

# Behandling af Atopisk Dermatitis hos gravide, ammende og patienter med graviditetsønske.

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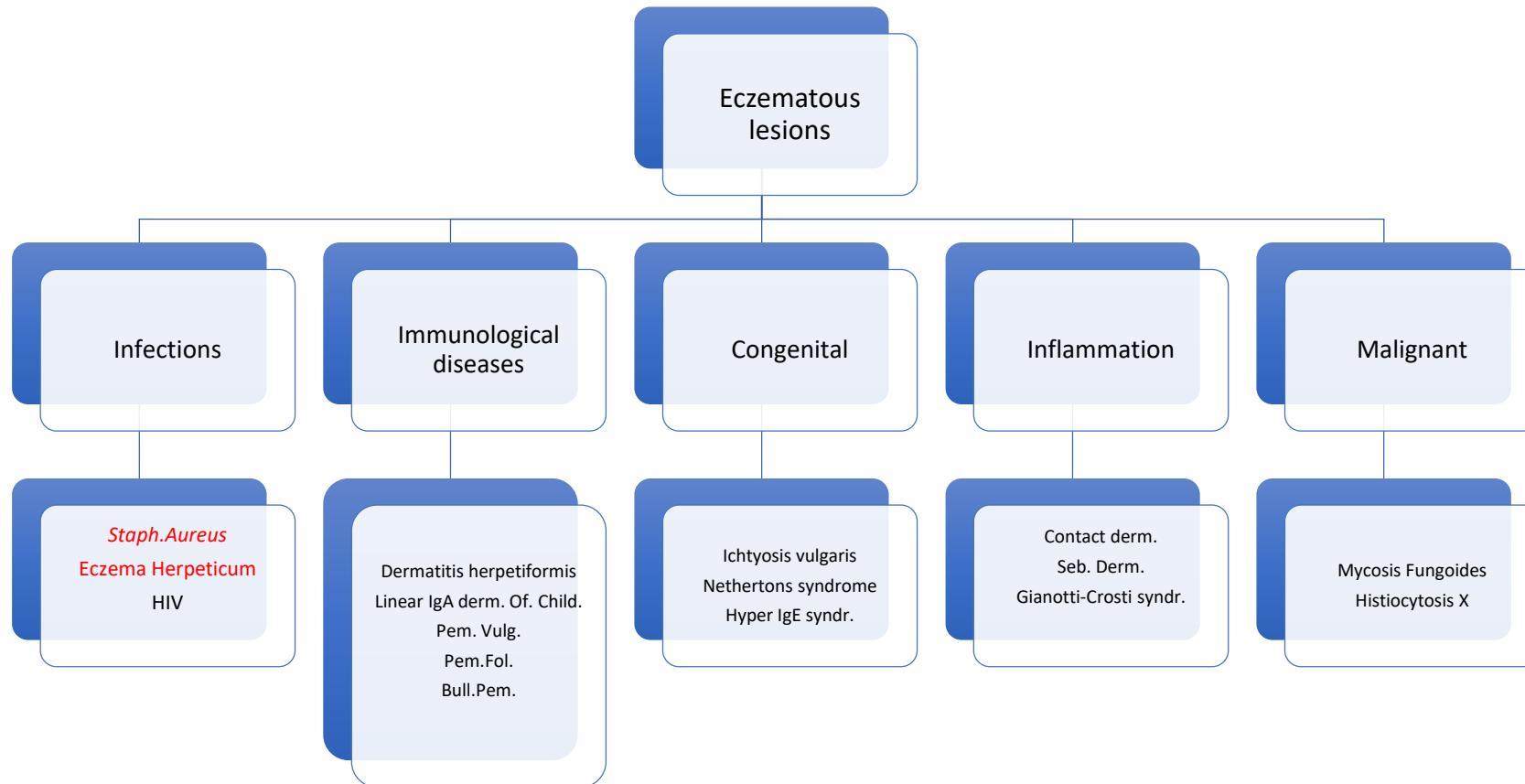
# Tre sider af atopisk dermatitis

- Differential diagnoser
- Systemisk behandling. Indikation og valg
- Behandling af gravide og ammende kvinder samt mænd der ønsker at være fædre.

# Udfordringen i diagnostik af AD

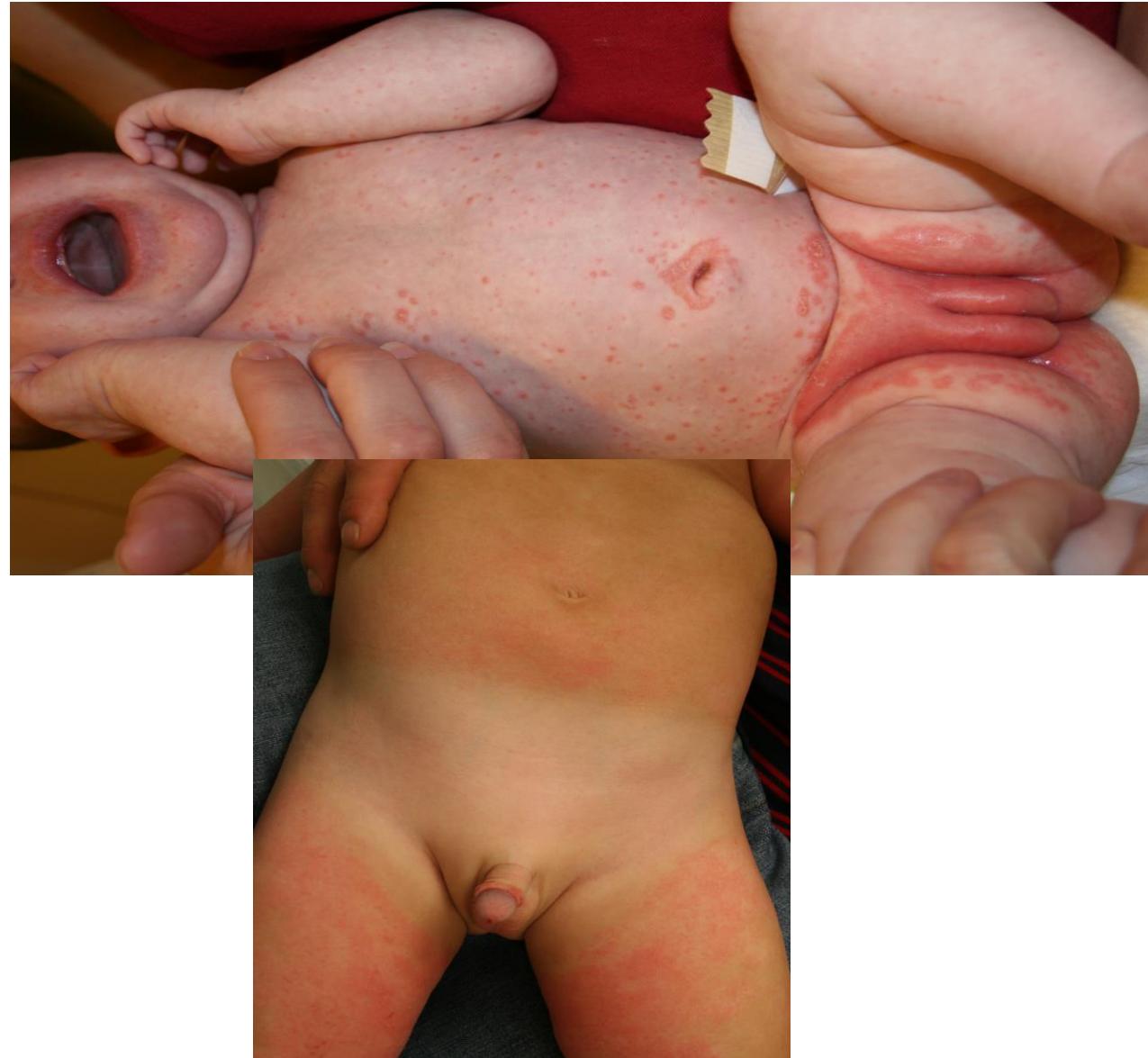


# What hides in AD?



# Seborrhoeic dermatitis

- In children it may be impossible to distinguish from AD
- Scaly, 'greasy', salmon red, diaper dermatitis.
- In the adult scales in the eyebrows, at the nasolabial folds, retroauricular area and scalp dandruf.



# Seborrhoeic dermatitis



'greasy red'



'burning red'

# Gianotti Crosti syndrome. Infantile papular acrodermatitis

- Skin reaction to infections.
  - Hepatitis B
  - Epstein Barr virus
  - Enterovirus
  - Echovirus
  - RS virus
- Last for weeks.



# infections

- Impetigo
- Eczema herpeticum



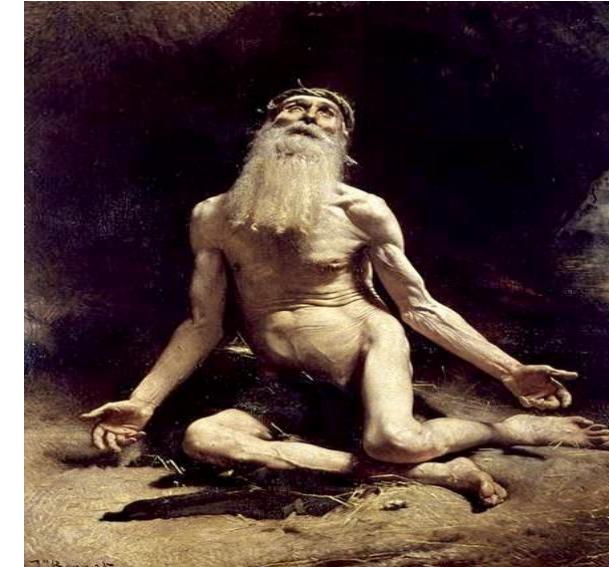
# Congenital diseases.

- Most common
  - Ichtyosis
  - Nethertons sydrome (ichtyosis linearis circumflexa)
  - Hyper IgE syndrome



[www.fao.com](http://www.fao.com)

(food and agricultural organizations of the united nations).



Bonnat 1880

# Ichtyosis Vulgaris

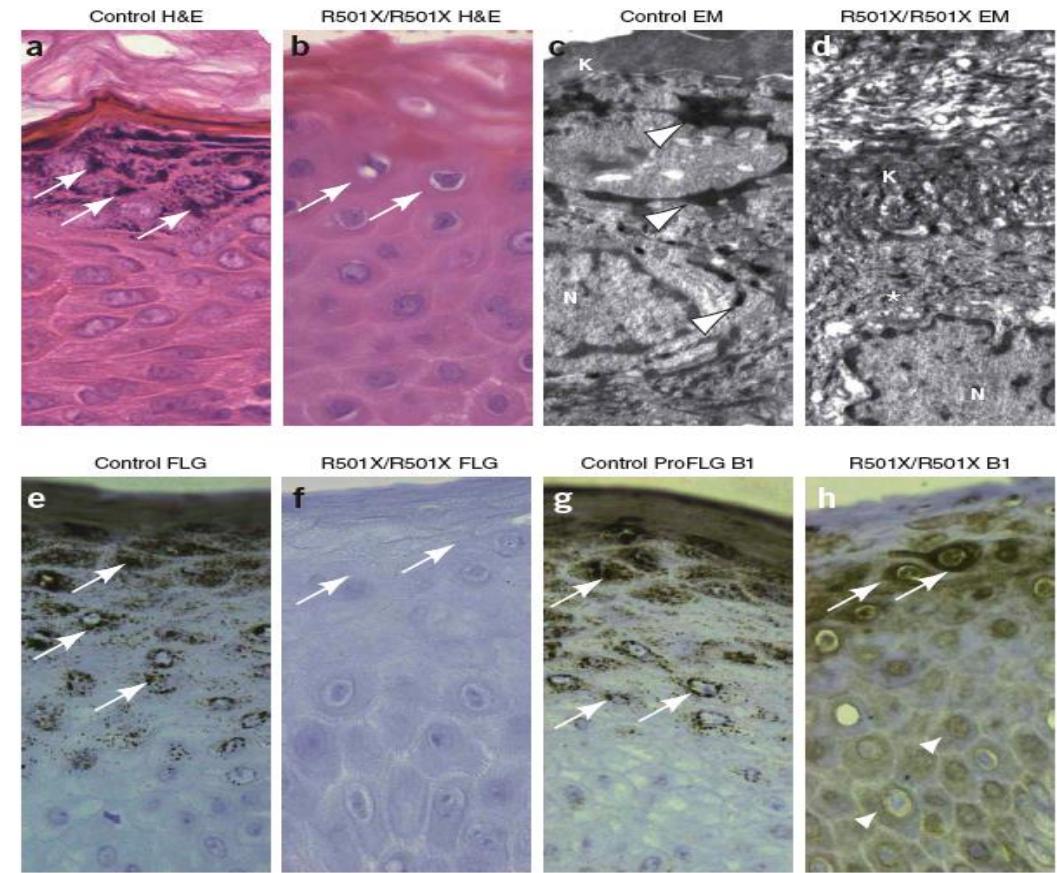
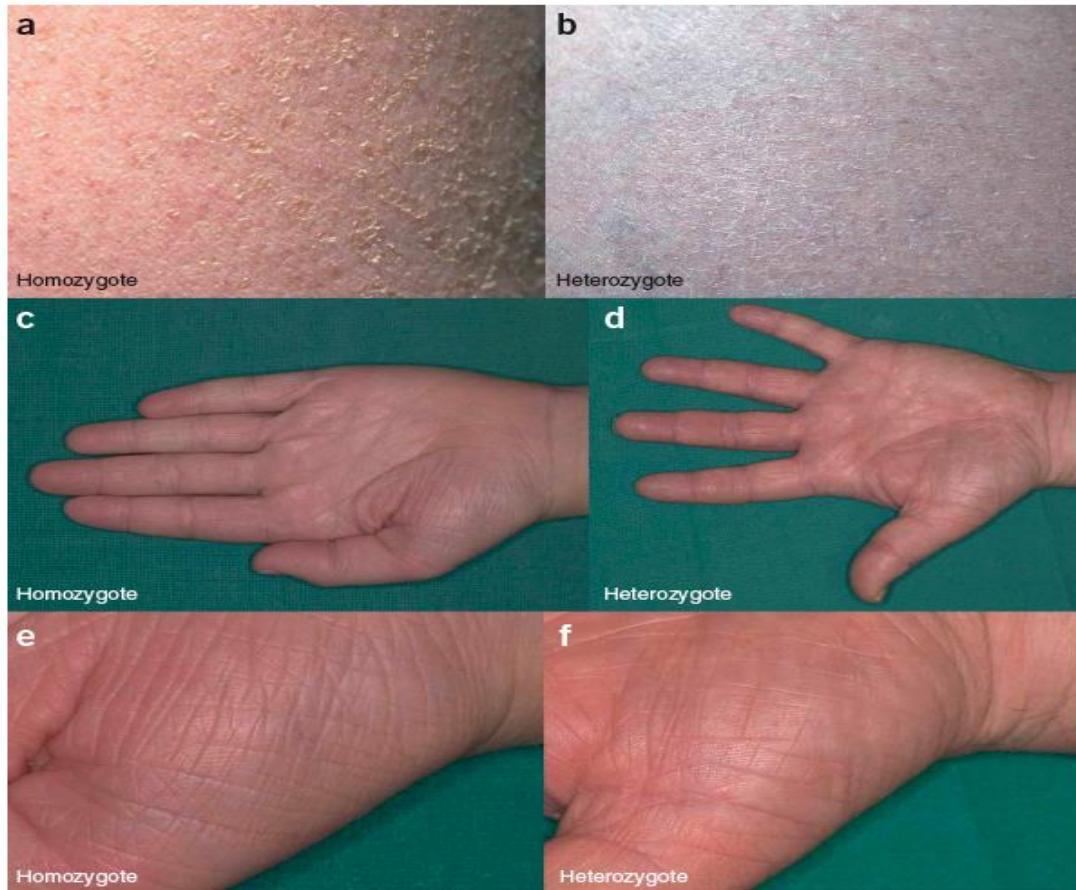
Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris

