

Storfiber, småfiber og autonom neuropati hos unge med type 1 diabetes



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Samarbejdsafdelinger
Børn og Unge afdelingerne i Aalborg, Randers og Aarhus
Steno Diabetes Center Nordjylland



Opsummering

 Diabetisk neuropati

 Metoder og resultater

 Perspektivering



Studie I

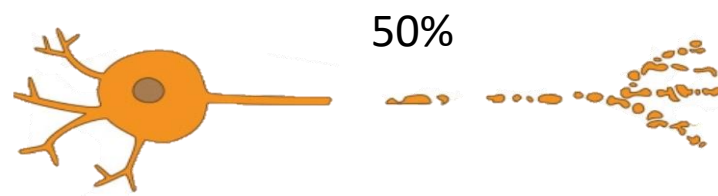


Studie II, III og IV

+ lidt ekstra



Studie I

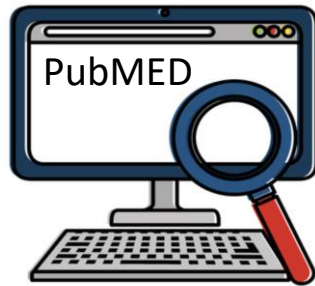




Systematisk review

Studie I

SEARCH Adolescents AND Type 1 diabetes AND Neuropathy or diagnostic methods



P

Population



Adolescents (10-19 years) with type 1 diabetes

I

Intervention



Diagnostic techniques assessing large fiber, small fiber, and autonomic neuropathy

C

Comparison



Normative reference data or an included control group

O

Outcome



Primary: prevalence of neuropathy
Secondary: results of comparison

n = 7589 participants

Pre-registered in PROSPERO
PRISMA guidelines

2448 studies imported for screening

Embase 1154

PubMed 609

Cochrane Library 685

431 duplicates removed

2017 studies screened

Title and abstract screening

1765 studies irrelevant

252 studies assessed for eligibility

Full text screening

210 studies excluded

- 133 Wrong population
- 52 Wrong intervention
- 8 Wrong comparators
- 7 Missing data
- 4 Duplicates
- 4 Wrong languages
- 2 Not available in full text

42 studies included

Quality synthesis

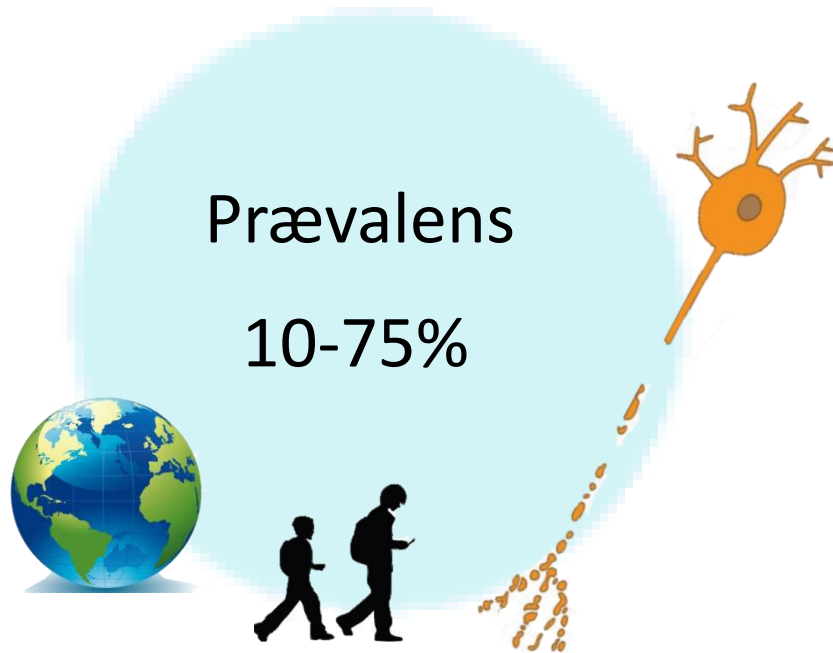
27 studies included

Quantitative synthesis

Fig. 1. Flow diagram of the selected studies.



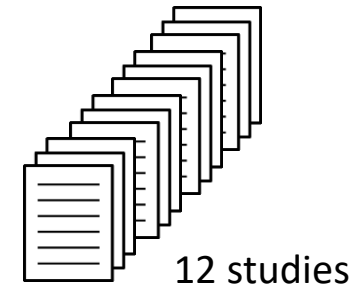
Studie I



Review > [J Diabetes Complications](#). 2021 Nov;35(11):108027.

doi: 10.1016/j.jdiacomp.2021.108027. Epub 2021 Aug 18.

Large fibre, small fibre and autonomic neuropathy in adolescents with type 1 diabetes: A systematic review

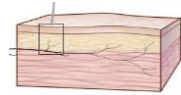
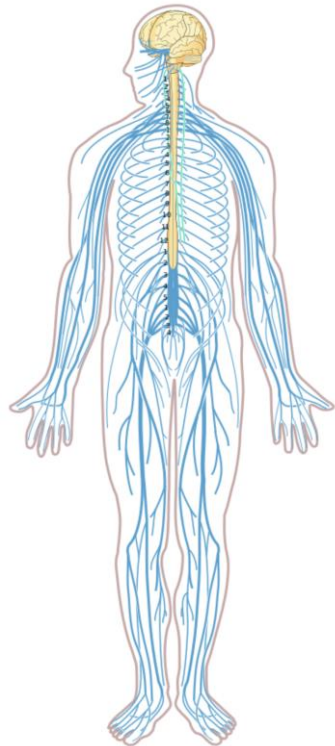


	Large fiber neuropathy and/or small fiber neuropathy	Cardiovascular neuropathy
Simple test	12-51%	12-75%
Confirmatory test "gold standard"	LFN: 10-57% SFN: 62%	41%

