# Systemic Sclerosis:

## *Results from a multicenter survey of Norwegian patients*

Thesis for the degree of philosophiae doctor (Ph.D.)

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# List of papers

**Paper I**
**Prevalence of systemic sclerosis in southeast Norway in the period 1999-2009**
Hoffmann-Vold AM, Midtvedt O, Molberg O, Garen T, Gran JT.
*Rheumatology (Oxford) 2012 Sep;51(9):1600-5.*


**Paper II**
**Survival and causes of death in an unselected and complete cohort of Norwegian patients with systemic sclerosis.**
Hoffmann-Vold AM, Molberg Ø, Midtvedt Ø, Garen T, Gran JT.
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**Paper III**
**Performance of the 2013 ACR/EULAR classification criteria for systemic sclerosis (SSc) in large, well-defined cohorts of SSc and mixed connective tissue disease.**
Hoffmann-Vold AM, Gunnarsson R, Garen T, Midtvedt O, Molberg O.
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**Paper IV**
**Predictive value of serial HRCT analyses and concurrent lung function tests in systemic sclerosis**
Hoffmann-Vold AM, Aaløkken TM , Lund MB, Garen T, Midtvedt O, Brunborg C, Gran JT, Molberg O.
*Submitted*

# Abbreviations

| | |
|---|---|
| ACA | Anti centromere antibody |
| ACR | American College of Rheumatology |
| ARA | Anti-polymerase III antibody |
| ATA | Anti-topoisomerase antibody |
| CI | Confidence interval |
| CTD | Connective-tissue diseases |
| dcSSc | Diffuse cutaneous SSc |
| DLCO | Diffusion capacity of carbon monoxide |
| DU | Digital ulcers |
| ED | Erectile dysfunction |
| ERS | European Respiratory Society |
| ESC | European Society of Cardiology |
| EULAR | European League Against Rheumatism |
| FEV1 | Forced expired volume in one second |
| FVC | Forced vital capacity |
| GI | Gastrointestinal |
| HRCT | High resolution computed tomography |
| ICD10 | International Classification of Diseases 10th version |
| ILD | Interstitial lung disease |
| IPF | Idiopathic pulmonary fibrosis |
| lSSc | Limited SSc |
| lcSSc | Limited cutaneous SSc |
| MCTD | Mixed connective tissue disease |
| MCP | Metacarpophalangeal joint(s) |
| mPAP | Mean pulmonary arterial pressure |
| mRSS | Modified Rodnan Skin Score |
| NOSVAR | Norwegian Systemic Connective Tissue and Vasculitis Registry |
| OR | Odds ratio |
| OUH | Oslo University Hospital |
| PAH | pulmonary arterial hypertension |
| PFT | pulmonary function tests |
| PH | pulmonary  hypertension |
| REK | Regional Committee for Research Ethics |
| RHC | Right heart catheterising |
| RNP | Ribonuclear protein |
| RP | Raynaud's phenomenon |
| SD | Standard deviation |
| SMR | Standardized mortality rate |
| SRC | Scleroderma renal crisis |
| SSc | Systemic sclerosis |
| US | United States |
| VA | alveolar volume |

# Summary

Systemic sclerosis (SSc) is a serious multiorgan disease, characterized by progressive fibrosis, vasculopathy and distinct serum auto antibodies (1, 2). Patients with SSc have an increased mortality risk and reduced quality of life (3-5). Interstitial lung disease (ILD) is a common manifestation in SSc and the leading cause of morbidity and mortality in the SSc population (3, 6). Classification of SSc was done with the 1980 American College of Rheumatology (ACR) classification criteria until 2013, when EULAR and ACR launched unified new classification criteria for SSc (7, 8).

The aim of the study was to estimate the prevalence of SSc in Norway, investigate survival and causes of deaths and to study fibrosis progression and lung function by serial assessments of high resolution computed tomography (HRCT) and concurrent pulmonary function tests (PFT). Additionally, we wanted to confirm the true value of the 2013 ACR/EULAR classification criteria for SSc.

We found a prevalence of SSc in Norway of 9.9/100 000, a value comparable to other Northern European countries, supporting the notion of a north-south gradient of SSc in Europe with the lowest prevalence in Northern Europe. Our data show that mortality in SSc is still increased compared to the background population and the major causes of death are pulmonary hypertension (PH) and ILD. When studying lung fibrosis and lung function in serial assessments, we demonstrate that a normal baseline HRCT was highly predictive against later fibrosis development, and that HRCT findings at baseline predicted fibrosis progression rates and the deterioration rates of pulmonary function. Male gender, SSc subtype, antibodies, baseline fibrosis and baseline lung function were main risk factors for fibrosis development and progression. The 2013 ACR/EULAR SSc criteria performed remarkably well in our cohort and the sensitivity was significantly better than the ACR1980 criteria using the combination of the ACR 1980 criteria and/or the Leroy & Medsger criteria as the "gold standard" for SSc.

Our results reinforce the view that SSc is a rare but serious disease with increased morbidity and mortality and that pulmonary disease is a devastating complication. Our data support the notion that the 2013 ACR/EULAR criteria are a major step forward and that their application should improve the quality of clinical and epidemiological SSc research in the years to come.

# 1. Background

## 1.1 General introduction

Systemic sclerosis is a rare, chronic connective tissue disease that affects the skin and internal organs, causes substantial morbidity and is associated with increased mortality (9, 10). The disease is characterized by micro vascular damage (vasculopathy) that leads to vessel obliteration, by fibroblast dysfunction with excessive collagen production, and by dysregulation of the immune system associated with the presence of specific autoantibodies, including anti-centromere antibody (ACA), anti-topoisomerase antibody (ATA) and anti-polymerase III antibody (ARA) (1, 2, 11-16). The etiology remains uncertain, but seems to be multifactorial. Both environmental and genetic factors have been suggested as potential risk factors for SSc (17-22).

The disease includes a heterogeneous group of patients with varying disease manifestations, and it is subdivided into limited (lSSc), limited cutaneous (lcSSc) and diffuse cutaneous (dSSc) SSc according to skin involvement (7, 23). Skleroderma sine sclerosis and overlap syndromes with other connective tissue diseases are also subtypes of SSc (24, 25).

Case assignment of SSc for research purposes have mostly been done with the ACR classification criteria from 1980 (7). Alternative classification systems were, however, increasingly used, particularly the Medsger & LeRoy three-subset system (23). In 2013, EULAR and ACR launched unified new classification criteria for SSc (8). In a multicenter SSc validation cohort, these criteria proved more sensitive than the 1980 ACR criteria. The criteria were also more specific, in terms of differentiating SSc from scleroderma like diseases. However, confirmation of the performance of the 2013 criteria in consecutive, unselected SSc patients, and the ability of the criteria to discriminate between SSc and mixed connective tissue disease (MCTD) as the most important and frequent scleroderma-related disease was not done.

The clinical symptoms of SSc depend upon the subtype and distribution of organ involvement (26, 27). Most frequently patients suffer from Raynaud's phenomenon (RP), gastrointestinal involvement (GI) and muscle and joint affection (11, 28). Digital ulcers (DU), ILD, PH and renal crisis (SRC) are also frequent manifestations (26, 29-31). Often there is a long delay from initial symptoms to detection and diagnosis conceivably due to insidious onset and symptom heterogeneity. SSc is in general progressive; however, progression rate varies

according to SSc subtype and the severity of organ manifestation at first presentation (1, 27). Although progressive lung disease with fibrosis development is the major determinant of morbidity and mortality in SSc, prospective data on fibrosis progression rate and risk factors for progressive disease are limited (32-35). There are, however, no prospective data assessing the functional impact of, and risk factors for, lung fibrosis development and progression in SSc (36, 37).

