

# Presentation of juvenile systemic sclerosis and difference to adult patients

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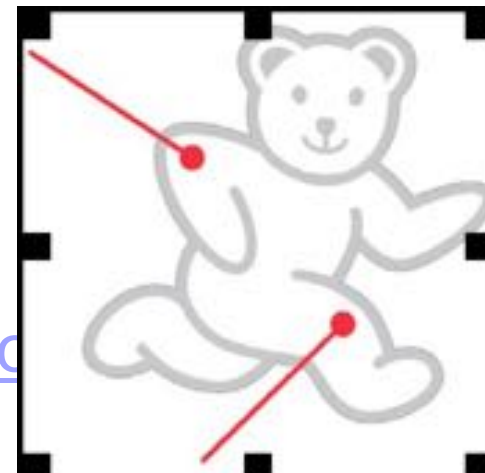
Teaching Unit of the Asklepios Campus of the  
Simmelweis Medical School, Budapest, Hungary

[www.kinderrheumatologie.de](http://www.kinderrheumatologie.de)

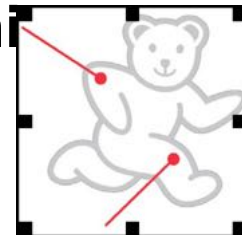
[www.sklerodermie.org](http://www.sklerodermie.org)

[www.uveitis-kindesalter.de](http://www.uveitis-kindesalter.de)

[www.orphan-diseases-in-pediatric-rheumatology.de](http://www.orphan-diseases-in-pediatric-rheumatology.de)



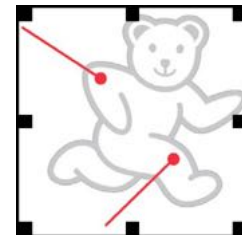
- Pediatric and Adolescent Rheumatologist
- Transition program with an associated adult rheumatologist
- Associated Occupationaltherapiest
- Associated Physiotherapiest
- Social worker
- Study nurses
- Assoziiertes Team
  - Uveitis (Uveitis specialised ophthalmologist)
  - Temporomandibular joint involvement (Orthodontist)
  - Pediatric orthopedic specialist
  - Pediatric dermatologist,.....
  - **Outpatient „Painteam“**
    - **Paediatrician specialised on chronic pain and hi**
    - **Paediatric Psychiatrist**
    - **Occupational therapy team**



# Cooperations/ Participation

- **Hamburger Elterninitiative Rheumakranker Kinder e.V.**  
[www.kinderrheuma.de](http://www.kinderrheuma.de)
- Deutsche Rheumaliga
- Lupus Erythematodes Selbsthilfegemeinschaft
- Scleroderma Foundation UK
- **FEDERATION OF EUROPEAN SCLERODERMA ASSOCIATIONS (FESCA)**
  - Advisor for pediatric issues
- Scleroderma Foundation – USA
- EMA /Enpra working group
- PRES Scleroderma working
- SCTC juvenile scleroderma working group

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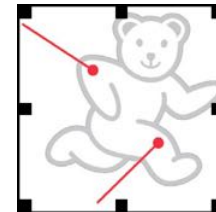


# Topics of the talk

- **Epidemiology of jSSc**
- Classification issues
- Specific pediatric issues
- Comparison of the pediatric data to adult population with diffuse subtype



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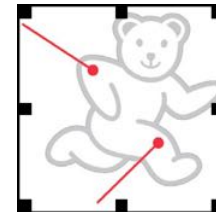


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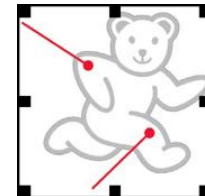
# Epidemiology and demographic of jSSc



- ◆ **Data regarding incidence and prevalence is rare**
- ◆ **According a cross-sectional study by Herrick et al.**

**( Arthritis Care 2010;62:213)**

- ◆ **Incidence rate 0.27 (95% CI 0.1-0.5) per million children**



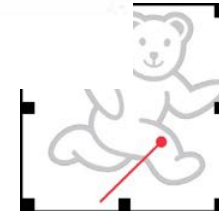
# Estimated Prevalence of jSSc using the USA claims data

