Contents

1 Introduction

Psoriasis is a common skin disease frequently seen by general practitioners and dermatologists. It is associated with psychological and physical burden, and chronic inflammation is considered the underlying pathological mechanism (1).

There is a growing range of literature linking psoriasis to other diseases and conditions, so-called comorbidities, with psoriasis arthritis being the most common comorbidity, seen in up to 30% of psoriasis patients (2). Since the 1970s, studies of the association between psoriasis and cardiovascular diseases and their risk factors have been conducted (3-8). Supporting these findings, widespread inflammation in the large arteries of psoriasis patients has been described (9, 10). Based on this knowledge, it has been proposed that patients with psoriasis, and especially those with severe forms, may require more aggressive control of cardiovascular risk factors than the general population (11-13), but this is still debated (14).

Not all studies have concluded that the association to cardiovascular diseases exists, and this applies especially to population-based studies (15-18). Furthermore, most prospective studies carried out so far have studied psoriasis as a risk factor and have reported that psoriasis patients are at increased risk of developing cardiovascular diseases and corresponding risk factors. Based on these findings, a concept named the "psoriatic march" has been proposed, where the systemic inflammation in psoriasis is thought to lead to insulin resistance, endothelial dysfunction and subsequently atherosclerosis and myocardial infarction (19). Studies showing shared pathogenic mechanisms between psoriasis and cardiovascular inflammation support this theory (20). However, while some studies propose that inflammatory elements from the psoriatic plaque in the skin migrate to the circulation, leading to a proatherosclerotic state (20, 21), others question the extent to which this increased risk of cardiovascular disease is directly attributable to psoriasis (13).

It is now well recognized that inflammation is a central mechanism in both psoriasis and cardiovascular diseases. However, the directionality of this association has not been fully elucidated, and we therefore wanted to assess if these cardiovascular conditions could increase the risk of developing psoriasis. This is based on the hypothesis that the

inflammation in these conditions could lead to psoriasis development, or alternatively, that a common underlying factor links all these conditions together.

2 Background

2.1 Psoriasis

2.1.1 Definition

Psoriasis affects equal numbers of women and men with onset at any age, but with one peak around 18-39 years of age and the second around 50-69 years of age (22). The disease is associated with both a physical and a psychological burden, and patients report symptoms such as pain, itch and bleeding (1). There is also a strong genetic component, with an estimated heritability in European populations of 50-90% (2).

Psoriasis is divided into five different types, the most common form being psoriasis vulgaris, with sharply demarcated plaques covered by silvery scales most often localized to the extensor surfaces and the scalp (Figure 1).

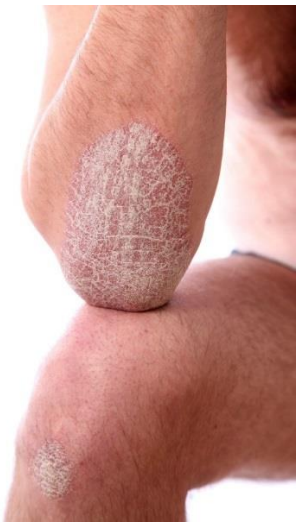

Figure 1. Psoriasis vulgaris at typically predilection sites
(Shutterstock. Reprinted by permission)

Other types include guttate psoriasis characterized by scaly teardrop-shaped spots; inverse psoriasis found in the skinfolds; pustular psoriasis either localized to the palms and soles (named pustulosis palmoplantaris) or generalized to the whole body surface, and finally erythrodermic psoriasis (1), which is a severe and potentially life-threatening form (2). Pustulosis palmoplantaris is sometimes regarded as a distinct disease entity different from psoriasis, but this is still under debate (23, 24).

The nails are affected in about 50% of psoriasis patients, with pitting, discolouration and thickening of the nail plates. There are no established diagnostic criteria for psoriasis, and the diagnosis is based on clinical examination with a recognition of clinical features consisting of distribution, configuration and morphology of skin changes (25). In addition, the patient's family history and potential trigger factors should be included in the medical history (1).

2.1.2 Severity assessment

Psoriasis is usually divided into categories of mild versus moderate/severe. To define the severity, different scoring instruments have been developed, where the Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA) are the most commonly used in Europe (26). The PASI score quantifies erythema, infiltration or thickness, scaling and the extent of lesions on the skin (27). BSA describes the percentage of the patient's skin affected by psoriasis, where the size of the patient's hand can be used as a measure, and one "handprint" reflects approximately 1% of their total BSA (28). In the evaluation of psoriasis severity, the patient's quality of life should also be assessed. In this respect, the Dermatology Life Quality Index (DLQI) is a validated dermatology-specific instrument assessing the burden of illness and life quality (29, 30). These scoring tools should be used both to measure disease severity and to monitor treatment response.

According to a European consensus (26), mild psoriasis is defined by BSA ≤10 and PASI ≤10 and DLQI ≤10, whereas moderate to severe psoriasis is defined by BSA >10 and PASI >10 and DLQI >10. Mild psoriasis is usually controlled by topical therapy, whereas moderate to severe psoriasis requires systemic therapy. In addition, UV-treatment is used in refractory cases of mild psoriasis and in moderate to severe cases as the only treatment or as a supplement to systemic treatment. However, some aspects of psoriasis can result in a DLQI >10 even if the severity of skin involvement is mild. In these cases, psoriasis can be considered moderate to severe and treatment should be chosen according to this (26).

2.1.3 Prevalence and incidence

There is considerable variation in the estimated prevalence of psoriasis both within and between countries (22, 31). The lowest prevalence is found in populations close to the equator, like Egypt, Tanzania, Sri Lanka and Taiwan, while higher prevalence is found both in Australia and Europe (22). Consistent with this, a study from USA found a prevalence of 3.2% among adults aged 20 years and older. This study also found the highest prevalence among Caucasians, with lower numbers for African Americans and Hispanics (32). In Norway, a self-reported prevalence of 5.8% was found in the third survey of The Nord-Trøndelag Health Study (HUNT3) (33), and as high as 11.4% in the Tromsø Study (34). Additionally, studies suggest that the incidence is rising; in a cohort study from USA the registered annual incidence rate of psoriasis almost doubled from 50.8 to 100.5 per 100 000 in the period between the 1970s and 2000 (35).

Different methodologies used in different studies make it difficult to draw conclusions on whether the reported geographical differences represent true differences. The sampling techniques include questionnaires, clinical examination and registry data, and the case definitions used are based on self-report, physician or dermatologist's diagnosis. There are also differences in the definition of prevalence with use of point prevalence, period prevalence and lifetime prevalence. In addition, some study populations have included children, while others have only studied adults (22, 31). The lack of diagnostic criteria for psoriasis will also be a challenge in such studies. Further, the fact that many psoriasis patients do not seek medical care, or do not have access to a dermatologist, probably leaves several undiagnosed (36).

Even if some of the differences in prevalence estimates could be due to methodological differences, the prevalence studies are considered supportive of the theory that a combination of genetic and environmental factors contributes to the development of psoriasis (37).

2.1.4 Pathophysiology

Psoriasis is influenced by genetic factors, but also by environmental triggers that can induce or exacerbate psoriasis. These triggers could be trauma, infections or medication

that initiate release of self-nucleotides in genetically susceptible individuals (2, 38). The pathogenesis is complex, where T-helper (Th)1 and Th17 cells are found to be key players (39). Dendritic cells are activated and produce interleukin (IL)-23, which regulates the development and maintenance of the Th-17 population in addition to IL-12, which induces Th1. Th1 cytokines such as γ-interferon (IFN- γ), tumour necrosis factor-α (TNF- α) and IL-12 are all elevated in psoriatic lesions. Th-17 produces IL-17 and IL-22, and all these cytokines activate keratinocytes, promote epidermal hyperplasia and recruit inflammatory cells (Figure 2).

