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Päivi Hirsso

ALOPECIA; ITS PREVALENCE AND ASSOCIATION WITH CARDIOVASCULAR DISEASES, RISK FACTORS AND QUALITY OF LIFE —CROSS-SECTIONAL POPULATION-BASED STUDIES

FACULTY OF MEDICINE,
DEPARTMENT OF PUBLIC HEALTH SCIENCE AND GENERAL PRACTICE,
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Abstract

Alopecia has been suggested to be associated with coronary artery diseases (CAD). However, the mechanism underlying this association has remained unclear. The purpose of the present study was to examine the relationships between metabolic syndrome-related risk factors, cardiovascular diseases (CVD) and alopecia among Finnish population. In addition, health-related quality of life (HRQOL) was studied in respect of alopecia among both genders.

The data come from the national Finrisk survey alopecia sub-study (4 066 men aged 25–74 years old) and two community samples of men and women (aged 55 and 63 years) living in the city of Oulu in 2001 and 1998, respectively. The degree of alopecia was assessed using the Norwood-Hamilton classification scale for men and the Ludwig scale for women.

This study showed a high prevalence of alopecia in the general male Finnish population varying from 17% to 73% among men aged 25–74 years, and its association with CVD particularly in age-groups older than 55 years. In addition, insulin resistance, as a metabolic syndrome-related risk factor, was associated with alopecia in middle-aged men. Among men younger than 35 years, low-grade inflammation was associated with alopecia, especially combined with central obesity. Further, in middle-aged general Finnish population, obesity associated most closely with low-grade inflammation, which is in line with the findings among young men with alopecia.

Compared to subjects with no alopecia, HRQOL dimension scores (RAND-36) were significantly lower in physical functioning, role limitations due to physical health and general health among women with alopecia, and in physical functioning and social functioning among men with alopecia. Regression analyses of HRQOL-related factors revealed that alopecia was associated with role limitations due to physical health in women but not in men.

An association between alopecia and CVD was strengthened in this study. In addition, low-grade inflammation and insulin resistance were associated with alopecia, especially with early onset alopecia. In elderly women, alopecia seemed to be associated with morbidity in vascular diseases. In the future, recognition of the risk factors for cardiovascular disease among subjects with alopecia is a challenge for primary health care that may prevent the development of arterial diseases.

Keywords: alopecia, cardiovascular diseases, health-related quality of life, insulin resistance, low-grade inflammation

Hirsso, Päivi, Hiustenlähtö; sen esiintyvyys ja yhteys sydän- ja verisuonisairauksiin, riskitekijöihin ja elämänlaatuun — väestöpohjaiset poikkileikkaustutkimukset

Lääketieteellinen tiedekunta, Kansanterveystieteen ja yleislääketieteen laitos, Oulun yliopisto, PL 5000, 90014 Oulun yliopisto; Oulun yliopistollinen sairaala, PL 10, 90029 OYS; Yleislääketieteen yksikkö, Oulun yliopistollinen sairaala, PL 22, 0029 OYS; Oulun kaupungin terveyskeskus, PL 8, 90015 Oulun kaupunki; Oulun Diakonissalaitos, Liikuntaklinikka, Kajaaninkatu 17, 90100 Oulu

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Tiivistelmä

Hiustenlähdön yhteys sydän- ja verisuonisairauksiin on ollut tiedossa jo pitkään, mutta yhteyden taustalla olevat patofysiologiset mekanismit ovat edelleenkin epäselviä. Tässä väitöskirjatyössä tutkittiin hiustenlähdön yhteyksiä metaboliseen oireyhtymään ja siihen liittyviin riskitekijöihin suomalaisessa väestössä yleisesti. Lisäksi tutkittiin elämänlaadun yhteyttä hiustenlähtöön 63-vuotiailla miehillä ja naisilla.

Tutkimukseen käytettiin kolmea aineistoa; kansallisen Finrisk 2002 tutkimuksen alopecia (hiustenlähtö) alaotos (4066 iältään 25–74-vuotiasta miestä) ja kaksi aineistoa Oulun kaupungista (Oulussa asuneet 55- ja 63-vuotiaat miehet ja naiset vuonna 2001 ja 1998). Hiustenlähdön laajuus määriteltiin miehillä Norwood-Hamiltonin ja naisilla Ludwigin luokitteluasteikon mukaan.

Hiustenlähdön esiintyvyys suomalaisessa miesväestössä vaihteli 17 %:sta (25–34-vuotiaat) 73 %:iin (65–74-vuotiaat) ja se näytti liittyvän sydän- ja verisuonisairauksiin 55-vuotiailla ja sitä vanhemmilla miehillä. Lisäksi alentunut insuliiniherkkyys metabolisen oireyhtymän merkkinä oli yhteydessä hiustenlähtöön keski-ikäisillä miehillä. Varhain alkanut hiustenlähtö (alle 35-vuotiaat) liittyi matala-asteiseen tulehdukseen erityisesti keskivartalolihavilla kaljuuntuvilla nuorilla miehillä. Samansuuntainen tulos tuli esille myös väestötutkimuksessa 55-vuotiailla oululaisilla miehillä ja naisilla, jonka mukaan matala-asteinen tulehdus oli yhteydessä erityisesti yleiseen lihavuuteen eikä pelkästään vyötärölihavuuteen.

Terveyteen liittyvän elämänlaadun osa-alueiden pisteet (RAND-36) 63-vuotialla hiustenlähdöstä kärsivillä naisilla olivat merkittävästi matalampia kolmella osa-alueella; fyysiset toiminnot, fyysisen terveydentilan aiheuttamat muutokset roolitoiminnoissa ja yleinen terveys. Samanikäisillä kaljuuntuvilla miehillä merkittävästi matalammat terveyteen liittyvät elämänlaadun osakomponentit olivat fyysisten ja sosiaalisten toimintojen alueella. Tilastollisessa regressioanalyysissä ilmeni, että hiustenlähtö selitti fyysisen terveydentilan aiheuttamia rajoituksia roolitoimintoihin erityisesti kaljuuntuvilla naisilla, mutta ei miehillä.

Hiustenlähdön yhteys eri sydän- ja verisuonisairauksiin vahvistui tässä tutkimuksessa. Varhainen hiustenlähtö on ilmeisesti merkki sekä matala-asteisesta tulehduksesta että alentuneesta insuliiniherkkyydestä. Myös naisilla hiustenlähtö näyttäisi liittyvän suurempaan sairastavuuteen. Terveydenhuollon tulisi jatkossa tarkemmin paneutua sydän- ja verisuonisairauksien riskin kartoittamiseen hiustenlähdöstä kärsivien potilaiden kohdalla.

Asiasanat: elämänlaatu, hiustenlähtö, insuliiniherkkyys, matala-asteinen tulehdus, sydän- ja verisuonisairaus

To My Family

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This thesis work was carried out in the years 2003-2007 at the Department of Public Health Science and General Practice, the Unit of General Practice, Oulu University Hospital, Oulu Health Centre and the Department of Sports Medicine of the Deaconess Institute of Oulu. The thesis is based on data from the National FINRISK 2002 Survey and two ongoing projects with an overall objective to identify risk factors associated with type 2 diabetes and cardiovascular diseases among two age cohorts of subjects living in the city of Oulu.

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Abbreviations

AGA	androgenetic alopecia
AR	androgen receptor
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
DHT	dihydrotestosterone
DM	diabetes mellitus
FPHL	female pattern hair loss
HDL	high-density lipoprotein
HOMA-IR	homeostasis model assessment of insulin resistance
HRQOL	health-related quality of life
hs-CRP	high sensitive C-reactive protein
IDF	International Diabetes Federation
IGR	impaired glucose regulation
IGT	impaired glucose tolerance
IL	interleukin
IR	insulin resistance
LDL	low-density lipoprotein
MetS	metabolic syndrome
MI	myocardial infarction
MPHL	male pattern hair loss
NCEP	National Cholestrol Education Program
OGTT	oral glucose tolerance test
PCOS	polycystic ovary syndrome
QOL	quality of life
QUICKI	quantitative insulin sensitivity check index
SBP	systolic blood pressure
SHBG	serum hormone binding globulin
T2DM	type 2 diabetes mellitus
TG	triglycerides
WHO	World Health Organization
WHR	waist-to-hip ratio

List of original articles

I Hirsso P, Rajala U, Hiltunen L, Jokelainen J, Näyhä S & Keinänen-Kiukaanniemi S (2007) Prevalence of alopecia and its association with cardiovascular diseases in the Finnish male population aged 25-74 years; results from the Finrisk 2002 study. Eur J Dermatol 17: 93-94

II Hirsso P, Laakso M, Matilainen V, Hiltunen L, Rajala U, Jokelainen J & Keinänen-Kiukaanniemi S (2006) Association of insulin resistance linked diseases and hair loss in elderly men. Finnish population-based study. Cent Eur J Publ Health 14: 79-82

III Hirsso P, Rajala U, Hiltunen L, Laakso M, Koskela P, Härkönen P & Keinänen-Kiukaanniemi S (2006) Association of low insulin sensitivity measured by QUICKI with hair loss in 55-year-old men. A Finnish population-based study. Diabetes, Obes Metab 8: 466-468

IV Hirsso P, Rajala U, Hiltunen L, Jokelainen J, Keinänen-Kiukaanniemi S & Näyhä S (2007) Obesity and low-grade inflammation among young Finnish men with early-onset alopecia. Dermatology 214: 125-129

V Hirsso P, Timonen M, Jokelainen J, Hiltunen L, Laakso M, Hedberg P, Ruokonen A, Koskela P, Härkönen P, Keinänen-Kiukaanniemi S & Rajala U (2006) Association between high-sensitive measurement of C-reactive protein and metabolic syndrome as defined by the IDF, the NCEP and the WHO criteria. Diabetes Care 29: 2177-2178

VI Hirsso P, Rajala U, Laakso M, Hiltunen L, Härkönen P & Keinänen-Kiukaanniemi S (2005) Health related quality of life and physical well-being among a 63-year-old cohort of women with androgenetic alopecia; A Finnish population-based study. Health Qual Life Outcomes 3: 49

In addition, unpublished results which are related to published articles.

Contents

1 Introduction

In past years, alopecia has been suggested to be associated with coronary artery disease (CAD) in men (Cotton 1972, Hambly 1977, Lesco *et al.* 1993, Herrera *et al.* 1995, Ford *et al.* 1996, Lotufo *et al.* 2000). The reasons for the high prevalence of CAD among men with alopecia are unclear. However, the high prevalence of certain cardiovascular risk factors such as elevated blood pressure (BP), high cholesterol and insulin levels (Trevisan *et al.* 1993, Ford *et al.* 1996, Lotufo *et al.* 2000, Matilainen *et al.* 2000) might partly explain the association between alopecia and CAD. The metabolic syndrome (MetS), the components of which include insulin resistance (IR), hypertension, dyslipidemia, hyperglycemia and abdominal obesity, is known to be a risk factor for cardiovascular disease (CVD) (Lempiäinen *et al.* 1999, Lehto *et al.* 2000, Isomaa *et al.* 2001). Until now, it has been unclear whether MetS is more common among men with alopecia than among those with no alopecia.

Outside Finland, a number of studies have focused on the prevalence and heredity of alopecia (Trevisan *et al.* 1993, Herrera *et al.* 1995, Schnohr *et al.* 1995, Ford *et al.* 1996, Rhodes *et al.* 1998, Muro-Mercon *et al.* 2000, Lotufo *et al.* 2000 Paik *et al.* 2001, Severi *et al.* 2003), whereas in Finland the prevalence of alopecia remains unknown, although CVD are common in Finland overall. Further, Finnish investigators have previously reported an association between alopecia and MetS-related disorders in general (Matilainen *et al.* 2000) and with severe CAD in men whose alopecia has started at an early age (Matilainen *et al.* 2001). Therefore, the prevalence of alopecia and its association with the components of MetS, impaired glucose regulation (IGR) and CVD were examined in this study.

There are only a few studies of female alopecia in respect of CVD and related disorders (Matilainen *et al.* 2003, Mansouri *et al.* 2005). Therefore, this study also focused on the association of female alopecia with IR and health-related quality of life (HRQOL). It was hypothesized that not only the mental aspects but also certain physical aspect of women's health, such as the presence of IR, have an important role in the determination of HRQOL among women with alopecia.

The pathophysiology of alopecia is complex and not completely understood. However, recent experimental and clinical advances in the research of hormones and genes enable us to explain some steps leading to alopecia. The most common appearance of alopecia is an androgen-dependent condition called androgenetic alopecia (AGA). The role of androgens is confusing because of their paradoxical

effect on the growth of hair follicles at different body sites (Hoffman 2002). Genetic background behind alopecia has been suggested, but it is unclear which genes are involved in the alopecia process. Quite recently, it was shown that the same mutation in the androgen receptor (AR)-gene is associated with both alopecia (Hillmer *et al.* 2005, Levy-Nissenbaum *et al.* 2005) and early severe CAD (Alevizaki *et al.* 2003), in genetically susceptible men and women. Interestingly, although the AR is known to be increased in balding scalp (Sawaya and Shalita 1997), it is, however, located on the X chromosome (Lubahn *et al.* 1988). Besides androgens and the genetic background of alopecia, few studies have reported an association of IR with testosterone and serum hormone-binding globulin (SHBG) levels at population level (Kapoor *et al.* 2003, Laaksonen *et al.* 2004).

This study consists of three epidemiological population-based studies which were used to measure the associations between alopecia and cardiovascular risk factors. These studies in question, including a large national survey of men aged 25-74 years and two representative population samples of 55- and 63-year-old subjects living in Oulu, provided an excellent opportunity to measure different factors related to alopecia at epidemiological level.

2 Review of the literature

2.1 Definition of alopecia

Alopecia is defined as the hair loss of the scalp affecting most men and about 30% of women during their lifetime. According to the literature, the term AGA is often used for alopecia in general, as more than 90% of alopecia is due to AGA (Norwood 1975, Rebora 2001, Trueb 2002). In addition to AGA, there may be other less common reasons behind alopecia (Rebora 2001), such as reversible episode of telogen effluvium, eczema seborrecum, alopecia areata, scalp/hair trauma, lichen planus or thyroid deficiency (Bertolino 1993). The diagnosis AGA can be made with a through history and physical examination, as well as laboratory tests to support relevant findings and scalp biopsies (Headington 1984). However, these are difficult and expensive to carry out in epidemiological studies, and therefore in this study the term "alopecia" is used for both AGA and the phenomenon of hair loss in general. The other terms used in literature for alopecia are male pattern hair loss (MPHL) or baldness in men, and female pattern hair loss (FPHL) or female alopecia in women. The term "hair loss" is also widely used, but dermatologists have criticized it as not being scientific.

2.2 Classification of alopecia

Since 1950, various classifications have been recommended for male (Hamilton 1951, Buechner *et al.* 1964, Setty 1970, Norwood 1975, Blanchard and Blanchard 1989 in Rebora 2001, Bouhanna 2000) and female alopecia (Ludvig 1977). Of these, the most commonly used are the Hamilton (Hamilton 1951) and the Norwood modification of the Hamilton classification scale (Hamilton-Norwood) (Norwood 1975) for male and Ludwig classification scale for female alopecia (Ludwig 1977). The Hamilton-Norwood classification scale has been validated earlier (Norwood 1975, Lesco *et al.* 1993, Ellis *et al.*1998, Taylor *et al.* 2004, Gan & Sinclair 2005). Both the Hamilton-Norwood and Ludwig classification scales are presented in Table 1.