Frances J D Smith<sup>1</sup>, Alan D Irvine<sup>2</sup>, Ana Terron-Kwiatkowski<sup>1</sup>, Aileen Sandilands<sup>1</sup>, Linda E Campbell<sup>1</sup>,  
Yiwei Zhao<sup>1</sup>, Haihui Liao<sup>1</sup>, Alan T Evans<sup>3</sup>, David R Goudie<sup>4</sup>, Sue Lewis-Jones<sup>5</sup>, Gehan Arsecularatne<sup>5</sup>,  
Colin S Munro<sup>6</sup>, Ann Sergeant<sup>6</sup>, Gráinne O'Regan<sup>2</sup>, Sherri J Bale<sup>7</sup>, John G Compton<sup>7</sup>, John J DiGiovanna<sup>8,9</sup>,  
Richard B Presland<sup>10,11</sup>, Philip Fleckman<sup>11</sup> & W H Irwin McLean<sup>1</sup>

**nature**  
**genetics**

- Ichtyosis Vulgaris
  - Dry skin
  - Keratosis pilaris, ulerythema oophrygenes, palmar hyperlinearity, fine desquamation
  - X-linked ichtyosis vulgaris (steroid sulfatase mutation)
  - FLG null-mutation

# Ichthyosis vulgaris



# Nethertons syndrome



Dragos et al, Acta Derm Ven Alp Pan Adr, 2000 vol9, no 2



[www.globalskinatlas.com](http://www.globalskinatlas.com)

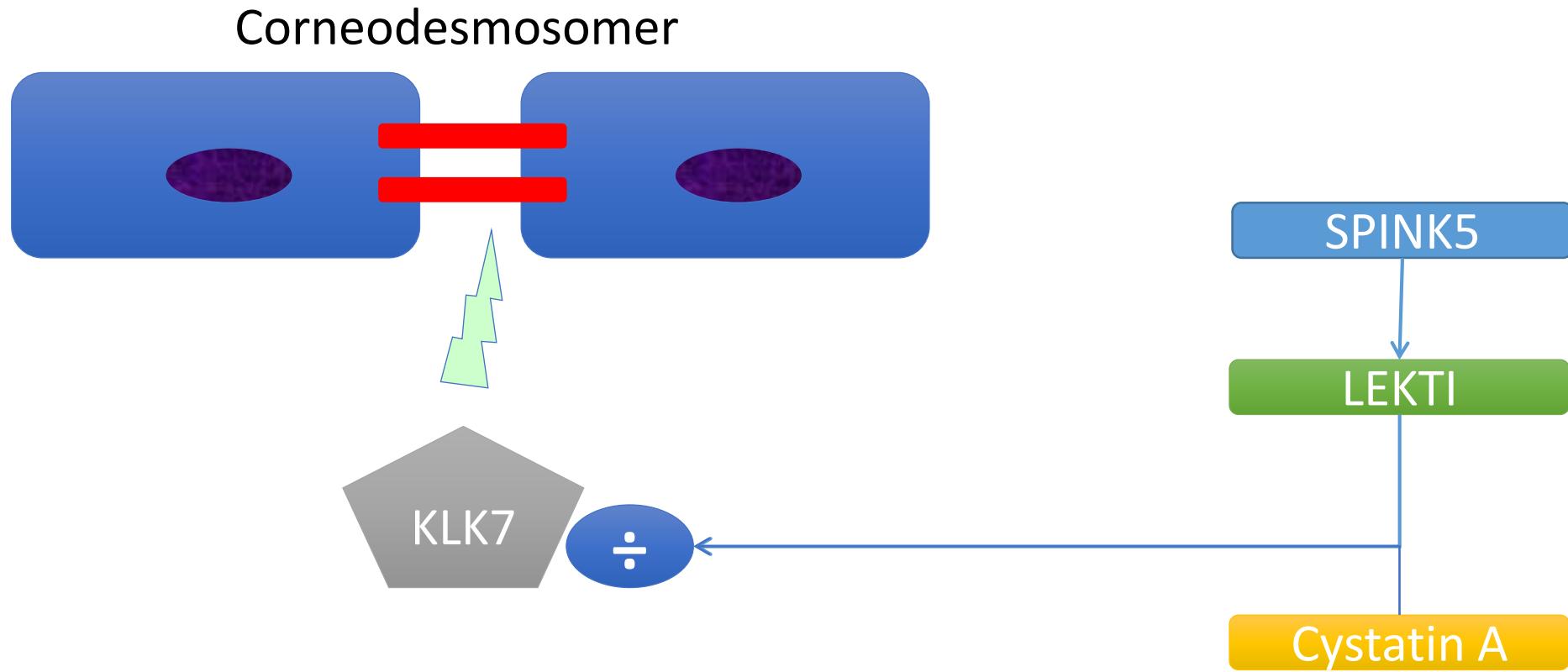
## Symptoms

Ichtyosis

Hair abnormalities (*pili torti*,  
*trichorrehxis invaginata*,  
*trichorrhesis nodosa*)

Atopic dermatitis.

# Proteases og Protease inhibitors



# Hyper IgE syndrome

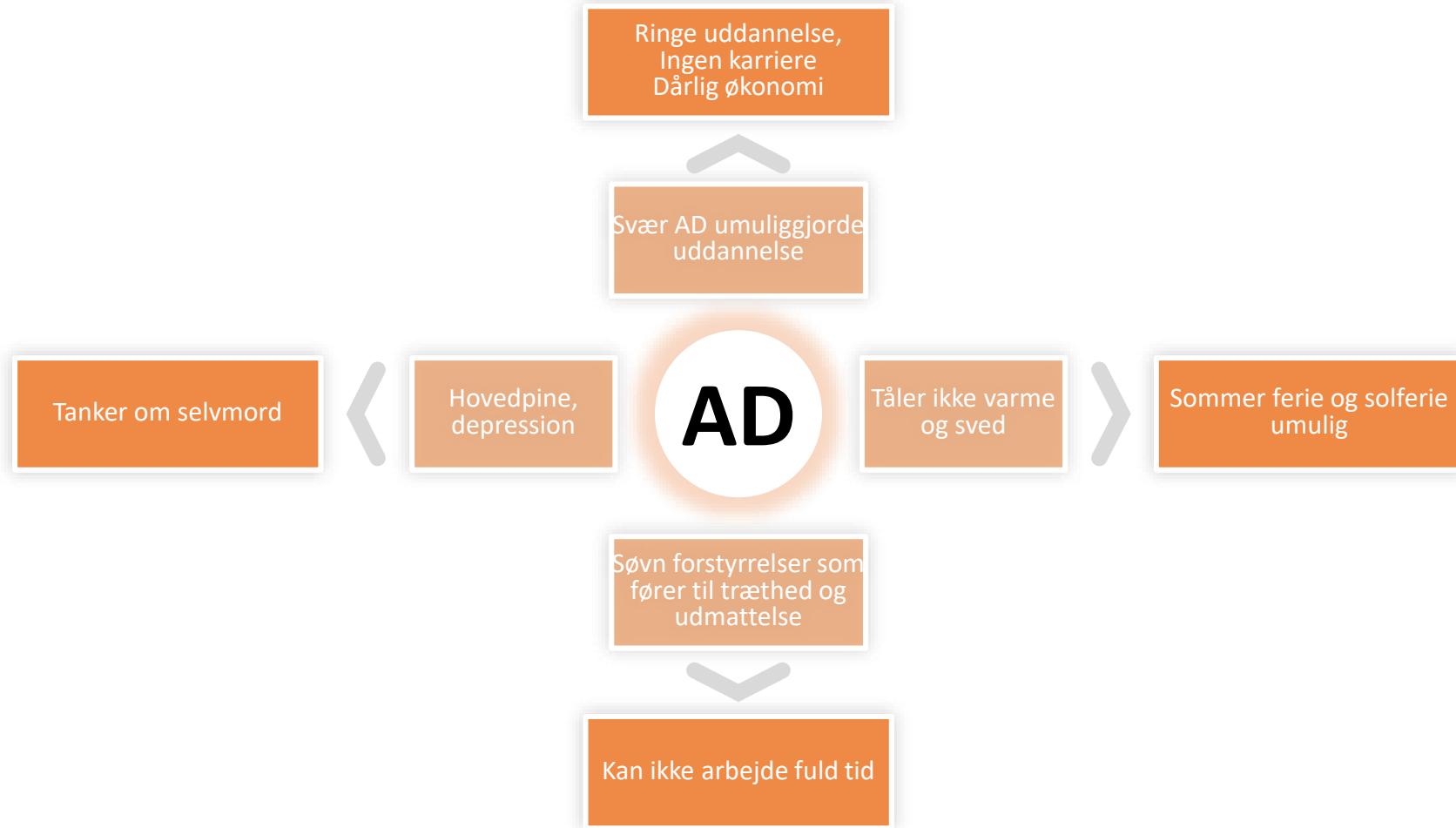
## Jobs syndrome

- (AD)-HIES
  - Autosomal dominant *STAT3*
  - Severe eczema, recurrent abscesses and pneumonias, nail and mucocutaneous candidiasis
- (AR)-HIES
  - Autosomal recessive *DOCK8*
  - Infections primarily associated with cellular immunodeficiencies, cutaneous viral infections.

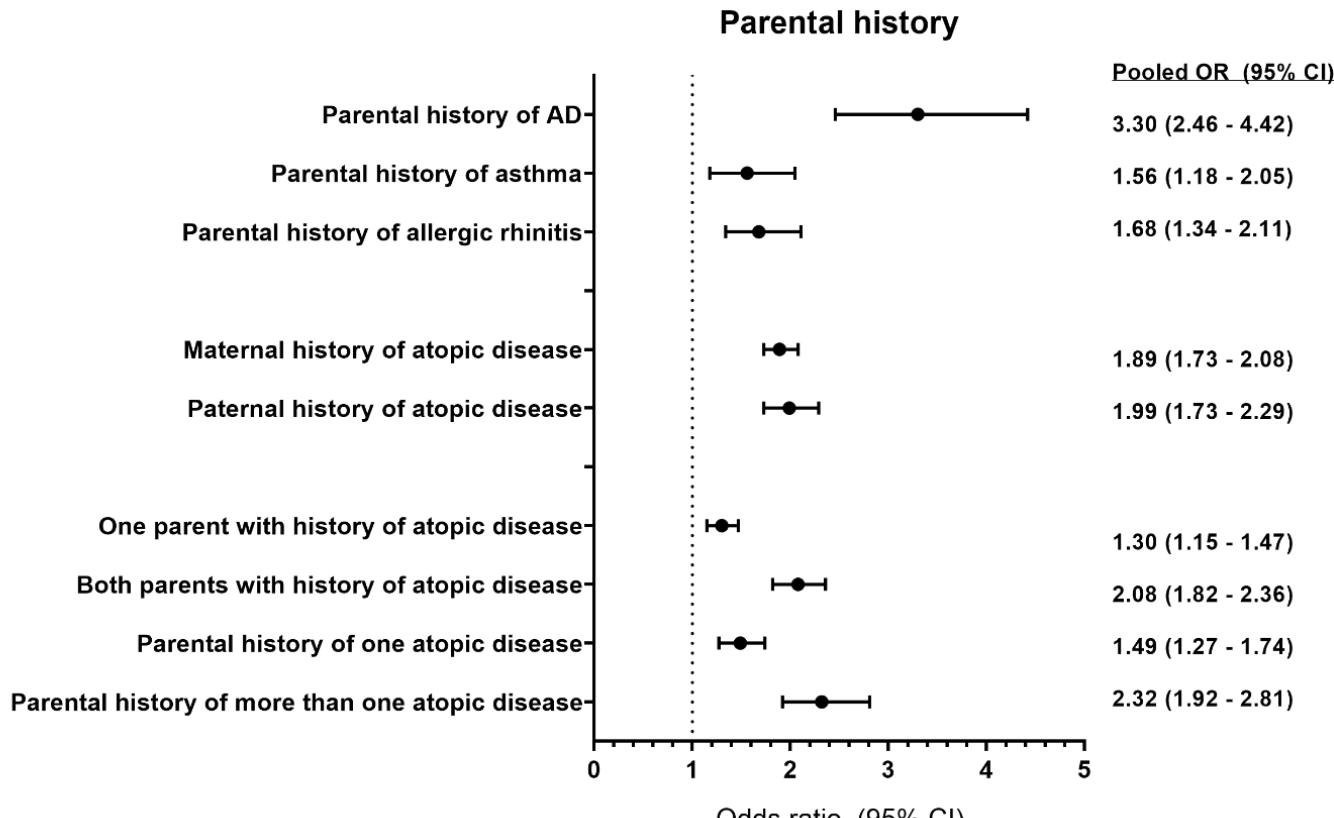


**Figure 9.** Older patients with hyper-IgE syndrome show thickened doughy texture of the skin, markedly dilated pores, and a broad-based nose. This patient also has angular cheilitis, a very common finding in hyper-IgE syndrome. Many patients also exhibit distinctive varioliform scarring on their faces.

