Rigshospitalet
Juliane Marie Centret

# Prader-Willis syndrom

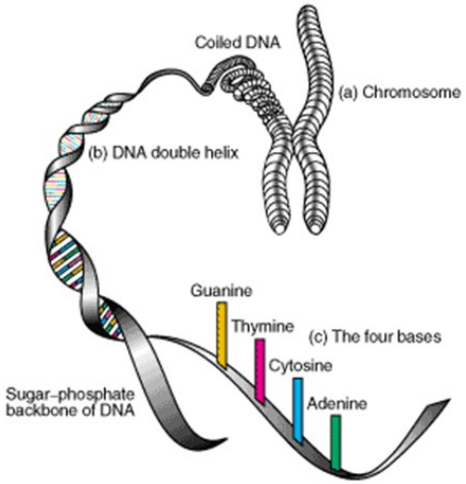
# - why do WE not GOVY?

Sjældne-symposion, 27. februar 2026

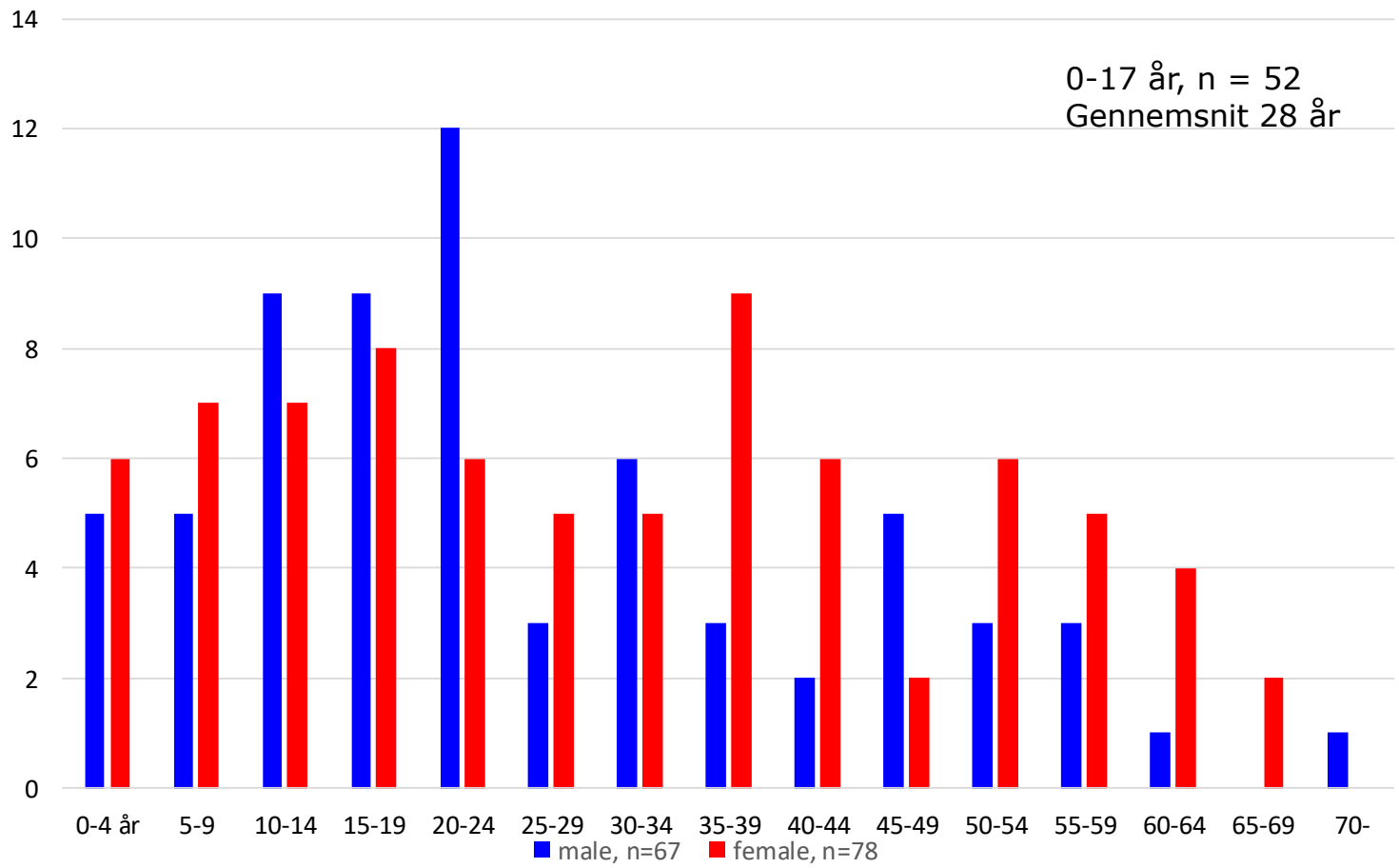
Stense Farholt

# Prader-Willis syndrom (PWS)

- Beskrevet i 1956
- Sporadisk
- Genetisk, 15q
- Sjælden
  - P = 1 : 21.000
  - I = 2-3 pr år i DK
- Ingen kønsforskel
- Ingen raceforskel
- ~ 180 i Danmark




# DK: Alder og køn, n = 145, november 2025



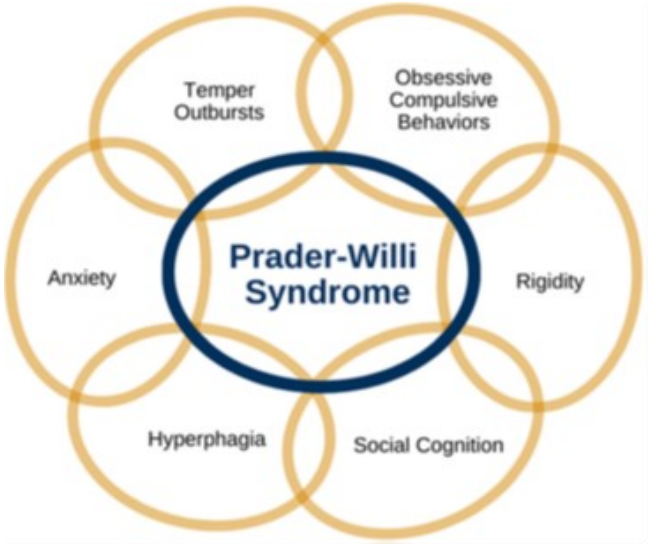
# Prader-Willis syndrom

- **Udseende**
- **Global udviklingshæmning**
  - Neonatal hypotoni
  - Forsinket motorisk udvikling
    - Går ca 2½ år gamle
  - Kognitivt
    - median IQ 63
  - Sprog
- **Endokrinopatier**
  - Væksthormonmangel
    - Vækstthæmning og abnorm body composition
  - Kønshormonmangel
    - Hypogonadisme
  - Andre?
- **Adfærd …..**