T. Beukelman, F. Xie, I. Foeldvari-

JSRD 2018, 3: 189-190

Year	N of Total Children	Diagnosis Code for Systemic Sclerosis	No Diagnosis Code for Localized Scleroderma	Use of Methotrexate, Mycophenolate Mofetil, or Cyclophosphamide	Estimated Prevalence per 1,000,000 Children [95% CI]
2010	5,888,868	254	186	23	3.9 [2.5-5.9]
2011	6,231,475	249	185	22	3.5 [2.2-5.3]
2012	6,278,116	217	170	26	4.1 [2.7-6.1]
2013	4,950,018	175	120	17	3.4 [2.0-5.5]
2014	4,933,522	138	91	14	2.8 [1.6-4.8]

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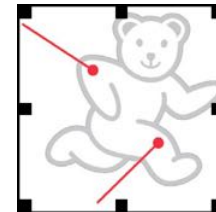


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# Proposed classification criteria for juvenile systemic scleroderma

Zulian et al. Arthritis Rheum 2007;57:203-12

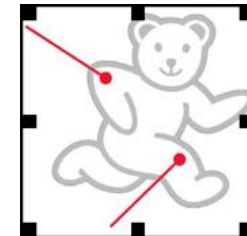
**First and Second International Workshop on Juvenile Scleroderma  
June 2001 and 2004 Padua, Italy**

**Steering Committee: F. Zulian (Padua), I. Foeldvari (Hamburg), J. Harper (London),  
A. Peserico (Padua), N. Ruperto (Pavia)**

- Major criteria
    - ♦ Sclerosis\* / induration\*
  
  - Definite disease
    - 1 major and 2 minor criteria
- ♦ Minor criteria
    - ♦ Vascular changes\*
    - ♦ Pulmonary involvement\*
    - ♦ Gastrointestinal involvement\*
    - ♦ Renal involvement\*
    - ♦ Cardiovascular involvement\*
    - ♦ Musculoskeletal involvement\*
    - ♦ Neurologic involvement\*
    - ♦ Serology\*

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\* Per definition typical for SSc

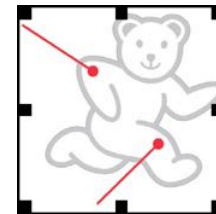


# New Classification of Systemic Sclerosis

Arth Rheum 2013,65: 2737-47

- The maximum possible score is 19
- Patients with a score of  $\geq 9$  are classified as having SSc.
- The definitions of the items used in the criteria are defined in the publication.

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# New Classification of Systemic Sclerosis

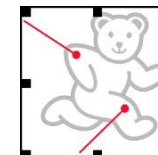
Arth Rheum 2013,65: 2737-47

Item	Sub-item(s)	Weight/score†
thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints ( <i>sufficient criterion</i> )	–	9
thickening of the fingers ( <i>only count the higher score</i> )	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
nailtip lesions ( <i>only count the higher score</i> )	Digital tip ulcers	2
	Fingertip pitting scars	3
angiectasia	–	2
abnormal nailfold capillaries	–	2
pulmonary arterial hypertension and/or interstitial lung disease ( <i>maximum score is 2</i> )	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
cytotoxic related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti-RNA polymerase III) ( <i>maximum score is 3</i> )	Anticentromere	3
	Anti-topoisomerase I	
	Anti-RNA polymerase III	

These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening of the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, localized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of  $\geq 9$  are classified as having definite SSc.

