# Co-morbidities in Inflammatory Dermatological Diseases

## Psoriasis, Hidradenitis Suppurativa, and Cardiovascular Risk Factors

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This review has been accepted as a thesis together with 4 previously published original papers by University of Copenhagen 31.12.2013 and defended on 7.11.2014.

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Dan Med J 2015;62(9)B5143

The 4 original papers are:

1. Miller IM, Ellervik C, Yazdanyar S, and Jemec GB. *Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors*. Journal of the American Academy of Dermatology. 2013 Dec;69(6):1014-24.
2. Miller IM, Skaaby T, Ellervik C, and Jemec GB. *Quantifying cardiovascular disease risk factors in patients with psoriasis: a meta-analysis*. British Journal of Dermatology.2013 Dec;169(6):1180-87.
3. Miller IM, Ellervik C, Vinding GR, Zarchi K, Ibler KS, Knudsen KM, Jemec GB.*Association of Metabolic Syndrome and Hidradenitis Suppurativa.* JAMA Dermatol.2014 Sep 17. Epub ahead of print.
4. Miller IM, Ellervik C, Zarchi K, Vinding GR, Ibler KS, Knudsen KM, and Jemec GB. *The Association of Metabolic Syndrome and Psoriasis: a Population- and Hospital-based Cross-Sectional Study*. J Eur Acad Dermatol Venereol. 2014 Jul 1. Epub ahead of print.

*"…and burning with curiosity,*
*Alice ran across the field after the White Rabbit…"*
*Alice's Adventures in Wonderland*

An innovative English animated short film presenting the nature of science and a summary of the PhD in laymans terms using an "Alice-In-Wonderland"-theme was displayed as part of the PhD presentation at the PhD defence. The film was created by Iben M. Miller in collaboration with animator Lais Christensen, sound mixer Dennis Bahnson, and professor Gregor Jemec, and can be found on http://www.regionsjaelland.dk/Sundhed/forskning/Forskere/Sider/Forsvar.aspx or requested by emailing the author of this thesis.

**BACKGROUND**

PSORIASIS

Psoriasis (PS) is a chronic immune-mediated inflammatory dermatological disease most characteristically manifested morphologically by sharply demarked erythematous, scaly plaques predilection sites being elbows, knees and scalp[1-4]. PS affects about 125 million people world-wide with prevalences varying from 2-4 % in Caucasians, and is characterised by equal gender distribution and a bimodal onset with a peak around 20 and 60 years respectively[1,2].

PS is multifactorial, and the etiology is not yet fully understood. Histologically, PS is characterized by hyperkeratosis with abnormal keratinization resulting in thickening of the epidermis (acanthosis), neo-angiogenesis in dermis making the appearance of the blood vessels dilated and tortuous, and infiltration of inflammatory cells in the dermis[2].

Attempts to illuminate the pathogenesis have revealed several regions in the human genome (e.g. Psoriasis Susceptibility Loci PSORS1-12) associated with a higher risk of developing PS. Triggering factors e.g. infection or psychological/physical stress, however, appear to be required for the manifestation of PS in predisposed individuals. Further investigations suggest dysregulation in the immune system as the core in PS pathogenesis with most emphasis on the Th1-driven immune response with a subsequent inflammatory cascade of events involving a broad range of immune cells and cytokines; Th17 lymphocytes, Il-17 and IL-12/23 overproduction being the prominent[2,3].

The severity of PS can be assessed by different score systems e.g. the Psoriasis Area Severity (PASI) score and Physician Global Assessment (PGA)[2]. From a clinical perspective a broad range of different phenotypes of psoriasis exist; the most common type is psoriasis vulgaris (chronic plaque psoriasis). Other types include guttate, erythrodermic, inverse, nail, seborrhoic and pustular psoriasis.

Treatment of PS relies mainly on immunosuppression/modulation i.e. topical corticosteroids, and tacrolimus/pimecrolimus, systemic cyclosporine, and biological therapy (TNF-alpha-inhibitors i.e. etanacept, adalimumab, infliximab or anti-IL12/23 i.e. ustekinumab). Other treatment options inhibits hyperproliferation/inflammation including topical synthetical vitamin D (calcipotriol), topical tar, systemic methotrexate, systemic A vitamin analogs (retinoids), and phototherapy (UVB, UVB01, or Psoralen combined with UVA).

The quality of life is significantly impaired, and associations with a number of co-morbidities have been reported; psoriatic arthritis, malignancies (non-melanoma skin cancer and lymphomas), Crohns disease, smoking, excessive alcohol consumption, cardiovascular disease, and associated risk factors e.g. MetS[5,6]. The

suspicion of a possible association between PS and CVD, and associated risk factors began over 100 years ago[7], and numerous investigations on CVD, subclinical atherosclerosis, and a broad spectrum of associated risk factors have been performed since, but results remain conflicting[8-99]. Furthermore, CVD and PS share CV risk factors (e.g. smoking, life style) which can blur the conclusions[100].

HIDRADENITIS SUPPURATIVA

Hidradenitis Suppurativa, also called Acne Inversa, is a chronic inflammatory dermatological disease manifesting itself by recurrent comedones, painful boils, nodules, fistulae, and subsequent scarring in the apocrine-gland bearing skin i.e. axillae, ano-genital area, and inframammary folds[101]. HS is diagnosed by the Dessau criteria as modified at the HS Foundation meeting in San Francisco 2009, where three criteria must be met; 1) Typical lesions 2) Typical topography, and 3) Chronicity and recurrences.

The prevalence varies from 0.05% to 4% in Caucasians. It is a much under- and misdiagnosed disease with a diagnostic delay of approximately 12 years. A letter correspondences between the historical figure Karl Marx and his doctor revealed that Marx might in fact have had misdiagnosed HS[102]. HS characteristically develops in the early 20s, and affects women more frequently than men (3:1).

The patho-etiology remains enigmatic; however, histologically studies suggest hyperkeratosis of the pilosebaceous unit with subsequent occlusion and eventually rupture of the hair follicle/apocrine glands leading to inflammative infiltrate, hair-follicle destruction, granuloma, scarring, and fistula formation in the dermis[103]. Furthermore, genetics, mechanical and hormonal factors, involvement of TNF-alpha, biofilm, IL-12/23/Th17/Th-1 pathway and Toll-like receptor2 have been suggested to contribute indicating autoimmunity involving the adaptive as well as innate immune system[104-106].

The severity of HS can be assessed by the Hurley or Sartorius score. Recently, different subtypes of HS have been proposed[107].

The treatment of HS is challenging yielding off-label medicine including topical antibiotics i.e. clindamycin or the peeling agent resorcinol, systemic antibiotic/immunmodulating tetracycline, anti-androgens or the combination of systemic clindamycin with the anti-tuberculose medicine rifampicin. Furthermore, immunusuppressants or anti-inflammatory pharmacotherapy such as cyclosporine, prednisolone, retinoids, and recently biologics have been suggested as possible therapy[101,108]. Surgical treatment i.e. laser or skin transplantation is also considered an option[101].

HS has been found to be associated with different co-morbidities e.g. acne, pilonidal cysts, certain types of cancers, Crohns disease[109] and smoking[101]. Furthermore, two recent hospital-based studies reported an association with metabolic cardiovascular risk factors[110,111].

CARDIOVASCULAR DISEASES AND CARDIOVASCULAR RISK FACTORS

Cardiovascular diseases (CVD) are a versatile group of disorders of the heart and blood vessels (both arterial and venous blood vessels). CVDs represent 30% (17.3 million people in 2008) of all global deaths, and are the number one cause of death worldwide[112]. Deaths due to CVDs are believed to reach 23.3 million by 2013[112] . The arterial cardiovascular diseases are mainly attributed to atherosclerosis, and include ischemic heart disease

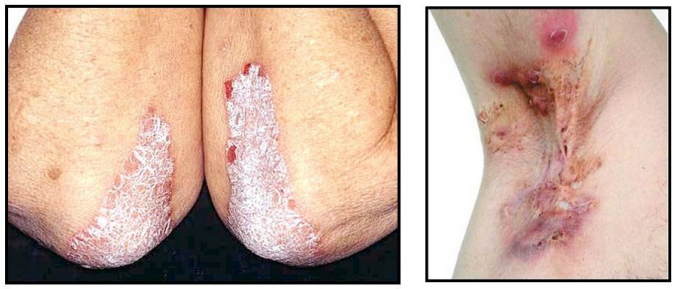


Figure1. Morphology of psoriasis (left) and hidradenitis suppurativa (right)

| | Psoriasis | Hidradenitis Suppurativa |
|---|---|---|
| **Pathophysiology** | Th1-mediated inflammation | Th1–mediated inflammation? |
| **Morphology** | Scaly, red plaques mainly on elbows, knees and scalp | Painful boils, nodules, fistula and scarring on apocrine-gland-bearing skin i.e. axilla, groin, ano-genital areas |
| **Treatment** | **Topical**<br>Corticosteroids, vitamin D<br>**Systemic**<br>Methotrexate<br>Cyclosporine<br>Retinoids<br><br>**Biological therapy**<br>e.g. TNFalpha-inhibitors | **Topical**<br>Clindamycin, resorcinol<br>**Systemic**<br>Clindamycin/rifampicine<br>Cyclosporine<br>Retinoids<br>Tetracycline<br>**Biological therapy**<br>TNFalpha-inhibitors? |
| **Prevalence** | 2-3% | 1-4% |

Table1. Characteristics of psoriasis and hidradenitis suppurativa

(angina pectoris, myocardial infarction), cerebrovascular disease (stroke, transient ischemic attacks), and peripheral arterial disease[112] (WHO). The venous CVDs include deep vein thrombosis and pulmonary embolism. Other mentionable CVDs are arrhythmias and congestive heart failure. This thesis focuses on arterial cardiovascular diseases (Study I), and associated risk factors (Study I-IV).

The spectrum of cardiovascular (CV) risk factors of arterial CV diseases is wide, and can be divided into three categories; behavioural, metabolic, and other[112]. Behavioural CV risk factors include smoking, unhealthy diet, physical inactivity, and harmful use of alcohol. Metabolic CV risk factors include diabetes, hypertension, dyslipidemia, and obesity. Other known CV risk factors are age, male gender, psychological factors (e.g stress), genetics, excess homocysteine, and socio-economic status[112]. The metabolic CV risk factors are components of the metabolic syndrome. This thesis focuses on the cardiovascular risk factors constituting the metabolic syndrome.

THE METABOLIC SYNDROME AND ITS COMPONENTS

Historically, the Metabolic Syndrome (MetS) also called Insulin Resistance Syndrome/Syndrome X/ the Deadly Quartet, has been of interest in over 80 years [113,114]. Through time the conceptual perceptions of MetS have changed. Today MetS is considered to be a cluster of cardiovascular risk factors i.e. diabetes/insulin resistance, hypertension, dyslipidemia and obesity that may occur in adults as well as children.

MetS affects 15-25% of the general population, and is a significant socio-economic burden globally. Various definitions of MetS have

been proposed through the years[115] including National Cholesterol Educational Programme Adult Treatment Panel (NCEP-ATPIII), the International Diabetes Foundation (IDF), the World Health Organization (WHO), the European Group for the study of Insulin Resistance (EGIR), the American Association of Clinical Endocrinologists (AACE), and recently a harmonized definition of MetS based on revisions of the NCEP-ATPIII definition was proposed. The harmonized definition was a result of a collaboration between American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI), IDF, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity[116]. The NCEP-ATPIII definition was designed to have clinical utility, and is thus simple to assess for the physician in an everyday clinical setting.

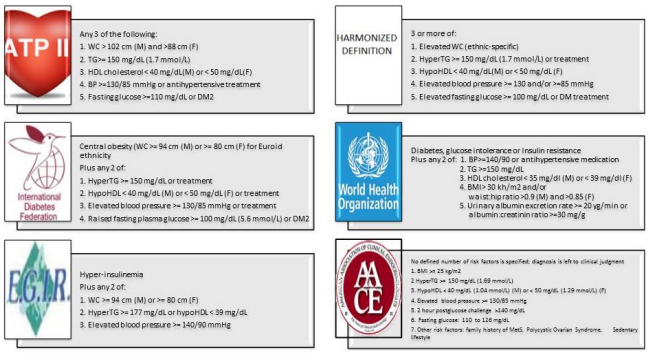



Figure2. Definitions of metabolic syndrome

The pathophysiology of MetS is complex, and still not fully understood. Several etiologic factors have been considered to contribute; IR and obesity are both believed to be cardinal features[117,118]. However, additional factors such as increases in cellular oxidative stress, dietary pattern, chronic inflammation, endothelial dysfunction, chronic stress leading to hypercortisolism and dysregulation of the hypothalamic-pituitary-adrenal axis and autonomic nervous system, dysfunctional renin-angiotensin-aldosterone system activity, low vitamin D, and genetic predisposition may also be involved[118-121].
Insulin-resistant subjects typically present with dissociative" hepatic IR meaning that insulin fails to decrease the Fox01 (forkhead box protein 01)-mediated gluconeogenesis on a level of gene transcription with a subsequent increase in glucose output. At the same time there is an increased insulin-mediated hepatic de novo lipogenesis which in turn results in a high free fatty acid flux, increased TG synthesis and intrahepatic lipid storage. Adipose tissue IR manifests in insulin failing to inhibit adipose tissue lipolysis with subsequent free fatty acid release in the circulation directly into the portal system and liver increasing the hepatic IR (the "portal theory")[118]. The "free radical theory" suggests that due to obesity-mediated inflammatory cytokines and dysfunctional mitochondria there is an imbalance between the generation of Reactice Oxygen Species (ROS) and the anti-oxidant defence system resulting in altered lipid peroxidation and DNA/cellular damage[118].
The incidence of MetS has increased during the past decades. It could be argued that this is based on an increase in obesity worldwide. This might be due to overconsumption and decrease in physical activity i.e. sedentary lifestyle. Although, the absolute consumption of total dietary fat has been found to remain stable the past 30 years, the dietary pattern of lipids as well as protein, and carbohydrate on a qualitative level i.e. western diet might contribute to the increase in obesity[118].
Recently, additional abnormalities such as prothrombotic state, non-alcoholic fatty liver disease, and Polycystic Ovarian Syndrome has been suggested to be part or play a part in MetS.
The individual elements in MetS confer an elevated risk of cardiovascular diseases. Although under debate, MetS is thought to confer an attributable risk of CVD greater than each parameter on its own. Several studies have shown a 1.5 to 3 times greater risk of CVD in MetS[121]. There is evidence suggesting both peripheral(e.g. vascular beds in limbs) and central (e.g. ischemic heart disease and stroke) vascular involvement in MetS[122]. The cardiometabolic risk does not seem to be entirely dependent on obesity as 30% of obese are metabolically undisturbed[118]. The primary therapy of MetS is life style intervention combined with pharmacotherapy for each CV risk factor if needed.
Despite the diverging definitions of MetS, four key parameters/components are repeatedly involved namely as mentioned above: diabetes, hypertension, dyslipidemia and obesity.

**Diabetes Mellitus**

Diabetes Mellitus (DM) ensues when euglycemia cannot be maintained. There are two major types of DM; Insulin-dependent DM (DM1), and non-insulin-dependent DM (DM2). The main physiological abnormalities are insulin resistance (IR) and impaired insulin secretion eventually leading to hyperglycemia, which may over time subsequently manifest micro- and macrovascular injuries (e.g. retinopathy, nephropathy, neuropathy, hypertension, and CVD)[123]. The prevalence of diabetes in America in 2012 was 9.3% (29.1 millions), where it is the 7$^{th}$ leading cause of death[124]. However, the underlying mechanisms differ according to the DM type. DM1 is believed to be an autoimmune disease caused by the immune-mediated destruction of pancreatic β-cells with subsequent lack of insulin production. The core of diabetogenesis of DM2 is impairment in the ability of insulin target tissue to respond to insulin. DM2 is associated with obesity, and inflammation is thought to play a role. The diagnose of DM relies on a broad range of glucose-tests in the blood e.g. glucose, HbA1c, and Oral Glucose Challenge[125].
Glucose control is thought to generate a "metabolic memory" suggesting it takes several years before glucose control translates into cardiovascular protection making early detection and therapy pivotal[126].

**Hypertensio Arterialis**

Hypertension, also referred to as arterial hypertension or hypertensio arterialis, is a chronic condition in which the blood pressure in the arteries is elevated creating an elevated vascular resistance, which subsequently requires the heart to work harder to circulate blood through the blood vessels[123]. Blood pressure is measured by the systolic (heart muscle contraction) and diastolic blood pressure (heart muscle relaxing). Approximately 25% of the population is affected, and hypertension is classified as either primary (essential/idiopathic) hypertension or secondary hypertension. Primary hypertension accounts for 90–95% of cases, and has no obvious underlying medical cause. Secondary hypertension, the remaining 5–10%, is caused by other conditions affecting various organs (e.g. the kidneys, arteries, heart or endocrine system).
The pathophysiology of hypertension is multifactorial and associated with functional and structural macrovascular and microvascular alterations including arterial stiffening, and vasomotor tone

abnormalities leading to disturbed tissue perfusion and susceptibility to ischemia. Cumulative metabolic burden and oxidative stress can lead to chronic endothelial injury and dysfunction, promoting these structural and functional vascular alterations[127]. Global deaths attributed to hypertension accounts for 16.5% (9.4 million deaths), of which 51% and 45% is caused by stroke and ischemic heart disease, respectively[112].

**Dyslipidemia**

Dyslipidemia is an abnormal level of lipids in the blood. There are several types of lipids, the most prominent being: Triglyceride (TG), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), and total-cholesterol.

Lipid metabolism is complex. In short, the lipids directly used for energy production are fatty acids, which are either synthesized in the liver/intestine or come from dietary lipids, and stored in the adipose tissue as TG. Dietary lipids are transported from the intestine to the peripheral tissues and liver. TG is transported packaged as lipoproteins; HDL and LDL. Thus, lipoproteins consist of TG, cholesterol and apoproteins, and are classified according to their TG-content (hydrophobic). The higher TG-content, the lower the density[128].

TG expressed as lipoproteins, enables the bidirectional transport of adipose fat and blood glucose between the liver and peripheral tissue; the main function of HDL particles is to remove fat from the artery wall atheroma and transport it back to the liver for excretion or re-utilization, and hence protect against atherosclerosis. LDL can transport their content of many fat molecules into artery walls, attract macrophages, and thus drive atherosclerosis.

Diagnosis of dyslipidemia is based on venous blood sampling, traditionally fasting. However, non-fasting values have demonstrated valid[129]. Interpretation of measurements of lipids in blood is complicated as there is a difference between the blood concentration on a quantitative level vs. qualitative level. Hence, a measurement of LDL cholesterol might be normal, but due to different subfractions of LDL e.g. small dense LDL, which are more susceptible to oxidation and penetrate the arterial intima more easily than larger LDLs, a person might still have more atherogenic lipoprotein distribution than usual. Lipoprotein analysis allow for such an exploration[128].

**Obesity**

Obesity affects approximately 35% of the population, and is consistently increasing with worldwide costs around $147 annually[130]. The increase in incidence could be partly due to economic growth and subsequent westernized lifestyle. Obesity is defined by Body Mass index (BMI) (general obesity) or Waist Circumference (WC) (abdominal obesity). It is a complex state in which there is over-accumulation of adipose tissue. The etiology is multifactorial, and involves genetics, hormones, diets, physical activity and environment. Adipose tissue is no longer considered inert, but is considered a metabolically active endocrine tissue involved in pathophysiology of immunity and inflammation.

The visceral adipose tissue is thought to secrete adipo-cytokines (e.g.adiponectin, leptin, resistin, visfatin as well as pro- and anti-inflammatory cytokines (e.g. TNF-alpha, IL-6), growth factors that promote angiogenesis and vascular remodelling (e.g. Vascular Endothelial Growth Factor, Plasminogen Activator Inhibitor 1), and other regulators of appetite, coagulation, and glucose/lipid metabolism. Obesity is associated with a chronic low-grade inflammation in which there is elevation of pro-inflammatory cytokines. However, it is still not yet fully understood how obesity triggers this inflammation. Obesity is a part of MetS, however, not all obese individuals have metabolic disturbances[130].

