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Psoriasis, ankylosing spondylitis and diabetes: The HUNT Study, Norway

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Abstract

Psoriasis is a common, chronic inflammatory skin disease associated with several comorbidities, including psoriatic arthritis and cardiovascular diseases. Emerging comorbidities include ankylosing spondylitis and diabetes, and potential underlying biological relationships could be partly explained by excessive chronic inflammation and shared genetic susceptibilities. However, the associations are not clear and have not been thoroughly explored in Norwegian populations. The aim of this study was to investigate the association of psoriasis with ankylosing spondylitis and diabetes. We did a cross-sectional study in two surveys of the population-based Nord-Trøndelag Health Study (HUNT3; 2006-2008, and HUNT4; 2017-2019). All inhabitants aged 20 years or older were invited to participate in the surveys, and a total of 50 800 adults participated in HUNT3 (54%) and 56 044 participated in HUNT4 (54%). We classified participants as having psoriasis, ankylosing spondylitis and diabetes according to self-reported information from HUNT3 and HUNT4. Odds ratios (OR) of psoriasis according to ankylosing spondylitis and diabetes were estimated with 95% confidence intervals (CI) using log-binominal regression analysis in HUNT3 and HUNT4. In HUNT3, psoriasis was associated with both ankylosing spondylitis OR 2.0 (95% CI 1.6-2.5) and diabetes OR 1.6 (95% CI 1.4-1.9). The corresponding associations in HUNT4 were OR 2.9 (95% CI 2.4-3.5) and OR 1.9 (95% CI 1.6-2.1), respectively. In conclusion, we found that psoriasis was positively associated with ankylosing spondylitis and diabetes in both HUNT3 and HUNT4. However, we did not investigate differences in associations between subtypes of disease (e.g. plaque psoriasis versus pustular psoriasis), and this would be useful in future studies. Increased awareness of comorbidities associated with psoriasis could improve the clinical follow-up and management of the disease. Our results emphasize a broad clinical approach to psoriatic patients where regular attention to symptoms of ankylosing spondylitis and diabetes could be recommended.

Background

Psoriasis

Psoriasis is a chronic immune-mediated inflammatory skin disease, which affects both genders equally. The prevalence differs across the world, ranging from 1% in the UK (1) to 6-11% in Norway (2, 3). Two peaks in the age of onset of psoriasis have been reported; one at late twenties, and a second at 50-60 years (4, 5). The majority (75%) of patients have onset before the age of 40 years, and 30-50% have onset before 20 years of age (4). Age of onset is usually earlier in women (4).

The underlying pathophysiology is complex and not yet fully understood. We know that psoriasis involves various cells in both the innate and adaptive immune system, especially T-cells, neutrophils, keratinocytes, and dendritic cells (4). Psoriasis is sometimes referred to as an autoimmune disease, yet, no triggering antigen has been identified (6, 7). However, psoriatic skin tends to overexpress a certain antimicrobial peptide called *cathelicidin*, and this protein has been suggested to act as a T-cell autoantigen in psoriasis (8, 9). The appearance of the disease is often triggered by environmental factors such as medication, psychological stress, infections, trauma, alcohol, and smoking (10). In addition, higher BMI has been suggested to have a causal effect upon incident psoriasis (11). The genetic basis of psoriasis is supported by investigations in families. A large study which included analysis of 2035 family histories in Germany reported that the risk of developing psoriasis if both parents were affected was 41% (12), indicating a strong genetic component. Further, twin studies have reported a substantially higher (2-3.5 fold) concordance of psoriasis in monozygotic twins compared to dizygotic twins (13, 14). Genetic studies of families and populations have identified >70 genetic loci associated with psoriasis (14). A majority of these genes have been implicated to have immune-related functions, underscoring the importance of the innate and adaptive immune systems in the pathogenesis of psoriasis. In contrast, psoriasis have been associated with relatively few genes that encode skin-specific proteins (4). Taken together, psoriasis is considered to be an immune-mediated disease, with a polygenic predisposition combined with environmental triggers (4).

Psoriasis is a clinical diagnosis and the disease can be grouped into several subtypes. Chronic plaque psoriasis (psoriasis vulgaris) is the most common variant and affects 90% of psoriatic patients (10). The plaques are usually symmetrically distributed and characterized by thick, silvery and sharply demarcated lesions, and show a predilection for extensor surfaces, such as

knees, elbows, and the scalp (4). The genitalia are involved in up to 45% of patients, and the face is usually not affected (4). Plaques may exist for months to years at the same location. Periods of complete remission do occur, and remissions up to five years have been reported (4). Other subtypes of psoriasis include guttate (droplet) psoriasis, inverse psoriasis (localized in skin folds), pustular psoriasis (localized or generalized), and erythrodermic psoriasis (very rare). In this study, we will refer to psoriasis as one disease regardless of subtype.

