psoriasis was 2.1%.

Autoimmune skin diseases were rare (N=81, 4.2%), and the most common of them was vitiligo (N=32, 1.7%).

All 1932 subjects had at least one melanocytic naevus. Cherry angiomas were diagnosed in 1158 (60.0%), seborrhoeic keratosis in 855 (44.3%) and dermatofibromas in 248 (22.2%). Twelve cases of solar keratosis (0.6%), seven basal cell carcinoma (0.4%) and one malignant melanoma (0.1%) were recognized.

5.3 The severity of skin diseases (I)

Almost all study cases with any skin disorder found upon study investigation (N=1156) required treatment or further evaluation. Of these cases, 56% were classified as mild and predicted to resolve with self-treatment; 41% (N=472) had skin disease severe enough to be referred to a general practitioner or occupational health care, and 3% (N=38) to secondary care for further evaluation.

Most cases of atopic eczema and psoriasis, as measured by EASI and PASI indexes, respectively, were classified as mild in severity. Mean EASI was 4.7 (0.1 to 36) and mean PASI 3.1 (0.1 to 13.7). One in every three of all study cases with psoriasis had nail deformities and joint symptoms.

5.4 Multiple melanocytic naevi, skin type and longitudinal history of sun exposure (II)

Multiple melanocytic naevi (defined as >50 naevi) were found in 222 individuals (11.6%) as a part of the 46-year survey. Most (N=1436, 74.4%) had 10–50 naevi and 271 (14%) fewer than ten. Most of the participants (N=1284, 69.1%) had self-reported skin type III, 282 (15.2%) type IV and 248 (13.3%) type II. Very sensitive skin type (I) was self-reported by 44 (2.4%) of the study cases.

One in every three of the study cases (N=588, 31.5%) retrospectively reported ten or more skin burns in their history. Holidays in hot climates were frequent; more than half of all respondents (N=1058, 58.0%) had travelled at least every other year during the past ten years. The majority (N=1184, 66.7%) of the study population used sunscreens regularly abroad but 232 (13.1%) had never used them. (II)

5.5 Risk factors associating with multiple naevi (II)

Skin types I–III, high numbers of sunburns (≥ 10 sunburns) and frequent holidays in hot climates were associated with the presence of multiple naevi ($p=0.01$, $p=0.04$ and $p=0.03$, respectively). Those who regularly used sunscreens were more likely to have multiple naevi compared with those who used sunscreens occasionally or did not use them at all ($p=0.001$). In contrast, study cases with diagnosed eczema or psoriasis were less likely to have multiple naevi than those without inflammatory skin diseases ($p<0.001$). After adjusting the results (by sex, education, skin types I–III, the regular use of sunscreens abroad and inflammatory skin diseases) the risk for multiple melanocytic naevi was 2.1-fold higher (95% CI 1.3 to 3.3) in those

with skin type I–III than in those with type IV. The regular use of sunscreens abroad increased the risk 2.0-fold (95% CI 1.2 to 3.4). In contrast, the presence of inflammatory skin diseases decreased the risk for multiple naevi by 50% (95% CI 0.3 to 0.7).

5.6 The effect of gender on the prevalence of skin diseases and multiple naevi (I,II)

Skin diseases were more common in males than in females; 676 males (75.6%) and 605 females (58.4%) had at least one skin disease ($p < 0.001$). Males were more likely to have several skin diseases ($p < 0.001$) and their skin findings required further treatment or follow-up more often than those of females ($p < 0.001$). Most eczemas were more common among males than females: seborrhoeic eczema (RR 3.8, 95% CI 2.6 to 5.5), eczema infectiosum (RR 3.5, 95% CI 1.5 to 8.1) and neurodermatis (RR 3.4, 95% CI 1.6 to 7.1). Skin infections like tinea pedis (RR 1.9, 95% CI 1.7 to 2.3), onychomycosis (RR 2.6, 95% CI 2.0 to 3.6) and folliculitis (RR 3.1, 95% CI 2.2 to 5.0) were also more common in males.

Most (68.6%) males had androgenetic alopecia. It was severe in 27%, moderate in 32% and mild in 38% of males.

The prevalence of multiple melanocytic nevi in males was 13.0% (N=116) and 10.3% (N=107) in females ($p < 0.13$). Over one in every three of males (N=291, 33.7%) reported a history of frequent sunburns and 29.5% (N=297) of females ($p < 0.06$). Males were less likely to report regular use of sunscreens ($p < 0.001$). In total, the risk for multiple melanocytic naevi was 1.5-fold greater in males than in females (95% CI 1.1 to 2.1).