Men with alopecia typically have a receding hairline and moderate to extensive alopecia, especially on the front and top of the head. Alopecia can start as early as the teenage years, and the remaining hair tends to feel a little finer and shorter than normal hair (Hamilton 1951).

Table 1. The classification scale of alopecia according to the Norwood modification of the Hamilton classification scale (men) and Ludwig's classification scale (women)

Grades	Definition of alopecia	Figure
Male		
I and II	no alopecia and mild alopecia	
III	Frontotemporal recession but the vertex not affected, or hair loss chiefly in the vertex	
IV	Bald areas are extensive but separated from each other by a band of moderately dense hair that extends across the top	
V	The vertex region of alopecia remains separated from the frontotemporal region of alopecia but the band of hair has become narrower	
VI	The frontotemporal and vertex regions of alopecia have become confluent and the area of alopecia has increased	
VII	The most severe form of male pattern alopecia	
Female		
I	No alopecia	
II and III	Perceptible thinning of the hair on the crown (II) Pronounced rarefaction of the hair on the crown (III)	

Women with alopecia experience overall thinning of their hair. Most of the hair loss is on the crown of the head or at the hairline. Female alopecia usually starts around age 30 and becomes noticeable around age 40. In women, the most commonly used scale is Ludwig's classification scale for alopecia (Ludwig 1977)

in which alopecia is described by three grades (I-III) of increasing severity of diffuse alopecia over the crown of the head but without the frontoparietal recession seen in men. However, postmenopausal women may develop MPHL (Venning & Dawber 1988).

2.3 Prevalence of alopecia

The prevalence of alopecia is known to increase steadily with advancing age in both men and women (Hamilton 1951, Paik *et al.* 2001, Birch *et al.* 2001). The studies concerning the prevalence of alopecia are presented in Table 2. Aforementioned studies have been either clinical or population-based, and have mostly used generally accepted classification scales (Hamilton 1951, Norwood 1975, Ludwig 1977).

In the population-based studies among Caucasian men aged 20-70(80) years, which have mostly used modified classification scales, the prevalence of alopecia has varied between 46% and 92% (Trevisan *et al.* 1993, Herrera *et al*.1995, Schnohr *et al.* 1995, Ford *et al.* 1996, Severi *et al.* 2003). In the case of the Hamilton-Norwood classification scale, the prevalence of alopecia was approximately 40% according to representative population studies (Muro-Mercon *et al.* 2000, Ellis *et al.* 2001a, Pathomvanich *et al.* 2002). Among women, the prevalence figures of alopecia according to Ludwig's classification scale have been clearly lower (Table 2), but alopecia becomes more common after the menopause (Venning & Dawber 1988).

Earlier studies have reported that the prevalence of alopecia varies between human races, being the most common among Caucasian races (Hamilton 1951, Setty 1970), which compares well with a representative clinical-based study reporting lower prevalence of alopecia among Korean men (14%) and women (6%) (Paik *et al.* 2001). On the other hand, among other than Caucasian races, the prevalence of alopecia among men is 30-40% according to the results of the most recent studies (Tang *et al.* 2000, Grover *et al.* 2005) that differ from those of earlier studies.

Table 2. The prevalence of alopecia (%) according to earlier studies.

Study, year	Country	Design	Classification scale	Study population	Prevalence (%)
Hamilton 1951	USA	clinical	Hamilton	312 males, 20-70 yr	59
Norwood 1975	USA	clinical	Hamilton-Norwood	1000 males, 20-70 yr	47
Lesco *et al.* 1993	USA	clinical	Hamilton	1437 males, 21-54 yr	32
Trevisan *et al.* 1993	Italy	population	Buechner	872 males, mean 46 yr	63
Venning & Dawber 1988	U.K.	clinical	Ludwig	564 pre/postmenopausal females	13 /37
Herrera *et al.* 1995	USA	population, follow-up	Modified Hamilton	2017 males, 35-74 yr	92
Schnohr *et al.* 1995	Danmark	population, follow-up	Modified Hamilton	5837 males, 30-79 yr	50
				7163 females	3
Ford *et al.* 1996	USA	population	Personal scores	3994 males, 26-76 yr	48
Girman *et al.* 1998	USA	population	Hamilton-Norwood	273 males, 18-59 yr	50
Rhodes *et al.* 1998	USA	population	Hamilton-Norwood	266 males, 18-49 yr	42
Muro-Mercon *et al.* 2000	Norway	population	Hamilton-Norwood	4101 males 26-50 yr	43
Lotufo *et al.* 2000	USA	population, follow-up	Hamilton simplified	1446 males 40-84 yr	39
Budd *et al.* 2000	France, U.K., Italy, Germany	population	Modified Hamilton-Norwood	1717 males 18-40 yr	46
Tang *et al.* 2000	Singapore	population	Norwood	254 males, 17-86 yr	38
Norwood 2001	USA	clinical	Ludwig	1006 females, 20-70 yr	19
Ellis *et al.* 2001	Australia	population	Hamilton-Norwood	1219 male	43
Birch *et al.*2001	U.K.	clinical	Ludwig	377 females, 18-99 yr	
				pre/postmenopausal	6/38
Paik *et al.* 2001	Korean	clinical	Norwood	5531 males	14
			Ludwig	4601 females, 20-70 yr	6
Pathomvanich *et al.* 2002	Thailand	clinical	Norwood	1124 males, 18-80 yr	39
Severi *et al.* 2003	Australia	population	Modified Hamilton-Norwood	1390 males, 40-64 yr	73
Chumlea *et al.* 2003	USA	population	Hamilton-Norwood	254 males, 18-49 yr	55
Grover *et al.* 2005	Indian	clinical	Hamilton-Norwood	2445 males, 20-70 yr	31
Gan & Sinclair 2005	Australia	population	Modified Hamilton-Norwood	203 males /193 females	45/32
				pre/postmenopausal	18/45

2.4 Heredity and the genetic aspect of alopecia

Since the days of Hippocrates, the reason behind the most common form of alopecia, AGA, has been assumed to be a combination of heredity and hormones. The interdependence of androgens, genetic factors and age was described to influence hair growth fifty years ago (Hamilton, 1951), but also, some other mechanism behind alopecia has been discussed.

Most studies on the heredity of alopecia are based on self-reported data, not clinical assessment of alopecia among family members (Paik *et al.* 2001, Tang *et al.* 2002, Chumblea *et al.* 2004). In addition, it is unclear whether early and late onset alopecia is inherited separately (Paik *et al.* 2001). An autosomal dominant mode of inheritance of alopecia has been suggested (Osborn D 1916 in Ellis *et al.* 1999), but a polygenic etiology seems to be more likely (Kuster & Happle 1984, Ellis *et al.* 1998). One study confirmed that additive genetic effects play a major role in the progression of alopecia, especially in early onset alopecia (Nyholt *et al.* 2003).

The genetic defects in alopecia are poorly understood. Candidate genes could be those involved in androgen production and the conversion of androgen into dihydrotestosterone (DHT), the excess production of which is known to exist in balding scalp (Dallop 1994). However, the genes of the enzyme 5α-reductase (testosterone is metabolized to DHT by 5α-reductase) have not been shown to be associated with the inheritance of alopecia (Ellis *et al.* 1998). Another possible gene associated with androgen effect in alopecia is the androgen receptor (AR) gene, which is located on the X-chromosome and therefore does not explain paternal heredity (Ellis & Harrap 2001). Although it has earlier been thought that alopecia is inherited from father to son, a recent study shows that maternal heredity is also involved with some form of alopecia in men (Hillmer *et al.* 2005).

In addition, insulin has been found in hair follicles, and, generally, it has been suggested that insulin may play a role in the regulation of androgen metabolism (Laaksonen *et al.* 2004, Pitteloud *et al.* 2005) and in the hair growth cycle (Philpott 1994). However, a study by Ellis did not confirm the association between insulin gene polymorphism and premature alopecia among men (Ellis *et al.* 1999). Other genes which may have a possible link to alopecia are the endothelial nitric oxide gene (Diani 1992) and genes involved in the insulin pathway (Ellis *et al.* 1999). Genes influencing alopecia may lead to the identification of a mechanism that may influence the early progression of CVD and IR in balding subjects.

2.5 Alopecia and cardiovascular diseases

The possible associations between alopecia and CVD have been extensively studied during the past fifty years (Table 3). However, the results of the oldest studies were contradictory due to small sample sizes and varying definitions of alopecia (Gertler and White 1954, Buechner *et al.* 1964 in Rebora 2001, Cotton 1972, Hambly 1977, Halim *et al.* 1978, Cooke 1979).

Yet, during the last two decades several studies have indicated that men with alopecia have a higher than normal risk for CAD, and that especially early onset alopecia is related to CAD in both cross-sectional and longitudinal studies (Table 3). Two case-control studies reported an elevated risk for a coronary event in men with alopecia (Lesco *et al.* 1993, Miric *et al.* 1998), and that the risk of myocardial infarction (MI) increased with the severity of alopecia on the vertex of the scalp (Lesco *et al.* 1993). In addition, among Finnish men with early onset alopecia, the coronary revascularization procedure was more common compared to those with late or no alopecia. (Matilainen *et al.* 2001).

According to follow-up cohort studies, early onset and rapid progression of alopecia predicted CAD and CAD mortality (Herrera *et al.* 1995) and higher risk of MI in men (Schnohr *et al.* 1995). In addition, Ford *et al.* showed that early severe alopecia (<55 years) predicted CAD mortality (1996). A retrospective cohort study reported that men with early onset alopecia (linked to severity of alopecia) had a higher risk for CAD compared to men with no alopecia (Lotufo *et al.* 2000). However, there are some limitations in the above-mentioned studies. Although the original study designs were prospective follow-up studies, the assessment of alopecia classification was not validated (Trevisan *et al.* 1993, Schnohr *et al.* 1995, Ford *et al.* 1996, Lotufo *et al.* 2000) and made by retrospective design (Trevisan *et al.* 1993, Lotufo *et al.* 2000). In addition, the prevalence of alopecia was surprisingly high in studies by Trevisan *et al.* and Herrera *et al*., which may cause a bias in their conclusions.

In women, female alopecia (grade II-III on Ludwig's scale) has been reported to be associated with CAD (Mansouri *et al.* 2005). In addition, it is known that alopecia is common among women with polycystic ovary syndrome (PCOS), and type 2 diabetes mellitus (T2DM) is associated with PCOS (Cela *et al.* 2003).

Table 3. The studies on the associations between alopecia and cardiovascular diseases or risk factors of cardiovascular diseases.

Study	Design	Country	Scale	Study population	Results
Gertler and White 1954*	clinical	no data	Hamilton	men with MI at the age of < 40 years	no association
Buecher 1964*	clinical	no data	Extensive frontal alopecia	40 men with heart disease, 153 controls	no association
Cotton 1972*	clinical	no data	Personal scores	91 men with CAD or MI, 98 controls	significant association between alopecia and CAD
Hamby 1977	clinical	no data	Frontoparietal alopecia	710 men	bald men have CAD
Halim 1978*	clinical	no data	Hamilton	48 men with MI, 48 controls	no association
Cooke 1979	clinical	U.K	Hamilton	351 with MI, 127 controls	association with CAD in age group 50-59 years only. No difference in blood pressure
Persson & Johansson 1984	population follow-up	Sweden	Personal scores	464 men	alopecia is a possible risk factor for CAD
Trevisan *et al.* 1993	population	Italy	Buechner	872 factory workers	fronto-occipital alopecia was associated with elevated cholesterol level and BP in young men
Lesco *et al.* 1993	clinical	USA	Hamilton-Norwood	955 men MI , 772 controls, all men < 55 years old	increased risk between vertex alopecia and MI, RR 3.4 (95% CI 1.7-7)
Herrera *et al.* 1995	population follow-up	USA	Hamilton	2017 men aged 35-74 years	rapid onset and progressive alopecia in men predicted CAD, OR 2.4 (95% CI 1.3-4.4)
Ford *et al.* 1996	population follow-up	USA	Personal scores	3932 men aged 26-76 years	risk of mortality among men under 55 years with severe alopecia with CAD, RR 2.5 (95% CI 1.0-6.2)
Schnohr *et al.* 1995	population follow-up	Denmark	Modified Hamilton	750 men with MI	alopecia was associated with higher risk of MI in men, RR 1.7 (95% CI 1.1-2.5)

Table 3. (Continued.)

Study	Design	Country	Scale	Study population	Results
Miric *et al.* 1998	clinical	Croatia	Personal Scores	842 men with MI and 712 controls	association between alopecia and MI, adjusted OR 1.9 (95% CI 1.4-2.2)
Lotufo *et al.* 2000	population follow-up	USA	Modified Hamilton	22071 male physicians aged 40-84 years	risk of CAD among men with vertex alopecia, RR 1.4 (95% CI 1.1-1.7)
Matilainen *et al.* 2000	population	Finland	Hamilton-Norwood	154 men with early onset alopecia and 143 controls aged 19-50 years	cluster of risk factors among men alopecia
Matilainen *et al.* 2001	clinical	Finland	Hamilton-Norwood	85 cases underwent coronary revascularization procedure, 85 controls	early onset alopecia associated with early severe CAD
Ellis *et al*. 2001, 1a)	population	Australia	Hamilton-Norwood	1219 male	no association between alopecia and established coronary risk factors; BMI, BP, cholesterol
Matilainen *et al.* 2003	population	Finland	Ludwig	324 women aged 63 years	risk of hypertension (RR 1.65 CI% 1.0-2.7) and microalbuminuria (RR 2.4 CI% 1.2-4.7) among women having alopecia grade II-III
Severi *et al.* 2003	population	Australia	simplified Hamilton-Norwood	1390 male aged 40-69 years	no association with androgen activity, body size and smoking
Mansouri *et al.* 2005	clinical	Iran	Ludwig	106 women aged under 55 years old with CAD	significant correlation between female alopecia and CAD and MI

2.6 General risk factors for cardiovascular diseases

2.6.1 Obesity

Obesity is usually the result from a combination of genetic factors and an inappropriate lifestyle, characterized by inadequate nutrition and lack of regular physical activity. It is closely associated with the development of T2DM (Goodpaster *et al.* 2003, Wang *et al.* 2005), hypertension, dyslipidemia, and CVD (Pi-Synier 2002, Empana *et al.* 2004, Dagenais *et al.* 2005).

In obesity, especially central obesity, visceral deposits constitute a highly active endocrine organ secreting many complex adipokines, which have a damaging effect on the vascular wall (Griffin *et al.* 1999). It is hypothesized that increased abdominal adipose tissue is responsible for a mild chronic inflammatory state, which may induce IR and vascular disorders, e.g. endothelial dysfunction and prothrombotic state (Yudkin *et al.* 1999, Hotamisligil 1999, Juhan-Vague *et al.* 2002, Kopp *et al.* 2003, Yki-Järvinen 2003).

2.6.2 Hypertension

The prevalence of hypertension increases with age (Burt *et al.* 1995). A high BP is known to be a strong risk factor for CVD (Chobanian *et al.* 2003), and the risk for CVD increases continuously from lowest to highest values for either systolic or diastolic BP (Grundy *et al.* 1997). Elevated BP is often associated with other risk factors, such as elevated blood lipid levels, obesity, smoking and DM (Chobanian *et al.* 2003). However, elevated BP may rarely also be associated with other mechanisms, e.g. hyperaldosteronism, chronic kidney disease, and renovascular hypertension (Chobanian *et al.* 2003).