Treatment of psoriasis is challenging, requires individualization and depends on the severity of the disease. The treatment includes topical therapies such as glucocorticosteroids, vitamin D derivates, phototherapy, and systemic drugs (15). In clinical trials, single agents are usually evaluated, but in practice most patients receive a combination of therapies. In the last two decades there has been tremendous advancements in treatment and management of psoriasis, however, there is no absolute cure as the exact mechanisms of the events that leads to psoriasis are not entirely known.

A growing number of epidemiological studies have established associations between psoriasis and a specter of comorbidities, including psoriatic arthritis, cardiometabolic diseases and psychiatric conditions (16-19), indicating that psoriasis is a disease not limited to the skin. Suggested links between psoriasis and the different comorbidities include systemic inflammation, cellular mediators, common risk factors and genetic susceptibilities (19). Observational epidemiological studies have examined the potential associations between psoriasis, ankylosing spondylitis and diabetes (16, 20, 21). However, the results are not clear and to our knowledge, the association between psoriasis and ankylosing spondylitis has not previously been explored in a Norwegian population-based study.

Ankylosing spondylitis

Ankylosing spondylitis is a chronic immune-mediated inflammatory arthritis which mainly affects the axial skeleton and the sacroiliac joints, and have a prevalence of roughly 1% in Norway (22). Prevalence rates of ankylosing spondylitis are known to vary greatly between populations, with the highest prevalence in northern Europe, largely because of different carrier frequencies of the human leukocyte antigen (HLA)-B27 (23). Extra-axial manifestations occur, and include acute uveitis, dysrhythmia, peripheral arthritis, psoriasis, enthesitis (inflammation of the site where tendons insert on bones), aortic and pulmonal affection, and gut inflammation (24). Age of onset is usually before 40 years, and the disease shows a male predominance (24).

Ankylosing spondylitis is considered to have a strong genetic component, with a monozygotic twin concordance of 63%, and more than 90% of the risk for developing the disease relies on genes (24, 25). The HLA-B27 allele is known to have a strong association with the disease and occurs in 6% of the general US population but in more than 90% of patients with ankylosing spondylitis (24). However, other genes play a part in the development, and even with the unusual high heritability of ankylosing spondylitis, the twin concordance rate is not 100%. Environmental triggers have been suggested to complement genetics in causing disease, and recent studies have highlighted the potential role of the microbiome and biomechanical stressors in triggering onset of disease (24).

Previous investigations of the association between psoriasis and ankylosing spondylitis are sparse. A Dutch meta-analysis suggested a pooled prevalence of psoriasis in ankylosing spondylitis to be 9.3% (95% CI, 8.1% to 10.6%) (20). However substantial variation in study outcomes between studies was observed (measures of heterogeneity, Q=608,17, $p<0.001$, $I^2=91\%$).

Diabetes

Diabetes is a group of metabolic disorders characterized by hyperglycemia due to defects in insulin secretion, action, or both (26). Diabetes affects ~250 000 patients in Norway, of which 28 000 have type 1 diabetes, and 220 000 are diagnosed with type 2 diabetes (27). However, many patients may be affected from type 2 diabetes without being aware of it (27). Inadequate treatment and consequently chronic hyperglycemia is associated with long-term organ damage and dysfunction, leading to organ failure, especially in kidneys, eyes, nerves, heart and blood vessels (26). Symptoms before adequate treatment may be polyuria, polydipsia, and weight loss, all due to hyperglycemia (26). Common long-term complications of diabetes include retinopathy, nephropathy leading to renal failure, peripheral neuropathy with risk of foot ulcers, amputations and Charcot joints (26). In addition, patients with diabetes have an increased risk of peripheral arterial-, cardiovascular-, and cerebrovascular diseases (26). As diabetes is a group of metabolic disorders, it can be classified into the following subtypes of which all is considered to be separate diseases, sharing the same pathologic mechanism, lack of insulin: 1) Type 1 diabetes, due to autoimmune β-cell destruction of the pancreas, usually leading to absolute insulin deficiency, 2) Type 2 diabetes, due to a combination of insulin resistance and β-cell

failure and consequently loss of insulin secretion, 3) Gestational diabetes mellitus, diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation, 4) Specific types of diabetes due to other causes, e.g., maturity-onset diabetes of the young (MODY), disease of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical diabetes (such as glucocorticoid use and after organ transplantation) (26). In this study, we will refer to diabetes as one disease regardless of subtype.