In contrast, rosacea was less common in males than females (RR 0.6, 95% CI 0.4 to 0.7), as were hand eczema (RR 0.73, 95% CI 0.5 to 0.9) and contact eczema (RR 0.1, 95% CI 0.03 to 0.6). Most types of benign skin tumour were also diagnosed less frequently in males, including dermatofibromas (RR 0.7, 95% CI 0.6 to 0.8), cherry angiomas (RR 0.8, 95% CI 0.8 to 0.9) and seborrhoeic keratosis (RR 0.9, 95% CI 0.8 to 0.9).

5.7 Association between education level and the prevalence of skin diseases and multiple naevi (I,II)

Compared with participants with a tertiary education level, study cases with only a basic level of education were more likely to have eczema infectiosum (RR 10.3,

95% CI 2.4 to 45.1), onychomycosis (RR 1.9, 95% CI 1.0 to 3.9) and tinea pedis (RR 1.6, 95% CI 1.1 to 2.4). In contrast, a higher education status was associated with a 2.1-fold greater risk for multiple melanocytic naevi (95% CI 1.5 to 3.0) as compared with a lower education level. Correspondingly, those with high childhood SES had a higher prevalence of multiple naevi compared to those with low childhood SES (13.4 %, 7.3%, respectively, $p < 0.05$).

5.8 The association between abnormal skin findings in toe web spaces and glucose metabolism (III)

The detailed skin status of feet and glucose metabolism was determined for all in the Skin Study population at the age of 46 years. The cases with previously diagnosed diabetes (N=81) were excluded from the study. Abnormal toe web spaces were seen in 492 (26.6%). FPG was elevated in 172 (9.5%) and HbA_{1c} in 397 (21.6%) of the subjects. An FPG level required for type 2 diabetes diagnosis (≥ 7.0 mmol/l) was reached by 21 (1.2%) participants and a diagnostic threshold HbA_{1c} level was reached by 15 (0.8%). According to OGTT findings, 1256 (80.8%) of the study cases presented with NGT, 121 (7.9%) with IFG, and 134 (8.6%) showed IGT. SDM was diagnosed in 43 (2.8%).

Elevated and diabetic levels of FPG and HbA_{1c} were more commonly found in subjects with abnormal toe web findings than in those who had healthy toe webs ($p = 0.002$, $p < 0.001$, respectively). Abnormal IFG, IGT or SDM in OGTT findings were also more common in these participants than those who had healthy toe webs ($p < 0.001$).

After adjustment, study cases with abnormal skin findings in toe webs had a 2.5-fold (95% CI 1.3 to 4.9) higher risk of having previously undiagnosed type 2 diabetes (SDM) detected by OGTT when compared to those with healthy toe webs. The risk was 6-fold (95% CI 1.4 to 27.6) higher if HbA_{1c} was used as a definition of SDM.

5.9 The predictive power of toe web finding in detecting type 2 diabetes (III)

Multivariate logistic regression analyses demonstrated that FINDRISC score and toe web space findings were both independent predictive factors for type 2 diabetes. When the FINDRISC model was modified by supplementing toe web findings as an additional variable, the β -coefficient for toe web findings was 0.82 which

corresponds to a score 3 in the FINDRISC model. The area under the receiver operating characteristic (ROC) curve, was 0.834 (95% CI 0.785 to 0.884) for the original FINDRISC score and 0.839 (95% CI 0.786-0.892) for the risk score modified with toe web findings.

5.10 Hs-CRP and skin diseases (IV)

Hs-CRP levels were normal (<1 mg/l) in 1174 (61.6%) of the subjects in the Skin Study population, slightly elevated (1–3 mg/l) in 533 (28.0%) and highly elevated (>3 mg/l) in 199 (10.4%). A higher proportion of females – 120/1022 (11.7%) presented with highly elevated hs-CRP, than did males – 79/884 (8.9%) ($p < 0.05$). The data of hs-CRP was missing in 24 subjects.

A highly elevated hs-CRP level was more common in study cases who had atopic eczema ($p < 0.05$), rosacea ($p = 0.001$) or tinea unguim ($p = 0.01$) diagnosed upon a dermatological evaluation when compared with those who did not have these diseases. Study cases who had any skin disease designated severe enough to require treatment had more common a highly elevated hs-CRP level than those with only slight skin disease ($p = 0.013$). There were more significant associations between skin diseases and elevated hs-CRP in females than in males, however, the two way interactions between skin diseases and sex were not statistically significant.

