Supplementary material

Content

Region Hovedstaden

By skin problems → Report the type of skin problem by diary or survey

If in doubt, contact PhD-student Anna Berg

Assess the type of skin problems

Eczema red, scolding, itching

Thick skin (lipohypertrophy)

Infection red, warm, swollen, yellow pus

Other type?

*Avoid site
*Lipid lotion
*Extra barrier

*Avoid site

*Avoid site
*Use proper hygiene

*Avoid site

*Contact doctor for inoculation and treatment

Contact your diabetes provider or PhD-student Anna Berg

By lack of effect, contact your diabetes provider or PhD-student Anna Berg

Skin Care Program

As part of the research project:

Prospective Study of Dermatological Complications Associated with Continuous Subcutaneous In-sulin Infusion and/or Continuous Glucose Monitoring in Pediatric Patients with Type 1 Diabetes

Gentle insertion and removal
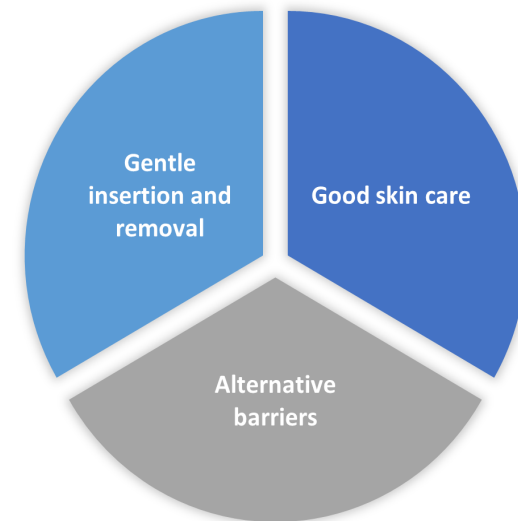
Good skin care

Alternative barriers
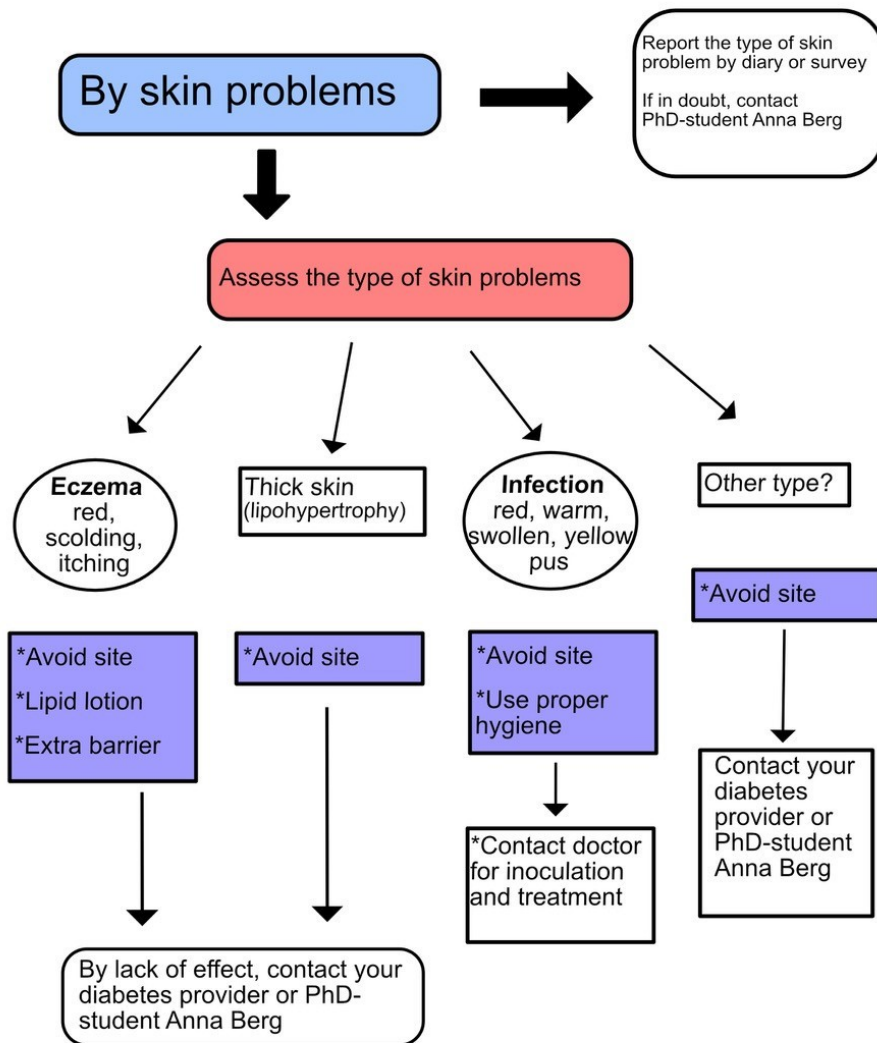
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Danish Diabetes Academy
Funded by the Novo Nordisk Foundation

Good skin care

Use unperfumed skin products and soap.

Use daily lipid lotion (the delivered Decubal Lipid 70%) on "pause sites" for the diabetes device. Pause sites are skin sites which are used for the device, although not currently.