# Konsekvenser af AD



# Risk of Developing Atopic Dermatitis According to Parental History of Atopic Disease



# Persistence: Williams HC 1998 Br J Derm

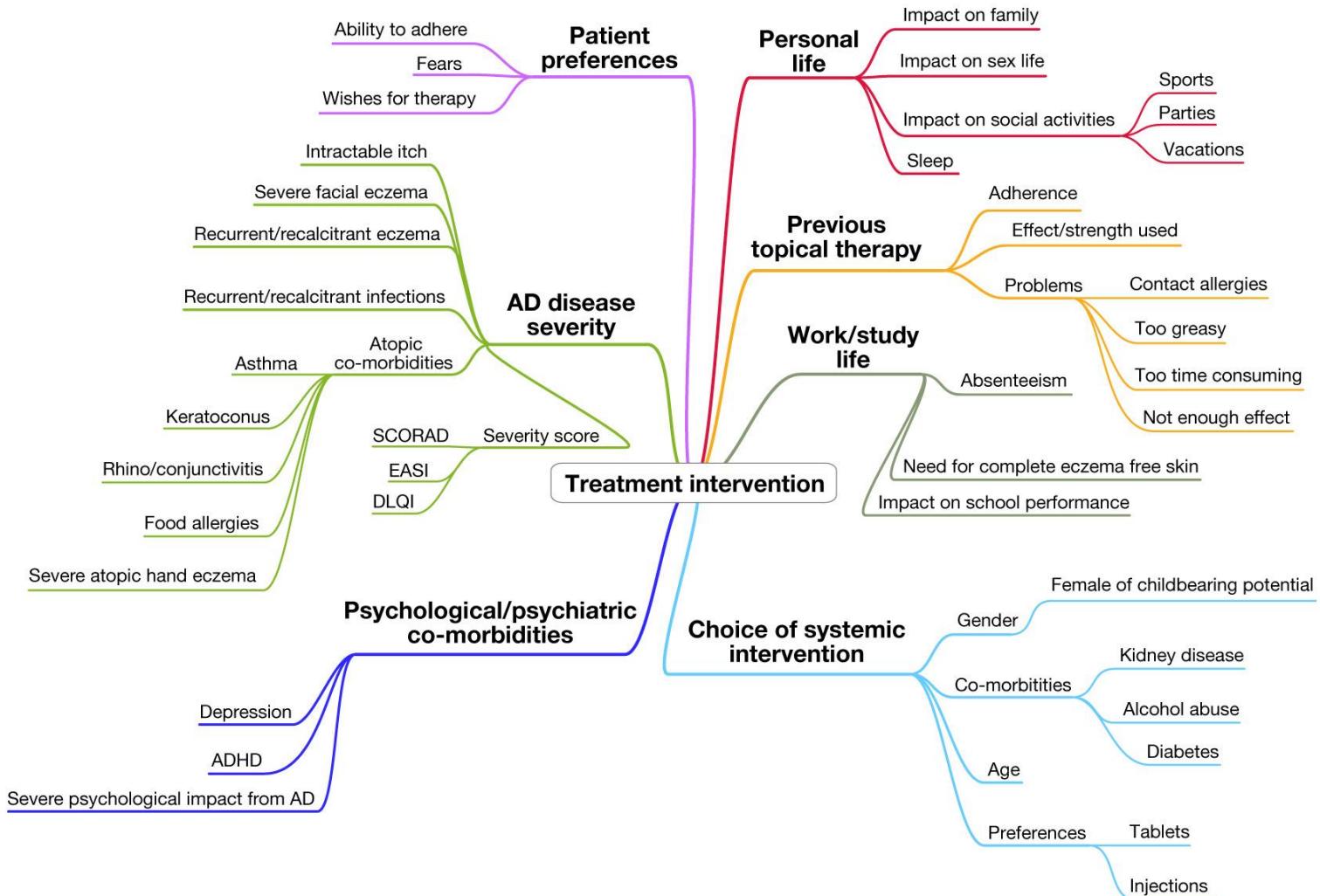
## (a) New cases examined or reported eczema

Onset of eczema at age (years)	Number (%) of children in whom eczema still present ( <i>n</i> = 6877)				
	At 1–7	At 11	At 16	At 23 <sup>a</sup>	Total
By 1 year (report)	229 (62·2)	138 (37·5)	114 (31·0)	107 (29·1)	368
1–7 years (report or examined)	—	60 (29·6)	36 (17·7)	36 (17·7)	203
10–11 years (report or examined)	—	—	26 (15·8)	27 (16·5)	164
15–16 years (report or examined)	—	—	—	23 (18·4)	125
22–23 (self report)	—	—	—	—	193
Total					1053

# **Hvordan vælger vi systemisk behandling**

## Effects of a protein-free oat plantlet extract on microinflammation and skin barrier function in atopic dermatitis patients

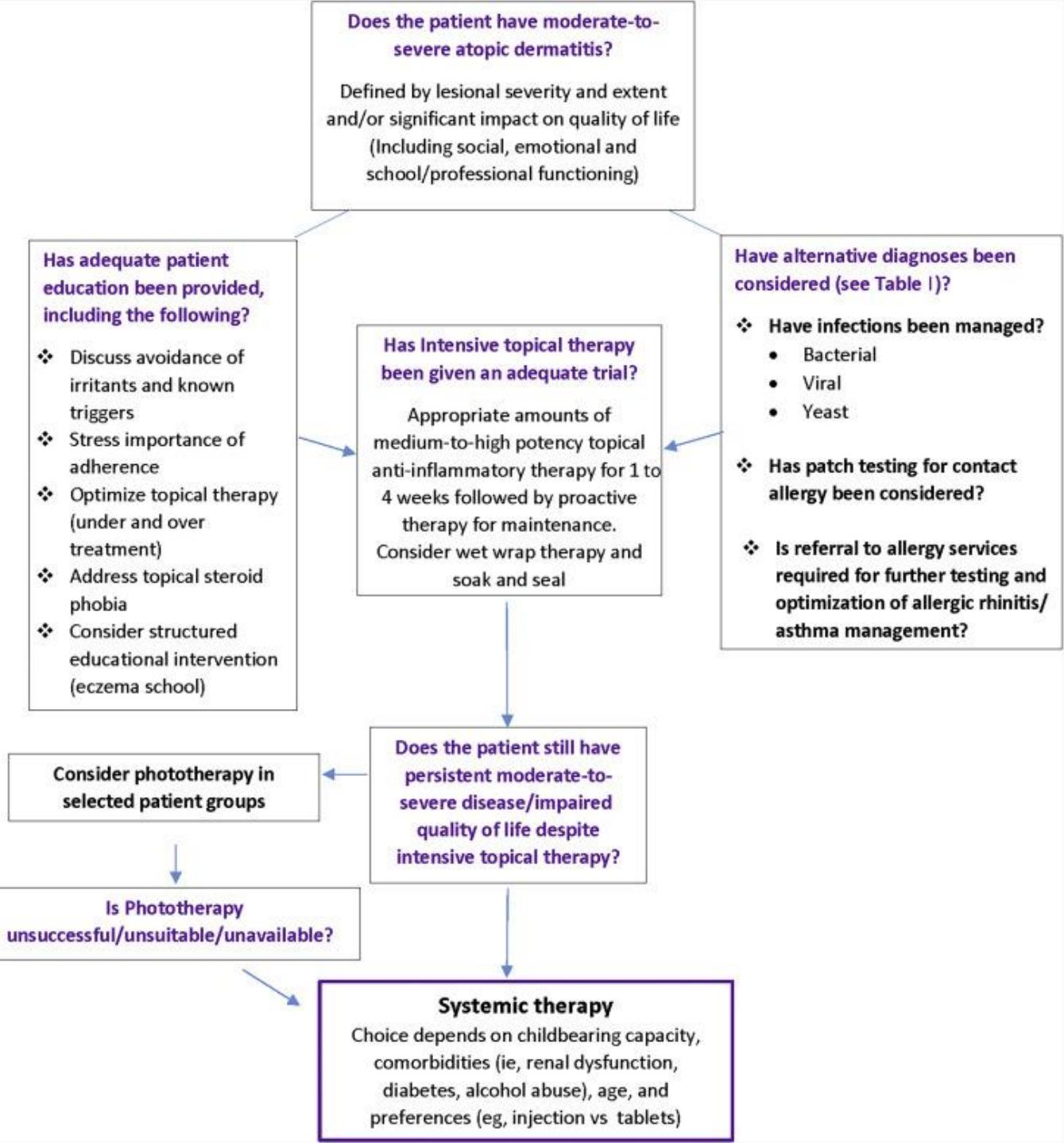
A. Wollenberg ✉, R. Fölster-Holst, M. Saint Aroman, F. Sampogna, C. Vestergaard



C.Vestergaard and M.Deleuran

## When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council

Eric L. Simpson, MD, MCR<sup>a,\*</sup>   Marjolein Bruun-Weller, MD, PhD<sup>b</sup>, Carsten Flohr, MD, PhD, MSc<sup>c</sup>, Michael R. Ardern-Jones, DPhil(PhD), FRCP(MD)<sup>d</sup>, Sébastien Barbarot, MD, PhD<sup>e</sup>, Mette Deleuran, MD, DMSc<sup>f</sup>, Thomas Bieber, MD, PhD, MDRA<sup>g,h</sup>, Christian Vestergaard, MD, PhD, DMSc<sup>i</sup>, Sara J. Brown, MD, FRCPE<sup>j,k</sup>, Michael J. Cork, PhD, FRCPI, Aaron M. Drucker, MD, FRCPC<sup>m</sup>, Lawrence F. Eichenfield, MD<sup>n,o,p</sup>, Regina Foelster-Holst, MD<sup>q</sup>, Emma Guttman-Yassky, MD, PhD<sup>r</sup>, Audrey Nosbaum, MD, PhD<sup>s</sup>, Nick J. Reynolds, MD, FRCPt<sup>t,u</sup>, Jonathan I. Silverberg, MD, PhD, MPH<sup>v,w,x</sup>, Jochen Schmitt, MD, MPH<sup>y</sup>, Marieke M.B. Seyger, MD, PhD<sup>z</sup>, Phyllis I. Spuls, MD, PhD<sup>aa</sup>, Jean-François Stalder, MD<sup>e</sup>, John C. Su, MD, MEpi, MA, MSt<sup>bb,cc</sup>, Roberto Takaoka, MD<sup>dd</sup>, Claudia Traidl-Hoffmann, MD<sup>ee,ff</sup>, Jacob P. Thyssen, MD, PhD, DmScigg, Jorien van der Schaft, MD, PhD<sup>hh</sup>, Andreas Wollenberg, MD, DrMed, DrHC<sup>ii</sup>, Alan D. Irvine, MD, DSc<sup>jj,\*\*</sup>  Amy S. Paller, MSc, MD<sup>v,kk,ll,\*\*\*</sup>  



# Indikationer for systemisk terapi

- Dårligt/manglende respons til topikal behandling
- Fysisk og psykisk påvirkning af sygdommen
- Nedsat livskvalitet
- Steroid bivirkninger (hudatrofi)



**Treatment recommendation for atopic eczema: adult**

- For every phase, *additional* therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with <sup>1</sup>
- Licensed indication are marked with <sup>2</sup>, off-label treatment options are marked with <sup>3</sup>

<b>SEVERE:</b> <b>SCORAD &gt;50 / or persistent eczema</b>	Hospitalization; systemic immunosuppression: cyclosporine A <sup>2</sup> , short course of oral glucocorticosteroids <sup>2</sup> , dupilumab <sup>1,2</sup> , methotrexate <sup>3</sup> , azathioprin <sup>3</sup> , mycophenolate mofetil <sup>3</sup> ; PUVA <sup>1</sup> ; alitretinoin <sup>1,3</sup>
<b>MODERATE:</b> <b>SCORAD 25-50 / or recurrent eczema</b>	Proactive therapy with topical tacrolimus <sup>2</sup> or class II or class III topical glucocorticosteroids <sup>3</sup> , wet wrap therapy, UV therapy (UVB 311 nm, medium dose UVA1), psychosomatic counseling, climate therapy
<b>MILD:</b> <b>SCORAD &lt;25 / or transient eczema</b>	Reactive therapy with topical glucocorticosteroids class II <sup>2</sup> or depending on local cofactors: topical calcineurin inhibitors <sup>2</sup> , antiseptics incl. silver <sup>2</sup> , silver coated textiles <sup>1</sup>
<b>BASELINE:</b> <b>Basic therapy</b>	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

# Systemiske behandlinger

- Cyclosporin A
- Methotrexat
- Azathioprin
- Mycofenolat mofetil
- Dupilumab
- (Prednisolone)



• Wollenberg A et al. JEADV. 2016;30:729-4.

# Hvad er biologisk behandling?

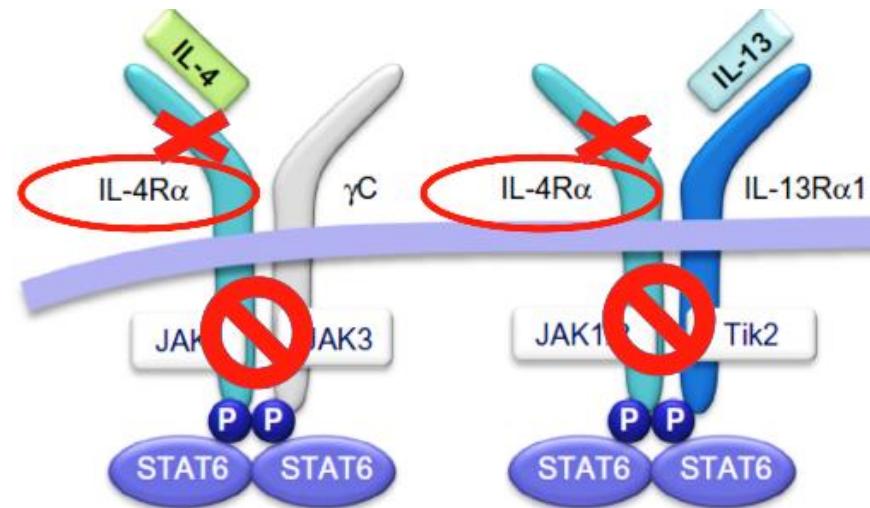
- Alle lægemidler der er produceret i levende biologiske organismer, eller som er levende biologiske organismer



*Wikipedia*

# Dupilumab

- Et humant monoclonalt antistof mod alpha subunit i interleukin-4/interleukin 13 receptoren<sup>1</sup>
- IL-4 og IL-13 er nøgleTh2 cytokiner i AD<sup>1</sup>