Driscoll et al. Genereviews.org, 2024

# ”The PWS behavioural phenotype”




**Hyperphagia**: intense persistent sensation of hunger accompanied by food preoccupations, an extreme drive to consume food, food-related behavior problems, and a lack of normal satiety

**Temper outbursts**: highly explosive episodes in which the person with PWS becomes very angry or upset in a way that seems excessive for the situation and also beyond the person's control

**Anxiety:** excessive worry and tension often related to schedules/ routines, food planning or food security, persons/items of special interest and excessive concerns about the possibility of change

**Obsessive compulsive behaviors:** repetitive, ritualistic behaviors, collecting and hoarding items, insistence on "sameness," need to know, ask, or tell

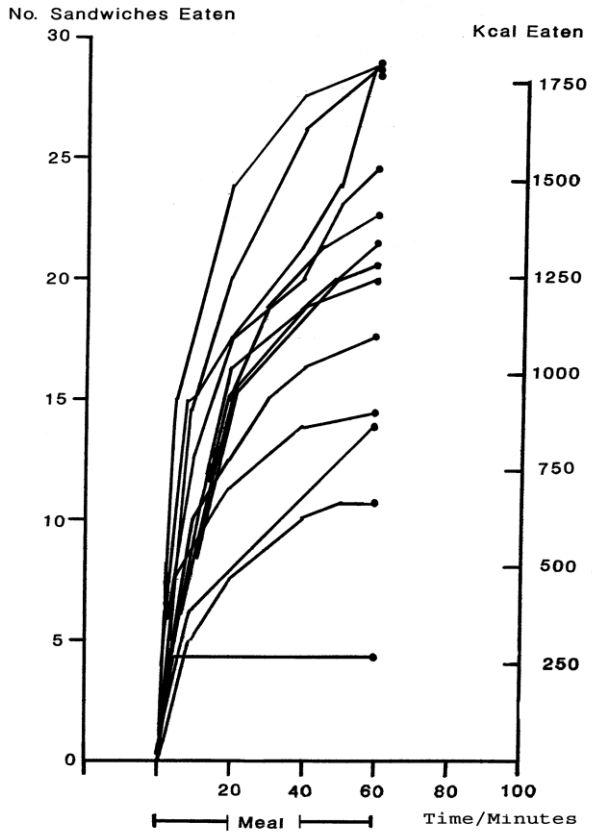
**Rigidity**: ardent inflexibility with certain routines, concepts, or ways of thinking; vigorous resistance to change; black and white thinking

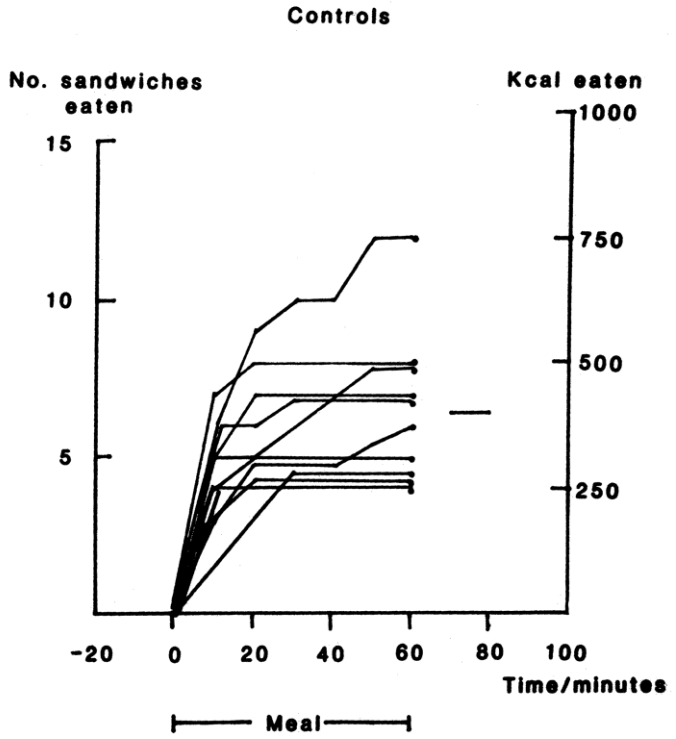
**Social cognition:** difficulties relating to others, challenges with reciprocal social communication, recognizing others' emotions, empathy and accurate interpretation of social cues.



