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How to Bridge the Gap between Research and Clinical Practice

Examples from Anorexia Nervosa Research

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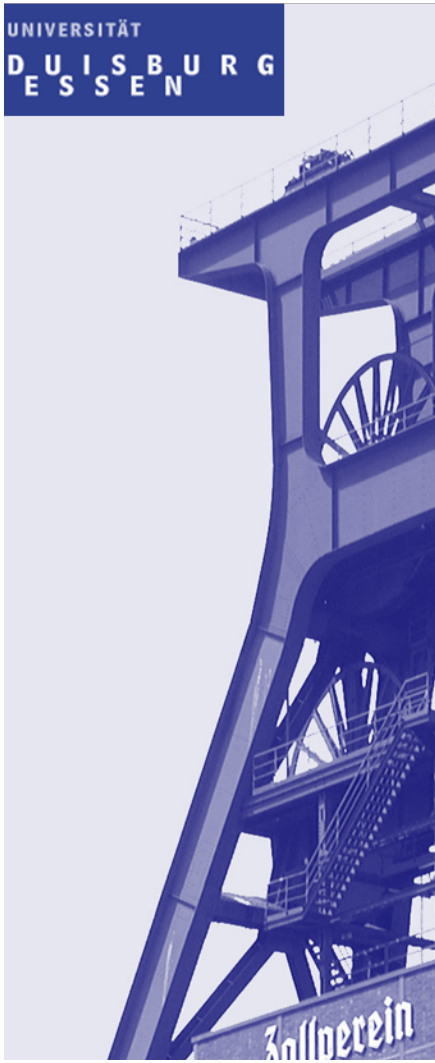

UNIVERSITÄT DUISBURG ESSEN

LVR-Klinikum Essen
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KTQ-Zertifikat

Conflicts of Interest

- Editor-in-chief of *European Childhood and Adolescent Psychiatry*
- Non-voting member of the ESCAP board
- Vice President of the European Association for the Study of Obesity
- Funding: DFG, BMBF, EU, NRW

Core Phenotype of Anorexia Nervosa

- **Special features**
  - **Comparatively rather homogeneous clinical symptomatology**
  - **Circumscribed age manifestation range**
  - **Moderate to high heritability**
  - **Low prevalence despite ubiquitous drive for thinness**
  - **Historic case reports (?)**

- **State and trait markers**

- **"… the intertwining of the primary behaviors with the psychological and somatic consequences of starvation represent the core symptomatology of AN."**

Hebebrand et al., J Neural Transm 2004;
Hebebrand and Bulik, Int J Eat Dis, *2011*

Overview

- **Do not hesitate to ask questions: Improving the weight criterion**
- **Make use of spin-offs: Systematic aspects of body weight regulation in anorexia nervosa**
- **Identifying major questions: Starvation independent findings**
- **Carpe diem: Neurobiology of starvation**
  - **Leptin as a central switch**
- **Struggle to make your opinions known: Discussion of current diagnostic criteria**
- **Identify your role: Genetic aspects**

DSM-IV TR Criteria for Anorexia Nervosa

- **A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).**

- **B. Intense fear of gaining weight or becoming fat, even though underweight.**