INFLAMMATORY DERMATOLOGICAL DISEASES AND THE ASSOCIATION OF CARDIOVASCULAR DISEASES AND RISK FACTORS

The growing interest of the association between dermatological diseases and cardiovascular risk factors dates back over 100 years[7]. A German article by Strauss et al. from 1897 linked psoriasis with diabetes[131]. The idea resurfaced in World War I when it was observed that the incidence of psoriasis decreased. It was speculated whether this was due to the scarcity of foods, especially fats linking psoriasis with lipid metabolism[132]. In line with this, Reed et al. found a possible association between psoriasis and cardiovascular diseases in 1961[133], followed by similar observations by McDonald[134].

Today inflammation is placed at the core of understanding atherosclerosis and thereby cardiovascular diseases and risk factors[135]. Additionally, recent studies suggest atrial fibrillation, which is a known risk factor of stroke, to be linked with both inflammation and psoriasis[136,137]. There is an overlap of the underlying inflammatory mechanisms with those of psoriasis e.g. they are both believed to be Th1/Th17-driven chronic inflammatory diseases. Other Th1-mediated inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, lichen planus, and recently HS have been linked to cardiovascular risk factors e.g. diabetes, hypertension, dyslipidemia, obesity, and smoking[100,110,138-140]. Surprisingly, insulin resistance has also been linked to Th2-driven inflammatory dermatological diseases e.g. acne[141]. However, results are inconsistent[142].

Treating psoriasis patients with the statins, which is considered to have both anti-cholesterol and anti-inflammatory properties, may have an effect on the skin symptoms supporting the theory of shared pathogenesis of psoriasis and CV risk factors[143]. Further studies underpinning the overlapping pathology suggest a possible association with surrogate markers of atherothrombotic disease; endothelial dysfunction, carotid intima-media thickening, and prothrombotic environment with hyperhomocysteinaemia and a hypercoagulative state in psoriasis patients[144-147]. However, results on subclinical atherosclerosis are conflicting with regard to psoriasis being an independent CV risk factor, and a studies excluding patients with CVDs or risk factors demonstrate diversity[148,149].

Another study suggested that possible lipid abnormalities are already present at the onset of psoriasis indicating that CV risk might be existent before the skin symptoms[80]. Furthermore, hypothesis on the impact of psoriasis subtype and severity on the alleged CV risk have been proposed aiding the understanding of the nature of the association[150,151].

In the matter of treatment, results on the effect of psoriasis treatment on CV risk remain inconclusive[152].

**Possible pathophysiology of the association between HS/PS and MetS**

The following paragraph is of a hypothesizing speculative nature. The speculations regarding a possibly pathophysiology of the association between HS/PS and MetS is an emerging, vivid field of science. Based on theories regarding the etiology in MetS mentioned above in supplement to hypothesis and theories that could provide a possible pathophysiological explanation, some main speculative categories of possible theories will be introduced. The

purpose of this is to provide a better fundament of discussion, to inspire and also give the thesis perspective beyond its main purpose. The main categories of possible pathophysiology chosen are; chronic inflammation and disease-specific immunology, pharmacotherapy, lifestyle and neuro-psychology, oxidative stress, and others.

*Chronic inflammation and Disease-specific immunology*
Both HS and PS are associated with elevation of the inflammatory marker CRP, and responding partly to e.g. TNF-alpha-inhibitors highlighting that both diseases are inflammatory. The chronic inflammation might be based on disease-specific immunology as well as inflammation produced by the associated obesity.
In short the immune system can be divided into the innate (rapid-response, unspecific) and the adaptive immune (slow-response, specific) system. The response of the innate immune system involves mannose-binding protein, compliment activation, phagocytes (macrophages), and Toll Like Receptors (TLR).
The response of the adaptive immune system involves lymphocytes i.e. B- and T-lymphocytes. The major difference between B and T lymphocytes is the type of antigen they recognize. B lymphocytes bind whole proteins and intact pathogens, whereas T lymphocytes recognize short peptide antigens bound to major histocompaibility complex molecules (MHC).
B-lymphocytes are responsible for immonoglobulines and subsequent antibody production. There are a number of different T-lymphocytes divided into two main categories; CD8+(T-cytotoxic cells) and CD4+ (T-helper cells). The CD4+ cells can be further subdivided into Th1 and Th2, the former secrete cytokines that activate macrophages, and the latter help B lymphocytes to make antibodies. Cytokines like TNF-alpha are involved in both the adaptive as well as the innate immune system[153].
Evidence suggests that HS and PS might both be autoimmune disorders involving the Th1-mediated pathway. Thus, both HS and PS involve chronic inflammation due to disease-specific immunological disturbances.
Furthermore, the obesity associated with HS/PS could subsequently lead to the production of pro-inflammatory cytokines creating an obesity-mediated chronic low-grade inflammative condition.
This chronic inflammation is speculated to burden the organism at large e.g. affect the entire endothelial and vascular system linking to MetS and CVD. It is furthermore speculated if the obesity-induced cytokines promoting angiogenesis and vascular remodelling further contribute to the psoriasis pathogenesis. Or alternatively, that the vascular remodelling in psoriasis might in fact not only apply to the skin, but also other organ systems.

*Lifestyle and neuro-psychology*
As mentioned HS/PS is associated with impaired quality of life and depression. The stigmatization these patients experience could eventually lead to behavioural changes such as sedentary lifestyle i.e. over-eating and physical inactivity with subsequent obesity leading to inflammation ect. Thus, the intake of food could be different quantitatively, but also qualitatively i.e. a tendency to eat more “comfort”-food (fatty foods, junk food ect).
Diet can act as a regulatory factor on the immune response and metabolism[118,130]. Hence, high fat intake in general causes excessive accumulation of adipose tissue, and furthermore might impair the immune system. Saturated fat is believed to be atherogenic i.e. can cause atherosclerosis. In contrast, the intake of fish is suggested to be inversely related with inflammation. The same inverse association is believed to account for high fruit/vegetables consumption. The fructose (e.g. sugar sweetened beverages) consumption has risen during the last decades, has been found to result in sustained elevations of postprandial TG levels, and is associated with weight gain, dyslipidemia, hepatic steatose, and IR. Furthermore, high amounts of eggs have been linked to hypercholesterolemia. Alcohol in small amounts is believed to be cardioprotective; however, in excessive amounts it can be associated with MetS; IR in particular[118]. Thus, a quantitatively and qualitatively different intake of nutrition’s could lead to further inflammation.
From a neuro-psychological perspective one could speculate whether cerebral foetal programming is altered in HS/PS patients leading to increased appetite. Alternatively, the psychological stress and stigmatization due to having HS/PS could lead to elevated cortisol-levels and activation of the hypothalamic-pituitary-adrenal axis and autosomal nerve system with subsequent tendency to MetS-components such as diabetes and hypertension.
Furthermore, the dietary pattern may influence the appetite e.g. excess protein impairs the transport of amino acids into cerebrum thereby reducing the catecolamine and serotonin production, which in turn may drive hunger[118]. Furthermore, it has been suggested that there are obesity-related alterations in the amino acid i.e. protein metabolism causing excess amino acids, some of which increase hepatic glucose output[118]. MetS has also been linked with depression[154]. Thus, a possible depression caused by stigmatization of having a skin disease could in theory contribute to MetS.

*Pharmacotherapy*
A broad range of the pharmacotherapy for PS or HS may affect MetS-components through known side effects. It is well-known that prednisolon might cause diabetes, cyclosporin may cause hypertension, and retinoids can increase cholesterol levels[155,156]. Methotrexate has been linked to CV protection[157]. This may be due to bone marrow suppression with subsequent thrombocytopenia and hence anti-coagulative state. Methotrexate may also seldomly induce diabetes or affect the liver function. Thus, the dermatological pharmacotherapy might be a contributor in driving MetS in PS/HS patients.

*Oxidative stress*
Oxidative stress, which is thought to play a part in MetS, is a state of oxidant/anti-oxidant imbalance meaning the amount of ROS in the body is larger than the anti-oxidant capacity of the body.
One could hypothesize that HS/PS patients have inherited mitochondrial dysfunction (e.g. foetal programming) leading to disturbances in basic metabolism, and subsequent susceptibility to gaining weight and increased mitochondria-mediated ROS creating oxidative stress. Oxidative stress is linked with endothelial damage, and could thus affect the whole vascular system.
One could also speculate that PS/HS patients might suffer from aquired mitochondrial dysfunction due to the sedentary lifestyle that could follow the stigmatization.
The dietary pattern may affect the mitochondrial capacity;excess protein amino acids may potentially impair mitochondrial beta-oxidation of lipids[118]. Physical inactivity is associated with impaired mitochondrial function, and exercise causes mitochondrial biogenesis in the liver and muscles resulting in an increase in numbers of mitochondria as well as increased mitochondrial function of already existing mitochondria[118,139].

Furthermore, the skin is part of the body´s anti-oxidant defence system, which is mediated partly by a xenobiotic (exogeneous chemicals e.g drugs, pollution, food additives) detoxification biotransformation system as well as ROS-scavenging enzymes. Hence, any disorders in the skin could in theory affect this functionality making individuals with dermatological disorders more susceptible to oxidative stress, and therefor MetS[139]. The skin also possesses an excretory function making sweat-mediated elimination of toxic substances possible, and thus adding to the anti-oxidant defence system[139]. It has been observed that sauna can protect against oxidative stress[139]. HS is believed to affect the apocrine sweat glands, the function of which is still not completely known as it is mainly the eccrine sweat glands producing sweat. However, HS may somehow be susceptible to reduced or altered sweat function leading to dysfunctional anti-oxidant system of the skin.
Moreover, sebum excretion in the skin mediates elimination of excess lipids[139]. It has been suggested that sebaceous glands of the skin is lacking or reduced in size in HS[158]. Thus, it could be speculated that this decreased sebum-mediated elimination of lipids contribute to dyslipidemia in HS.

*Other*
Low vitamin D levels have been associated with MetS[120]. PS has also been linked with vitamin D deficiency[159], and topical vitamin D is used for treatment. Furthermore, low vitamin D has been suggested to relate to Th cells. Thus, it could be speculated if vitamin D plays a part in the possible association of PS with MetS. Recently, a possible communicational pathway between the skin and the liver has been implied[160]; A study in mice showed that an Acetyl CoA binding Protein deficiency in the skin caused delayed adaption to weaning, including hepatic lipid accumulation. Furthermore, an imperfect epidermal barrier led to increased lipolysis in white adipose tissue. Hence, one could hypothethize that disorders in the skin including PS/HS could lead to hepatic dysfunction, and cause imbalance in the lipid metabolism with subsequent dyslipidemia contributing to MetS.

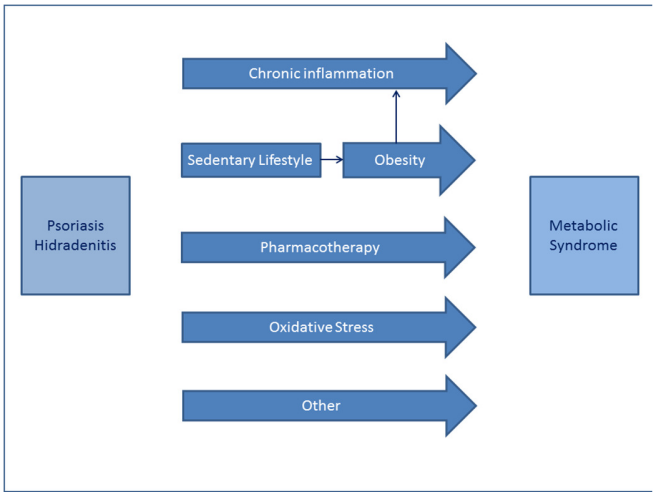



Figure3.
Illustration of speculations on possible pathophysiology of the Association between PS/HS and MetS

*Causality*
The association might not be causal as the association might be explained by another variable, a co-called confounder. If the association is causal, it might go in one direction or the other e.g. HS/PS might trigger obesity, but being obese might also trigger HS/PS. In fact, studies of obese psoriasis and hidradenitis patients undergoing gastric bypass surgery or low caloric diet show a decrease in psoriasis and hidradenitis, respectively after weight loss[161-163]. Cohort studies of psoriasis conveying information of time indicate a possible causal relationship (according to Hills criteria 4) between psoriasis and e.g. diabetes and CVDs[25,39]. However, results from cohort studies are conflicting[21]. No temporal studies of CVDs and associated risk factors have been performed with regard to HS yet.

**GENERAL METHODS IN THE THESIS**

*"Science is but an image of the truth"*
*Francis Bacon*

EPIDEMIOLOGY
Epidemiology *(Greek; epi: among, demos: people, logos: reason)* is the study of health and disease in populations. Contemporary epidemiology can be traced back to ancient Greek physician Hippocrates. Within epidemiology a distinction is made between experimental (interventional) and observational studies[164]. According to evidence-based medicine (EBM) which has dominated science of medicine the many last decades, the hierarchy of quality of evidence is based on the study design as illustrated by Figure4.

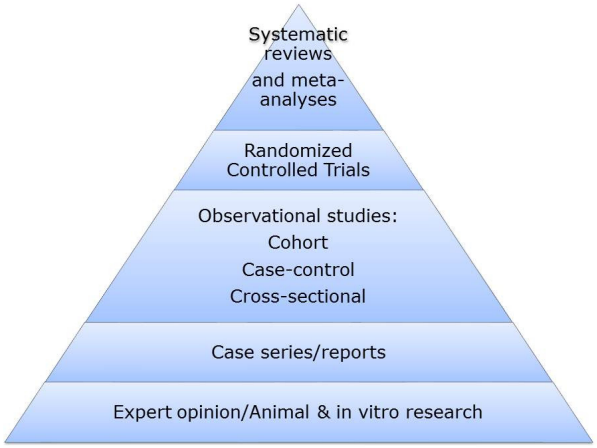



Figure4. The hierarchy of the quality level of study designs according to EBM

This Ph.D. thesis was built on two different study designs; meta-analysis and cross-sectional studies, both considered to be within the field of epidemiology.
A meta-analysis is a systematic review with a statistical summary estimate based on published literature on a specific subject, and can be created from experimental or observational data.
Observational studies are studies based on observations made without any intervention, and there are three types of studies: cohort, case-control and cross-sectional. The two former are longitudinal/temporal, whereas the latter does not contain the element of time.

Both the meta-analyses and the cross-sectional studies aim to investigate associations.

MEASURES OF ASSOCIATION

**Association and Causality**

In statistics, an association is any relationship between two variables that renders them statistically dependent. An association refers to any such relationship, whereas the term correlation describes a linear relationship. An association is not necessarily causal.

Causality (or causation) is the relationship between an event (the cause) and a second event (the effect), where the second event is understood as a consequence of the first. Causation has been subject to debate since at least 5th century BC where Aristotle defined it. A causal mechanism often involves the joint action of multiple components, referred to as multicausality depicted in the causal pie model[164].

Attempts have been made to make criteria to determine whether an association was causal or not (Table2). However, depending on which philosophy of science mind set you choose, these criteria are ambiguous[164].

Causality is ruled out when an effect precedes a postulated cause. Thus, according to Hills criteria 4, temporal study designs give more information than cross-sectional study designs on causality. Notably, no observational studies can determine causality on its own. An association is as stated above not necessarily causal.

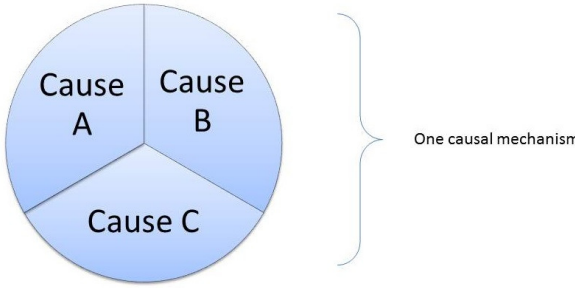



Figure5. Causal Pie Model

| "Causal criteria" of Hill |
|---|
| 1. Strength |
| 2. Consistency of results |
| 3. Specificity |
| 4. Temporality |
| 5. Biologic gradient (Dose-response-relationship) |
| 6. Plausibility |
| 7. Coherence |
| 8. Experimental evidence |
| 9. Analogy |

Table2. Hills criteria of causality

MEASURES OF ASSOCIATION AND STUDY DESIGN

When investigating an association, different measures are used to express the relationship depending on the study design and type of data (Table 3 & 4)[164].

The three observational study designs i.e. cross-sectional, case-control, and cohort differ especially with regard to the element of observational time. A cross-sectional study is a "snap-shot" of a source population i.e. all information obtained refers to the same point in time, In contrast, case-control and cohort studies are longitudinal/temporal studies and include information obtained more than one point in time. A cross-sectional study can assess disease prevalence. A cohort study can assess disease incidence. Prevalence is the proportion of cases with a specific disease at a given time (how widespread the disease is), whereas incidence is the number of new cases developing the disease in a given time period. Prevalence expresses a risk, incidence expresses a rate[164].

A case-control study can be thought of as a modified cohort study, the modification being the sampling/selection of the source population based on the outcome[164]. Due to this selection modification, a case-control study can assess the odds ratio, but not prevalence or incidence. In summary, statistical measures of association of dichotomous outcomes and exposures used in cross-sectional studies are odds ratio or relative risk comparing prevalence. Measures of association of dichotomous outcomes and exposures used in cohort studies are incidence rate ratio, odds ratio, or relative risk. Due to the above mentioned distinction in sampling, only odds ratio is used in case-control studies[164] (Table 3). The standard statistical continuous measure of association when comparing outcomes from two treatment groups is to look at the difference between the mean of each group taking the standard error of the mean into account.

This thesis uses OR for dichotomous outcomes, and Mean Differences for continuous outcomes.

| Study design | Dichotomous Outcome | Continuous outcome |
|---|---|---|
| Cohort | Incidence Rate Ratio<br>Relative Risk<br>Odds Ratio | Mean Difference |
| Case-control | Odds Ratio | Mean Difference |
| Cross-sectional | Odds Ratio<br>Relative Risk | Mean Difference |

Table3. Measures of Association

| Statistical term (Synonyms) | Definition |
|---|---|
| **Incidence** (Incidence Rate) (Incidence density rate) | Incidence is the number of new events per person-time, and conveys information on the development of disease onsets in a population per unit of follow-up time. The time contributed by each person is called "time at risk", and incidence is the number of individuals developing a disease per total time at risk experienced by the population at risk. |
| **Incidence Rate Ratio** (Rate Ratio) (Incidence density ratio) | Incidence rate ratio is the relative difference measure used to compare the incidence rates of events occurring in two different groups (Incidence rate1/Incidence rate2) e.g. Incidence rate of disease in a psoriasis group/ Incidence rate of disease in control group. If the exact time od disease is recorded for all individuals, the Hazard rate ratio can be calculated via regression models. The interpretation of a Hazard rate ratio is that of an incidence rate ratio. |
| **Prevalence** | Prevalence is the proportion of a population found to have a disease at a given point in time, and conveys information about how many people have the disease i.e. how widespread the disease is. |
| **Relative Risk** (Risk Ratio) | Relative risk is a relative difference measure describing the risk of a disease among the exposed group compared to risk of disease among the unexposed group e.g. risk of diabetes in a psoriasis group compared to the risk of diabetes in a control group. |
| **Odds Ratio** | Odds ratio is a relative difference measure describing the odds of a disease among the exposed group compared to odds of disease among the unexposed group e.g. odds of diabetes in a psoriasis group compared to odds of diabetes in a control group. |

Table 4. Statistical terms in observational studies

**Odds Ratio**

In general, measures of relative effect express the chance of an outcome in one group relative to that in the other. The odds of an event is the ratio of the probability of occurrence of an event or outcome to the probability of non-occurrence of the event or outcome. For example, an odds of 6 means that 6 people will experience the event or outcome for every one that does not (6:1). The OR is the ratio of these two odds comparing the odds of an event or outcome in the exposed to those unexposed.