Schwartz et al J Neurodevelopmental Disorders 2021

# Hyperfagi - ”sandwich-studiet”

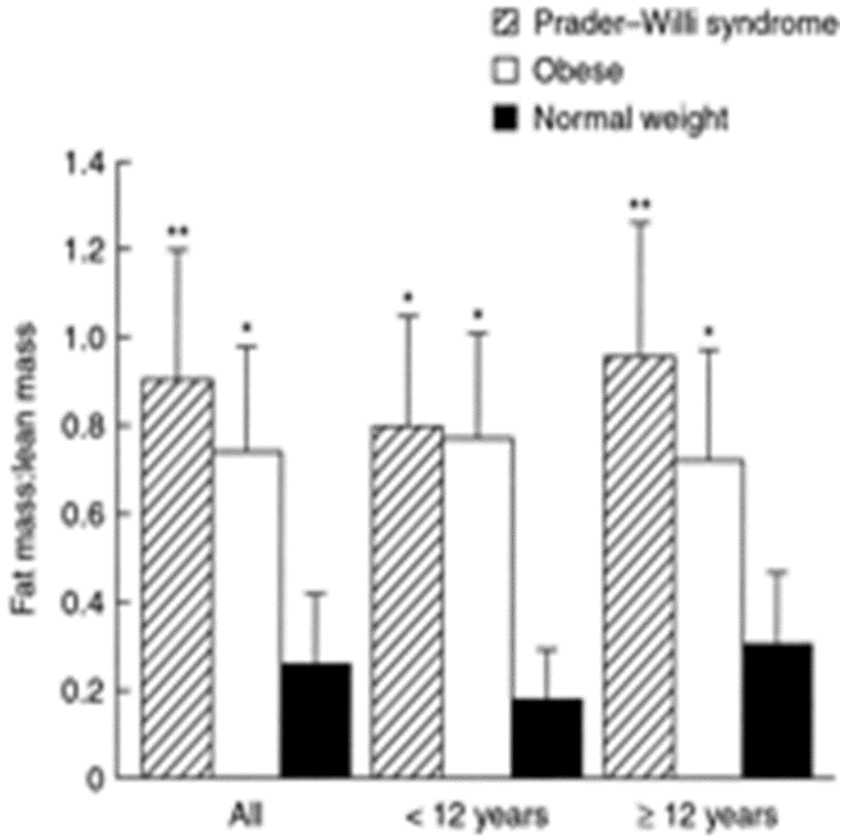



Stense Farholt

Holland et al., 1993. Int J Obesity 17:527-532

# PWS & kropssammensætning

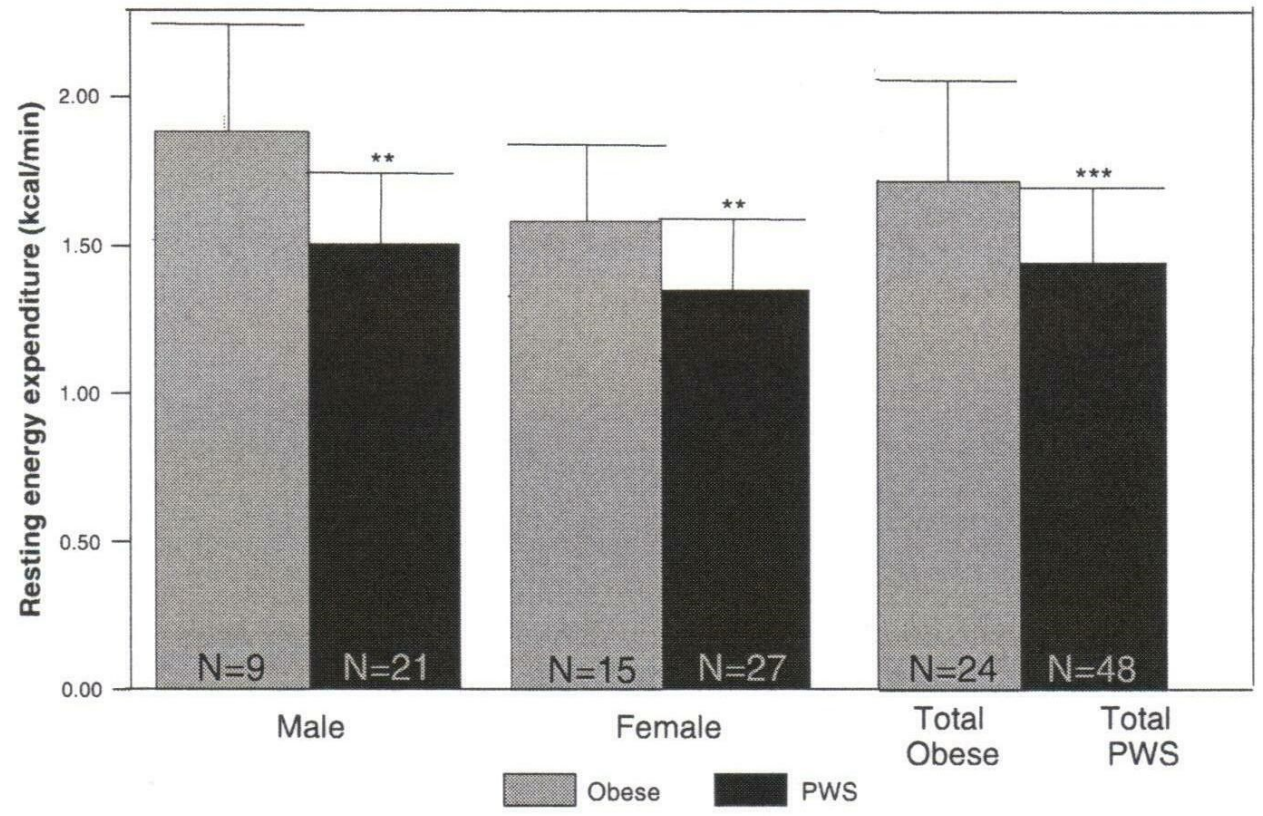



- Abnorm kropssammensætning
  - Høj fedtmasse
  - Lav muskelmasse
- Det gælder også de slanke



Burman et al. Endocrine Reviews, 2001; 22: 787-799
Höybye et al. J Clin Endocrinol Metab, 2002; 87:3590-3597

# Hvile-energiforbrug nedsat






Butler et al. Am J Med Genet 2007;143A:449-459

# Bodycomposition and resting metabolic rate

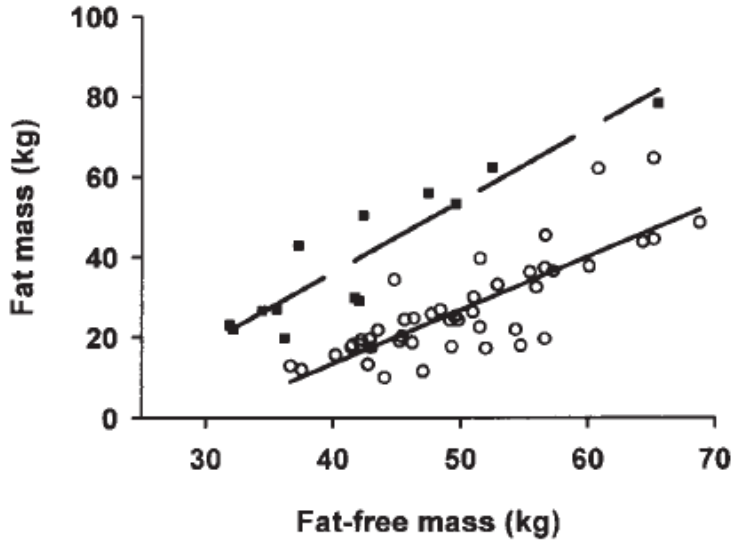



**FIGURE 1.** Relation between fat mass and fat-free mass measured by whole-body magnetic resonance imaging in healthy control women (○, solid regression line) and in female patients with Prader-Willi syndrome (■, dashed regression line). $r = 0.92$ ($P < 0.001$) in the PWS group and 0.81 ($P < 0.001$) in the control group.

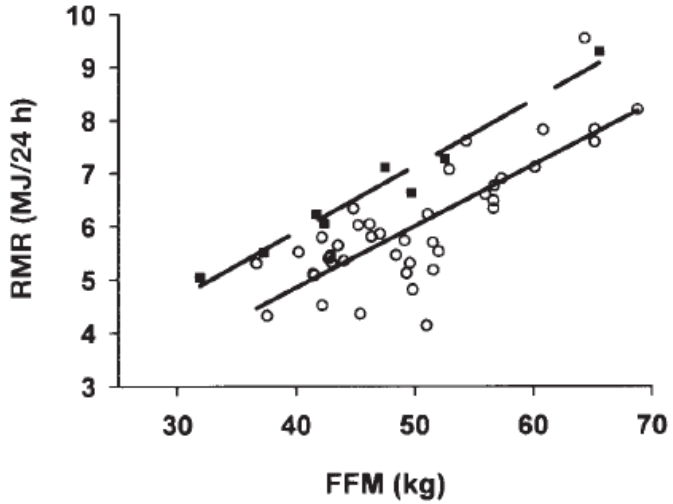



**FIGURE 2.** Relation between resting metabolic rate (RMR) and fat-free mass (FFM) measured by whole-body magnetic resonance imaging in healthy control women (○, solid regression line; $n = 41$) and in female patients with Prader-Willi syndrome (■, dashed regression line; $n = 8$). $r = 0.98$ ($P < 0.001$) in the PWS group and 0.80 ($P < 0.001$) in the control group.