- **C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.**

- **D. In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)**

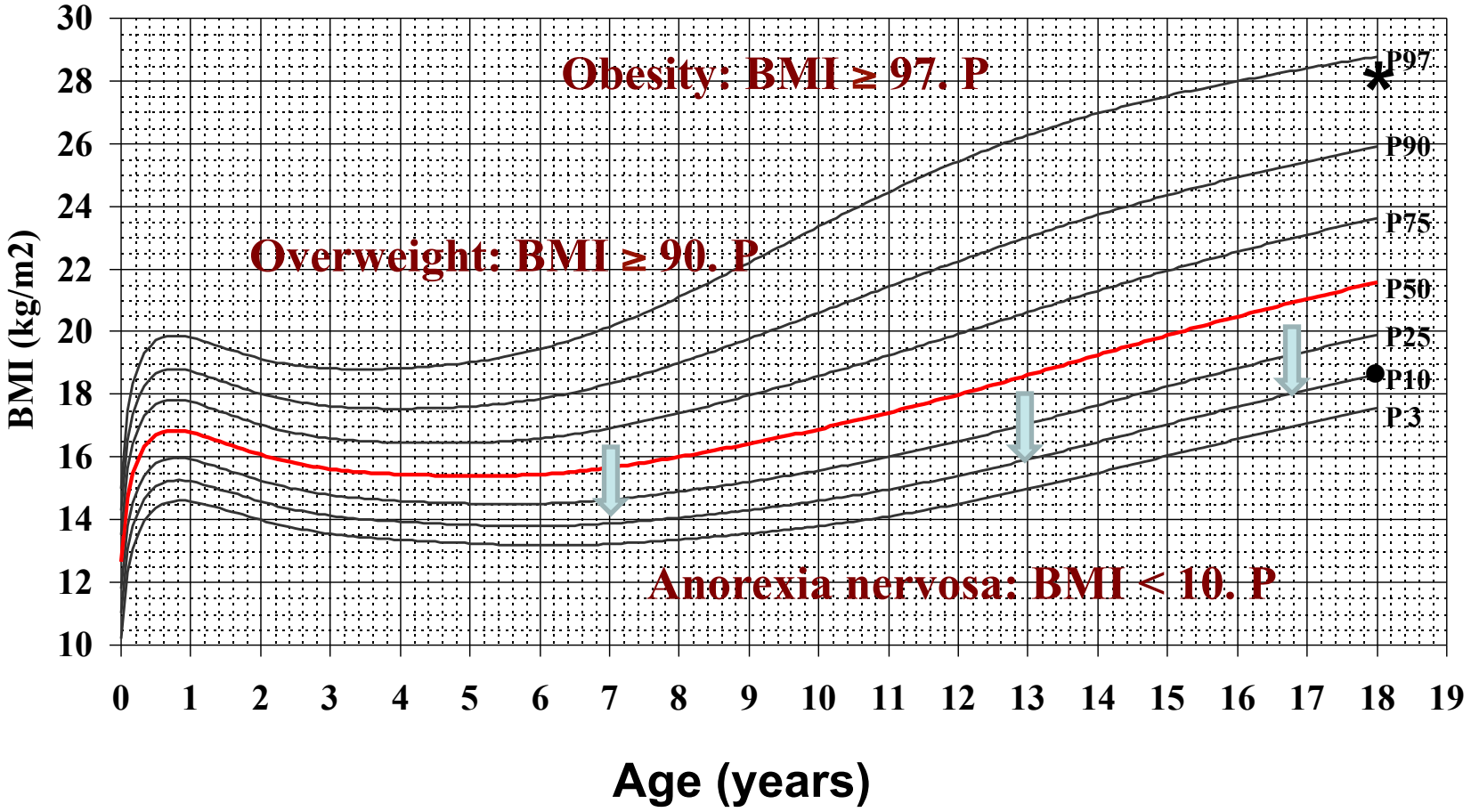
Do not hesitate to ask questions

Absolute BMI Values Corresponding to 10th BMI Centile (NHANES I)

	Age in years							
	10-12	13-14	15-16	18-20	21-23	24-26	27-29	33-35
Females	15.6	16.6	17.4	18.4	18.5	18.5	18.7	19.4
Males	15.3	16.6	17.8	19.7	20.0	20.2	20.5	21.3