An OR of 1 indicates that the estimated odds are the same in both the exposed and non-exposed group. The value greater than 1 indicates that the exposed group has a higher odds of having the outcome i.e. a positive association. The 95% CI determines whether this association is statistically significant or not. If 95% CI includes 1 the association is not statistically significant at a 5% level.

OR is a measure of a relative effect like Relative Risk (RR). In contrast to RR, the OR is difficult to interpret per intuition. An OR describes the ratio of the *odds* of an outcome in an exposed group in relation to a non-exposed group. This is not exactly the same as RR describing ratio of the *risk* of an outcome in an exposed group in relation to a non-exposed group. RR tells us how much risk is increased or decreased from an initial level. An OR does not entail information on the initial level i.e. the question of how much (the strength of the association) is less comprehensible.

| | Disease (outcome) | No disease (no outcome) |
|---|---|---|
| Exposed | a | b |
| Un-exposed | c | d |

$$OR = \frac{a/c}{b/d} = \frac{a/b}{c/d} = \frac{ad}{bc}$$

$$RR = \frac{a\,/\,(a+b)}{c\,/\,(c+d)} = \frac{a\,/(c+d)}{c\,/(a+b)}$$

Figure6. Calculations of OR and RR

The relationship between the relative risk (RR) and the odds ratio (OR) can be seen by graphing the odds ratio as a function of the risk of disease among the nonexposed. The relationship between OR and RR can be described as the following:

$$RR = \frac{risk\ of\ disease\ among\ the\ exposed}{risk\ of\ disease\ among\ the\ nonexposed} = \frac{p_1}{p_0}$$

$$OR = \frac{p_1/(1-p_1)}{p_0/(1-p_0)} = RR\frac{1-p_0}{1-p_1} = RR\frac{1-p_0}{1-RR\,p_0}$$

Figure7. The relationship between OR and RR

For a relative risk of 1.5, 2 and 3, the odds ratio will diverge from the relative risk as the risk among nonexposed increases and the divergence is greater the larger relative risk as seen in Figure 8. However, in general if the outcome is rare (<2% prevalence) the OR approximates the RR and can be interpreted as such. In contrast, when the outcome is common, the OR does not approximate the RR. An OR above 1 will always overestimate the size of the effect compared to a RR[165]. An OR below 1 will always underestimate the size of effect compared to a RR. The discrepancy between the odds ratio and the relative risk can be expressed as seen in Figure 8 and illustrated in Figure9.

$$\frac{(OR-RR)}{RR} = initial\ risk\ \times (OR-1)$$

Figure8. The discrepancy between the odds ratio and the relative risk. The term "initial risk" used by Daviet et al. is the risk of disease among non-exposed [165]

It has been suggested that if the outcome is common (e.g. MetS prevalence 25%) an OR above 1 can be interpreted as an RR when the OR is up to 3 without significant overestimation. In aggregate, although the qualitative interpretation (is there an association or not) of OR as an RR may not deviate when OR is below 3, quantitative judgments (the strength of the association) of OR should still be done with caution.

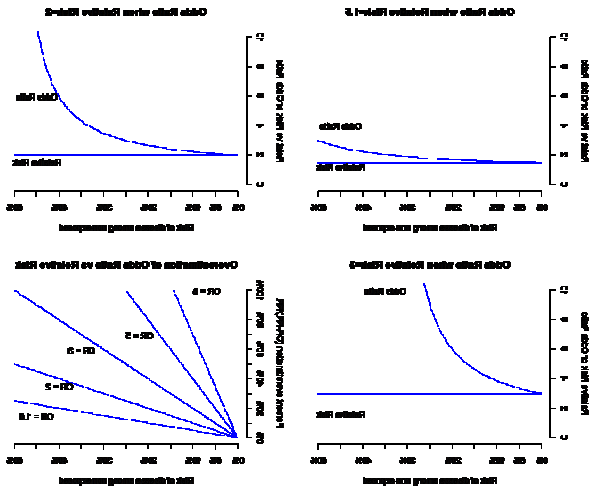


Figure9. Illustration of overestimation of OR in comparison to RR when OR>1

Furthermore, the interpretation of an OR differs according to the study design i.e. an OR in a temporal/longitudinal study (case-control or cohort) contains more information than a cross-sectional study (no temporal element i.e no information of time)[164]. A cross-sectional study answers the question "is there an association or not?" as do both case-control and cohort studies. Additionally, case-control and cohort studies answer the question "Does the exposure precede the outcome?". A cohort study furthermore answers the question "With what rate is this association developing?".

Why use OR instead of RR when OR is so difficult to interpret? The OR has a wide range of superior mathematical properties compared to RR, and some of these are; when making adjustments/controlling for possible confounding factors using multiple logistic regression, ORs and not RR can be derived (with 95% CI) from this class of models. Furthermore, an OR has symmetrical properties which is an advantage when studying associations[166]. The main reason for using OR in Study I was to get one summary estimate and thereby combining all types of observational studies in a metaanalysis. The main reason for using OR in study III and IV was to get a measure of association that was symmetrical, i.e. the direction of the association is not pre-assumed and can therefore be reverse.

**Mean Difference**

Mean Difference is less complicated as it is the difference between the means of two groups compared, and is used for continuous data (outcome). Thus, the name Difference of Means is really more appropriate. It is an absolute measure which quantifies the data.

If the outcome has been log-transformed (e.g. to transform non-normally distributed data like blood sample results into a normal distribution) the Difference of Means is expressed as a Ratio of Means (RM).

$$\exp(\log \text{Difference of Means}) = \exp(\log(x1) - \log(x2))$$
$$= \exp(\log(x1))/\exp(\log(x2))$$
$$= \exp(\log(x1))/\exp(\log(x2))$$
$$= x1/x2$$
$$= \text{Ratio of Means}$$

*x1: the mean of subjects*
*x2: the mean of non-subjects*

Figure10. Mathematical justification of Difference of Means expressed as RM

**Regression analyses in short**

This Ph.D. Thesis uses regression models in Study III and IV to adjust for background factors/possible confounders. A regression analysis is a statistical analysis assessing the association between two variables – possibly adjusting for additional variables[164]. It is used to find the relationship between two (or more) variables. Given data on a dependent variable y and one or more independent variables (e.g. x1, x2, ect) regression analyses involves finding the most suitable mathematical model to describe y as a function of x´s, or to predict y from the x´s. Regression assumes that a change in x will lead directly to a change in y.

Linear regression is used for continuous outcome, and is based on the assumption of a linear relationship between the effect measure and outcome. Logistic regression (binary logistic regression) is used for dichotomous outcome, and based on the assumption of a linear relationship between the logit of the outcome and the exposure (Figure11).

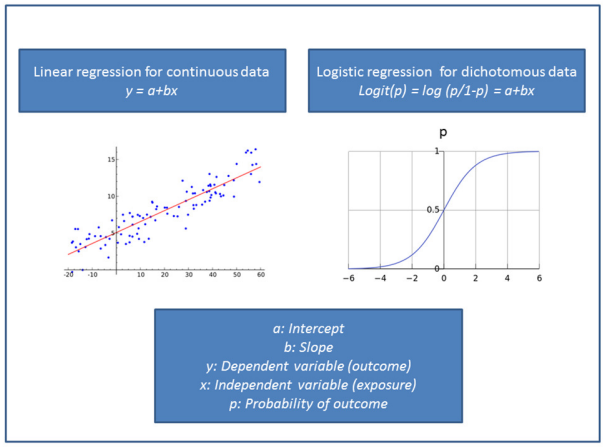



Figure11. Illustrations of regression models

**Errors**

Errors influencing epidemiologic studies can be divided into two types; random and systematic errors, the latter also called *bias*[164] (Figure10). Random errors are reduced to zero if the study is infinitely large. In contrast, systematic errors are maintained even when the study is infinitely large.

The main types of sources of biases in epidemiological studies are selection bias, information bias, and confounding.

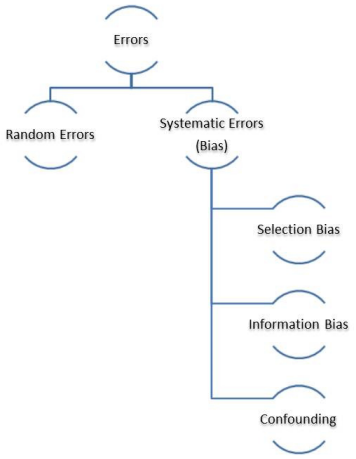



Figure12. Classification of Errors in Epidemiology

Selection bias stems from methods used to select subjects or factors that influence participation rate. Information bias are errors in the collection of information about either the exposure or the outcome e.g. misclassification bias.
Confounding is simply a mixing of effects, which skews the true association. A confounder must be associated with the exposure as well as the outcome (either as a cause or a by proxy cause). Furthermore, a confounder must not be an effect of the exposure.
Confounding is an epidemiological term, and whether there is an equivalent specific statistical test for confounding is ambiguous. The methods of controlling for confounding include randomization, restriction and matching depending on study design. Adjusting for confounding can be done via regression models.

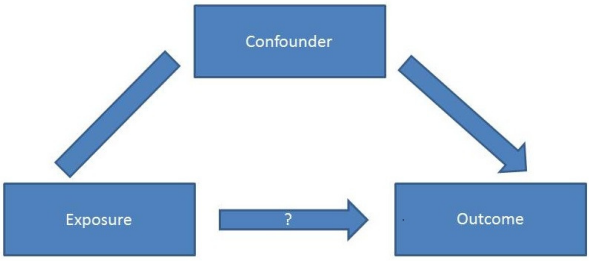



Figure13. Illustration of a confounder

**Effect measure modification**
In epidemiology, effect measure modification (effect modification) refers to the situation in which a measure of effect changes over values of a third variable[164]. Effect modification is, in contrast to confounding, a biological phenomenon in which the exposure has different impact in different groups. The counterpart in statistics is called interaction. Testing for interaction e.g. by stratification requires an adequate sample size in order to provide a meaningful analysis.

**3. META-ANALYSES (STUDY I & II)**
OBJECTIVES
The possible association between PS and CVD, and associated risk factors has been implied, but inconsistent results have been reported. Numerous systematic reviews of the association between psoriasis and cardiovascular morbidity and mortality have been performed, but meta-analyses on the subject are scarce[167-169].
The aim was to create an overview and a statistical summary of the previous body of literature.
Two meta-analyses on psoriasis were performed for dichotomous and continuous outcome respectively.
With regard to the association of HS and MetS as well as CVD, only one investigation[110] could be identified at the time this study was conducted making a meta-analysis not applicable.

Study I:
To create an overview and a statistical summary of previous literature describing the possible association between psoriasis, cardiovascular diseases, and associated metabolic risk factors for dichotomous outcome. Furthermore, relevant subgroup analysis will be performed.
Study II:
To create an overview of previous literature describing the association between psoriasis and metabolic cardiovascular risk factors in terms of quantifying the data i.e. continuous outcome. Furthermore, relevant subgroup analysis will be performed.

METHODS
Both meta-analyses were performed according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology group (MOOSE-guidelines)[170].

**Locating and selecting studies**
The two meta-analyses were based on the same systematic search of studies before 25th October, 2012. The search was conducted in collaboration with an information specialist using the databases MEDLINE, EMBASE, International Pharmaceutical Abstracts, PASCAL, and BIOSIS. The search strategy was constructed to find at least 1 term from 3 search blocks: the term "psoriasis"; synonyms for CVD, MetS, and its components; and terms aimed at identification of any clinical trial. Detailed search strategy can be found in Manuscript I or II, efile 1. Additional relevant articles were found by manual inspection.
The studies selected for inclusion were of original observational study design i.e. cross-sectional/case-control/cohort studies in English, German, Swedish/Norwegian/Danish. The study variable being psoriasis, and the CV risk factors being the outcome.
Study I dealing with dichotomous outcome included studies with the following outcome: CVD(ischemic heart disease i.e. myocardial infarction, angina, coronary artery disease, and cerebrovascular disease, peripheral vascular disease, atherosclerosis), associated risk factors (metabolic syndrome, diabetes, hypertension, dyslipidemia, obesity), and cardiovascular mortality.
Study II dealing with continuous outcome included studies with the following outcome: Lipid profile (Total cholesterol, LDL, HDL, TG, Systolic and Diastolic Blood Pressure, BMI (expressing general obesity), Waist Circumference (expressing abdominal obesity), non-fasting/fasting glucose and HbA1c (expressing diabetes)
Exclusion criteria were: abstracts, unpublished studies, lack of raw data, and overlapping studies.

**Data extraction**
Data extraction was performed by two and one reviewer, in study I and II respectively. The following data from each study was extracted: author; year of publication; journal; country/ethnicity; number of cases/controls (in Study I: additionally, number of exposed/non-exposed cases/controls). For Study II: additionally mean values and standard deviation. We referred to "skin psoriasis (PsO)" if the inclusion criteria was having skin psoriasis (mostly plaque psoriasis), and "psoriatic arthritis (PsA)" if the inclusion criteria was having psoriatic arthritis. We referred to "hospital-based" when recruitment of cases was from in/outpatient clinics. A study was classified as "population-based (overall)" if cases were recruited from the general population, as "population-based (insurance database)" if cases were recruited from health care databases, and "population-based (excluding insurance database)" if cases were recruited from the general population, but data did not come from a health insurance database.

**Definitions of end points in Study I (dichotomous outcome)**
Cardiovascular diseases were defined as ischemic heart disease including myocardial infarction, angina or coronary artery disease and cerebrovascular disease defined as stroke or transient ischemic attack. These diagnoses were based on data from medical charts, databases, or were self-reported. Atherosclerosis and peripheral vascular disease were defined by either medical charts, databases or self-reported diagnosis.
Cardiovascular mortality was defined by cardiovascular death in databases or medical charts.
Diabetes was defined via either relevant blood samples, anti-diabetic drugs, or diagnosis of diabetes either in medical charts, databases or self-reported.
Hypertension was defined as either physical examination (proximal blood pressure), diagnosis of hypertension either in medical charts, databases or self-reported.
Dyslipidemia was defined as either blood sample measuring (total-cholesterol or triglycerides), medical charts, databases or self-reported.
Obesity measured by BMI was defined mostly as BMI above 30 or 25 kg/m$^2$, either by physical examination or self-reported.
Obesity measured by abdominal fat was defined as a large waist measurement (mostly men > 102cm and women > 88cm).
The metabolic syndrome was mostly according to the NCEP-ATPIII-definition.

**Definitions of end points in Study II (continuous outcome)**
Lipid profile (total cholesterol (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), Triglyceride (TG) (mg/dL)), fasting/non-fasting blood glucose (mg/dL), and Hba1c (mmol/mol) were all measured in venous blood samples. Conventional conversion factors were used to make the units compatible. See Manuscript II for conversion factors.
Systolic and diastolic blood pressures (mmHg) were measured by physical examination. BMI was calculated as weight divided by height squared (kg/m$^2$) either from information based on physical examination or self-reported. Abdominal fat was expressed as waist circumference (cm) by physical examination.

**Statistical Analysis**
A meta-analysis is the process of using statistical methods to combine the results of different studies. The purposes of performing a meta-analysis can be to create an overview of previous body of literature, increase power and improve precision of an estimate, and moreover settle controversies arising from previous conflicting studies[171].
The principle of a meta-analysis is first to calculate a summary statistic for each study, and subsequently calculate a summary (pooled) effect estimate as a weighted average of the individual estimates (Figure14).

$$Weighted\ average = \frac{Sum\ of\ (estimate\ x\ weight)}{sum\ of\ weights}$$

Figure14. Weighted average in metaanalysis

A meta-analysis can use fixed or random effects statistics to gain the statistical summary[171]. Fixed effect meta-analysis is based on the assumption that the true effect estimate is the same in every study (no statistical heterogeneity). This implies that observed differences between study results are due to chance. In contrast, random effects meta-analysis assumes that the different estimates of the studies are not identical, but follow some sort of distribution. The most widely used method of random effects analysis is DerSimonian and Laird, which was used in Study I and II. The more information a study contains (i.e. the larger the study), the bigger the weight, the more contribution to the weighted average[171].
Thus, due to expected substantial heterogeneity, random effects statistics with the method of DerSimonian and Laird were used. This does not, however, mean that heterogeneity should no longer still be explored further.
The summary effect measures in these meta-analysis were OR (95%CI) (Study I) and Weighted Mean Difference (WMD) (95%CI) (Study II) for dichotomous and continuous outcome, respectively. As stated earlier, the OR is the ratio of the odds of an outcome in exposed vs. unexposed subjects. The Weighted Mean Difference is the absolute difference between the mean value in the exposed vs. non-exposed subjects.
Selecting the summary statistical effect measure in a metaanalysis, can be discusses based on three criteria: consistency, mathematical properties, and ease of interpretation[171]. Three types of observational studies (i.e. cross-sectional, case-control, and cohort) were included in the first meta-analysis for dichotomous outcome (Study I). As discussed in "General Methods of the Thesis" an OR is the only effect measure that can express an association in all types of observational studies and thus give values that are similar/consistant for all study types. Subsequently, the OR was selected as the summary effect measure in Study I in order to accommodate all types of observational studies accomplishing one statistical summary estimate for all included studies in. Furthermore, selecting an OR in Study I made comparing results of Study I with the ORs in Study III and IV more suitable. As we do not know if this possible association is of a causal nature or the

"direction" of this possible causality, the symmetrical mathematical properties discussed earlier is an major advantage of OR.
The limitation of using OR in Study I is that any time element in the data of temporal/longitudinal studies are lost. The thesis will discuss this "statistical time bias" in the limitation section below. Moreover, the OR is not easily interpreted.
We performed all meta-analyses with STATA statistical software 11.0 (Metrika Consulting, Stockholm, Sweden) using the "metan" command to calculate OR (95%CI), and WMD(95%CI) for dichotomous and continuous outcome, respectively.
Heterogeneity is any kind of variability among the different studies in a meta-analysis. A distinguishment can be made of the different types of heterogeneity; clinical heterogeneity (variability in participants, outcomes); Methodological heterogeneity (variability in study design/quality; Statistical heterogeneity (variability in effect measure) is a consequence of clinical and methodological heterogeneity.
The statistical heterogeneity was assessed with $I^2$ statistics[171,172], which is useful for quantifying inconsistency. Describes the percentage of the variability in effect estimates that is due to heterogeneity rather than random error. A rough interpretation of $I^2$ is: 30-60% moderate heterogeneity, 50-90% substantial heterogeneity, >75% considerable heterogeneity[171].
Furthermore, clinical and methodological heterogeneity was assessed by relevant subgroup analysis i.e. according to PsO or PsA. In addition, Study I provided subgroup analysis according to whether a study was hospital- or population-based, ethnicity, before/after obesity epidemic, study type, and study quality. The study quality assessment of each study was based on a modified version of the New-castle-Ottowa Scale[173]. See Manuscript I and II for further details on subgroup analyses.
Publication bias was assessed by visual inspection of funnel plots where asymmetry suggests possible publication bias[171]. In Manuscript I Eggers test was performed additionally[174].
Funnel plots are simple scatter plots of effect measures of each study (x-axis), and the size of each study (y-axis). In the absence of bias the plot should resemble a symmetrical inverted funnel. Publication bias, which is a type of selection bias, expresses the challenge that the likelihood of finding studies is related to the results of those studies. However, an asymmetry can also indicate reasons other than publication bias e.g. other selection bias (language bias), poor methodological quality of smaller studies, true heterogeneity (size of effect differs according to study size), or chance.
Eggers test is a test for asymmetry of the funnel plot. It is a test for the Y intercept = 0 from a linear regression of normalized effect estimate (estimate divided by its standard error) against precision (reciprocal of the standard error of the estimate). A p-value less than 0.1 suggests asymmetry i.e. publication bias.