Treatment of SSc is challenging and at present time there is no curative treatment. Therapeutic intervention should be initiated early, but unspecific symptoms often delay the onset of treatment. Data on key issues like fibrosis progression rate and risk factors for progressive disease are limited (26). This makes targeted treatment difficult, and until now there is still no promising anti fibrotic treatment for SSc available (38).

## 1.2 Epidemiology

SSc is a rare disease and few population based cohort studies on SSc epidemiology in Caucasians exist, but available data suggest that SSc usually develops in the age group 40 to 50, with different peak incidences for gender and race (39-41). There is a female excess in SSc in all population studies with ratios between 3:1 and 6:1 (40). The reason for this female predominance is not well understood.

Previous studies on SSc epidemiology have yielded annual incidence data varying between 0.6 and 19/100.000 (39, 40, 42-45). Moreover, in several studies increasing incidence rates have been reported over the last decades (42, 43, 45).

Prevalence rates have been reported ranging from 5/100.000 to 30/100.000 (39, 40, 42, 44, 45). The prevalence estimates from the US and Australia appear to be higher than for Japan and Europe (39-41, 45, 46). The available data also indicate that the prevalence of SSc in the south of Europe may be higher than in the north, with prevalence rates of 15.8/100.000 around Paris, France, 15.6/100.000 in Southern Croatia, 15.4/100.000 in Northwest Greece and 27.7/100.000 in Northwest Spain, compared to 8.8/100.000 in Northwest England and 7.1/100.000 in Iceland (47-51). Notably, a recent study from Southern Sweden found one of the highest prevalence figures (23.5/100.000) ever seen in Europe; arguing against the presence of a north-south European SSc gradient (52).

Nonetheless, it is clear from these studies that there are regional variations in SSc epidemiology data. It is not known if these variations reflect true population differences

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caused by differential exposures to environmental triggers and/or genetic factors. They might also reflect differences in completeness of case ascertainment in the different studies, geographic location or absence of classification criteria prior to 1980 and better physician and patient's awareness of the disease (11).

Of unknown causes, even higher prevalence rates have been observed in several geographical clusters and in the native Choctaw Indian population (53-56).

Summarizing, it has been difficult to conduct population-based studies revealing the true prevalence and incidence. The majority of previously published studies were carried out in rather small populations and were often based on single centre or county data (47-49, 51). Therefore, we wanted to utilize the inherent properties of the Norwegian health system (free access to health care, electronic patient databases, reliable population statistics and the unique Norwegian identity numbers with *"no loss to follow up*) and conduct a population based cohort study on the true prevalence of SSc in Norway.

**1.3 Survival**
The overall survival rates of SSc vary depending on the degree of skin severity and distribution of organ involvement. Nonetheless, SSc is clearly a disorder with increased mortality and SSc patients continue to carry one of the highest risks of mortality of all connective tissue diseases (57, 58).
The observed mortality rates differ considerably between studies. Reported standardized mortality ratios (SMR) range from 1.5 to 7.2 (5, 50, 59-62) and the 5- and 10-year cumulative survival estimates range from 80 to 90% and 60% to 85%, respectively (4, 62-65).

Moreover, the frequency of deaths caused by SSc itself varies from 30% to 80% (3, 39, 57, 62, 66-68). Very nicely demonstrated by *Steen et al.* in the Pittsburgh database, causes of death have changed over the past decades (3). Renal crisis was earlier the predominant cause of death, while in the last decade, pulmonary diseases were found to be the most frequent cause of death (3).

Factors previously associated with increased mortality have included male gender, older age at disease onset, dcSSc subtype and the presence of serum ATA as well as cardiovascular, pulmonary and renal disease involvement (4, 6, 29, 57, 69-75).

Since most of the previous mortality studies in SSc were conducted in single centres with selected cohorts, the large variations may, at least partly, be explained by selection bias. Therefore, we again wanted to use the advantages of the Norwegian health care system and conduct survival analyses in our population based SSc cohort for unbiased and complete data.

## 1.4 Classification criteria

Case assignment of SSc for research purposes were until 2013 mostly done with the 1980 ACR classification criteria (7). When these criteria for SSc were designed, the intention was "to be specific rather than sensitive to minimize false positive diagnoses". Since these criteria, by definition, were not applicable to the full spectre of SSc, alternative classification systems, among others, LeRoy & Medzger's modified criteria for early SSc were developed in 2001 (23, 25, 76). Interpretation of earlier epidemiology studies was therefore hampered by the inconsistent use of classification criteria and subset definitions (76-78). Another challenge was that SSc is a heterogeneous disease where the phenotype depends upon the disease subtype and the distribution of organ involvement. In the early disease phase, the symptoms can be mild and subtle, and delineation against other connective tissue diseases (CTD), particularly MCTD might be difficult (11, 79, 80).

Very recently, EULAR and ACR launched unified new classification criteria for SSc (8, 81-83). It is evident from the joint ACR/EULAR publication that the 2013 criteria are a significant step forward, however, to confirm their true value, we wanted to evaluate the performance of the 2013 criteria in our consecutive, unselected SSc cohort, and assess the ability of the criteria to discriminate between SSc and MCTD as the most important and frequent scleroderma-related disease.

## 1.5 Pathogenesis

The pathological process involves three distinct features; micro vascular damage (vasculopathy) that leads to vessel obliteration, fibroblast dysfunction with excessive collagen production, and dysregulation of the immune system resulting, among other things, in disease-specific serum autoantibodies, most often ATA and ACA antibodies (17, 79). Both environmental and genetic factors have been suggested as potential risk factors for SSc (18-20). Several possible environmental factors associated with SSc development, such as silica and solvents have been discussed (84, 85). Scleroderma-like syndromes have been described after exposure to different factors; including exposures with contaminated rapeseed oil in

1981 in Spain, exposure with vinyl chloride in the mid 60`s and development of nephrogenic systemic fibrosis after administration of gadolinium contrast material for magnetic resonance imaging in the setting of renal compromise (86-88). Lately, gastrointestinal (gut) micro biota has been discussed as an interesting possible environmental factor for other diseases (89-91). There is growing evidence that the bacteria in the gastrointestinal tract (the gut micro biota) might influence the development of autoimmunity in rodent models (91). However, there are only few studies on microbiota and autoimmune diseases and only one on microbiota in the skin of SSc patients (89). Research will be needed to identify specific bacterial species and to ascertain whether there are possible causal association between the development of SSc and the Gut microbiom.

**1.6 Skin disease**
The skin is almost always affected in SSc and characterized by excessive fibrosis development. Clinically, it is marked by loss of flexibility due to indurations of the skin. SSc subtypes are mostly classified by the extent of the skin involvement (92). In lcSSc the skin thickening does not extent proximal to the elbows and knees. Many of these patients have only involvement of the face and the fingers. In lcSSc development of telangiectasias and calcinosis cutis is often seen. In dcSSc the skin involvement extents over the knee and elbows and affects often the whole body except for the upper back. Sine scleroderma has no affection of the skin and lSSc is defined as early SSc with no skin affection yet (also called prescleroderma). The degree of skin involvement is quantified using the validated modified Rodnan Skin Score (mRSS) (93-95).

**1.7 Gastrointestinal manifestations**
After skin involvement, the GI tract is the second most commonly involved organ system in SSc with over 90% of patients being affected (96). It is a leading cause of morbidity and mortality and a major contributor to poor quality of life (6). It can affect any site in the GI tracts, from the mouth to the anus (97). Symptoms vary based on location on affection with a variable extent and severity. The pathogenesis is elusive, but there is evidence of prominent fibrosis and alterations of smooth muscle cells and nerve fibres (98). The liver is mainly spared as a primary target in SSc. However, increased frequency of chronic liver diseases have been reported, especially the coexistence of primary biliary fibrosis (PBC) (99-102).