Gentle insertion and removal

Insertion:

1. Find a suitable site with intact skin

2. If necessary, remove hair gently

3. Clean the site with water and soap and let it air-dry

4. Insert the device carefully without pulling too much in the patches

Removal:

1. Firstly, loosen the sides of the patch

2. Thereafter, carefully pull the patch with a low angle to remove it

3. Finally, use Niltac or other removal agents to remove adhesive

Alternative barriers

If there are problems due to too loose adhesion of the device, a protecting film (IV-3000) or tape (Mepore tape) can be put above to keep it secured, for instance also during sport or swimming.

If the skin is irritated or itchy, the following alternative barrieres can be used either under or above the device between number 3 and 4 in insertion recommendations.
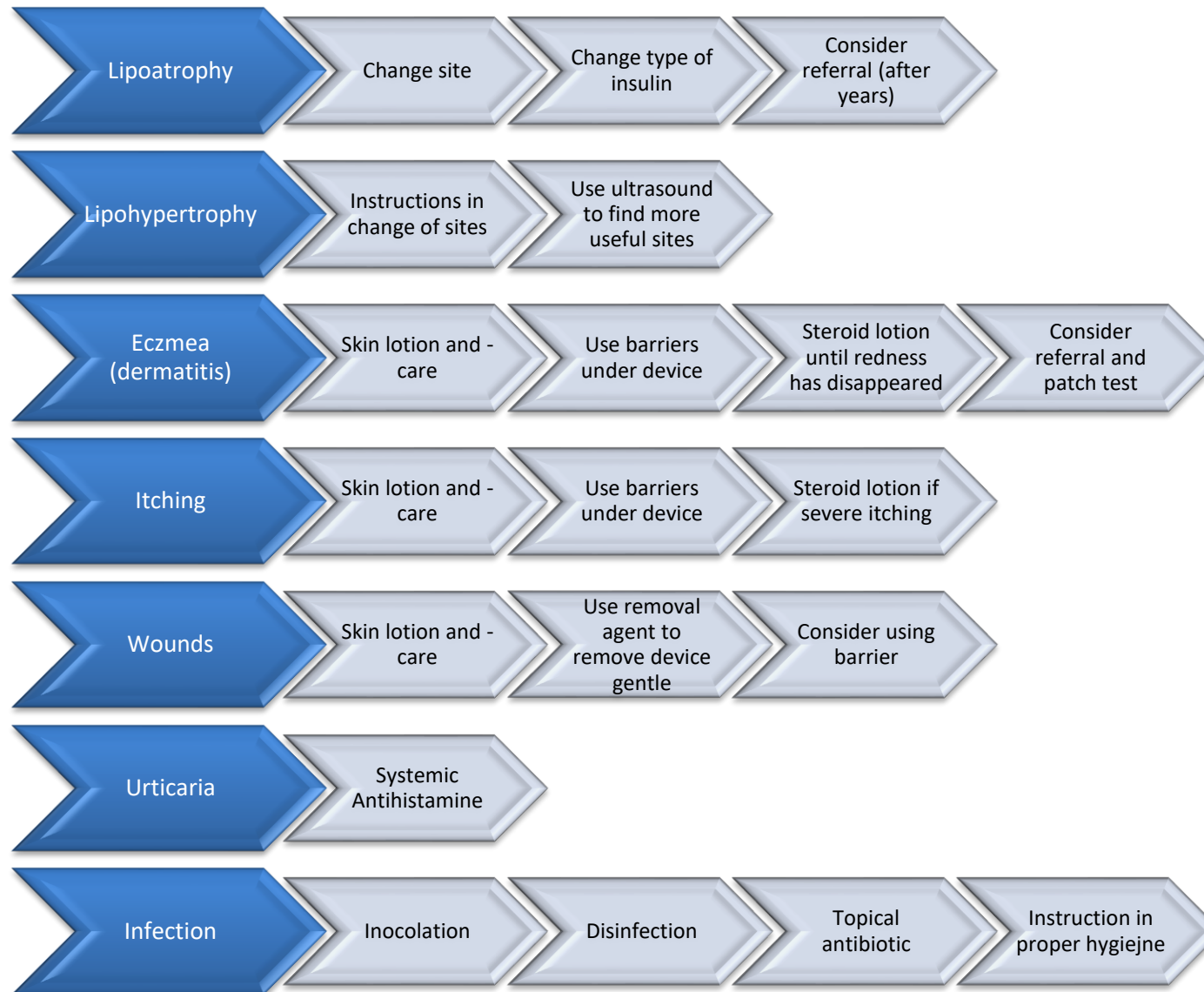
Liquid barrier that must dry before insertion: Welland WBF Wipe or Silesse Spray

Barrier film or thin patch: IV3000, Leukomed, Fixomull or tegaderm.

Thicker barrier patch: Duoderm or Compeed.

Ask your diabetes provider about the products and get them delivered next time you are at the thospital.

January 2020

Flowchart for developed skin problems – to health-care-professionals

Lipoatrophy	Change site	Change type of insulin	Consider referral (after years)	
Lipohypertrophy	Instructions in change of sites	Use ultrasound to find more useful sites		
Eczmea (dermatitis)	Skin lotion and -care	Use barriers under device	Steroid lotion until redness has disappeared	Consider referral and patch test
Itching	Skin lotion and -care	Use barriers under device	Steroid lotion if severe itching	
Wounds	Skin lotion and -care	Use removal agent to remove device gentle	Consider using barrier	
Urticaria	Systemic Antihistamine			
Infection	Inocolation	Disinfection	Topical antibiotic	Instruction in proper hygiejne

This is just an overview of possibilities and sequence of steps – **For all reactions, the site of reaction should be avoided** until proper healing and the **reaction should be reported as an adverse event** to the Danish Medicines Agency. The first steps will be continued.