**SUMMARY OF RESULTS**

**Study I:**
Of 835 references in the original search, 75 relevant articles were identified. Up to 503,686 cases and 29,686,694 controls were included.
Psoriasis was associated with cardiovascular disease in total (odds ratio [OR] 1.4; 95% confidence interval [CI] 1.2-1.7), ischemic heart disease (OR 1.5; 95% CI 1.2-1.9), peripheral vascular disease (OR 1.5; 95% CI 1.2-1.8), atherosclerosis (OR 1.1; 95% CI 1.1-1.2), diabetes (OR 1.9; 95% CI 1.5-2.5), hypertension (OR 1.8; 95% CI 1.6-2.0), dyslipidemia (OR 1.5; 95% CI 1.4-1.7), obesity by body mass index (OR 1.8; 95% CI 1.4-2.2), obesity by abdominal fat (OR 1.6; 95% CI 1.2-2.3), and the metabolic syndrome (OR 1.8; 95% CI 1.2-2.8), but not associated with cerebrovascular disease (OR 1.1; 95% CI 0.9-1.3) and cardiovascular mortality (OR 0.9; 95% CI 0.4-2.2).
Subgroup analyses; the strongest associations were seen in hospital-based studies and psoriatic arthritis. Population-based studies did not show significant associations, with the exception of dyslipidemia. Stratifying the population-based studies revealed that results for the population-based (insurance database) studies generally were significant compared with non-significant results for population-based (excluding insurance database) studies.
Subgroup analyses according to study quality, before/after the obesity epidemic did not change the statistical significance of the results. No uniform pattern could be detected with regards to ethnicity. With regards to study design, a non-significant association for cohort studies, and a significant association for case-control/cross-sectional studies were found.
The most prominent limitation was a considerable heterogeneity, which makes clinical interpretation and generalization challenging. Performing subgroup analyses reduced, but did not eliminate, heterogeneity. Funnel plots indicated publication bias as a possible source of heterogeneity. Furthermore, disregarding information of time in follow-up study designs was a limitation. This limitation is discussed below (statistical time bias).
In aggregate, psoriasis was associated with ischemic heart disease and cardiovascular risk factors. The association was only significant for hospital-based studies, except for dyslipidemia, which was also significant in population-based studies.

**Figures illustrating main results of Study I:**

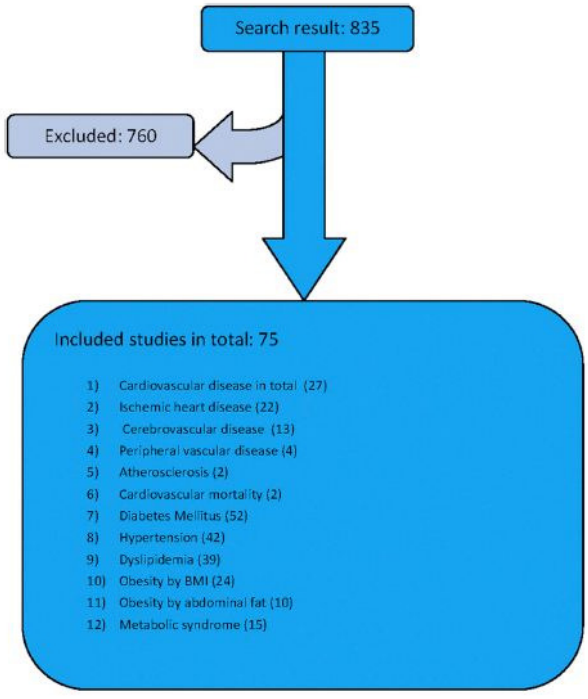


Figure15. Flow chart of search results, included and excluded references (Figure 1 in Manuscript I)

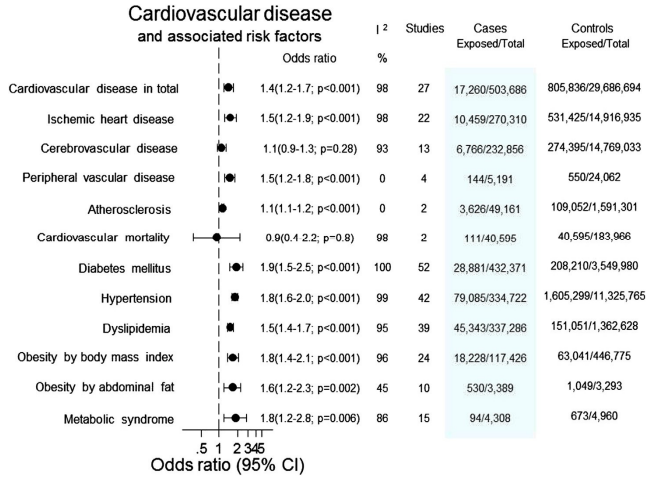



Figure16. Overall OR for end points by random effects model: OR > 1 indicates that cases have higher odds than controls. CI: Confidence Interval (Figure2 in Manuscript I). Corresponding forest plots can be found in efiles for Manuscript I.

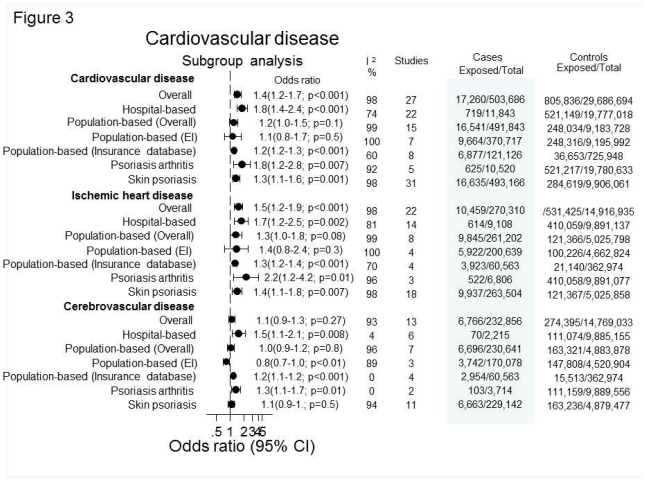



Figure17. Subgroup analysis: OR for subgroups for cardiovascular morbidity and mortality by random effects model. EI: Excluding insurance database.

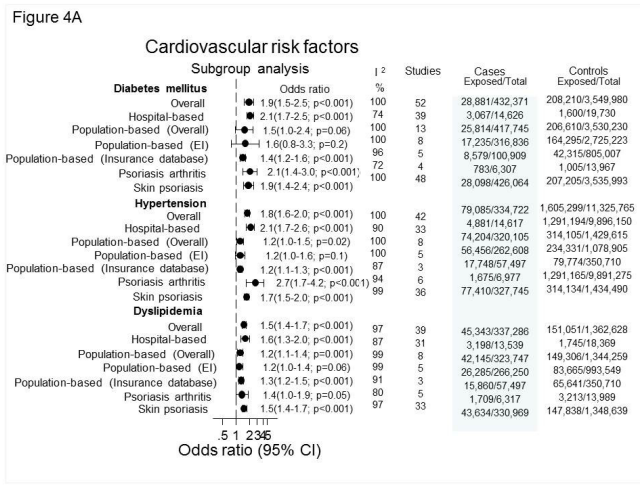



Figure18. Subgroup analysis: OR for subgroups of metabolic syndrome elements by random effects model (Diabetes, hypertension, and dyslipidemia)

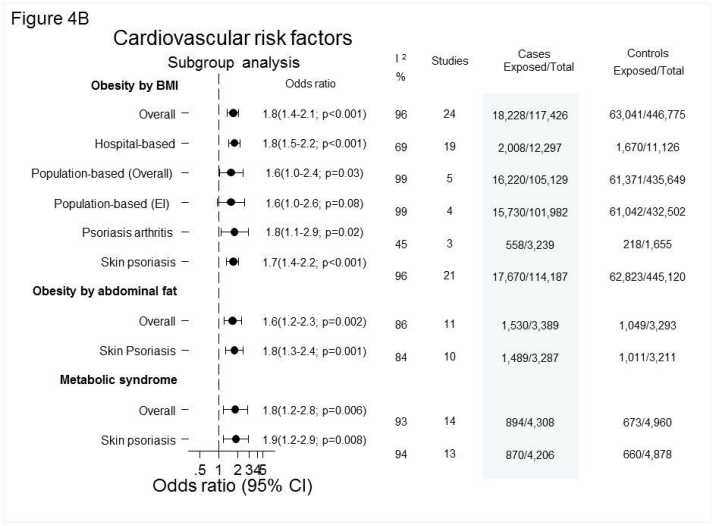



**Figure19.** Subgroup analysis: OR for subgroups of metabolic syndrome elements by random effects model **(Obesity by BMI, obesity by abdominal fat, and metabolic syndrome)**

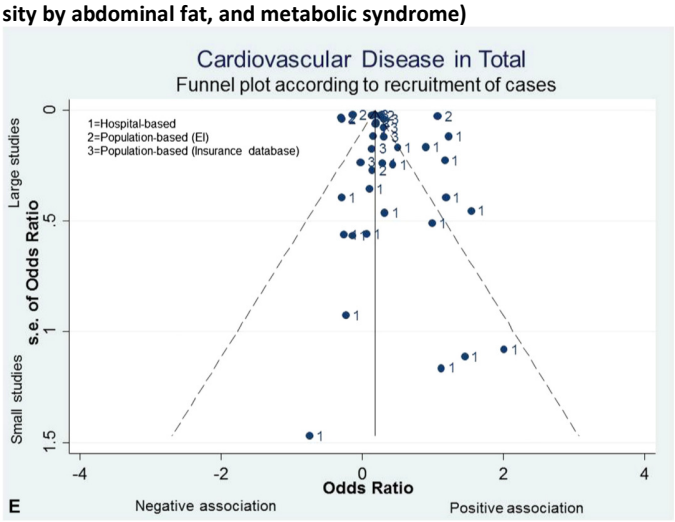



Figure20. Funnel plot of CVD according to recruitment of cases revealing a tendency towards true heterogeneity with regard to hospital- vs. population-based studies, and further suggesting some publication bias.

**StudyII:**

59 studies with up to 18,666 cases and 50,724 controls were included. Psoriasis cases had a higher total cholesterol (Weighted Mean Difference 8.83 mg/dL (Confidence Interval 95% 2.94;14.72, p = 0.003) (= 0.23 mmol/L), higher LDL cholesterol (9.90 mg/dL (1.56;18.20, p = 0.020)(= 0.25 mmol/L), higher TG (16.32 mg/dL (12.02;20.63, p = 0.000)(= 0.18 mmol/L), a higher systolic blood pressure 4.77 mmHg (95%CI 1.62;7.92, p = 0.003), a higher diastolic blood pressure 2.99 mmHg (95%CI 0.60;5.38, p = 0.014), higher BMI 0.73 kg/m$^2$ (0.37;1.09, p = 0.000), higher waist circumference (WC) 3.61 cm (2.12;5.10), higher fasting glucose 3.52 mg/dL (0.64;6.41, p = 0.017)(= 0.20 mmol/l), higher non-fasting glucose 11.70 mg/dL (11;24;12.15, p=0.000), and a higher HbA1c 1.09 mmol/mol (0.87;1.31, p = 0.000)(=2.2%).

Subgroup analyses; No uniform pattern was observed with regard to subgroups PsO and PsA.
The most prominent limitation was a considerable heterogeneity, which makes clinical interpretation and generalization challenging. Performing subgroup analyses reduced, but did not eliminate, heterogeneity. Funnel plots indicated publication bias as a possible source of heterogeneity.
In a preventive medicine perspective, the weighted mean differences between cases and controls are significant, and therefore relevant to the clinical management of psoriasis patients.

**Figures illustrating main results of Study II:**

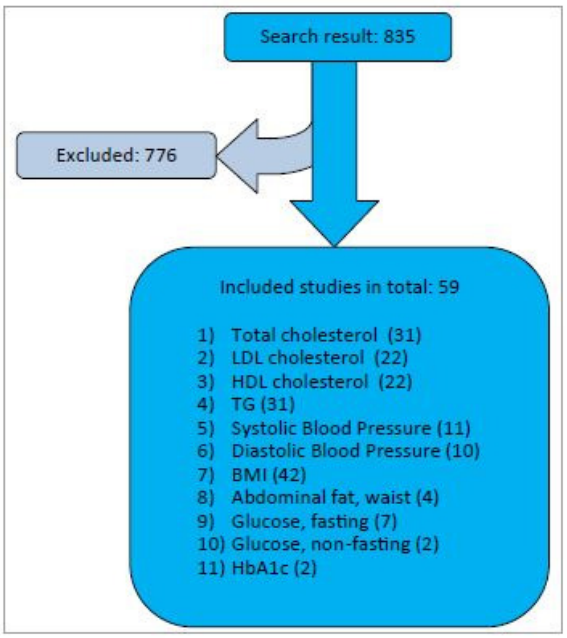



Figure21. Flow chart of search results, included, and excluded references (Figure 1 in Manuscript II)

Figure22a-k. Below; Forest plots of the 11 cardiovascular risk factors variables;(Figure 2 a-k in Manuscript II)

Figure 2a

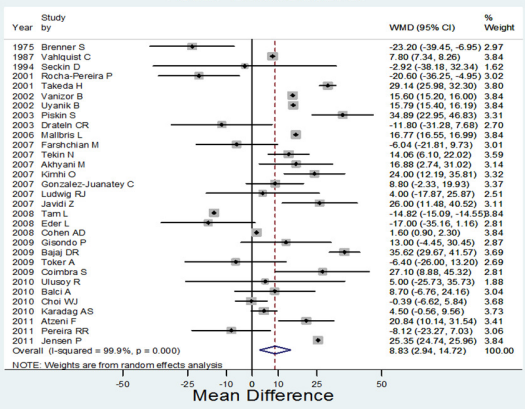



Figure 2b

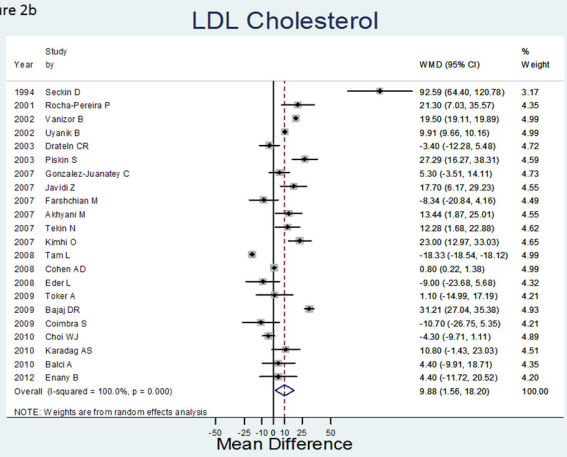



Figure 2c

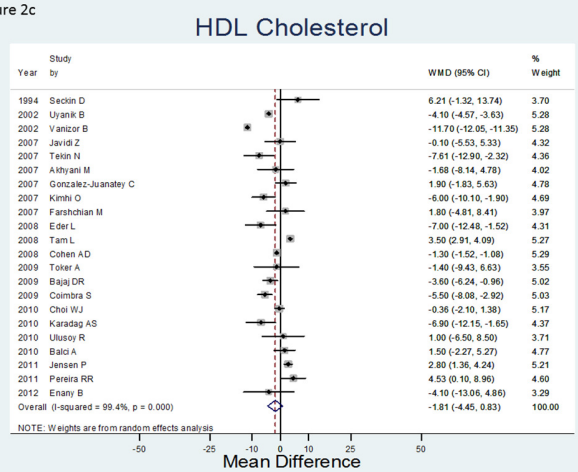



Figure 2d

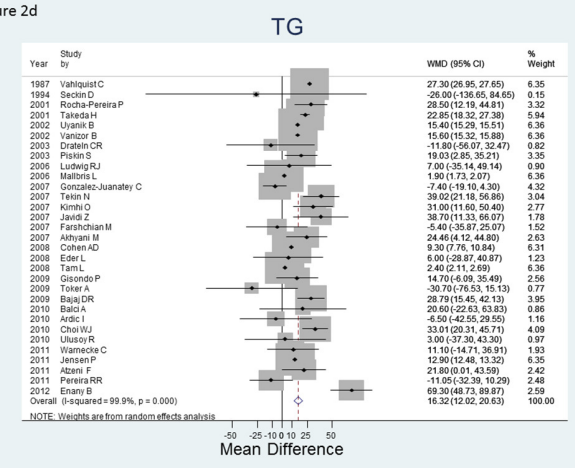


Figure 2e

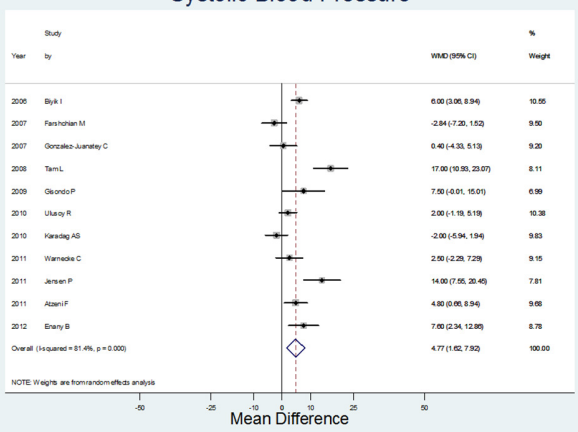



Figure 2h

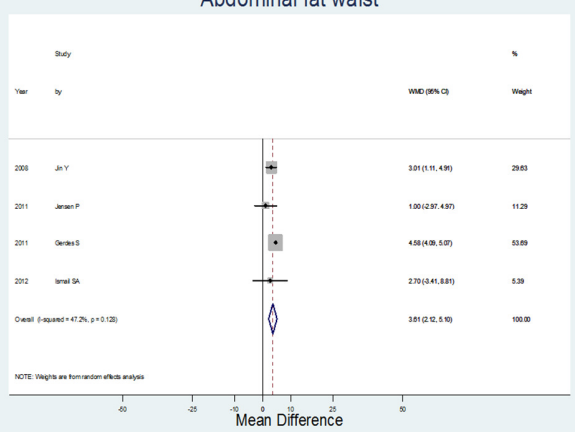



Figure 2f

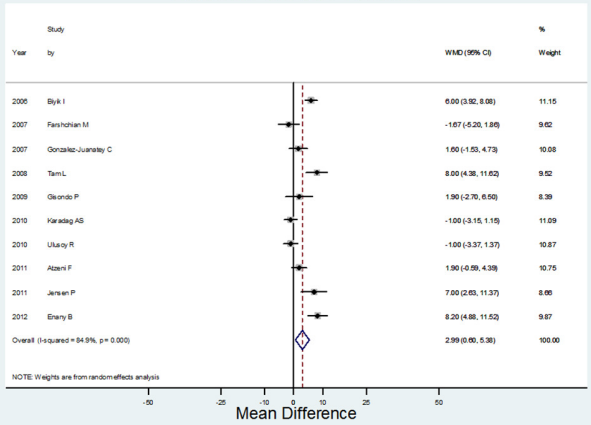



Figure 2i

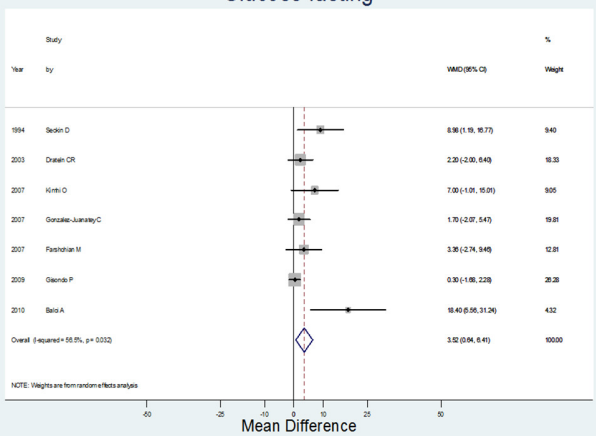



Figure 2g

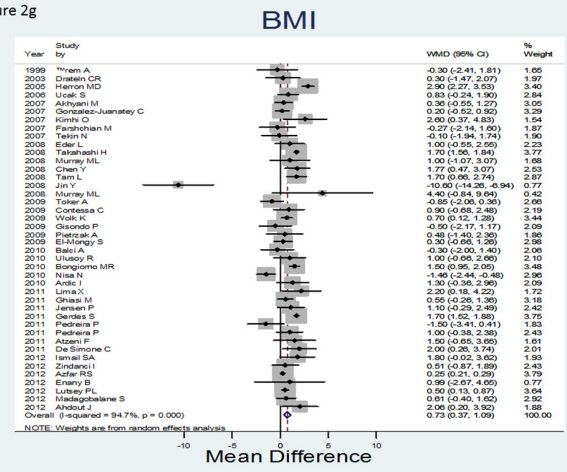



Figure 2j

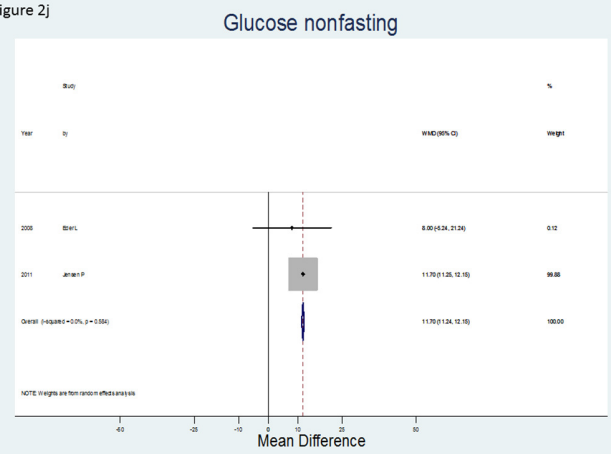
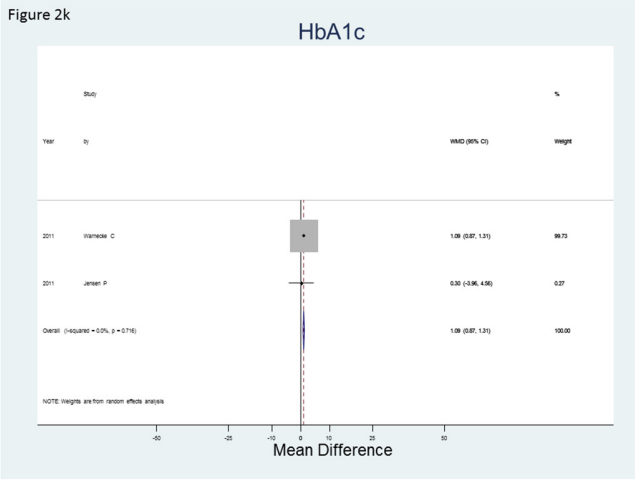