One possible mechanism by which hypertension enhances the development of CVD may be IR, which has been reported to be linked with elevated BP (Pollare *et al.* 1990, Natali *et al.* 1991, Denker & Pollock 1992, Facchini *et al.* 1992, Ferrannini *et al.* 1997).

2.6.3 Glucose intolerance

It is known that subjects with diabetes (Stamler *et al.* 1993, Haffner *et al.* 1996, Fox *et al.* 2005) have an increased risk for CVD. In addition, many prospective studies have shown that even subjects with IGT have a higher risk for the

development of CVD and CVD mortality than subjects with normal glucose tolerance (Alberti 1996, Edelstein *et al.* 1997, DECODE Study Group 2001, Wong *et al.* 2003). Based on several epidemiological studies, it has been suggested that hyperglycemia, per se, is atherogenic (Rewers *et al.* 1992, Coutinho *et al.* 1999, Aronson & Rayfield 2002, Meigs *et al.* 2002).

2.6.4 Dyslipidemia

Atherogenic dyslipidemia compromises increased plasma triglyceride (TG) levels as well as reduced high-density lipoprotein (HDL) cholesterol concentrations. The presence of smaller, denser low density lipoprotein (LDL) particles is also observed particularly in insulin-resistant and abdominally obese subjects although many of these individuals will display relatively normal LDL cholesterol levels. (Lamarche & Mauger 2005.) According to prospective studies an increase in plasma TG level (Hokanson & Austin 1996, Onat *et al.* 2006) and the low HDL cholesterol level (Hubert *et al.* 1983, Gordon *et al.* 1989, McNeill *et al.* 2005) independently predicted CVD. In addition, high serum concentration of low-density lipoprotein (LDL) cholesterol (Lamarche *et al.*1997 & 1999, Despres 2000) is associated with increased risk of CVD.

2.6.5 Metabolic syndrome

Clustering of cardiovascular risk factors published in 1988 (Reaven 1988) suggested that IR is the common underlying cause for "syndrome X" known as MetS. Other components of this syndrome are hypertension, dyslipidemia, hyperglycemia and abdominal obesity. There are several names for this syndrome, of which the most preferable is the Metabolic Syndrome recommended by the World Health Organization (WHO) in 1999. The term "insulin resistance syndrome" has been widely used for the risk factor clustering; however, nowadays the term "metabolic syndrome" is preferred. (Alberti & Zimmet 1998.)

Subjects with MetS are at higher risk of developing CVD and T2DM than those without MetS (Alberti & Zimmet 1998). An association between different components of MetS and CVD has been reported in several prospective studies (Lempiäinen *et al.* 1999, Lehto *et al.* 2000, Pyörälä *et al.* 2000, Isomaa *et al.* 2001, Lakka *et al.* 2002).

There are several definitions used for diagnosing MetS (Alberti & Zimmet 1998, Balkau & Charles 1999, NCEP 2001, Bloomgarden *et al.* 2003, Alberti *et*

al. 2006). The most widely used definitions have been provided by WHO with a focus on blood glucose status and IR (Alberti & Zimmet 1998), and the National Cholestrol Education Program (NCEP), with a focus on CVD (NCEP 2001). As there is no universally agreed definition, the different definitions have led to confusion and absence of comparability between studies. In addition, it has been difficult to measure MetS in different ethnic groups, especially in terms of the cut-point values of obesity (WHO Expert consultation group 2004). Because of this, the newest definition of MetS provided by the International Diabetes Federation (IDF) emphasizes the importance of central obesity defined by ethnic specific values (Alberti *et al.* 2006). The criteria defined by WHO, NCEP and IDF of MetS are presented in Table 4.

Table 4. The definitions of the metabolic syndrome defined by WHO, NCEP and IDF.

WHO 1998	NCEP	IDF 2005
Diabetes or IGT or IFG and/or IR		Waist circ. ≥ 94 (male) or ≥ 80 (female) cm
And two or more of the following:	Three or more of the following:	
Obesity: BMI > 30 or WHR > 0.9 (male) or > 0.85 (female)	Waist circ. > 102 cm (male), > 88 cm (female) identifying central obesity	Raised triglycerides > 1.7 mmol/L or specific treatment for lipid abnormality
Dyslipidemia: triglycerides ≥ 1.7 mmol/L or HDL chol < 0.9 (male) or < 1.0 (female) mmol/L	Triglycerides > 1.7 mmol/L, HDL chol < 1.0 mmol/l (male), <1.3. mmol/l (female)	Reduced HDL-chol: < 1.03 (male) or < 1.29 (female) mmol/L or specific treatment for lipid abnormality
Hypertension: blood pressure ≥ 140/90 mmHg	Elevated blood pressure ≥ 135/85 mmHg	Elevated blood pressure: systolic ≥ 130 mmHg, diastolic ≥ 85 mmHg or treatment of previously diagnosed hypertension
Microalbuminuria: albumin excretion ≥ 20 µg/min	Hyperglycemia: fasting plasma glucose ≥ 6.1 mmol/L	Hyperglycemia: fasting plasma glucose ≥ 5.6 mmol/L or previously diagnosed type 2 diabetes

IGT; impaired glucose tolerance, IFG; impaired fasting glucose, IR; insulin resistance, BMI; body mass index, WHR; waist to hip ratio

Individuals with MetS have a higher risk for CVD than those without the syndrome, but it has been debated whether the individual components of the syndrome are equally predictive of CVD (Kahn *et al.* 2005, McNeill *et al.* 2005). Some additional criteria have also been proposed to be added to the definition of MetS to increase its predictive value for future CVD. These include e.g. interleukin, high fibrinogen and/or raised plasminogen activator inhibitors in the

blood, which are markers of both endothelial dysfunction (Steinberg *et al.* 1996) and proinflammatory state, and can be indirectly verified by a surrogate measure of elevated high sensitivity C-reactive protein (hs-CRP) (Pearson *et al.* 2003), interleukin-6 and tumor necrosis factor-α (Fernandez-Real & Ricart 2003). Other alterations that are not included in the diagnostic criteria for the MetS are smoking (Eliasson *et al.* 1994), high lipoproteins apo B and C-III (Onat *et al.* 2003), non-alcoholic steatohepatitis (Medina *et al.* 2004), low adiponectin as an anti-inflammatory cytokine (Pischon *et al.* 2004, Maahs *et al.* 2005), some vascular and other changes associated with IR, such as microalbuminuria, obstructive sleep apnea and polycystic ovarian disease (Eckel *et al.* 2005).

2.6.6 Insulin resistance

The first description of the MetS was based on hypothesis that the syndrome was a clinical manifestation of IR (Reaven 1988). IR is said to be present when the biological effects of insulin are less than expected for both glucose disposal in the skeletal muscle and suppression of endogenous glucose production in the liver (Dinneen *et al.* 1992). IR is defined as impaired insulin action in target tissues, mostly skeletal muscle, liver and adipose tissue, which is influenced by a number of factors including age, weight and physical activity (Reaven 1988). IR is known to be the strongest predictor of the development of T2DM (Martin *et al.* 1992). Besides, hyperinsulinemia, as a marker of IR, has predicted CVD and mortality (Lempiäinen *et al.* 1999, Lakka *et al.* 2000, Hedblad *et al.* 2002).

The golden standard for the measurement of IR is the euglycemic hyperinsulinemic clamp (DeFronzo *et al.* 1979) which, however, is impractical for epidemiological studies. Among alternative methods, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (Matthews *et al.* 1985) and quantitative insulin sensitivity check index (QUICKI) (Katz *et al.* 2000, Hrebicek *et al.* 2002), are simple and economical methods that both provide an estimate of basal insulin resistance from mathematical modeling of plasma glucose and insulin concentrations. Earlier, fasting plasma insulin level was used as a marker of IR in epidemiological studies.

2.6.7 Low-grade inflammation

High sensitive C-reactive protein (hs-CRP) is an acute-phase reactant that is synthesized in the liver under interleukin-6 (IL-6) stimulation correlating to the

amount of visceral fat in subjects with MetS (Lemieux *et al.* 2001). Besides being a marker of inflammation, hs-CRP may contribute to atherosclerosis by modulating endothelium function (Pasceri *et al.* 2000). According to recent studies, hs-CRP is one of the best independent predictors of CVD (Ridker *et al.* 2003, Sattar *et al.* 2003, Rutter *et al.* 2004). Besides, one population-based survey suggests that hs-CRP may be a stronger predictor of cardiovascular events than LDL, and that measurement of hs-CRP adds important prognostic information to that described in the Framingham Risk Score (Ridker *et al.* 2002).

Obesity, especially visceral obesity with intra-abdominal adipose tissue, is suggested to be the main reason for the inflammatory state which could serve as a link between obesity and IR and later atherosclerosis (Gimeno & Klaman 2005, Eckel *et al.* 2005). As a result of the aforementioned studies, hs-CRP has been recommended to be used in measuring the future risk of CVD among subjects with MetS (Pearson *et al.* 2003).

2.6.8 Androgens

According to resent studies, low testosterone and SHBG levels associated with IR (Rajala *et al.* 2007) and predicted the presence of MetS (Laaksonen *et al.* 2004, Kapoor *et al.* 2005), in which IR is the essential feature. Thus, it has been suggested that hypotestosteronemia could have an independent role in the pathogenesis of MetS by causing IR (Oh *et al.* 2002, Muller *et al.* 2005, Pitteloud *et al.* 2005) and that SHBG is the mediating link between total testosterone and IR (Nestler 1993, Pitteloud *et al.* 2005).

2.7 General risk factors for cardiovascular diseases in subjects with alopecia

2.7.1 Obesity, hypertension, lipid levels and metabolic syndrome

A few studies in men have examined the risk factors for CVD in relation to alopecia, with inconsistent results (Trevisan *et al.* 1993, Ford *et al.* 1996, Matilainen *et al.* 2000, Ellis 2001, Severi *et al.* 2003).

Concerning obesity, two earlier studies reported that BMI and waist circumference were not associated with alopecia (Ellis *et al.* 1998, Severi *et al.* 2003). Furthermore, the results concerning hypertension have been contradictory

among men with vertex alopecia compared to men with no alopecia (Trevisan *et al.* 1993, Lotufo *et al*.2000). The former study reported higher BP in men with alopecia, while the latter study found no association between alopecia and BP. The most recent definition of dyslipidemia was not in use when data collecting was made in earlier studies (Trevisan *et al.* 1993, Lotufo *et al.* 2000). In the aforementioned studies, hypercholesterolemia (self-reported cholesterol level ≥ 6.45 mmol/L or cholesterol lowering medication) was associated with alopecia in men. Instead, HDL-chol or triglycerides were not associated with alopecia.

Until now, it was not known whether MetS is more common among men with alopecia than among those without alopecia. Matilainen *et al.* (2000) defined a cluster of IR-associated risk factors as a combination of obesity, hypertension and dyslipidemia in men with alopecia (Matilainen *et al.* 2000).

The studies concerning solely women with alopecia are rare. There is one population-based study that reported a link between alopecia and obesity among elderly Finnish women (Matilainen *et al.* 2003).

2.7.2 Insulin resistance

Finnish case-control studies suggest an increased risk of hyperinsulinemia and severe CAD among elderly men with alopecia compared to men with no alopecia (Matilainen *et al.* 2000, Matilainen *et al.* 2001). However, there is no knowledge of whether alopecia is associated with IR generally.

In women, an association between alopecia and high fasting insulin level has been reported among Finnish women aged 63 years (Matilainen *et al.* 2003). In addition, alopecia is common in women with PCOS (Futterweit *et al.* 1988, Carey *et al.* 1993, O'Driscoll *et al.* 1994 in Cela *et al.* 2003) who also have other symptoms of hyperandrogenemia (acne, hirsutism) (Cela *et al.* 2003). IR might be a factor behind these phenomena (Dunaif *et al*.1985)

2.7.3 Low-grade inflammation

An inflammation process, which in the case of alopecia has been reported to be microscopic follicular inflammation, is suggested to be in important in the pathogenesis of alopecia (Jaworsky *et al.* 1992, Whiting 1993, Mahe 2000). A high number of proinflammatory cytokines has been found in the hair follicles of subjects with alopecia (Mahe 2000). In addition, subjects with alopecia have other clinical and histological features of inflammation, as well as fibrosis limited to the

area of androgenetic hair loss (Zinkernagel &Trueb 2000, Mahe 2000). However, studies concerning inflammation are rare and other disturbances linked to endothelial dysfunction have not been reported.

2.7.4 Androgens

In men, one potential mechanism between alopecia and CVD is androgen metabolism. Testosterone is known to be the major circulating androgen of which only a small fraction exits as free steroids in the circulation system – normally, 70% is bound to SHBG and 19% to albumin. Free testosterone can be metabolized into dihydrotestosterone (DHT), which is five times more potent than testosterone, and associated in the pathogenesis of e.g. androgenetic alopecia. (Kaufman 1996 & 2002, Trueb 2002.) High levels of DHT and increased expression of AR have been reported in the scalps of men with alopecia (Schweikert 1974). AR is a steroid receptor and responsible for determining the cellular sensitivity to androgens (Janne *et al.* 1993), and it is known to be associated with alopecia (Ellis 1998, Levy-Nissenbaum *et al.* 2005).

In women, alopecia is undoubtedly a feature of hyperandrogenism; women with alopecia are more likely to have elevated androgen levels or show an increased amount of other features of androgen excess (Futterweit *et al.* 1988, Vexiau *et al.* 2000, Cela *et al.* 2003). Also, PCOS with increased total testosterone and premenopausal depletion of estrogens is associated with alopecia, hirsutism and other signs of masculinization (Redmont & Bergfeld 1990, Azziz 2003). Women with alopecia and PCOS have indices of changes in their hormonal profiles (elevated median testosterone, androstenedione, free androgen index and lower SHBG) (Futterweit *et al.* 1988, Cela 2003). However, women with typical female pattern alopecia have no clinical symptoms of hyperandrogenism and their serum testosterone levels are usually within the normal range (Schmidt *et al.* 1991, Sawaya & Shalita 1998, Birch *et al.* 2006). In some women with a potent contribution of genetics behind alopecia, hormonal changes are not involved in the alopecia process (Birch *et al.* 2006).

It is generally assumed that both male and female alopecia is a result from an abnormal sensitivity of scalp hair follicles to circulating androgens in genetically susceptible men and women (Kaufman 2002). Androgens act as mediators of terminal hair growth in the body and affect the scalp and other body areas in different ways. The most studied steroid hormone in respect of hair growth is the peripheral conversion of testosterone into DHT, which is catalyzed by the enzyme

5α-reductase (Kaufman 1996) and binds strongly to AR in frontal hair follicles in the balding scalp (Hibberts *et al.* 1998).

2.8 Alopecia and other diseases

In men, alopecia has been reported to be linked with benign prostatic hyperplasia (Oh *et al.* 1998, Hawk *et al.* 2000) and prostatic cancer (DeMark-Wahnefried *et al.* 1997 & 2000, Giles *et al.* 2002). Further, a link between alopecia and associated diseases may be the AR gene mutation (short repeat lengths of both CAG and GGN), because the same mutation has been found in both alopecia (Ellis *et al.* 2001b, Hillmer *et al.* 2005, Levy-Nissenbaum *et al.* 2005), early severe CAD (Alevizaki *et al.* 2003) and prostatic cancer (Stanford *et al.* 1997, Hsing *et al.* 2000, Chang *et al.* 2002, Suzuki *et al.* 2003). However, the results in Finnish male population were contradictory to the studies concerning association between AR gene mutation and prostatic cancer (Mononen *et al.* 2002).