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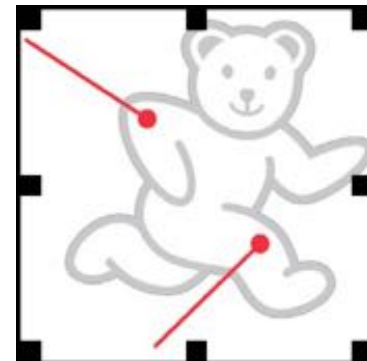


Performance of the adult Systemic Sclerosis classification in juvenile systemic sclerosis patients. Results from the juvenile systemic sclerosis inception cohorte –

[www.juvenile-scleroderma.com](http://www.juvenile-scleroderma.com)

I. Foeldvari<sup>1</sup>, J. Klotsche<sup>13</sup>, M. Katsicas<sup>2</sup>, M. Teresa Terreri<sup>3</sup>, R. Cimaz<sup>4</sup>, M. Kostic<sup>5</sup>, F. Sztajnbok<sup>6</sup>, D. Nemcova<sup>7</sup>, M. Moll<sup>8</sup>, M. Jose Santos<sup>9</sup>, T. Avcin<sup>10</sup>, J. Brunner<sup>11</sup>, S. Nielsen<sup>12</sup>, T. Kallinich<sup>13</sup>, K. Minden<sup>13</sup>, J. Müller<sup>14</sup>, M. Janarthanan<sup>15</sup>, Y. Uziel<sup>16</sup>, A. Giraldo<sup>17</sup>, D. Eleftheriou<sup>18</sup>, K. Torok<sup>19</sup>, N.Helmus<sup>1</sup>

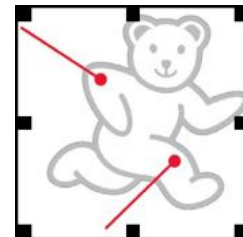
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# Inception Cohort for juvenile systemic Sclerosis (jsSc)

- **Data of juvenile systemic sclerosis patients are prospectively collected with a standardized assessment including quality of life**
- **The aim of collecting data in patients with recent onset jSSc is to learn more about the evolvement of organ involvement and the quality of life in these patients**
- **The project should help to improve the care of these patients throughout the world**

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# Inception Cohort for juvenile systemic Sclerosis (jsSc)

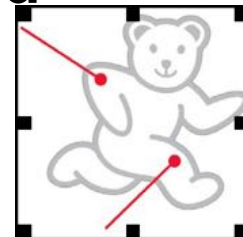
- **Inclusion criteria**

- ⇒ **Patients diagnosed with juvenile systemic sclerosis ( fulfilling the adult classification criteria)**
- ⇒ **Developed the first non-Raynaud symptom before the age of 16 years**
- ⇒ **Age at inclusion younger than 18 years of age**

- **Method**

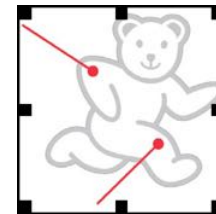
- ⇒ **Assessment every 6 months according to a standardized protocol**
- ⇒ **Assessment of organ involvement and patient related outcomes**

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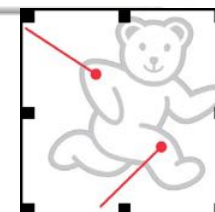


# Results

- All paediatric patients in the cohort fulfil the adult classification, as the main criteria of the paediatric classification, proximal skin sclerosis from MCP joint, already gives sufficient points to be classified as SSc.
- The pediatric patients had a mean score of:
  - 15.3 at  $\leq 6$  months (n=13)
  - 15.5 at  $\leq 12$  months (n=19)
  - 17.2 at  $\leq 24$  months (n=25)
  - 17.4 at  $\leq 48$  months (n=35).
- The cluster analysis showed 3 clusters of patients



Padua Criteria		Class I n=17 %	Class II n=21 %	Class III n=48 %
Major	Proximal skin sclerosis	100,0	100,0	100,0
Minor	Sclerodactyly	100,0	100,0	100,0
Peripheral vascular	Raynauds	100,0	0,0	95,8
	Nailfold changes	100,0	23,8	56,3
	Digital tip ulcers	87,5	0,0	2,1
Gastrointestinal	Dysphagia	0,0	0,0	0,0
	Reflux	58,8	33,3	22,9
Cardiac	Arrythmias	29,4	14,3	8,3
	Heart failure	5,9	0,0	0,0
Renal	Renal crisis	0,0	0,0	0,0
	New arterial hypertension	0,0	0,0	0,0
Respiratory	Fibrosis	23,5	28,6	6,3
	Decreased DLCO	70,6	9,5	0,0
	PH	0,0	4,8	12,5
Neurologic	Neuropathy	0,0	0,0	0,0
	Carpal tunnel	0,0	0,0	0,0
Musculoskeletal	Tendon friction	0,0	9,5	4,3
	Arthritis	17,7	47,6	2,1
	Myositis	0,0	0,0	0,0
Immunologic	ANA	100,0	57,9	85,4
	SSc AB	35,3	0,0	52,2