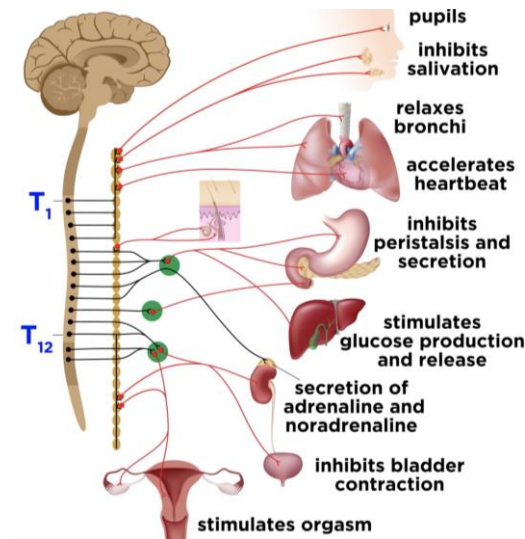




Diabetisk neuropati – påvirkning af nerverne



Motor	Sensory	Sensory	Autonomic		
Myelinated	Myelinated	Thinly myelinated	Unmyelinated	Thinly myelinated	Unmyelinated
$A\alpha$	$A\alpha/\beta$	$A\delta$	C	C	
Storfiber		Småfiber		Autonom	
Muscle control	Position perception Vibration, Touch	Cold perception Pain	Warmth perception Pain	Heart rate, blood pressure, sweating, gastrointestinal peristalsis, bladder	



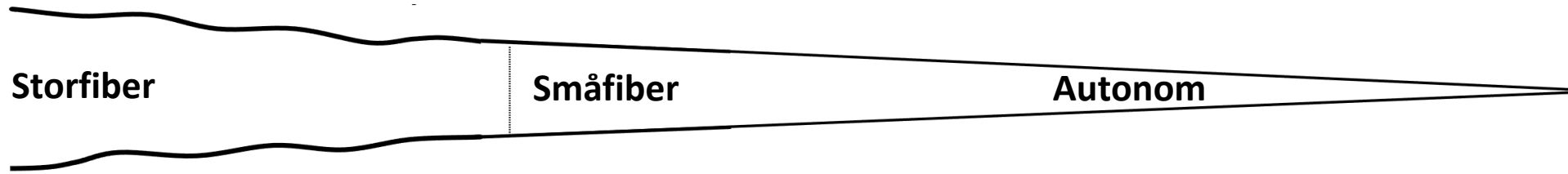
Funktionel



Strukturel

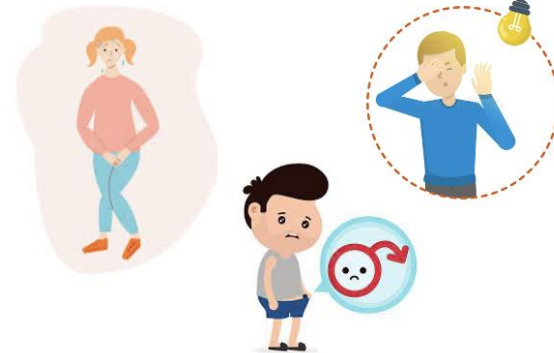
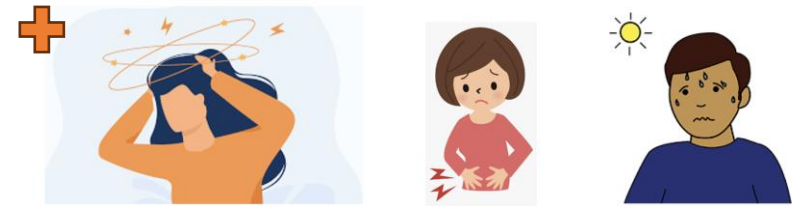
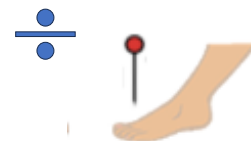
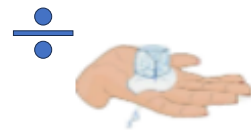
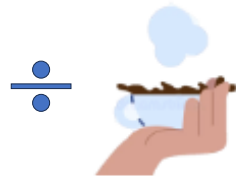