Goldstone. Am J Clin Nutr, 2002

# Den allervigtigste behandling!!

- Kaloriebehov
  - 60-90% af det normale
  - Aftalt mængde. KAN ikke afviges
- Gode råd
  - Sunde kostvaner fra starten
  - Kostplan, når den øgede madlyst viser sig
  - CSS-diætist
  - Følg de officielle kostråd

Stense Farholt

https://foedevarestyrelsen.dk/kost-og-foedevarer/alt-om-mad/de-officielle-kostraad

# Den allervigtigste behandling!!

- Kaloriebehov

**Hvis hyperfagien ikke kontrolleres, vil det føre til (ekstrem) fedme, helbredsproblemer og i værste fald død**

- Sunde kostvaner fra starten
- Kostplan, når den øgede madlyst viser sig
- CSS-diætist
- Følg de officielle kostråd

Stense Farholt

https://foedevarestyrelsen.dk/kost-og-foedevarer/alt-om-mad/de-officielle-kostraad

# Hvad frarådes?


Stense Farholt

# Kostkontrol → Adfærdsregulering

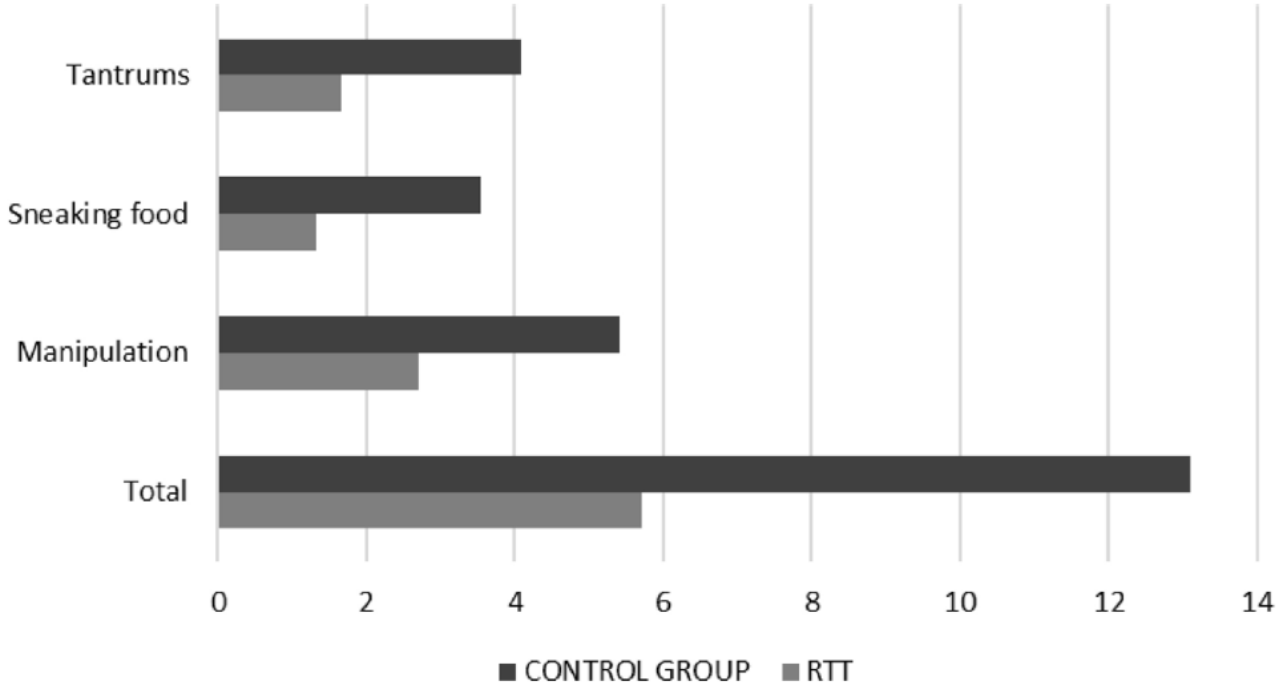
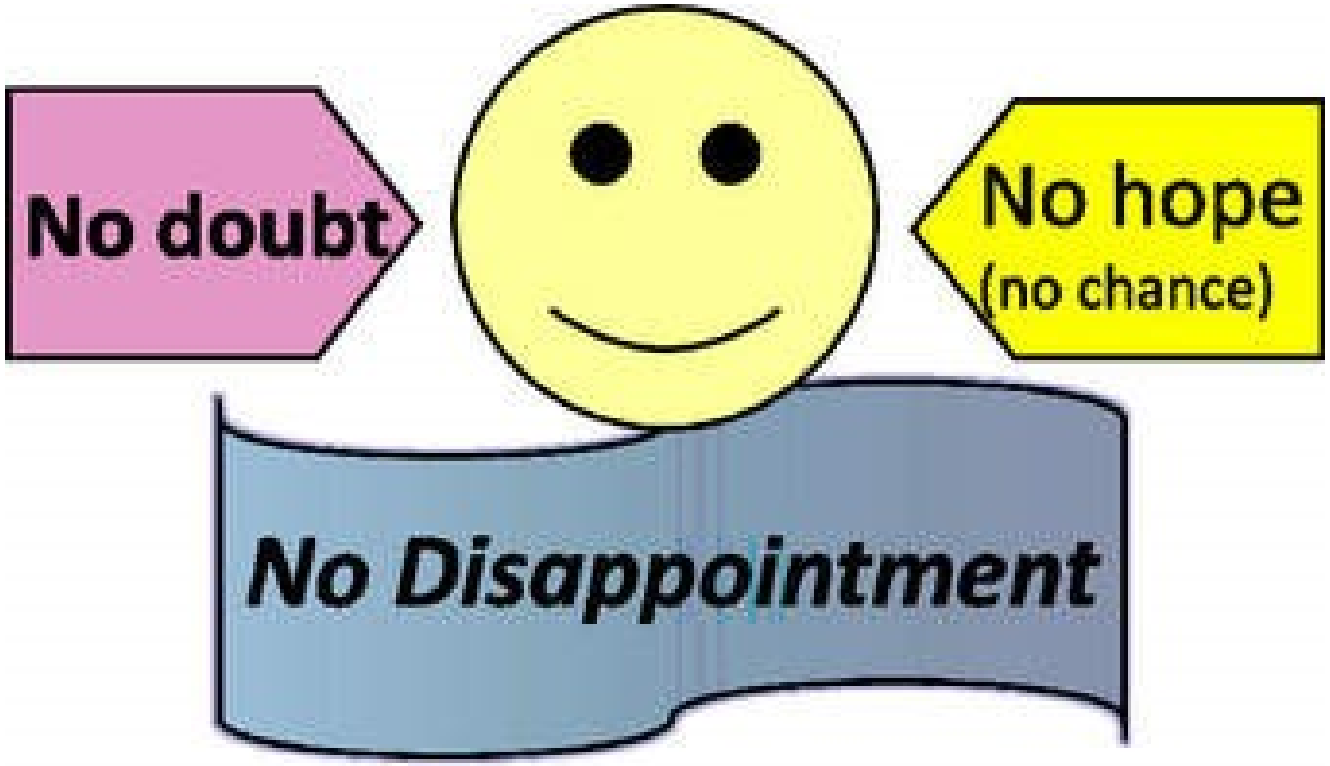



**Figure 1** Behaviours related to hyperphagia in individuals with PWS under regular transdisciplinary treatment (RTT) compared to a control group without RTT.