Meta-analysis of 38 studies including 92 2870 diabetic cases and 12 808 071 non-diabetic controls demonstrated a strong association between psoriasis and diabetes, with estimated odds ratio (OR) 1.7 (95% CI 1.5-1.9) (16). However, heterogenicity in this metanalysis was high (I^2 = 98.5%, P<0.001) and subgroup analysis was conducted with OR 1.9 (95% CI 1.5-2.2), 1.4 (95% CI 1.2-1.6) and 1.8 (95% CI 1.5-2.2) in case-control, cohort and cross-sectional studies, respectively (16). A Danish meta-analysis of observational studies including 503 686 cases and 29 686 694 controls suggested that psoriasis was associated with diabetes with OR 1.9 (95% CI 1.5-2.5) (21). The strongest associations were seen in hospital-based studies, and population-based studies did not show significant associations between psoriasis and diabetes (21).

Shared genetic susceptibilities between psoriasis, ankylosing spondylitis and diabetes

For both psoriasis, ankylosing spondylitis and diabetes the underlying pathophysiology is complicated and not yet fully understood. However, genome-wide association studies (GWASs) support the hypothesis that there is a underlying shared genetic risk between the diseases (17, 18, 28, 29). This includes identification of genes encoding the endoplasmic reticulum aminopeptidase *ERAP-1*, *ERAP-2*, and insulin regulated aminopeptidase (*IRAP* or *LNPEP*), which are common for ankylosing spondylitis, insulin-dependent diabetes, psoriasis, and Crohn's disease (17, 18). Furthermore, psoriasis share specific risk alleles with ankylosing spondylitis, supporting the hypothesis that there is a common underlying pathogenesis for these diseases (18).

Objectives

Population-based studies of the associations between ankylosing spondylitis and diabetes in individuals with psoriasis are sparse in Norwegian populations. We therefore aimed to examine these associations in two surveys of the Nord-Trøndelag Health Study (the HUNT Study) in Norway.

Hypothesis

Based on epidemiological and genetic data our hypothesis was that individuals with psoriasis have an increased odds of ankylosing spondylitis and diabetes compared to non-psoriatic individuals.

Materials and methods

Study population

The HUNT Study is an extensive population-based study conducted within the county of Trøndelag (previously Nord-Trøndelag), Norway. HUNT includes both personal and family medical information from >150,000 individuals collected during four recruitment phases spanning four decades since 1984 (HUNT 1, 2, 3 and 4) (30). All inhabitants aged 20 years or older were invited to participate in the surveys, which included multiple questionnaires, standardized clinical examinations, urine and non-fasting venous blood samples. In the present study we used information from HUNT3 (2006-2008) and HUNT4 (2017-2019). In HUNT3, 93 860 persons were invited, and 50 800 (54%) chose to participate. In HUNT4, 103 782 persons were invited, and 56 044 (54%) chose to participate. Among participants in HUNT3, we excluded 22 individuals with missing on the psoriasis question, 1688 individuals with missing on ankylosing spondylitis and 22 with missing on diabetes. Among participants in HUNT4, we excluded 2671 individuals with missing on the psoriasis question, 2963 individuals with missing on ankylosing spondylitis and 929 with missing on diabetes.

Classification of psoriasis

Psoriasis was defined by a positive answer to the question: "Have you had or do you have psoriasis?" This question was included in a general health-related questionnaire sent to all participants. A total of 2 928 (5.8%) participants reported to have psoriasis in HUNT3, and 3 535 (6.6%) reported to have psoriasis in HUNT4. The psoriasis question has previously been validated in the HUNT3 population (31).

Classification of ankylosing spondylitis

Ankylosing spondylitis was defined by a positive answer to the question: "Have you had or do you have Bechterew's disease (spondyloarthritis)?" This question was included in a general health-related questionnaire sent to all participants. A total of 758 (1.5%) participants reported to have ankylosing spondylitis in HUNT3, and 805 (1.5%) reported to have ankylosing

spondylitis in HUNT4. The ankylosing spondylitis question has previously been validated in the HUNT2 and HUNT3 populations (23).