Symptomer på neuropati



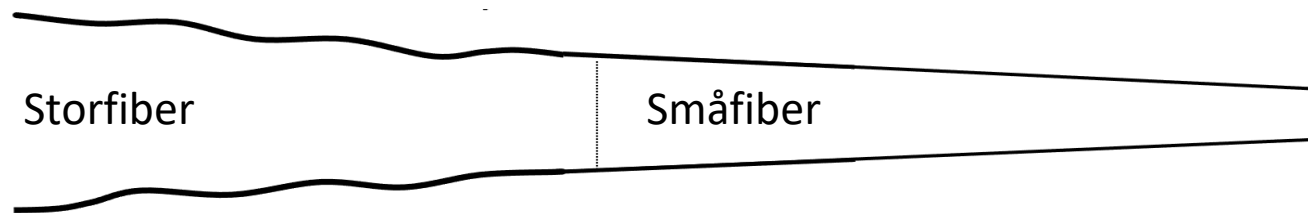
÷ Mistet følesans 

+ *Neuropatisk smerte*





Neurologisk undersøgelse



↓ Touch sensation



↓ Proprioception



↓ Vibration sense



Hyporeflexia



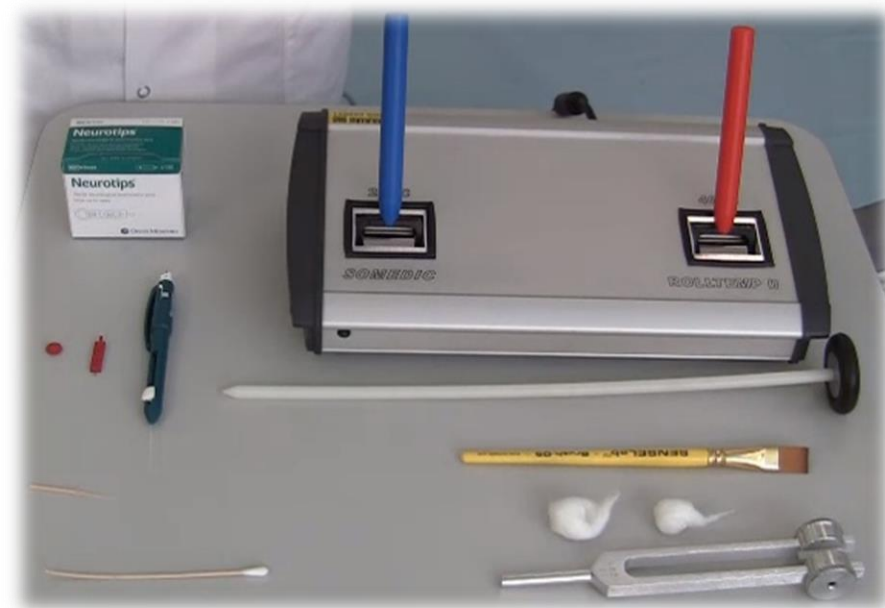
Muscle atrophy



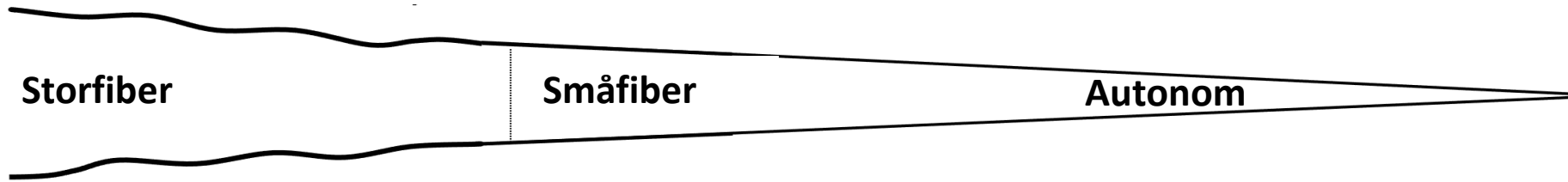
↓ Muscle strength

↓ Pain sensation (NeuroTip)

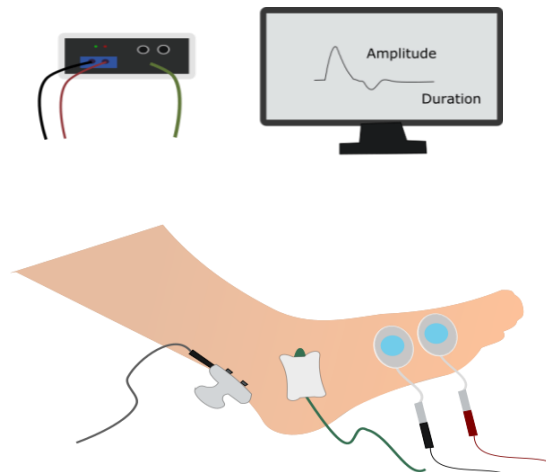
↓ Cold / warm sensation



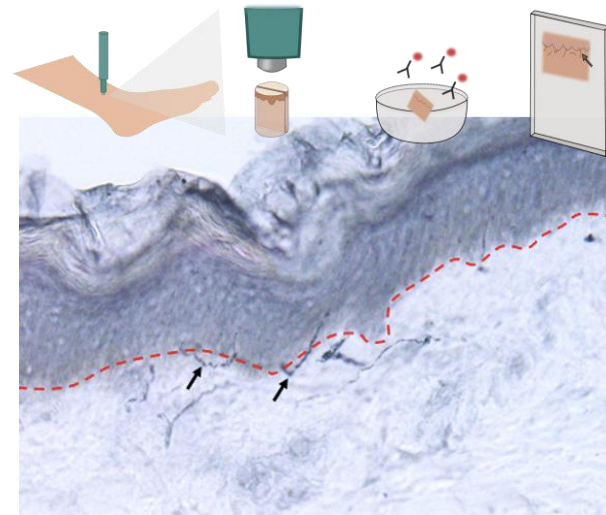
Diagnostiske tests



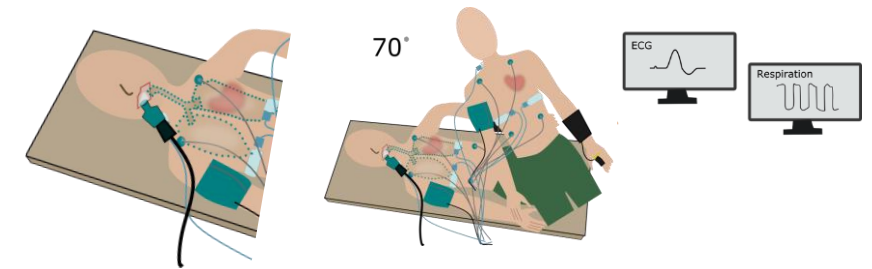
Nerveledningsundersøgelse
Nerve conduction studies



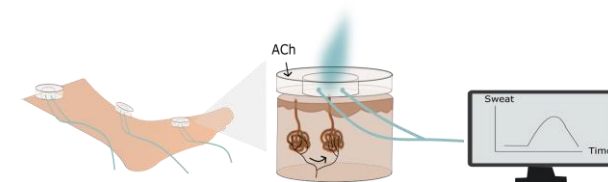
Hudbiopsi
Intraepidermal nerve fiber density