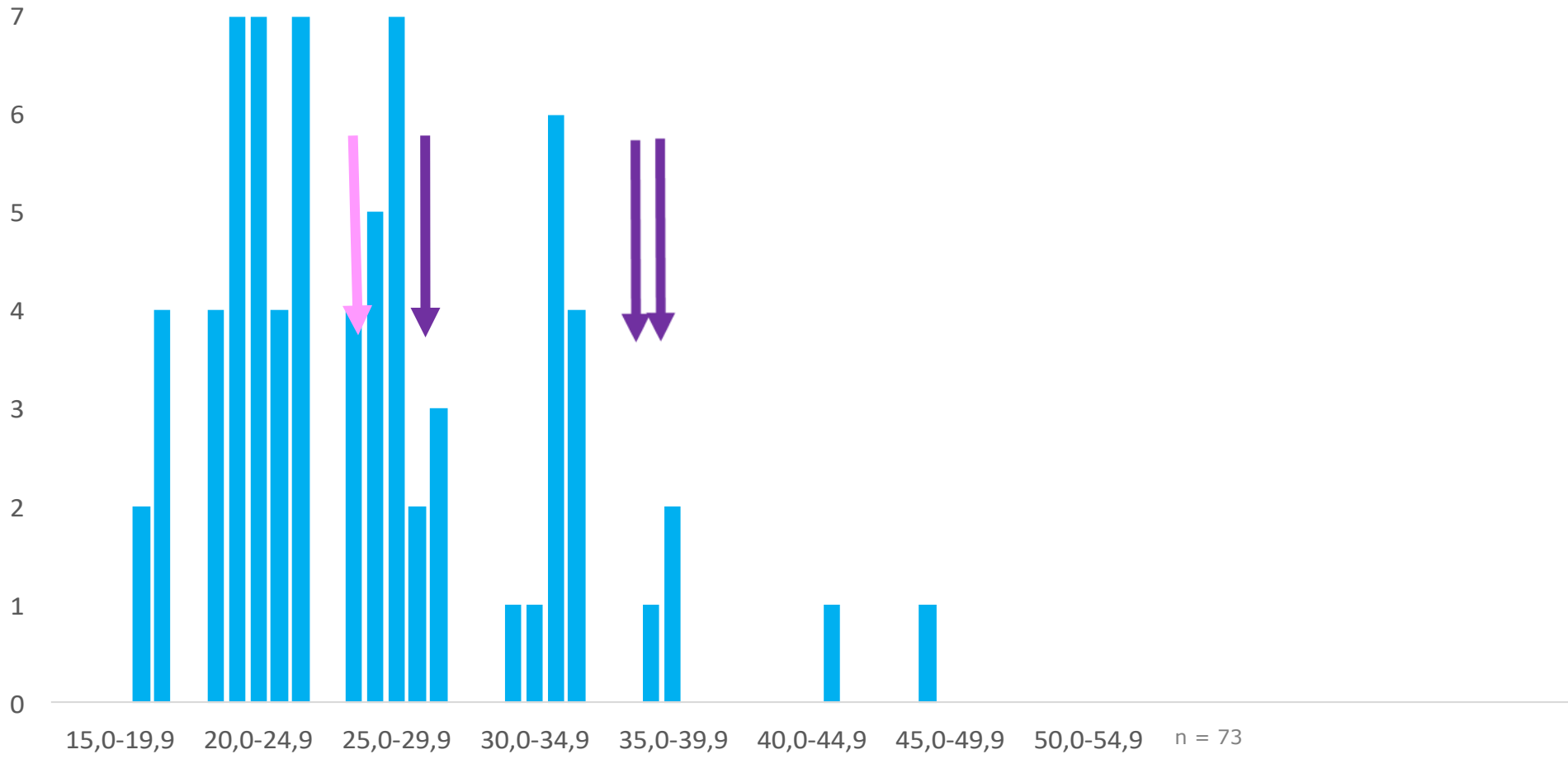
2023 Pedemonti et al

# Ingen ”huller i stakittet”



# BMI in adult PWS in DK

Median 24,9 and mean 26,05 kg/m$^2$




Sode-Carlsen et al 2010
Farholt et al, unpublished. Opgjort 2016

34,4 (n=72), Dykens, 2007
34,7 (n=38), Mogul, 2008
34,1 (n=22), Kido 2012
29,2 (n=22), Hirsch, 2014