Classification of diabetes

Diabetes was defined by a positive answer to the question: "Have you had or do you have diabetes?" This question was included in a general health-related questionnaire sent to all participants. A total of 2264 (4.5%) participants reported to have diabetes in HUNT3, and 3334 (6.0%) reported to have diabetes in HUNT4. The diabetes question has previously been validated in the HUNT1 population (32).

Statistical analysis

We used log-binominal regression analyses to calculate OR (with 95% CIs) for the association between psoriasis and ankylosing spondylitis and diabetes. We selected potential confounders based on *a priori* considerations of factors that are related to both psoriasis, ankylosing spondylitis and diabetes. All estimated associations were adjusted for possible confounding by age (years), sex (women, men), smoking (never, former, current and unknown) and BMI (continuous). All statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 26.0 (Chicago, IL, U.S.A.).

Ethics and personal protection

This study was approved by the Regional Committees for Medical and Health Research Ethics in Mid-Norway (2015/586). The participation in the HUNT Study is voluntary, and a written informed consent is signed before inclusion. Every participant may withdraw their consent at any time. Before data are made accessible to researchers the files are de-identified, i.e. name and identification number are converted into project numbers. We have used HUNT Cloud as our computer environment for storage of HUNT data.

Results

Characteristics of the HUNT3 and HUNT4 populations are presented in Table 1. The self-reported prevalence of psoriasis in HUNT3 and HUNT4 were 5.8% and 6.6%, respectively. Individuals with psoriasis in HUNT3 were slightly older, reported more tobacco use, and had slightly higher BMI and systolic- and diastolic blood pressure compared to individuals without psoriasis. We observed the same tendency in HUNT4. The participants without psoriasis had

somewhat more female participants than the psoriatic group in both HUNT3 and HUNT4, but overall in HUNT3 and HUNT4, women were slightly overrepresented with the highest attendance in the middle-aged group.

Table 1. Characteristics of the HUNT3 and HUNT4 participants according to psoriasis.

	HUNT3 (n = 50 778)		HUNT4 (n = 53 373)	
	No psoriasis (n = 47 850)	Psoriasis (n = 2928)	No psoriasis (n = 49 838)	Psoriasis (n = 3535)
Female, n (%)	26 206 (54.8)	1536 (52.5)	27 125 (54.4)	1904 (53.9)
Age, mean (SD), years	53.0 (16.2)	55.2 (14.2)	53.9 (17.5)	57.7 (15.8)
Smoking status				
Never, n (%)	20 183 (43%)	883 (31%)	22 551 (46%)	1072 (30%)
Former, n (%)	15 014 (32%)	1093 (38%)	22 329 (45%)	1936 (55%)
Current, n (%)	11 287 (24%)	890 (31%)	4736 (10%)	513 (15%)
BMI, mean (SD), kg/m^2	27.1 (4.4)	28.0 (4.6)	27.1 (4.7)	28.2 (5.1)
BP, mean 2nd and 3rd measurement (SD), mmHg				
Systolic	131 (19)	132 (19)	128 (19)	130 (18)
Diastolic	73 (11)	74 (11)	73 (10)	74 (10)

Abbreviations: HUNT, Nord-Trøndelag Health Study; SD, standard deviation; BMI, body mass index; BP, blood pressure.

Ankylosing spondylitis and psoriasis

In HUNT3, individuals with psoriasis had an OR for ankylosing spondylitis of 2.0 (95% CI 1.6-2.5) compared to non-psoriatic participants (Table 2). The associations did not change substantially after adjustment for age, sex, smoking and BMI, OR 1.9 (95% Cl 1.5-2.4). In HUNT4, the association between ankylosing spondylitis and psoriasis was notable stronger than in the HUNT3, OR 2.9 (95% CI 2.4-3.5). Additional adjustment for age, sex, smoking and BMI did not substantially change the association between ankylosing spondylitis and psoriasis, OR 2.8 (95% CI 2.3-3.4).

Diabetes and psoriasis

In HUNT3, individuals with psoriasis had an unadjusted OR for diabetes of 1.6 (95% Cl 1.4-1.9) compared to non-psoriatic participants (Table 2). The associations did not change substantially after adjustment for age, sex, smoking and BMI, OR 1.5 (95% CI 1.3-1.8). In HUNT4, the association between diabetes and psoriasis was slightly stronger than in the HUNT3, OR 1.9 (95% CI 1.6-2.1). Additional, adjustment for age, sex, smoking and BMI did not substantially change the association between ankylosing spondylitis and psoriasis, OR 1.7 (95% Cl 1.5-1.9).