Autonome tests
Cardiovascular reflex tests (CARTs)
Tilt table test



Quantitative sudomotor axon reflex test



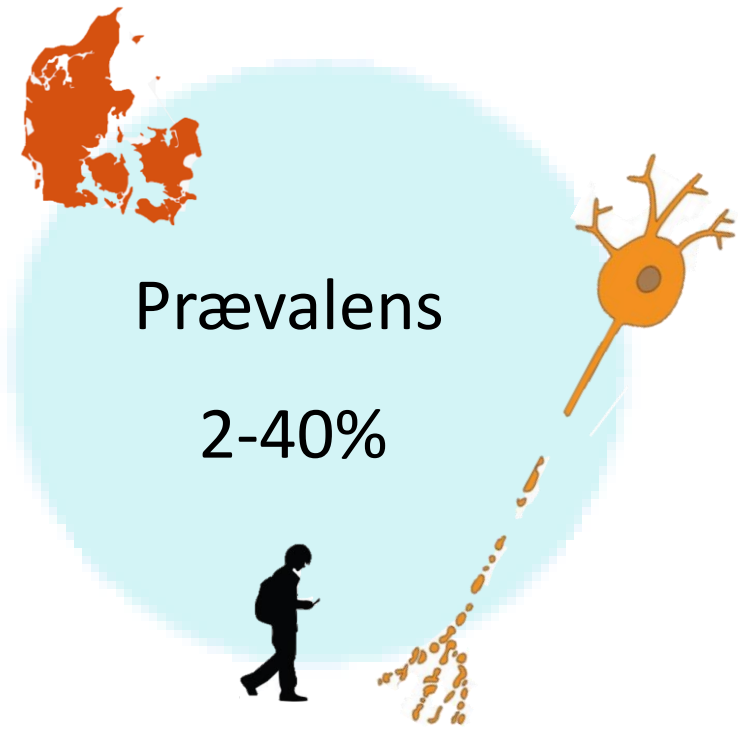


Unge med type 1 diabetes, n = 60

15-18 årige med diabetes varighed > 5 år



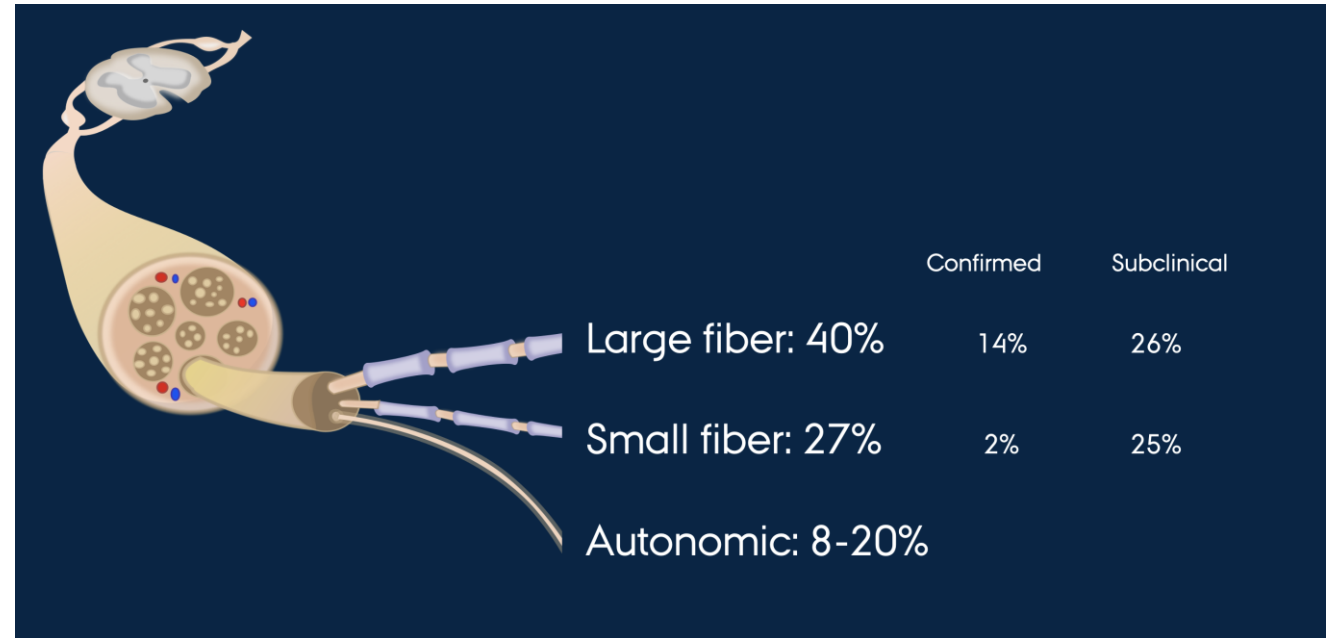
Studie II



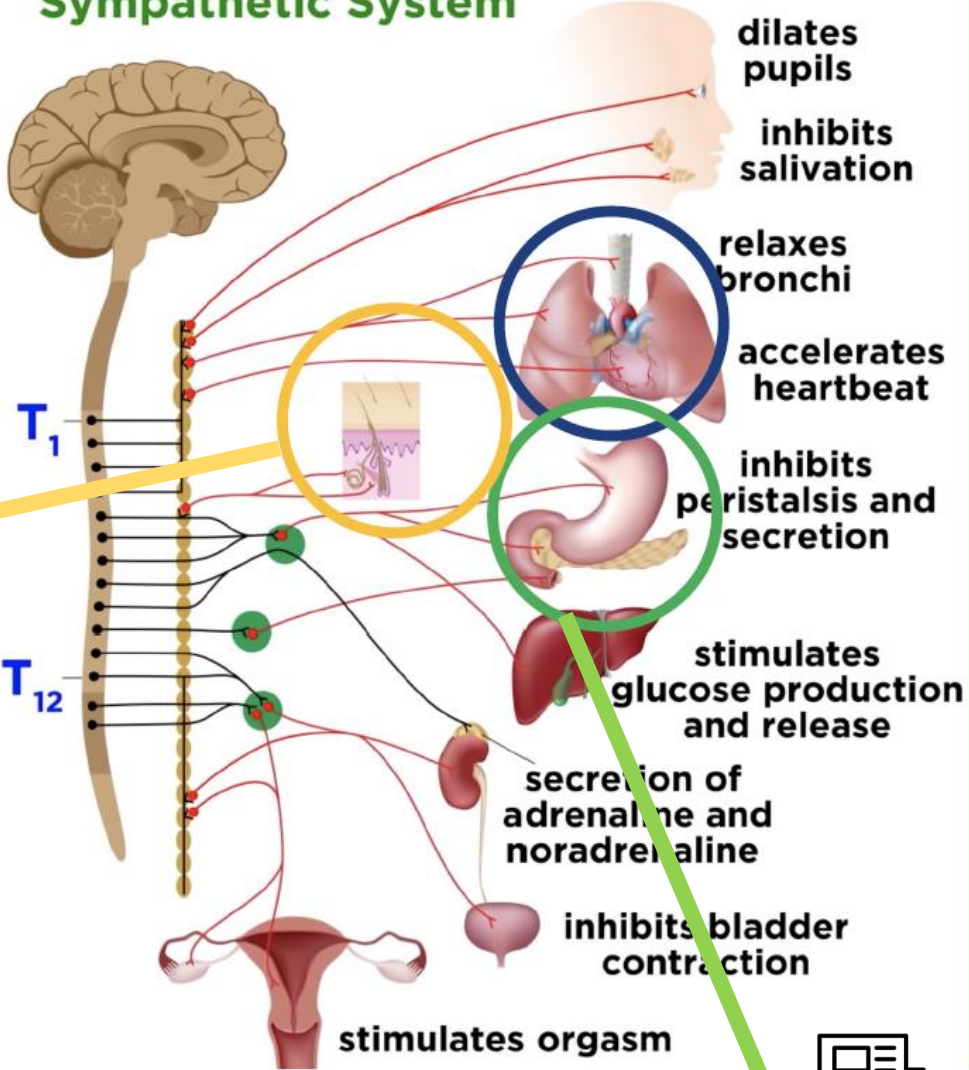
> *Diabetes Res Clin Pract.* 2023 Jul;201:110736. doi: 10.1016/j.diabres.2023.110736. Epub 2023 Jun 3.