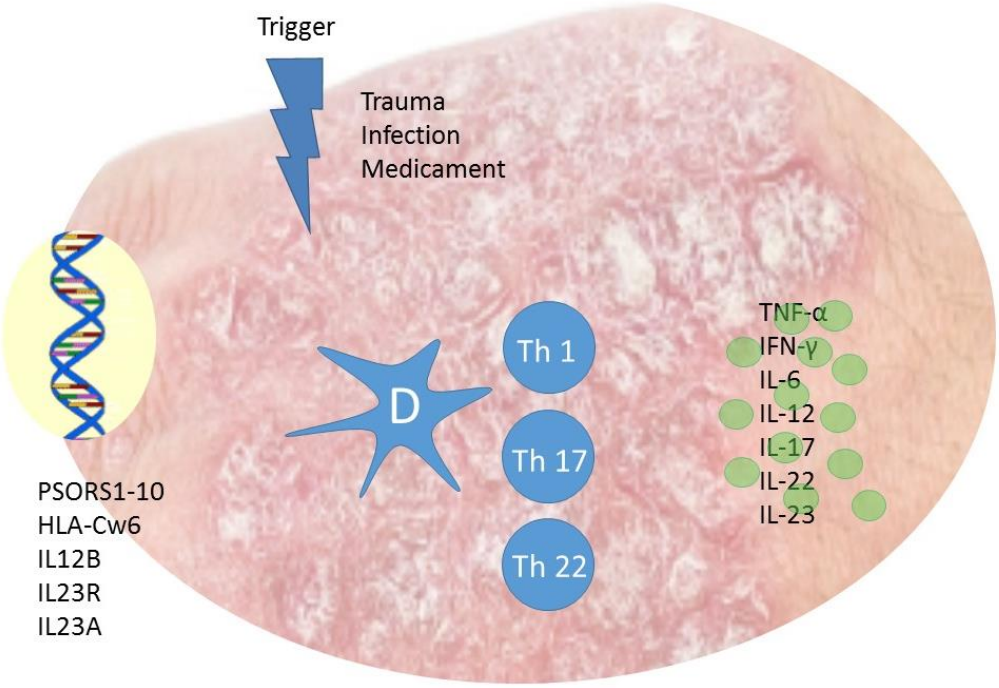

Figure 2. Simplified illustration of psoriasis pathogenesis. Genetic factors such as PSORS1-10 and environmental triggers activate dendritic cells (D) and T-helper cells (Th) which produce cytokines such as tumour necrosis (TNF)-α, interferon (IFN)-γ and a broad range of interleukines (IL).

TNF-α plays a central role in the pathogenesis by activating a signal pathway which affects proliferation and anti-apoptotic effects of lymphocytes and keratinocytes in

addition to formation of microabcesses (39). These mechanisms lead to the clinical manifestations of psoriasis, the scales being a result of hyperproliferation of the epidermis with premature maturation of keratinocytes; the redness is due to an increased number of capillaries near the skin surface and the thickness of the lesion is a combination of a dermal inflammatory infiltrate and a thickened epidermis (40).

2.2 Chronic inflammation

Inflammation is the body's response to injuries and infections. It is usually short term, leads to tissue repair, and is characterized by swelling, redness, pain and increased temperature. However, a more prolonged inflammation, where few of the classic aspects of inflammation are observed, is referred to as low-grade or chronic inflammation (41). Chronic inflammation can lead to conditions such as type 2 diabetes, atherosclerosis, non-alcoholic fatty liver disease and neurodegenerative diseases, and hence, inflammation could be a 'friend or foe' (42-44).

Chronic inflammation is well established as an underlying mechanism of insulin resistance and type 2 diabetes, with pancreatic cell death and changes in the liver and in adipose tissue (45). Low-grade chronic inflammation is also an underlying condition in atherosclerosis (42). There has been some dispute about whether inflammation is a risk factor or merely a marker of the disease process in atherosclerosis (46), but in a recent extensive study, inflammation as the key driving factor is considered finally proven (47, 48). Non-alcoholic fatty liver disease is the most common liver disorder in the world and is caused by accumulation of triglycerides in the liver followed by inflammation, leading to a state of chronic hepatic inflammation (49, 50). Even in Alzheimer's disease and age-related brain degeneration, inflammation plays a key role, with interaction between the immune system and the nervous system (51).

Obesity is associated with a chronic inflammatory state and is often considered the main source of the chronic inflammation seen in these diseases (42, 51-53). In rheumatoid arthritis, there has been some controversy about whether obesity is an aggravating factor (54), but it seems that obesity has an unfavourable impact on disease activity (55), and could be a risk factor for developing this disease as well (56). In genetically predisposed

subjects, multiple insults like smoking, insulin resistance, hormones from adipose tissue, nutritional factors and microbiota act together to induce these diseases (45, 49, 57, 58).

2.3 Obesity

Obesity is a growing health problem and is associated with increased risk of diabetes, myocardial infarction, hypertension, stroke, some forms of cancer, sleep apnoea, gallstone disease, osteoarthritis and neurodegenerative diseases (59).

Obesity is often defined by body mass index (BMI), where a BMI <18.5 kg/m^2 is classified as underweight, 18.5-24.9 kg/m^2 as normal weight, 25-29.9 kg/m^2 as overweight, and a BMI ≥30.0 kg/m^2 is classified as obesity. BMI is considered the most useful measure to estimate the prevalence of obesity on a population level (60). However, BMI does not distinguish between weight associated with muscle mass or fat mass, and it does not reflect fat mass in intra-abdominal depots, which are most strongly related to increased risk of obesity-related illnesses. Waist circumference and waist-hip ratio are therefore considered better predictors of cardiovascular disease risk, based on the knowledge that increased visceral adipose tissue is associated with metabolic abnormalities such as decreased glucose tolerance, reduced insulin sensitivity and adverse lipid profiles (61). There are, however, differences in risk associated with waist circumference, both between sexes and between populations. Sex-specific cut-off points for different populations have therefore been suggested. Table 1 displays the sex-specific waist circumference and risk of metabolic complications associated with obesity in Caucasians, but a combined use of BMI and abdominal adiposity measures has also been recommended (60, 61).

In 2013, the American Medical Association recognized obesity as a disease (62), although the use of a disease label is still debated (63). The World Obesity Federation argues that obesity is a disease process in the same way as hypercholesterolemia and hypertension, and states that obesity should be considered a chronic relapsing disease process (59).

Table 1. Waist circumference and risk of metabolic complications in Caucasians (60).

Risk of metabolic complications	**Waist circumference (cm)**	
	Men	**Women**
Increased	≥94	≥80
Substantially increased	≥102	≥88

The prevalence of overweight and obesity is increasing worldwide, and some authors describe it as a pandemic (64). According to a report from the Global Burden of Disease Study 2013, the proportion of adults with overweight or obesity had increased from 29% to 37% in men and from 30% to 38% in women in the period between 1980 and 2013. An increase was also seen in children and adolescents; in 2013 24% of boys and 23% of girls were overweight or obese (65). The numbers are even higher in USA where a recent survey among adults showed that 35% of all men were obese and 6% were morbidly obese (BMI ≥40), whereas 40% of all women were obese and 10% were morbidly obese (66). An increase has also been reported in Norway; in the Tromsø Study, the prevalence of obesity increased from 10% to 21% in men and from 12% to 19% in women from 1994 to 2008 (67). Also in the HUNT Study, there has been an increase in mean BMI from HUNT1 to HUNT3 (68).

There is evidence that the obesity epidemic has been levelling off in the period between 1999 and 2010, especially in children and adolescents. The tendency of levelling off is also seen among children in Norway, where the Child Growth Study shows that the proportion of 8- to 9-year-olds with overweight or obesity has stabilized from 2008 to 2015 (69). However, the prevalence was still increasing among adults in Asia (70).

Suggested explanations for the obesity epidemic have been a lifestyle favouring sedentary behaviour and easy access to inexpensive energy-dense food (70).

2.4 Metabolic syndrome

The metabolic syndrome is a constellation of risk factors for diabetes and cardiovascular diseases, and over the years, several different definitions have been proposed. WHO

proposed the first definition in 1998, where insulin resistance was considered the major underlying risk factor and a prerequisite for the definition (71). The National Cholesterol Education Program Adult Treatment Panel III (ATP III) published their criteria in 2001, which did not require insulin resistance per se. Instead, the basis for the diagnosis was the presence of three out of five factors: abdominal obesity, elevated triglyceride, reduced high-density lipoprotein cholesterol (HDL), elevated blood pressure and elevated fasting glucose (72). Later, the International Diabetes Federation (IDF) made abdominal obesity necessary as one of five factors for the diagnosis in their definition (73), before an agreement between several major organizations was finally made in 2009 with the presence of three out of five risk factors constituting the diagnosis of metabolic syndrome (71) (Table 2).

Table 2. Criteria for the diagnosis of the metabolic syndrome (71).