After adjustment, study cases with atopic eczema had a 2-fold (95% CI 1.2 to 3.9) greater OR of having highly elevated hs-CRP levels when compared with those who did not have atopic eczema. The OR for highly elevated hs-CRP was 1.7-fold (95% CI 1.1 to 2.5) greater in those who had rosacea and 2.0-fold (95% CI 1.2 to 3.2) greater in those with tinea unguim than in those without. More severe skin disease (denoted by the need for further follow-up or treatment) was associated with an OR of highly elevated hs-CRP 1.6-fold (95% CI 1.2 to 2.3) higher than disease not requiring further follow-up.

Further adjustment for BMI and systemic diseases resulted in an OR for highly elevated hs-CRP that was 2.4-fold (95% CI 1.3 to 4.6) greater in subjects with atopic eczema than those in those without. The OR for highly elevated hs-CRP was 1.9 -fold (95%CI 1.1 to 3.1) greater among those with tinea unguim than those without. The need for treatment of skin diseases was associated with highly elevated hs-CRP (OR 1.5, 95% CI 1.0 to 2.1).

Study cases with hs-CRP \geq 10 mg/l (unpublished data)

Hs-CRP levels were \geq 10 mg/l in 30 study cases; 12 of these were male and 18 female. A closer analysis of the association between subjects' CRP level and the incidence of skin diseases was performed by excluding cases with hs-CRP \geq 10 mg/l. In logistic regression analysis, after adjusting for tobacco smoking, sex, the use of oral contraceptives, education level, physical activity, BMI and systemic diseases, the OR for highly elevated hs-CRP was nearly 3-fold (2.9, 95% CI 1.5 to 5.6) greater in subjects with atopic eczema than in those without atopic eczema. The OR for highly elevated hs-CRP was also higher (OR 2.2 95% CI 1.3 to 3.6) in those with onychomycosis than in those without the disease. The OR for highly elevated hs-CRP was 1.5 (95% CI 1.0 to 2.9) in cases with any of the sebaceous gland disease when compared with cases without sebaceous gland disease.

6 Discussion

6.1 High prevalence of skin diseases in Northern Finland Birth Cohort 1966 (I)

It has previously been shown that skin patients are common in general practice (Julian 1999, Lowell *et al.* 2001) and the results of the present study strongly support this statement. The prevalence of skin diseases as well as the need of treatment was even higher in our study than in previous population-based studies (Augustin *et al.* 2011, Johnson & Roberts 1978, Rea *et al.* 1976). One reason for this may be that the diagnosis of cutaneous findings was based on a dermatologist's evaluation. In one of the previous studies the diagnoses were made by a nurse, and some findings that were considered "slight" were not recorded at all (Rea *et al.* 1976). We performed a comprehensive clinical examination, and all skin findings, including minor cutaneous abnormalities, were recognized. Furthermore, all social classes were represented in our study, whereas e.g. a previous wide cohort study among German workers included only employed people with health insurance, which may have led to selection bias (Augustin *et al.* 2011). It is important to bear in mind the differences in age ranges and diagnostic criteria for skin diseases when comparing the results of the present study to those of previous epidemiological studies.

In this study the skin findings of a high proportion of subjects required further care. However, there is no consensus on which case cutaneous findings require treatment or care; in the present study the decision on whether further evaluation was required was based on the subjective evaluation of an examiner and followed the accepted clinical guidelines in dermatology. Further evaluation was seen as necessary if the finding required therapeutic treatment such as a prescription drug or confirmation of the diagnosis. Aside from these factors, many different aspects can contribute to such a decision. For example, the effect of a case of hand eczema on a patient's fitness to work, the effect of facial eczema on quality of life or the prognosis in skin tumours cases.

In all clinical studies with participation rate less than 100%, including ours (participation rate 62%), there is a risk of selection bias. It is possible that subjects with relevant diseases are more likely to be enrolled. Nevertheless, in the present study, cohort members were invited to participate in the multidisciplinary overall health investigation, which included several other clinical evaluations other than

those involving the skin. Therefore, it is unlikely that study cases with skin diseases would have been overrepresented in this study, despite the high overall prevalence of skin diseases.