Lipoatrophy

Change site

It is important that the affected site is not used anymore, and that more different skin sites are being used.

Change type of insulin

Lipoatrophy is an immune reaction to insulin, and therefore changing the type of insulin may help. If there is a tendency for lipoatrophy by multiple types of insulin, quarterly change of insulin type may help.

Consider referral (after years)

If many months or years' worth of attempts in changing the type of insulin have not resulted in remission of the site and it has cosmetic implications for the participant, lipofilling by referral to plastic surgeon can be considered.

Lipohypertrohy

Instructions in change of sites

Lipohypertrophy is caused by insulins anabolic effect in the tissue, which influences insulin absorption. Therefore, these areas must be avoided. The reaction can be prevented by changing sites more often according to the manufacturer's recommendations.

Use ultrasound to find more useful sites

If too few skin sites are known, ultrasound can be used to find more skin sites with sufficient depth of subcutis for devices.

Eczema

Skin lotion and -care

Proper skin care with use of clean, dry sites for infusion set, insulin pump or glucose sensor seem to have a positive influence on reactions. A lipid cream with up to 70% lipid can be placed on skin areas not currently being used for a device, aka 'the pause sites'.

Use barriers under device

To avoid exposure of skin to the ingredients from the diabetes device, a barrier can be used underneath. The first step is a barrier lotion, spray or film. Failing that a patch can be used (IV-3000/Tegaderm/Mepitel). A punch a hole can be made in the patch for the catheter or filament to go through.

Steroid lotion until redness has disappeared

Steroid lotion (type ll or lll) can be used to treat the current eczema by applying the lotion daily until the eczema-reaction disappears (max 4 weeks).

An alternative to steroid lotion is the use of fluticason spray on skin, which has shown to be effective in studies on children and adolescents[1].

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[1] Paret et al. "Out of the box" solution for skin... *Acta Diabetol.* (2019)

Consider referral and patch test

If eczema continues to arise despite the above steps in more than 14 days, the participant should be referred to the dermatological department, Gentofte Hospital, with consideration of the need to perform patch testing.

Itching

Skin lotion and -care

See above

Use barriers under device

See above

Steroid lotion if severe itching

Steroid lotion as for eczema can be used daily in case of severe itching in a period with daily applying of steroid lotion although maximum in 4 weeks.

Wounds

Skin lotion and -care

See above

Use removal agent to remove device gentle

Some wounds are caused by destruction of tissue by removal of former used diabetes devices and/or removal agents such as Niltac. Oil, or similar products can be used to support more gentle removal.

Consider using barrier

Wounds can be caused by too strong adhesion that disrupts the skin barrier. If so, a barrier under the Eczema area can be used to protect the skin from the strong adhesive.

Infection

Inoculation

Inoculation of the area including a test of antibiotic resistance

Disinfection

Clearance of infection by use of disinfection with, for instance, hibiscrub on the area.

Topical antibiotic

If lack of effect by clearance, topical antibiotics can be used after the test of antibiotic resistance

Instruction in proper hygiene

Proper hygiene can prevent further infections.

Contact info

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Supplementary tables

Supplementary Table S1 – Insulin pump cohort including device types, prior experience, and skin problems

	Control (N=40)	Intervention (N=57)	Overall (N=97)
Type of initiated insulin pump			
Medtronic 670G	2 (5.0%)	10 (17.5%)	12 (12.4%)
Medtronic 780G	5 (12.5%)	6 (10.5%)	11 (11.3%)
Omnipod	21 (52.5%)	15 (26.3%)	36 (37.1%)
Tandem	12 (30.0%)	18 (31.6%)	30 (30.9%)
Medtrum	0 (0%)	8 (14.0%)	8 (8.2%)
Former use of insulin pump			
Yes	11 (27.5%)	26 (45.6%)	37 (38.1%)
No	29 (72.5%)	31 (54.4%)	60 (61.9%)
Skin problems with earlier insulin pump			
Yes	7 (17.5%)	19 (33.3%)	26 (26.8%)
No	4 (10.0%)	7 (12.3%)	11 (11.3%)
Missing	29 (72.5%)	31 (54.4%)	60 (61.9%)

Supplementary Table S2 – Glucose sensor cohort including device types, prior experience and skin problems

	Control (N=37)	Intervention (N=110)	Overall (N=147)
Type of initiated glucose sensor			
Dexcom G6	11 (29.7%)	32 (29.1%)	43 (29.3%)
Libre	21 (56.8%)	57 (51.8%)	78 (53.1%)
Medtronic sensor	5 (13.5%)	14 (12.7%)	19 (12.9%)
Glucomen Day	0 (0%)	2 (1.8%)	2 (1.4%)
Medtrum sensor	0 (0%)	5 (4.5%)	5 (3.4%)
Former use of glucose sensor			
No	21 (56.8%)	57 (51.8%)	78 (53.1%)
Yes	16 (43.2%)	53 (48.2%)	69 (46.9%)
Skin problems with earlier glucose sensor			
No	7 (18.9%)	16 (14.5%)	23 (15.6%)
Yes	9 (24.3%)	26 (23.6%)	35 (23.8%)
Missing	21 (56.8%)	68 (61.8%)	89 (60.5%)

Supplementary Table S3 – Confirmatory models for effect of intervention on primary outcome any eczema or wound

	Cox regression models†	
	HR [95%CI]	p-value
Univariate	0.77 [0.47-1.28]	0.313
Multivariable§	0.83 [0.50-1.39]	0.478

Abbreviations:
† All coefficients in table are shown as effect of intervention (skin care program) on presence of eczema or wound from cox regression and is presented as Hazard ratio (HR) with [95%CI]. Besides exact p-values are presented.
§ Multivariable analysis are corrected for: atopic disease, age, sex in full group, former pump and sensor use, days since initiation of pump or sensor and atopic disease.