# Hypothalamus

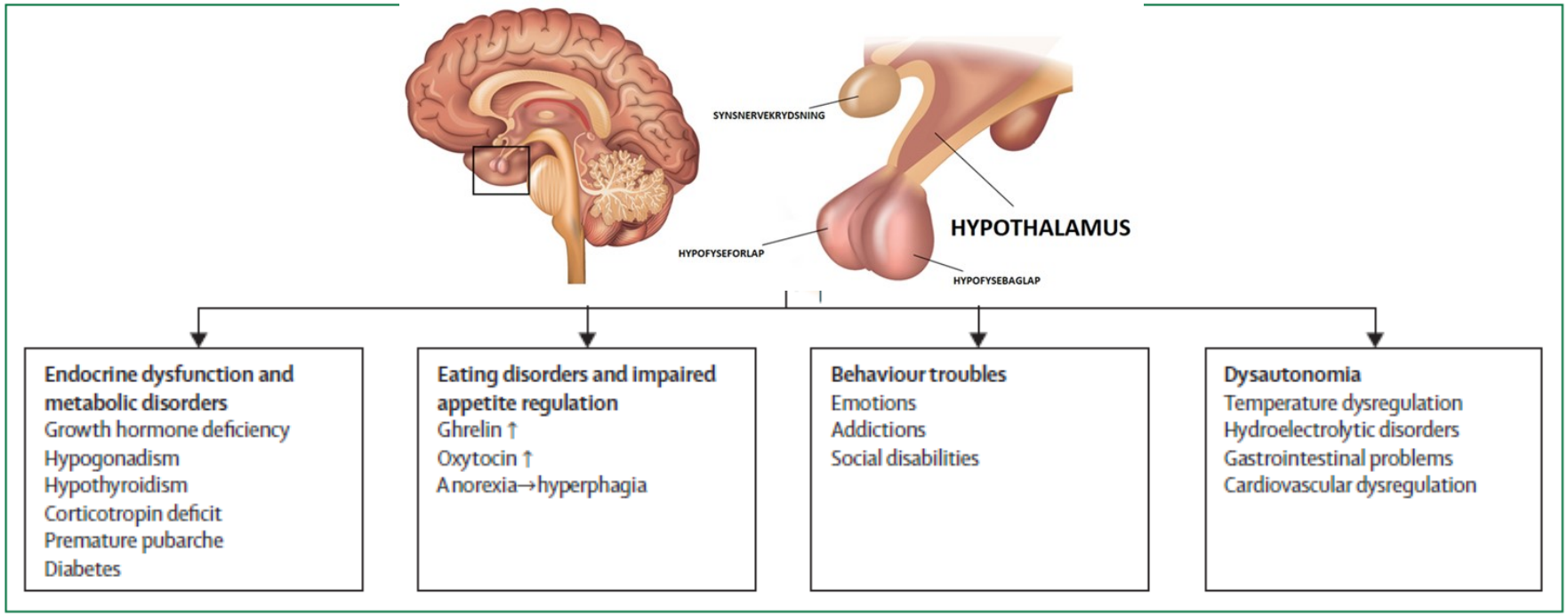
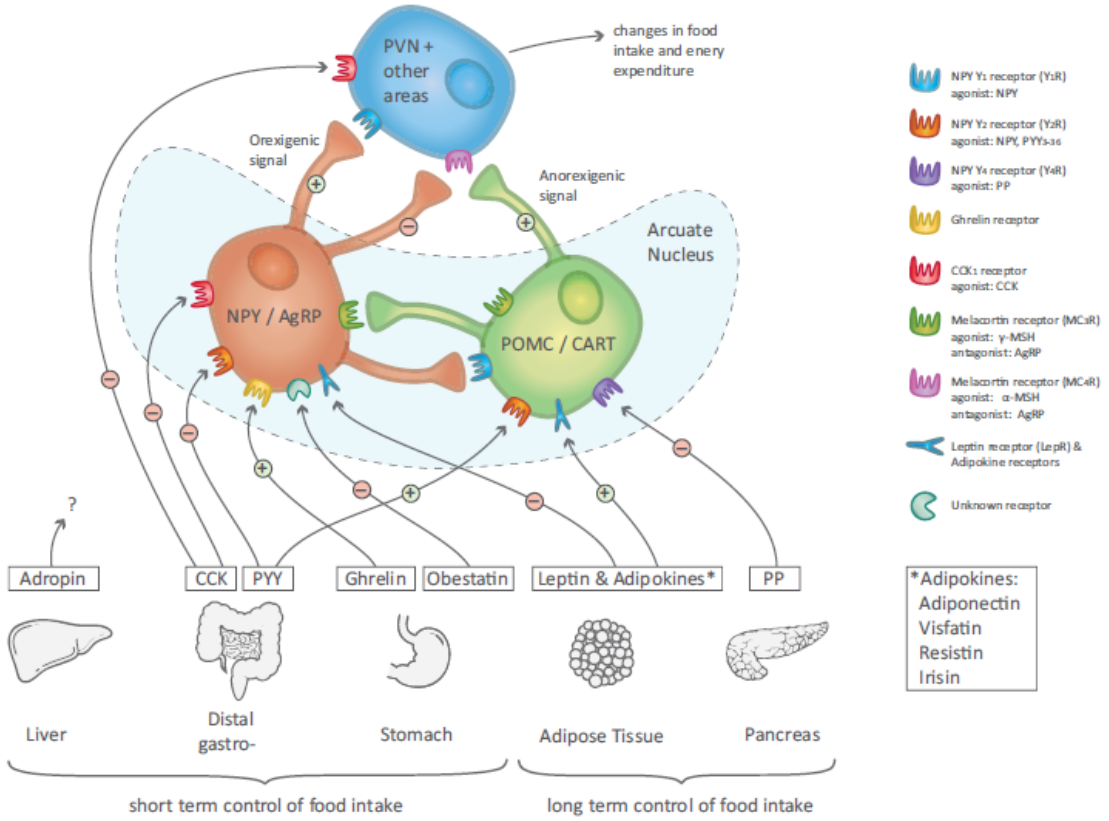



***Figure 4*: Impaired development and function of the hypothalamus explains most of the typical features of Prader-Willi syndrome**
The hypothalamus controls endocrine and metabolic function, appetite regulation, emotion, and behaviour and is linked to the autonomic nervous system. Impaired development and function of the hypothalamus explains most of the typical features of Prader-Willi syndrome.