As with previous reports (Augustin *et al.* 2011, Johnson & Roberts 1978, Plunkett *et al.* 1999, Rea *et al.* 1976), the most common cutaneous findings in the present study were benign skin tumours, skin infections, sebaceous gland diseases and eczemas. Melanocytic naevi were present in every study case, seborrhoeic keratosis in 44% and dermatofibromas in 22%. In another dermatological cohort study performed in the Netherlands (N=966) seborrhoeic keratosis were found in 38% (N=86/226) of the subjects aged 24–49 years, a similar result to that of the present study (Kennedy *et al.* 2003b). Tinea pedis was surprisingly common in the present population (prevalence 26%). Previous estimates of its prevalence in developed countries have varied between 5 and 15% (Augustin *et al.* 2011, Elewski & Hay 1995). However, in the present study, diagnosis of tinea pedis was based solely on the clinical picture; samples for fungal culture were not taken, which may explain the higher prevalence.

The prevalence of rosacea was 15%, while in other studies it has varied between 1 and 20% (Tan & Berg 2013). This relatively high prevalence may be explained by the fact that rosacea is associated with fair skin types. This would also be consistent with the high prevalence estimates in Estonia and Sweden (Abram *et al.* 2010, Berg & Liden 1989, Gibson *et al.* 1997). Acne was seen in 8% of the present cohort. In a 1970s community based-study in Sheffield, England (N=2155) acne was diagnosed in 5% of females and in 3% of males (Cunliffe & Gould 1979). In another UK study, performed in 1999 (N=749) 12% of females over 25 years of age had mild, moderate or severe acne (Goulden *et al.* 1999). There is evidence of an increasing prevalence of adult acne (Goulden *et al.* 1999) and the finding of the present study may support that trend.

The prevalence of atopic eczema was 4.2% in this study, which is higher than previously reported in Central European and Asian countries (0.3–2.9%)(Augustin *et al.* 2011, Muto *et al.* 2003). However, the prevalence of atopic eczema in adults is reportedly higher in Scandinavia than in the southern part of Europe (Augustin *et al.* 2011, Vinding *et al.* 2014). For example in a Danish study (N=16 547) the prevalence of self-reported atopic eczema in the adult population was unexpectedly high, at 14.3% (Augustin *et al.* 2011, Vinding *et al.* 2014). The high prevalence of atopic eczema in Scandinavia has also been reported in the comprehensive International Study of Asthma and Allergies in Childhood (ISAAC) (Beasley *et al.* 1998). The prevalence of psoriasis was 2% in the current study, which is in line

with the results of a USA study (N=27 220) which reported a prevalence of 2.2% (Stern *et al.* 2004) and with global findings, which vary from 0.6 to 4.8% (Gelfand *et al.* 2005).

Actinic keratosis was diagnosed in 12 in the present study, basal cell carcinoma in seven and melanoma in one. Although the prevalence of skin cancer is constantly increasing (Rogers *et al.* 2015) it was rather unexpected that so many premalignant and malignant skin tumours were detected among the relatively young cohort members.

6.2 Multiple naevi and their risk factors in Northern Finland Birth Cohort 1966 (II)

The prevalence of multiple melanocytic naevi in the present study was 11.6%. At corresponding latitudes, a study carried out in Northern Sweden (N=201), at a similar latitude, found 6% of study cases with multiple naevi (over 100 naevi) (Karlsson *et al.* 2000) and, in the southern part of Sweden (N= 379) the prevalence has been reported as 22% (Augustsson *et al.* 1991). In Germany (at a lower latitude) the prevalence of multiple naevi has been reported as 18% (>50 naevi) and in the UK as 23% (>100 naevi) (Bataille *et al.* 2000, Garbe *et al.* 1994). The highest naevus counts have been recognized in Australia (N=205), where 31% of study cases were seen with over 50 naevi (Youl *et al.* 2002). In general, the average naevus number is higher in those living nearer the equator (Rodvall *et al.* 2007). Given that the present study was performed in high latitudes, the result of 11.6% can be considered moderately high. However, these studies are not directly comparable with each other because of the different definitions of multiple naevi (>50 vs >100 naevi) and also other methodological differences.

Holidays in sunny climates were reasonably common in the present study population (58% of the participants at least every other year). Sun exposure is the main known environmental risk factor for naevus development and is especially harmful to individuals who are not accustomed to intensive UV exposure in their everyday lives. Sunburns induce naevus development and are extremely harmful in childhood (Garbe *et al.* 1994, Kennedy *et al.* 2003b). Over 30% of study participants reported more than ten sunburns in their history. Thus it is not surprising that the study cases with several sunburns and frequent holidays in the sun had higher numbers of naevi compared to those who did not have these risk factors in their past.