Figure 2k




**DISCUSSION (META-ANALYSES)**

**In aggregate**

In aggregate, psoriasis was positively associated with CVDs in total (ischemic heart disease + stroke), and associated risk factors, but not with cerebrovascular disease, and CV mortality. The significant ORs of the positive associations ranged from 1.1 to 1.9. Previous meta-analyses also found significant positive associations between psoriasis and CVDs and associated risk factors (Table 6). In agreement with the OR of CVDs in total of 1.41(1.20-1.66) in Study I a meta-analysis by Xu et al.[169] on cohort studies found a relative risk of 1.20(1.10-1.31) for composite vascular end point (MI+stroke). Previous meta-analyses by Semerasekera et al. [175] (cohort studies included), Armstrong et al. [176] (all types of observational studies), and Xu et al.[169] (cohort studies included) on myocardial infarction also found positive associations. (See Table 6 for further details)

Additionally, previous meta-analyses on the associated metabolic cardiovascular risk factors of diabetes, hypertension, and obesity is in agreement with the ORs of 1.9(1.5-2.5), 1.8(1.6-2.0), and 1.6(1.2-2.3) to 1.8(1.4-2.1), respectively in Study I. Hence, Armstrong et al. [168](all types of observational studies included) found an OR of 1.59(1.38-1.83) for diabetes, Armstrong et al. [177](all types of observational studies included) and Armesto et al.[167] found ORs of 1.58(1.42-1.76) and 1.66(1.36-2.04) for hypertension, respectively, and Armstrong et al. [178] (case-control and cross-sectional studies included) found an OR of 1.66 (1.46-1.89) for obesity (see Table 6 for further details). Moreover, Armstrong et al. [179] (case-control and cross-sectional studies included) found an OR of 2.26(1.70-3.01) for MetS compared to an OR of 1.8(1.2-2.8) for MetS in Study I.

This thesis did not find psoriasis to be associated with cerebrovascular disease and CV mortality. In contrast, previous meta-analysis on stroke found a positive association; Semerasekera et al.[175] (cohort studies included) found an incidence rate ratio of 1.13(1.01-1.26), Armstrong et al.[176] a risk ratio for mild psoriasis of 1.12(1.08-1.16) and severe psoriasis 1.56(1.32-1.84), and Xu et al. [169] (cohort studies included) a relative risk of 1.20(1.10-1.31). Effects measures in previous meta-analysis were in general smaller for stroke than that of e.g. MI and associated cardiovascular risk factors. Notably, Semerasekera et al. [175] did a subgroup analysis revealing a statistically significant association between severe psoriasis and stroke, however, not for mild psoriasis(Incidence rate ratio of 1.59(1.34,1.89) vs. 1.15 (0.98.1.35)). This may be suggestive of a dose-response relationship with regard to severity of psoriasis and stroke.

Along this line, previous metaanalyses by Semerasekera et al. and Armstrong et al. found a significant association between CV mortality and severe psoriasis, however, not for mild psoriasis (see Table 6).

On a quantitative level, psoriasis had a more un-favourable lipid profile with higher levels of total cholesterol, LDL cholesterol, and TG. Furthermore, levels of diastolic and systolic blood pressures, BMI, fasting/non-fasting glucose, and HbA1c were higher when compared to controls. There was no statistical difference in HDL Cholesterol between cases and controls.

The magnitude of the CV risk factors identified in quantitative meta-analyses is of importance, both in terms of practical management as well as pathophysiologically.

A follow-up study of the effects of statins on CV events when LDL cholesterol was reduced by 54 mg/dl(=1.4 mmol/l), TG by 21 mg/dl(=0.24 mmol/l), and HDL cholesterol increased by 1.97 mg/dl(=0.05 mmol/l) suggesting that a small difference in lipid profile matter when preventing CVD[180]. The present study showed a WMD of 0.25 mmol/l and 0.18 mmol/l in LDL and TG respectively, and while the differences in LDL are considerably lower than reported following statin use, the TG changes are similar indicating abnormal lipid levels amendable to meaningful prophylaxis.

In contrast, non-significant results were found with regard to HDL cholesterol. HDL works on a smaller scale i.e. the cardioprotective level for HDL is >1 mmol/l as compared to <3 mmol/l for LDL. The difference in HDL between cases and controls may consequently be smaller than that of LDL. This non-significant result may be interpreted as either lack of statistical power, or lack of clinical significance. The mutual influence of quantitative and qualitative aspects of lipids is however complex. The absence of major differences between the quantity of these lipids may therefore be speculated to be of less importance if the quality i.e. composition or function of lipids is affected[16,181].

A recent meta-analysis of preventive treatment of hypertension suggests that lowering systolic blood pressure by 10 mm Hg or diastolic blood pressure by 5 mm Hg reduces cardiovascular heart disease events (fatal and non-fatal) by 22% and stroke by 41%[182]. Studies on pre-hypertensive individuals have shown a reduction in the number of cerebrovascular incidents following implementation of antihypertensive medicine[183]. The National High Blood Pressure Education Program Coordinating Committee published its first statement on the primary prevention of hypertension, and noted that even small changes in blood pressure as low as 2 mmHg could reduce mortality[184]. Seen in this perspective, the WMD of 4.77 and 2.99 mmHg systolic and diastolic respectively, are most likely of clinical relevance to patients suffering from psoriasis.

BMI is a general measurement of obesity, and WC a more specific indirect measurement of visceral obesity. It is suggested that the expanded visceral fat could act as an endocrine gland and produce cytokines hence insulin resistant state. Subcutaneous fat may act as a protective metabolic buffer. In contrast, visceral fat could be a marker of "dysfunctional" adipose tissue associated with fat stored at undesired sites such as the liver, the heart, and the pancreas causing dysfunction in these organs leading to e.g. MI, DM[185].

It has been suggested that a mean weight loss of 4.2 kg may reduce the risk of diabetes by 58%[186]. Our study found a WMD in

BMI of 0.73 kg/m2, which would equal approximately 2.24 kg in an average 1.75 meter tall person. The observed difference in weight between psoriasis patients and controls is therefore approximately half of this and its significance similarly unclear.
The research field of diabetes, insulin resistance and cardiovascular disease is expanding rapidly. Blood glucose has been suggested as a biomarker of MI[187], and lowering glucose levels by Glucose-Insulin-Potassium-infusion has been found to reduce the damage of MI even in non-diabetics[188]. On the other hand glycaemic control of diabetics with cardiovascular disease has failed to prove beneficial in the prevention of additional vascular events[189]. In addition, not all diabetic patients are at a similar risk for CVD[190]. Glucose control is thought to generate a "metabolic memory" suggesting it takes several years before control translates into cardiovascular protection[126].
Studies of glycaemic control have suggested that a reduction of HbA1c of 0.9% or fasting plasma glucose of 1.53 mmol/l reduces overall cardiovascular events by 9%, mainly due to a decrease in MI rather than stroke[126]. The current study showed a WMD of 2.2%, 0.2 mmol/l, and 0.65 mmol/l of HbA1c, fasting, and non-fasting blood glucose respectively. While the difference with regard to HbA1c is of obvious clinical importance, the mean differences in glucose levels may seem of lesser clinical importance. It has however, been indicated that transient hyperglycemia mediates persistent gene-activating events promoting inflammation and CVD. Thus, interpreting mean glucose differences may be too simple a translation as compared to looking at incidences of transient hyperglycaemia[126].
Furthermore the dose-response relationship between fasting blood glucose levels below those diagnostic of diabetes with cardiovascular events has been found to be J-shaped i.e. risk levels increase only beyond specific glucose thresholds[191,192.]
In subgroup analysis, hospital-based studies and insurance database studies demonstrated an association whereas population-based (overall and excluding insurance database) did not, with the exception of dyslipidemia. This subgroup analysis was only performed in Study I.
Furthermore, higher ORs in PsA were observed when compared to PsO in Study I, but no uniform pattern was found in Study II. A metaanalysis by Armstrong et al. found a higher OR for PsA than for skin psoriasis with regard to hypetension (See Table 6). Additionally, subgroup analysis in Study I according to ethnicity, study quality, or obesity epidemic did not significantly change the results.
The higher OR of hospital-based vs. population-based psoriasis cases compared to controls may represent a dose-response relationship between psoriasis and the comorbidities reflecting possible causality (according to Hills criteria), or suggest that the associations are present in severe disease only. This is in agreement with previous meta-analyses finding higher effects measures for severe vs. mild psoriasis (see Table 6). Supporting the findings of higher ORs for hospital-based psoriatics is a study of CV mortality yielding a significant increased risk for in- but not outpatients[193].
The higher ORs for psoriasis arthritis as compared with skin psoriasis may similarly reflect a dose-response relationship if psoriatic arthritis is assumed to represent a more severe degree of the psoriasis disease. PsA may also, however, represent a different disease entity, or simply indicate that joint pain causes immobility leading to sedentary lifestyle with subsequent CV risk.

**Strengths and limitations**

The major strengths of the meta-analyses were the large number of cases and controls yielding high power, and furthermore the elucidating subgroup-analyses.
The major strength of the large sample sizes is indirectly at the same time the major limitation as it leads to considerable heterogeneity amongst the large number of studies included.
One could argue that the need for extensive meta-analyses precedes the expected challenge of a considerable heterogeneity. Heterogeneity was expected due to the large number of studies, and was addressed by using random effects analysis.
The study quality assessment in Study I showed lower heterogeneity in subgroup analyses suggesting that methodological heterogeneity is an important contributing factor.
Some publication bias, i.e. unpublished negative results, appeared to be present. The funnel plots in Study I revealed a tendency of true heterogeneity with regard to hospital- vs. population-based studies (Figure18).
Despite the methods used to accommodate the considerable heterogeneity, this issue still remains, and subsequently challenges the reliability to generalize and clinically interpret the results. Similarly, previous meta-analysis have all found large heterogeneity (Table 6).
Despite the suggested dose-response relationship of the severity of psoriasis (i.e. hospital vs. population-based results) the results cannot demonstrate causality between psoriasis and the investigated comorbidities as both meta-analyses are based on observational studies.
Notably, the higher OR for hospital-based compared to population-based cases might express a possible surveillance/detection bias i.e. there might be a decreased threshold of detecting comorbidities in hospital-based patients.
Possible selection bias was also addressed by subgroup analysis in Study I. The majority of studies were hospital-based ,i.e., specialist diagnosis of psoriasis. An association was found in the hospital-based and population-based studies relying on health insurance databases. In contrast, no association was found between cases from the general population compared to controls, except for dyslipidemia. Misclassification bias might be a possible explanation of this i.e. diagnostic accuracy is lower in population-based studies as the vast majority of psoriasis diagnoses were self-reported vs. specialist diagnoses in in/outpatient clinics. The socioeconomic status of patients with or without health insurance may be a further source of selection bias.
Detection bias is another consideration, i.e., hospital access may provide a more correct and earlier diagnosis of both psoriasis and comorbidities.
Another limitation is the absence of data on possible use of anti-hypertensive/cholesterol/diabetic medicine, which could influence the quantitative meta-analysis.
Furthermore, the limitation of statistical time bias is present in Study I Selecting OR as the summary effect measure reduces the information in large-scale cohort studies to information similar to that of case-control/cross-sectional studies by disregarding the information on time at risk, and thereby the potential differences in time at risk between exposed and non-exposed individuals. Figure 23 and Table 5 illustrate this statistical time bias.
Subgroup analyses excluding cohort studies did not significantly change the main results of the meta-analysis. The subgroup meta-analyses on cohort studies were, however, non-significant. This is in general in contrast to other metaanalyses of cohort studies suggestive of a presence of statistical time bias in Study I (Table 6).

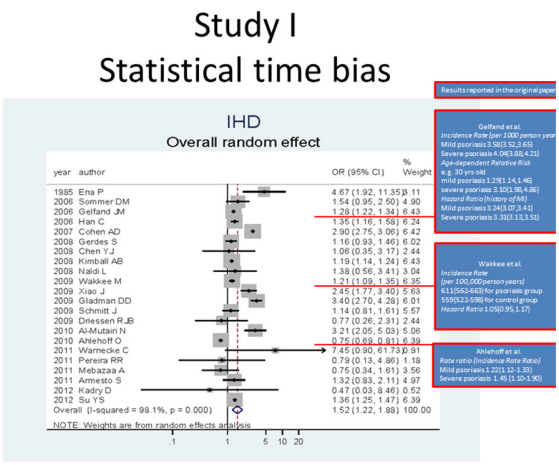



Figure 23 Statistical Time Bias in Study I.
Illustration of how the methodology of the meta-analysis in Study I may influence the originally reported results. The illustration has made with studies[21,39,56] included in the metaanalysis of ischemic heart disease (IHD) in Study I.

*Below:*

Table 5 Statistical Time Bias in Study I.
Illustration of how the methodology of the meta-analysis in Study I may influence the originally reported results. The illustration has made with studies[21,39,56] included in the metaanalysis of ischemic heart disease (IHD) in Study I.

Table 6 Overview of previous metaanalyses[38,169,175-179,194].
Comparison of methodology and results of previous meta-analyses of psoriasis and cardiovascular diseases and associated risk factors.

| Table 5 Statistical Time Bias in Study I | | | | | | |
|---|---|---|---|---|---|---|
| **Author** | **Study design** | **Methodology in original article** | **Results reported in original article** | **Methodology in Miller et al metaanalysis (Study I)** | **Results in Miller et al metaanalysis (Study I) OR(95% CI)** | **Comments to the methodology in metaanalysis (Study I)** |
| Wakkee et al 2009, JID | Cohort | Effect measures: Incidence Rate Hazard Ratio<br><br>Outcome: Ischemic heart disease | Incidence Rate/100,000 person years<br><br>611(562-663) for psoriasis group 559(522-598) For reference group Adjusted Hazard Ratio 1.05(0.95,1.17) Mean follow-up time: 6 years | Odds Ratio (OR) was estimated based on number of new events in psoriasis vs. control group | 1.21(1.09,1.35) | Disregarding any element of time could bias the result Assumption: one patient has one event |
| Ahlehoff et al 2010, J Int Med | Cohort | Effect measures: Rate ratio =incidence rate ratio) was adjusted via a time-dependent Poisson regression model<br><br>Outcome: Myocardial infarction (MI) | Rate Ratio<br><br>1.22(1.12,1.33) for mild PS 1.45 (1.10,1.90) for severe PS Mean follow-up time: 9.2 years for controls, 5 years for psoriasis | Odds Ratio was estimated as one estimate for the whole psoriasis group (mild+severe) based on data of number of new events in the psoriasis vs. control group | 0.75 (0.69,0.81) | Disregarding any time element could bias the result Assumption: one patient has one event |
| Gelfand et al 2006, JAMA | Cohort | Effects measures: Incidence rate Relative Risk (new events of MI) Hazard ratio (of history of MI)<br><br>Outcome: MI | Incidence Rate/ 1000 person years 3.58(3.52,3.65) for mild PS 4.04(3.88,4.21) for severe PS Age-dependent Relative Risk e.g. 30 yrs old 1.29(1.14,1.46) for mild PS 3.10(1.98,4.86) for severe PS<br><br>Hazard Ratio 3.24(3.07,3.41) for mild PS 3.31(3.13,3.51) for severe PS<br><br>Mean follow-up time: 5.4 years | Odds Ratio was estimated from the ”history of MI ” in psoriasis patients vs. controls. The data of new events was not used. | 1.28(1.22, 1.34) | No use of follow-up data. Retrospective data (history of MI) was used instead. |