In women, one study reported an association between PCOS and AR gene CAG repeats (Mifsud *et al.* 2000). An association between alopecia and PCOS has been described in section 2.7.4. Interestingly, longer alleles of the GGN repeat of the AR gene have been associated with endometrial cancer (Sasaki *et al.* 2005).

2.9 Alopecia and health-related quality of life

2.9.1 The concept of health-related quality of life

Health-related quality of life (HRQOL) is described as "a state of complete physical, mental and social well-being", which is a positive definition and also includes the psychological consequences related to a physically undesirable state (WHO 1948). In addition, HRQOL is a more specific definition than "quality of life" (QOL) and is influenced by a person's experiences, beliefs, expectations and perceptions (Testa & Simonson 1996). Moreover, in measuring HRQOL one should also take into account the positive state of well-being, in addition to the negative state of disease or lack of health or well-being (Ware Jr. 1987).

Although the concept of QOL has meant different things to different health researchers, there is a general agreement that it consists of at least physical, psychological and social core dimensions, which can be divided further into subdimensions (Aro *et al.* 1993). Furthermore, different measurements may

include complementary dimensions, e.g. general estimate of perceived or self-rated health status (Hays *et al.* 1993, Stewart *et al.* 1988, Ware & Sherbourne 1992) and energy/vitality (Hays *et al.* 1993, Ware Jr & Sherbourne 1992). The final dimensions of HRQOL used depend on the purpose of the study, the study population and the available instruments.

2.9.2 Measuring quality of life

A large number of instruments – global, generic and disease-specific – have been developed for HRQOL assessment. The HRQOL instruments can be classified according to comprehensive structure as global, one-dimensional and multidimensional instruments (Aro *et al.* 1993).

The concept of a global self-rated health question, "Do you consider you health to be excellent, good, fair, or poor?" has received much attention in health research. This does not provide information on different dimensions of health, but in this simple form it has proven to be a good predictor of one's subjective health (Blank & Diderichsen 1996) and mortality (Idler & Benyamini 1997).

One-dimensional scales are used in measuring one specific dimension related to HRQOL; e.g. the scales of the New York Heart Association (NYHA) (Lindholm *et al.* 2004), Activities of Daily Living (Lawton *et al.* 1969) and BDI-21 for depression (Beck 1967).

Generic multidimensional scales offer a broader measure for assessing HRQOL in terms of physical, mental, and social health dimensions, but they do not always address the life areas that are important in the case of a specific illness. The most widely used international generic scale questionnaires include SF-12 (Stewart *et al.* 1988), SF-36 (Ware Jr & Sherbourne 1992), RAND-36 (Hays *et al.* 1993), Nottingham Health Profile (Wiklund 1990), Sickness Impact Profile (SIP, Bergner *et al.*1981) and 15-D (Sintonen 1989).

2.9.3 Alopecia and HRQOL questionnaires

Several cross-sectional studies have examined the association between alopecia and QOL (Table 5). The results of these studies are difficult to compare because of the different methodologies used. Measurements of QOL have varied because there is a lack of alopecia-specific measurements of QOL for clinical and epidemiological studies.

The international generic scales of standardized QOL instruments used in the studies among alopecia subjects include the Nottingham Health Profile (NHP) (van der Donk *et al.* 1994), general health measure (SF-12) (Muro-Mercon *et al.* 2000, Budd *et al.* 2000) and mental health survey (MHI-5) (Muro-Mercon *et al.* 2000). Because alopecia clearly reduces the QOL but does not affect the general health status, special questionnaires have been developed to assess the QOL effects of alopecia on a subject's life, e.g. Hairdex questionnaire (Fischer *et al.* 2001), Dermatology Life Quality Index (DLQI) (Williamson *et al.* 2000) and Women's Androgenetic Alopecia Quality of Life Questionnaire (WAA-QOL) (Dolte *et al.* 2000).

2.9.4 Studies concerning life satisfaction and quality of life among subjects with alopecia

Alopecia is not a disease in the traditional sense. However, it is likely to have psychological and social effects and also influence the subject's QOL.

The negative psychological impact of alopecia has been documented in both males and females (Cash *et al.* 1992 and 1993, van der Donk *et al.* 1991a,b & 1994, Wells *et al.* 1995, Maffei *et al.* 1999, Girman *et al.* 1998). However, the association between alopecia and different psychological effects seems to be stronger among women (Cash *et al.* 1993, van der Donk 1991b & 1994, Girman *et al.* 1999, Fischer *et al.* 2001). In addition, some studies have reported the psychosocial effects of alopecia in men, such as stress and decrease in body image satisfaction (van der Donk *et al.* 1991a, Cash 1992). Some studies concerning alopecia and QOL-related factors (e.g. psychological impairment, low self-esteem, low body-image, social self-consciousness) reported treatment satisfaction among subjects with alopecia (van der Donk *et al.* 1991a,b & 1994, Schmidt 2003). These aspects are important in measuring outcomes, e.g. the effect of treatment on a patient's life, but they do not examine the impact of the severity of alopecia or other health factors on QOL among persons with alopecia.

Table 5. The studies of alopecia with quality of life related aspects among males (M) and females (F).

Reference	Classification scale	Design	Country	Sex (n)	Age	Questionnaire
van der Donk *et al.* 1991	Hamilton	Clinical	Netherlands	M (168)	20-40	IOA, NPV, DQ, BC
van der Donk *et al.* 1991	Ludwig	Clinical	Netherlands	F (58)	18-47	NPV, DQ, BC, SRQ, Zung
van der Donk *et al.* 1994	Ludwig	Clinical	Netherlands	F (58)	18-45	open and closed questions in an interview
Cash *et al.*1992	Hamilton-Norwood	Population	USA	M (145)	18-70	HLEQ, TSBI, LOC, S-CS, BIS
Cash *et al.* 1993	Hamilton-Norwood	Clinical	USA	M (212)	36	HLIQ, HLEQ, MBSRQ, SDS-13, TSBI,
	Ludwig			F	31	LOC, S-CS, IES
Maffei *et al.* 1994	Hamilton	Clinical	Italy	M (64)	18-58	PDQ-R, SCL-90
	Ludwig			F (54)		
Wells *et al.* 1995	Not reported	Not reported	UK	M (182)	19-73	SES, BECK-21, EPQ-R
Girman *et al.* 1998	Not reported	Population	USA	M	18-50	MHGQ, MSHL, MHI-5, SF-12
Girman *et al.*1999	Ludwig and Savin	Clinical	USA	F (120)	22-66	WAA-QOL
Budd *et al.* 2000	Hamilton-Norwood	Population	France, Germany, UK, Italy	M (1717)	18-40	HGQ, IHL, MHI-5, SF-12,
Williamson *et.al*. 2000	Not reported	Clinical	UK	M (65)	24-72	DLQI, CES-DS
				F (13)		
De-Muro Mercon 2000	Hamilton-Norwood	Population	Norway	M (4101)	20-50	SF-12, MHI-5
Schmidt *et al.* 2001	Ludwig	Not reported	Germany	F (55)	19-66	Hairdex, Befo-S, FSOZU-KZZ
Franzoi *et al.* 2001	Not reported	Population	USA	M (91)	23-66	PRQ, PAQ
Schmidt 2003	Ludwig	Clinical	Germany	F (74)	19-68	Hairdex, Befo-S, FSOZU-KZZ
Alfonso *et al.* 2005	Not reported	Population	Germany, France, Italy, Spain, UK	M (729)	18-45	Modified from Gallup Spain, not validated questionnaires

Befo-S = Berne Coping Test (Hessel 2000, see Schmidt *et al.* 2001), BC = Body-Cathexis List (Tucker 1981, see van der Donk *et al.* 1991a), BECK-21 = 21-item Beck Depression Inventory (Beck 1967), BIS = body image satisfaction (Brown *et al.* 1990, see Cash *et al.*1992), CES-DS = Center for Epidemiologic Studies Depression Scale (Andresen 1994, see Williamson *et al.* 2000), DLQI = Dermatology Life Quality Index (Finlay 1994, see Williamson *et.al.* 2000), DQ = Delft Questionnaire (Appels 1985, see van der Donk *et al.* 1991a), FSOZU-KZZ = Social Support Questionnaire (Fydrich, see Schmidt *et al.* 2001), Hairdex = Condition-Specific Health-Related QOL measurement tool (Fischer 2000), HGQ = Hair Growth Questionnaire (Barber 1998, see Budd *et al.* 2000), HLIQ = Hair Loss Information Questionnaire (Cash *et al.* 1993), HLEQ = Hair Loss Effect Questionnaire (Cash *et al.* 1992), IES = 5-item Impact of Event Scale (Horowitz *et al.* 1979, Zilberg *et al.* 1982, see Cash *et al.* 1993), IHL = Impact of Hair Loss on Men's HRQOL (Gagnon 1993, see Budd *et al.* 2000), IOA = Inventory List on Association with Others (Van Dam-Baggen *et al.* 1987, see van der Donk *et al.* 1991a), LOC = 24-item Levenson Locus of Control Scale (Levenson 1973, see Cash *et al.* 1993), MHI-5 = Mental Health Survey (Berwich 1991, see Girman *et al.* 1998), MHGQ = Male Hair Growth Questionnaire (Barber 1998, see Girman *et al.* 1998), NPV = Dutch Personality Questionnaire (Luteijn *et al.* 1985, see van der Donk *et al.* 1991), PAQ = Physical appearance questionnaire (Franzoi *et al.* 2001), PDQ-R = Personality Disorders Questionnaire – Revised (Hyler 1987, see Maffei *et al.* 1994), PRQ = Personal reaction questionnaire (Fenigstein 1975, see Franzoi *et al.* 2001), TSBI = Texas Social Behavior Inventory (Helmreich *et al.* 1974, see Cash *et al.* 1994), SCL-90 = Symptoms Checklist -90 (Derogatis 1973, see Maffei *et al.* 1994), S-CS = 13-item Self-Consciousness Scale (Scheier *et al.* 1985, see Cash *et al.* 1994), SDS-13 = 13-item Social Desirability Scale (Zook *et al.* 1985, see Cash *et al.* 1993), SF-12 = General Health Survey (Ware *et al.* 1987), SRQ = self-rating questionnaires (van der Ploeg *et al.* 1980, see van der Donk 1991c), WAA-QOL = Women's Androgenetic Alopecia Quality of Life Questionnaire (Dolte *et al.* 2000), Zung = Self-Rating Scale for Depression (Zung)

2.10 Summary of the literature

Alopecia is common among Caucasian races, with prevalence among men varying from 30% at the age of 30 years to 50% at the age of 50 years. In women, it manifests a decade later than in men. (Hamilton 1951.) Various factors have been suggested to influence alopecia, such as androgens, genetic factors with polygenic inheritance, age and disturbances in enzyme mediators (Ellis *et al.* 1998 & 1999 & 2005, Ellis & Harrap 2001, Kaufman 2002).

The definition of alopecia has been discussed, as the classification scales used in population-based studies merely measure the degree of alopecia, but not any conditions behind it (Rebora 2001). However, more than 90% of subjects with alopecia suffer from AGA. The most utilized and acceptable definitions for degree of alopecia assessments are the Hamilton classification scale modified by Norwood and the Ludwig scale for men and women, respectively.

A positive association between the severity of alopecia and the risk of CVD in men has been reported. However, prospective studies on the topic have some limitations (Rebora 2001). Further, few studies have reported an association between alopecia and MetS-related disorders, such as hypertension, obesity and hyperinsulinemia (Trevisan *et al.* 1993, Lotufo *et al.* 2000, Matilainen *et al.* 2000 & 2002). On the other hand, central obesity is associated with systemic low-grade inflammation (Yudkin *et al.* 1999), and on the other hand, the presence of microinflammation in the hair follicle of scalp has been confirmed (Mahe 2002). The question remains of whether mircoinflammation in the scalp is part of a systemic inflammation.

There are only a few studies on women with alopecia. Most studies address the psychological disturbances associated with alopecia and report a high prevalence of depressive symptoms and low self-esteem among women with alopecia. Compared to women, men do not generally experience hair loss as being as stressful.

3 Purpose of the present study

The overall aim was to obtain additional information about the relationship between alopecia and both cardiovascular risk factors and cardiovascular diseases. Additionally, health-related quality of life among Finnish subjects with or without alopecia was evaluated.

More specifically, the aims of the study were to address the following questions:

1. To describe the prevalence of alopecia in Finnish men (Articles I, II-IV) and in one age cohort of women (Article VI)
2. To describe and analyze the association of alopecia with vascular diseases (Articles I, III-IV)
3. To describe and analyze the association of alopecia with insulin resistance and insulin resistance-linked factors (Articles II-III)
4. To describe and analyze the association of alopecia with low-grade inflammation (Article IV)
5. To describe and analyze the association of low-grade inflammation with some metabolic syndrome-linked factors at population level (Article V)
6. To describe and analyze the association of alopecia with health-related quality of life (Article VI)

4 Subjects and methods

The present work consisted of three separate cross-sectional population samples; the Finrisk 2002 alopecia sub-study and two other study populations, the Oulu 45 study (55-year-old subjects) and the Oulu 35 alopecia sub-study (63-year-old subjects).

4.1 Design and subjects

4.1.1 Finrisk 2002 survey

Part of the present study is based on a sample of the national Finrisk survey performed in Finland at 5-year intervals for surveillance of chronic non-communicable diseases and their risk factors. The alopecia sub-study monitors the prevalence and heredity of significant alopecia in a Finnish male population (Article I) and the cardiovascular risk factors associated with early onset alopecia (Article IV).

The survey protocol followed closely the WHO MONICA protocol (WHO MONICA 1988) and the most recent recommendations of the European Health Risk Monitoring Project (Tolonen *et al.* 2002). Six teams, with four trained nurses in each, carried out the survey. The survey included a self-administered questionnaire and a health check, where anthropometric measurements, BP measurements and blood sampling were carried out.

The data were collected by sending a postal questionnaire to a total of 13 437 men and women aged 25-74 years, who were selected by random sampling from population registers and stratified by sex and age from five geographical areas. The response rate in the postal inquiry was 67%, but the actual response rate dropped to 61%. (Laatikainen *et al.* 2003) The alopecia classification was performed on 4 066 men. Figure 1 presents the formation of the study population. In the prevalence study (Article I), the study population consisted of 4 066 men. In the study concerning alopecia and low-grade inflammation (Article IV), the study population was restricted to 727 men younger than 35 years at the time of the study, with men reporting alopecia grade III or more being further divided according to the age of the most abundant hair loss (<25 years/25-34 years).