PBC is reported in 2-2.5% of all SSc patients and SSc has been estimated to occur in 4-15% of patients with PBC (100, 103-105).

## 1.8 Cardiovascular diseases

Traditionally, SSc had been considered as a fibrotic disease but over the last decades vasculopathy was revealed as an important key stone of SSc's pathogenesis. Vascular disease imply a high burden for SSc patients and can manifest in SSc patients as Raynauds phenomenon, digital ulcers, telangiectasias, renovascular complications (including renal crisis) and pulmonary arterial hypertension (28, 29, 106-108). Patients may additionally suffer from erectile dysfunction (ED) (109-111). Nailfold capillaroscopy is increasingly used for the detection and imaging of microvascular changes and represents a safe and readily available imaging tool (112-115). Capillaroscopy has also been incorporated in the 2013 classification criteria for SSc (8).

Cardiac involvement is common in SSc and can affect any cardiac structure both in lcSSc and dcSSc patients (116-119). The pathogenesis involves vasospastic mechanisms. Symptoms vary based on location on affection. When cardiac involvement gets symptomatic the prognosis is poor. Therefore, screening for sub clinical cardiac disease is essential but unfortunately, optimal screening tools are unknown.

## 1.9 Pulmonary manifestations

Pulmonary diseases in SSc are the leading causes of deaths in SSc. There are two types of lung diseases in SSc (ILD and PH) with different pathogenesis, clinical features, predictors and treatment. The identification and predictive values for the detection of PH including isolated pulmonary arterial hypertension (PAH) has not been addressed in this thesis (120-123).

### 1.9.1 Interstitial lung disease

ILD is a common manifestation in SSc and the leading cause of morbidity and mortality in the SSc population with 35% of all SSc related death directly attributable to pulmonary fibrosis (3, 6). Previous published data have shown that major lung involvement in SSc occurs early in the disease course (26, 124). ILD`s clinical course is heterogeneous and pulmonary manifestations vary widely; from limited non-progressive lung involvement to major pulmonary inflammation and fibrosis progressing to respiratory failure and death (32, 33, 75,

125). ILD can appear in both lcSSc and dcSSc; data from the EULAR multicenter SSc database showed that 53% of the enrolled patients with dcSSc and 35% with lc SSc had ILD. Several risk factors have been detected to predict ILD in SSc (35, 75, 126-129). The presence of an abnormal forced vital capacity (FVC) early in the disease has been reported as one of the most important risk factors for end stage lung disease (26, 130, 131). It has also been discussed whether the autoantibody profile may be a more powerful predictor for organ involvement than the disease subtype (27).

SSc-ILD has typically an insidious onset with subtle clinical symptoms that are often non-specific and a challenge to patients and physicians (132). PFTs play an important role in staging and serial monitoring of ILD in SSc (131). ILD in SSc is mostly associated with a restrictive ventilator defect, but coexistence of pulmonary vascular disease or extra-pulmonary restriction may make the interpretation difficult. Usually, spirometric volumes are the most readily available measures and are highly reproducible but have clear limitations. PFT abnormalities are not specific for ILD, and wide normal ranges make baseline values difficult to evaluate (unless pre-morbid values are available). Benchmarking PFT at baseline is, nonetheless, critical for predicting outcome in SSc-ILD. In fact, serial PFT data suggest that forced vital capacity (FVC) decline to 50-70% within five years predict end-stage ILD and mortality (26, 127).

HRCT is the primary tool used to determine the extent of lung affection in systemic sclerosis in SSc-patients with abnormal PFTs and/or clinical ILD symptoms (34, 37, 133, 134). The advent of HRCT has greatly enhanced the detection of ILD, with HRCT changes seen in up to 55-65% of SSc patients and up to 96% of those with abnormal pulmonary function tests (37). The high diagnostic sensitivity of HRCT allows the detection of ILD at an earlier stage than ordinary chest radiographs and adequate staging to when and who commence with treatment (30, 133). It identifies the type of lung parenchyma abnormalities involved and allows for quantitative assessment of individual ILD components (34, 133, 134). Notwithstanding, there is no gold standard for differentiating between irreversible and reversible HRCT abnormalities, but the accumulated evidence suggest that reticular pattern changes may be considered as equivalents to lung fibrosis, and therefore represent the irreversible end of the abnormality spectre. Ground glass abnormalities typically represent the reversible end of the spectre. They are not specific for a distinct pathology, but may represent inflammatory processes in the lung parenchyma.

The potential value of quantitative HRCT fibrosis measurements in SSc was recently highlighted by Goh et al. (30). By combining cross-sectional HRCT analyses with follow-up PFT and survival data, they constructed a readily available prognostic algorithm for SSc-ILD, including both PFTs and HRCT findings. ILD is divided into a limited disease, an intermediary disease and an extensive disease, defined by baseline fibrosis </>20% and a baseline FVC>/<70%. It was shown that extensive disease was associated with high risk for mortality, also validated by Moore and co-workers (30, 69)

Nonetheless, there is a substantial deficiency of data on key issues like fibrosis progression rate and risk factors for progressive disease. Little has been published on the utility and predictive value of serial HRCT in SSc (133). To date, there are no data on pulmonary fibrosis progression combining detailed lung fibrosis progression analyses with lung function tests in large longitudinal and prospective cohorts (37, 135).

Therefore, we wanted to determine the lung fibrosis progression rate and to analyse predictors for favourable and unfavourable lung outcome in a large, prospective SSc cohort by investigating pair wise data combining serial HRCT, PFT and clinical investigations.

### 1.9.2 Pulmonary hypertension

PH is common in SSc and occurs in two forms; isolated PAH and PH secondary to ILD. PAH is a disease of the small pulmonary arteries, characterized by progressive increase in pulmonary vascular resistance, ultimately causing right heart failure and death. It is defined by mean pulmonary artery pressure (PAP) >25 mmHg at rest measured by right heart catheterising (RHC) (31, 136). PAH is typically seen in patients with longstanding lcSSc without significant ILD (136, 137). No population data on PAH prevalence exist, but referral centre data indicate that it occurs in 10-15% of the patients. PAH has a major impact on quality of life (138) and takes often a rapid and devastating course.

## 2. Aims of the study

**General aim**

Estimate the frequency and mortality of SSc, assess the lung fibrosis progression rate and identify predictive value for fibrosis progression in SSc and perform the 2013 classification criteria in an unselected, population based SSc cohort.

Our specific aims were:

1. Estimate incidence, prevalence and gender ratio of SSc in south east Norway and evaluate possible geographic differences compared to earlier investigated populations

2. Estimate the mortality and the causes of death of SSc patients compared to an age- and sex- adjusted control group, representing the general population

3. Assess the sensitivity of the 2013 ACR/EULAR classification criteria for SSc on defined subgroups of SSc and in MCTD as a scleroderma related disease

4. Evaluate the predictive value of serial HRCT, assess lung fibrosis progression rate and risk factors for progressive lung disease in SSc using pair wise serial HRCT analyses and concurrent pulmonary function tests

# 3. Patients and Methods

### 3.1 Patient cohorts

The Norwegian health system has inherent properties that make it highly suitable for population based studies (free access to health care, electronic patient databases, reliable population statistics and the unique Norwegian identity numbers with *"no loss to follow up"*). Over the last years, we have taken advantage of this and established two observational population based cohorts. First, the prospective SSc cohort at Oslo University Hospital (OUH) (Norwegian Systemic Connective Tissue Disease and Vasculitis Registry [NOSVAR]) that has been the basis for the performance of the 2013 classification criteria and for the detailed, serial HRCT analyses and concurrent pulmonary function tests in SSc and is described below. Second, the Southeast Norway SSc cohort formed the basis for the analyses of the prevalence and mortality of SSc in Norway.