Supplementary Table S4 - Coefficients from Competing Cox Regression on time to eczema and wounds

		Time to Eczema		Time to Wound	
	Effect of group	HR [95% CI]	p-value ($p_{corrected}$)	HR [95% CI]	p-value ($p_{corrected}$)
Full cohort (N = 171)	Univariate	0.85 [0.46-1.55]	0.590 (1.000)	0.38 [0.18-0.80]	0.010 (0.080)
	Multivariable†	0.89 [0.47-1.70]	0.730 (1.000)	0.37 [0.17-0.77]	0.008 (0.080)
Insulin pump cohort (N = 93)	Univariate	0.87 [0.38-2.03]	0.750 (1.000)	0.55 [0.21-1.41]	0.210 (0.560)
	Multivariable§	1.02 [0.40-2.59]	0.970 (1.000)	0.43 [0.14-1.30]	0.140 (0.448)
Glucose sensor cohort (N = 137)	Univariate	0.59 [0.27-1.27]	0.180 (1.000)	0.36 [0.13-1.01]	0.053 (0.212)
	Multivariable§	0.70 [0.29-1.64]	0.410 (1.000)	0.35 [0.12-1.00]	0.050 (0.212)

Coefficients from competing risk cox regression taking the risk of the other outcome (respectively eczema and wound) into account.
† Multivariable analysis is adjusted for: age, sex in both models and for atopic disease in eczema-specific model.
§ Multivariable analyses are adjusted for age, sex, former use of device in both models and for atopic disease in eczema-specific model

Supplementary Table S5 – Coefficients from GEE on effect of intervention on itching severity at pump and sensor sites.

		OR [95% CI]	P-value
Insulin pump cohort (n = 65)	Model A†	0.76 [0.38-1.54]	0.4503
	Model B§	0.76 [0.36-576.93]	0.4548
Glucose sensor cohort (n = 114)	Model A†	0.69 [0.37-1.28]	0.2390
	Model B§	0.69 [0.37-475.75]	0.2298

†Model A is only adjusted for baseline itch level at respectively site of insulin pump or glucose sensor

§Model B is adjusted for former device use, atopic disease, and baseline itch level at respectively site of insulin pump or glucose sensor

Supplementary Table S6 – Coefficients from GEE for the influence of skin care program components on eczema or wound in full cohort

	Eczema (GEE)		Wound (GEE)	
	OR [95%CI] †	p-value	OR [95%CI] †	p-value
Use of disinfection	0.62 [0.42-0.92]	0.017	0.69 [0.41-1.17]	0.170
Use of lipid cream (reference never)				
Seldom	0.63 [0.33-1.22]	0.168	1.21 [1.00-1.45]	0.044
Often	0.88 [0.47-1.63]	0.686	0.81 [0.62-1.05]	0.105
Always	0.72 [0.38-1.35]	0.304	0.60 [0.32-1.10]	0.099
Use of removal	0.79 [0.42-1.46]	0.445	0.98 [0.62-1.56]	0.935

Abbreviations: GEE; Generalized Estimating Equations
† Coefficients are shown as the per protocol effect of different explanatory variables in rows with Odds Ratio (OR) with 95% confidence interval for OR in brackets [] and exact p-values. The GEE-models here are univariate

Supplementary Table S7 – Coefficients from GEE for the influence of different products on later eczema or wound and itching.

		Eczema or Wound (GEE)		Itching (GEE)	
		OR [95%CI] †	p-value	OR [95%CI]†	p-value
Pump cohort	Use of disinfection	0.73 [0.31-1.73]	0.476	1.39 [0.87-2.25]	0.172
	Use of lipid cream (reference never)				
	Seldom	0.59 [0.18-1.88]	0.369	0.46 [0.21-0.98]	0.043
	Often	0.61 [0.20-1.83]	0.380	0.45 [0.21-0.97]	0.042
	Always	0.84 [0.29-2.39]	0.740	0.40 [0.20-0.81]	0.011
	Use of removal	0.79 [0.26-2.40]	0.680	0.97 [0.96-0.99]	0.002
	Number of pump sites	0.78 [0.55-1.12]	0.185	0.99 [0.83-1.18]	0.910
	Use of liquid barrier	0.66 [0.23-1.86]	0.428	1.08 [0.62-1.87]	0.795
	Use of patch under	0.96 [0.19-4.83]	0.963	0.27 [0.12-0.62]	0.002
	Use of patch over	0.92 [0.25-3.40]	0.906	1.03 [0.23-4.63]	0.968
Sensor cohort	Use of disinfection	1.08 [0.51-2.26]	0.848	0.96 [0.58-1.58]	0.870
	Use of lipid cream (reference never)				
	Seldom	0.21 [0.06-0.80]	0.022	0.92 [0.33-2.6]	0.879
	Often	0.50 [0.18-1.38]	0.180	0.50 [0.21-1.21]	0.125
	Always	0.38 [0.14-1.06]	0.065	0.51 [0.21-1.26]	0.144
	Use of removal	0.59 [0.18-1.93]	0.381	1.06 [0.7-1.62]	0.773
	Number of sensor sites	0.66 [0.45-0.97]	0.036	0.32 [0.17-0.59]	<0.001
	Use of liquid barrier	0.52 [0.21-1.29]	0.159	0.50 [0.28-0.88]	0.017
	Use of patch under	1.57 [0.44-5.58]	0.482	0.99 [0.47-2.05]	0.968
	Use of patch over	0.79 [0.35-1.77]	0.563	1.25 [0.66-2.36]	0.496