Measure	**Categorical cut points**
Waist circumference	Population- and country-specific definitions
Triglycerides	≥1.7 mmol/L (or drug treatment for elevated triglycerides)
HDL	<1.0 mmol/L in men; <1.3 mmol/L in women (or drug treatment for reduced HDL)
Blood pressure	Systolic ≥130 and/or diastolic ≥85 mmHg (or antihypertensive drug treatment or history of hypertension)
Fasting glucose	≥5.6 mmol/L (or drug treatment of elevated glucose)

While the ATP III criteria used ≥102 cm in men and ≥88 cm in women as the cut-off for waist circumference, the IDF recommended cut-off values for Europeans of ≥94 cm in men and ≥80 cm in women. Since the risk associated with waist circumference is different across populations, recommended thresholds differ around the world (71).

Although metabolic syndrome often is referred to as one single entity, it should be underlined that it is a syndrome, not a disease. There is no single pathogenesis for metabolic syndrome, and it might be a constellation of factors that are linked together by a common underlying mechanism (74).

2.5 Psoriasis and associated cardiovascular diseases and risk factors

2.5.1 Psoriasis and cardiovascular diseases

Several studies report positive associations between psoriasis and coronary artery disease (75-77), and between psoriasis and myocardial infarction (6, 77-79). As many studies have failed to adjust for traditional risk factors such as smoking and obesity, there is uncertainty about whether cardiovascular disease risk is directly attributable to psoriasis (13, 78). The positive association seems to weaken or disappear when restricting to population-based studies (15-17), and conflicting results are found even within the same cohorts (6, 18, 80-82).

Shared pathogenic mechanisms between psoriasis and atherosclerosis are found, with IFN-γ and TNF-α being the dominant pro-inflammatory signals linking the two conditions together (83). Neutrophils play a role in the development of atherosclerosis by contributing to endothelial dysfunction, monocyte recruitment and foam cell formation. In addition, neutrophils have been shown to play an important role in psoriasis pathogenesis by releasing IL-17 (84). Human leukocyte antigen (HLA) related genes associated with early and severe psoriasis are associated with an increased amount of atherosclerotic plaques, but it is not clear whether these genes play a direct role in atherogenesis in these patients (85). However, even if some studies have found overlapping genetic variants with psoriasis and coronary artery disease (86), the majority of the studies have shown no such association (87, 88). Treatment of psoriasis has improved non-calcified coronary plaque (89) and vascular inflammation (90), supporting the hypothesis of shared pathogenic mechanisms, but a recent trial using a TNF-α antagonist showed no reduction in cardiovascular inflammation in psoriasis patients (91).

2.5.2 Psoriasis and metabolic syndrome

Individuals with metabolic syndrome have about twice the risk of developing cardiovascular disease over the next five to ten years compared to individuals without the syndrome as well as about a five-fold increased risk of type 2 diabetes mellitus (71). The prevalence of metabolic syndrome is estimated at 20-25% in the adult population

worldwide (92), and several studies suggest that psoriasis patients have an increased odds ratio of metabolic syndrome (93-95). Most published studies are cross-sectional or case-control, but a recent study from Korea with a prospective design found that metabolically unhealthy individuals had an increased risk of incident psoriasis. The study also found this risk to be increased in both obese and non-obese individuals (96).

Metabolic syndrome and psoriasis have common inflammatory pathways with inflammation mediated by Th-1 and Th-17 (97), and overlapping genetic disposition is found in some studies (88) but not in others (87, 98).

2.5.3 Psoriasis and obesity

Several studies have shown a dose-response relationship between the severity of psoriasis and obesity (99-102). This positive association is found even among children with psoriasis (103-106). Most published studies are cross-sectional, but one prospective study found psoriasis patients to have an increased hazard ratio of obesity (80).

For several years, a substantial remission or reduction of psoriasis in patients with weight loss after bariatric surgery has been reported (107-109), and this association has been confirmed by studies of diet and weight loss (110-112). Correspondingly, an increased response to systemic treatment has been found after weight loss (113, 114). These studies indicate that obesity influences the severity of psoriasis, but less is known about whether obesity could induce psoriasis onset.

Two prospective studies from the Nurses' Health Study in the USA found increased risk of incident psoriasis related to BMI, waist circumference and waist-hip ratio (115, 116), while a recent Norwegian study did not find clear evidence for a relation between BMI and risk of psoriasis (117). Their results suggested, however, a threshold around 28 kg/m^2 where the risk of psoriasis was increased, compared to individuals with a BMI < 28 kg/m^2. Also, a prospective study from Korea showed a weak positive association between obesity and incident psoriasis (96), whereas a nested case-control study from the United Kingdom General Practice Research Database reported a 30% increased risk of psoriasis in obese individuals compared to individuals with normal weight (118).

Adipose tissue has a more complex function than previously known. White adipose tissue in particular has been identified to be an essential endocrine organ secreting adipokines, and is mainly found around the visceral compartments. Adipokines that display pro-inflammatory activities, namely leptin, visfatin and resistin, are also increased in psoriasis while the anti-inflammatory adipokine adiponectin is decreased (119, 120). In addition, the stromal-vascular fraction of adipose tissue includes macrophages, which are the main producers of psoriasis-signature cytokines such as IL-6 and TNF-α (121) (Figure 3).

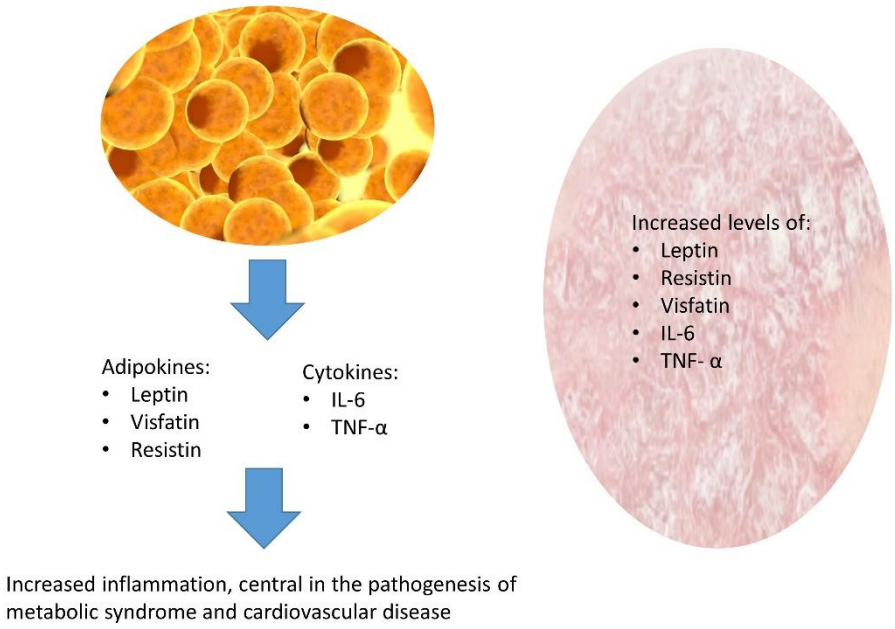

Figure 3. Adipose tissue and psoriasis displays common adipokines (such as leptin, visfatin and resistin) and cytokines (such as IL-6 and TNF-α).

The latter are pro-inflammatory mediators, which also induce insulin resistance and may lead to altered lipid metabolism, hypertension, endothelial dysfunction and increased risk of cardiovascular disease (122). However, whether the adipose tissue is a risk factor for development of diseases, such as psoriasis, or whether its activity is secondary to

psoriasis onset is still under debate (121). Of note, genetic studies have suggested that a combination of genetic factors and adiposity could increase the risk of developing psoriasis (123, 124). This finding was supported by a recent twin study from Denmark, indicating a common genetic aetiology of psoriasis and obesity (125).

2.5.4 Psoriasis and hyperlipidaemia

Changes in lipid levels due to altered lipoprotein metabolism and retention are considered a central step in the initiation of an atherosclerotic lesion, which in turn increases the risk of cardiovascular events (21). A positive association has been found in several (93, 126, 127), but not all (128, 129) cross-sectional and case-control studies investigating psoriasis and dyslipidaemia. When prospectively studying hyperlipidaemia in relation to incident psoriasis, some found an increased risk (130), while others found no increased risk of psoriasis (118).