### 3.1.1 The prospective OUH SSc cohort:

Since 2008, all the hospital databases at OUH are regularly screened to identify new eligible patients (i.e. patients with International Classification of Diseases (ICD-10) diagnoses compatible with SSc; M34.0, M34.1, M34.2, M34.8 or M34.9), which has been used in all Norwegian hospitals since 1999. This systematic database monitoring (and accompanying chart review by at least two SSc experts) allows for early detection of suspect SSc cases. All patients with an ICD-10 diagnosis compatible with SSc are continuously registered in NOSVAR. Patients who do not fulfil any criteria (predominantly SSc sine scleroderma and pre-scleroderma) are followed-up at the OUH outpatient clinic.

### 3.1.2 The south east Norway SSc cohort

We aimed to identify and enrol every SSc patient living in Norway between 01.01.1999 and 31.12.2012 in this cohort. Through collaboration with all hospital-based rheumatologists in south east Norway, we established an unselected and large population based SSc cohort, which included every identifiable patient in south east Norway.

Different acquisition routes were used to identify every Norwegian patient with an ICD-10 SSc diagnosis code (i.e. M34, see below).

*3.1.3 The MCTD cohort*

The MCTD cohort included 178 patients, 147 patients enrolled in the unselected Norwegian nationwide MCTD cohort from 2005-08 and 31 included from the prospective OUH cohort NOSVAR from 2008-13 by *Gunnarsson et al.* (139, 140). Inclusion criteria for the MCTD cohort were; (141) (1) age = 18 years at inclusion, (2) fulfilment of at least one of three MCTD criteria sets (Sharp, Alarcón-Segovia and/or Kasukawa, and (3) exclusion of other CTDs (142).


**3.2 Case finding strategy for SSc patients in southeast Norway**

By January 2010 Norway's population consisted of 4801055 inhabitants. The denominator study population consisted of every person registered in the Norwegian Central Register with a home address in one of the 10 counties in southeast Norway with a total population of 2707012 (56% of the total Norwegian population). There are eight Departments of Rheumatology and one department of dermatology in these ten counties.

Five different acquisition routes (see below) were used to identify all the patients in the study area between 01.01.1999 and 31.12.2009 who had been registered with a SSc diagnosis code (M34) according to the 10th revised version of the International Classification of Diseases (ICD-10), which has been used in all Norwegian hospitals since 1999.

Patients with an ICD-10 diagnosis code consistent with SSc were identified by the following five, partly overlapping acquisition routes:


1. The prospective SSc cohort (NOSVAR) of the Department of Rheumatology, at OUH was interrogated.
2. All the other seven Departments of Rheumatology in southeast Norway were asked to interrogate their hospital database.
3. All the rheumatology consultants practicing within the study region were invited to provide details of any patients under their care whom they considered to have SSc.
4. The one rheumatology department for children in Norway (located at OUH) was asked to interrogate their database for juvenile SSc patients.
5. The Department of dermatology at the OUH was asked to interrogate their database for SSc patients not taken care of by the rheumatology department.

All the hospital records were reviewed to evaluate whether the patient fulfilled the 1980 ACR and/or the Medsger & LeRoy classification criteria (7, 23). Finally, the records of every patient who fulfilled the criteria were re-examined to exclude other connective tissue diseases. All data were recorded retrospectively. Patients with CTD other than SSc and patients with localized scleroderma or morphea were excluded.

### 3.3 Inclusion criteria for the prospective OUH cohort

The OUH cohort NOSVAR was initiated before the 2013 ACR/EULAR classification criteria for SSc were developed. Thus, SSc patients were until 2013 included if they satisfied the ACR classification criteria from 1980 and/or Medsger & Leroy's criteria from 2001 (7, 23). The patients were categorized into three SSc subtypes: 1. lSSc; defined by RP plus SSc-type nailfold capillary pattern or SSc specific auto antibodies, 2. lcSSc with skin thickening distal to the elbow/knee and 3. dcSSc with skin thickening proximal to the elbow/knee.

After 2013, all SSc patients were enrolled if they fulfilled the 2013 classification criteria for SSc (8). Briefly, the criteria are based on a scoring system where the first criterion alone, skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal (MCP) joints, gives the 9 points needed to classify the patient as SSc. If the first criterion is not met, the patient can gain 9 points by seven other items (8).

### 3.4 Prevalence and Survival analysis

*3.4.1 Prevalence*

The point prevalence of SSc was calculated at December 31st 2009.

*3.4.2 Assessment of SMR and survival rates*

Using the personal identification numbers, we were able to identify every death and all the reported causes of death in the SSc cohort between 01.01.1999 and 01.01.2010. The vital status at the end of the study was established by contacting the Norwegian Central Person Register and by chart review. To calculate the SMR Statistics Norway provided a control group from the general Norwegian background population. Altogether 15 random controls were selected for each individual SSc patient. The controls were matched with the SSc patient for gender, year of birth and living area. Additionally, all the 15 controls were alive on the date of patient's disease onset. For calculation of the SMR in the follow up period we

excluded all controls dying during the period of diagnostic delay and reduced the number of controls per patient accordingly.

### 3.4.3 Causes of death
The causes of death were based on information from medical charts, death certificates and autopsy. When the information from the different sources was not consistent, we used data from the medical chart and not from the death certificate. On three death certificates, SSc was not mentioned as a contributing cause of death (cause of death unknown). Causes of death of the control group were given by Statistics Norway. The causes of death of SSc patients were classified as SSc-related mortality and mortality unrelated to SSc. SSc related deaths were defined as deaths related to progressive, active SSc or deaths caused by organ failures directly related to SSc affection. Deaths unrelated to SSc were of all other causes and divided into several subgroups. If there was no notification on the death certificate or in the patient chart, the cause of death was defined as "unknown".

### 3.5 Clinical parameters
Clinical parameters were recorded in a standardised form and included: patient's age, gender, smoking history, RP, skin involvement, organ involvement (including pitting scars and teleangiectasias), nailfold capillaroscopy, SSc-related antibodies, onset of RP and non-RP and vital status (28). PH was defined by the European Society of Cardiology (ESC) criteria (i.e. mean PAP > 25 mm HG by right heart catheterisation at rest) (31). ILD was assessed by HRCT and PFTs. The presence of ILD was defined by findings of fibrosis on HRCT and a FVC <70 % of the expected value (30).
Disease onset was defined as the first non-RP symptom. The period of time from disease onset until study end at the time of death was defined as the disease duration.

### 3.6 Pulmonary function test
All included SSc patients underwent at least two PFTs, one at baseline and one at follow up. PFTs were systematically performed within 1 months of corresponding HRCT examination, following standard protocols. Lung function tests included dynamic spirometry and gas diffusing capacity. Recorded spirometric variables were: FVC, forced expiratory volume in 1 s ($FEV_1$) and $FEV_1$/FVC. Gas diffusing variables were the DLCO and DLCO divided by alveolar volume (DLCO/VA). Lung function values were expressed in absolute values and as

percentage of predicted. Reference values were those recommended by the European Respiratory Society (ERS) (143).

### 3.7 Acquisition and review of HRCT images

Low-dose thin-section CT images were obtained in the supine position during breath-holding and deep inspiration.

The images were reviewed independently and in random order by one experienced chest radiologists and one rheumatologist with training in interpretation of HRCTs. The observers were blinded to lung function and the patient's clinical condition. In case of differing interpretations, final conclusions were reached by consensus. Reticular pattern (fine intralobular fibrosis without evident cysts; microcystic; and macrocystic) and super-imposed ground-glass opacities were defined as equivalent to fibrosis (144).