Hebebrand et al., Int J Eat Dis 1996

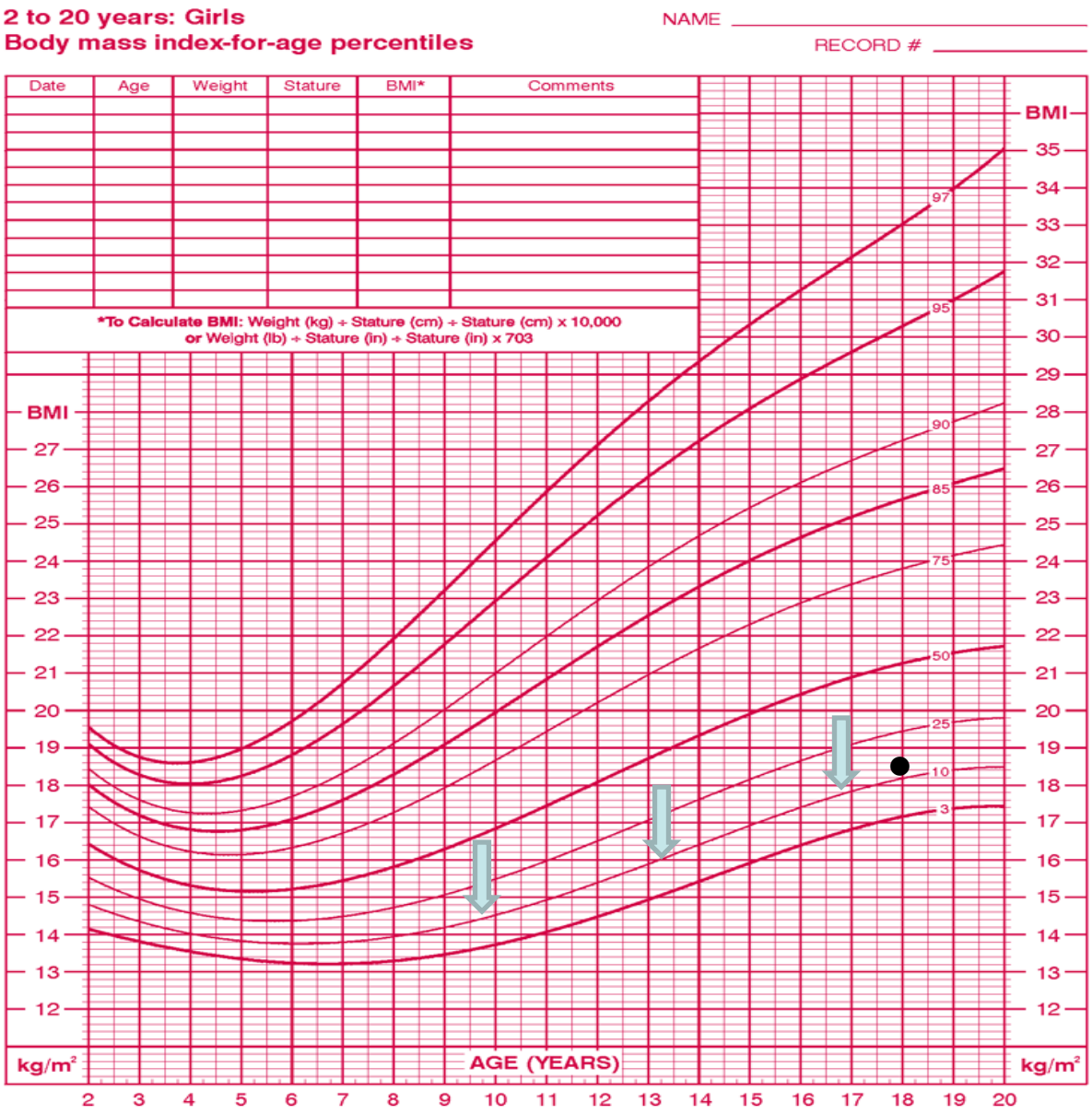
German BMI Percentiles (Females)



Kromeyer-Hauschild et al. (2001); Monatsschrift Kinderheilkunde 149: 807

US BMI Percentiles (Females)