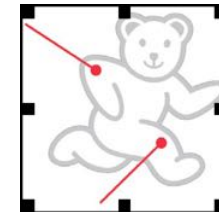


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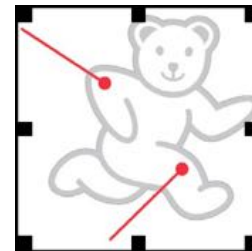


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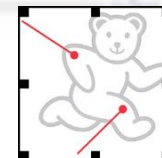


Are there clinical differences  
between male and female patients?

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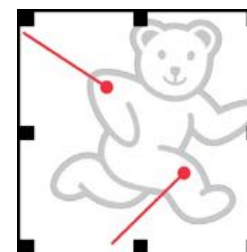


	Female	Male	P-Werte
	N=66	N=14	
Female to Male Ratio	[66/0]	[0/14]	
Diffuse subtype	48 (72.7%)	10 (71.4%)	0.982
Diffuse overlap	6	0	
Limited subtype	18 (27.3%)	4 (28.6%)	
Limited overlap	5	0	
Caucasian	59 (89.4%)	12 (85.7%)	0.834
African	4 (6.1%)	2 (14.3%)	
Asian	2 (3%)	0 (0%)	
Indigenous	1 (1.5%)	0 (0%)	
Mean Disease duration (years)	3.6 (± 3.1)	3.3 (± 2.9)	0.671
Mean age of onset of Raynaud's (years)	9.4 (± 4.1)	9.3 (± 3.9)	0.913
	8 non-Raynaud	0 non-Raynaud	
Mean age of onset of non-Raynaud's (years)	10.0 (± 4.1)	9.1 (± 3.9)	0.834
Disease modifying drugs	75.8% (50/66)	85.7% (12/14)	0.418



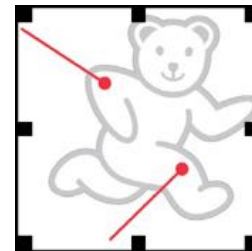
	Female	Male	P-Werte
	<b>N=66</b>	<b>N=14</b>	
6 Minute Walk Test (Mean, SD)	441.4m (±116.1) n=18	286.7m (±179.8) n=3	<b>0.035</b>
Muskuloskeletal	55.4% (36/65)	92.9% (13/14)	<b>0.009</b>
Total contractures	38.1% (24/63)	78.6% (11/14)	<b>0.006</b>
Tendon Friction Rub	6.7% (4/60)	33.3% (3/9)	<b>0.013</b>
Patient global disease activity	41.9 (0-100) n=34	58.3 (30-80) n=6	<b>0.041</b>
Physician global disease activity	34.3 (0-90) n=38	58.3 (30-80) n=6	<b>0.037</b>
Physician global disease damage	26.2 (0-70) n=37	68.3 (40-80) n=6	<b>0.001</b>

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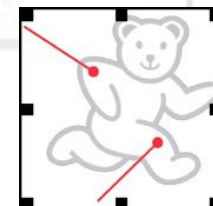