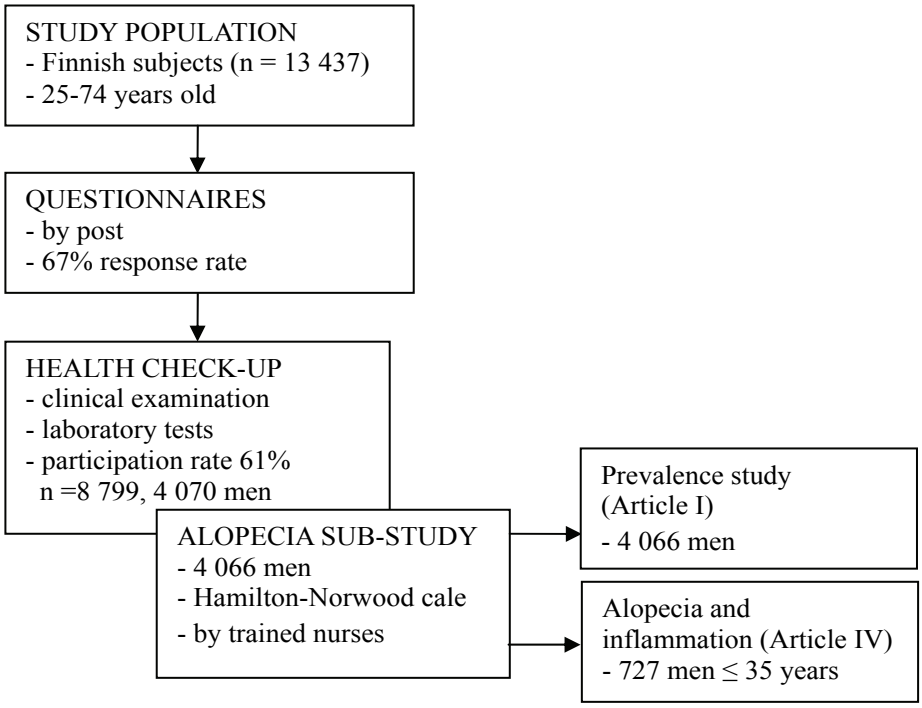

Fig. 1. The study population in the Finrisk 2002 survey

Based on the available information from the national register, the non-attenders were young men from urban environment (Laatikainen *et al.* 2003). The 412 men who only filled in the questionnaire but did not participate in the check-up were analyzed for some characteristics to evaluate the significance of dropouts. Employment status did not differ between the attenders and those who only returned the postal questionnaire.

4.1.2 Oulu studies

The Oulu studies consisted of the age cohorts of 55 and 63 years old, those born in 1945 (Oulu 45 study) and those born in 1935 (Oulu 35 alopecia sub-study) (Figure 2).

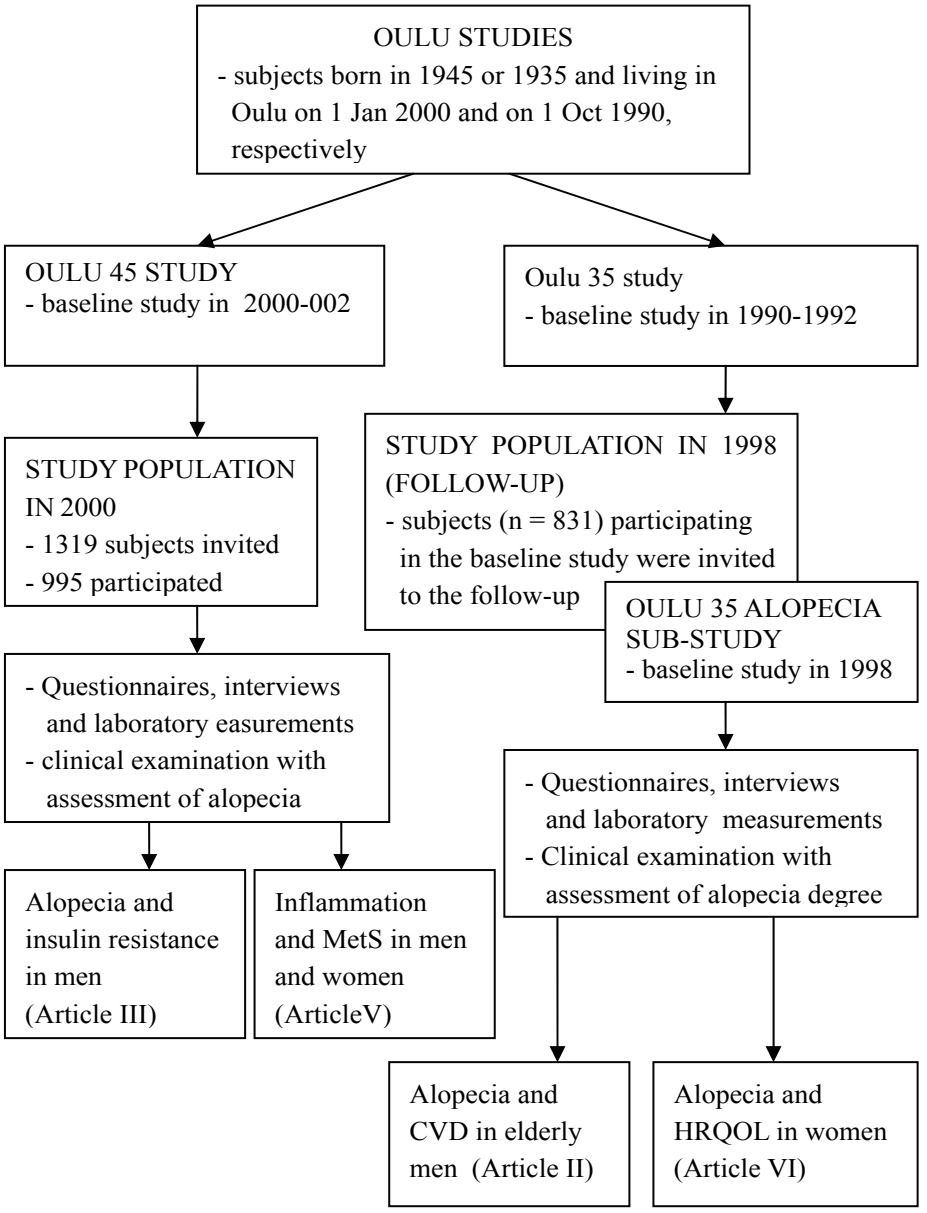

Fig. 2. The study populations in Oulu

The Oulu 45 study (55-year-old subjects)

The possible links between alopecia grades III or more and IR (Article III) were examined using the cross-sectional Oulu 45 study. Further, the existence of low-grade inflammation was investigated at population level (Article V). The study was carried out to assess the prevalence of CVD, IFG, IGT and T2DM among this age-cohort overall and in the case of having alopecia, and, in the future, to evaluate this population prospectively. Questionnaires, interviews, clinical examinations and laboratory tests were used to collect the data.

The Oulu 45 study consisted of persons born in 1945 and living in the City of Oulu in Northern Finland in 2001 (n=1 332). The original study population comprised 1 300 subjects, of whom 995 (74.5%) participated in the examinations. Forty-four per cent (n=439) of the participants were men and 56% (n=556) were women. The classification of alopecia was available for 421 (96%) men. Table 6 presents the formation of the study population. The characteristics of the Oulu 45 study participants are provided in Table 7. In article III, only men were selected from the original population, and they were further divided into two groups based on alopecia classification. In study V, all the women and men who had attended the examination were used in the analyses.

Table 6. Formation of the study populations in the Oulu 45 and Oulu 35 study.

Population	Total	Men	Women
Oulu 45 study			
In register in 2001	1332		
Died or moved	32	18	14
Study population in 2002-2004	1300		
Declined	305		
Available participants	995	439	556
Alopecia classification	923	421	502
Oulu 35 study			
In register	1012	458	552
Study population in 1990-1992	1008	456	554
Participants in 1992	831	345	435
Died after the base study	28		
DeclinedDecined	210		
Participants in 1996-1998	593	246	347
Alopecia classification	551	221	330

The Oulu-35 alopecia sub-study (63-year-old subjects)

The Oulu 35 alopecia sub-study was used to examine the association between alopecia grades III or higher and CVD among elderly men (Article II) and HRQOL among elderly women having alopecia grades II-III (Article V). Questionnaires, interviews, clinical examinations and laboratory tests were used to collect data during the follow-up period in 1996-1998 to assess, among other things, the prevalence of DM and IGT.

The baseline study population in articles II and VI consisted of all 831 subjects born in 1935 and living in Oulu (Qiao 1996, Rajala 1997, Rajala *et al.* 2001) who were invited to attend a follow-up study in 1996-1998; 593 (71%) of them participated. Of those, the classification of alopecia was assessed for men (221 cases out of 245 participants) and women (330 cases out of 347) as in a cross-sectional design. The formation of the study population is presented in Table 6 (Oulu 35 study) and the background characteristics in Table 7 (Oulu 35 follow-up study). In article II, the analyses were performed among men only and, in article VI, among women.

Table 7. The background characteristics of Oulu study populations.

Variable	Oulu 45 study		Oulu 35 follow-up study	
	Men	Women	Men	Women
	n=439	n=556	n=246	n=347
Marital status (%)				
Married	74.8	62.7	88.0	65.8
Unmarried	12.9	17.5	3.7	7.5
Widows	1.4	6.4	2.1	13.1
Divorced	10.8	16.2	6.2	13.6
Current smokers (%)	31.3	21.3	19.3	14.6
Education (%)				
Primary school	16.0	14.3	49.2	61.8
Vocational courses/school	44.3	47.5	31.1	22.0
Vocational college	18.5	25.3	12.3	9.0
University	21.2	12.9	7.4	7.2
Elevated triglycerides[1)]	29.4	19.0	29.5	23.3
Low HDL-chol[2)]	9.0	10.5	17.6	21.2
Hypertension (%)[3)]	62.6	54.1	64.5	68.4
Known diabetes (%)	3.7	2.9	7.5	4.4
Coronary artery disease (%)	5.7	3.3	13.9	13.2

[1)] Triglycerides: ≥ 1,7 mol/l [2)] HDL-chol < 1.29 (men) < 1.03 (women)

[3)] Hypertension: BP 140/90 or antihypertensive drug or diagnosed hypertension by physician

4.2 Methods

Postal questionnaires, clinical interview and examinations as well as laboratory measurements were used in data collecting.

4.2.1 Questionnaires

The Finrisk 2002 survey

In the Finrisk 2002 survey (studies I and IV), information on health behavior and medical history was collected using a standardized, self-administered questionnaire. These include questions about chronic diseases, medical treatment and smoking. The subjects were asked to indicate whether they had suffered any medical conditions diagnosed by a physician during the past 12 months (myocardial infarction, angina pectoris, stroke, cerebral hemorrhage, cerebral vascular thrombosis, elevated BP or manifest or latent DM), or whether they had undergone a coronary bypass operation or angioplasty or used antihypertensive, antidiabetic or cholesterol-lowering drugs. (Laatikainen *et al.* 2003.)

The Oulu studies

In the Oulu studies, the contents and structure of questionnaires were very similar in the Oulu 45 study and Oulu 35 alopecia sub-study.

The Oulu 45 study

In the Oulu 45 study (Articles III and V), the self-administered questionnaires included questions about sociodemographic background, physical activity, smoking habits, alcohol consumption, self-reported diseases and medication. Self-reported diseases diagnosed by physician were inquired in the questionnaires (hypertension, ischemic heart disease and diabetes) and the “yes” responses were used in the analyses.

The Oulu 35 alopecia sub-study

In the Oulu 35 follow-up study (Rajala *et al.* 2001), a self-administered questionnaire was mailed to the participants and the collected data were used in

the Oulu 35 alopecia sub-study (Articles II and VI). The *sociodemographic* questionnaire included questions about the respondents' current marital status (married, unmarried/divorced or widowed) and educational attainment (elementary, secondary or university). *Self-reported diseases* were asked about in the questionnaires as follows: "Do you have DM/hypertension diagnosed by a physician?" and "Do you use any antidiabetic medication?" Prevalent chronic disease (hypertension, ischemic heart disease, diabetes, stroke, intermittent claudication, arthritis) was based on medical diagnosis as reported by the participants on the questionnaire or on the use of medication for any of these diseases as reported during the clinical examination. *Smoking* habits were also determined.

Self-perceived health and the participants' own opinion of their overall *physical fitness* and *life satisfaction* were also assessed, ranging from good, moderate to poor. A sum score of overall physical capacity was constructed based on the questions concerning their ability to walk up one flight of steps, a few flights of steps, half a kilometer or two kilometers or to run one hundred meters. The total score ranged from 0 to 20, a higher score indicating poorer physical capacity (Article VI).

Depressive symptoms were measured using the Beck Depression Inventory (BDI) (Beck 1967) with scores $\geq$ 10 defined as indicative of depressive symptoms.

Health-related quality of life (HRQOL) (Article VI) was measured using the Finnish version of the RAND 36-Item Health Survey 1.0 (RAND-36) (Hays *et al.* 1993). This self-reported measure is composed of eight separate scales assessing physical functioning (10 items), role limitations due to physical health (4 items), role limitations due to emotional problems (3 items), energy/fatigue (4 items), emotional well-being (5 items), social functioning (2 items), pain (2 items) and general health (5 items). All scale scores range from 0 to 100, with 100 representing the most favorable functioning/well-being, and the minimal clinically important difference is cautiously suggested to be 3-5 points. RAND-36 includes the same items as the Item Short-Form Health Survey SF-36 (Jenkinson *et al.* 1993), but the scoring algorithm has been slightly modified.

4.2.2 Clinical examinations

Finrisk 2002 survey

According to the Finrisk survey protocol (Laatikainen *et al.* 2003), BP was measured three times at one-minute intervals from the right arm of the sitting subject after five minutes' rest using a standard mercury sphygmomanometer with a cuff size of 14 cm x 40 cm. The mean of the measurements was used in the analysis. SBP was recorded at the first sound heard and DBP at Korotkoff's fifth sound. Heart rate was recorded between the first and second measurement. (Article IV)

Height, body weight, BP, heart rate and circumferences of the upper arm, hip and waist were measured by trained nurses. For the measurement of body weight and height the subjects wore light clothing and took their shoes off, and the above circumferences were measured with any tight clothing removed and the subjects standing with their legs slightly apart. Waist circumference was measured midway between the lowest ribs and the iliac crest during expiration and hip circumference two fingers above the pubic bone. Additional measures used were BMI and WHR. WHR was used as a measure of abdominal obesity (Article IV).

The assessment of alopecia degree

Alopecia grade was determined for 4 066 men (60.6% of those invited) by trained nurses, using the Hamilton classification scale modified by Norwood (Norwood 1975). The original grades (I – VII) were merged to obtain larger categories: no alopecia (grades I - II) and alopecia (grades III-VII), the latter category being further divided into moderate (III to V) and severe alopecia (VI to VII). Additional questions elicited the age of the most abundant hair loss if there had been significant loss. The respondents were asked about the age at which their most abundant hair loss had started if there had been significant hair loss, and about the family history of hair loss (Articles I and IV).

The Oulu studies

Anthropometric measures were measured in the clinical examination, and BMI and WHR were calculated. BP was measured from both arms in sitting position with a standardized automatic mercury sphygmomanometer (OMRON, HEM-

757). Two measurements of BP were made by a nurse (Oulu 45 study) or a physician (Oulu 35 alopecia sub-study). The mean value of these two measurements was used in the analyses. Hypertension was defined as either SBP ≥ 160 mmHg or DBP ≥ 90 mmHg or being on antihypertensive medication regardless of the BP values. Antihypertensive medication was recorded in an interview conducted by a nurse.

The assessment of alopecia degree

The alopecia grade of the subjects was assessed by a trained nurse as part of the clinical examination using the Hamilton-Norwood scale (Article II). The original grades I-VII were merged to form larger categories: no alopecia (grades I-II) and alopecia (grades III-VII).