CDC 2000 growth curves



10th Percentile

US Prevalence rates of BMI < 18.5 kg/m²

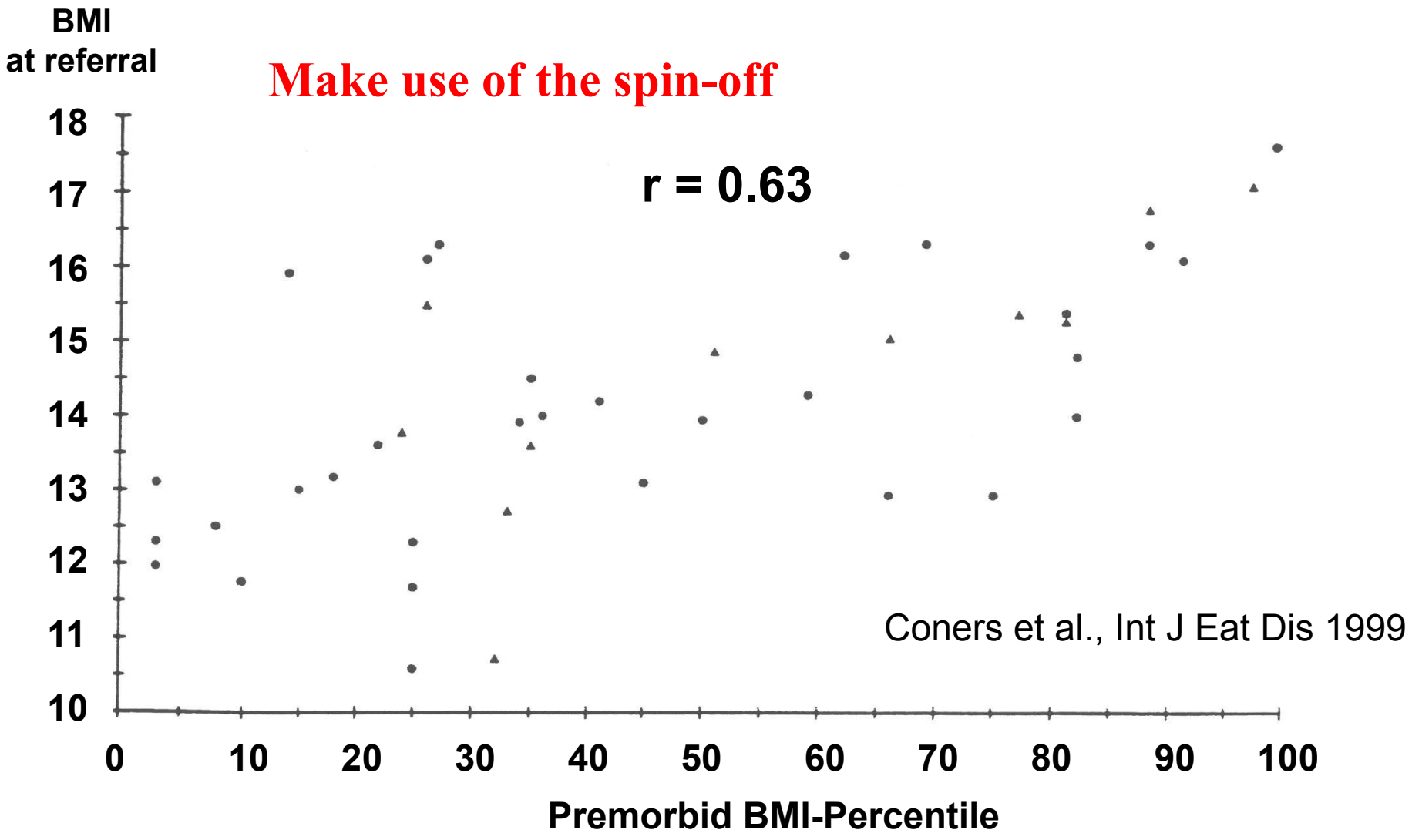
Table 3: Age-adjusted percent distribution (with standard errors) of underweight (BMI < 18.5 kg/m²) for adults 18 years of age and over: United States, average annual, 2005–2007 [60]

Age range	Males	Females
18–24 years	2.9 (0.46)	4.8 (0.40)
25–44 years	0.6 (0.08)	2.7 (0.17)
45–64 years	0.5 (0.07	1.7 (0.16)
65–74 years	1.0 (0.19)	1.9 (0.25)
75 years and over	2.4 (0.42)	4.4 (0.36)

BMI was computed using respondent-reported height and weight, without shoes.