The dyslipidaemia observed in psoriasis is probably caused by inflammation where cytokines such as TNF-α, IL-1, IL-6 and IL-8 are central in the production of lipids. This, in combination with endothelial cell dysfunction which has been associated with TNF-α and IL-17, could lead to atherosclerosis and cardiovascular events (21).

2.5.5 Psoriasis and hypertension

Hypertension is the strongest risk factor for cardiovascular disease (131). Psoriasis was positively associated with hypertension in a meta-analysis of cross-sectional and case-control analyses, with a stronger association for severe psoriasis than for mild psoriasis. The study concluded that most studies failed to completely adjust for important confounders, and the association could therefore be weaker (132). While large studies have found a positive association (133, 134), others have found weak or no association between psoriasis and hypertension (99, 118, 128, 135). In one prospective study, women with hypertension carried an increased risk of developing psoriasis with the highest risk among those with duration of hypertension of six years or more (136).

The exact mechanism underlying this possible association is not fully elucidated (132), but chronic inflammation as well as increased oxidative stress in psoriasis patients which may influence the vasodilatory mechanisms of the endothelium, are hypothesized (136, 137).

2.5.6 Psoriasis and diabetes

Diabetes is a major risk factor for coronary heart disease (138). In cross-sectional studies psoriasis is found to be positively associated with diabetes, with the strongest association for severe psoriasis (139). Prospective cohort studies have found psoriasis to be a modest risk factor for diabetes (140, 141), and a Danish nationwide cohort study found an increased incidence rate ratio of new-onset diabetes which was increasing with psoriasis severity, but was unable to adjust for BMI or smoking (142). There are few studies of the association between diabetes and incident psoriasis. However, a study from the General Practice Research Database (GPRD) found no increased risk of psoriasis in individuals with diabetes (118).

Psoriasis and diabetes share common risk factors like low-grade inflammation, several biomarkers and environmental factors like smoking (140). Low-grade inflammation can predict the risk of type 2 diabetes, and IL-6 and TNF seem to be central markers (143). In addition, leptin and adiponectin are probably involved in both psoriasis and type 2 diabetes (144).

2.5.7 Psoriasis and CRP

C-reactive protein (CRP) is a measure of inflammation in the body, and high-sensitivity CRP (hsCRP) is often used to predict cardiovascular disease, although it is probably at the most a moderate predictor compared with most established risk factors (145, 146). Levels of CRP are elevated in patients with psoriasis compared to controls, and some find an increase in PASI associated with increased CRP levels (98, 145).

3 Aims

3.1 General objective

The objective of this thesis was to investigate the associations between psoriasis and cardiovascular diseases and cardiovascular disease risk factors in a general population.

3.2 Specific aims

The aims of the studies were:

I. To examine the cross-sectional association between severity of psoriasis and cardiovascular morbidity including objectively measured cardiovascular disease risk factors in a general population.

II. To investigate the association of BMI, waist circumference, waist-hip ratio and 10-years weight change with the risk of developing psoriasis in a large prospective population-based study.

III. To investigate if metabolic syndrome and its components were associated with risk of incident psoriasis in a general population.

4 Materials and methods

4.1 The Nord-Trøndelag Health Study (HUNT)

Nord-Trøndelag is located in the central part of Norway (Figure 4), and was one of 19 counties until 1 January 2018 when it merged with Sør-Trøndelag to create a new county named Trøndelag. Prior to the merger, the population was 137 858 (147).

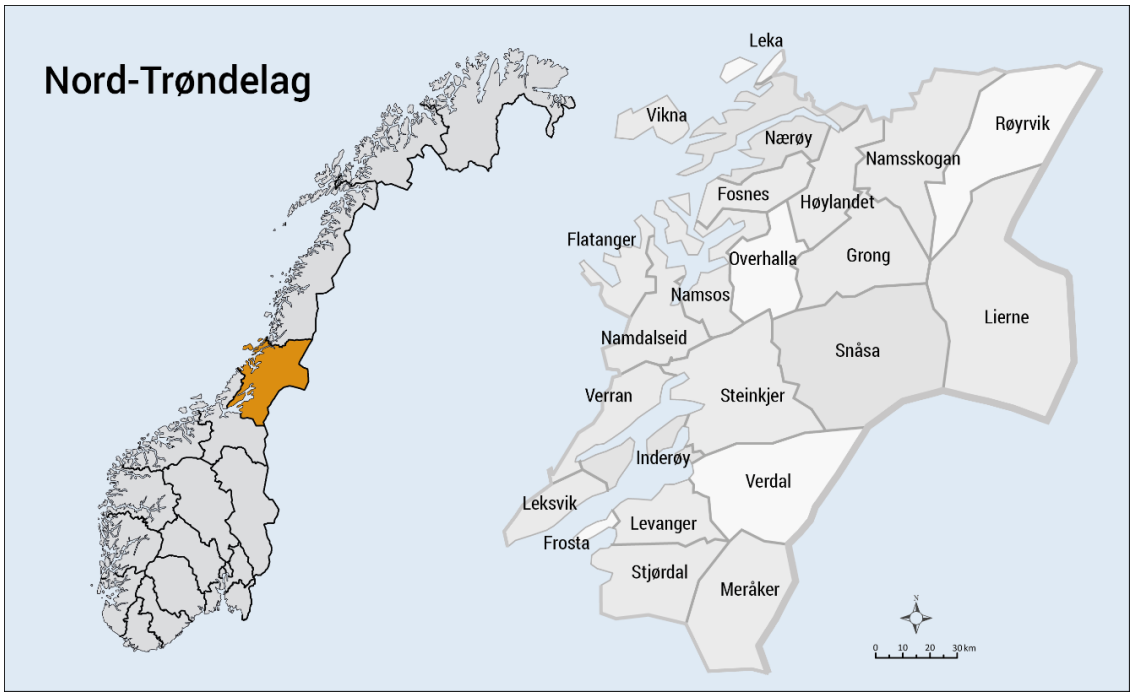

Figure 4. Nord-Trøndelag County. *(Illustration: Stina Aasen Lødemel/Allkunne CC BY-SA, kartgrunnlag Kartverket CC BY-SA 4.0 NO. Reprinted by permission)*

The population is considered homogenous, with mortality and health status fairly representative of Norway (148). So far, three surveys of the adult population aged 20 years or older have been completed: in 1984-1986 (HUNT1), in 1995-1997 (HUNT2) and in 2006-2008 (HUNT3). In paper I we used information from HUNT3, in paper II we used information from HUNT1, 2 and 3, and in paper III we used information from HUNT2 and 3. The unique personal identification number of all Norwegian citizens enabled us to link this information to other registries.

In HUNT1, the number of participants was 77 212 (participation rate: 89.4%). This survey was designed with a focus on investigating hypertension, diabetes, chest X-ray screening of tuberculosis and quality of life. Questionnaires were completed, and blood pressure, height and weight were measured. In addition, a capillary non-fasting blood glucose was measured in participants aged 40 years and older.

HUNT2 was extended to include a wider range of diagnoses and public health issues. In this survey, the number of participants was 65 237 (participation rate: 69.5%). The questionnaires were more comprehensive, the anthropometric measures included weight, height, waist and hip circumference, urine samples were analysed, and blood samples were analysed and stored.

The HUNT3 study was even more extensive, with questionnaires including more diagnoses. The same measurements were carried out, and the blood analyses included several variables. The number of participants was 50 807 (participation rate: 54.1%), and a biobank was established (149).

4.2 The Norwegian Prescription Database

The Norwegian Prescription Database contains information about all prescription drugs dispensed in Norway since 2004. This information can be linked to other registries on an individual level, for which a licence from the Norwegian Data Inspectorate is required (150). In paper I, we linked the data to the Norwegian Prescription Database to be able to assess the severity of psoriasis. We received information about the date of retrieval of the following systemic treatments: methotrexate (tablets and injections), acitretin, fumaric acid, cyclosporine, 5-methoxypsoralen, etanercept, adalimumab, ustekinumab and efalizumab. Infliximab is administered at hospitals, and information on this drug was therefore not available in the Prescription Database. It has been shown that during a four-year period, all patients treated with infliximab had previously been treated with methotrexate (151), and would therefore be captured by information on this medication.

4.3 The National Education Database

In the National Education Database, all individually based statistics on education have been gathered since 1970 (152). We linked information from HUNT3 to the National Education Database to obtain information on educational attainment in paper I since there was no information on this in HUNT3.