Table 2. Odds ratio for ankylosing spondylitis and diabetes in psoriasis versus no psoriasis.

	HUNT3				HUNT4			
	No psoriasis	Psoriasis			No psoriasis	Psoriasis		
	Cases, *n*	Cases, *n*	Crude OR (95% CI)	Adjusted OR* (95%CI)	Cases, *n*	Cases, *n*	Crude OR (95% CI)	Adjusted OR* (95% CI)
Ankylosing spondylitis	678	80	2.0 (1.6-2.5)	1.9 (1.5-2.4)	627	120	2.9 (2.4-3.5)	2.8 (2.3-3.4)
Diabetes	2065	196	1.6 (1.4-1.9)	1.5 (1.3-1.8)	2694	334	1.9 (1.6-2.1)	1.7 (1.5-1.9)

Abbreviations: HUNT, Nord-Trøndelag Health Study; OR, odds ratio.
*Adjusted for age, sex, smoking and BMI.

Discussion

Interpretation of main findings

In this population-based, cross-sectional study, psoriasis was positively associated with ankylosing spondylitis and diabetes. There was no substantial difference in the OR of ankylosing spondylitis and psoriasis, or diabetes and psoriasis, when we adjusted for age, sex, smoking, and BMI, suggesting that these associations are strong regardless of these known risk factors for psoriasis.

To the best of our knowledge, this is the first observational, epidemiological study to show a positive association between psoriasis and ankylosing spondylitis in a Norwegian population-based cohort. Our results are supported by a Ducth meta-analysis, were the pooled prevalence of psoriasis in ankylosing spondylitis was found to be 9.3% (95% CI, 8.1%-10.6%) (20).

However, this study reported substantial heterogeneity between study outcomes, indicating that the results should be interpreted with caution. Our estimate of OR between psoriasis and ankylosing spondylitis is relatively high. Lack of other large population-based studies makes it difficult to compare our results with other studies. However, as psoriasis is described to occur in 10-15% of patients with ankylosing spondylitis (33, 34), our estimate doesn't seem unrealistic.

The positive association between diabetes and psoriasis are supported by several other studies, including systematic reviews and meta-analysis (16, 21, 35, 36). However, the majority of these studies were hospital-based and population-based studies are few. Previously reported results may therefore represent a population more prone to illness than the general background population. The potential association between psoriasis and diabetes has previously been investigated in psoriasis subtypes (mild versus moderate/severe subtype) in HUNT3 by Snekvik et. al (36). Their results are in line with this study, were a positive association between mild psoriasis and diabetes was observed (OR 1.5, 95% CI 1.2-1.7) (36). They found no association between moderate/severe psoriasis and diabetes (OR 1.1, 95% CI 0.7-2.9). However, only 251 participants were classified to have moderate/severe psoriasis compared to 2 643 participants with mild psoriasis, suggesting that the result could change if the number of participants with moderate and severe disease were increased by enhancing statistical power. Our study did not split psoriasis into subtypes nor by severity of the disease, and suggests a similar association between psoriasis and diabetes in HUNT3 with OR 1.6 (95% Cl 1.4-1.9). Although, several studies have found positive associations between psoriasis and diabetes, a British cohort study found no significant difference in comorbidity related to cardiovascular diseases (including diabetes, hypertension, ischemic heart disease, and hyperlipidaemia) in patients with psoriasis alone, compared to their matched cohort (37). However, this study included relatively few patients with psoriasis (n = 290) and was not adjusted for BMI, a potential confounder.

The association between psoriasis, ankylosing spondylitis and diabetes is complex, and yet not fully understood. A combination of genetic susceptibility, common risk factors and common underlying pathophysiology including systemic inflammation have been suggested to explain these associations (17, 18, 28, 29). Psoriasis, ankylosing spondylitis and type 2 diabetes are all inflammatory conditions mediated by T1 lymphocytes producing cytokines such as TNF-∝ (24, 38). The efficacy of several therapeutics that target TNF-∝ in patients with psoriasis and ankylosing spondylitis emphasizes these findings. Anti- TNF-∝ treatment strategies have also

been studied in type 2 diabetes, but the results are controversial whereupon some studies report improvement of insulin resistance while other studies don't (38). The inflammatory molecules produced in psoriasis could thus influence conditions such as ankylosing spondylitis and diabetes, and vice versa.