# **SOLO 1 & SOLO 2**

*The NEW ENGLAND JOURNAL of MEDICINE*

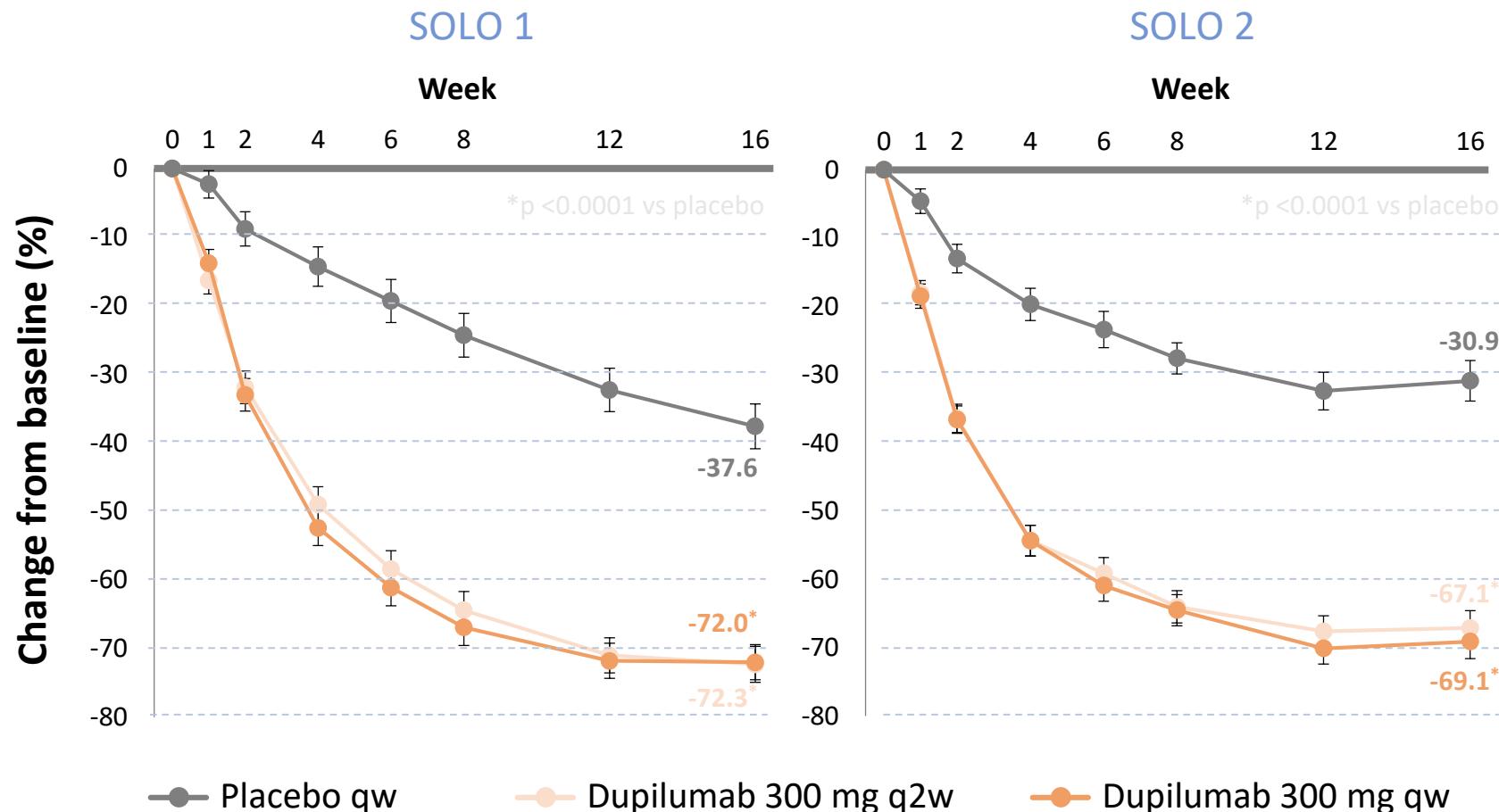
**ORIGINAL ARTICLE**

## **Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis**

E.L. Simpson, T. Bieber, E. Guttman-Yassky, L.A. Beck, A. Blauvelt, M.J. Cork,  
J.I. Silverberg, M. Deleuran, Y. Kataoka, J.-P. Lacour, K. Kingo, M. Worm,  
Y. Poulin, A. Wollenberg, Y. Soo, N.M.H. Graham, G. Pirozzi, B. Akinlade,  
H. Staudinger, V. Mastey, L. Eckert, A. Gadkari, N. Stahl, G.D. Yancopoulos,  
and M. Ardeleanu, for the SOLO 1 and SOLO 2 Investigators\*

# SOLO 1 & SOLO 2

## EASI: % change from baseline



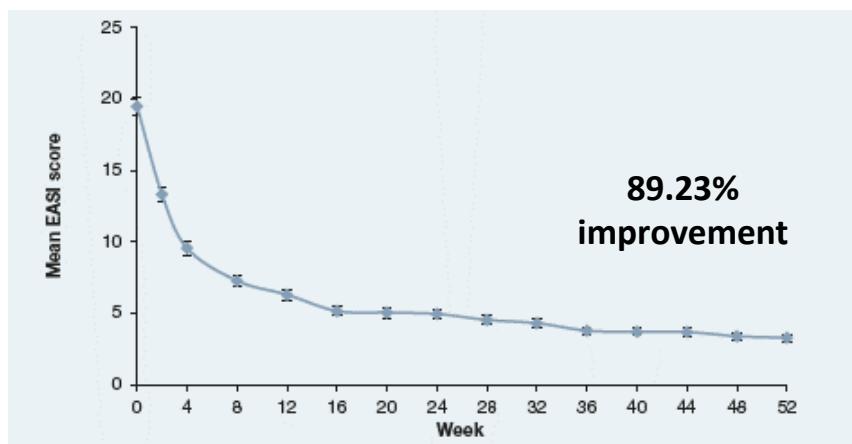
LS= least squares; SE= standard error.

- Simpson EL, et al. N Engl J Med. 2017;376:1090-1.

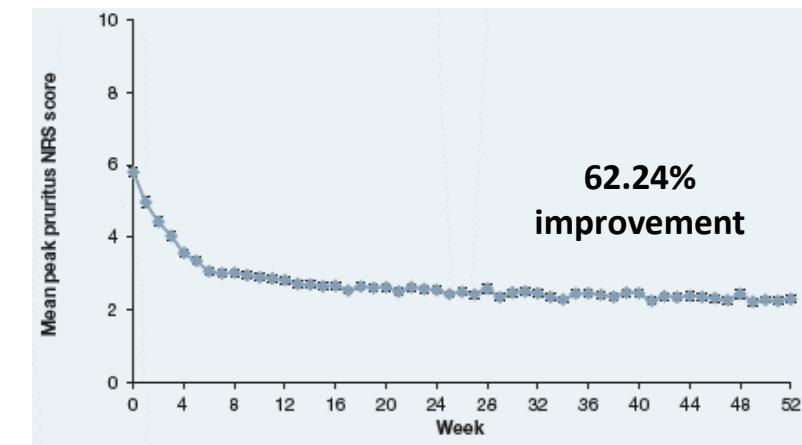
# Long-term safety and efficacy of open-label dupilumab

- 459 voksne patienter med moderat-til-svær AD behandlet open label med 300 mg dupilumab weekly i 52 uger
- Dupilumab havde langtids effect på AD og forbedrede livskvaliteten hos patienterne

Mean EASI score



Mean NRS

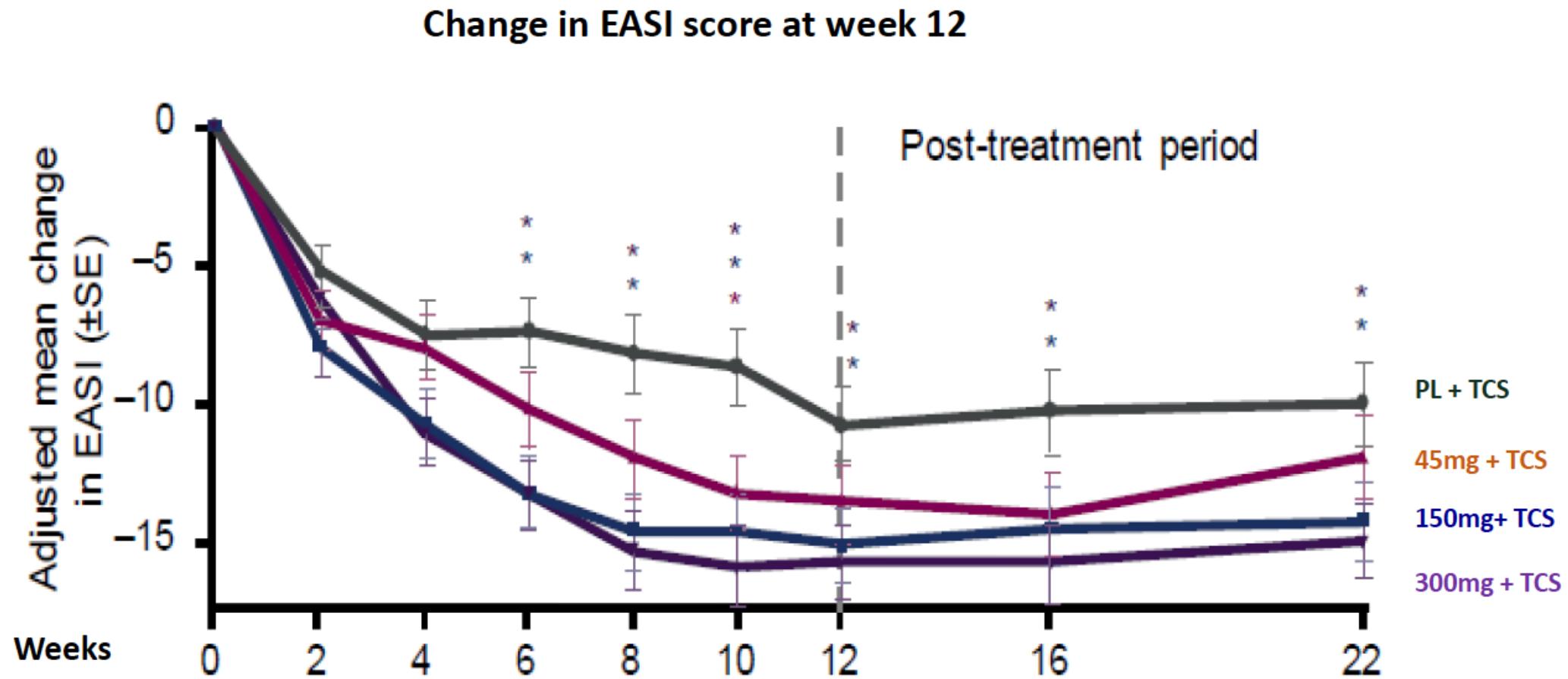


Mean EASI and peak pruritus NRS scores are shown as mean  $\pm$  SE.

EASI, Eczema Area and Severity Index; NRS, numerical rating scale; SE, standard error.

- Ingen svære bivirkninger

# Tralokinumab fase II Studie i AD



# IL-31 – Kløe cytokinet

- II
- E
- S
- S

## Experimental Dermatology

 Free Access

### Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis

- K

Øystein Grimstad, Yasushi Sawanobori, Christian Vestergaard, Janine Bilsborough, Uffe Bang Olsen,  
Christian Grønhøj-Larsen, Kouji Matsushima

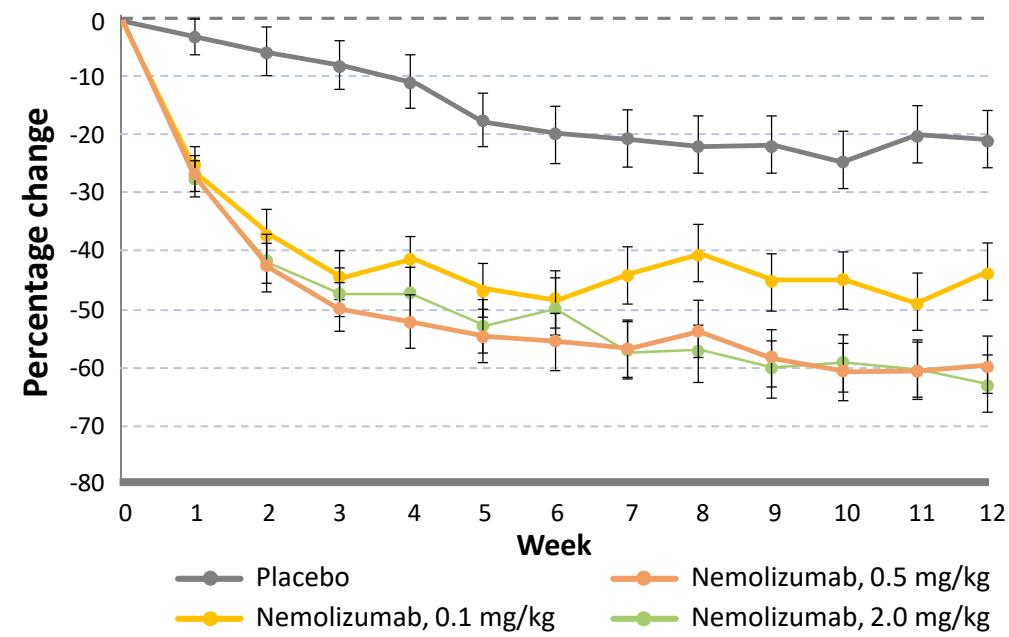
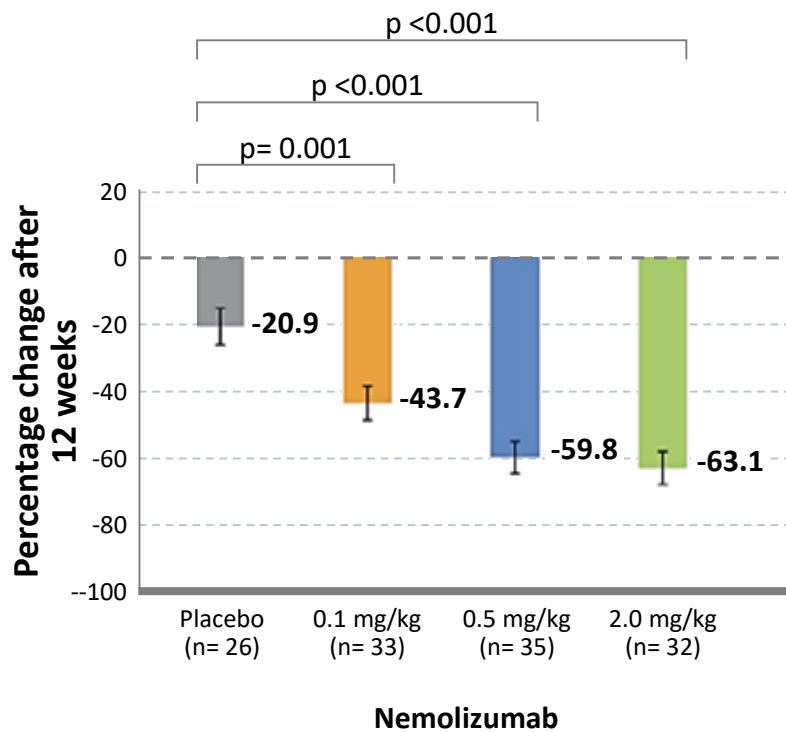
First published: 08 December 2008 | <https://doi.org/10.1111/j.1600-0625.2008.00766.x> | Cited by: 124

Cornelissen C, Luscher-Firzlaff J, Baron JM, et al. (2011) Eur J Cell Biol, Epub Oct 5  
Niyonsaba F, Ushio H, Hara M, et al. (2010) J Immunol 184: 3526-34

Cornelissen C, Marquardt Y, Czaja K, et al. (2012) J Allergy Clin Immunol 129: 426-33

Nygaard U, Hvid M, Johansen C, Buchner M, Fölster-Holst R, Deleuran M, Vestergaard C JEADV 2016.