4.4 Study variables

4.4.1 The psoriasis question and validation study

Information on psoriasis diagnosis was obtained from the HUNT3 questionnaire by the question: "Do you have or have you had any of the following?" where "Psoriasis (Yes, No)" was a response option. A total of 2 928 participants answered yes to this question.

Furthermore, those who answered yes to the psoriasis question in HUNT3, were asked about the age at onset of the disease. In paper II and III, we used this information to determine follow-up time from participation in HUNT2 until onset of psoriasis between HUNT2 and HUNT3.

To assess the validity of the main psoriasis question, which was the basis for our further studies of psoriasis in HUNT, we conducted a validation study. We invited a random sample of 150 individuals with self-reported psoriasis and 700 individuals without self-reported psoriasis, and respectively 110 and 434 participated. We carried out clinical interviews and extensive skin examinations, and defined psoriasis as having clinical findings at the day of examination in combination with a positive history. For those with remission on the examination day, the diagnosis was confirmed either by a former skin biopsy or by collecting the medical record from a dermatologist. These results were compared to the answer from the questionnaire, and a sensitivity of 56% and a specificity of 99% was found, with a positive predictive value of 78% and a negative predictive value of 96% (33).

4.4.2 Anthropometric measurements

Height and weight were measured with participants wearing light clothes and no shoes. In HUNT1 and HUNT2 weight was rounded to the nearest half kilo whereas in HUNT3 it was registered with one decimal. Height was given in centimetres in HUNT1 and HUNT2 and in centimetres with one decimal in HUNT3 (153). BMI was calculated as weight divided by the squared value of height (kg/m^2) and classified into categories of underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30.0 kg/m^2).

Waist and hip circumference was measured with a steel band in HUNT2, and with a non-stretchable measuring band in HUNT3. Waist circumference was measured at the height of the umbilicus and hip circumference at the widest part of the hip, both recorded to the nearest whole centimetre. Waist-hip ratio was calculated as waist circumference (cm) divided by hip circumference (cm). In paper II, we classified people into four categories based on the distribution of waist circumference and waist-hip ratio using the sex-specific quartiles as cut-offs. For waist circumference the cut-offs were 86, 90, and 96 cm in men and 73, 79, and 87 cm in women; for waist-hip ratio the cut-offs were 0.86, 0.89, 0.92 in men and 0.75, 0.79, and 0.82 in women. In the same paper, we used information on body weight from HUNT1 in a subsample, for whom we calculated change in body weight before baseline by subtracting weight at HUNT1 from weight at HUNT2. Furthermore, we categorized weight change into five groups: <-2.0 kg, -2.0 to 1.9 kg, 2.0 to 4.9 kg, 5.0 to 9.9 kg and ≥10.0 kg.

4.4.3 Blood pressure

Blood pressure was measured with a Dinamap Critikon based on oscillometry. The measurement was done after the participants had been seated for two minutes with the cuff on the arm, and the mean of the second and third reading was used. In paper I and III, blood pressure was dichotomized into ≥130 mmHg systolic and ≥85 mmHg diastolic pressure as defined by the metabolic syndrome. In paper III, we additionally divided blood pressure into three categories: systolic blood pressure <120, 120-139 and ≥140 mmHg and diastolic blood pressure <80, 80-89 and ≥90 mmHg.

4.4.4 Laboratory measurements

The blood samples were analysed at the Central Laboratory at Levanger Hospital, and the time between last meal and blood sampling was recorded. In HUNT2, glucose was measured by an enzymatic hexokinase method and total cholesterol, HDL cholesterol and triglycerides were measured with an enzymatic colorimetric methods using Architect cSystems ci8200, Abbott Diagnostic, Ireland. In HUNT3, a Hitachi 911 Autoanalyser (Hitachi, Mito, Japan) with reagents from Boehringer Mannheim (Mannheim, Germany) was used: total cholesterol was analysed by an enzymatic cholesterol esterase method and HDL cholesterol was analysed by an accelerator selective detergent method. In the same study triglycerides were analysed by a glycerol phosphate oxidase method, glucose by a hexokinase/G-6-PDH method and hsCRP by a latex immunoassay method (153). We calculated non-HDL cholesterol as the difference between serum cholesterol and HDL cholesterol. Non-HDL cholesterol includes a combination of cholesterol in low-density lipoprotein (LDL) and triglyceride-rich lipoproteins (remnants) (154).

4.4.5 Metabolic syndrome

Metabolic syndrome was used in the analyses in papers I and III, and we utilized a modified version of the NCEP-ATPIII criteria (155). At least three of the following criteria were required to be classified with metabolic syndrome:

1) Blood pressure ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or self-reported treatment for elevated blood pressure.
2) Non-fasting blood glucose ≥ 11.1 mmol/L or answering yes to the question "Have you had or do you have diabetes?"
3) HDL cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women.
4) Non-fasting triglycerides ≥1.7 mmol/L.
5) Waist circumference ≥ 102 cm for men and ≥ 88 cm for women.

4.4.6 Other variables

From the questionnaires, we also collected information on self-reported diagnoses of diabetes, myocardial infarction and angina pectoris, in addition to self-reported medication for hypertension and time since last meal. Information on smoking was constructed in HUNT from reported answers about smoking status and categorized as 'never', 'former' and 'current'. Level of education was collected in HUNT2 and categorized as <10 years, 10-12 years and ≥13 years.

4.5 Ethics

Participants in the HUNT Study and the psoriasis validation study signed written informed consent, and the Regional Committee for Medical and Health Research Ethics approved all studies carried out in this thesis (2014/1791). The Norwegian Data Inspectorate and the National Prescription Database approved linkage between the HUNT studies, the National Education Database and the Norwegian Prescription Database.

4.6 Study design and analyses

4.6.1 Paper I

Paper I is a cross-sectional study using data from HUNT3 (Figure 5). We assessed the severity of psoriasis by defining mild psoriasis if participants did not receive systemic treatment for their disease, and moderate/severe psoriasis if they had received systemic treatment between 2004, the year the Norwegian Prescription Database was established, and the day at study participation.

We used linear regression to calculate adjusted mean differences of the cardiovascular risk factors in participants with mild and moderate/severe psoriasis compared to people without psoriasis. Due to non-normal distribution, the triglycerides and hsCRP were log transformed and calculated as geometric means and percentage change. Logistic regression was used to calculate odds ratios (ORs) for the association between psoriasis and overweight, hypertension (blood pressure ≥130 mmHg systolic or ≥85 mm Hg

diastolic or self-reported treatment for elevated blood pressure), total cholesterol >6 mmol/L and metabolic syndrome, in addition to self-reported diagnosis of diabetes, myocardial infarction and angina pectoris. The precision of the estimates was assessed by 95% confidence intervals (CI) and accompanied by p-values. We first conducted crude analyses and then adjusted for the following potential confounders based on *a priori* knowledge: age (years), sex (women, men), education (<10 years, 10-12 years and ≥13 years), BMI (continuous) and smoking (never, former, current and unknown). We treated missing information on smoking as an unknown category to keep as many cases as possible in the analyses.

In additional analyses, we stratified by sex and evaluated possible statistical interaction between psoriasis and sex using a likelihood ratio test. We also did several sensitivity analyses where we first excluded those with self-reported psoriasis arthritis. Second, we excluded those who had eaten in the last two hours before blood sampling or with missing data on time since last meal from the analyses of blood lipids and blood glucose. Third, and finally, we excluded people who reported to be on antihypertensive medication from the analyses of blood pressure.