**ARE THERE DIFFERENCES IN THE CLINICAL  
PRESENTATION ACCORDING ANTI-SCL70 POSITIVITY  
AND ANTI-SCL70 NEGATIVITY?**

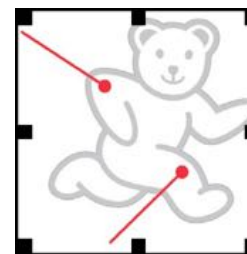
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	Anti-Scl 70 negative	Anti-Scl 70 positive	P-value
	N=53	N=24	
female to Male Ratio	5.6:1 (45/8)	3:1 (18/6)	0.628
diffuse subtype	39 (73.6%)	17 (70.8%)	0.867
diffuse overlap	5	0	
limited subtype	14 (26.4%)	7 (29.2%)	
limited overlap	4	0	
Caucasian	49 (92.4%)	20 (83.3%)	0.834
African	4 (7.5%)	2 (8.3%)	
Asian	0 (0%)	1 (4.2%)	
Hispanite	0 (0%)	1 (4.2%)	
mean Disease duration (years)	3.7 (± 3.1)	3.4 (± 3.0)	0.671
mean age of onset of Raynaud's (years)	9.5 (± 3.8) 6 non-Raynaud	9.7 (± 4.1) 1 non-Raynaud	
mean age of onset of non-Raynaud's (years)	9.8 (± 4.0)	10.3 (± 4.0)	0.846

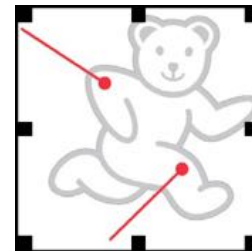


	Anti-Scl70 negative	Anti-Scl 70 positive	P-value
	<b>N=53</b>	<b>N=24</b>	
disease modifying drugs	71.7% (38/53)	87.5% (21/24)	0.129
ANA	75.5% (40/53)	86.4% (19/22)	0.294
Anti-scl 70	0% (0/53)	100% (24/24)	0.001
Anti-centromere	6.1% (2/33)	15.4% (2/13)	0.312
CRP elevated ( $\geq 10$ mg/l)	8.5% (4/47)	35% (7/20)	<b>0.007</b>
Normal findings in ultrasound	58.1% (18/31)	23.1% (3/13)	<b>0.034</b>
Number of joints with increased range	57.7% (30/52)	29.2% (7/24)	<b>0.021</b>



# ARE THERE DIFFERENCES IN THE CLINICAL PRESENTATION ACCORDING THE AGE AT INCLUSION IN THE COHORT?

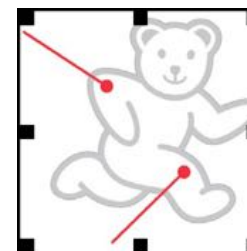
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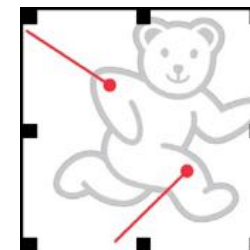
	< 10years at first visit	> 10years at first visit	P-value
	N=16	N=64	
female to Male Ratio	3:1 (12/4)	5.4:1 (54/10)	0.688
diffuse subtype	14 (87.5%)	44 (68.7%)	0.574
diffuse overlap	0	6	
limited subtype	2 (12.5%)	20 (31.2%)	
limited overlap	1	4	
caucasian	14 (87.5%)	57 (89.1%)	0.972
african	1 (6.25%)	5 (7.8%)	
indian	0 (0%)	2 (3.1%)	
arabite	1 (6.25%)	0 (0%)	

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	< 10years at first visit	> 10years at first visit	P-value
	N=16	N=64	
mean Disease duration (years)	2.3 (± 1.8)	3.9 (± 3.2)	0.539
mean age of onset of Raynaud's (years)	4.3 (± 2.3) 0 non-Raynaud	11.0 (± 3.0) 8 non-Raynaud	0.027
mean age of onset of non-Raynaud's (years)	4.8 (± 2.1)	11.2 (± 3.3)	0.074
disease modifying drugs	81.2% (13/16)	76.6% (49/64)	0.688
angiectasia	54.5% (6/11)	21% (8/38)	0.030
gastrointestinal beside esophageal	12.5% (2/16)	1.6% (1/64)	0.039
physician global disease activity	57.9 (10-90) n=7	33.7 (0-80) n=37	0.037

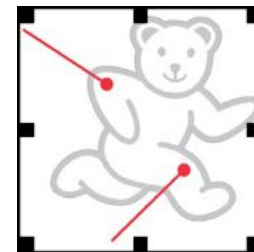
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# Is there a change in organ involvement pattern after 12 or 24 months ?