Neuropathy in adolescents with type 1 diabetes: Confirmatory diagnostic tests, bedside tests, and risk factors

Vinni Faber Rasmussen¹, Mathilde Thrysoe², Jens Randel Nyengaard³, Hatice Tankisi⁴, Páll Karlsson⁵, John Hansen⁶, Klaus Krogh⁷, Christina Brock⁸, Konstantinos Kamperis⁹, Mette Madsen¹⁰, Wolfgang Singer¹¹, Esben Thyssen Vestergaard¹², Kurt Kristensen¹³, Astrid Juhl Terkelsen¹⁴

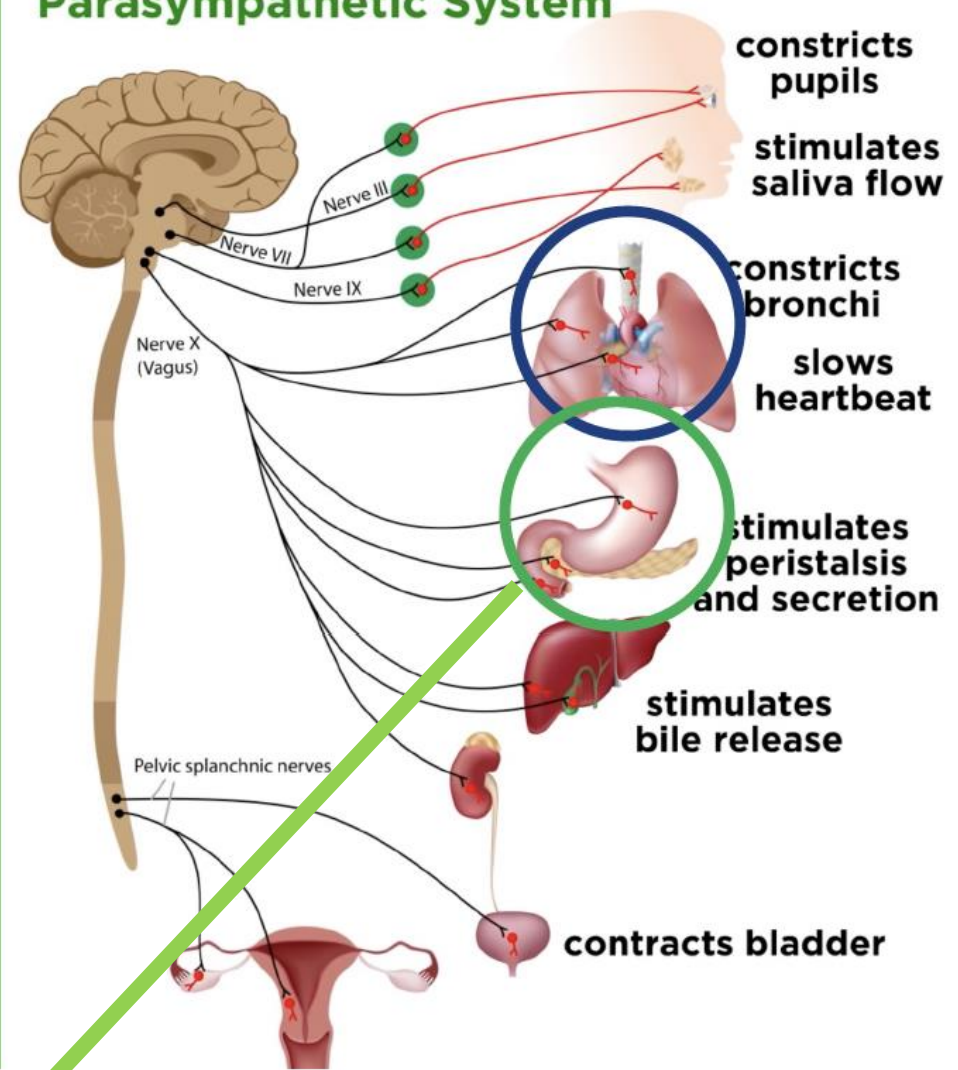


Sympathetic System



Studie IV

Parasympathetic System

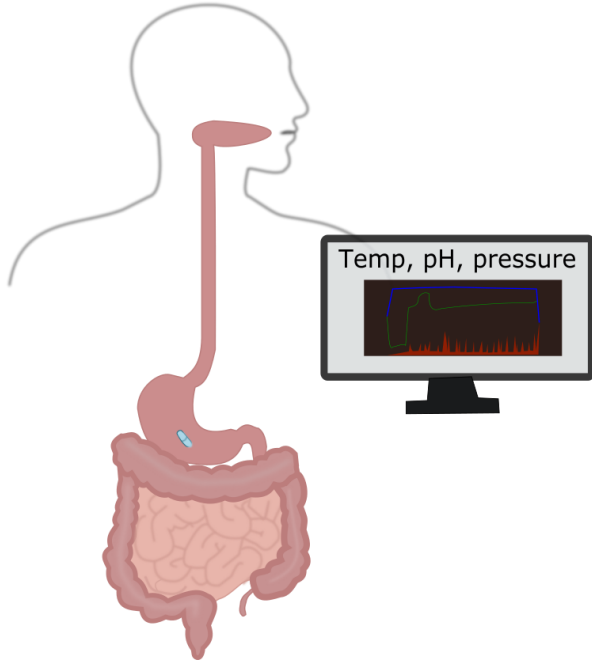


Studie III

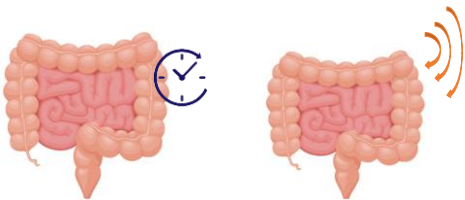


Gastrointestinal neuropati