The extent of involvement was evaluated independently for each thin-section image, and each image was assigned a score based on the percentage of lung parenchyma that showed evidence of fibrosis. Area measurements were done precisely by drawing a freehand region of interest (ROI) on the PACS screen. The overall extent of fibrosis was scored, and related to the total volume of lung parenchyma. The relationship between the overall volume of fibrosis and total lung volume was evaluated for HRCT at baseline and at follow up. To assess the sequential changes over time for each patient, the % rate of abnormal HRCT findings were compared with % rates on the other HRCT scan.

Patients were stratified in four subgroups by the extent of fibrosis on HRCT at follow up with 0% fibrosis at baseline and follow up (group 1), 1-20% fibrosis at baseline and follow up (Group 2), 1-20% at baseline and >20% fibrosis at follow up (Group 3) and >20% at baseline and follow up (Group 4) (30, 133).

### 3.8 Statistics

Statistical analyses were performed by SPSS version 16-21 and STATA version 13. Causes of death were analyzed using standard descriptive statistics. Kaplan-Meier survival curves and significance was tested with the log rank test. Items with significant effects on survival were entered into the Cox proportional hazards model. The SMR was calculated as the ratio between the observed rate of death in the SSc cohort and the observed rate of death in the

comparable age- and gender-matched control group from Statistics Norway, representing the Norwegian background population.

The association between potential risk factors and outcome was quantified by odds ratio (OR) with its 95% confidence interval (CI). Further, all independent risk factors significantly associated with survival or outcome measures from the univariate analysis at a significance level of 20% were considered as candidates in the multivariate logistic regression analysis. A manual backward stepwise elimination procedure using a multivariate logistic regression model was performed to identify independent risk factors for survival and outcome measures. Multivariate analyses were preceded by estimation of correlation between risk factors. Demographics, clinical and lung characteristics were analyzed using standard descriptive statistics. Differences in clinical findings between patients were analysed using Pearson Chi-square test for contingency tables for categorical variables and independent sample t-test for continuous variables. Descriptive statistics were applied to analyse the number of patients of both cohorts meeting the newly established classification criteria for SSc. Sensitivity and specificity were calculated with confidence limits by using 2x2 tables with chi-square test.

### 3.9 Ethics

This study was approved by the regional committee (REK) of health and medical research ethics south east Norway (regional komité for medisinsk og helsefaglig forskningsetikk Sør-Øst (No.2009/1035)).

# 4. Results

### 4.1 Paper I

Using the acquisition routes described, we identified a total of 369 patients diagnosed with SSc according to the ICD-10 coding system. Chart review revealed that 52 patients were miscoded and suffered from connective tissue diseases other than SSc (145). Another five patients were excluded as they did not fulfil the inclusion criteria. Since every person living in Norway has a unique Norwegian identity number, no patients were registered twice. Thus, the total number of SSc patients in the study area who fulfilled the ACR classification criteria for SSc and/or the Medsger& LeRoy's criteria was 312, including five patients with juvenile onset.

The mean age at onset of the first non-Raynaud SSc symptom was 46.6 yrs. (SD 14.5 yrs.) for women and 47.2 yrs. (SD 15.4 yrs.) for men. The patients with dcSSc were younger at disease onset than the other subgroups and had shorter disease duration than lcSSc patients, but somewhat longer than lSSc patients. The female to male ratio of SSc in the study area was 3.8:1. Forty three SSc patients died during the study period. The total number of SSc patients living in the study area by December 31$^{st}$ 2009 was thus 269. Of these patients, 35, 183 and 51 were classified as lSSc, lcSSc and dcSSc, respectively. The overall ratio of lSSc to dSSc was 4.6:1. The ratio of limited to diffuse disease in women and men was 5.1:1 and 3.3:1. Approximately 95 % of the patients included were Caucasians.

The point prevalence of SSc, according to the Medsger&LeRoy and ACR criteria, in southeast Norway by December 31$^{st}$ 2009 was estimated to 9.9/100.000 (95% CI 8.8-11.2), 4.2/100.000 (95% CI 3.2-5.4) for males and 15.6/100.000  (95% CI 13.6-17.8) for females. We observed a distinct geographical variation in the prevalence of MCTD in Norway. The prevalence of SSc in the different Norwegian counties varied between 5.2 and 14.4/100.000 (95% CI 2.8-8.8 and 10.3-19.6). The point prevalence for SSc by the ACR criteria alone was 7.2/100.000 (95% CI 6.3-8.3).

## 4.2 Paper II

The total study cohort consisted of 95% Caucasians and included 312 patients fulfilling the ACR classification criteria for SSc and/or the Medsger& LeRoy's criteria. 43/312 patients (14%) died during the study period (146). The deceased patient group consisted of 6 males with lcSSc and 9 males with dcSSc and 20 females with lcSSc and 8 with dcSSc. Male patients with dcSSc had a significantly higher mortality (43%) compared to females with dcSSc (17%) and to males and females with lcSSc (12% and 10%, respectively) (p-value 0.03).

Chart review showed a higher frequency of ILD, PH associated with ILD (PH-ILD) and PAH in the 43 patients who died than in the surviving patients. Odds Ratio analyses identified ILD and PH (PAH and PH-ILD) as factors associated with mortality. Male gender and dcSSc subtype were also factors associated with a poor prognosis, whereas ACA was negatively associated with mortality. Multivariate logistic regression analysis showed that PAH (OR=8.0, 95% CI: 3.4-18.8) followed by ILD (OR=3.1, 95% CI: 1.5-6.6) were the strongest predictors for mortality.

The overall SMR of the observation period was 2.03. The all-cause SMR was higher in males than in females, SMR for dcSSc was 5.33 compared to 1.62 for lcSSc.

The Kaplan-Meier cumulative 5-year overall survival for SSc patients was 95%, and the 10-year survival was estimated to 86%. The 5- and 10- year survival rates for lcSSc were estimated to 98 and 93%, and to 91% and 70% for dcSSc, respectively.

The death was attributable to SSc in 24 of the 43 deceased patients (56%). Sixteen of the 43 deceased patients had death causes not attributable to the disease (37%) while three SSc patients died of sudden death of unknown causes (7%).
In total, 54% of the SSc attributable deaths were due to cardiopulmonary diseases, with pulmonary fibrosis (20%) and PAH/PH (20%) as the most frequent causes. All five patients dying from pulmonary fibrosis had extensive fibrosis according to the staging system by *Goh et al* (30). All patients dying of PAH/PH had pre-capillary PH, no signs of post-capillary PH were noted. Another 25% of the patients died of SSc associated gastrointestinal causes while renal causes accounted for the death of five patients (20%). Three of the five patients with renal failure were diagnosed with SRC during their disease course (12.5%). They all died within three years after their SRC diagnosis. The 16 cases with non-SSc related causes of

death included malignancies (n=6), infections (n=2), coronary arterial disease (n=2), obstructive lung diseases (n=2), stroke (n=2) and bleeding anaemia (n=2).

## 4.3 Paper III

The OUH cohort included 425 consecutive SSc patients; 328 fulfilling the Leroy & Medsger criteria (23) (294 with lcSSc, 24 with prescleroderma and 10 with sine SSc) and 97 patients with dcSSc. Since prescleroderma and sine SSc, by definition, would not be captured by the 1980 ACR criteria, only 391 patients were classifiable by these criteria. Hence, the frequency of patients meeting the ACR 1980 criteria was 75% (293/391). The mean age at disease onset was 48 years (SD 15.0) and the female to male ratio was 4:1. Altogether, 82 of the consecutive SSc patients had disease duration <1 year at study inclusion and in 239 the disease had lasted less than three years. Median disease duration of the whole SSc group was 8 years, (range 0-44). ILD was identified in 174 patients (41% of the whole group) and 60 (14%) had PH, verified by RHC.

The 2013 EULAR/ACR classification criteria for SSc were met by 409 (96%) of the SSc patients, 97 of these (23%) were classified as SSc due to bilateral skin thickening proximal to the MCP joints. The remaining 312 patients reached 9 points or more by fulfilling other parameters defined by the criteria.