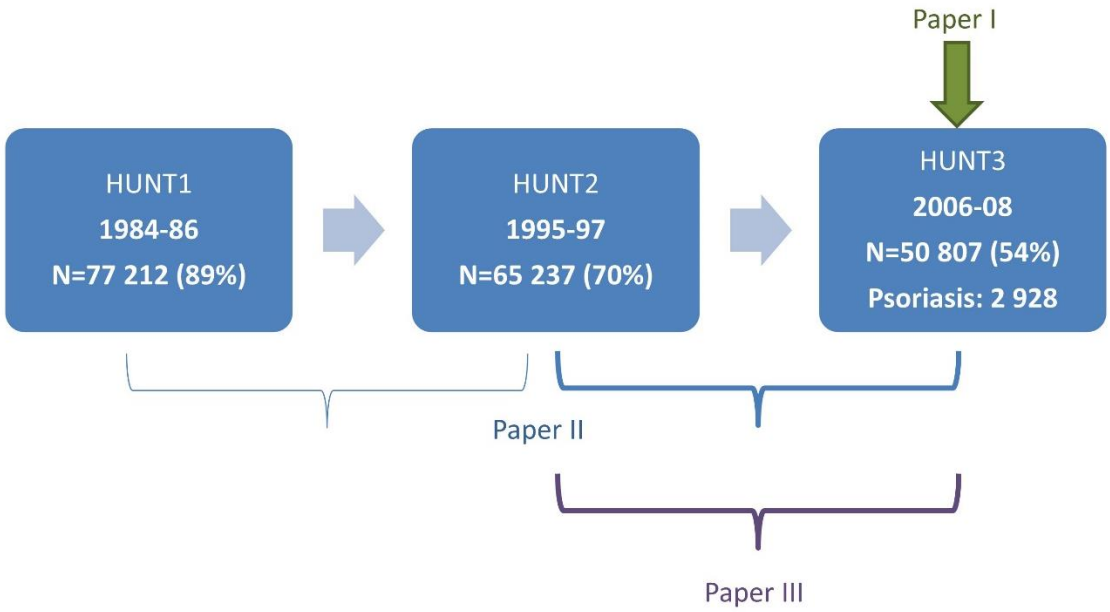

Figure 5. Participation in HUNT and design of our studies.

4.6.2 Paper II

Paper II is a prospective study using HUNT2 as baseline with follow-up until HUNT3. We also included information about weight and BMI from HUNT1 in a subset (Figure 5). Cox regression was used to calculate hazard ratios as estimates of relative risk (RR) for incident psoriasis, and the precision of all estimates were evaluated by 95% CI. We evaluated departure from the proportional hazards assumption by tests of Schoenfeld residuals and graphical inspection of log-log plots. In the main analyses, we used complete case strategy and selected potential confounders based on *a priori* knowledge. The estimated associations were adjusted for possible confounding by age (years), sex (women, men), smoking (never, former and current), and education (<10 years, 10-12 years and ≥13 years). We also did additional analyses where we adjusted for physical activity and alcohol consumption, although the rationale for these factors as confounders is less clear. Additional adjustments were made for physical activity (no, low, medium, high and unknown) and alcohol consumption (no, 1-4 times per week, ≥5 times per week, abstainer and unknown).

The relative risk of psoriasis was calculated within categories of BMI, waist circumference and waist-hip ratio measured at HUNT2 compared to a reference category. In addition, we used information of change in weight and BMI categories between HUNT1 and HUNT2 in a subset of the participants. We also estimated relative risks associated with the continuous measures of the anthropometric variables, using both the original scale and sex-specific normalized values (z scores). Z scores, or standard deviations scores, were calculated as the observed value minus the sex-specific mean value, divided by the sex-specific standard deviation. We calculated the population attributable fraction which quantifies the proportion of psoriasis that could be attributed to overweight and obesity, based on the assumption that the estimated association reflect a causal association between high BMI and psoriasis.

In additional analyses we stratified by sex, since adipose tissue could have differential biological effects and be distributed differentially among women and men. Possible statistical interaction (i.e. departure from multiplicative effect) was evaluated in a likelihood ratio test using a product term of sex and the anthropometric factors. We performed a sensitivity analysis excluding people with reported psoriasis onset the first

year after HUNT2 to reduce influence of imprecise report of age at onset and possible reverse causality due to existing undiagnosed disease.

4.6.3 Paper III

Paper III is also designed as a prospective study using HUNT2 as baseline with follow-up until HUNT3 (figure 5). As in paper II, we used Cox regression to calculate hazard ratios as estimates of RR for incident psoriasis, and evaluated the precision of all estimates by 95% CI. Departure from the proportional hazards assumption was also in this study evaluated by tests of Schoenfeld residuals and graphical inspection of log-log plots. We conducted crude analyses and adjusted for potential confounders based on *a priori* knowledge: age (years), sex, education (<10 years, 10-12 years, ≥13 years and unknown), and smoking (never, former, current and unknown). Missing information on smoking and education was treated as unknown categories to keep as many persons as possible in the analyses.

We estimated the RR of incident psoriasis within categories of metabolic syndrome (yes/no) and number of metabolic factors compared to a reference category. In addition, we divided metabolic syndrome into its components and estimated RR in categories of waist circumference, blood lipids, blood pressure and raised blood glucose/diabetes. We also used standard deviation (z-scores) to estimate RRs associated with the continuous measures.

In additional analyses, we stratified metabolic syndrome by sex and age groups and evaluated interaction in a likelihood ratio test. We also did analyses excluding those who had eaten in the last two hours before blood sampling and those with missing information on time since last meal from the analyses of blood lipids and blood glucose. From the categorical analyses of blood pressure, we excluded individuals on antihypertensive medication or missing information on this question. For the continuous measures of blood pressure, we added 10 mmHg to systolic pressure and 5 mmHg to diastolic pressure in additional analyses. Furthermore, we excluded people with psoriasis onset the first year after baseline, in addition to repeating all analyses in a complete case strategy excluding unknown categories of education and smoking.

All analyses were carried out using Stata for Windows (Version IC 14.1, StataCorp, College Station, Texas, USA).

5 Main results

5.1 Paper I: Psoriasis and cardiovascular disease risk factors

Out of 50 245 participants, we identified 2 643 individuals with mild psoriasis and 251 individuals with moderate/severe psoriasis. Individuals in the mild psoriasis group had a BMI that was 0.7 kg/m^2 (95% CI 0.5, 0.9) higher than those without psoriasis, whereas individuals in the moderate/severe psoriasis group had a BMI that was 1.8 kg/m^2 (95% CI 1.2, 2.3) higher than individuals without psoriasis. We observed the same association for waist circumference, with a 1.9 cm (95% CI 1.5, 2.4) higher circumference among those with mild psoriasis and a 4.7 cm (95% CI 3.3, 6.2) higher circumference among those with moderate/severe psoriasis compared to individuals without psoriasis. Individuals with psoriasis also displayed increased hsCRP, with an increase of 6.9% (95% CI 2.6, 11.4) in the mild psoriasis group and 48.8% (95% CI 30.6, 69.6) in the moderate/severe psoriasis group. However, for systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides and non-fasting glucose there was no clear association.

When studying the association between psoriasis and self-reported diagnoses, we found that individuals with moderate/severe psoriasis had increased ORs for overweight and metabolic syndrome, with ORs of 1.94 (95% CI 1.42, 2.67) and 1.91 (95% CI 1.47, 2.49) respectively. We also found positive associations between psoriasis and self-reported diabetes, myocardial infarction and angina pectoris.

5.2 Paper II: Obesity, waist circumference, weight change and risk of incident psoriasis

We prospectively assessed the risk of incident psoriasis associated with obesity, waist circumference and weight change among 33 734 individuals, out of whom 369 developed psoriasis during follow-up. Increases of one standard deviation in BMI (3.81 kg/m^2), waist circumference (11.14 cm) and waist-hip ratio (0.08) were all associated with increased risk of incident psoriasis, with RRs of 1.22 (95% CI 1.11, 1.34), 1.26 (95% CI 1.15, 1.39) and 1.18 (95% CI 1.07, 1.31) respectively. When BMI was categorized into normal weight, overweight and obese, we found the obese group to

have nearly twice the risk of psoriasis compared to the normal weight group with an RR of 1.87 (95% CI 1.38, 2.52). Individuals in the fourth quartile of waist circumference had an RR of 1.95 (95% CI 1.46, 2.61) compared to the first quartile.

We further assessed 10-year weight change from HUNT1 to HUNT2 in 25 148 individuals who had participated in all three HUNT surveys, and found an RR of incident psoriasis of 1.20 (95% CI 1.07, 1.35) for every standard deviation (5.96 kg) increase in weight change. When categorizing weight change in groups of weight reduction (<-2.0 kg), unchanged weight (-2.0 to 1.9 kg), modest increase (2.0 to 4.9 kg), moderate increase (5.0 to 9.9 kg) and more extensive increase (≥10.0 kg), we found a dose-response relationship with the highest RR of 1.72 (95% CI 1.15, 2.58) among those with a weight increase of 10.0 kg or more. Regarding BMI categories from HUNT1 to HUNT2, individuals who were overweight in both surveys had an RR of psoriasis of 1.53 (95% CI 1.07, 2.19) compared to those who were of stable normal weight. Correspondingly, those who were obese at both surveys had an RR of 2.16 (95% CI 1.29, 3.62). Finally, calculation of the population attributable fraction suggested that 23.6% of psoriasis cases in the study population could be attributed to overweight or obesity.