# Nemolizumab: Effekt på kløe



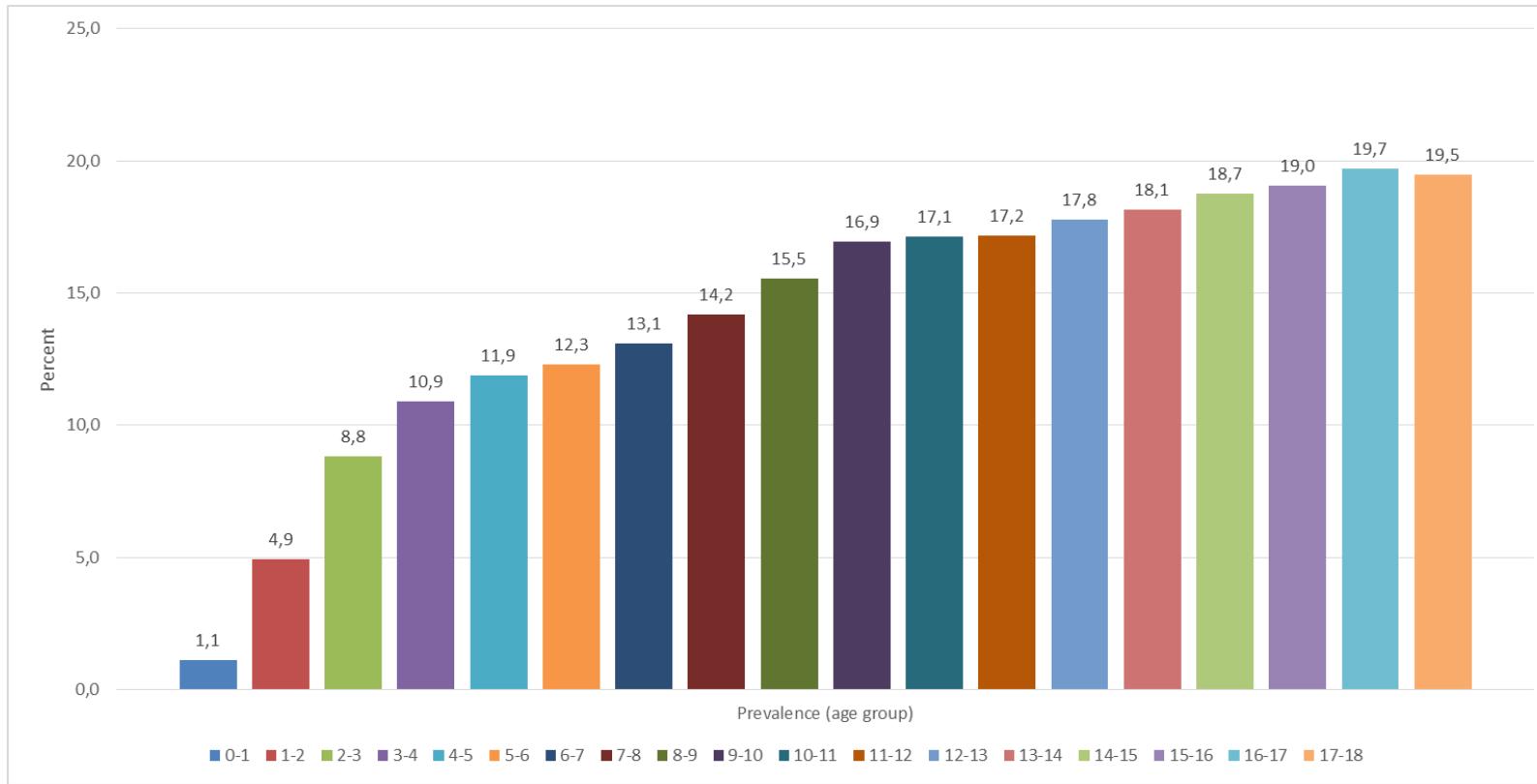
• Ruzicka T, et al. N Engl J Med 2017;376:826-35.

# AD treatment and pregnancy



Familydoctor.org

# Estimated nationwide 'AD ever' prevalence in Denmark



## More than 30 million Europeans suffer from AD

### 80 million children in EU

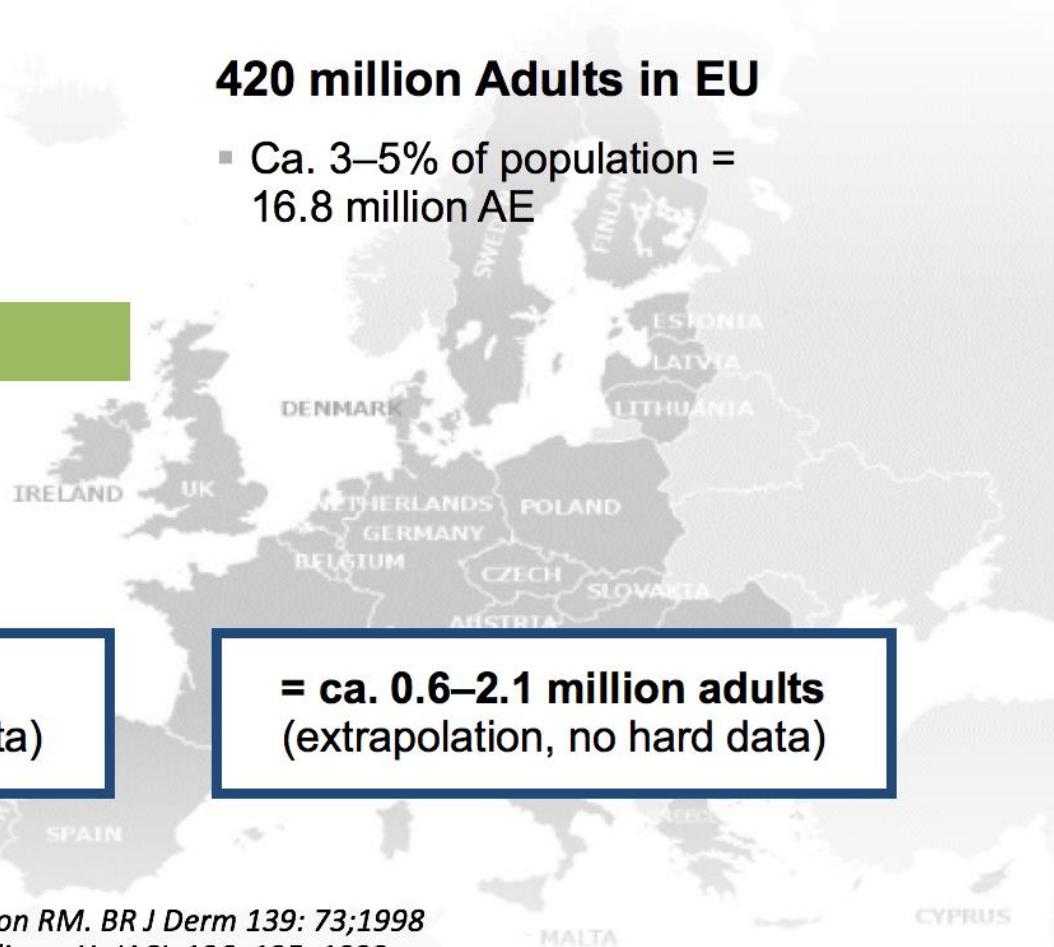
- Ca. 10–20% of population with AE = 16 million



= ca. 320,000 children  
(extrapolation, no hard data)

### 420 million Adults in EU

- Ca. 3–5% of population = 16.8 million AE



= ca. 0.6–2.1 million adults  
(extrapolation, no hard data)

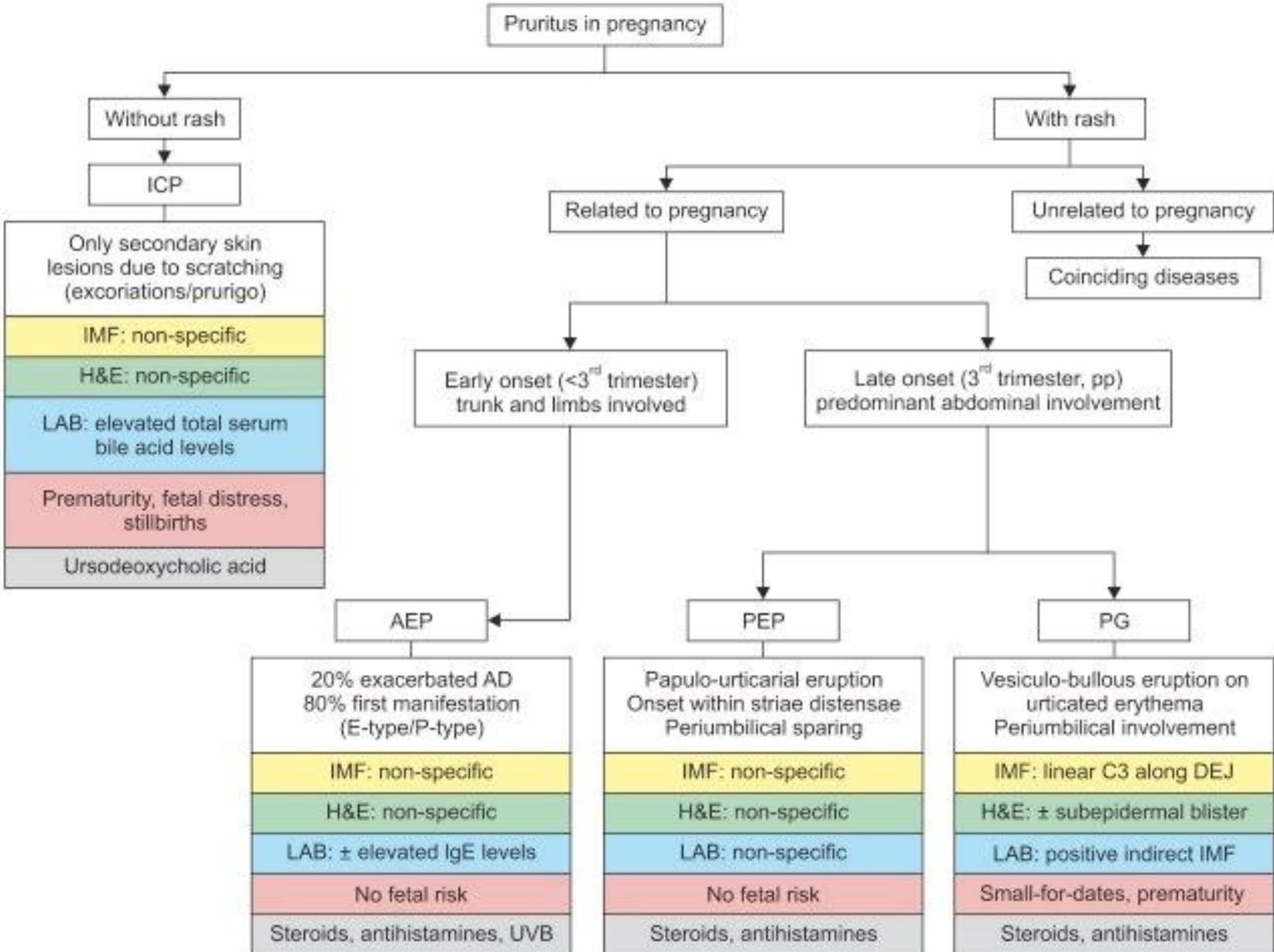
Emerson RM. *BR J Derm* 139: 73;1998

Williams H. *JACI*. 126: 125: 1999

Hanifin JM. *JACI*. 132: 1132; 2013

Silverberg J & Simpson EL. *Ped All Imm*. 5: 276; 2013

Courtesy of Prof. Jan Gutermuth

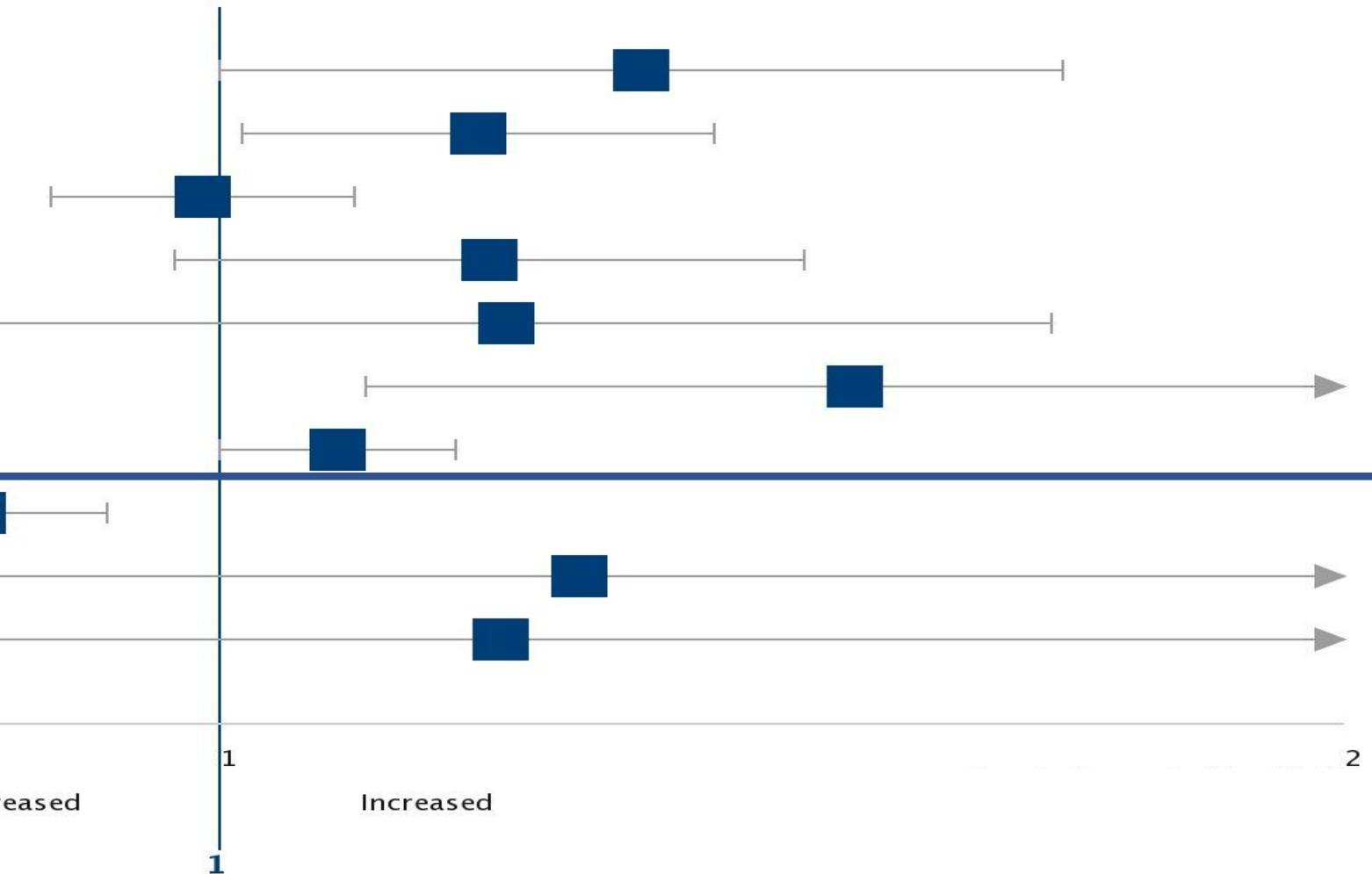


# Graviditets komplikationer og outcome ved Atopisk Dermatitis

PhD studie af Carsten Hamann, Dermatologisk Afdeling, Gentofte Hospital,  
Københavns Universitet.