Studie III



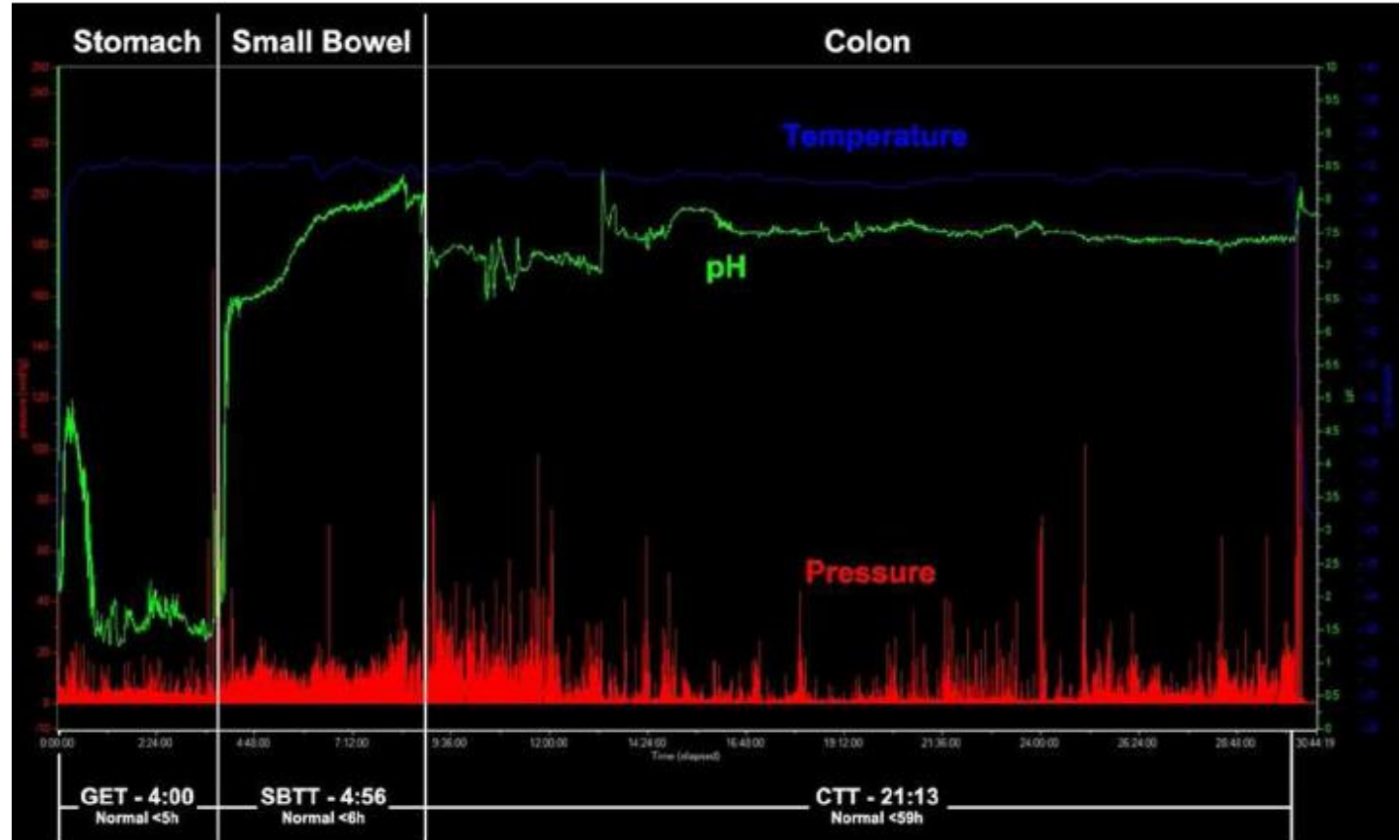
28% af de unge med T1D havde forlænget transittid og/eller en lavere motilitets index



Article

Early Gastrointestinal Neuropathy Assessed by Wireless Motility Capsules in Adolescents with Type 1 Diabetes

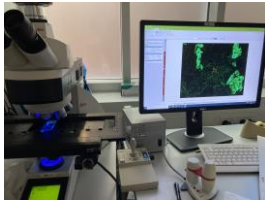
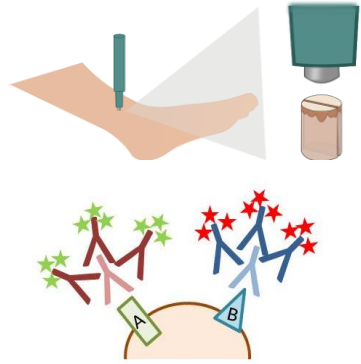
Vinni Faber Rasmussen ^{1,2,3,*}, Mathilde Thrysoe ¹, Páll Karlsson ^{1,4}, Esben Thyssen Vestergaard ^{3,5}, Kurt Kristensen ³, Ann-Margrethe Ronholt Christensen ^{6,7}, Jens Randel Nyengaard ^{4,8}, Astrid Juhl Terkelsen ^{1,9}, Christina Brock ¹⁰ and Klaus Krogh ¹¹