A sun-sensitive skin type (types I–III) was associated with a 2.0-fold higher risk of multiple naevi than skin type IV. It has been previously reported that people with fair skin type have a higher risk for multiple naevi (Valiukeviciene *et al.* 2005). This is supported by the findings of the present study. Also reflecting the findings of previous studies, regular use of sunscreens was associated with an increased risk of high naevus count (Autier *et al.* 1999). However, there have been other findings that contradict this; the use of sunscreens was associated with a lower risk of multiple naevi in children (Moreno *et al.* 2016). One explanation for the present finding could be that people who use sun lotions tend to stay in the sun for longer, leading to greater exposure to UV radiation.

In the present study, having an inflammatory skin disease decreased the risk for multiple naevi. The previous literature concerning on this topic is sparse, but in a Swedish study (N=448) patients with severe atopic eczema (N=51) had significantly lower total body naevus count compared to those without atopic eczema (N=379) (Broberg & Augustsson 2000). The authors of that report suggested that an immunologic mechanism in atopic eczema or the use of local or systemic medication could have affected the development of naevi (Broberg & Augustsson 2000).

6.3 Association between gender and the prevalence of skin diseases and multiple naevi (I, II)

Compared to females, males had more skin diseases, they were diagnosed more often with multiple skin diseases and their need for follow up or treatment was higher. Eczemas like seborrhoeic eczema and eczema infectiosum as well as most of the skin infections (onychomycosis, tinea pedis and folliculitis) were more common in males than females. Such a male predominance has been reported in several other population-based studies (Johnson & Roberts 1978, Plunkett *et al.* 1999, Rea *et al.* 1976). There may be biological and behavioural explanations for this. For example, folliculitis affects men more commonly because they have more terminal hair follicles than women (Abeck 2009). The higher rate of onychomycosis and tinea pedis in males may result from the use of occlusive shoes in industrial workplaces or from exercise-related nail injuries (Perea *et al.* 2000). Another hypothesis is that females take better care than males of their appearance and therefore, diagnosis and treatment of cutaneous diseases is more likely to be either delayed or ignored by males.

In the present study, androgenetic alopecia was diagnosed frequently in males; 70% of males had hair loss and one in every three had a severe form of baldness. Male pattern hair loss has geographical variation in prevalence: in the USA 42% of 266 males aged 18–74 years reported a moderate-to severe form of hair loss (Rhodes *et al.* 1998). In a Korean study (N=5531), the prevalence of male pattern hair loss was clearly lower, at 14% (Paik *et al.* 2001). Two main aetiological factors contribute to the development of androgenetic alopecia: hormonal factors and genetic predisposition (Sinclair, 1998), with the latter being thought to explain the geographical differences. The findings of the present study suggest that the genes affecting baldness phenotype may have been accumulated in Northern Finland.

Males had 1.5-fold greater risk than females for multiple melanocytic naevi. This is in line with the previous reports (Dogan 2007, Green *et al.* 1989). In the present study it appears that this sex difference was mostly due to behavioural differences between the genders: The male participants declared more sunburns and lesser use of sunscreens.

A female predominance was found in hand eczema, contact eczema, rosacea and benign skin tumours. This does not conflict with the previous literature (Plunkett *et al.* 1999). For example, the higher prevalence cherry angiomas in females may be due to hormonal factors (Luba *et al.* 2003). Occupational gender differences may partly explain the female predominance in hand eczema, since, for example, hairdressers, nurses and cleaners expose themselves to water and some of the irritant chemicals that are associated with irritant contact dermatitis. The latter is the most common type of hand eczema and is often work-related (Nettis *et al.* 2002).

6.4 Association between educational level and the prevalence of skin diseases and multiple naevi (I, II)

An important finding was that study cases with a lower educational level had more certain skin diseases compared to those with higher educational status. This relationship has been reported previously (Rea *et al.* 1976) but has not yet been fully explained. It could in part be due to behavioural factors or financial reasons. For example, the availability of health services varies and highly educated people may have the option to seek private health care. An association between atopic eczema and SES has been reported previously (Bergmann *et al.* 2000) but this was not confirmed by the present study, possibly because of the low number of cases of atopic eczema.

There was a higher risk of multiple naevi in study cases with higher education than those with lower education. This result remained significant after adjusting for the frequency of holidays in sunny climates and sunbathing habits. The association between malignant melanoma and SES is well known (Harrison *et al.* 1998), but the present study was the first to report an association between higher SES and multiple naevi. It is possible that highly educated people participate more regularly in outdoor leisure activities such as golf, sailing or other outdoor sports. In any case, more education is required to increase awareness of people about the potential risks of sun exposure. There are encouraging reports from Australia of reductions in the rates of skin cancers following prevention programmes (Stanton *et al.* 2004, Staples *et al.* 1998).