In study III, the hair status of 421 men, who made up the final study population, was assessed by both a trained nurse and with a self-assessment questionnaire as part of the clinical examination. The self-assessed data were used in analyses after the validation of the methods (kappa 0.78, agreement 89%). Additionally, the participants were asked: "Which of the following most closely approximates your hair pattern at age 55?" and were given seven possible choices to indicate the degree of their hair status using the Hamilton-Norwood scale. The original grades I-VII were merged to form larger categories: no alopecia (grades I-II) and alopecia (grades III-VII). Additional questions were asked about the age of the most abundant hair loss if any significant had occurred, as well as the family history of hair loss.

Among the women (Article VI), alopecia grades were assessed by a trained nurse using Ludwig's scale, and re-classified further into two groups for analysis. The original class I was referred to as the no alopecia group, while the original classes II and III (moderate or marked hair loss) were combined as the alopecia group.

4.2.3 Laboratory measurements

The Finrisk 2002 survey

Serum total cholesterol (chol), HDL-chol and TG concentrations were determined using enzymatic (chol, TG) and direct enzymatic (HDL) methods (Thermo

Electron Oy). The subjects had been requested to fast for four hours before the laboratory tests. High sensitive-CRP was measured with an immunoturbidometric assay (Orion Diagnostica) which has a detection limit of 0.2 mg/l. The determinations mentioned above were performed in the laboratory of Analytic Biochemistry of the Finnish National Public Health Institute.

The Oulu studies

Serum lipids, glucose and insulin

The following biochemical data concerning the traditional cardiovascular risk factors were recorded: fasting chol, HDL-cholesterol, TG and insulin concentrations as well as fasting glucose from a blood sample taken after an overnight (10 h) fast. In the Oulu 45 study, apart from the previously diagnosed diabetic patients (n=33, 3.4%), 938 persons had their glucose tolerance measured. All the subjects who did not have previously diagnosed DM were invited to participate in a two-hour glucose tolerance test. The prevalence of newly diagnosed T2DM was 5.7% (n=55).

In the Oulu 35 alopecia sub-study, subjects with IGT and normal glucose tolerance were combined as non-diabetic subjects (Article II) and subjects with impaired fasting glucose (IFG), IGT or DM were considered to have IGR (Article VI).

A standardized 75-g oral glucose tolerance test was performed according to the instructions of the WHO Study Group. (Articles II-III, V-VI). Serum immunoreactive insulin concentrations were measured by RIA using the Phadeseph Insulin RIA 100 kit (Pharmacia Diagnostics AB, Uppsala, Sweden) (Articles II and VI) and by AxSYM Insulin assay (Articles III and V), which has no cross-reactivity with proinsulin (Abbot Laboratories, Japan). Insulin levels were not analyzed from the samples of diabetic patients treated with insulin.

Urine samples

Urine albumin and creatinine concentrations were measured from an overnight spot urine sample. The highest deciles of the urinary albumin-to-creatinine ratio ($\geq$ 2.5 mg/mmol) were used as a measure of microalbuminuria. (Studies II and VI).

High sensitive C-reactive protein

Plasma hs-CRP was determined by time-resolved fluorometry using an Innotrac Aio! analyzer (Innotrac Diagnostics Oy, Turku Finland). The detailed performance characteristics of hs-CRP assay have been published earlier (Hedberg *et al.* 2004). The values of hs-CRP concentrations have been recommended for the assessment of CVD risk (Pearson *et al.* 2003).

Definition of insulin resistance

To measure insulin sensitivity, HOMA-IR (Study V) or QUICKI (Study II, III and VI) was used. HOMA-IR is a method for assessing β-cell function and IR from fasting glucose and insulin or C-peptide concentrations (Matthews *et.al*. 1985). It is calculated as $[(IB_f \times GB_f)]/22.5$, where IB_f is the fasting insulin level and GB_f is the glucose level. QUICKI can be determined from fasting insulin and glucose values according to the equation: QUICKI=1/[log(I0) + log(G0)], in which I0 is fasting insulin and G0 is fasting glucose (Katz *et al.* 2000, Hrebicek *et al.* 2002).

Definition of metabolic syndrome

The MetS was identified by using three definitions of the syndrome: that of the World Health Organization (WHO) criteria (Alberti & Zimmet 1998), the National Cholesterol Education Program (NCEP 2001) and the International Diabetes Federation (IDF) (Alberti *et al.* 2006). Different criteria of the metabolic syndrome are presented in Table 4 on page 31.

A cluster of MetS for analysis was performed according to modified instructions of the WHO definition without the information on microalbuminuria (Alberti & Zimmet 1998): IGR or DM and/or IR defined as the lowest quartile of QUICKI with two or more of the other components: BP ≥ 140/90, TG ≥ 1.7 mmol/l and/or HDL < 0.90, WHR > 0.90, and/or BMI > 30 kg/m².

4.2.4 Ethical questions

The Ethics Committee for Research in Epidemiology and Public Health approved the study protocol of FINRISK 2002 survey and the participants provided their written consent. In the Oulu studies, informed consent was obtained from all

subjects after the purpose of the study was explained to them. The study protocols were approved by the Ethics Committees of the University of Oulu.

4.2.5 Statistical analyses

The summary statistics for normally distributed continuous variables were expressed as mean and standard deviation and as median with interquartile range (25^{th} and 75^{th} percentiles) for non-normally distributed variables.

Descriptive comparisons of the groups defined by degree of alopecia were presented as cross-tabulations and percentages for the categorical variables and assessed with Student's t-test when the distribution was normal, or with the Mann-Whitney U-test in the case of non-normal distribution of the continuous variables (Articles II, III). For categorical variables, the chi-square test for heterogeneity was used. The differences between alopecia grades I-II vs. III-VII, and the scores of the HRQOL dimensions were tested by the Mann-Whitney U-test (Article VI). The HRQOL dimensions on which the women with alopecia scored lower than the women with no alopecia were analyzed in more detail. After bivariate comparisons, multivariate logistic regression analyses were conducted to analyze the independent associations of risk factors with dependent variable: alopecia in article II and the lowest quartile of HROL in article VI. The possible interactions between alopecia and risk factors were tested by interaction terms (Article VI).

Since the study focused on inflammation, a special analysis was devoted to the associations of hs-CRP with the classic risk factors. The means of the risk factors were compared between the categories of hs-CRP, using classes of 0.0-0.9, 1.0-2.9 and 3.0+ mg/l, as recommended by the Center for Disease Control and the American Heart Association (Pearson *et al.* 2003) (Articles IV and V).

The age-specific prevalence figures (in classes 25-34, 35-44,…, 65-74 years) were adjusted for age by the direct method using the Finnish male population in 2002 as standard, the confidence intervals for the figures being calculated by the binomial formula (Article I).

Binary regression analyses with a logarithmic link function were used to describe the relationship between separate components of MetS as a response variable and elevated hs-CRP-level (3.0+ mg/l) after adjustment by the potential confounding factors smoking, alcohol consumption, physical activity and educational status, and the adjusted risk factors were calculated. The predictive power of the different components of MetS and their differences were studied

using the area under the receiver-operator characteristic (ROC) curve. The analyses were performed separately for both sexes (Study V). All statistical analyses were done using SPSS 11.5 (Statistical Package for Social Science) software and SAS (SAS Institute Inc., Gary, North Carolina, USA).

5 Results

5.1 The prevalence and heredity of alopecia in Finnish population (Articles I-III, VI)

Forty-seven per cent of the men (1 871 out of 4 066) reported alopecia, i.e. Hamilton-Norwood class III or higher (Table 8). The prevalence of alopecia increased with age, from 17% among the youngest (25-35 years) to 73% among the oldest (65-74 years), and similar trends were seen at all levels of the scale (Article I).

Forty-two percent of the men with alopecia reported that their hair loss had started before the age of 35, accounting for three quartiles of those who were aged 35-44 years at the same time of the survey but only a quintile of those who were 65-75 years old (Table 9). Twenty-two per cent of the men with alopecia grade III or more reported the onset of abundant hair loss at an age younger than 35 years. The men with such alopecia reported in most cases the hair loss to have occurred one decade prior to their the current age. The affected men consistently reported a family history of alopecia more often than the men with no alopecia (Table 10).

The prevalence of alopecia among 55-year-old men was 55% (Article III), and those with alopecia reported a family history more often than those men with no alopecia (50% vs. 24% in fathers and 7% vs. 3% in mothers).

The prevalence of alopecia among 63-year-old men was 58.4% (Article II). Among women aged 55 and 63 years, the prevalence of alopecia was 17% and 31%, respectively (Article VI).

Table 8. The distribution of alopecia in Finnish men according to the Hamilton-Norwood classification scale.

Grade	Age group (years)										Total	
	25-34		35-44		45-54		55-64		65-74			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
I-II	601	83	544	65	487	54	424	40	139	27	2195	53
I	332	46	251	30	177	20	130	12	26	5	916	22
II	269	37	293	35	310	34	294	28	113	22	1279	31
III-VII	126	17	310	35	527	46	834	60	478	73	1871	47
III	39	5	64	7	82	9	108	10	35	7	328	8
IV	37	5	96	11	129	14	155	15	103	20	520	13
V	31	4	73	9	82	9	122	11	82	16	390	10
VI	18	3	63	7	121	13	207	20	114	22	523	13
VII	1	0.1	10	1	13	1	42	4	44	8	110	3

Table 9. Distribution of the respondents by age of onset of the most abundant hair loss, classified according to age at survey.

Age of onset hair loss	Age at survey (years)					Total
	25-34 (n=126) %	35-44 (n=306) %	45-54 (n=427) %	55-64 (n=634) %	65-74 (n=378) %	(n=1871) %
-25	47	18	11	12	8	14
25-34	53	56	26	18	12	28
35-44		25	41	26	19	26
45+			22	44	61	32
All	100	100	100	100	100	100

Table 10. Percentage of alopecia among family members of men with alopecia/without alopecia.

Family member	Age at survey (years)					Total
	25-34 % / %	35-44 % / %	45-54 % / %	55-64 % / %	65-74 % / %	% / %
Father	65 / 38	63 / 34	66 / 33	61 / 30	55 / 19	62 / 25
Brother	31 / 13	52 / 23	64 / 27	60 / 31	57 / 29	57 / 25
Mother	4 / 2	3 / 2	7 / 3	6 / 5	6 / 3	5 / 3
Sister	2 / 1	0 / 2	3 / 2	2 / 2	4 / 2	2 / 2
Son			4 / 1	21 / 10	33 / 18	16 / 6
Daughter		1 / 0	0 / 1	0 / 1	1 / 0	

5.2 Association of alopecia with cardiovascular diseases (Articles I- IV, VI)

The association of alopecia with CVD was studied in Article I. The age-adjusted prevalence of all reported CVD is presented in Table 11 and as a figure in Article I. A significant association was found between alopecia and vascular diseases (CVD, hypertension). No difference by alopecia categories was found for the prevalence of cerebrovascular disorders and hypercholesterolemia (2.2% and 32% in both groups, respectively).

Specifically, among men younger than 35 years (Article IV) no significant differences were observed between the alopecia categories in the prevalence of cerebrovascular conditions, heart failure, T2DM or glucose intolerance or in the use of antihypertensive drugs. A higher proportion of men with alopecia of at least grade III reported an elevated BP during the last 12 months compared to men

having no alopecia (9% vs. 4%). Similar percentages (41%) of men in both categories were current smokers.

Further, middle-aged men with alopecia did not report more hypertension or T2DM compared with men with no alopecia. In addition, their oral glucose tolerance tests (OGTT) were similar (Article III). However, men with alopecia grades III-VII reported more often CAD than men with no alopecia (11% vs. 4%, $p < 0.006$).

Elderly men with alopecia reported more frequently hypertension and use of antihypertensive medication than those with no alopecia (62% vs. 45%, $p = 0.016$ and 58% vs. 26%, $p = 0.0003$, respectively) (Article II). Sixty-three-year-old women with alopecia had more often T2DM than those with no alopecia (14% vs. 6%). Furthermore, no differences were seen in the occurrence of self-reported CAD and hypertension (Article VI).

5.3 Association of alopecia with insulin resistance and components of the metabolic syndrome (Articles II-IV)

Among men with alopecia younger than 35 years (Article IV), overall obesity was common and DBP tended to be higher than in those with no alopecia. The men reporting alopecia occurring between the ages 25 to 34 showed significantly greater BMI, WHR and waist circumference than men reporting alopecia before the age of 25 years (Table 12).

In middle-aged men, alopecia was significantly associated with lower insulin sensitivity measured by QUICKI as a marker of IR compared with the men having no alopecia. There were no differences in the other components of MetS between the study groups (Table 1 in article III). The presence of MetS was quite common in both alopecia and no alopecia groups (36% vs. 31%, respectively), but the difference was not statistically significant (Article III). The results of elderly men (aged 63 years) were in line with those of the middle-aged age group (Table 1 in Article II).

The prevalence of impaired glucose regulation (IGR; cluster of self-reported DM and IFG, IGT and DM according to OGTT) defined by WHO was different in women aged 63 years with alopecia compared to women with no alopecia (43% vs. 30%, $p=0.01$) (Article VI).

Table 11. Self-reported prevalence and confidence intervals (95% CI) of cardiovascular diseases and self-reported risk factors among Finnish males aged 25-74 years with alopecia classified according to Hamilton classification scale modified by Norwood.

Disease	Grades I-II % (95% CI)	Grades III-VII % (95% CI)	p
CVD	23.5 (21.5-25.1)	26.0 (24.2-27.9)	0.033
Hypertension	33.7 (31.7-35.7)	36.9 (34.5-39.2)	0.039
CAD	6.6 (5.4 - 7.7)	7.9 (6.9-8.9)	0.087
Hypercholesterolemia	32.0 (30-34)	32.4 (30.2-34.6)	ns.
T2DM or IGR	4.5 (3.6- 5.5)	5.3 (4.5-6.2)	ns.
Cerebrovascular disorders	2.2 (1.5-2.9)	2.2 (1.7-2.8)	ns.

CVD: the cluster of cardiovascular diseases; hypertension or coronary artery disease or type 2 diabetes mellitus or impaired glucose tolerance or hypercholesterolemia or cerebrovascular disorder; Hypertension: elevated blood pressure or antihypertensive drug; CAD: coronary artery disease; Hypercholesterolemia: increased lipid parameters or treatment for lowering cholesterol level; T2DM: type 2 diabetes; IGR: impaired glucose regulation; Cerebrovascular disorders: stroke, cerebral hemorrhage or cerebrovascular infarction

5.4 Association of alopecia with low-grade inflammation (Article IV)

The role of low-grade inflammation was studied among young men with early onset alopecia (Article IV). The mean values of hs-CRP among the men having alopecia and no alopecia have been presented in Table 12. The median of hs-CRP was twice as high among the men with alopecia compared to those with no alopecia, although the difference did not reach statistical significance.

Serum lipids, BP and anthropometric measures showed otherwise little variation between the categories of CRP, but the mean WHR increased slightly with increasing hs-CRP (0.91, 0.94 and 0.94 in the classes of 0-0.9, 1.0-2.9 and 3.0+ mg/L, respectively). This association virtually disappeared after adjustment for BMI (0.92, 0.92 and 0.92 in the respective classes), but a further analysis of the data stratified by alopecia classification (alopecia grades III or more and grades I-II) revealed a significant increase in WHR with increasing hs-CRP in the men with alopecia but no trend at all in the men with no alopecia. The model-based means of WHR are shown in Article IV, Figure 1.