5.3 Paper III: Metabolic syndrome and risk of incident psoriasis

We analysed the risk of incident psoriasis in relation to metabolic syndrome and its different components. In total 34 996 individuals were included in the study, and 374 of them developed psoriasis during follow-up. Metabolic syndrome was associated with an RR of incident psoriasis of 1.66 (95% CI 1.30, 2.14), but after excluding waist circumference from the definition and adjusting for BMI this was attenuated to 1.33 (95% CI 0.97, 1.81). We found a dose-response relationship between an increasing number of the metabolic factors and RR of incident psoriasis. When analysing the different components of metabolic syndrome, we found no increased RR of psoriasis in any of the components except for increased waist circumference, which gave an RR of psoriasis of 1.68 (95% CI 1.30, 2.17). Furthermore, we had information on non-fasting total cholesterol, which is not included in metabolic syndrome. A raised total

cholesterol of >6 mmol/L gave an RR of psoriasis of 1.26 (95% CI 1.01, 1.57), but this was attenuated to 1.18 (95% CI 0.88, 1.58) after excluding those who had eaten in the last two hours before blood sampling or with missing information on time since last meal.

6 Discussion

6.1 Summary of main findings

The aim of our studies has been to investigate the relationship between psoriasis and cardiovascular diseases and risk factors from an epidemiological perspective. Our main findings could be summarized as:

- A positive cross-sectional association between psoriasis and BMI, hsCRP, metabolic syndrome and cardiovascular diseases.
- A positive association between adiposity and risk of incident psoriasis.
- A positive association between metabolic syndrome and risk of incident psoriasis, with high waist circumference as the dominant factor.

6.2 Methodological considerations

In an epidemiological study, it is a goal to present a valid and precise estimate of the effect of an exposure on the occurrence of a disease in the population, or of the frequency of a disease. Precision and validity are components of accuracy. The two types of error in epidemiologic studies are random error and systematic error, linking respectively to precision and validity (156).

6.2.1 Precision

An estimate is described as precise if there is little random error. As a measure of precision, we used confidence intervals, which give us information on precision and the strength of association.

One way to reduce random error and thereby increase the precision of a study is to increase the sample size (157). In our study, there was a high number of participants, contributing to high precision indicated by relatively narrow confidence intervals. However, stratifying and sub-grouping led to a relatively low number of participants in some groups, and hence a wider confidence interval. In particular, in the category of moderate/severe psoriasis, there were relatively few individuals, leading to imprecise estimates.

6.2.2 Validity

The validity of a study is divided into internal validity, where inference is relevant to the members of the source population, and external validity, where we draw inference to the external populations. The systematic error will not be affected by changing the study size, and the main types of systematic errors are selection bias, information bias and confounding (156).

6.2.2.1 Selection bias

Selection bias appears if the relation between exposure and outcome is different for those who participate and those who are eligible in a study. If the attendance in a population-based study is high, selection bias could be reduced.

In the cross-sectional study (paper I), we used data from HUNT3 which included questions on a broad range of diseases and conditions, and in which psoriasis was a tiny part. We thus find it unlikely that the participation differed for individuals with and without psoriasis. Findings from a study comparing psoriasis prevalence in HUNT3 with diagnostic codes from general practitioners in Nord-Trøndelag showed only slightly lower psoriasis prevalence in the general practitioners' population than in the HUNT3 study (148).

In the prospective studies (papers II and III), participants must have attended both HUNT2 and HUNT3 to be included. This could potentially lead to selection bias if the relation between exposures and outcome were different for those who participated and those who did not participate at follow-up in HUNT3. Ideally, we should have information on those participating in HUNT2 but not in HUNT3; whether they for instance had a higher morbidity or mortality than those participating in both studies. It is reason to believe that individuals with high BMI and metabolic syndrome may have a higher degree of morbidity and mortality between the surveys. This could make this group of individuals less likely to participate at follow-up, resulting in an underestimation of the association between obesity/metabolic syndrome and psoriasis.

6.2.2.2 Information bias

Information bias occurs if the information collected from the study subjects is incorrect, for instance because of measurement errors. For discrete variables, measurement error is often called misclassification.

We based our studies on self-reported diagnosis of psoriasis. This question was validated, with a positive predictive value of 78% (33), which implies that 8 out of 10 answering yes to this question do in fact have psoriasis. However, the sensitivity was 56%, which shows that some cases may remain undetected in the study cohort. This could be a major problem with a very common disease, but psoriasis is a relatively rare disease where the false negative cases will tend to be attenuated in the larger total population. The proportion of subjects misclassified with respect to psoriasis diagnosis will hence be low in the non-case group.

We also used self-reported year of psoriasis onset in the prospective studies, and hence some could possibly have undetected psoriasis already at baseline. Thus, we cannot rule out that a part of the association between obesity and psoriasis could be caused by reverse causality. In an effort to account for this, we did sensitivity analyses excluding participants with onset the first year after baseline.

In the cross-sectional study (paper I), we used systemic treatment as a proxy for psoriasis severity. Hence, individuals with severe psoriasis using only UV treatment would be misclassified into the mild psoriasis group. However, the number of individuals with moderate/severe psoriasis was low compared to the number with mild psoriasis, and a few severe cases misclassified into the mild group would therefore tend to be attenuated by the many mild cases. Furthermore, our strict definition of moderate/severe psoriasis ensured that individuals in this group really were severely affected. Use of self-reported information on smoking status, use of blood pressure medication and diagnosis of diabetes and heart diseases could also be misclassified. If misclassification of psoriasis diagnosis in paper I depends on the outcome variables, or vice versa, that misclassification of these diseases and risk factors depends on the psoriasis diagnosis, this would lead to differential misclassification. Psoriasis patients could potentially consult their physician more often than individuals without psoriasis,

and could therefore more likely be screened for comorbidities, leading to diagnoses of diabetes, heart diseases or treatment for hypertension. However, it is less likely that individuals with hypertension or other cardiovascular diseases would be screened for psoriasis unless they present with a skin complaint. Nevertheless, we found the strongest associations for objective and standardized measurements like BMI and waist circumference, which also reduce the possibility that our results can be explained by this type of bias.

In the prospective studies (papers II and III), the assessments of the exposures were made before the onset of disease. There could have been measurement errors in laboratory values, blood pressure and anthropometric measurements. For instance, in some individuals blood pressure will be increased when measured in a clinical setting ("white coat hypertension"). However, the use of standardized methods where blood pressure was measured three times and the mean of the second and third reading was used would minimize these measurement errors.

BMI does not necessarily reflect adiposity, as a higher muscle mass would also lead to a higher BMI. Individuals, and in particular men, could be placed into a high BMI category simply because they have high muscle mass. Further, when categorizing continuous variables, there is a risk of losing some information. The classification into categories of BMI could lead to individuals with BMI close to the cut-off values having almost identical BMI and still being placed in different categories. We also studied weight change according to change in BMI categories from HUNT1 to HUNT2. Some individuals could potentially present a small change in weight, but still change weight class. Others could have a more extensive weight change, but remain in the same BMI category between the two surveys. Therefore, in order to avoid losing information due to categorizing, we also studied BMI and weight change as continuous variables.

The use of metabolic syndrome as a risk factor has some limitations. Metabolic syndrome is a constellation of different characteristics rather than a distinct entity. When evaluating a patient's cardiovascular risk, one might rather evaluate the total risk load and utilize continuous rather than dichotomous variables (158). For instance, the definition does not take into account cardiovascular risk factors such as age, sex and

smoking. In addition, an individual could have all measurements towards the most pathological part of the scale, while another could have values just above (or for HDL just below) the cut-off, and both would be diagnosed with metabolic syndrome. An individual who meets all five criteria would also have a higher risk than one meeting three criteria, but again, both will have metabolic syndrome. In our analyses, we assessed both the number of metabolic factors and the continuous values of the risk factors with respect to risk of psoriasis. However, when individual component are considered in isolation, they are not necessarily regarded as pathological, such as an isolated blood pressure of 130/85 mmHg without other risk factors in combination. We used a strict cut-off value for glucose when defining metabolic syndrome. In the NCEP-ATPIII criteria, the cut-off for raised fasting plasma glucose is 5.6 mmol/L. Because we did not have fasting blood samples we set this cut-off to 11.1 mmol/L, which has been used in previous studies of hyperglycaemia and metabolic syndrome (159, 160) and also used as a positive screen in the HUNT study. Using a less strict cut-off would have defined more people as having metabolic syndrome.