There was also slight evidence of an association between childhood SES and naevus number. This emphasizes that naevus acquisition is a long-lasting cumulative process that starts in childhood. However, no association was found between childhood living area and number of naevi despite the hypothesis that subjects from the countryside would have been exposed to more UV radiation and experienced more sunburns than those who had spent their childhood in urban areas.

6.5 Skin findings in toe web spaces act as a marker of abnormal glucose metabolism (III)

This study employed a novel design to uncover the potential association between skin diseases (toe web findings) and glucose metabolism and therefore construct a method to enhance the early detection of type 2 diabetes. Interestingly, study cases with erythema, macerations or other local skin findings in toe webs had a 2.5- fold greater risk to have undiagnosed type 2 diabetes defined by OGTT than those who had healthy toe web skin. The risk difference was even greater (6-fold), when HbA_{1c} was used to define undiagnosed diabetes.

This approach was highly justified, as over half of all patients with type 2 diabetes are undiagnosed (Beagley *et al.* 2014). In Finland it is estimated that 150000 people with diabetes are unaware that they have the disease (the report of Finnish Diabetes Association 2016). In such cases, treatment for diabetes is delayed, and this may lead to the development of preventable complications. Therefore, there is a clear need for inexpensive and simple clinical screening tools for diabetes.

The predictive power of abnormal toe web findings for diabetes was tested by comparing it with the recognized FINDRISC score, which has been reported to detect 66% of males and 70% of females with undiagnosed diabetes (Lindstrom &

Tuomilehto 2003). This analysis found that the predictive power of toe web findings when added in the FINDRISC was comparable with that of the original FINDRISC score; both were independent predictive factors for type 2 diabetes in the present study population. When toe web findings was added to the modified FINDRISC score as an additional variable it improved slightly the area under the curve. The β -coefficient for toe web finding correlated with BMI and waist circumference in the score when analysed in multivariate logistic regression analysis. This result has potential benefits for the detection of type 2 diabetes, in that abnormal skin findings in toe webs can be noticed by individual patients without any doctoral visit. Also, toe web checking is a rapid, non-invasive, and inexpensive tool for screening people at high risk of type 2 diabetes.

Although this study was not designed to confirm fungal infections or take culture samples from toe webs, it is rather probable that most of the abnormal findings in toe web spaces were symptoms of tinea pedis since its typical symptoms are maceration, cracks and erythema located in interdigital space of the toes. There are some explanations as to why patients with diabetes are susceptible to fungal skin infections (Foss *et al.* 2005, Galdeano *et al.* 2013, Legge *et al.* 2008, Mahajan *et al.* 2003, Perez & Kohn 1994, Yosipovitch *et al.* 1998). Hyperglycaemia increases the skin pH, which favours the increase of microbe populations. Also, insulin imbalance resulting from hyperglycaemia leads to keratinocyte dysfunction (Spravchikov *et al.* 2001, Wertheimer *et al.* 2000). Both these changes predispose to fungal skin infections.

6.6 The association between skin diseases and low-grade inflammation (IV)

This study found that low-grade inflammation is connected to several skin diseases, such as atopic eczema, rosacea and onychomycosis. This association has only been previously investigated in a disease specific manner, for example, with regard to psoriasis or rosacea (Dowlatshahi *et al.* 2013, Duman *et al.* 2014). Nevertheless, many cutaneous disorders have an inflammatory background (Dowlatshahi *et al.* 2013, Silverberg & Greenland 2015).

Low-grade inflammation has been an area of interest in recent decades because of its association with many non-communicable diseases. Hs-CRP measurement is an accurate marker for systemic inflammation and has been used to predict future cardiovascular events (Rifai & Ridker 2001). Elevated hs-CRP also has a

documented association with depression, obesity and PCO (Boulman *et al.* 2004, Liukkonen *et al.* 2006, Maachi *et al.* 2004).