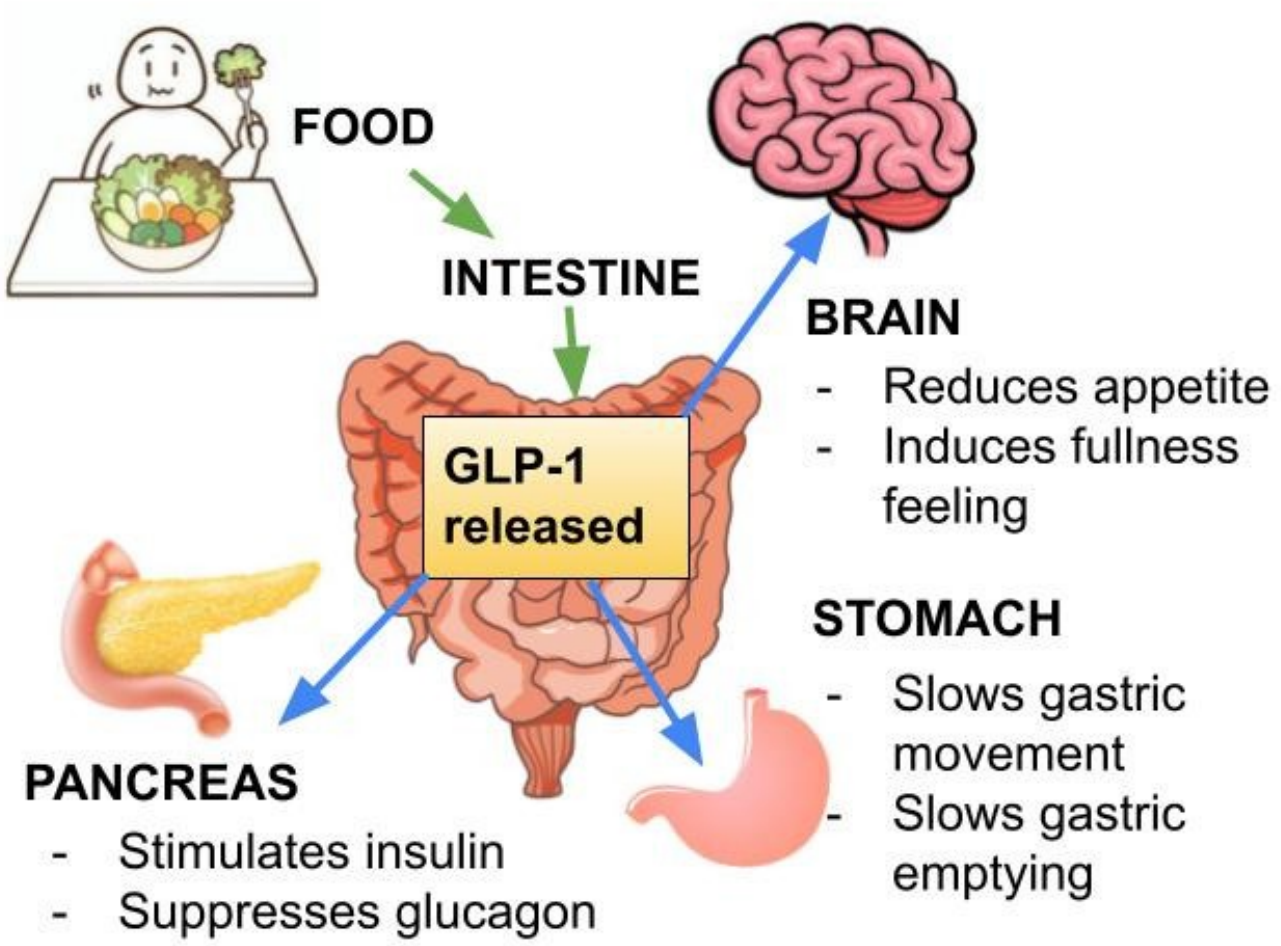
Tauber & Hoybye 2021

# Appetit-regulering: Neuroendokrine faktorer






Vlaardingerbroek et al 2021


FOOD
INTESTINE
GLP-1 released
BRAIN
- Reduces appetite
- Induces fullness feeling
STOMACH
- Slows gastric movement
- Slows gastric emptying
PANCREAS
- Stimulates insulin
- Suppresses glucagon

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https://doi.org/10.1210/clinem/dgac549
Advance access publication 1 October 2022
**Clinical Research Article**

# Liraglutide for Weight Management in Children and Adolescents With Prader–Willi Syndrome and Obesity

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[9]Toulouse Institute for Infectious and Inflammatory Diseases (Infinity) INSERM UMR1291 – CNRS UMR5051, University of Toulouse III, 31024 Toulouse Cedex 3, Toulouse, France

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## Abstract

**Context:** Prader–Willi syndrome (PWS) is characterized by lack of appetite control and hyperphagia, leading to obesity. Pharmacological options for weight management are needed.

**Objective:** To determine whether liraglutide treatment for weight management is superior to placebo in pediatric individuals with PWS.

**Methods:** This was a multicenter, 52-week, placebo-controlled trial with a 16-week double-blinde years; Tanner stage 2-5) and children (n = 24, aged 6-11 years; Tanner stage <2) with PWS a randomized 2:1 to liraglutide 3.0 mg (or maximum-tolerated dose) or placebo for 16 weeks, after wl continued for 52 weeks. All patients followed a structured diet and exercise program throughou change in body mass index (BMI) standard deviation score (SDS) from baseline to 16 and 52 we weight-related parameters, hyperphagia, and safety.

**Results:** Change in BMI SDS from baseline to weeks 16 and 52 was not significantly different betw treatment difference: −0.07 at week 16 and −0.14 at week 52) and children (−0.06 and −0.07, resp parameters between treatments were not significant. At week 52, hyperphagia total and drive scor liraglutide vs no treatment. The most common adverse events with liraglutide were gastrointestinal

**Conclusion:** Although the coprimary endpoints were not met, changes in hyperphagia total and d studies on liraglutide in this population.

*The Journal of Clinical Endocrinology & Metabolism*, 2023, **108**, 1676–1685
https://doi.org/10.1210/clinem/dgad014
Advance access publication 14 January 2023
**Clinical Research Article**

## Diazoxide Choline Extended-Release Tablet in People With Prader-Willi Syndrome: A Double-Blind, Placebo-Controlled Trial

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*J.L.M. and E.G. are co-first authors of this work.

## Abstract

**Context:** Prader-Willi syndrome (PWS) is a rare neurobehavioral-metabolic disease caused by the lack of paternally expressed genes in the chromosome 15q11-q13 region, characterized by hypotonia, neurocognitive problems, behavioral difficulties, endocrinopathies, and hyperphagia resulting in severe obesity if not controlled.

**Objective:** The primary end point was change from baseline in hyperphagia using the Hyperphagia Questionnaire for Clinical Trials (HQ-CT). Other end points included Global Impression Scores, and changes in body composition, behaviors, and hormones.

**Methods:** In DESTINY PWS, a 13-week, randomized, double-blind, placebo-controlled, phase 3 trial, 127 participants with PWS aged 4 years and older with hyperphagia were randomly assigned 2:1 to diazoxide choline extended-release tablet (DCCR) or placebo.

**Results:** DCCR did not significantly improve hyperphagia (HQ-CT least-square mean (LSmean) (SE) −5.94 (0.879) vs −4.27 (1.145); $P = .198$), but did so in participants with severe hyperphagia (LSmean (SE) −9.67 (1.429) vs −4.26 (1.896); $P = .012$). Two of 3 secondary end points were improved (Clinical Global Impression of Improvement (CGI-I); $P = .029$; fat mass; $P = .023$). In an analysis of results generated pre-COVID, the primary (HQ-CT; $P = .037$) and secondary end points were all improved (CGI-I; $P = .015$; Caregiver Global Impression of Change; $P = .031$; fat mass; $P = .003$). In general, DCCR was well tolerated with 83.3% in the DCCR group experiencing a treatment-emergent adverse event and 73.8% in the placebo group (not significant).

**Conclusion:** DCCR did not significantly improve hyperphagia in the primary analysis but did in participants with severe baseline hyperphagia and in the pre-COVID analysis. DCCR treatment was associated with significant improvements in body composition and clinician-reported outcomes.