| Table 6 Overview of previous metaanalyses | | |
|---|---|---|
| **Meta-analysis by** | **Methodology clues** | **Summary of results** |
| Armstrong et al, 2013<br>JAAD | Case-control or cross-sectional studies were included.<br>Statistical analysis:<br>Pooled Odds Ratio(OR) based on crude ORs from original paper. Random effects models of DerSimonian and Laird. | 12 studies were included<br>Metabolic Syndrome<br>• OR 2.26(1.70,3.01)<br>Substantial heterogeneity |
| Semarasekera et al, 2013<br>JID | Cohort studies were included.<br><br>Statistical analysis:<br>Relative Risk estimates (standardized mortality ratio (SMR), hazard ratio (HR), and Incidence Rate Ratio (IRR)).<br>Random effects models of DerSimonian and Laird. | 14 studies were included<br>CVD mortality (SMR or HR)<br>• SMR 1.03(0.86,1.25) for mild psoriasis<br>• SMR 1.37(1.17,1.60) for severe psoriasis<br>• HR 1.57(1.26,1.96) for severe psoriasis<br>MI (HR or IRR)<br>• 1.40(1.03,1.89) for all psoriasis<br>• 1.34(1.07,1.68) for mild psoriasis<br>• 3.04(0.65,14.35) for severe psoriasis<br>Stroke (HR or IRR)<br>• 1.13(1.01,1.26) for all psoriasis<br>• 1.15(0.98,1.35) for mild psoriasis<br>• 1.59(1.34,1.89) for severe psoriasis<br>Substantial heterogeneity |
| Armstrong et al, 2013<br>JAMA derm | Cohort, case-control and cross-sectional studies were included.<br><br>Statistical analysis:<br>Using the inverse variance method to calculate pooled OR (from crude OR for prevalence studies) and pooled relative risk (RR) (for incidence studies). DerSimonian and Laird was used for the pooled RR.<br>Both fixed and random effects models. | 27 studies were included<br>Diabetes<br>• OR 1.59(1.38,1.83) (prevalence studies)<br>• OR 1.53(1.16,2.04) for mild psoriasis<br>• OR 1.97(1.48,2.62) for severe psoriasis<br>• RR 1.27(1.16,1.40) (incidence studies)<br>Substantial heterogeneity |
| Armstrongetal, 2013<br>AHA | Cohort, case-control, nested case-control, and cross-sectional studies were included.<br><br>Statistical analysis:<br>Pooled risk ratio (=relative risk)(RR) was calculated.<br>Using the inverse variance method applied with fixed and random effects models of DerSimonian and Laird. | 9 studies were included<br>CV Mortality<br>• RR 1.03(0.86,1.25) for mild psoriasis<br>• RR 1.39(1.11,1.74) for severe psoriasis<br>MI<br>• RR 1.29(1.02,1.63) for mild psoriasis<br>• RR 1.70(1.32,2.18) for severe psoriasis<br>Stroke<br>• RR 1.12(1.08,1.16) for mild psoriasis<br>• RR 1.56(1.32,1.84) for severe psoriasis |
| Armstrong et al, 2013<br>J Hypertension | Cohort, case-control, nested case-control, and cross-sectional studies were included.<br><br>Statistical analysis:<br>Pooled OR for prevalence studies.<br>Studies assessing prevalence were analyzed separately from studies assessing incidence.<br>No other information was given. | 24 studies of psoriasis were included<br>5 studies of Psoriatic arthritis were included<br>Hypertension<br>• OR 1.58(1.42,1.76)<br>• OR 1.30(1.15,1.47) for mild psoriasis<br>• OR 1.49(1.20,1.86) for severe psoriasis<br>• OR 2.07(1.41,3.04) for psoriatic arthritis<br>No metaanalysis was performed for the 2 incidence studies<br>Substantial heterogeneity |

| | | |
|---|---|---|
| Xu et al, 2012<br>BJD | Cohort studies were included.<br><br>Statistical analysis:<br>Relative risk (RR) was calculated based on adjusted relative risks/hazard ratios reported in original report.<br>Random effects models of DerSimonian and Laird. | 7 studies were included<br>Composite vascular end point (MI+stroke)<br>• RR 1.20(1.10,1.31)<br>MI<br>• RR 1.22 (1.05,1.42)<br>Stroke<br>• RR 1.20 (1.10,1.31)<br>Substantial heterogeneity |
| Armstrong et al, 2012<br>Nutrition and Diabetes | Case-control and cross-sectional studies were included.<br><br>Statistical analysis:<br>Pooled OR was calculated based on either crude OR from original report or log-transformed effect size and 95%CI.<br>Random effects models of derSimonian and Laird/inverse variance method was used. | 16 studies were included in the metaanalysis<br>Obesity<br>• OR 1.66(1.46,1.89)<br>Substantial heterogeneity |
| Armesto et al, 2011<br>JEADV | Lack of information. | 10 studies included<br>Hypertension<br>• OR 1.66(1.36,2.04)<br>Substantial heterogeneity |
| Miller et al, Study I, 2013<br>JAAD | Cohort, case-control, and cross-sectional studies were included.<br><br>Pooled OR was calculated based on number of exposed/unexposed cases and number of exposed/unexposed controls.<br>Random effects models of derSimonian and Laird method was used. | 75 studies were included<br>CVD in total<br>• OR 1.4(1.2,1.7)<br>Ischemic heart disease<br>• OR 1.5(1.2,1.9)<br>Cerebrovascular disease<br>• OR 1.1(0.9,1.3)<br>Peripheral vascular disease<br>• OR 1.5(1.2,1.8)<br>Atherosclerosis<br>• OR 1.1(1.1,1.2)<br>CV mortality<br>• OR 0.9(0.4,2.2)<br>Diabetes<br>• OR 1.9(1.5-2.5)<br>Hypertension<br>• OR 1.8(1.6,2.0)<br>Dyslipidemia<br>• OR 1.5(1.4,1.7)<br>Obesity<br>• OR (BMI) 1.8(1.4,2.1)<br>• OR (Abdominal fat) 1.6(1.2,2.3)<br>Metabolic syndrome<br>• OR 1.8(1.2,2.8)<br><br>Subgroup analyses were performed e.g. hospital or population based recruitment of cases.<br>Substantial heterogeneity |

**CROSS-SECTIONAL STUDIES (STUDY III & IV)**

OBJECTIVES
To investigate if there is a possible association between hidradenitis suppurativa (HS) and MetS, and furthermore psoriasis (PS) and MetS on a hospital- and population-based level.

METHODS
Both cross-sectional studies were reported using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines of communicating observational studies[195].

**Ethical statement**
This study was accepted by the ethics committee of region Zealand (project number SJ-191, SJ-113, SJ-114) in Denmark. Written informed consent was obtained from all study participants. The investigation was conducted according to the principles of the Declaration of Helsinki.

**Study Design**
Study III and IV were based partly on The Danish General Suburban Population Study (GESUS)[196]. GESUS was initiated in January 2010 with on-going enrolment and is a cross-sectional study of the adult Danish suburban general population in Naestved Municipality (70 km south of Copenhagen). All citizens aged 30+ and a random selection of 20-30 years were invited. Methods of GESUS included the GESUS-questionnaire(see Appendix), physical examinations, and non-fasting venous blood samples performed by trained staff at Naestved Hospital.
Study III and IV were both cross-sectional studies of the association of HS/PS (referred to as the exposure), respectively, and MetS (referred to as the outcome) was performed investigating four different groups of HS/PS subjects;

1) HS subjects identified in a hospital-based sample (referred to as hospital HS subjects)
2) HS subjects identified in a population sample (referred to as population HS subjects)
3) PS subjects identified in a hospital-based sample (referred to as hospital PS subjects)
4) PS subjects identified in a population sample (referred to as population PS subjects)

StudyIII: Two cross-sectional studies examining the possible association between HS and MetS on a hospital as well as population-based level respectively.
Study IV: Two cross-sectional studies examining the possible association between PS and MetS on a hospital as well as population-based level respectively.
The comparison group (non-HS subjects) in both HS studies were defined as participants from GESUS without HS.
The comparison group (non-PS subjects) in both PS studies were defined as participants from GESUS without PS.
All subjects underwent the exact same survey (i.e. GESUS-questionnaire, physical examination and blood samples).

***The Exposure***
*The population HS-subjects*

The population HS subjects were identified in The Danish General Suburban Population Study (GESUS)[196].
The definition of the population HS subjects was based on the GESUS questionnaire where the diagnose of HS was made on the basis of a combination of the following two questions 1) "yes" to the question "have you had boils within the previous 6 months?" as well as 2) reporting of a minimum of 2 boils (in 5 possible locations: axillae, groin, genitals, mammae, other locations e.g. perianal, neck, abdomen)(see GESUS questions H_19_01, H_19_02, H_19_03, H_19_04, H_19_05, H_19_06). The first HS question has previously been validated[197]. The sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) were further explored in two different HS definitions using the first question only or adding information of number of boils.
These calculations of SE, SP, PPV, and NPV were made by comparing the hospital HS subjects with 35 physician-verified non-hidradenitis subjects (psoriasis) from the Department of Dermatology at Roskilde Hospital who also filled in the GESUS-questionnaire, and were examine by a physician in the field of dermatology to verify the dermatological disease.
The HS definition used for this thesis was as mentioned above the combination of the two HS-questions. Thus, SE was 90%, SP was 97%, PPV was 96%, and NPV was 92%. This definition was chosen due to the higher SP.

| *Defining HS according to the combination of "yes" to the question "*Have you had outbreak of boils during the last 6 months?" and a minimum of 2 boils | Controls (Psoriasis) (By clinical examination) | HS Cases (By clinical examination) | |
|---|---|---|---|
| ASSAY NEGATIVE (patients did not forefill HS definition in GESUS questionnaire | 34 | 3 | 37 |
| ASSAY POSITIVE (patients forefilled HS definition in GESUS questionnaire) | 1 | 27 | 28 |
| | 35 | 30 | |

*Specificity=34/35=97.1%*
*Sensitivity=27 /30=90.0%*
*PPV=27/28=96.4%*
*NPV=34/37=91.9%*
*2 subjects were excluded (one had both HS and PS, one had a missing answer)*

| *Defining HS only according to "yes" to the question "*Have you had outbreak of boils during the last 6 months?" | Controls (Psoriasis by clinical examination) | HS Cases (HS by clinical examination) | |
|---|---|---|---|
| ASSAY NEGATIVE (patients did not forefill HS definition in GESUS questionnaire | 32 | 0 | 32 |
| ASSAY POSITIVE (patients forefilled HS definition in GESUS questionnaire) | 3 | 30 | 33 |
| | 35 | 30 | |

*Specificity=32/35=91,43%*
*Sensitivity=30/30=100%*
*PPV=30/33=90,90%*
*NPV=32/32=100%*

Table7. Calculations of SE, SP, PPV, and NPV for the two definitions of the population HS-subjects.

*The hospital HS subjects*
The hospital HS subjects were recruited from the Department of Dermatology at Roskilde Hospital in Denmark (serving the region of Zealand which includes Neastved Municipality), and were included if they had the ICD-10-diagnose-code of HS (L73.2), and were undergoing either systemic or laser treatment for HS indicating moderate/severe disease. The diagnose of HS was confirmed by physical examination by a physician from the Department of Dermatology. Subjects were invited to undergo the exact same survey (i.e. GESUS-questionnaire, physical examination and blood samples) in the same location (Naestved Hospital) by trained staff as participants of GESUS. The participation rate was 34%. The distribution of age (mean age participants vs. non- participants 43 vs. 39 years) and gender (Male:Female in participants vs. non- participants 21%:79% vs. 29%:71%) did not differ between participants and non-participants
The comparison group (non-HS subjects) in both HS studies were defined as participants from GESUS without HS.

*The population PS-subjects*
The population PS-subjects were similarly identified in The Danish General Suburban Population Study (GESUS)[196], and the data used from GESUS for this study were within the period 1st January 2010 to 2nd August 2012. The population PS subject-definition was based on the GESUS-questionnaire where the definition of PS was based on participants answering "yes" to the question: "Do you suffer from or have you suffered from psoriasis?" (see GESUS question M_20_17). The sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) of this question was explored. These calculations were made comparing the hospital PS subjects with 30 physician-verified non-psoriasis subjects (hidradenitis suppurativa) from the Department of Dermatology at Roskilde Hospital who also filled in the GESUS-questionnaire. Thus, SE was 100%, SP was 87.7%, PPV was 87.5%, and NPV was 100%.

| | Controls (Hidradenitis by clinical examination) | PS Cases (PS by clinical examination) | |
|---|---|---|---|
| ASSAY NEGATIVE (patients did not forefill PS definition in GESUS questionnaire | 26 | 0 | 26 |
| ASSAY POSITIVE (patients forefilled PS definition in GESUS questionnaire) | 4 | 35 | 39 |
| | 30 | 35 | |

*Specificity=26/30=86.7%*
*Sensitivity=35/35=100.0%*
*PPV=35/39=89.7%*
*NPV=26/26=100.0%*

Table8. Calculations of SE, SP, PPV, and NPV for population PS-subjects

The hospital PS-subjects were recruited from the Department of Dermatology at Roskilde Hospital in Denmark (serving the region of Zealand which includes Naestved), and were included if the ICD-10-diagnosis-code was PS (DL40), and were undergoing treatment with biologics indicating moderate/severe disease. The diagnosis of PS was physician-verified. Subjects were invited to undergo the exact same survey (i.e. GESUS-questionnaire, physical examination and blood samples) as the participants in GESUS. The participation rate was 49%. The distribution of sex was approximately the same for participants and non-participants (male 71% vs. 75%, female 28% vs. 25%). The mean age of participants was, however, slightly higher when compared to non-participants (51 vs. 46 years).
For comparison in both studies non-PS-subjects were defined as participants from GESUS without PS.

***The Outcome***
The definitions of the outcome MetS were based on the methods of GESUS involving the GESUS-questionnaire (self-reporting), physical examination and non-fasting venous blood samples[196].
The MetS involve four key parameters: diabetes, hypertension, dyslipidemia, and obesity. The methods used to define the outcomes of Study III and IV are listed in detail in Table9[116,198-201]. A modified version of the MetS NCEP-ATPIII criteria was used. This definition is very simular to the harmonized definition of MetS.
As the cross-sectional studies (Study III+IV) were conducted retrospectively from the initiation and ongoing collection of data in GESUS, a MetS definition that utilized the maximum information of the data already collected was selected. In this respect the NCEP-ATPIII definition was chosen. Furthermore, NCEP-ATPIII is easily utilized in a clinical setting, which makes the results more translatable to everyday clinical practice. Last, the vast majority of studies included in the first meta-analysis (Study I) used the MetS definition of NCEP-ATPIII making the results from the cross-sectional studies more comparable to Study I.

| Outcome | Outcome type | Definition of outcome |
|---|---|---|
| MetS | *Binary* | MetS according to a modified version of the US National Cholesterol Education Program Adult Treatment Panel III(NCEP-ATP III) three or more of the following criteria;<br>1. Abdominal obesity: waist circumference >102 cm for men, and >88 cm for women. Based on physical examination.<br>2. Dyslipidemia I: Hypo-HDL-cholesterolemia: plasma HDL-cholesterol < 40 mg/dl (< 1.03 mmol/l) for men, and < 50 mg/dl (<1.28 mmol/l) for women. Based on blood sample.<br>3. Dyslipidemia II: Hypertriglyceridemia: plasma triglyceride >= 1.7 mmol/l (>=150 mg/dl). Based on blood sample.<br>4. Hypertension: physical examination measurement of blood pressure >= 130/85 mmHg or self-reported use of anti-hypertensive medicine<br>5. Diabetes: HbA1Ac >=48 mmol/mol (IFCC) (>=6.5%(DCI)) or non-fasting-glucose plasma glucose>=12.2 mmol/l or self-reported diagnose of diabetes |
| Diabetes | *Binary* | 1. Diabetes defined by self-reported diagnosis of diabetes or by blood sample (HbA1c >=48 mmol/mol (IFCC) (>=6.5%(DCI)) or non-fasting plasma glucose>=12.2 mmol/l) |
| | | 2. Diabetes type defined by self-reported use of insulin or non-insulin-antidiabetic medicine |
| | *Continuous* | 3. Quantification based on venous blood samples of HbA1c (mmol/mol) and non-fasting plasma glucose (mmol/l) |
| Hypertension | *Binary* | 1. Hypertension defined by self-reported antihypertensive medicine or by measurement of hypertension >=140/90 mmHg according to definition of hypertension |
| | *Continuous* | 2. Quantification based on physical examination measurements of systolic and diastolic blood pressure (mmHg) |
| Dyslipidemia | *Binary* | 1. HyperTG by blood sample according to ATPIII criteria>=1.7 mmol/l(>=150 mg/dl) |
| | | 2. HypoHDL by blood sample according to ATPIII criteria<1.03 mmol/l(<40 mg/dl) for men, and <1.28 mmol/l(<50mg/dl) for women. |
| | *Continuous* | 3. Quantification by blood samples measuring triglycerides (TG), High Density Lipoprotein (HDL) cholesterol in mmol/l, Total cholesterol, Low Density Lipoprotein (LDL) in (mmol/l). |
| Obesity | *Binary* | 1. General obesity defined as Body Mass Index (BMI) >= 30 kg/m$^2$. BMI was calculated from weight (kg)/(height$^2$ (m$^2$)).Based on physical examination. |
| | | 2. Abdominal obesity defined as waist circumference(WC) according to ATPIII criteria >102cm for men, and >88 cm for women.Based on physical examination. |
| | *Continuous* | 3. Quantification of obesity based on physical examination of BMI (kg/m$^2$), and WC(cm) |

Table1: Definitions of the outcome

Table9. Definitions of Outcome
(see also Table1 in Manuscript III and IV)

**Extended Background on Methods of GESUS**
GESUS was initiated in January 2010 with on-going enrolment along the creation of this thesis, and ended on 10th October 2013. It is a cross-sectional study of the adult Danish suburban general population in Naestved Municipality (70 km south of

Copenhagen; including postal codes 4160, 4171, 4250, 4262, 4684, 4700, 4733, and 4736).

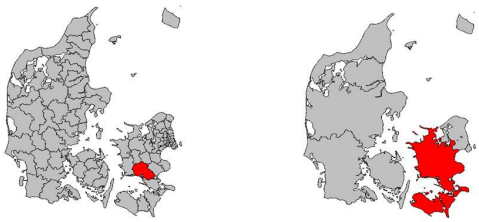


Figure24: Areas of GESUS-inclusion (left) and hospital based subjects (right)

Inclusion criteria were Danish citizenship and residence. All citizens aged 30+ and a random selection of the population aged 20-30 years were invited. If they did not respond within three weeks, an additional invitation was sent. A completed paper-questionnaire (referred to as the GESUS-questionnaire, see appendix) in Danish was a prerequisite for attending the health examination.
The GESUS-questionnaire was similar to ones used for the Copenhagen Heart Study, but additionally included questions about skin. The GESUS-questionnaire was tested in a pilot-study on 60 volunteers and finally validated by the Danish Unit of Patient Conceived Quality, Institute of Public Health.
The physical examination was performed by trained health professionals at the Department of Clinical Biochemistry, Naestved University Hospital, Denmark, on weekdays 3.30 pm to 9.00 pm.
The physical examinations relevant for this thesis were carried out as follows;
Blood pressure: After 5 minutes of rest, two consecutive digital measurements of blood pressure were performed on the left upper arm, and the blood pressure of the second measurement was registered.
Obesity: Using a tape measure, WC (cm) was measured at the lowest rib. Height (cm) was measured without shoes with a stadiometer. Weight (kg) was measured, and BMI was calculated as kg/m$^2$.
Blood samples: Fresh venous blood samples (50ml) were drawn in the non-fasting state. Venosafe plastic tubes (Terumo, Leuven, Belgium) were used and 25ml of blood were spun and kept overnight at 4 degrees of Celsius until biochemical analysis the next morning. Assays were followed up daily for precision and several times annually for accuracy with a Scandinavian quality control programme.
Triglycerides (TG), Total Cholesterol, and High Density Lipoprotein (HDL) were measured in mmol/l. Low-density lipoprotein cholesterol (LDL)(mmol/l) was calculated from the Friedewald equation if TG was < 5 mmol/l.
Plasma glucose and HbA1c were measured in mmol/l and mmol/mol respectively.
GESUS-data were checked for serious error and inconsistencies.

Participants: The overall participation rate in GESUS was 49%. Compared to non-participants, participants were more frequently women, had a higher median age, higher frequency of suburban residence, higher frequency of marriage/registered partnerships, and a lower frequency of comorbidities. Compared to an urban population, the suburban participants were less physical active, smoked less and consumed less alcohol. Furthermore, they had higher anthropometric measures (BMI and waist-hip-ratio), less undiagnosed hypertension but more undiagnosed diabetes, less frequency of elevated total cholesterol and LDL but higher frequency of decreased HDL and elevated TG.
A more detailed description of GESUS can be found in Bergholdt et al.[196]

**Exploring possible confounders**
The following possible confounders were explored:

1) General obesity defined by BMI based on physical examination
2) Inflammatory load defined by high-sensitivity C-reactive-protein (hs-CRP in mg/l) based on venous blood samples
3) Physical activity level defined by self-reported physical activity at work and in leisure time
4) Diet and drink intake defined by self-reported intake of atherogenic i.e. saturated fat, fish, fruit/vegetables, eggs and alcohol.