The 16 SSc patients that did not meet the 2013 EULAR/ACR criteria had complete data on all the parameters defined by the criteria. They were classified as lcSSc (2 patients), pre-scleroderma (6 patients) or sine SSc (8 patients).

The mean age of the MCTD patients at onset was 35 years (SD 15.7) and the female to male ratio was 4:1. Puffy fingers were present in 134/178 MCTD patients (75%), 54 (30%) had sclerodactyly, DU were recorded in 12 patients (7%) and four (2%) had SSc-related antibodies. ILD was identified in 44 patients (25%) and 5 (3%) had PH, as verified by RHC. The 2013 ACR/EULAR criteria for SSc were met by 18 patients (10%) in the MCTD cohort. All these 18 patients had RP, 17 had sclerodactyly, 4 had DU and 15 ILD, but none had PH.

The sensitivity for the new classification criteria was accounted to 96 % (95% CI 93.39, 97.36) and the specificity to 90% (95% CI 84.85, 94.05).

**4.4 Paper IV**

Of the 425 consecutive SSc patients enrolled in the prospective OUH SSc cohort, 305 had at least two pairs of lung HRCTs and corresponding PFTs available. The mean age at onset of first non-RP in these 305 patients was 48 years (SD 15.0). The mean time from non-RP onset until baseline HRCT was 4.2 years (SD 4.5) and the time lag between baseline HRCT and baseline PFTs was 0.01 years (SD1.5). Mean observation time between baseline and follow up HRCT was 3.1 years (SD 2.6) and the total disease duration, from non-RP onset to study end or death was 10.8 years (SD 7.8). Altogether, 67 patients (22%) died in the time period from the follow-up HRCT to the end of the study.

At baseline, lung fibrosis was identified in 197/305 (65%) of the patients, while 108 patients had no signs of fibrosis. Strikingly, none of the 108 SSc patients without lung fibrosis at baseline had developed fibrosis on the follow-up HRCT, obtained mean 3.4 years later (group 1). The 108 patients with no fibrosis were predominantly female (88%), had lcSSc (84%) and were ACA positive (70%) (group 1). In contrast, the 40 patients with >20% fibrosis at baseline were mostly dcSSc (55%), ATA positive (48%), and had a higher frequency of PH (28%) (group 4). Smoking habits did not differ across the groups. Of the 157 patients with 1-20% fibrosis at baseline, 11 progressed to >20% fibrosis at follow up (group 3). These 11 patients were characterized by significantly shorter mean disease duration at baseline (1.3 years) than all the other groups.

At baseline HRCT, the mean fibrosis was 6.8% (SD 13.0). At the follow-up HRCT, fibrosis had progressed by 1.6% (SD 5.5). The mean fibrosis progression rate was highest (17.2%) in the 11 patients progressing from 1-20% fibrosis at baseline to >20% fibrosis at follow-up. The group with >20% fibrosis (n=40) at baseline and follow-up had higher fibrosis progression rate (2.7%) than the 146 patients with 1-20% fibrosis at baseline and follow-up (fibrosis progression rate 1.1%) (p-value <0.001).Only 19 patients had >10% fibrosis progression from baseline to follow-up.

Mean baseline FVC % in the total SSc cohort was 92.7% (SD 20.9). The group with >20% baseline fibrosis had the lowest FVC % (69.9%). At follow-up, FVC % had declined by 4.8 % (SD 12.7) in the total cohort. FVC decline >10% was observed in 85/305 patients (28%), with highest frequency (46%) in the 11 patients with 1-20% fibrosis at baseline and >20% fibrosis at follow-up. Mean unadjusted DLCO % at baseline was 66.5% (SD 20.8) and the mean decline in DLCO % from baseline to follow-up was 8.2 % (SD 13.8). Patients with >20%

fibrosis at follow-up had lower mean DLCO % at baseline than the other groups, but there was no significant difference between the groups with respect to mean DLCO decline or frequency of DLCO decline >15%.

Disease duration at baseline HRCT was <3 years in 58% of the patients (177/305), 4-10 years in 23% and >10 years in 19%. Percentage fibrosis at baseline did not differ between these three groups, but the group with <3 years disease duration had significantly higher fibrosis progression rate (2.2%) than the 4-10 years (0.8%) and >10 years (0.5%) groups. Moreover, 13/19 patients with >10% fibrosis increase had <3 years disease duration.

Univariate analyses showed significant associations between *no lung fibrosis at follow-up* and anti-centromere antibodies (ACA), and between *>20% fibrosis* and male gender, dcSSc, anti-topoisomerase antibodies (ATA) and PH. Both the primary outcomes were also associated with baseline values for FVC and DLCO. Univariate analyses of the secondary outcomes (*FVC<70%*, and *FVC decline >10% from baseline to follow-up*) were also performed. In the multivariate analyses, predictors for *no lung fibrosis* were ACA (OR 4.7) and baseline DLCO (OR 1.0), while *>20% fibrosis* was predicted by baseline values for fibrosis (OR 1.2) and FVC (OR 0.96) (Table 4). *FVC<70%* was predicted by baseline fibrosis (OR 1.0), FVC (OR 0.9) and by ACA (OR 0.3). *FVC decline >10%* was also predicted by ACA (OR 0.4), and with the development of PH (OR 2.2).

During the period from the follow-up HRCT to the end of study, 67 SSc patients (22%) had died. The deceased patients were significantly older at disease onset than the survivors, and had more often dcSSc and PH. Baseline values of FVC % and DLCO % were significantly associated with survival, and FVC % decline was higher among the deceased patients. The frequency of patients with >20% fibrosis at baseline was higher in deceased than surviving patients. Other lung fibrosis parameters were not significantly associated with survival.

# 5. General discussion

## 5.1 What is the role of epidemiologic research?

Although systemic sclerosis is one of the most enigmatic and challenging rheumatic diseases associated with a huge burden of morbidity and mortality surprisingly little has been known about causes, aetiology and pathophysiology. Fortunately, over the last decades research on SSc has increased tremendously and results are elucidating several aspects of this devastating disease, including clinical aspects, genetic and environmental factors and changes in the molecular level (17, 147-149). Disease management has also improved, clinicians and researchers dedicated to SSc are more aware of the heterogeneity of the disease, monitoring and possible treatment for different organ manifestations. Additionally, international collaboration has been established and has, among others, resulted in a large SSc cohort, the EUSTAR database (6, 27, 150). Many items, including data about SSc frequency, mortality and different organ affection have been published.

So why is further epidemiologic research interesting in an era marked by basic research progress and large international cohorts? Can epidemiologic researches from Norway, with its limited population add novel knowledge to the SSc society? Obviously, my answer is "yes, it is" for both questions. Firstly, although research of the last decades has lead to enormous advances in understanding of the disease we still do not know the cause and there no curative treatment exists. We really need future research into molecular mechanisms to improve our knowledge and find effective treatment. However, to know who to treat how, we need to classify and diagnose the right patients at the right time. In the era of evolving knowledge and awareness of SSc and new classification criteria, we really need updated and valid epidemiologic data about the true incidence, prevalence and mortality. For creating reliable epidemiological data of SSc, unselected and complete population based cohorts are the preferred basis for deriving those. Secondly, we want again elucidate that Norway is particularly suitable for epidemiologic studies because of the special Norwegian health care properties . Furthermore, Norway is a relatively small northern European country, its population is ethnically homogeneous, with less than 10% of the 4 800 000 inhabitants being of non-European ancestry and it has a climate and environmental exposures that differs from other northern European countries. All these items result in good prerequisite for reliable epidemiologic data and the possibility for novel knowledge.

In conclusion, we think that we have delivered novel and interesting data of the prevalence and the survival of SSc in a complete and unselected cohort causing the basis for more research.