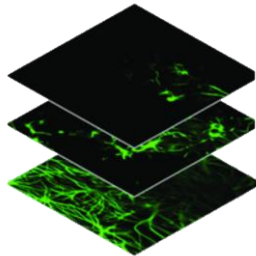
3D-kvantificering af nerverne i svedkirtler

Studie IV

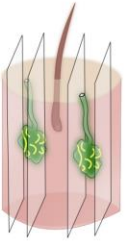


1 μm intervals

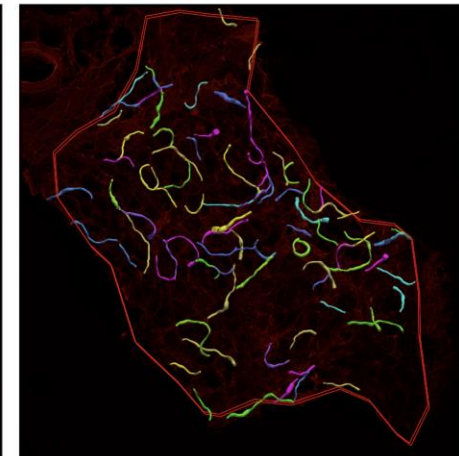
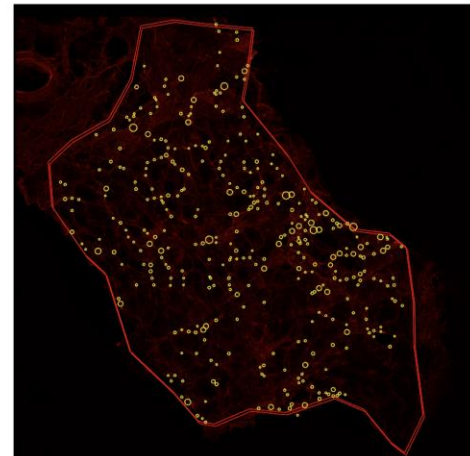
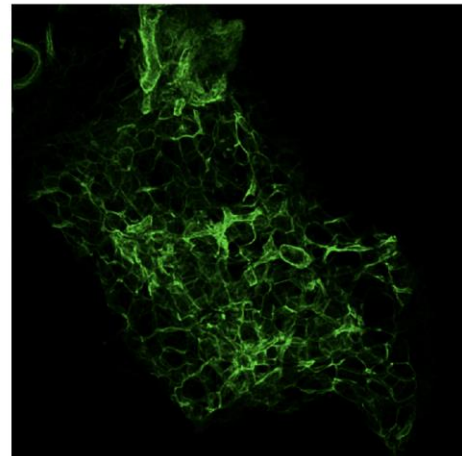
Volume



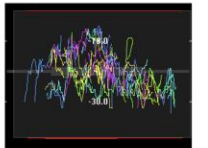
Total nerve fiber length



34% af de unge med T1D havde reduceret nerve fiber densitet i svedkirtlerne



Orthogonal view



> Clin Auton Res. 2023 Dec;33(6):691-703. doi: 10.1007/s10286-023-00973-7. Epub 2023 Sep 8.

Sweat gland nerve fiber density and association with sudomotor function, symptoms, and risk factors in adolescents with type 1 diabetes

Vinni Faber Rasmussen^{1 2 3}, Ann Schmeichel⁴, Mathilde Thrysoe⁵, Jens Randel Nyengaard^{6 7}, Ann-Margrethe Rønholt Christensen^{8 9}, Esben Thyssen Vestergaard^{10 11}, Kurt Kristensen^{10 11}, Astrid Juhl Terkelsen^{5 12}, Páll Karlsson^{5 10 6}, Wolfaana Sinaer⁴

$$\text{Sweat gland nerve fiber density} = \frac{\text{Total nerve fiber length in sweat gland}}{\text{Sweat gland volume}}$$



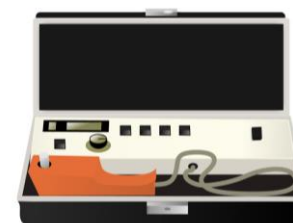


Screening



ISPAD

International Society for Pediatric and Adolescent Diabetes



1.2.5 | Neuropathy

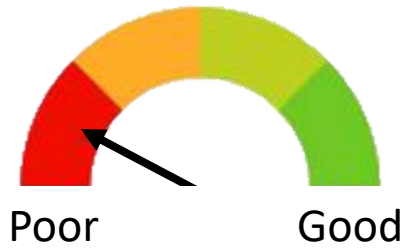
- Screening for peripheral neuropathy should start from age 11 years with 2 to 5 years diabetes duration and annually thereafter. **C**
- Specific tests to evaluate diabetic neuropathy include assessment of sensation, vibration and reflexes in the feet for peripheral neuropathy, and orthostatic, heart rate variability for cardiac autonomic neuropathy. **E**



Mørketal?



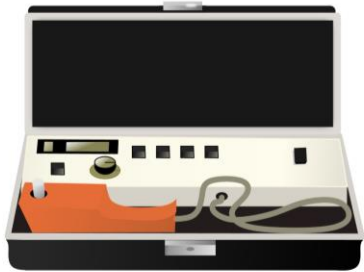
Nyt screeningsprogram?



Storfiber

Småfiber

Autonom



Conduction velocity
Acceptable, AUC=0.73

HR response to deep breathing
Acceptable, AUC=0.72



Ingen behandling, men vi kan...