**Obesity**

- Physical examination: BMI (kg/m2): -25, 25-30, 30-

**Inflammation**[1]

- Veneous blood sample: hs-CRP (mg/L): <0.9, 1.0-2.9,3.0-9.9, >10

• 1: Ridker PM. C-Reactive Protein. A Simple Test to Help Predict Risk of Heart Attack and Stroke. Circulation. 2003;108:e81-e85

**Physical activity level**

- Self-reported physical activity level: based on GESUS multipel choice questions "Physical activity in spare time/work ?" (see GESUS questions A_01_01 and A_01_02)

| Freetime/ Work | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 1 | Low | Low | Moderate | Moderate |
| 2 | Low | Low | Moderate | Moderate |
| 3 | Moderate | Moderate | High | High |
| 4 | Moderate | Moderate | High | High |

**Diet/drink**

•Self-reported intake of atherogenic (saturated) fat: intake of either butter products for bread/cooking or fast food minimum once a week ("what kind of fat do you use on the bread or for cooking?" and "How many times a week do you eat fast food?", see GESUS questions K_70_01 and K_75_06)

•Self-reported intake of fish: no intake reported to "How many times a week do you eat fish on the bread or for dinner?" (see GESUS questions K_74_03 and K_75_04)

•Self-reported intake of vegetables/fruits: "How many times a week do you eat vegetables/fruit?", where<6 per day was considered atherogenic (see GESUS questions K_76_01 and K_77_01)

•Self-reported intake of eggs: "How many eggs do you eat per week?", where >3 per week is considered atherogenic (see GESUS question K_78_01)

•Self-reported intake of alcohol, where >14/>7 units a week ( men/women) was considered atherogeneic (see GESUS question K_73_05 and K_73_08)

Table10. Definitions of possible confounders

The possible confounders were chosen based on the hypothesis on possible pathophysiology behind the association investigated (See Background).

**Exploring the Severity of HS**
The definition of severity of HS for the population HS subjects were based on self-reported information on number of boils/locations of boils, and subsequent scarring (see GESUS questions H_19_01, H_19_01, H_19_02, H_19_03, H_19_04, H_19_05, H_19_06, H_19_07), and was inspired by the Hurley Score, which is considered almost static[202] (see Appendix). Mild HS: minimum 2 boils, and no subsequent scarring, moderate HS: minimum 2 boils and subsequent scarring, and severe HS: minimum 2 boils in minimum 2 locations, and subsequent scarring. The severity of HS for the hospital HS subjects was assessed by the Sartorius score based on physical exami-

nation[202] (see Appendix). Furthermore, we explored the severity of HS in both population - as well as hospital HS subjects as number of boils i.e. a dynamic scale.

**Exploring the Severity and Duration of PS**

The definition of severity of PS for the population PS-subjects was based on self-reported information on whether receiving systemic treatment for their psoriasis or not (see GESUS question L_96_59). Mild PS: PS-subjects not receiving systemic PS-treatment. Moderate/severe PS: PS-subjects receiving systemic PS-treatment. The severity of PS for the hospital PS-subjects was assessed by the PASI score based on physical examination by a physician (see Appendix). The duration of PS was assessed by self-reported duration of PS (see GESUS question M_20_18).

**Statistical analyses**

HS/PS-subjects and non-HS/PS-subjects were compared using logistic regression adjusting for age, sex and smoking status yielding an adjusted Odds Ratio (OR with 95%CI) for binary outcomes, and linear regression of log-transformed outcomes adjusting for age, sex and smoking status yielding an adjusted Ratio of Means (RM with 95%CI) for continuous outcome. Smoking status was self-reported (see GESUS question R_56_01 and R_56_02).

Binary effects measure (OR) expresses if there is an association or not, and the strength of association. Continuous effect measure (RM) expresses the quantification of the association i.e. translation of the association into clinical management. P-values <0.05 were considered to be statistically significant.

The ORs and RMs for population HS/PS-subjects were expressed as $OR_{pop}$ and $RM_{pop}$, and similarly $OR_{hos}$ and $RM_{hos}$ for hospital HS/PS-subjects.

The influence of possible confounders on the association between HS/PS and MetS was examined by including these in the regression model and assessing the effect on the odds ratio.

The relationship between severity of HS/PS and MetS was explored using the same regression method as above analysing only HS/PS-subjects. All statistical analyses were performed in SAS version 9.3.

Due to differences in background factors between exposed vs. non-exposed groups (HS/PS vs. non-HS/PS subjects), and the knowledge from previous literature that age, sex, and smoking can act as confounders in cardiovascular risk, the effects measures were adjusted accordingly. In the supplementary e-file 1 and 2 of Manuscript III and IV, crude ORs and RMs are additionally displayed.

With regards to testing for interaction (or effect modification), this thesis has focused on suspicion of interaction based on previous literature i.e. men vs. women in the outcomes HDL and waist.

Testing for ”all kinds of interaction” on all the data could be perceived as ”going fishing”. The hospital group is very small, and one could argue that it is even too small to perform interaction tests on. The population group is on the other hand very large i.e. contains a vast portion of information making interaction tests able to detect quite small statistically significant interactions, that might blur the results more than actually make them more clinically meaningful.

SUMMARY OF RESULTS

**Study III:**

Thirty-two hospital HS subjects, 326 population HS subjects, and 14,851 population non-HS subjects were identified. When compared to non-HS subjects the odds ratios for hospital HS subjects and population HS subjects respectively were 3.89(1.90-7.98) and 2.08(1.61-2.69) and for MetS, 5.74(1.91-17.24) and 2.44(1.55-3.83) for diabetes, 6.38(2.99-13.62) and 2.56(2.00-3.28) for general obesity, and 3.62(1.73-7.60) and 2.24(1.78-2.82) for abdominal obesity. With regards to dyslipidemia significant results were found for hypoHDL with ORs of 2.97(1.45-6.08) and 1.94(1.52-2.48) for hospital HS subjects and population HS subjects respectively when compared to non-HS subjects. With regards to hyperTG only the result for the population HS subjects compared to non-HS subjects was significant with an OR of 1.49(1.18-1.87). The OR for hypertension, which was only significant for hospital HS subjects compared to non-HS subjects, was 2.14(1.01-4.53). The quantitative results (RMs) are depicted in Figure26.

Obesity and inflammation acted as possible confounders. The ORs were higher for hospital HS subjects compared to population HS subjects.

Interaction in HDL and waist could not be ruled out with regards to sex.

Similarly to more widely spread inflammatory diseases, HS is associated with the metabolic syndrome. As this is a cross-sectional study, causality remains to be explored.

| | **Hospital HS-subjects n=32** | **Population HS-subjects n=326** | **Population non-HS-subjects n=14851** |
|---|---|---|---|
| **Age** ((years) mean (range)) | 42 (22-64) | 47 (22-78) | 56 (20-96) |
| **Sex** Female vs. Male, Number (%) | 25 vs 7 (78 vs. 22) | 218 vs 108 (67 vs. 33) | 8090 vs 6761 (54.5 vs. 45.5) |
| **Smoking Status, Number (%)** | | | |
| Present Smoker | 17(55) | 133(42) | 2683(19) |
| Past Smoker | 13(42) | 114(35) | 5633(40) |
| Never Smoked | 1(3) | 70(22) | 5684(41) |
| **Ethnicity, Number(%)** Caucasian | 31(97) | 315(97) | 14624(98.5) |
| **CRP** (median(mg/l)(range)) | 5.1 (0.2-119.0) | 2.1 (0.1-38.0) | 1.4 (0.1-136.0) |
| **HS Severity , Number(%)** | | | |
| Mild | 4 (12.5) | 165 (50.6) | Not Applicable (N/A) |
| Moderate | 5 (15.6) | 90 (27.6) | N/A |
| Severe | 23 (71.9) | 71 (21.8) | N/A |
| **Sartorius (median (range))** | 29 (5-176) | N/A | N/A |
| **Number of boils (median(range))** | 12 (1-171) | 3 (2-106) | N/A |
| **Comorbidities, Number (%)** | | | |
| MetS | 17 (53.1) | 105 (32.2) | 3192 (21.5) |
| Diabetes | 4 (12.5) | 23 (7.1) | 728 (4.9) |
| Hypertension | 18 (56.3) | 157 (48.2) | 9007 (60.6) |
| HypoHDL | 15 (46.9) | 108 (33.1) | 2687 (18.1) |
| HyperTG | 16 (50.0) | 159 (48.8) | 6428 (43.3) |
| General Obesity | 16 (50.0) | 107 (32.8) | 2799 (18.8) |
| Abdominal Obesity | 20 (52.5) | 168 (51.5) | 5524 (37.2) |

Table11. Background factors and characteristics of hospital HS subjects, population HS subjects, and population non-HS subjects

**Figures illustrating results from study III:**

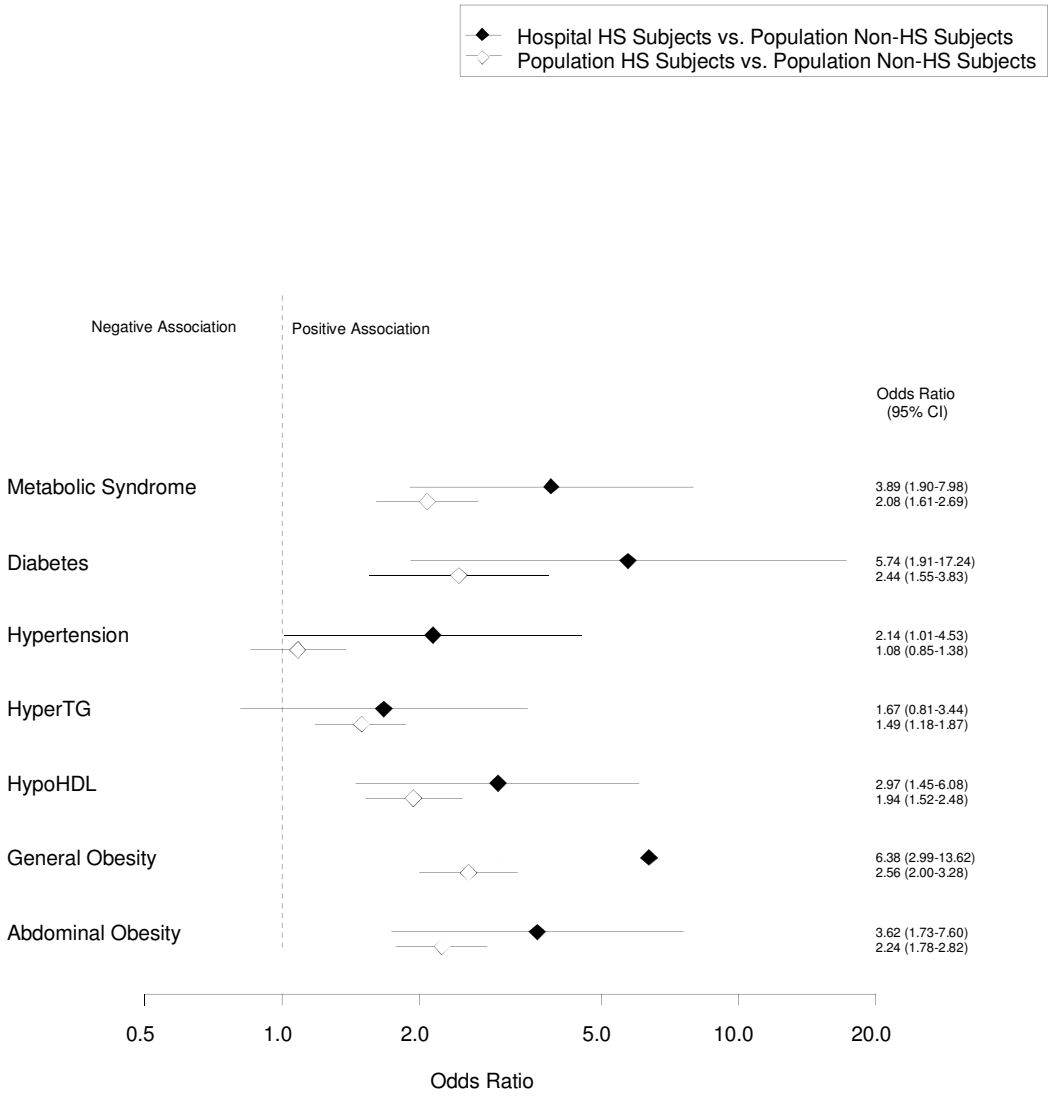



Figure25. Age, sex, and smoking adjusted ORs for binary outcome.

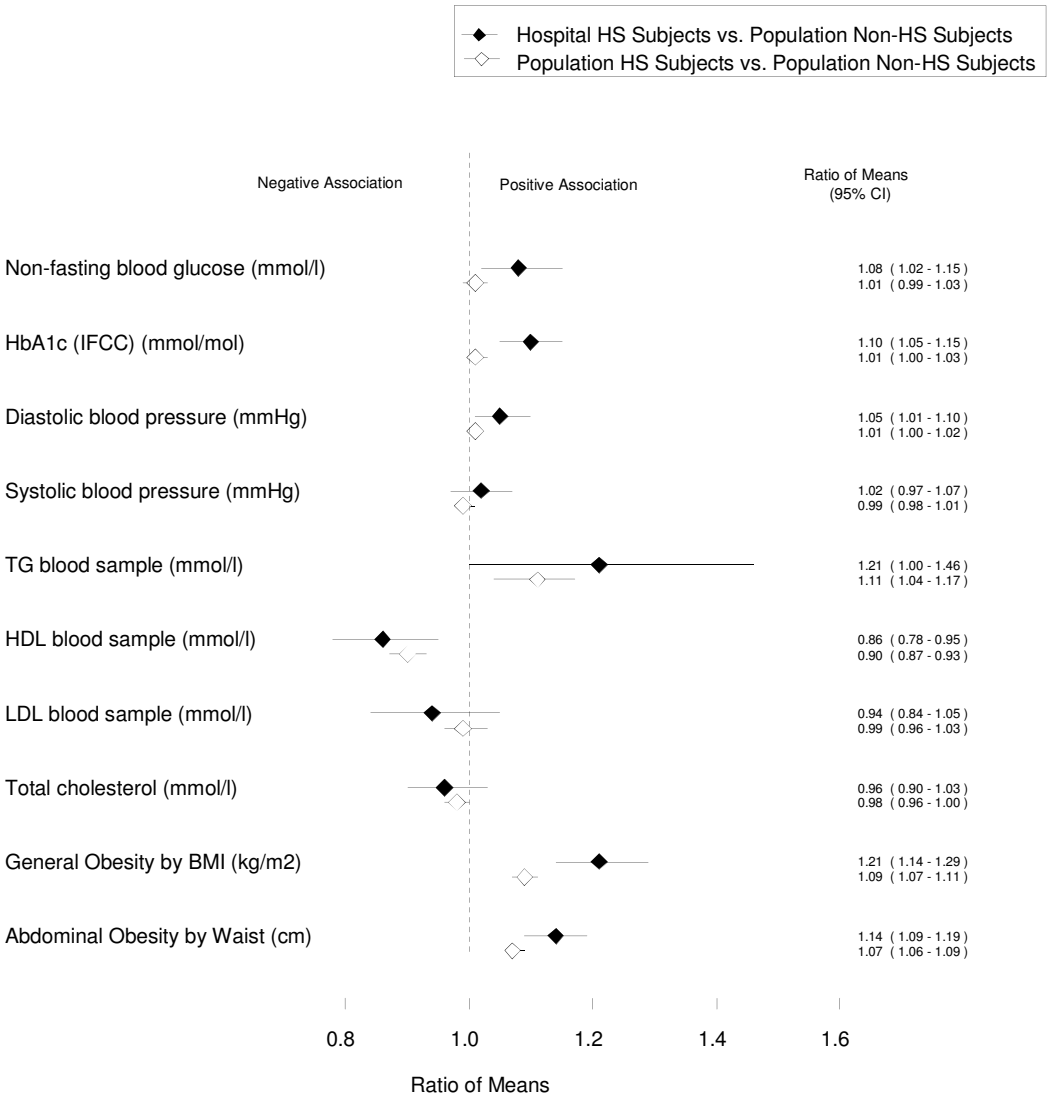



Figure26. Age, sex, and smoking adjusted RM for continuous outcome.

**Study IV:**

Thirty-six hospital PS-subjects, 860 population PS-subjects, and 14,016 non-PS-subjects were identified. The Odds Ratios (ORs) for hospital PS-subjects and population PS-subjects vs. population non-PS subjects respectively were 5.14(2.47-10.69) and 1.29(1.09-1.53) for MetS, 4.55(1.91-10.85) and 1.16(0.65-1.59) for diabetes, 1.92(0.87-4.22) and 1.00(0.86-1.17) for hypertension, 4.34(1.86-10.10) and 1.15(1.00-1.34) for hyperTG, 3.88(1.96-7.69) and 1.19(1.01-1.42) for hypoHDL, 5.77(2.89-11.52) and 1.19(1.00-1.41) for general obesity, and 2.92(1.45-5.88) and 1.34(1.16-1.55) for abdominal obesity.
The quantitative results (RMs) are depicted in Figure28.
Obesity acted as a possible confounder. A uniform pattern of higher ORs for hospital PS subjects when compared to population PS subjects was observed.
No uniform pattern was seen with regards to PS severity and duration.
No signs of interaction in HDL and waist was seen with regards to sex.
The data suggested an association between MetS, and the individual parameters on hospital-based level, with the exception of hypertension. On a population-based level the associations were only significant for MetS, hypoHDL, and abdominal obesity.
As this is a cross-sectional study, causality cannot be demonstrated.

| | **Hospital PS-subjects n=36** | **Population PS-subjects n=860** | **Population non-PS-subjects n=14016** |
|---|---|---|---|
| **Age** (Mean years (min-max)) | 52 (25-77) | 56 (22-87) | 55 (20-96) |
| **Gender, Number(%)**<br>Female vs. Male | 11 vs 25<br>(31 vs 69) | 466 vs 394<br>(54 vs 46) | 7669 vs 6347<br>(55 vs 45) |
| **Smoking Status (%)**<br>Present Smoker<br>Past Smoker<br>Never Smoked | <br>32<br>44<br>24 | <br>23<br>46<br>31 | <br>19<br>40<br>41 |
| **Ethnicity % (number)** Caucasian | 36(100) | 850(99) | 13799(99) |
| **CRP** (Median(mg/l)(min-max)) | 1.2 (0.3-29) | 1.5 (0.1-73) | 1.4 (0.1-136) |
| **PS Severity, Number(%)**<br>Mild/moderate<br>Severe<br>PASI (Median(range)) | <br>8(24)<br>26(76)<br>2.6(0.4-14) | <br>660(79)<br>176(21)<br>N/A | <br>N/A<br>N/A<br>N/A |
| **PS Duration** (Mean(range)) | 24(5-49) | 27(1-71) | N/A |
| **Comorbidities,Number(%)**<br>MetS<br>Diabetes<br>Hypertension<br>HypoHDL<br>HyperTG<br>General Obesity<br>Abdominal Obesity | <br>23 (66)<br>7 (19)<br>25 (69)<br>17 (47)<br>28 (78)<br>21 (58)<br>21 (58) | <br>226 (33.5)<br>49 (7)<br>531 (62)<br>180 (21)<br>406 (47.5)<br>185 (23)<br>379 (44) | <br>3032 (27)<br>680 (6)<br>8434 (60)<br>2544 (18)<br>6025 (43)<br>2636 (20)<br>5158 (37) |

Table12. Background factors and characteristics of hospital PS subjects, population PS subjects, and population non-PS subjects.