**5.2 What does the lower prevalence in Norway tell us?**

We showed a lower prevalence (9.9/100.000) of SSc than in Southern Europe (15.4-27.7/100.000), the US (27.6-44.3/100.000) and Australia (23.3/100.000) but comparable to other Northern European countries (7.1-8.8/100.000) (40). Until *Andreasson et al* published substantial higher prevalence data in southern Sweden (23.5/100.000) in July 2013 (52), we were convinced of a north south gradient of SSc in Europe. The health system of Sweden and Norway is comparable and both cohorts were complete, unselected and population based. So what does the lower prevalence in Norway compared to Sweden tell us? Our speculation that similar prevalence rates between the Northern European countries might be due to common genetic variants in the region has obviously to be reconsidered.

Could the awareness of SSc explain the differences? In our study, we observed variation in prevalence rates ranging from 5.2 to 14.4/100.000 in the ten Norwegian counties included in the study area. It appeared that the three counties with the lowest observed prevalence rates also had the lowest number of rheumatologists per capita, indicating that the observed differences could be due to missed SSc diagnoses due to lower awareness. Notably, the total population in these three counties only made up 20% of the total denominator population. Thus, any missed diagnoses would only have a minor impact on the overall observed SSc prevalence data. We believe that it is rather unlikely, that the awareness of rheumatologists in southeast Norway is significantly lower than in southern Sweden. However, the awareness of SSc in the primary health care system might be higher in southern Sweden and might explain, at least partly, the higher prevalence.

As we know, the mechanisms behind SSc are not well understood, but involve genetic and environmental factors (151). The genetic contribution appears modest and, as mentioned, it is rather unlikely the only explanation for the different prevalence rates (17-19). Therefore, environmental factors come up as interesting aspects. Lately, there has been increasing focus on the microbiota in autoimmune diseases and there is growing evidence that the gut micro biota influence the development of autoimmunity (91). It has been supposed that people who are genetically predisposed to autoimmunity, harbour gut microbial communities that might

influence the onset and/or severity of a disease (90, 152, 153). Additionally, factors, like dietary changes exist that modulate the composition and function of the gut microbiom. Until now, there are no data on the gut microbiota in SSc, however, we know that there exist differences in diet and body mass index (BMI) varies worldwide. Therefore, might disturbance of the gut microbiota, as an environmental factor, explain the different prevalence rates world wide?

In conclusion, we still do not know how to explain the lower prevalence of SSc in southeast Norway compared to southern Sweden, the US and Australia and further research is warranted. Especially, research will be needed to identify potential environmental factors.

### 5.3 Has mortality changed over the last decades?

We know that mortality is increased in SSc and that SSc patients continue to carry one of the highest risks of mortality of all systemic inflammatory diseases. However, few mortality data are derived from population based cohort studies and there has not been consistent use of classification criteria making it difficult to compare results from studies with different study designs and different cohorts. Earlier reported standardized mortality ratios (SMR) ranged from 1.5 to 7.2, with corresponding 5- and 10-year cumulative survival estimates of 80-95% and 60-85%, respectively. Both the observed SMR of 2.03 and the 5- and 10- year survival rates of 95% and 86% in the present study indicate that the mortality of SSc in southeast Norway is lower than reported in most other countries including other Scandinavian countries. In a study from Sweden, published in 1998, the 5- and 10- year survival rates were 86% and 69% and the overall SMR 4.6. Data from Denmark, also from 1998, showed 5- and 10- year survival rates of 81% and 71%, and an overall SMR estimated to 2.9 (4, 5). Why is the survival higher in Norway? We do believe that there are several possible explanations. Most obviously, the relatively low mortality mainly reflects that the South-East Norway cohort was population based and therefore included proportionally more patients with mild and early disease than cohorts from referral centres. This is also supported by the inclusion of SSc patients fulfilling the 1980 ACR criteria and/or the Medsger and LeRoy criteria for early SSc in the Norwegian cohort. In comparison, both the Swedish and the Danish cohort included only SSc patients fulfilling the 1980 ACR criteria and might have missed SSc patients with a milder and earlier disease course. In comparison with Northern American and southern European cohorts, our data might also reflect the rather homogenous population of

Caucasian descent, with a milder disease evolution and progression leads to increased survival of our cohort compared to cohorts with heterogeneous ethnicity (39, 154).

Nonetheless, we do know that survival rates have been reported to have improved over the last decades (3). It has been suggested that this is due to earlier diagnosis and improvement in treatment of SSc patients, especially treatment of SRC. Renal crisis used to be the predominant cause of SSc-related death, but in the last decade pulmonary diseases have taken over. Our data of causes of deaths are in line with these reports. In the Southeast Norway cohort 56% of deaths were attributable to SSc with ILD (20%), PH (20%), and GI disease (25%) as the most frequent causes while SRC was the least cause of death and accounted only for 12.5% of all SSc related deaths. We do not have mortality data from different decades from our Norwegian cohort, however, comparison with the achieved data from Sweden and Denmark from the mid-90s might hypothetically reflect increased survival in the Scandinavian countries over the last two decades.

In conclusion, although mortality data vary in some degree and despite that survival has improved in different reports over the last decades, our results reinforce the view that SSc is still a disease with increased mortality and that cardiopulmonary disease are now the leading causes of death.


**5.4 Who do we classify with the new criteria?**
Classification criteria were initially proposed to enhance research by developing approaches for creating groups with similar patients. The main aims were to reach high sensitivity and specificity. In SSc the main goals were to include all SSc patients (sensitivity) and to exclude patients with scleroderma like disorders (specificity) (155). Historically, this has been challenging due to the heterogeneity of SSc and the wide range of clinical manifestations and the occurrence of different auto antibodies. The first classification criteria, the 1980 ACR criteria were not designed to identify patients with lcSSc, lSSc and sine scleroderma patients. Other criteria included these, like Medsger& Leroy's criteria, but they were never validated. However, they included increasingly auto antibodies and nailfold capillary pattern. The varying use of different classification criteria were leading to inconsistency of research results as discussed earlier in this thesis.

Very recently, EULAR and ACR launched unified new classification criteria for SSc (77, 78). In a multi-centre SSc validation cohort, these criteria proved more sensitive than the 1980

ACR criteria for the full spectrum of SSc (8). We showed in our consecutive, unselected SSc patients a high sensitivity of the new criteria. Only 4% of the cohort patients remained unclassifiable. These unclassifiable SSc cases had early disease. However, the 2013 EULAR/ACR criteria did not discriminate completely between SSc and MCTD as the most important and frequent scleroderma-related disease. Ten percent of the MCTD patients met the 2013 SSc criteria, even in the absence of two criteria items (telangiectasias and nailfold capillaroscopy findings). We do believe that this high frequency mainly reflects the protean nature of MCTD and the potential evolution of MCTD into a more SSc-predominant phenotype over time. This answers the initial question: With the 2013 criteria for SSc, we will mainly classify SSc patients, however, we will still miss some SSc patients and might misclassify some patients with scleroderma like disorders. The clinical challenge of discerning especially MCTD from SSc will therefore, also in the future require detailed clinical work-up on a case to case basis and, in some cases, even longitudinal follow-up data.

A future challenge will be the development of unified SSc subset classification criteria. We know that the clinical course, organ affection and survival often depend on the SSc subtype with dcSSc as the most severe subtype. Until now, the most widely accepted method is to divide patients clinically after skin involvement according to the distribution of skin thickening distal or proximal to the knee and/or elbow. However, measuring the skin thickening with the mRRS is dependent on the clinicians experience and regular application of the same clinician. Over the last decade, several different auto antibodies associated with lc and dcSSc have been detected, but not all are commercially available yet (1, 14, 29, 79). Fortunately, new SSc subset classification criteria combining typical clinical and serological profiles will be a useful tool for the enhanced early detection, patient treatment and monitoring in the future.