Abbreviations: GEE; Generalized Estimating Equations

† Coefficients are shown as the per protocol effect of different explanatory variables in rows with Odds Ratio (OR) with 95% confidence interval for OR in brackets [] and exact p-values from a univariate model.

Supplementary Table S8– Descriptive results on use of barriers, skin sites etcetera at first and last study visit

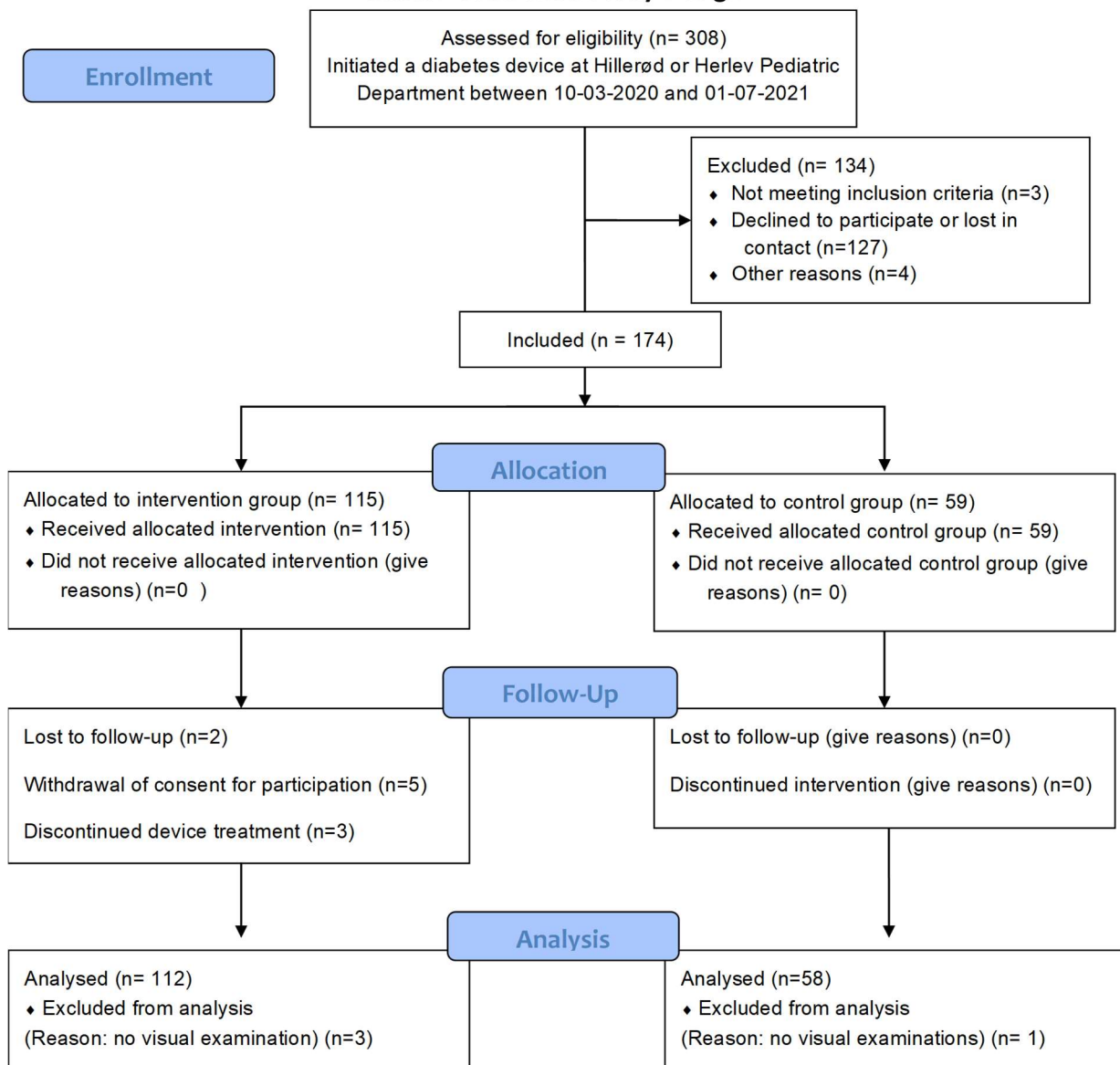| Insulin pump cohort	Intervention		Control	
	Baseline (N=49)	Last visit (N=48)	Baseline (N=34)	Last visit (N=39)
Used skin sites for insertion of insulin pump				
2 sites	36 (73.5%)	40 (83.3%)	22 (64.7%)	24 (61.5%)
3–4 sites	2 (4.1%)	5 (10.4%)	8 (23.5%)	11 (28.2%)
>4 sites	2 (4.1%)	1 (2.1%)	0 (0%)	4 (10.3%)
Missing	9 (18.4%)	2 (4.2%)	4 (11.8%)	0 (0%)
Liquid barrier under infusions set/insulin pump				
Yes	9 (18.4%)	16 (33.3%)	6 (17.6%)	17 (43.6%)
No	40 (81.6%)	32 (66.7%)	27 (79.4%)	22 (56.4%)
Missing	0 (0%)	0 (0%)	1 (2.9%)	0 (0%)
Patch under insulin pump				
Yes	3 (6.1%)	7 (14.6%)	5 (14.7%)	4 (10.3%)
No	32 (65.3%)	30 (62.5%)	25 (73.5%)	29 (74.4%)
Missing	14 (28.6%)	11 (22.9%)	4 (11.8%)	6 (15.4%)
Extra patch above insulin pump				
Yes	4 (8.2%)	0 (0%)	1 (2.9%)	2 (5.1%)
No	31 (63.3%)	37 (77.1%)	29 (85.3%)	31 (79.5%)
Missing	14 (28.6%)	11 (22.9%)	4 (11.8%)	6 (15.4%)
Glucose sensor cohort	Intervention		Control	
	Baseline (N=111)	Last visit (N=94)	Baseline (N=38)	Last visit (N=38)
Used skin sites for insertion of glucose sensor				
2 sites	88 (79.3%)	83 (88.3%)	29 (76.3%)	34 (89.5%)
3–4 sites	3 (2.7%)	3 (3.2%)	0 (0%)	1 (2.6%)
>4 sites	1 (0.9%)	2 (2.1%)	0 (0%)	1 (2.6%)
Missing	19 (17.1%)	6 (6.4%)	9 (23.7%)	2 (5.3%)
Liquid barrier under glucose sensor				
Yes	17 (15.3%)	19 (20.2%)	1 (2.6%)	17 (44.7%)
No	87 (78.4%)	74 (78.7%)	33 (86.8%)	21 (55.3%)
Missing	7 (6.3%)	1 (1.1%)	4 (10.5%)	0 (0%)
Patch under glucose sensor				
Yes	6 (5.4%)	7 (7.4%)	2 (5.3%)	1 (2.6%)
No	81 (73.0%)	53 (56.4%)	26 (68.4%)	30 (78.9%)
Missing	24 (21.6%)	34 (36.2%)	10 (26.3%)	7 (18.4%)
Extra patch above glucose sensor				
Yes	24 (21.6%)	14 (14.9%)	13 (34.2%)	9 (23.7%)
No	63 (56.8%)	46 (48.9%)	15 (39.5%)	22 (57.9%)
Missing	24 (21.6%)	34 (36.2%)	10 (26.3%)	7 (18.4%)