Table 12. Anthropometric measures, serum lipids, blood pressure and C-reactive protein among men younger than 35-years with alopecia (Hamilton-Norwood grades III-VII) compared to men with no alopecia (grades I-II). Dunnett's test was made for men reporting alopecia grades III-VII occurring before the age of 25 years and between the ages 25 and 34.

	Grades I-II n=601		Grades III-VII n=126			Onset of alopecia <25 years n=58		Onset of alopecia at 25-34 years n=68		Dunnett's test Grades III-VII <25 yr vs. I-II	Dunnett's test Grades III-VII 25-35 yr vs. I-II
	Mean	Sd	Mean	Sd	p	Mean	Sd	Mean	Sd	p	p
Height (m)	1.79	0.07	1.79	0.07	ns.	1.79	0.07	1.78	0.06	ns.	ns.
Weight (kg)	82.2	14.4	85.3	14.8	<0.05	84.5	15.6	86.0	14.2	ns.	<0.10
BMI (kg/m²)	25.7	4.0	26.8	4.0	<0.05	26.2	3.9	27.1	4.3	ns.	<0.05
Upper arm circ.	31.5	3.4	32.2	3.3	<0.05	32.1	3.5	32.4	3.1	ns.	<0.10
Hip circ.(cm)	96.9	7.7	98.5	7.4	<0.05	98.0	7.5	98.9	7.4	ns.	<0.10
Waist circ.(cm)	88.9	11.3	91.4	11.4	<0.05	89.9	11.0	92.8	11.7	ns.	<0.05
WHR	0.92	0.06	0.93	0.07	<0.10	0.92	0.07	0.94	0.06	ns.	<0.05
CHOL (mmol/l)	5.1	1.0	5.0	1.1	ns.	4.8	1.0	5.2	1.0	<0.05	ns.
HDL (mmol/l)	1.3	0.3	1.3	0.3	ns.	1.3	0.2	1.4	0.3	ns.	ns.
TG (mmol/l)	1.4	1.1	1.4	1.2	ns.	1.3	0.7	1.6	1.5	ns.	ns.
SBP(mmHg)	128.8	11.9	128.5	12.1	ns.	126.8	11.4	129.9	12.7	ns.	ns.
DBP(mmHg)	74.2	10.6	75.7	10.9	ns.	74.3	9.6	76.9	11.9	ns.	<0.10
CRP (mg/L)	0.10*	0.10-0.86**	0.25*	0.10-0.66**	ns.	0.25*	0.10-0.55**	0.27*	0.10-0.75**	ns.	ns.

*Median **Interquartile range

5.5 The association of inflammation with different components of the metabolic syndrome at population level (Article V)

The association of inflammation with the components of MetS in Finnish population was studied by comparing the definitions of MetS defined by IDF, NCEP and WHO. Earlier, alopecia has been known to be linked with IR as well as some components of MetS and diseases linked to MetS (Trevisan *et al.* 1993, Matilainen *et al.* 2000 & 2002).

5.5.1 Prevalence of metabolic syndrome in middle-aged subjects (Article V)

The prevalence of MetS in women was 31, 17 and 19% according to the IDF, NCEP and WHO criteria, respectively. Among men, the corresponding prevalences were 19, 15 and 24%. The prevalence of MetS and its components based on the NCEP, WHO and IDF definitions is shown in Table 13. It is noteworthy that 76.1% of the women fulfilled the criteria for the essential component (i.e., high waist circumference) of the IDF definition of MetS. Of men with MetS according to the IDF criteria, 50.0% were also classified as having MetS based on the WHO criteria. The corresponding prevalence in women was 34.8%.

Among women, IDF-, NCEP-, and WHO-defined MetS was significantly associated with increased risk [adjusted risk ratio of having elevated hs-CRP 1.77 (95% CI 1.40-2.23), 2.00 (1.59-2.53) and 2.07 (1.65-2.60), respectively] after adjustment for smoking, alcohol consumption, physical activity, and educational status. Among men, the corresponding risk ratios were 1.10 (0.76-1.58), 1.87 (1.38-2.54) and 2.23 (1.69-2.94).

5.5.2 Association of high sensitive C-reactive protein with components of metabolic syndrome (Article V)

In this middle-aged general population, BMI associated most closely with hs-CRP (the largest area under curve being 0.6305 in men and 0.7547 in women). In addition, HOMA-IR was moderately associated with hs-CRP in both genders (0.6284 and 0.6749, respectively), albeit being inferior to BMI in women. Interestingly, the other measurements of obesity were significantly inferior to BMI.

Thirty percent of the men and 35.3% of the women with central obesity, the essential component of MetS as defined by IDF, had hs-CRP levels of > 3 mmol/L. In addition, 45.6% of the men and 51.2% of the women with hyperglycemia and/or IR, the essential component of MetS as defined by WHO, had hs-CRP levels of > 3 mmol/L.

5.6 Alopecia and health-related quality of life (Article VI)

In the cohort of elderly Finnish subjects, HRQOL measured by RAND-36 seemed to be lower in women compared to men. Further, HRQOL was lowest in women with alopecia. However, also men with alopecia scored lower than men or women with no alopecia.

The background characteristics of the study population concerning factors linked to HRQOL are presented in Table 14. Women with alopecia scored significantly lower in physical functioning, role limitations due to physical health and general health perceptions dimensions of HRQOL compared to women with no alopecia. In addition, a nearly statistically significant difference was observed in the pain score between the groups. (Article VI, table 3). In 63-year-old men with alopecia grades III or more, an association between alopecia and HRQOL related to physical and social functioning was found (Table 15).

Table 13. Prevalence of the metabolic syndrome and its different components using the NCEP, the WHO 1999 and the IDF 2005 definitions.

NCEP			WHO 1999			IDF 2005		
Variable	Men %	Women %	Variable	Men %	Women %	Variable	Men %	Women %
Three or more of the following								
Waist circ. (cm) > 102 (men), > 88 (women)	19.6	54.0	DM or IGT or IFG and/or IR	38.6	29.9	Waist circ. (cm) ≥ 94 (men) or ≥ 80 (women) cm	36.8	76.1
Triglycerides > 1.7 mmol/L	29.4	19.1	And two or more of the following:					
			BMI > 30 or WHR > 0.9 (men) or >0.85 (women)	58.2	31.7	Triglycerides > 1.7 mmol/L or drug	34.7	24.6
HDL chol < 1.0 mmol/l (men), <1.3. mmol/l (women)	10.0	10.5	Triglycerides ≥ 1.7 mmol/L or HDL chol < 0.9 (men) or < 1.0 (women) mmol/L	29.4	19.9	HDL-chol: < 1.03 (men) or < 1.29 (women) mmol/L or drug	17.7	15.9
BP ≥ 135/85 mmHg or drug	75.1	69.4	BP ≥ 140/90 mmHg	59.8	48.2	SBP ≥ 130 mmHg, DBP ≥ 85 mmHg or drug	80.4	75.1
fB-gluc ≥6.1 mmol/l	20.1	10.5	Urine albumin excretion ≥ 20 µg/min	-	-	fB-gluc ≥ 5.6 mmol/L or earlier T2DM	20.6	10.9
Metabolic syndrome	14.8	17.3	Metabolic syndrome	24.4	15.3	Metabolic syndrome	15.6	24.7

IGT: impaired glucose tolerance, IFG: impaired fasting glycemia, IR: insulin resistance defined by the lowest quartile of QUICKI

Table 14. The background characteristics of male and female subjects aged 63 years.

Variable	Women			Men		
	Grades III-VII	Grades I-II		Grades III-VII	Grades I-II	
	n=105	n=225		n=129	n=92	
	% (n)	% (n)	p	% (n)	% (n)	p
Marital status			0.163			0.028
married	59(61)	69(154)		84(108)	96(88)	
not married/divorced	27(28)	18(41)		13(17)	3(3)	
widow	14(14)	13(29)		2(3)	1(1)	
Educational level			0.115			0.149
elementary	89(92)	80(181)		78(100)	83(76)	
secondary	5(5)	11(25)		16(20)	8(7)	
tertiary	6(6)	8(19)		6(8)	10(9)	
Self-perceived health			0.030			0.017
good	41(43)	54(121)		45(57)	59(54)	
moderate	48(50)	42(94)		47(60)	40(37)	
poor	11(11)	4(10)		5(11)	0.5(1)	
Self-rated physical fitness			0.001			0.054
good	26(27)	46(104)		35(45)	51(47)	
moderate	54(56)	44(99)		54(70)	40(37)	
poor	20(21)	10(22)		11(14)	9(8)	
Life satisfaction			0.044			0.156
satisfied	66(69)	79(176)		73(94)	83(76)	
moderately satisfied	32(34)	20(45)		26(33)	17(16)	
dissatisfied	2(2)	1(3)		2(2)	0	
BDI[1)]			0.311			0.166
no depression	76(78)	83(173)		88(103)	94(77)	
depressive symptoms	22(21)	17(35)		12(14)	6(5)	
CVD[2)]			0.118			0.116
no	47(51)	58(130)		56(72)	66 (61)	
yes	51(54)	42 (95)		44 (57)	34 (31)	

[1)] BDI = Beck's Depression Inventory; cut point ≥10. [2)] CVD = Cardiovascular diseases.

Table 15. Means/medians and standard deviation (SD) / interquartile range of health related quality of life dimensions of men with alopecia and no alopecia.

Scale	Alopecia (n=129)		No alopecia (n=92)		p
	Mean	SD	Mean	SD	
Physical functioning	84.8	15.5	88.0	13.5	0.049
Role limitations due to emotional problems	85.0	28.5	89.3	21.5	0.310
Energy/fatigue	73.5	17.9	76.1	16.1	0.268
Emotional well-being	80.9	16.4	82.5	14.5	0.491
Social functioning	88.1	18.5	93.5	13.0	0.017
Pain	76.6	23.4	77.0	22.0	0.895
General health	58.5	16.0	62.2	18.2	0.121
Role limitations due to physical health	76.3*	75-100**	78.9*	75-100**	0.971

*Median **25^{th} - 75^{th} percentiles

Table 16. Odds ratios for impaired quality of life among men aged 63 years. Odds ratios for risk of comparison to the lowest quintiles in the dimensions of quality of life.

Variable	Functioning	
	Physical	
BDI[1)]	14.3	(1.95-105.2)
Alopecia[2)]	1.1	(0.32-3.66)
Marital status	2.8	(0.14-56.5)
Self-perceived health	0.07	(0.01-0.37)
	Social	
BDI[1)]	6.4	(1.16-35.9)
Alopecia[2)]	1.2	(0.36-3.71)
Marital status	2.0	(0.16-25.6)
Self-perceived health	0.25	(0.11-0.56)

[1)] BDI = Beck's Depression Inventory; depressive symptoms ≥10.

[2)] Alopecia; classes III-VII

Multivariate logistic regression analyses were performed to analyze the independent association of alopecia with the HRQOL dimensions for both genders. Two different adjusted models are presented for women in Table 4 in Article VI. In model A, glucose status is presented as IGR, and in model B, glucose metabolism is described with QUICKI. Of the background characteristics, marital status and education (Table 17) and depressive symptoms are known to be associated with HRQOL, so they were included in the models as confounding factors. In both models, alopecia was independently associated with

role limitations due to the physical health dimension of HRQOL. In physical functioning and general health, no such association between alopecia and HRQOL was seen. In addition, depressive symptoms were independently associated with role limitations due to physical health and general health. The model for men is presented in Table 16, and no such association between alopecia and lower HRQOL in the dimensions of physicial functioning or social functioning were observed.

6 Discussion

Alopecia is an unpleasant phenomenon for most of the affected men and women. In addition to individual concern, the recent data suggest that alopecia is linked to an increased CVD risk (Table 3). However, the exact nature of the association between alopecia and CVD is still unclear. This study investigated the possible mechanisms behind the increased prevalence of CVD among balding men and also addressed whether balding women have the same tendency for CVD than men. The novel finding of this study was an association between low-grade inflammation and early onset alopecia (< 35 years), which may be one pathophysiological mechanism in the background of increased risk of CVD among men with alopecia.

6.1 Study population

This study utilized three population-based samples of Finnish people. The National Finrisk 2002 survey consisted of men and the Oulu studies of both men and women. The target populations were homogenous, stable and representative samples of Finnish men and women, obtained from the National Population Registry of Finland.

The Finrisk survey is carried out every five years using independent, random and representative population samples from different parts of Finland. The 61% participation rate can be considered acceptable. Participation rates in the Oulu studies were 74% in the Oulu 45-study and 71% in the Oulu 35 study, which are representative population samples of two age groups, giving the study the relevance of an epidemiological survey (Goudy 1976 in Lydeard 1996).

The participation rate cannot be considered completely unbiased since non-participants often differ from participants (Criqui *et al.*1978, Streiner *et al.* 1989, p 36-37, van Loon *et al.* 2003, Tolonen *et al.* 2005); the associations might thus be underestimated due to of missing data from non-participants. In the present study, there is no specific knowledge about the reasons for non-participation. In the Finrisk 2002 survey, generally, younger men are predominantly healthier than older men. In addition, due to the sampling method, younger age groups were relatively overrepresented in the sample, but not in the participation, compared with the other age groups in Finland.

6.2 Study design

The purpose of the study was to investigate associations between alopecia and previously known cardiovascular risk factors and related diseases. However, cross-sectional studies do not provide evidence for causal relationships of alopecia with cardiovascular risk factors and CVD; the findings of the cross-sectional studies allowed only description of the factors associated with alopecia.

In the Finrisk 2002 study, a large sample size allowed the stratification of data by age. This is important when assessing whether the present findings are representative of the entire Finnish male population. Due to the study design, the moderate participation rate (61%) allows fairly good generalization of the results to the Finnish population.

The Oulu studies are comparable with each other because the same validated methods were used in both of the studies. Both studies are cross-sectional in respect of alopecia, and the participation rates allow generalization of the results to Finnish middle-aged men as well as elderly men and women.

6.3 Measurements

Anthropometric measurement

In study IV, WHR was selected as the measure of abdominal obesity instead of waist circumference because WHR is a useful tool for defining abdominal obesity in research (Folsom *et al.* 2000). In addition, according to previous Finnish studies, WHR seems to be a better predictor for acute coronary events and progression of carotid atherosclerosis than BMI (Lakka *et al.* 2001, Lakka *et al.* 2002). Waist circumference and WHR are better tools for assessing intra-abdominal obesity and total fat than BMI (Ashwell *et al.* 1985, Rankinen *et al.* 1999, Despres 2001). Although waist circumference appears particularly useful in clinical settings as an easily measured variable (Despres 2001), it also correlates to the same extent with body height, which is why tall persons may be falsely categorized into the abdominally obese to group (Seidell *et al.* 2001).

Blood pressure

Validation of BP is difficult because the levels of BP fluctuate a lot and are unstable at individual level (Parati *et al.* 2005). BP was measured in standardized

conditions with standard methods by a trained nurse or physician. To minimize possible errors the mean values of BP measurements were used. The diagnosis of hypertension was based on the information about self-reported and measured elevated BP and the use of antihypertensive drugs.