In conclusion, our data support the notion that the 2013 ACR/EULAR criteria are a major step forward and that their application should improve the quality of clinical and epidemiological SSc research in the years to come. We have still to be aware of scleroderma like disorders that can be misclassified as SSc.

**5.5 How do we follow our SSc patients with and without lung fibrosis?**
Interstitial lung disease is common in SSc but the clinical course is heterogeneous and severity varies widely; from limited non-progressive lung involvement to major pulmonary

inflammation and fibrosis progressing to respiratory failure and death. It is important to identify SSc patients with poor lung outcome early and to identify predictors for future fibrosis progression. HRCT and PFTs are the hallmarks in the detection of ILD in SSc and in the prediction of outcomes. Intuitively, it appears that lung HRCT has huge potential in SSc. Screening by HRCT early in the disease course would not only allow for early detection of ILD, but also exclude the presence of SSc-ILD at that stage. However, the value of (early) lung HRCT screening in SSc is not known. Notwithstanding, high awareness and routine monitoring are essential for early detection, but we are still lacking guidelines for monitoring SSc patients with and without lung fibrosis. How do we follow SSc patients without ILD? Do we need follow up HRCTs and/or PFTs on these? How do we monitor patients with diagnosed ILD? Do we need follow up HRCTs and PFTs on those?

To answer these questions, we performed detailed, serial HRCT analyses of fibrosis progression in a prospective SSc cohort with comprehensive follow-up data on HRCTs, PFTs and clinical data. Our major findings were that 1. A baseline HRCT without fibrosis is highly predictive of a fibrosis free disease course. However, FVC declines mildly and DLCO is declining significantly in those patients. 2. Extensive lung fibrosis occurs very early in the course of SSc, progresses more rapidly than limited fibrosis and is associated with declining PFT values and DLCO and the development of PH. We also found that high proportion of lung fibrosis and deterioration of lung function during the disease course were predicted by male gender, dcSSc subtype, and presence of ATA, high extent of baseline fibrosis, low baseline FVC % and low DLCO% predicted.

How do these results answer our initial questions? Firstly, our data suggest that patients with no fibrosis at baseline might not need any further HRCT scan but do benefit from lung function follow up and need further DLCO measurements based on mildly declining FVC and significant declining DLCO during the disease course. Secondly, patients with fibrosis at baseline need follow up investigations including HRCT and PFTs. It is very important to diagnose SSc patients early since lung fibrosis develops very early in the disease course. We are unfortunately not able to answer the question how often and how long patients need follow up investigations. Nonetheless, these are the first results combining serial lung imaging and lung function on SSc patients from a large and prospective and nearly unselected follow up cohort. We need clearly follow up studies to confirm those findings and to create guidelines for monitoring of SSc patients with and without fibrosis.

In conclusion, we report the high predictive value of HRCT imaging and good long term outcome for patients with no fibrosis at baseline and that fibrosis occurs early, while progression of lung fibrosis can occur during the disease course. DLCO declined regardless of lung fibrosis. Male gender, dcSSc subtype, ATA, FVC % predicted <70 % and increased fibrosis at baseline are predictors for poor lung outcome and reduced survival.

## 6. Main Conclusions

1. The observed SSc point prevalence in southeast Norway of 9.9/100.000 is comparable to most previous data from other northern European countries.

2. The low prevalence observed support the possibility of a north-south gradient of SSc in Europe.

3. Mortality in SSc is high, particularly in the subset of patients with dcSSc and male gender.

4. The major causes of death were PH and lung fibrosis.

5. Our data support the notion that the 2013 ACR/EULAR criteria are a major step forward and that their application should improve the quality of clinical and epidemiological SSc research in the years to come

6. A normal baseline HRCT was highly predictive against future lung fibrosis

7. Extensive fibrosis occurred early in the disease course and was associated with high fibrosis progression rate and declining PFTs throughout the disease course.

8. Male gender, dcSSc subtype, ATA, FVC % predicted <70 % and increased fibrosis at baseline were predictors for poor lung outcome and reduced survival.

# 7. Clinical implications and future perspectives

## 7.1 Clinical implication

The main clinical implication of this study is that we need to diagnose SSc patients early and follow these with tight and planned controls. SSc is a rare but serious disease, development of ILD and PH is frequent and mortality due to these complications is high. Lung fibrosis develops early in the disease course and therefore diagnosis and tight controls are important, especially early in the disease course. Patients with no fibrosis at baseline might not need any follow up HRCT but will benefit from PFT controls since in the present study all SSc patients declined in DLCO even patients with no fibrosis. Declining DLCO can be associated with the development of PH and therefore all SSc patients need control of lung and cardiac function also later in the disease course.

Our data support the notion that male SSc patients and dcSSc patients need particularly follow up due to higher likelihood of developing lung fibrosis and due to higher mortality. The 2013 classification criteria might help to classify all SSc patients leading to possible earlier diagnosis, targeted treatment and facilitated monitoring. Still, we have to increase the awareness of SSc in the primary health care system even more in order to make early diagnosis possible.

## 7.2 Future perspectives

We have come further in SSc research but not far enough. We have neither found the cause of SSc nor very important genetic and/or environmental factors associated with SSc. However, it is rather unlikely that we will find only one, single cause or triggering factor in the future. Nonetheless, our goal has to be to increase the awareness of SSc and make early diagnosis of all eligible patients possible, treat as good as we can and increase patients quality of life and survival. Therefore, further broad research is required, from unselected and complete cohorts, from large international collaborations and on molecular levels.

Our research group wants to contribute with further research on our unique and unselected cohorts. The basic approach of our next project is to go from bedside to bench; meaning that our research will focus on the major clinical challenges in SSc and primarily aim for data that are of immediate benefit and relevance to the SSc society.

In the first part, we assemble a unique, nationwide SSc cohort; the NORSE Cohort and describe how we will use this large, complete and unselected cohort for high-quality studies on the frequencies and impact of ILD, PAH, GI involvement and cancer. In addition, we will use our established prospective OUS SSc cohort, which is one of the largest worldwide, for inter-disciplinary studies on immunological and imaging biomarkers on PAH, ILD and GI involvement. Data from these "proof-of concept" studies will then be sought validated in the NORSE cohort.
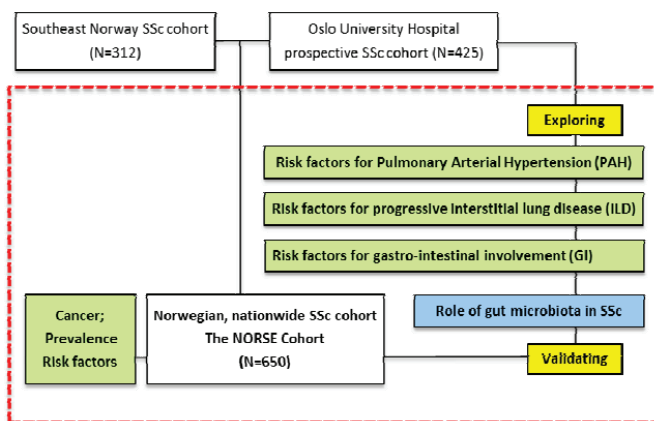


In collaboration with the University of California (UCLA), USA and the Jebsen Centre for Inflammation Research OUH, we will approach the hypothesis that gut microbiota play a role in SSc. If the preliminary analyses indicate associations between microbiota, GI involvement and other clinical parameters, these will be sought validated in the NORSE cohort. The project plan includes a one-year stay at UCLA to work on microbiota.

We believe that the results of this future project should contribute important clinical data of immediate relevance for the patients and the physicians treating them. The more explorative part of the work will hopefully contribute to better understanding of the mechanisms behind PAH development and the influence of microbiota in SSc.

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