Reducere risikofaktorer →

Behandle symptomer

Fokusere på sygdomslære



↑ HbA1c → ↓ Sweat responses

↑ Diabetes duration → ↑ Gastric motility index

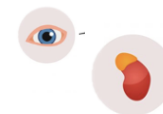
↓ Time in range for blood glucose → ↑ Colonic motility index

RR: Previous smoking



↑ LDL → sweat responses

RR: Cholesterol ≥ 5



RR: Other microvascular complications



RR: Basal insulin dose per kg per day > 0.5

RR: Total insulin dose per kg per day > 1.0



Undgå

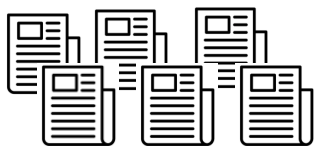


Diabetisk neuropati →

- Invaliderende symptomer
- Reduceret livskvalitet
- Øget risiko for amputationer, kardiovaskulære hændelser og død





+ lidt ekstra



Research Article

Cranial Nerve Affection in Adolescents with Type 1 Diabetes Assessed by Corneal Confocal Microscopy, Smell and Taste Tests

Vinni Faber Rasmussen ^{1,2,3}, Dorthe Rasmussen,⁴ Mathilde Thrysoe,¹ Páll Karlsson,^{1,5} Mette Madsen,^{6,7} Kurt Kristensen,³ Jens Randel Nyengaard,^{5,8} Astrid Juhl Terkelsen,^{1,9} Esben Thyssen Vestergaard ⁶ and Therese Ovesen ¹⁰

Treatment-induced neuropathy of diabetes in an adolescent with rapid reduction in HbA1c and weight loss: Persistent neuropathic findings at follow-up after 1.5 years

Vinni Faber Rasmussen , Mathilde Thrysoe, Hatice Tankisi, Páll Karlsson, Esben Thyssen Vestergaard, Kurt Kristensen, Jens Randel Nyengaard, Klaus Krogh, Christina Brock, Astrid Juhl Terkelsen

First published: 10 February 2022 | <https://doi.org/10.1002/ccr3.5415>

> *J Pediatr Urol.* 2024 Apr 23:S1477-5131(24)00199-2. doi: 10.1016/j.jpuro.2024.04.007.
Online ahead of print.

Bladder dysfunction in adolescents with type 1 diabetes

Vinni Faber Rasmussen ¹, Mathilde Thrysoe ², Páll Karlsson ³, Mette Madsen ⁴, Esben Thyssen Vestergaard ⁵, Jens Randel Nyengaard ⁶, Astrid Juhl Terkelsen ⁷, Konstantinos Kamperis ⁵, Kurt Kristensen ⁸

Open access

Original research

BMJ Open Cross-sectional study investigating the association between inflammatory biomarkers and neuropathy in adolescents with type 1 diabetes

Vinni Faber Rasmussen ^{1,2,3}, Verena Hirschberg Jensen ⁴, Mathilde Thrysoe,² Esben Thyssen Vestergaard,⁵ Joachim Størling,^{4,6} Kurt Kristensen¹

Submitted

Neurofilament light chain – ny biomarkør?

Neuropati – nogen indflydelse på livskvalitet?



**Tak for jeres
opmærksomhed**

Vejledere og samarbejdspartnere

Collaborators

Danish Pain Research Center (DPRC)

Nanna Brix Finnerup, Irene Brix Finnerup, and the entire team

Dept. of Pediatrics and Adolescents Aalborg, Randers, and Aarhus

 Steno Diabetes Center Nordjylland

 midt Regionshospitalet Randers

 midt Steno Diabetes Center Aarhus

Steno Diabetes Center Aarhus Steno Diabetes Center North Denmark

Supervisors



Professor Astrid Juhl Terkelsen (Main Supervisor)

The Danish Pain Research Center, Department of Clinical Medicine, Aarhus University & Department of Neurology, Aarhus University Hospital.

Associate Professor Esben Thyssen Vestergaard

Department of Pediatrics and Adolescents and Steno Diabetes Center Aarhus (SDCA), Aarhus University Hospital, and Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Associate Professor Kurt Kristensen

Steno Diabetes Center Aarhus (SDCA), Aarhus University Hospital, Denmark

Professor Jens Randel Nyegaard

Core Centre for Molecular Morphology, Section for Stereology and Microscopy, Department of Clinical Medicine, Aarhus University & Department of Pathology, Aarhus University Hospital, Denmark

**SDCA**
Steno Diabetes
Center Aarhus



Collaborators, Denmark

Pall Karlson (PhD Med., Associate professor), Core Center for Molecular Morphology, Stereology and Microscopy, Aarhus University, Denmark

Troels Staehelin Jensen (MD, PhD, Professor), Danish Pain Research Center, AU. The International Diabetic Neuropathy Consortium, Aarhus University Denmark

Hatice Tankisi (MD, Ph.D, Clinical Professor), Department of Clinical Neurophysiology, Aarhus University Hospital, Denmark

Klaus Krogh (MD, PhD, Consultant, Clinical professor), Gastroenterology, Aarhus University, Denmark

Christina Brock Gastroenterology, Aalborg University Hospital, Denmark

Therese Ovesen (MD, DMSc, Professor), Orto-rhino-laryngology, Aarhus University, Denmark

Tina Parkner (MD, Associate professor), Department of Clinical biochemistry, Aarhus University, Denmark

Konstantinos Kamperis (MD, PhD, Linical Associate Professor), Department of Pediatrics, Aarhus University Hospital, Denmark

Departments of Pediatrics and Adolescents, Randers, Aalborg and Aarhus Hospital, Denmark.

STENO DIABETES CENTER AARHUS

STENO DIABETES CENTER NORDJYLLAND

Sponsors

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Collaborator, USA

Wolfgang Singer (MD, Professor), Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA



Practical helpers

Dorthe Rasmussen (Laboratory technologist, smell and flavour), Orto-rhino-laryngology, Aarhus University, Denmark

Jane Knudsen (Laboratory research technician), Pediatric department, Aarhus University Hospital, Denmark

Mathilde Thrysoe (Medical student), Aarhus University, Denmark