Results from the Juvenile Scleroderma  
Inception Cohort

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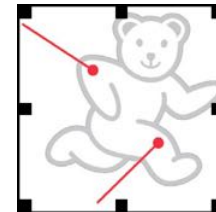


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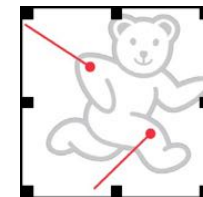


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# Publications selected for comparison

- 2. Scalapino K, Arkachaisri T, Lucas M, Fertig N, Helfrich DJ, Londino AV, Jr., et al. Childhood onset systemic sclerosis: classification, clinical and serologic features, and survival in comparison with adult onset disease. *J Rheumatol*. 2006;33(5):1004-13.
- 4. Martini G, Foeldvari I, Russo R, Cuttica R, Eberhard A, Ravelli A, et al. Systemic sclerosis in childhood: clinical and immunologic features of 153 patients in an international database. *Arthritis Rheum*. 2006;54(12):3971-8.
- 5. Foeldvari I, Zhavania M, Birdi N, Cuttica RJ, de Oliveira SH, Dent PB, et al. Favourable outcome in 135 children with juvenile systemic sclerosis: results of a multi-national survey. *Rheumatology (Oxford)*. 2000;39(5):556-9.
- 24. Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis*. 2007;66(6):754-63.

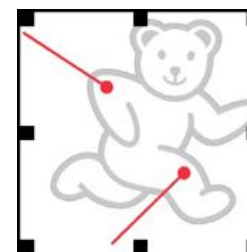


Organ involvement	Inception Cohort n=80	Foeldvari et.al (5) n=135	Martini et.al (4) n=153	Scalapino et al (2) n = 111	EUSTAR aSSc (24) n=1349*
Age at onset in years	9.0** 9.4***	8.8	8.1	11.1	42.9*
Disease duration at diagnosis in years	3.7	ND	1.9	2.8	7.4*
Follow up in years	3.7*	5.0	3.9	14.4	ND
Subtype diffuse	72.5%	ND	91%	35%	100%
Subtype limited	22.5%	ND	9%	36%	-
Overlap feature	14%	ND	ND	29%	5.6%
Sex female /male	4.7:1	2.8:1	3.6:1	4.1:1	6.7:1
Ethnical background (% Caucasian)	91.1%*	Mostly caucasian	ND	92%	

diffuse; \*\* onset of Raynauds; \*\*\* onset of non Raynauds

ND = not documented

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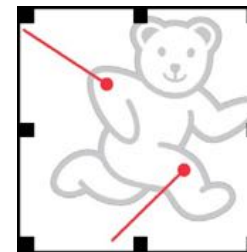


Organ involvement	Inception Cohort n=80	Foeldvari et.al. (5) n=135	Martini et.al (4) n=153	Scalapino et al (21) n = 111	EUSTAR aSSc (24) n=1349*
ANA positive	77%*	ND	80%	97%	92%*
Anticentromere positive – diffuse*/limited	6%*	ND	7.1%	8%	6%*
Anti-scl 70 positive- diffuse* /limited	30.4%*	ND	34%	20%	60.8%*
Raynauds	100%*	72%	84%	97%	96%*
Capillary changes	62%*	ND	39.9%	ND	62%*
Digital infarcts/ulceration	55%*	28.6%	29%	ND	42.7%*

\*diffuse; \*\* onset of Raynauds; \*\*\* onset of non Raynauds

ND = not documented

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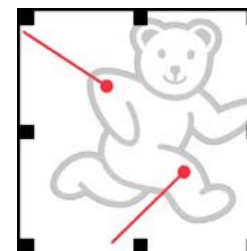