6.2.2.3 Confounding

Confounding can be considered as a confusion of effects, where the effect of the exposure is mixed with the effect of another variable. This can lead to an overestimation or underestimation of the effect, or can even change the apparent direction (156). To be defined as a confounder, the factor must be a risk factor for the outcome and also associated with exposure under study, but not be an intermediate step in the causal pathway between the exposure and the disease. Confounders should not be chosen based on statistical associations found in the data, but rather from subject-matter knowledge (161). Construction of causal diagrams, or directed acyclic graphs (DAGs), is a good tool in the selection of confounders.

In our studies of the association between risk factors and psoriasis, we chose age, sex, education (as a proxy for socioeconomic status) and smoking as confounders. In addition, we adjusted for BMI when this was relevant. In paper III, we also adjusted for BMI in different models: as a categorical variable, as a continuous variable and in linear

splines. We did extra analyses where we adjusted for waist circumference, as we were uncertain if BMI would cover all aspects of adiposity. However, one should be careful with respect to entering strongly related variables into the same multiple-regression model, as this may create a problem with collinearity when controlling for the effect of the other variable. Therefore, we excluded waist circumference from metabolic syndrome in extra analyses in order to be able to adjust for obesity. In paper II, we adjusted for physical activity and alcohol in additional analyses, although the rationale for choosing these as confounders was less clear. Even if alcohol consumption seems to be high in psoriasis patients, it is highly unclear whether alcohol is a risk factor, or merely a consequence of psoriasis (162, 163).

To avoid excluding people with missing data on possible confounders from the analyses, we classified people with missing data on smoking and education as a separate 'unknown' category in multivariable adjusted analyses. This measurement error could potentially increase the amount of residual confounding in our results, but additional complete case analyses gave unchanged results.

Even if we had access to important confounders in our material, we can never rule out residual confounding. Such residual confounding could for instance be due to unknown environmental or genetic common causes of psoriasis and the exposure variable of interest.

6.2.2.4 External validity (generalizability)

The external validity of a study depends on the study's internal validity. If the internal validity in a study is low, the conclusions about causality will likely be wrong and no generalization can be made. However, representative study populations are not required to draw scientific inference about cause and effect; hence, a study with high internal validity will often be generalizable with or without a representative study population (164, 165). We do not find it likely that the associations between waist circumference/BMI and psoriasis will be different across populations and assume that our main findings would be generalizable to other populations and countries.

6.3 Interpretation of main findings

In paper I, we found that psoriasis was positively associated with increased levels of BMI, waist circumference and hsCRP, and we found an increased prevalence of overweight, metabolic syndrome, diabetes, myocardial infarction and angina pectoris in psoriasis patients using a cross-sectional design. These findings are in line with several previous studies (16, 95, 139), while population-based studies in particular have shown weak or no association between psoriasis and cardiovascular comorbidities (15-17). Population-based studies are likely to include a greater proportion of individuals with mild psoriasis, which might explain the weak associations in their results. We found the strongest associations among individuals with moderate/severe psoriasis, which is in agreement with others (6, 93), while several other studies lack information on severity (166-168).

We did not find substantial associations between psoriasis and blood pressure, blood lipids or blood glucose levels, which is in contrast with several other studies (16, 126, 132). However, it has been pointed out that some of the associations formerly found could be biased because of incomplete adjustment for confounders such as obesity and smoking (95, 132, 169). There are also some studies reporting no association between psoriasis and these factors (128, 170). The findings of inflammatory molecules common in psoriasis and several of the cardiovascular diseases and their risk factors have supported the hypothesis that a link exists, but the temporal relationship is still unclear.

In paper II, we found overweight and obesity to be associated with risk of incident psoriasis, and this is in line with two former studies of women (115, 116) and a study from the United Kingdom General Practice Research Database (118). The consistent dose-response relationship across multiple measurements such as waist circumference, waist-hip ratio and weight gain further strengthens our results. Interestingly, our results also suggest that weight loss could reduce psoriasis risk, which is in agreement with former studies showing improvement of already established psoriasis in relation to weight loss (107-109, 112). Former cross-sectional studies of psoriasis and obesity have been supported by the evidence that levels of adipokines and pro-inflammatory cytokines correspond in both conditions (121). It is likely that adipose tissue could be a risk factor for psoriasis, or that they share a common genetic aetiology, which is further

supported by genetic studies (123-125). Obesity is modifiable, and assuming that the estimated associations reflect causal relations between high BMI and psoriasis, our results suggest that 23.6% of the psoriasis cases could have been prevented if there were no one with overweight or obesity in our population.

In paper III, we extended the research question from paper II to include all aspects of metabolic syndrome. We found that metabolic syndrome is associated with increased risk of incident psoriasis, which is in line with one former study from Korea (96). However, while we found increased waist circumference to be the dominant factor in this association, the former study concluded that metabolic health status, regardless of obesity, was associated with increased risk of incident psoriasis. After dividing metabolic syndrome into the different components, we found no increased risk of psoriasis for any other factors than waist circumference. This finding is in contrast with a previous study showing an association between hypertension and risk of incident psoriasis (136). The results from paper III confirm the results from paper II identifying obesity as an important risk factor for psoriasis. Nevertheless, metabolic syndrome still displayed an increased relative risk of psoriasis after controlling for adiposity, which might be due to a combined effect of these risk factors. The common biological mechanisms identified in obesity and psoriasis could also be applied as a link between metabolic syndrome and psoriasis, but when it comes to studies of possible common genetic background between psoriasis and metabolic syndrome, results are conflicting (86, 87, 98).

7 Conclusions and future perspectives

7.1 Conclusions from papers I-III

We found that participants with psoriasis have higher BMI and higher hsCRP than participants without psoriasis, an association that was strongest for individuals with more severe disease. In addition, we found higher prevalence of overweight, metabolic syndrome, diabetes, myocardial infarction and angina pectoris in psoriasis cases. In this cross-sectional study from a general population, we did not find any clear association between psoriasis and blood pressure, blood lipids or blood glucose.

Using a prospective design, we found that overweight/obesity, and particularly waist circumference, was associated with subsequent risk of developing psoriasis, and we found a consistent dose-response relationship across multiple obesity-related measurements. Additionally, weight gain was associated with increased psoriasis risk, and our results suggest that weight loss could reduce the risk of psoriasis.

In a prospective design, we found that metabolic syndrome was associated with increased risk of incident psoriasis, a risk that was attenuated after adjusting for adiposity. Among the different components of metabolic syndrome, waist circumference was the only factor showing a clear increased risk of psoriasis.

7.2 General conclusion across the papers

In this work, we have identified adiposity and possibly metabolic syndrome as risk factors for psoriasis. Supporting this finding, is the apparent increase in psoriasis incidence and prevalence in recent years, which corresponds with the worldwide obesity epidemic. The findings of more cardiovascular disease among psoriasis patients could be due to the inflammation common in all these conditions, supported by the increased levels of hsCRP among psoriasis cases in our study. In addition, hsCRP was highest among individuals with moderate/severe psoriasis, reflecting a more severe inflammation.

A chronic inflammatory state in the body can lead to different diseases depending on the individual’s genes. We propose that obesity with its production of pro-inflammatory

cytokines and adipokines could be the driver of this inflammatory state. Or, alternatively, that there are some inflammatory mechanisms further upstream leading to both obesity and other conditions such as psoriasis and cardiovascular diseases. Hence, not only psoriasis, but all inflammatory conditions, could potentially lead to other inflammatory conditions including cardiovascular diseases.

7.3 Future perspectives

Onset of psoriasis in an individual is probably caused by a combination of environmental factors and genes. In these studies, we have investigated factors that could possibly influence disease onset, with adiposity being a central factor. It would be of interest to know if these risk factors have different impact in individuals with different genetic susceptibility. The HLA-CW6 allele is identified as probably the most important psoriasis susceptibility locus, and is associated with an earlier onset and a more severe clinical course (171, 172). The extensive HUNT biobank, which includes DNA sampling, gives us the opportunity to identify participants positive and negative for this allele. By doing this, we could examine if the disease risk factors could have different influence with regard to developing psoriasis in genetically different individuals.

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