**Figures illustrating the results of study IV:**

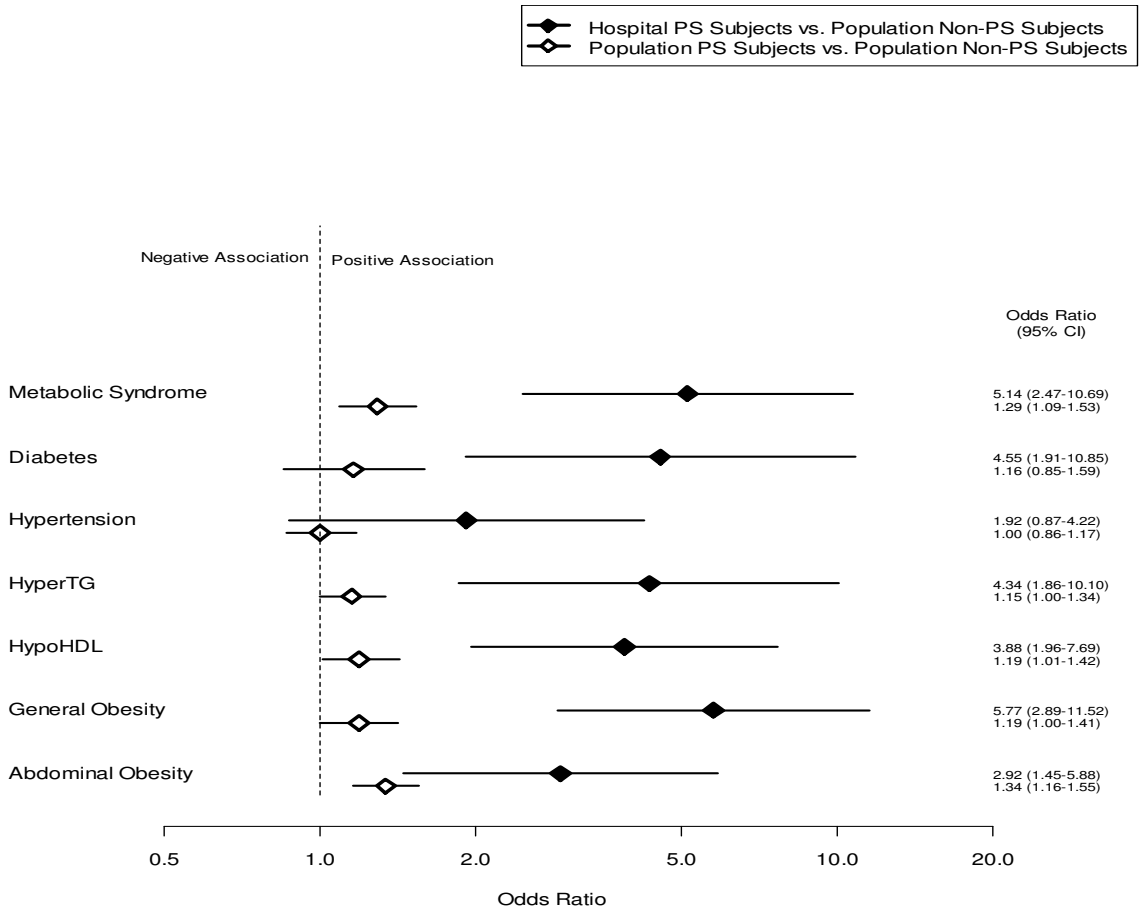



Figure27. Age, sex, and smoking adjusted ORs for binary outcome

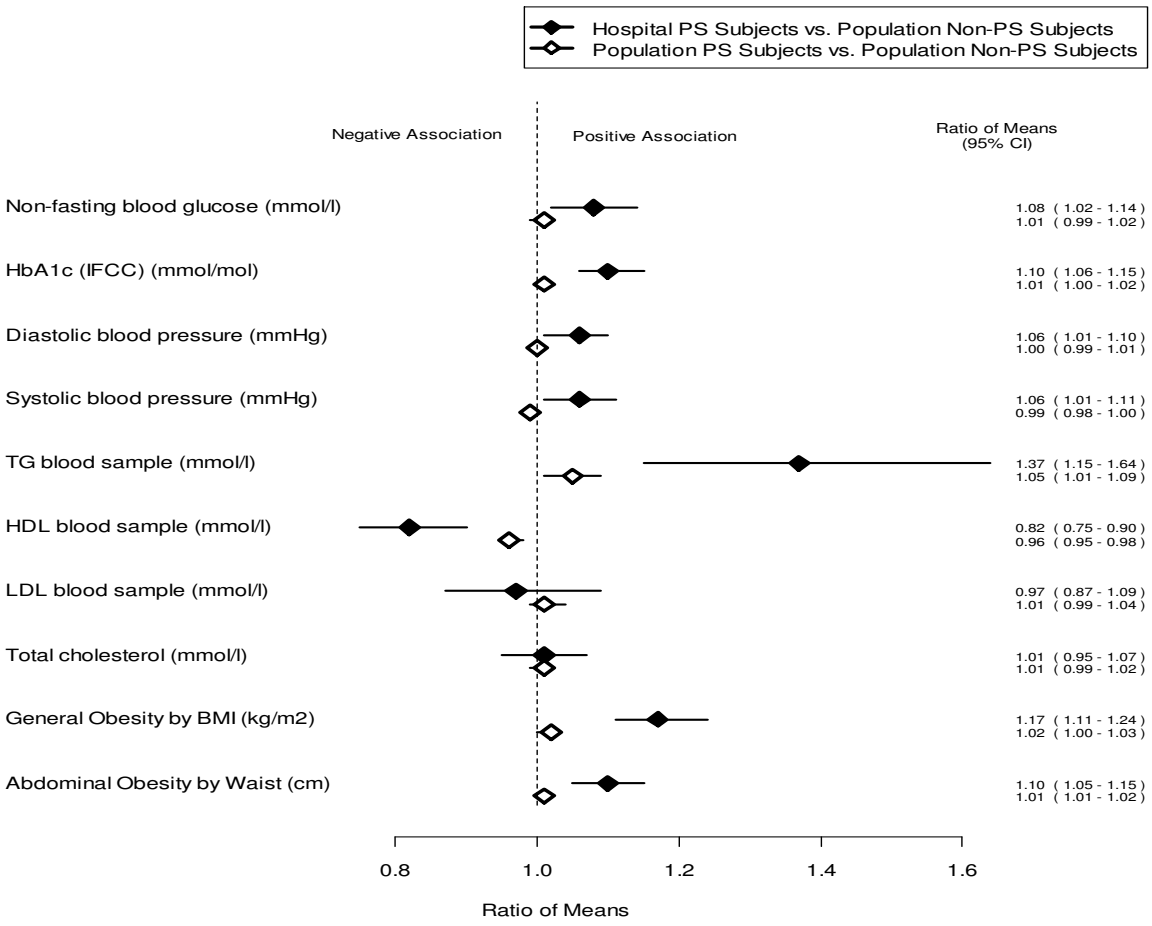



Figure28. Age, sex, and smoking adjusted RMs for continuous outcome

**DISCUSSION (CROSS-SECTIONAL STUDIES)**

With regard to hidradenitis (HS) the results suggest an association between HS and MetS as well as the individual parameters of diabetes, hypoHDL, general and abdominal obesity on a hospital- and population-based level. Positive associations were also found with regards to hypertension and dyslipidemia. Hypertension was however only statistically significant in the hospital HS subjects. According to binary data (using acknowledged cut-off values) for hyperTG only the association for the population HS subjects was statistically significant. However, statistically significant differences in the TG-levels between hospital HS subjects and non-HS subjects were found looking at continuous data. The findings of a positive association between HS and MetS is in concordance with two previous hospital-based studies( ref gold+sabat).

With regard to psoriasis (PS), the study suggests a significant association between PS and MetS on a hospital as well as a population-based level. Examining the individual MetS-parameters positive associations were also found. Associations on a hospital-based level were significant, with the exception of hypertension. On a population-based level, only hypoHDL and abdominal obesity were significant.

A uniform pattern for both dermatological diseases (HS/PS) of higher ORs for hospital- dermatological subjects when compared to population dermatological subjects was observed. This uniform pattern could indicate that HS/PS severity, duration or subtype may play a role. The observation may also be an expression of dilution of the population based HS/PS sample due to misclassification bias. However, the SP and SE was 97% and 90% for HS, and 87% and 100% for PS respectively based on a hospital sample. The higher ORs for hospital dermatological subjects may similarly indicate detection bias i.e. HS/PS patients within the hospital system are more likely to have already been diagnosed with the outcome, which influences self-reported diagnosis. However, detection bias was expected to be minimized by outcome definitions as they including both self-reported diagnosis as well as physical examination and blood samples. Notably, possible surveillance/detection bias could be considered with regard to self-reported outcome i.e. hospital-based HS/PS-patients may be more likely to get a diagnose of diabetes, hypertension ect. compared to population-based HS/PS-patients as they are more frequently in contact with health care.

Looking at Mets parameters individually, ORs for diabetes was significant for HS, and consisted of mostly non-insulin diabetes. The OR for diabetes was significant for hospital PS-subjects, and included both insulin and non-insulin treated diabetes. The association of diabetes with population PS subjects was positive, however non-significant, and included mostly non-insulin diabetes.

Quantification analysis indicated that non-fasting glucose was 1% higher in population HS subjects, and 8% higher in HS/PS hospital subjects compared to non-dermatological subjects. HbA1c was 10% higher in HS/PS hospital subjects, and 1% higher in HS population subjects compared to non-dermatological subjects. Previous studies have suggested that an approximately 1% reduction in HbA1c may decrease risk of myocardial infarction by 14-16% indicating that the abnormalities seen in the HS patients have clinical relevance[126]. Further indirect support for this association is provided by the observation that metformin treatment may ameliorate HS[203]. Previous results with regards to the effects of anti-diabetic drugs on psoriasis have been just as ambiguous as these current results on PS[204].

A significant association for HS and general and abdominal obesity was found in both the hospital- and population based HS subjects. In PS-subjects a positive association was found with regards to abdominal obesity on both a hospital- and population-based level, and with regards to general obesity only significance in PS hospital subjects was found.

When quantified, BMI was 21% and 17% higher in HS and PS hospital subjects respectively, and 9% higher in HS-population-subjects. When quantifying abdominal obesity, WC was 14% and 10% larger in HS/PS hospital subjects, and 7% and 1% larger in HS/PS population subjects compared to non-dermatological subjects. It has been suggested that trimming of the WC by 4.4 cm from 102 cm i.e. a 4.3% reduction, may reduce the risk of diabetes by 58%[186]; similarly indicating clinical relevance and a substantial potential for intervention.

The association of an atherogenic lipid profile i.e. hyperTG and hypoHDL was significant for hypoHDL, however, hyperTG was only significant for population HS subjects, and borderline significant for population PS-subjects.

When quantified hospital HS/PS subjects had an 21% and 37% higher, and population HS/PS subjects an 11% and 5% on a population-level higher TG level compared to non-dermatological subjects. Similarly, HDL was 14% and 18% lower in hospital HS/PS subjects, and 10% and 4% lower in population HS/PS subjects compared to non-dermatological subjects. A follow-up study of the effects of statins in 17,802 healthy individuals showed a significant reduction of cardiovascular events when TG was reduced by 17%, and HDL increased by 4%[180].

Having hypertension was only significant with regard to hospital HS subjects, and with regards to PS subjects altogether non-significant.

When quantifying blood pressure in the hospital HS subjects, only the diastolic blood pressure was significantly increased by 5%, and both the diastolic and systolic blood pressure was 6% higher in hospital PS-subjects when compared to non-PS-subjects.

A recent meta-analysis of preventive treatment of hypertension suggested that lowering diastolic blood pressure by 5 mmHg from 90 mmHg to 85 mmHg i.e. 6% reduction would reduce cardiovascular heart disease and stroke by approximately 20% and 30% respectively[182]. However, this may not be relevant unless the blood pressure is actually in a “pathological” hypertensive level.

These findings on HS are in concordance with and expand the findings of a previous hospital-based study[110]. In aggregate, these data therefore strongly imply that the comorbidities of HS are clinically significant, and that an increased clinical awareness of the HS diagnosis and its comorbidities is warranted in this potentially substantial group of patients.

With regard to PS, these results imply that the comorbidities of PS are clinically significant in hospital PS-subjects, and for some outcomes i.e. hypoHDL and abdominal obesity also population PS-subjects. This is in general in concordance with the meta-analysis in Study I, which implied significance for hospital-based cases only.

Obesity and inflammatory load were identified as possible confounders in HS, and the latter in PS. These possible confounders might explain the associations partly – but not exclusively, indicating a complex and overlapping relationship. Surprisingly, we found that physical activity level, diet/drink and the severity of HS/PS, and PS duration did not influence the associations. The observation of no influence of the severity of the dermatological disease is in contrast to the previous supposition that hospital HS/PS subjects have higher ORs because of more severe disease, implying either detection bias as previously discussed or an insufficiently sensitive measure of disease severity. It is therefore speculated that HS/PS subtypes may influence the association to MetS more strongly than severity.
In contrast to HS, inflammation was not found to be a possible confounder in PS. However, the hospital PS-subjects underwent biological treatment i.e. reduced inflammation making the difference in CRP between PS-subjects and non-PS-subjects minimal, which limited the possibility to explore inflammation as a possible confounder.

**Strength and limitations**
The major strength of our study was the large population-based sample size and the inclusion of both hospital- and population PS-subjects. The broad recruitment reduced selection bias, and opened the possibility of a broader range of disease severities, thus aiding the generalization (external validity) of the results. The diagnosis of the hospital HS/PS-subjects was physician-verified. Misclassification bias in the population subjects was evaluated by exploration of the HS and PS diagnosis definition yielding a SP and SE of 97% and 90% for HS, and 87% and 100% for PS, respectively. As the self-reported questions used to identify HS subjects refer to symptoms (i.e. boils) rather than the actual diagnose (i.e. do you suffer from HS?), the design maximized the inclusion of the un- and misdiagnosed HS subjects in the population, which is particularly pertinent for underdiagnosed diseases such as HS. The combined methods of self-reporting, blood samples and physical examination aimed to optimize methods in the hope of reducing false negatives with regard to outcome (MetS). Finally, essential confounders were recognized and explored.
Potential limitations merit consideration. First, it is pivotal to recognize that as this study is cross-sectional, we cannot demonstrate causality between HS/PS and MetS. Furthermore, the population is suburban and the majority of the participants were Caucasian and +30 years old. This may limit the generalizability. The low number of hospital HS/PS-subjects results in a large variation of estimates, and low power to detect an association. It is speculated that the low participation rate of HS is an expression of limited resources of HS patients due to the physical and mental burden of the disease. As with all questionnaire-information there is a risk of recall bias. Furthermore, blood samples were non-fasting. However, differences in fasting vs. non-fasting lipids have been shown to be minimal[129]. Additionally, lack of validation of the PS/HS severity models used (mild/moderate/severe HS/PS, number of boils) could cause misclassification bias with regard to HS/PS Severity. Furthermore, possible surveillance/detection bias is present as mentioned above. Last, methods of defining the investigated confounders could be questioned e.g. CRP as the only indicator of inflammation might not be fully adequate.

In conclusion, the data suggest an association between HS and the MetS in both hospital and population HS subjects. This increased disease burden due to comorbidities indicates that HS patients require general medical attention beyond the skin. Furthermore, the data suggests an association between PS, MetS, and its parameters in hospital-based PS subjects, with the exception of hypertension. For population-based PS subjects only the associations with MetS, hypoHDL and abdominal obesity were significant. Thus, clinical screening of hospital PS-patients for MetS may be relevant, but at the same time awareness not to unnecessarily stigmatize PS patients from the general population should be kept in mind.

**INTEGRATED DISCUSSION IN SHORT**
The association of inflammatory dermatological diseases i.e. psoriasis and hidradenitis suppurativa and metabolic syndrome was supported by both meta-analysis and cross-sectional studies.
A uniform pattern for both dermatological diseases (HS/PS) of higher ORs for hospital- than population-based dermatological subjects when compared to non-dermatological subjects was observed. This uniform pattern could indicate that HS/PS severity, duration or subtype may play a role.
Meta-analysis showed an association between PS and MetS as well as all the parameters of MetS. However, only significant for hospital-based studies when compared to population-based studies, with the exception of dyslipidemia. The cross-sectional study demonstrated similar results for PS with associations significant for hospital-based subjects, with the exception of hypertension, and with regard to population-based subjects only significant associations for certain MetS-parameters. The cross-sectional study for HS demonstrated significant associations for all MetS-parameters, with the exception of hypertension (population-based) and hyperTG (hospital-based).
When comparing the burden of MetS as a comorbidity in HS vs. PS ORs are higher for HS. Furthermore Study I suggested that the associations in psoriasis are only significant with regards to hospital-based studies implying that the burden of these comorbidities is greater for HS than for PS.
Quantitatively, HS and PS did not differ offhand. Except for hyperTG, which appear somewhat larger for PS hospital subjects than for HS hospital subjects. However, with regards to the population-based subjects it is the other way around. One could, however, speculate whether HS and PS influence the lipid metabolism in different ways.
Furthermore, with regard to the lipid profiling, there is no difference between HS/PS subjects total cholesterol and LDL compared to non-dermatological subjects. However, the thesis found hypoHDL. If total-cholesterol and LDL are "normal", but HDL is lower than "normal", this could mean that there could be higher than normal levels of alternative lipoproteins e.g. VLDL. Hence, lipoprotein analyses exploring the function and qualitative aspects of lipids are warranted to investigate this field further.
Obesity (in HS and PS) and the inflammatory load (in HS) were found to be possible confounders, and may thus explain the association. Thus, the association between HS/PS and MetS-parameters might be caused by the association with obesity. It does not make sense to say that obesity might indirectly cause the association between HS/PS and MetS (per criteria) as obesity is indeed one of the possible criteria in MetS. Similarly,

the association between HS and MetS might be indirectly caused by the inflammation. Referring to the causal pie model, the association is most likely multicausal and complex.

**CONCLUSION**

This thesis found an association between inflammatory dermatological diseases i.e. psoriasis and hidradenitis suppurativa and metabolic cardiovascular risk factors, i.e. metabolic syndrome by meta-analyses as well as cross-sectional studies. Clinical implications of these findings; according to the results of this thesis, it is recommended as a minimum to screen HS and PS patients attending in/outpatient clinics for the metabolic syndrome.

Furthermore, it is recommended to screen HS patients for metabolic syndrome in the primary sector i.e. in the general population. With regard to PS patients in the general population, it may be relevant to screen for MetS, but at the same time awareness not to unnecessarily stigmatize these PS patients is warranted.

As the skin in a communicative organ, dermatological diseases in general have a great impact on the patients' lives. HS and PS are both dermatological diseases with a large impairment in quality of life. This thesis suggests that the burden of these diseases not only rely in the psychological impact of having a visible disease and the skin-specific physical burdens, but furthermore demonstrates a major disease burden due to comorbidities i.e. metabolic syndrome increasing the cardiovascular risk of psoriasis and hidradenitis patients. Thus, indicating that HS/PS patients require general medical attention beyond the skin.

Future longitudinal studies with similar methods as the cross-sectional studies (i.e. a combination of self-reported diagnosis, physical examination, and blood samples including lipoprotein function analysis) are needed to explore the temporal relationship of the association between hidradenitis and metabolic syndrome. Longitudinel studies on psoriasis, CVDs, and some elements of the metabolic syndrome have been performed, however, methods of defining both the diagnosis of psoriasis and the outcome could be optimized. Further exploration of the influence of dermatological subtypes, and the possible effect of pharmacotherapy are needed. Furthermore, investigations on the pathophysiological mechanism with which these associations work need exploring e.g. mitochondrial and endothelial dysfunction.

**SUMMARY**

In conclusion, this thesis demonstrated an association between inflammatory dermatological diseases i.e. psoriasis and hidradenitis suppurativa and the metabolic syndrome putting these two patients groups at cardiovascular risk. Therefore, it is recommended as a minimum to screen hidradenitis and psoriasis patients attending in/outpatient clinics for the metabolic syndrome aimed at prevention of cardiovascular disease. The increased risk of metabolic syndrome adds to the range of well-known disease-related burdens e.g. the physical skin symptoms, the psychological impact thereof, and other comorbidities, thus highlighting that both hidradenitis and psoriasis patients require general medical attention beyond the skin.

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