Blood samples

For blood samples participants were advised to fast for at least four hours (Articles I and IV) and ten hours (overnight) (Articles II-III, V-VI) before the visit at the clinic. It may be debated whether a four-hour fasting period might be too short for reliable measurements of certain risk factors such as lipids from blood samples (Article IV).

Health-related quality of life

RAND-36, a well-documented questionnaire (Hayes *et al.* 1993) designed to measure several aspects of well-being, was used to assess quality of life in the study population. In this analysis, the study population was divided further into different groups according to the degree of alopecia. It can be speculated whether a general HRQOL instrument is appropriate for measuring HRQOL in this population, as the effects may be more disease-specific. However, the general QOL scale was preferred because of the population-based study design.

The scaling properties and validity of the Finnish RAND-36 have been tested among randomly selected Finns (3 000 subjects aged 18-79 years and 400 subjects aged 65-79 years) (Aalto *et al.* 1999). The results were comparable with the results obtained for RAND-36 in international studies, but in the Finnish study, the general health scale correlated more strongly with physical health. RAND-36 has well-documented reliability and validity and is useful in describing HRQOL in epidemiological studies on unselected populations (Hemingway *et al.* 1997).

Assessment of alopecia

There has been a lot of discussion on the valid assessment of alopecia (Rebora 2001, Gutherson & Scheidegger 2005). The degree of alopecia was assessed by using a standard classification scale (Norwood) by a trained nurse in all the other studies except Study III in which self-reported data were used. However, the self-

assessment of alopecia degree using the Hamilton-Norwood classification scale has been validated in earlier studies with a good reliability (Lesco *et al.* 1993, Ellis *et al.* 1998, Taylor *et al.* 2004, Can & Sinclair 2005). The validation of the Hamilton-Norwood classification scale in this study is in line with these earlier validations. In addition, the validation in this study was performed on the total study population as opposed to studies by Lesco *et al.* (1993) and Ellis *et al.* (1998), in which the validation was only performed on to sub-samples of the study population.

The question "the age at which most abundant hair loss had started, if there had been significant hair loss" is not validated. It may be that the subjects recalled an episode of telogen effluvium as the moment when which the "hair loss" started. However, a population-based cross-sectional study in which check-up was done by nurses prevents diagnosing possible other reasons behind significant alopecia. Naturally, the possibility for e.g. an episode of telogen effluvium might also exist. It was not possible to determine the exact diagnosis for alopecia as only the severity of alopecia was measured based on the Hamilton-Norwood classification scale. Because of this, instead of "hair loss" the term "alopecia" was used, which at epidemiological level generally means AGA as more than 90% of alopecia is due to AGA (Norwood 1975, Rebora 2001, Trueb 2002).

Maternal heredity of alopecia may be underestimated because female-pattern alopecia is different and difficult to recognize from male-pattern alopecia. Besides, it is possible that a recall bias exists in reporting the age of the most intensive hair loss among older age groups. Among younger men, this should not be a significant factor within the relatively narrow age band (25-34 years).

For women, the classification of alopecia according to Ludwig's scale has been widely accepted.

6.4 Results

6.4.1 Prevalence and heredity of alopecia among Finnish population (Articles I-IV, VI)

This is the first study (Article I) based on a large unselected population to report the prevalence of alopecia among the general Finnish male population (47%). The prevalence of alopecia in the Oulu 45 study (55%) and the Oulu 35 alopecia sub-study (58%) was in accordance with the age-specific rates of alopecia (60% in

those aged 55-64 years) in the Finrisk 2002 survey (Articles II, III and I, respectively).

The prevalence of significant alopecia in this study was comparable to that found for other Caucasian male populations (Ford *et al.* 1996, Lotufo *et al.* 2000, Ellis *et al.* 2000) and not very different from the figures reported elsewhere for young men (Lesco *et al.* 1993, Rhodes *et al.* 1998, Muro-Mercon *et al.* 2000). The prevalence rate of alopecia among women was comparable with earlier studies in Caucasian races (Norwood 2001). The increase in the prevalence of alopecia with age has been reported earlier (Hamilton 1951, Norwood 1975, Rhodes *et al.* 1998, Paik *et al.* 2001) and is consistent with the observations of this study.

The finding that in nearly one half of Finnish men, the most abundant hair loss occurs before the age of 35 years, with young men reporting such hair loss much more often than older men, is new in Caucasian races. One survey in four countries (Italy, Germany, UK, France) reported earlier that men aged 18-40 years noticed their hair loss at the age of 23.9 years (Budd *et al.* 2000). This age trend could be accounted for by a cohort effect of early hair loss increasing from younger to older generations, but a possibility of memory bias exists. Such bias is suggested by the fact that the men under 60 years of age consistently reported that their hair loss had started one decade earlier.

Comparison of the prevalence rates of alopecia across different studies is not straightforward. Some studies present prevalence rates based on self-reported status (Muro-Mercon *et al.* 2000, Lotufo *et al.* 2000, Ellis *et al.* 2000, Budd *et al.* 2000) while others use different methods (modified) of alopecia classification (Trevisan *et al.* 1993, Schnohr *et al.* 1995, Herrera *et al.* 1995, Ford *et al.* 1996, Lotufo *et al.* 2000, Severi *et al.* 2003). In addition, there are ethnic differences between study populations (Tang *et al.* 2000, Paik *et al.* 2001) or differences in age classification (Schnohr *et al.* 1995, Rhodes *et al.* 1998, DeMuro-Mercon *et al.* 2000), which do not allow any direct comparisons. The current study is one of the few studies based on a representative population (Ford *et al.* 1996, Budd *et al.* 2000, Ellis *et al.* 2001).

6.4.2 Association of alopecia with cardiovascular diseases (Articles I- IV, VI)

Based on the results of the current study, alopecia is associated with CVD, especially with hypertension and CAD, also showing a significantly increasing

trend after the age of fifty (Article I). Epidemiologic studies reporting this kind of association are rare. Earlier, men with alopecia have been reported to suffer from higher BP (Trevisan *et al.* 1993, Lotufo *et al.* 2000, Matilainen *et al*. 2000) and severe CAD (Lesco *et al.* 1993, Matilainen *et al.* 2001), observations which are in accordance with this study.

Articles II and III show limited results between alopecia and vascular diseases among 55- and 63-year-old men, which may be due to lack of power (small sample size). Small sample size can lead to greater probability of type II error, where the null hypothesis is not rejected although it is actually false (Hennekens & Buring 1987, p 256). In addition, the risk of alopecia increases overall with age, and regardless of diseases or medication; there is also a tendency to hair loss in the healthy population.

In the future, the focus of interest in the pathology of alopecia may be in the field of the mutation of the AR gene which has been found in the hair follicle of the scalp in a subject with alopecia (Schweikert 1974, Ellis 1998, Ellis *et al.* 2001b, Hillmer *et al.* 2005, Levy-Nissenbaum *et al.* 2005). The same mutation of the AR gene has been reported to associate with early severe CAD (Alevizaki *et al.* 2003). It may be that especially early onset alopecia is associated with CVD (Rebora 2001). However, developing CVD takes a longer period of time, for and it can be supposed that the men who have significant alopecia at the age of 50 have had thinning hair for some years or even one or two decades earlier (Whiting 1993). Prospective studies among younger men with progressive alopecia are needed to verify these results.

6.4.3 Association of alopecia with insulin resistance (Articles II-III)

This is the first population-based study in which low insulin sensitivity measured among 55- year-old men was observed to be associated with alopecia. As there seems to be a connection between alopecia and low insulin sensitivity, it is possible that especially men with alopecia might have a higher risk of IR-linked diseases (Article III). Among elderly men, association between alopecia and hyperinsulinemia (marker of IR) was rare (Article II), which could be explained by small sample size and the relationship between aging and alopecia.

It has been suggested that IR is the common denominator for CVD and atherosclerosis. The mechanism underlying the association between alopecia and cardiovascular risk factors has remained unknown, but the suggested explanations

include endothelial dysfunction and associated IR (Pinkney *et al.* 1997) followed by decreased microcirculation and local tissue hypoxia in the area of hair follicles in the scalp (Goldman *et al.* 1996, Klemp 1989).

6.4.4 Association of inflammation with alopecia, metabolic syndrome and its components (Articles IV-V)

Alopecia is known to be associated with CAD (Table 3, page 26). In addition, inflammation, measured by hs-CRP, is known to be one of the predictors of future CVD (Ridker *et al.* 2003, Ridker & Morrow 2003). With respect to the underlying inflammatory state in the vascular system overall and locally in the area of hair loss suffering scalp, the present study assessed (Article IV) whether young men with and without early-onset alopecia differed regarding the association their alopecia and hs-CRP concentrations. In addition, it was studied if the findings differ from the alopecia sub-study at population level (Article V) with respect to low-grade inflammation and components of MetS.

The increase of WHR with increasing hs-CRP in the men with alopecia but not in other men was a novel finding. Further, central obesity was more pronounced among men reporting the most intensive hair loss after the age of 25 years than in those who reported such hair loss before that age. This was unexpected, since a genetic predisposition to alopecia would presuppose a more pronounced pattern in men with alopecia emerging at an early age. A recall bias arising from a young man's dissatisfaction with his body image is possible. It can also be hypothesized that young men, when becoming aware of their hair loss, change their lifestyles, e.g. by increasing physical exercise and adopting a healthier diet.

An elevated concentration of hs-CRP has been shown to associate with obesity (Yudkin *et al.* 1999). The present study confirms this association also among Finnish middle-aged population (Article V). Particularly, abdominal deposition of fat is thought to be an important factor contributing to an inflammatory metabolic state (Ridker *et al.* 2003), elevated BP (Yudkin *et al.* 1999), hyperglycemia (Mendall *et al.* 1996), abnormal lipid profiles (Mendall *et al.* 1996, Yudkin *et al.* 1999) and IR (McLaughlin *et al.* 2002).

IR is one of the potential mechanisms by which obesity might lead to MetS and ensuing CVD, since for instance the proinflammatory cytokines produced by adipose tissue are suggested to be the underlying "common soil" for both IR and the vascular abnormalities, i.e. endothelial dysfunction and increased risk of

thrombosis, associated with it (Yudkin *et al.* 1999, Caballero 2003). The observed link between the indicators of obesity and low-grade inflammation especially in young men with grade III or greater alopecia could be attributed to proinflammatory cytokines (e.g., IL-1, TNF-α), which have been found in both the arterial wall (Willerson & Ridker 2004) and the hair follicle (Jaworsky *et al.* 1992, Whiting 1993, Mahe *et al.* 2003). Based on this study, it can be suggested that among men with alopecia, the ”microinflammation” in the hair follicle causing alopecia might be a local manifestation of a systemic inflammation predicting MetS and, possibly, CVD.

6.4.5 Alopecia and health-related quality of life (Article VI)

According to this study, an association between HRQOL and alopecia was stronger among women than among men with alopecia. These findings are not quite consisted with previous studies (Table 4). The result of this study could be explained by the suggestion that alopecia is not such a tragic event at the age of 63 years.

The results of the previous studies concerning the QOL of alopecia subjects are somewhat difficult to compare with the current results because of methodological and other differences, such as age, limited criteria of QOL and the selection of study populations (van der Donk *et al.* 1994, Schmidt *et al.* 2001 & 2003). The earlier results are contradictory to the results of this study, which might be explained by population differences and differences in evaluating of HRQOL. Moreover, in Article VI, the women were not seeking treatment for alopecia and it seems that although alopecia is a stressful event especially for women, no differences in emotional aspects of RAND were found in this population.

Besides emotional problems related to alopecia (Cash *et al.* 1993, Maffei *et al.* 1994, van der Donk *et al.* 1994), women with alopecia may have physical problems and chronic diseases, which need to be properly evaluated and treated. According to the results of this study, it is especially the physical rather than the mental health dimensions that affect the HRQOL of women with alopecia. However, depressive symptoms overall seemed to be associated with low HRQOL in both men and women, a result that is in accordance with some earlier observations studies (Hays 1993, Saarijärvi *et al.* 2002). These findings might be explained by the similarities in the measurement of the psychological dimensions of HRQOL and BDI.

6.5 Strengths and limitations

Strengths of this study include the large and representative population samples of a national survey and two age cohorts in Finland. In the Finrisk 2002 alopecia sub-study, the measurements were validated by using the same group of nurses in every study as well as standard methods recommended for epidemiological studies (WHO 1988, Tolonen *et al.* 2002). In addition, the nurses practiced all the measurements thoroughly during a two-week training phase. In the Oulu studies, the same study nurses performed all measurements after training to reduce internal variability (the inter-rater variation was low).

All analyses were implemented systemically and consistently with recommended methods in all three study populations. The methods used are also appropriate for cross-sectional analyses. Furthermore, the normality of the dependent variables was tested in all statistical analyses. All laboratory determinations were performed in a laboratory with a standardized quality control system.

The cross-sectional study design is overall a limitation, and prospective studies are needed in the future. The participation rate was acceptable in the Oulu studies but only moderate in the Finrisk 2002 survey. Another limitation of the study was that the questionnaire data were self-reported, which could attribute to recall bias. To minimize this bias, trained nurses provided the participants advice on filling out the questionnaires.

The laboratory determinations were not performed in the same laboratory and the results are thus not comparable. In the Finrisk 2002 survey, fasting blood glucose and insulin were not measured, but this does not invalidate the conclusions of this study. Also, there were no data of hormonal levels available at the time of analyzing the data, i.e. the levels of testosterone and serum hormone-binding globulin, which also represent risk factors for CVD (Laaksonen *et al.* 2004, Kapoor *et al.* 2005). A minor limitation is the missing information on microalbuminuria (Finrisk 2002, Oulu 45 study). However, microalbuminuria among non-diabetic subjects is uncommon (Zavaroni *et al.* 1996) and its association with other components of MetS is not consistent (Jager 1998, Mykkänen *et al.* 1998). A limitation in the Oulu 35 study was that the alopecia classification was made in the second phase so that causal relationships in the Oulu 35 follow-up study could not be studied. The original study design of the Oulu 35 study may have been improved by including other parameters in the

baseline, such as waist circumference and, as the most important parameter, alopecia degree.

In women, the age of menopause was not recorded. It can be assumed that the entire study population of the Oulu 35 follow-up study was at menopause during the data collection. The use of HRT is limited at this age among Finnish women, and specific drug information concerning hormonal therapy was not used.

7 Conclusions

The conclusions to the specific study questions are:

1. In Finnish men aged 25 to 74 years, there is a high prevalence of alopecia grade III-VII (47%), which increases with age. Alopecia seems to be strongly connected with paternal heredity. In addition, a high prevalence of early-onset alopecia (> 35 years, 42%) was found. Among women aged 63 years, female pattern alopecia is relatively common (30%).
2. Alopecia was associated with CVD in the general male population. Among 63-year-old women, alopecia was associated with impaired glucose regulation.
3. Alopecia was associated with visceral obesity among young men and with IR among middle-aged men. Among women aged 63 years, alopecia was associated with IR and abdominal obesity.
4. Low-grade inflammation was associated with alopecia in young men with central obesity.
5. Low-grade inflammation was associated with BMI and IR of the components of MetS among 55-year-old Finnish subjects.
6. Of the HRQOL-related factors, IR and IGR in women and depressive symptoms in both men and women had a marked association with impaired quality of life. The odds ratio of alopecia itself was 2.2-2.5-fold for being in the lowest quintiles of the role limitation due to the physical health dimension of HRQOL in women. No such independent association was found in men.

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