Supplementary Figures

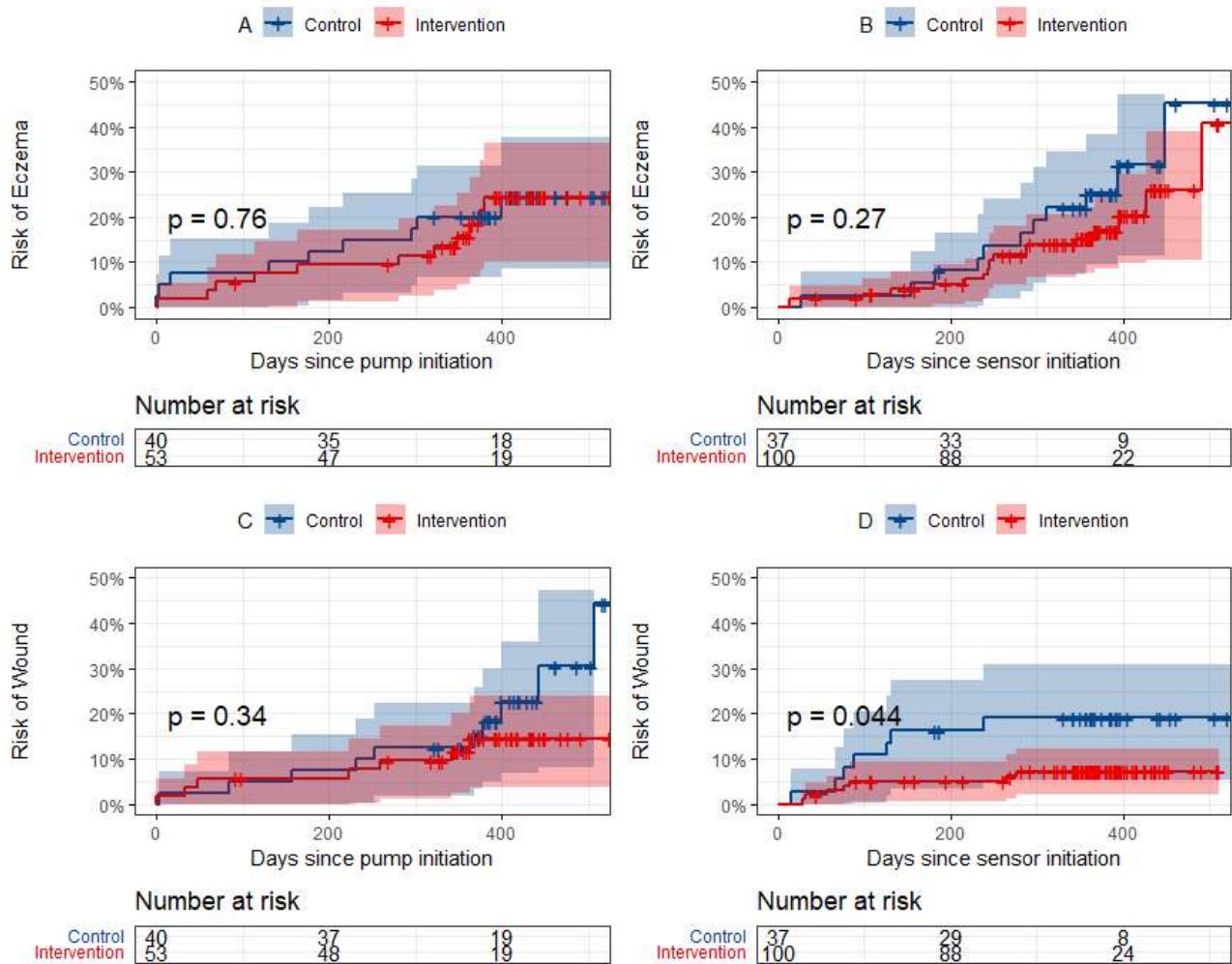Supplementary Figure S1 – Consort flow diagram for inclusion process