To best of our knowledge, no association has previously been demonstrated between increased hs-CRP and atopic eczema in an unselected adult study population. In a previous UK study among young adults (N=3898) those with atopic eczema showed higher hs-CRP levels than their controls (Hayes *et al.* 2016). However, the association disappeared after adjusting the results (adjusted for sex, age, ethnicity, SES, Strengths and Difficulties Questionnaire, Edinburgh Postnatal Depression Scale and BMI) (Hayes *et al.* 2016) whereas in the current study the association remained significant after adjustment for sex, BMI, educational level, tobacco smoking, physical activity, systemic diseases and the use of oral contraceptives. Recent studies have reported an elevated risk for cardiovascular events in patients with atopic eczema (Andersen *et al.* 2016, Silverberg *et al.* 2015, Su *et al.* 2014). However, in a cohort study of females in the USA, atopic eczema was not independently associated with nonfatal myocardial infarction or stroke (Drucker *et al.* 2016). The most likely explanation for the higher cardiovascular risk profile in patients with atopic eczema is its comorbidities; atopic eczema is known to be associated with many cardiovascular risk factors such as smoking, lower levels of physical activity, higher BMI, and hypertension (Silverberg & Greenland 2015). However, future studies are needed to confirm whether low-grade inflammation contributes to this association.

Fungal nail infection is common disease and is, on average, seen in 10% of the population (Elewski & Hay 1995, Heikkilä & Stubb 1995). The present study found an association between highly elevated hs-CRP and onychomycosis. In our opinion, onychomycosis, which is easily ignored because its mild symptoms, should be considered not only as local tissue damage but also as a possible source of systemic inflammation. However, this novel finding requires confirmation by further studies. Rosacea was also associated with low-grade inflammation, which supports the conclusions of a previous Turkish study that reported increased hs-CRP levels in rosacea patients (Duman *et al.* 2014).

Surprisingly, no association between low-grade inflammation and psoriasis was found even though this relationship has been reported in several studies (Dowlatshahi *et al.* 2013). This may have been because most cases of psoriasis in the present study were mild. It is known that hs-CRP is higher in patients with severe psoriasis than in those with mild disease (Coimbra *et al.* 2010, Rocha - Pereira *et al.* 2004).

In this study, subjects with hs-CRP ≥ 10 mg/l were initially included into the statistical analyses. Some of these high levels could have been due to hidden infections such as flu, and this may have increased the number of false positive cases in the study. However, high CRP levels may also be a consequence of the present skin disease and the exclusion of subjects with high CRP could have increased the number of false negative cases.

A further logistic regression analysis was performed on a subpopulation after excluding subjects with hs-CRP levels ≥ 10 mg/l. This exclusion had only a slight effect on the results; the association between severe skin diseases and highly elevated hs-CRP was slightly weaker but the corresponding OR for highly elevated hs-CRP in patients with atopic eczema and onychomycosis increased (see Results).

It would be ideal to research the potential association between CRP levels and chronic disorders in the absence of obvious concurrent infections or (other) inflammatory conditions. Furthermore, when high hs-CRP levels (≥ 10 mg/l) are detected, it is recommended to repeat the measurements after two weeks to determine whether the elevation was caused by the disease in question or by confounding factors (Pearson *et al.* 2003). However, in the present study repetitive measurements were not possible because of the study design; this was the main reason for the inclusion of all subjects in the analyses, regardless of hs-CRP level.

6.7 Strengths of the described studies

Most previous dermatoeidemiological studies have analysed the prevalence of a certain skin disease such as acne or atopic eczema in a specific population or patient groups such as servicemen, children or subjects with mental health problems (Berg & Liden 1989, Herd *et al.* 1996, Parisi *et al.* 2013, Susitaival *et al.* 1994). The major strength of the present study is its general, unselected population which allows the generalization of the results to other middle-aged Caucasian populations. Another strength is that it covered skin diseases in general rather than focusing on a limited disease group. Instead of using self-reporting questionnaires (Montnemery *et al.* 2005, Wallenhammar *et al.* 2004) these results were based on the findings of whole-body skin evaluations performed by dermatologists. Furthermore, the interobserver reliability was found to be highly satisfactory. This provides high standard diagnostics. When appropriate, dermatoscopy was used to evaluate the findings and confirm the diagnosis. A further strength of this study is the unique birth cohort, which has recorded all health data and lifestyle information of all study participants since birth, and, that of their mothers since pregnancy. This longitudinal data set

has enabled us to survey the impact of multiple medical and non-medical factors on study endpoints, and to comprehensively investigate the associations between these factors and the occurrence and severity of skin diseases.

Glucose metabolism and low-grade inflammation were quantified using high quality laboratory measurements. Diabetes can be identified via OGTT or by measuring FPG or HbA_{1c} but all these methods were employed in the present study. Although OGTT is a time-consuming method, it was included because of its sensitivity in screening for prediabetes.