Methodological considerations

The main goal of an epidemiological study is to present valid and accurate estimates, and this is critically depended on the validity of the methods (39). Small error in estimation gives small differences between the observed value and the true value. The two types of error in epidemiological studies are random error and systematic error (39). Random error can be harder to predict and is considered the opposite of precision. One way to increase precision is to reduce random error by increasing number of participants. Systematic errors are perhaps easier to predict and are considered the opposite of validity. The main types of systematic errors are selection bias, information bias and confounding. We used confidence intervals as a measure of precision and the strength of association. A major strength of our study is the large sample size, which enable more precise estimates, indicated by relatively narrow confidence intervals. However, there were relatively few participants in HUNT3 (n = 758) and in HUNT4 (n = 805) who responded "yes" to the question about ankylosing spondylitis, and hence wider confidence interval and imprecise estimates.

Selection bias

Selection bias can appear in studies with groups of participants that differ in ways other than intervention or exposures, and therefor proper randomization is not achieved. If the attendance in a population-based study is high, selection bias could be reduced. This study has the advantage of a population-based design, which carries less risk of selection bias compared to hospital-based studies. In addition, Trøndelag county is located in the middle of the country, and is considered representative for the whole country when it comes to age distribution, geography, economy, industry, morbidity and mortality (40). A potential limitation of our study is the rather high number of non-responders whereas the participation in both HUNT3 and HUNT4 was 54%. Also, the participation varied within age groups of the population; for example in HUNT3, in the age group of 20-29 years, participation was 26% among men and 38% among women, whereas in the age group of 60-69 years, participation was 68% among men and 75% among women (30). Despite this, it seems unlikely that that psoriasis played a major role in the decision whether the invited would participate or not.

Information bias

Information bias refers to error in the collection of information, and includes misclassification bias, observer bias, recall bias and reporting bias. In this study, we classified psoriasis based on self-reported information in HUNT3 and HUNT4. This question has been systematically validated by our group's experienced dermatologists through a clinical skin examination (3). They confirmed the diagnosis in 78% of the psoriatic cases (3), which indicates a small risk of diagnostic misclassification. The self-reported diabetes question also represent a solid basis for the diagnosis, with a reported positive predictive value of 96% (32). However, our study is hampered by a potential misclassification of ankylosing spondylitis, where the self-reported information has been validated to be inaccurate and often false-positive (23). Further, the incidence of ankylosing spondylitis was higher in the HUNT Study than previously reported in a mixed population from Norway (23). This indicates that the self-reported diagnosis of ankylosing spondylitis is prone to bias and cannot be considered to be an entirely reliable source. Several studies have questioned whether axial psoriatic arthritis and ankylosing spondylitis (with or without psoriasis) are different clinical presentations of the same disease (41, 42), and if so, this could potentially explain the high number of false positives. To reduce the potential for misclassification in future studies, ankylosing spondylitis could be defined by linkage to information from electronic health records (EHRs). Further, in this study, we did not stratify according to disease subtype. Psoriasis and diabetes could be stratified into several subtypes to increase the precision of our results by linkage to EHRs.

Confounding

Confounding is defined as a factor X that is associated with the exposure in the studied population, and considered a risk factor for the outcome under study, but must not be a consequence of neither the exposure nor outcome (39). This can lead to an overestimation or underestimation of the effect. In our study we chose age, sex, smoking and BMI as confounders. However, there was no substantial difference in the OR of psoriasis and ankylosing spondylitis, or psoriasis and diabetes, when we adjusted for age, sex, smoke, and BMI, suggesting that these associations are strong regardless of these risk factors for psoriasis, and possible confounders were small. Nonetheless, the results should be interpreted with caution as there might be possibilities of unknown and unmeasured confounders. This includes genetic factors and lifestyle factors shared between psoriasis, ankylosing spondylitis and diabetes.

Conclusion

In this large population-based study, we found that psoriasis was positively associated with ankylosing spondylitis and diabetes in both HUNT3 and HUNT4. However, we did not investigate differences in associations between subtypes of disease and this would be useful for a more stratified insight into psoriasis comorbidities in future studies. Increased awareness of comorbidities associated with psoriasis could improve the clinical follow-up and management of the disease. Our results emphasize a broad clinical approach to psoriatic patients where regular attention to symptoms of ankylosing spondylitis and diabetes could be recommended.

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Contributors

ML, KH, MS and IS conceived the study concept and managed the project. PB and ML performed statistical analysis with the HUNT dataset. PB conducted the literature review with support from ML, MS and IS. PB drafted the initial version of the manuscript. All authors were involved in the interpretation of the data and contributed to and approved the final version of the manuscript.

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Conflicts of interest

None declared.

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