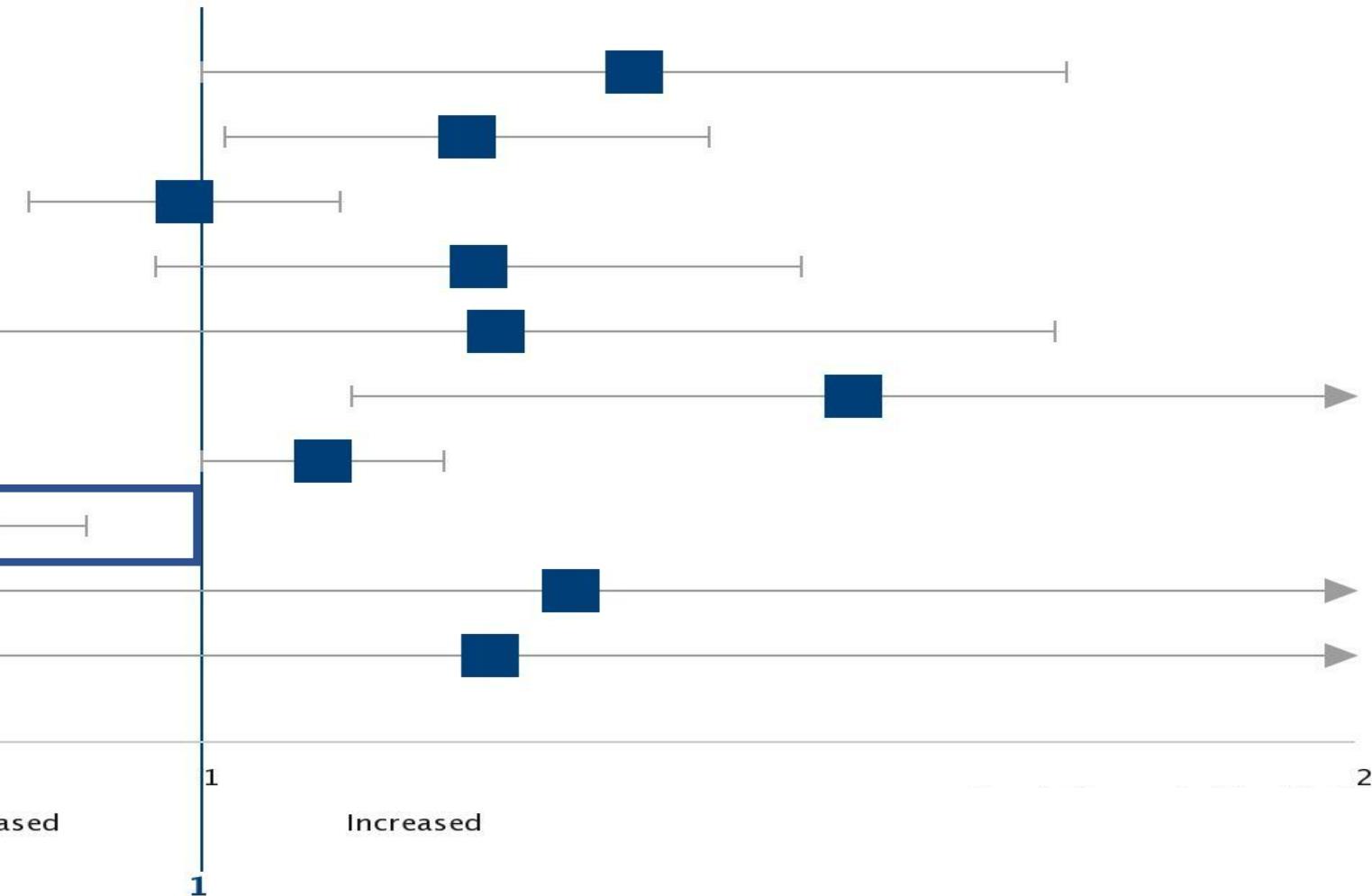
## Prenatal outcomes

Preexisting HTN complicating pregnancy



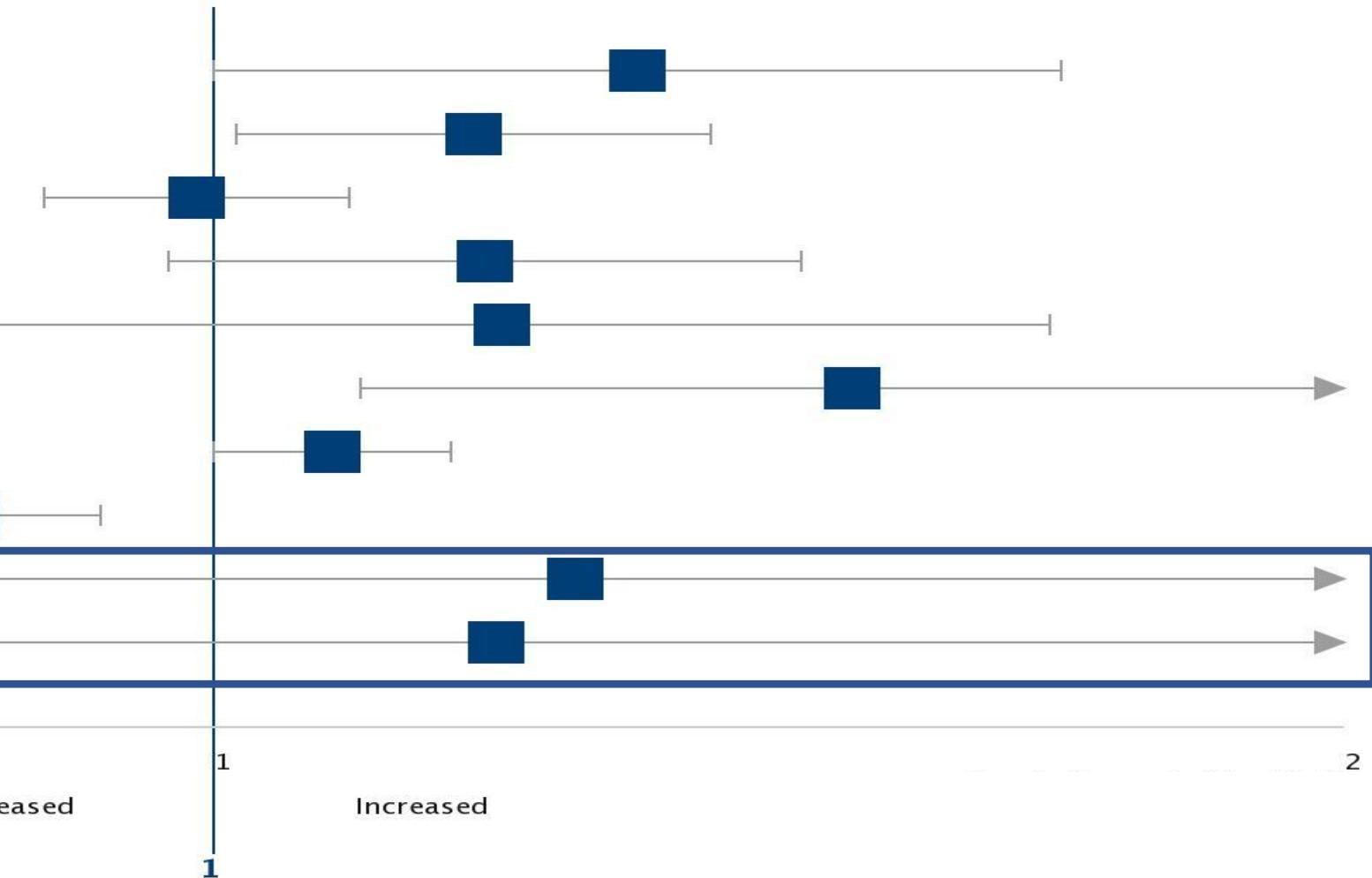
## Prenatal outcomes

Preexisting HTN complicating pregnancy

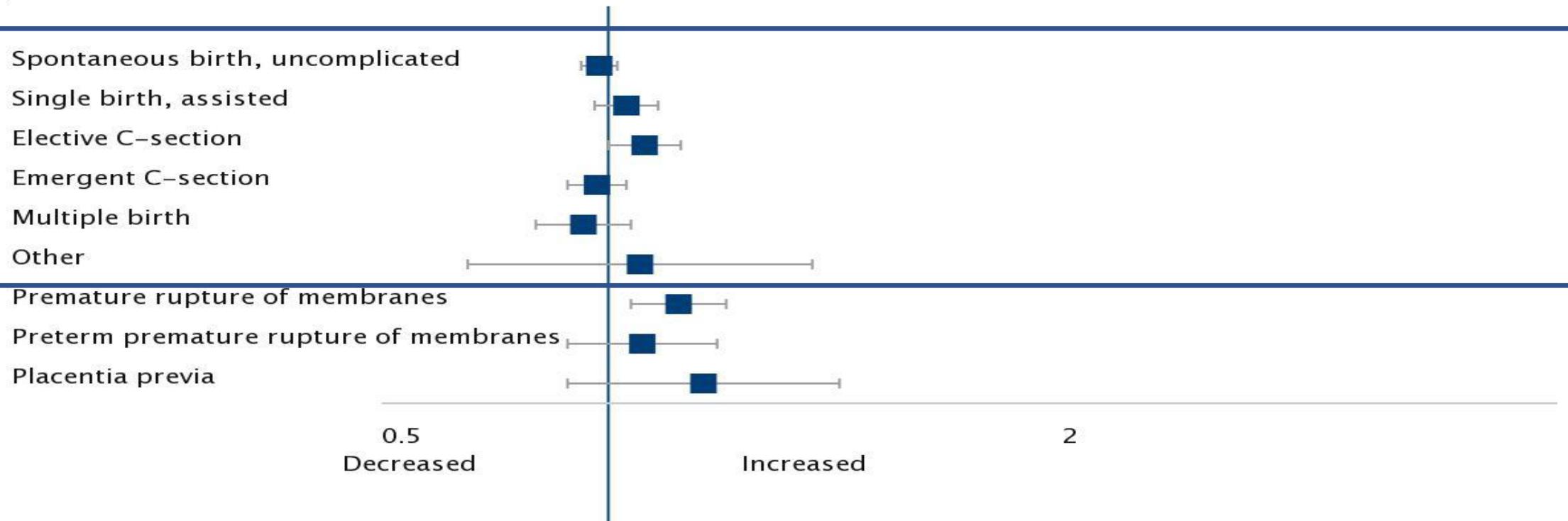


## Prenatal outcomes

Preexisting HTN complicating pregnancy



## Obstetric outcomes



## Obstetric outcomes

Spontaneous birth, uncomplicated

Single birth, assisted

Elective C-section

Emergent C-section

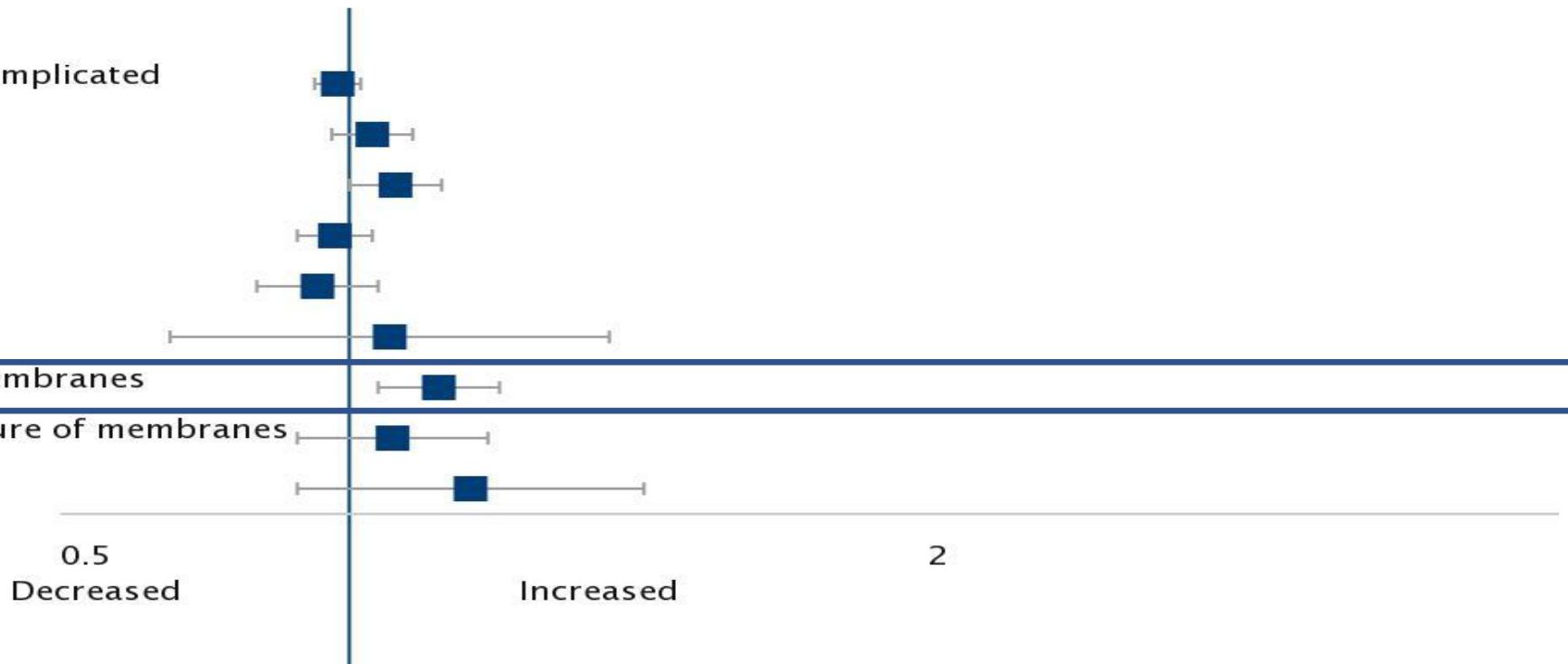
Multiple birth

Other

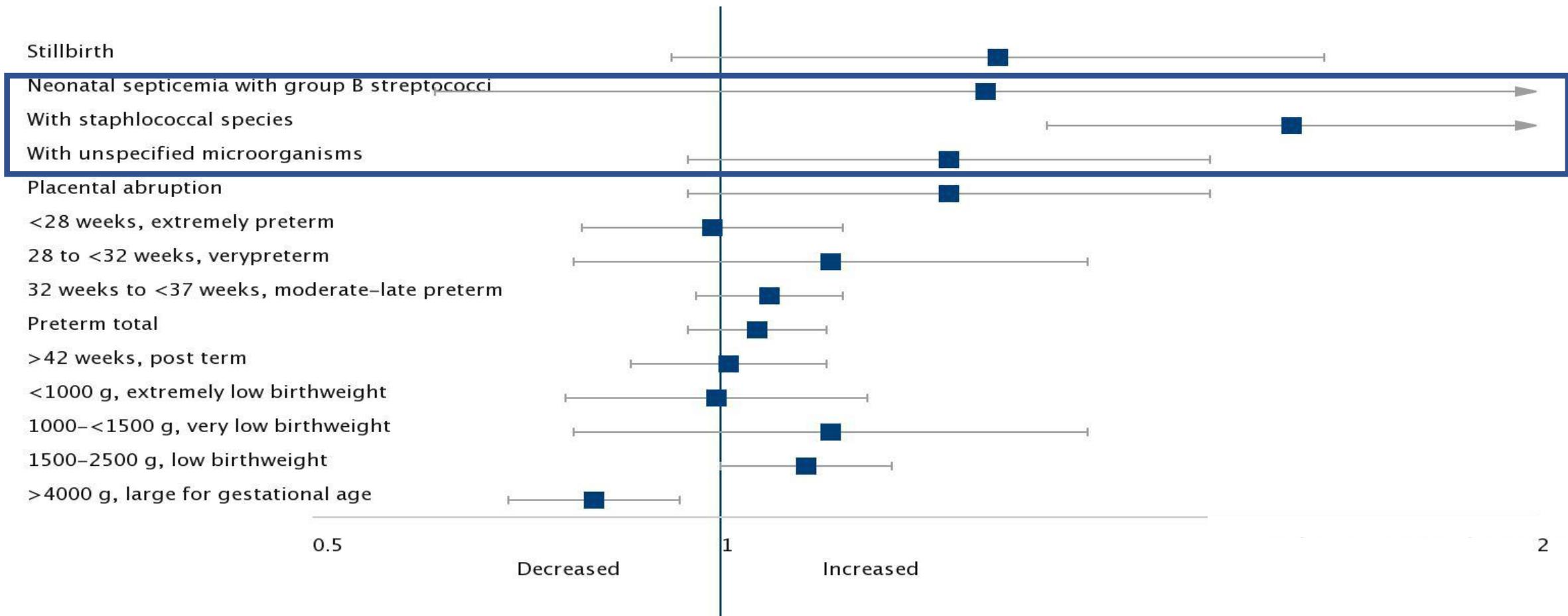
Premature rupture of membranes

Preterm premature rupture of membranes

Placenta previa

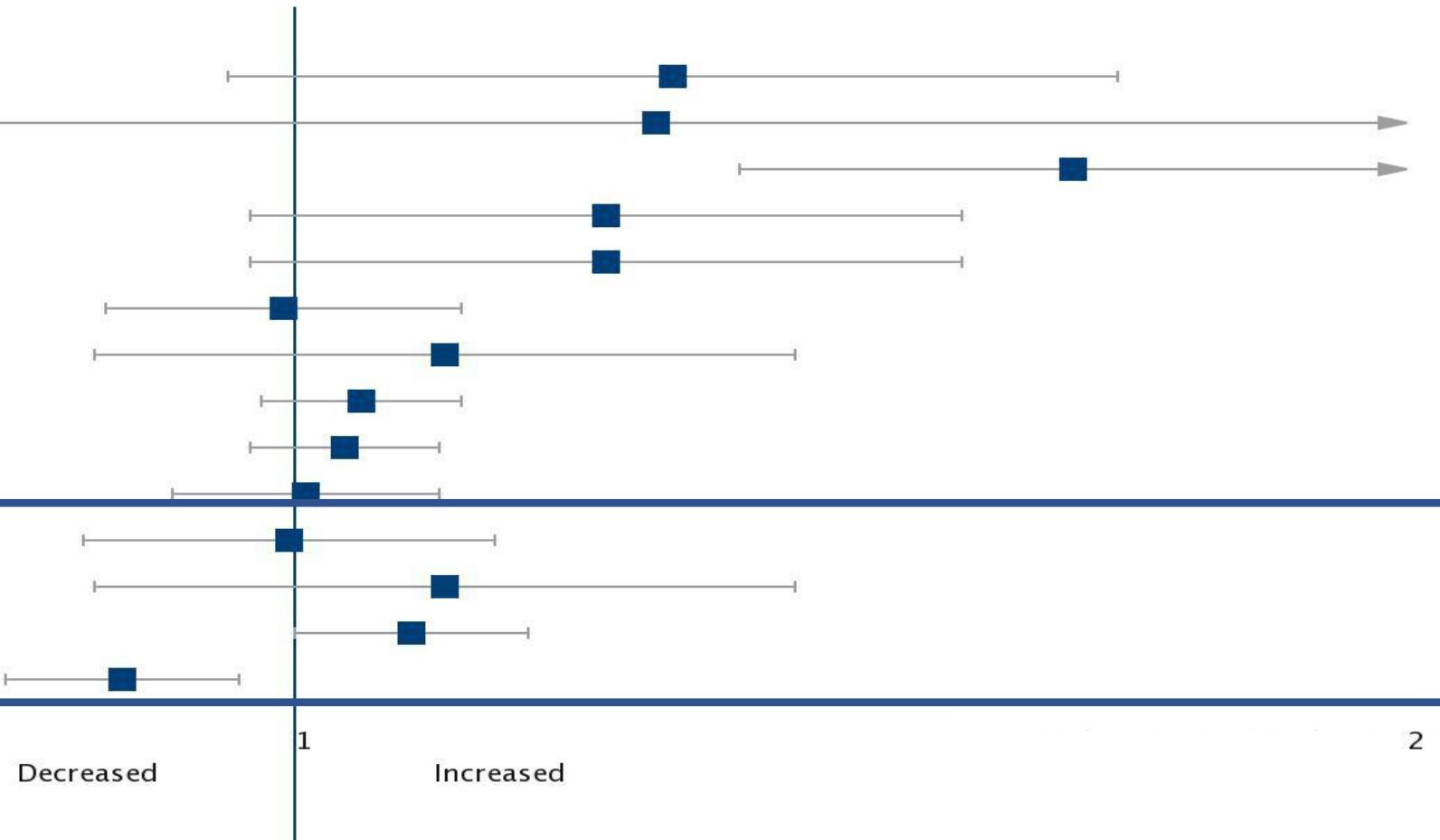


## Birth outcomes



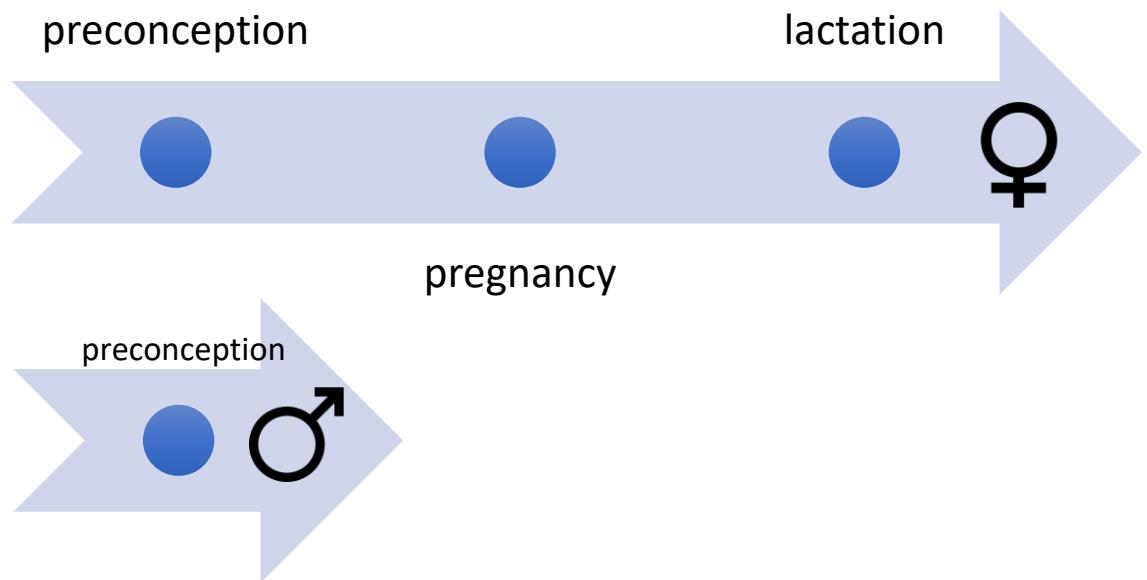
## Birth outcomes

- Stillbirth
- Neonatal septicemia with group B streptococci
- With staphylococcal species
- With unspecified microorganisms
- Placental abruption
- <28 weeks, extremely preterm
- 28 to <32 weeks, very preterm
- 32 weeks to <37 weeks, moderate-late preterm
- Preterm total