**CONSORT 2010 Flow Diagram**

Cluster-Controlled Study Design

Enrollment

Assessed for eligibility (n= 308)
Initiated a diabetes device at Hillerød or Herlev Pediatric
Department between 10-03-2020 and 01-07-2021

Excluded (n= 134)
- Not meeting inclusion criteria (n=3)
- Declined to participate or lost in contact (n=127)
- Other reasons (n=4)

Included (n = 174)

Allocation

Allocated to intervention group (n= 115)
- Received allocated intervention (n= 115)
- Did not receive allocated intervention (give reasons) (n=0)

Allocated to control group (n= 59)
- Received allocated control group (n= 59)
- Did not receive allocated control group (give reasons) (n= 0)

Follow-Up

Lost to follow-up (n=2)

Withdrawal of consent for participation (n=5)

Discontinued device treatment (n=3)

Lost to follow-up (give reasons) (n=0)

Discontinued intervention (give reasons) (n=0)

Analysis

Analysed (n= 112)
- Excluded from analysis
(Reason: no visual examination) (n=3)

Analysed (n=58)
- Excluded from analysis
(Reason: no visual examinations) (n= 1)

Kaplan-Meier plots for risk of eczema or wound for respectively pump and sensor starters stratified by intervention or control group. The p-value on the diagram is from the log-rank test.
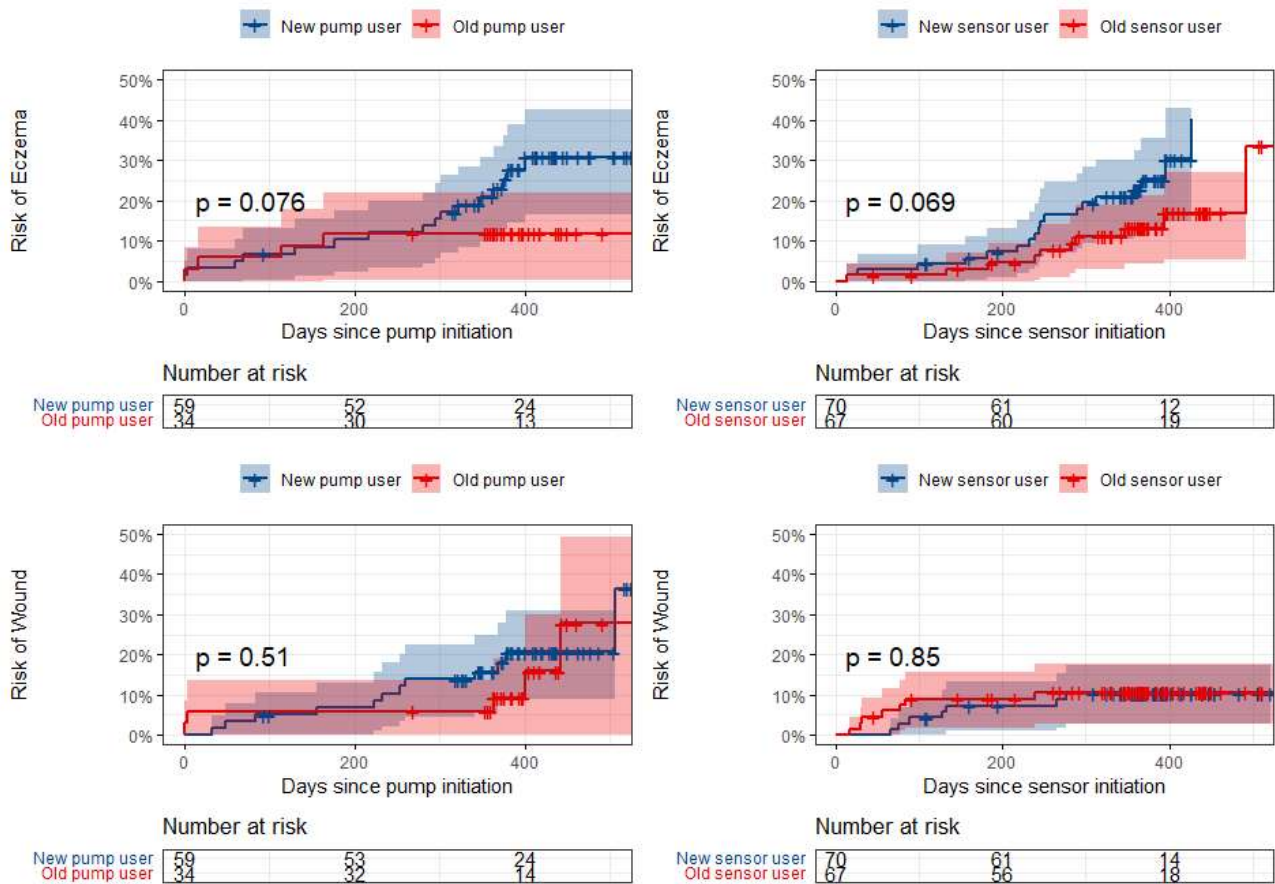
Kaplan-Meier plots for risk of eczema or wound for respectively pump and sensor starters stratified by experience of device use prior to initiation of this device. The p-value on the diagram is from the log-rank test.
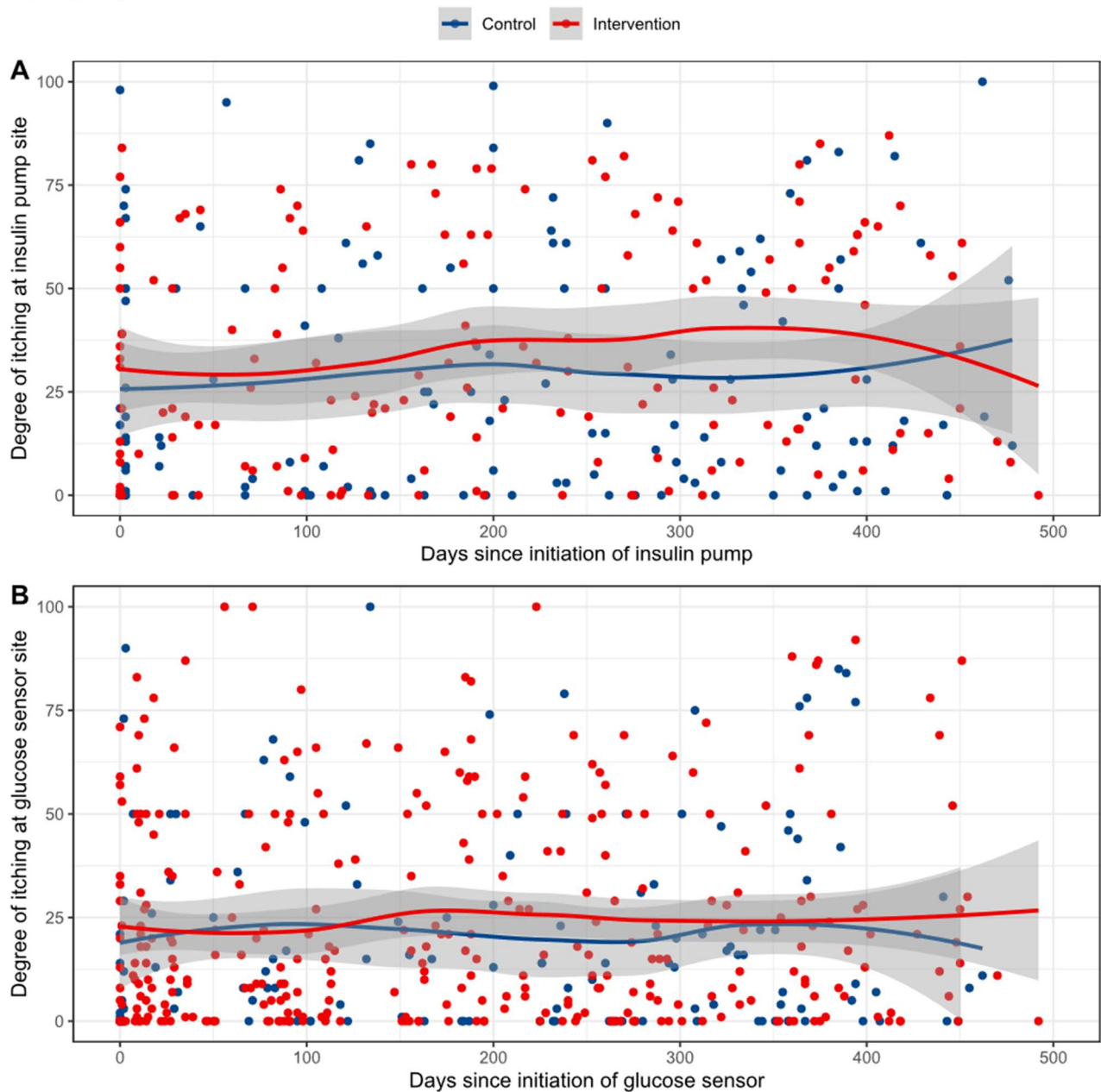
The y-axis represents the degree of itching on a VAS-scale from 0-100, the x-axis represents the exact number of days since initiation of device, and each dot represent one measure of itching and its respectively day. The smooth curves (made with "loess" function in R) show the average and tendencies for direction and correlation including 95% confidence levels in shaded gray. Panel A show itching at insulin pump sites for all participants in insulin pump cohort and panel B show itching at glucose sensor sites for all participants in glucose sensor cohort.