Organ Involvement	Inception Cohort n=80	Foeldvari et.al. (5) n=135	Martini et.al (4) n=153	Scalapino et al (2) n = 111	EUSTAR aSSc (24) n=1349*
Pulmonary	41.4%*	50%	42%	55%	67%*
Pulmonary hypertension	7%*	ND	7.2%	7%	22%*
Abnormal HRCT/fibrosis	31%*	ND	23.5%	ND	53.4%*
Reduced DLCO	17%*	ND	27.5%	ND	64%*
Reduced FVC	28%*	ND	41.8%	16% (severe FVC<50%)	ND
Cardiovascular	46.6%*	44%	29%	17%	27.3%*or more

diffuse; \*\* onset of Raynauds; \*\*\* onset of non Raynauds

ND = not documented

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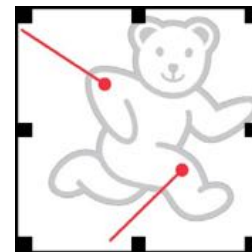


rgan involvement	Inception Cohort n=80	Foeldvari et.al. (5) n=135	Martini et.al (4) n=153	Scalapino et al (2) n = 111	EUSTAR aSSc (24) n=1349*
CNS	0%*	16%	4 %	ND	0%
Renal	7%*	13%	10%	4%	9% or more
Raised creatinine/proteinuria	5%*	ND	4.6%	4%	9%*
hypertension	0%*	ND	2.6%	4%	19.3%*
Renal crisis	0%*	0.7%	0.7%	4%	4.2 %*

diffuse; \*\* onset of Raynauds; \*\*\* onset of non Raynauds

D = not documented

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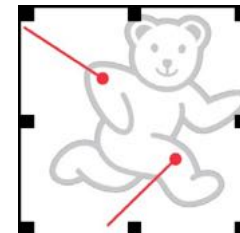
# „Promotion for our project“

- I would like to invite you to participate on the  
**Juvenile Inceptions Cohort Project**  
[www.juvenile-scleroderma.com](http://www.juvenile-scleroderma.com)

- If interested, please contact us:  
[foeldvari@t-online.de](mailto:foeldvari@t-online.de)  
or  
[inceptioncohort@kinderrheumatologie.de](mailto:inceptioncohort@kinderrheumatologie.de)



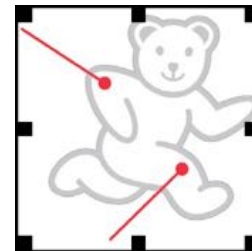
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# Conclusion

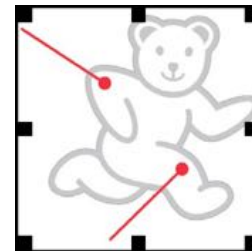
- Pediatric onset jSSc has a distinct feature with the around 75% diffuse subtype of patients
- 15 to 29% of patients with overlap features
- Rare occurrence of renal crisis, less pulmonary hypertension
- The follow up in the inception cohort shows a stabilisation of the organ involvement pattern, with a significant improvement in patient related outcomes
- We need more patients with longer follow up with standardized assessment to answer lot of open questions

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Thanks for Your interest  
Looking forward to your questions 😊

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# New Classification of Systemic Sclerosis

## Arth Rheum 2013,65: 2737-47

Table 2 Definitions of items/sub-items in the American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis

	Definition
skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
swollen fingers	Swollen digits—a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
digital ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischaemia, rather than trauma or exogenous causes.
telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
abnormal nailfold capillary pattern consistent with systemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary haemorrhages at the nailfold. May also be seen on the cuticle.
secondary pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterisation according to standard definitions.
interstitial lung disease	Pulmonary fibrosis seen on high-resolution CT or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of 'Velcro' crackles on auscultation, not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase colour change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
Anti-centromere related auto antibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti-topoisomerase I antibody (also known as anti-Scl-70 antibody), or anti-RNA polymerase III antibody. Positive according to local laboratory standards.

systemic sclerosis.