- >42 weeks, post term
- <1000 g, extremely low birthweight
- 1000–<1500 g, very low birthweight
- 1500–2500 g, low birthweight
- >4000 g, large for gestational age



# Background 1

- AD affects 15-20% of all children.
- 20% Persists or re-appears in adulthood.
- Of these 50% are women – pregnancies?
- Treatment is often forgotten or even avoided.
- Treatment of Men with AD who wish to father a child is neglected.
- Pregnancy is not a disease but a condition that demands extra care.



# Background 2

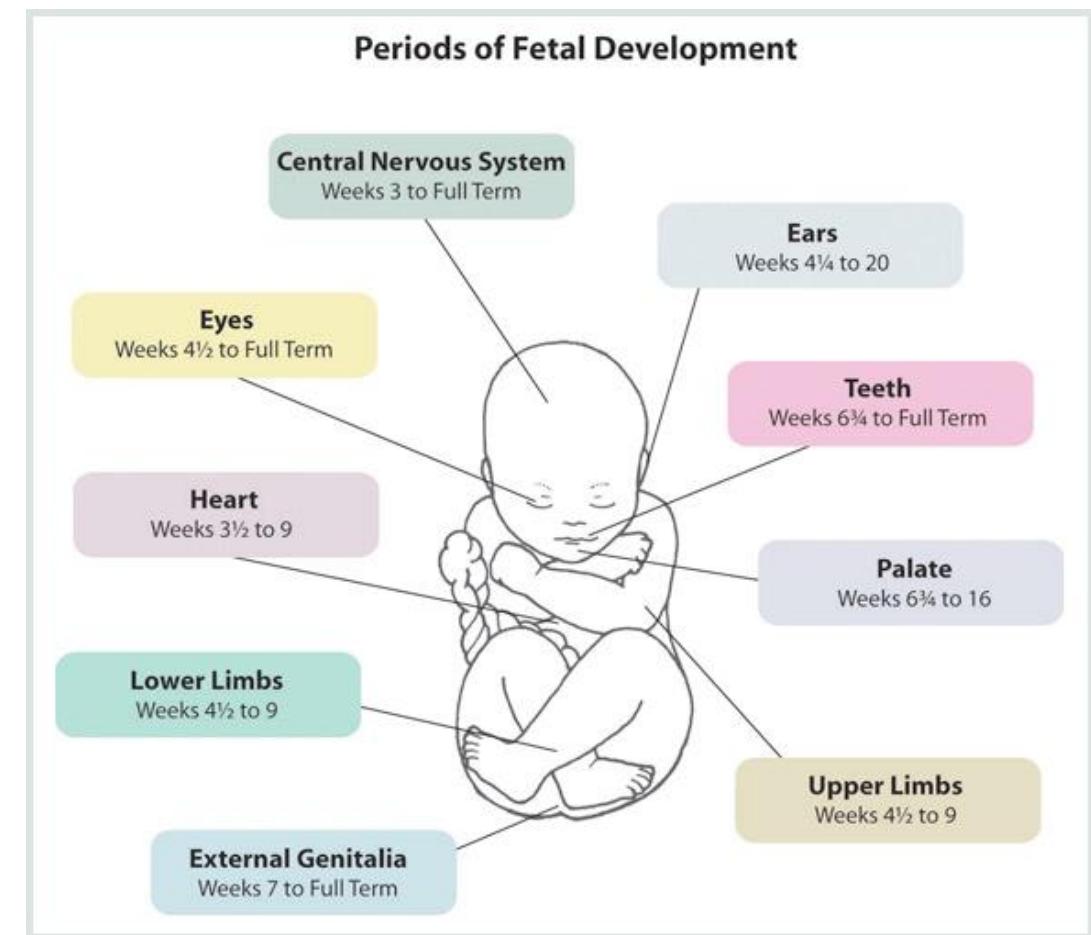
- 3.2 mill stillborn every year ( $\approx 3\%$  of all births) 5-32/100.000 birth depending on country
- 8 mill. (6%) born with serious birth defects.
  - Congenital heart defects
  - Neural tube defects
  - Downssyndrom
- 5% are due to environmental factors including
  - Airpollution, Cigarette smoking, pesticides, solvents, radiation, chemicals

Stanton C, et al. Lancet. 2006;367: 1487-1494.

Liu LC, et al Taiwan J Obstet Gynecol. 2014;53: 141-145

Baldacci S, et al Epidemiol Prev. 2018;42: 1-34.