6.8 Limitations of the described studies

All NFBC 66 cohort members were invited to participate in the 46-year survey, but not all did, and this may have led to sample selection bias. Despite the large study population, the numbers of subjects with particular skin diseases were rather low. Diagnoses of skin diseases were achieved during a single outpatient visit and there was no opportunity to take skin biopsies, use microbiologic culture or to obtain information of subjects' previous medical history at the time of skin evaluation. Subjects self-reported their history of sun exposure and sunbathing habits and this may have led to underestimations regarding these risk factors. Furthermore, each subject's glucose status and low-grade inflammation assessment was based on analysis of a single blood sample, even though repetitive tests are recommended to confirm a resultant diagnosis. In particular, CRP is influenced by several factors and a result obtained from a single measurement may weaken the conclusions. Moreover, although an association was found between abnormal toe web findings and glucose metabolism, the findings cannot be generalized beyond the middle-aged populations.

6.9 Future prospects

The work presented here has demonstrated an unexpectedly high overall prevalence of skin disorders and a high demand of treatment. Further studies investigating the epidemiology of skin diseases are needed to strengthen these findings in other populations and other geographic regions. Meta-analysis of data collected from different continents would provide valuable information on the epidemiology of skin diseases. From a clinical point of view, dermatological evaluations should be a regular feature of the clinical examination of patients in the primary care setting. Since skin disorders are so commonplace, it must be ensured that enough

dermatologists are available to meet demand. In some cases tele-medicine methods could improve the recognition and treatment of skin findings, by making an expert second opinion of an expertise more easily available.

Multiple melanocytic naevi are a major risk factor for cutaneous melanoma. In this study they were more common in highly-educated subjects. Effective preventative programmes to educate the population about the potential effects of sun exposure, such as those launched in Australia, should also be investigated in Finland.

The association between abnormal toe web skin findings and undiagnosed diabetes in a middle-aged population cannot be generalized to all age groups. The study should be repeated with a sample of older subjects. Furthermore, prospective clinical trials are needed to confirm the predictive value of toe web findings in recognizing people at high risk of diabetes.

The clinical importance of the relationship between elevated hs-CRP and skin diseases requires further studies. The potential causative connections between skin diseases, elevated hs-CRP and particular systemic diseases such as atherosclerosis and depression, which are known to be associated with increased levels of inflammatory markers, should be studied.

Studies using birth cohort data, an appreciated epidemiological research setting, could further investigate the longitudinal development of dermatologic and allergic diseases. One future aim is to investigate the prevalence of IgE-mediated allergy among NFBC 1966 members by means of skin prick tests and by combining the cohort data concerning environmental and life-style factors with them.

Moreover, one additional future aim is to investigate the effect of separate skin disorders at any age on fitness to work, sickness absence and living standard in adulthood.

7 Conclusions

A comprehensive population-based skin study was performed among nearly 2000 subjects (aged 46–47 years) from the Northern Finland Birth Cohort 1966. The main results were as follows:

- A high prevalence of skin diseases serious enough to need a further follow-up or treatment was found.
- Benign skin tumours, skin infections, eczemas and sebaceous gland diseases were the most common cutaneous findings of the dermatological evaluation.
- Skin diseases were more common in males than in females, and males had more need of further treatment or follow-up.
- Socioeconomic status was linked to the prevalence of particular skin diseases.
- In the prospectively followed birth cohort multiple melanocytic naevi were present in 11.6% of the study population, while the risk of their presence was increased by higher education, male sex, fair skin type and the retrospectively evaluated regular use of sunscreens, and decreased by the presence of concurrent inflammatory skin disease.
- Skin findings in toe webs were associated with increased risk of previously undiagnosed type 2 diabetes when OGTT (2.5-fold higher risk) and HbA_{1c} (6-fold higher risk) were used as a definition of occult diabetes.
- The predictive power of FINDRISC increased slightly when the toe webs finding was added in the original FINDRISC score in the cross-sectional study.
- Elevated hs-CRP, a marker of low-grade inflammation, was present in many skin diseases, particularly in atopic eczema, onychomycosis and rosacea.

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Original publications

- I Sinikumpu S-P, Huilaja L, Jokelainen J, Koironen M, Auvinen J, Hägg PM, Wikstöm E, Timonen M, Tasanen K (2014) High prevalence of skin diseases and need for treatment in a middle-aged population. A Northern Finland Birth Cohort 1966 Study. *Plos One* 9:e99533
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- IV Sinikumpu S-P, Huilaja L, Auvinen J, Jokelainen J, Puukka K, Ruokonen A, Timonen M, Tasanen K (2017) The association between systemic low grade inflammation and skin diseases. A cross-sectional survey in the Northern Finland Birth Cohort 1966 Study. *Acta Derm Venereol* doi:10.2340/00015555-2795.

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