**Key Words:** Prader-Willi syndrome, hyperphagia, DCCR

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DOI: 10.1111/dom.70282

COMMENTARY

# Recommendations for real-world evidence of efficacy and safety of GLP-1 agonists in Prader-Willi syndrome: Report of a workshop held by the Foundation for Prader-Willi Research and International Prader Willi Syndrome Organisation

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[3]Center of Academic Medicine, Division of P

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## Effects of Exenatide on Weight and Appetite in Overweight Adolescents and Young Adults with Prader-Willi Syndrome

**Parisa Salehi, M.D.[1], Isabel Hsu, M.D., Ph.D.[2], Colleen G. Azen, M.S.[3], Steven D. Mittelman, M.D., Ph.D.[2,4], Mitchell E. Geffner, M.D.[2,4], and Debra Jeandron, M.D.[2]**

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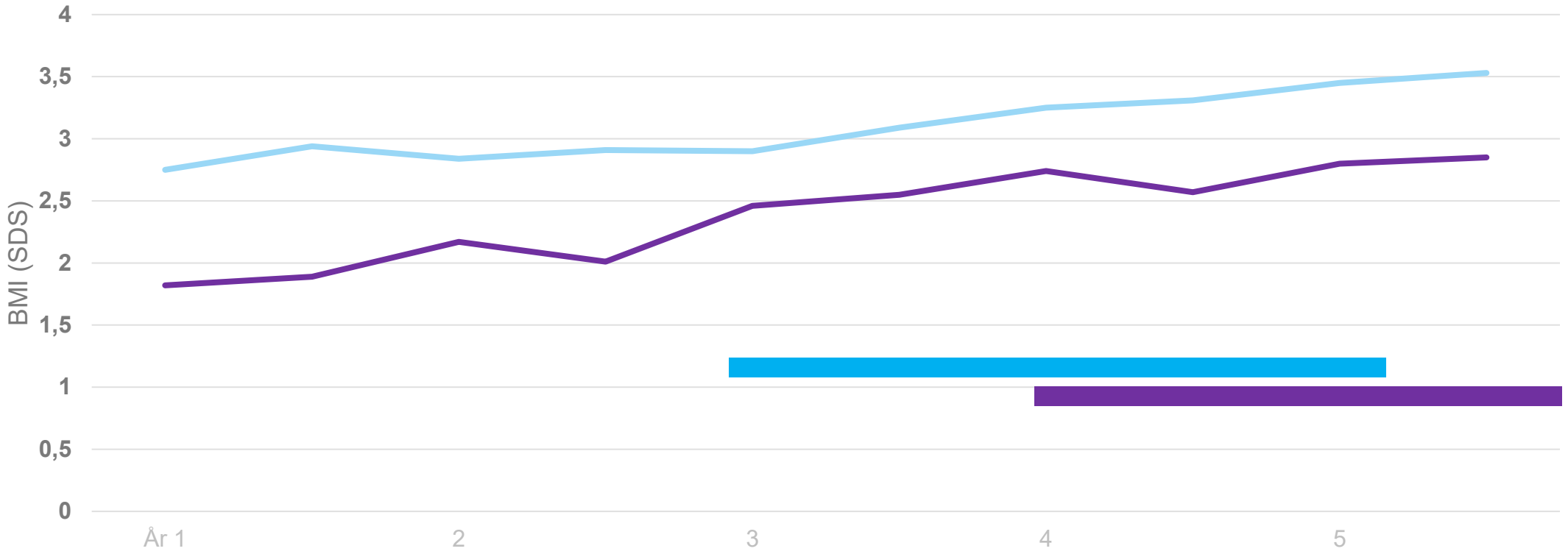
## Abstract

**Background—**Prader-Willi Syndrome (PWS) is associated with hyperphagia and hyperghrelinemia with major morbidity due to obesity without effective medical treatment targeting hyperphagia. Exenatide [Byetta (synthetic Exendin-4); AstraZeneca, Wilmington DE] is a GLP-1 receptor agonist which reduces appetite and weight, and may be an effective treatment in PWS.

**Objective—**To determine the effect of a 6-mo trial of exenatide on appetite, weight, and gut hormones in youth with PWS.

**Methods—**Ten overweight and obese subjects with PWS (13-25 yr) were recruited for a 6-mo open-label, non-randomized, longitudinal study conducted at Children's Hospital Los Angeles. Exenatide was given using standard diabetes dosing without dietary modifications. Weight, BMI, truncal fat, appetite, and plasma acylated ghrelin were measured over 6 mo. Mixed meal tolerance tests were done at 0 and 6 mo.

# Erfaring med PWS og Semaglutid i DK: BMI falder ikke



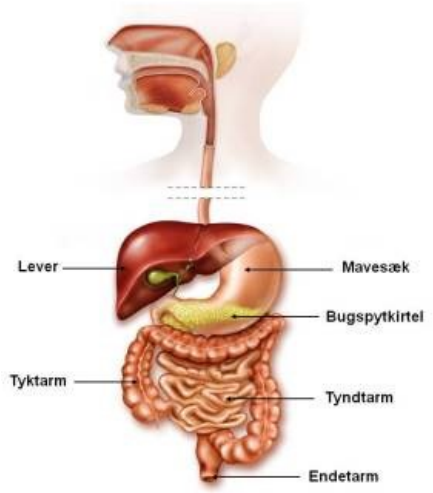
# GLP1 receptor agonist og PWS

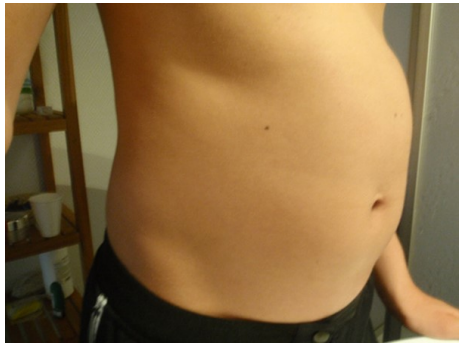
- **Fordele**
  - Hyperfagi-score reduceres hos nogle
  - Bedre glycæmisk kontrol
- **Ulemper**
  - Utilstrækkelige videnskabelige data
  - Safety uafklaret
    - Nedsat ventrikeltømning
      - Øget risiko for ventrikelruptur?
  - Fører ikke til vægttab
  - Ingen RCCT vedr Semaglutid og PWS
  - Slækkes på støtten til at overholde kostplan?
  - Økonomi



Finer et al 2025

# Mavetarm-kanalen



- Refluks
- Manglende evne til at kaste op
- Øget forekomst af forstoppelse
- Signaler om afføringstrang?
- Gastroparese
- Ileus, pseudo-obstruktion?
- CAVE! Overspisning – risiko for ventrikelruptur

- Nedsat ventrikeltømnings-hastighed
  - Arenz et al 2010
  - Høybye et al 2006
- Øget GITT
  - Kuhlmann et al 2014

# Status på nuværende tidspunkt

- …. existing obesity and diabetes assets are not effective for genetic obesity such as PWS (Sarkar et al, 2024, meta-analyse)

- FPWR og IPWSO
  - Fraråder brug af GLP1-ra ved PWS

# Landsforeningen for Prader-Willi syndrom


## Fagråd




http://prader-willi.dk