Morris JK et al PLoS One. 2018;13



[www.drugs.ie](http://www.drugs.ie)

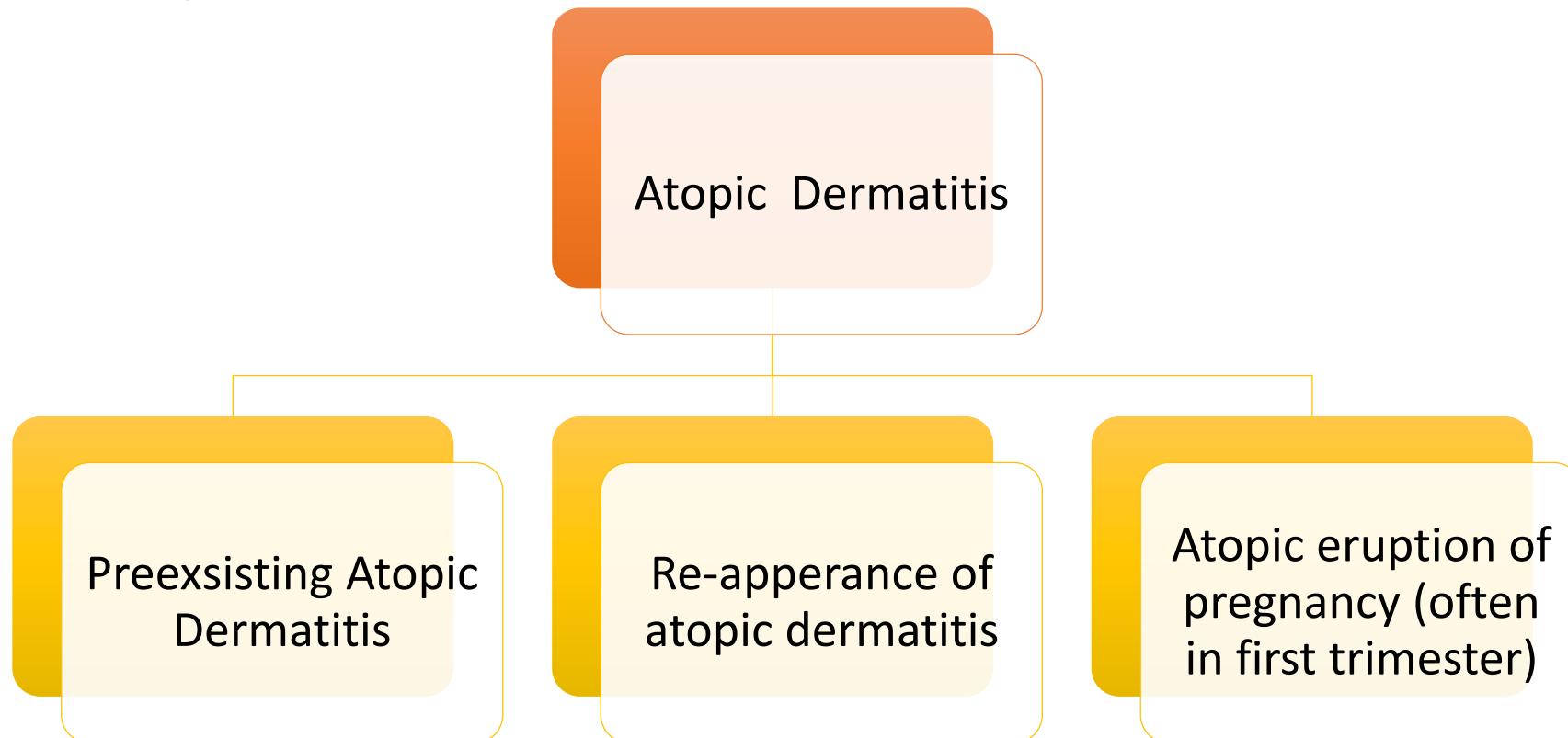
**POSITION STATEMENT****European task force on atopic dermatitis position paper:  
treatment of parental atopic dermatitis during  
preconception, pregnancy and lactation period**

C. Vestergaard<sup>1,\*†</sup> A. Wollenberg,<sup>2,3,†</sup> S. Barbarot,<sup>4</sup> S. Christen-Zeuch,<sup>5</sup> M. Deleuran,<sup>1</sup> P. Spuls,<sup>6</sup> C. Flohr,<sup>7</sup> M. Trzeciak,<sup>8</sup> L. von Kobyletzki,<sup>9</sup> J. Seneschal,<sup>10</sup> C. Paul,<sup>11</sup> T. Bieber,<sup>12</sup> T. Werfel,<sup>13</sup> R. Fölster-Holst,<sup>14</sup> U. Darsow,<sup>15</sup> U. Gieler,<sup>16</sup> Å. Svensson,<sup>9</sup> M. Cork,<sup>17</sup> J.-F. Stalder,<sup>4</sup> L. De Raeve,<sup>18</sup> B. Kunz,<sup>19</sup> D. Simon,<sup>20</sup> P. Chernyshov,<sup>21</sup> D. Hijnen,<sup>22</sup> C. Gelmetti,<sup>23</sup> J. Ring,<sup>15,24</sup> A. Taieb,<sup>10</sup> M. de Bruin-Weller,<sup>25</sup> J.P. Thyssen<sup>26</sup>

# Clinical presentation



Atopicdermatitis.net



# Topical cortico-steroids

- 1st line treatment
- Worries:
  - Orofacial cleft
- Studies
  - Cochrane review of 14 studies including 1.601.515 pregnancies
  - No association with preterm delivery, birth defects, low APGAR
  - Non significant association with low birth weight

## Topical corticosteroids

Women	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis
Pregnant		TCS class II or III are recommended. If the use exceeds 200 g/month, additional UV treatment should be considered. Class IV may be used as rescue therapy, or over longer periods on limited skin areas. Fluticasone propionate should be avoided.
Lactating		Should be applied immediately after breastfeeding, and nipples should be cleaned gently and carefully before feeding.
Men	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis

# Topical Calcineurin Inhibitors (TCI)

- No studies on the effect in pregnancies.
- Recommendation based the following.
  1. No systemic absorption of tacrolimus (except Nethertons sdr.)
  2. The use of tacrolimus and CyA in organ transplant women showed no association with congenital malformations, but increased risk of prematurity – which was attributed to maternal disease.
  3. Pimecrolimus has not been studied

## Topical Calcineurin inhibitors

Women	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis
	Pregnant	No restrictions compared to the ETFAD position paper on atopic dermatitis
	Lactating	Should be applied immediately after breastfeeding, and nipples should be cleaned gently and carefully before feeding
Men	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis

The recommendation is for tacrolimus since there is not ample data for pimecrolimus available.

# Topical antiseptics and antibiotics

- Very poor evidence
- Evidence is indirectly i.e. Octenindin used for bacterial vaginosis in pregnancy without any associated diseases.
- Triclosan is a known endocrine hormone disrupter in rats.

- Topical fucidic acid may be used.
- Aminoglycosides should be avoided

## UV therapy

No restriction apart from the normal use  
No evidence for extra use of folic acid.

# Systemic immuno suppressants

## Methotrexate

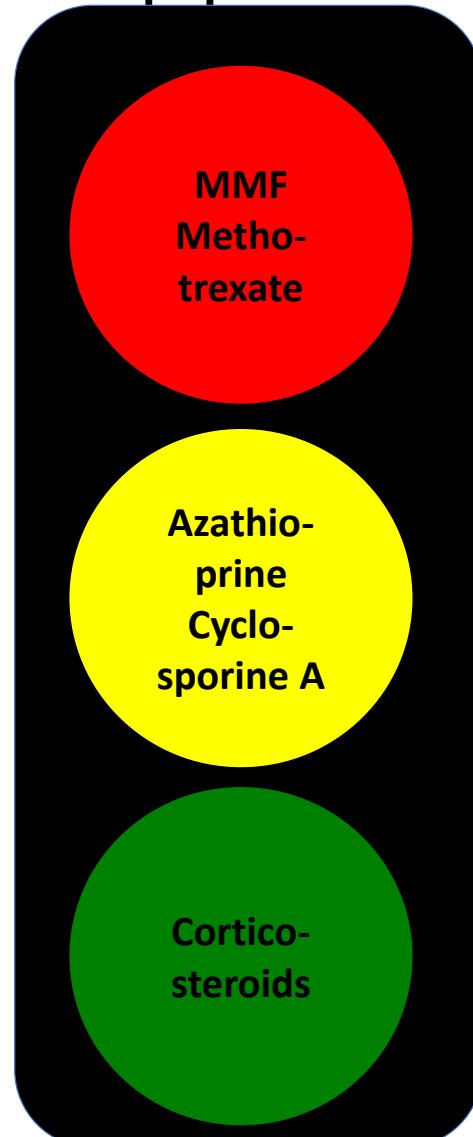
Women	Preconceptive	Therapy must be stopped 6 months prior to desired time of conception if no local/national guideline exists. Local/National guidelines supersedes this recommendation
	Pregnant	Contraindicated
	Lactating	Contraindicated
Men	Preconceptive	Therapy must be stopped 3 months prior to desired time of conception

## Azathioprine

Women	Preconceptive	May be used
	Pregnant	May be used under strict indications if no other therapy is possible. It is not recommended to initiate therapy during pregnancy where other therapies should be used.
	Lactating	May be used, but it is recommended to discard milk produced within 4 hours after drug intake.
Men	Preconceptive	No restrictions.



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## Mycophenolate mofetil

Women	Preconception	Therapy must be stopped 3 months prior to desired time of conception
	Pregnancy	Contraindicated
	Lactating	Contraindicated
Men	Preconception	Therapy must be stopped 3 months prior to desired time of conception

## Cyclosporine A

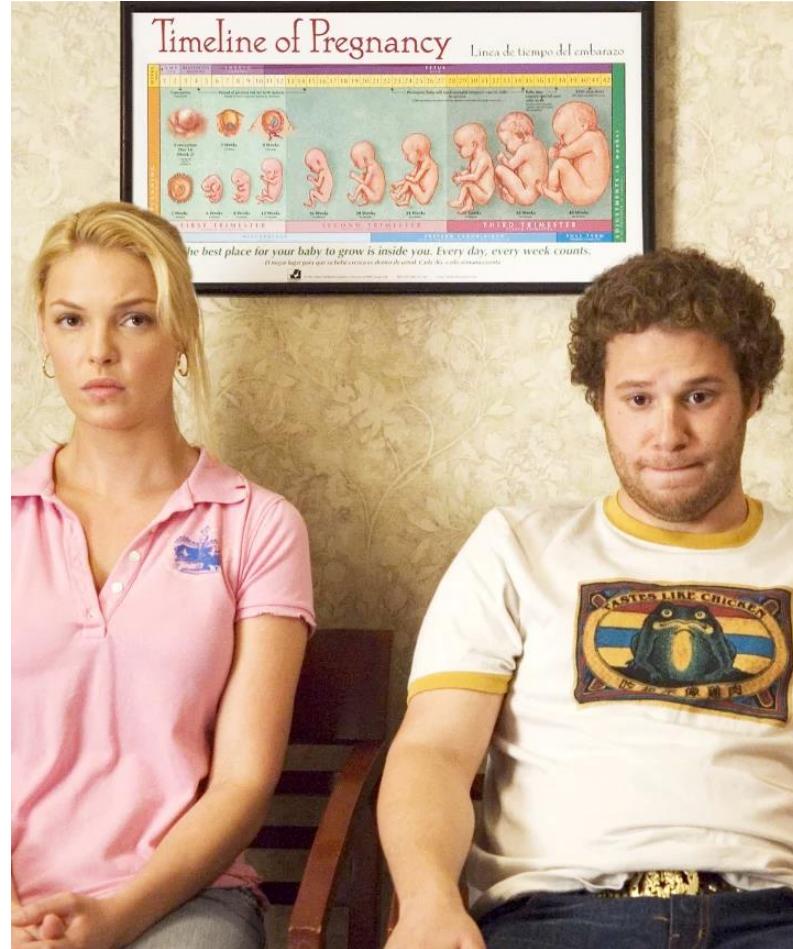
Women	Preconceptive	May be used
	Pregnant	May be used under strict indications, is first-line therapy for long-term control
	Lactating	May be used under strict indications
Men	Preconceptive	No restrictions

## Systemic corticosteroids

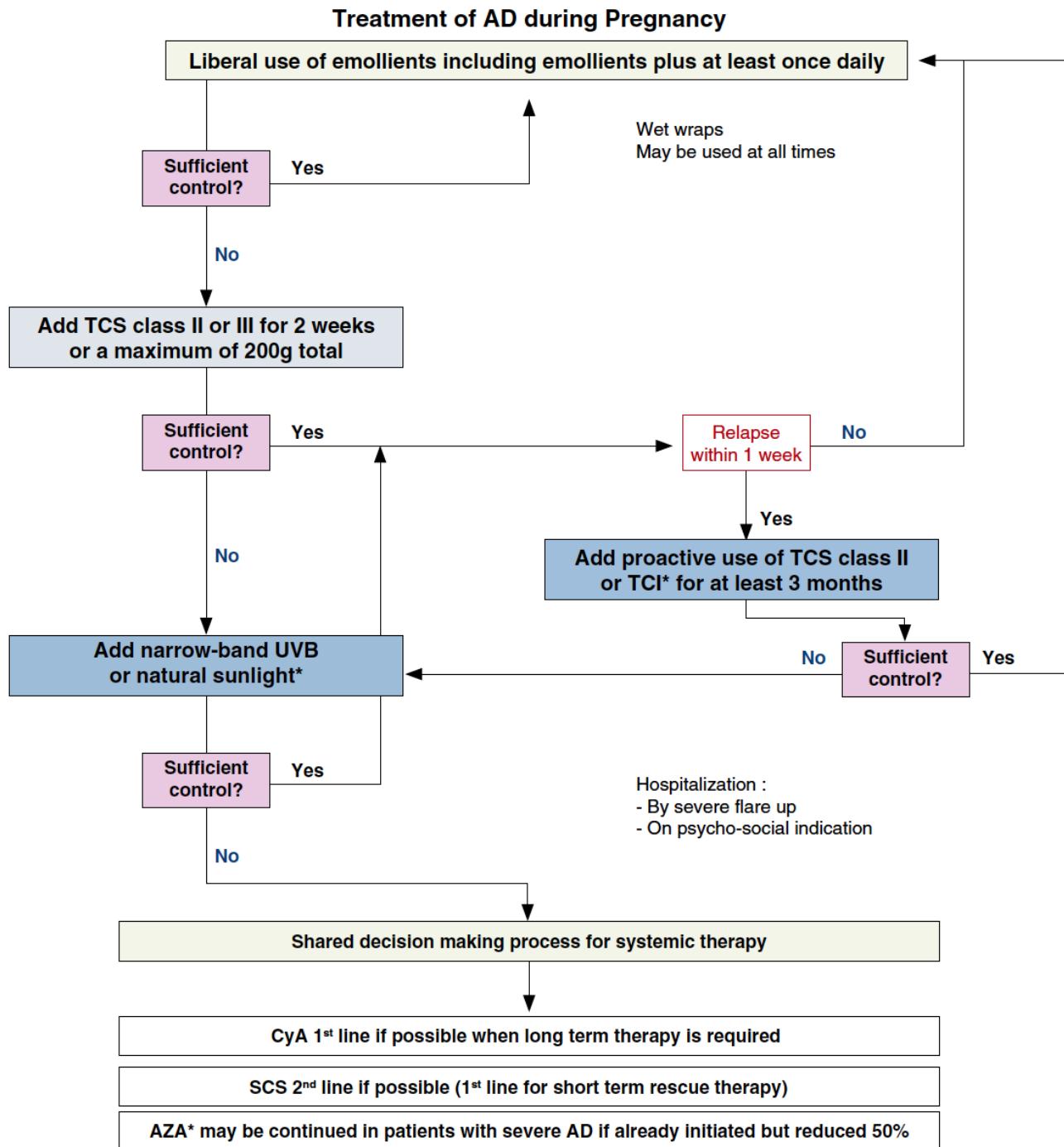
Women	Preconceptive	May be used as rescue therapy, or as bridging until effect of other systemic or biological medicaments
	Pregnant	May be used as rescue therapy, or for short periods of time (2–3 weeks), not exceeding 0.5 mg/kg/day. Prednisolone is the preferred drug
	Lactating	May be used as rescue therapy
Men	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis

# Unplanned pregnancy

- It is crucial to have the patient well informed.
- In case of MMF or MTX women of childbearing potential should also start efficient contraceptive treatment
- In case of pregnancy
  - Stop treatment
  - Intensify topical treatment
  - Refer to obstetrician and teratology information center.



Universal Pictures



Klar til AD ambulatoriet?