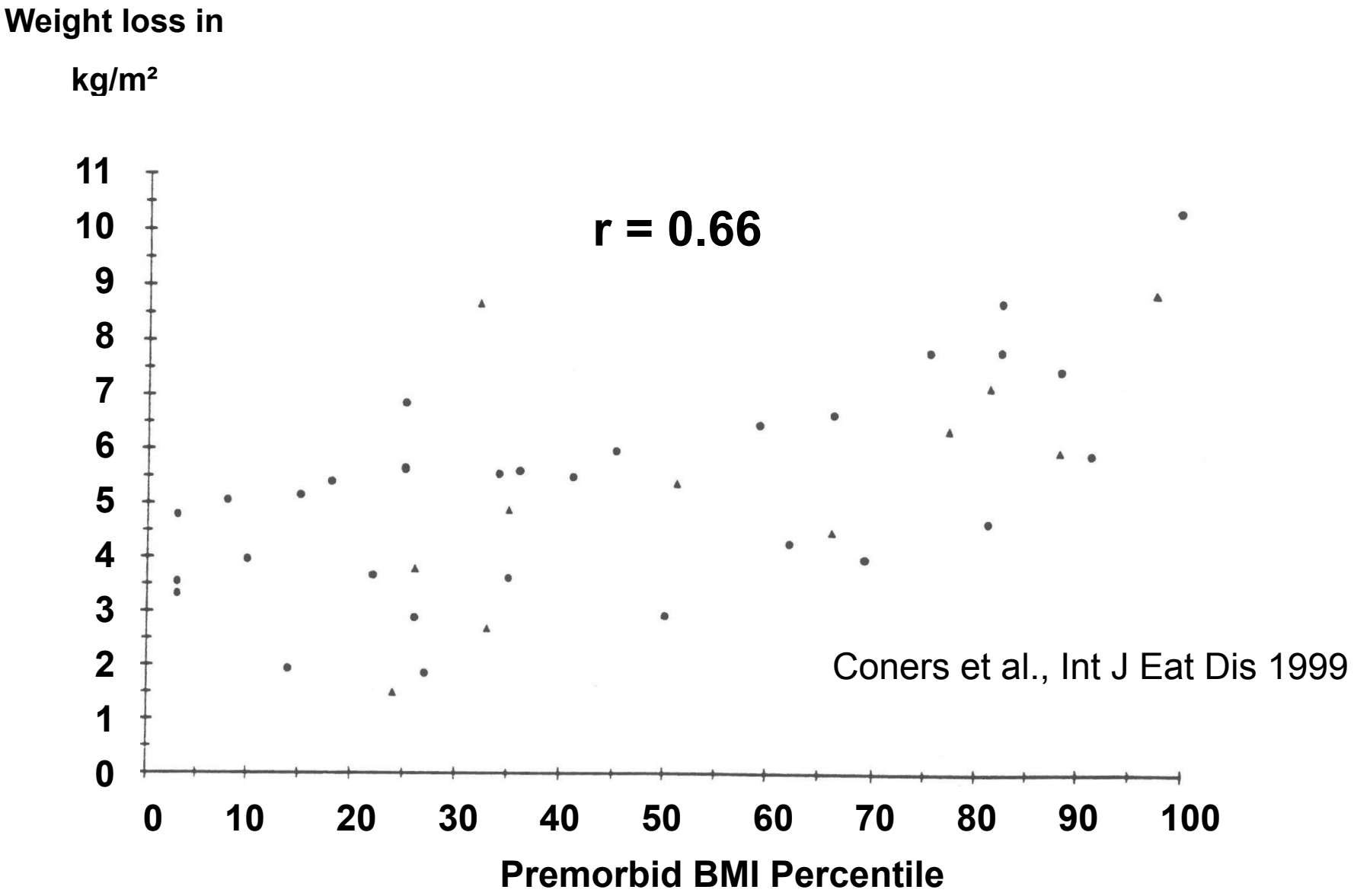
Hebebrand and Bulik, 2011

Referral and Premorbid BMI



Coners et al., Int J Eat Dis 1999

Referral-BMI and Weight Loss



Coners et al., Int J Eat Dis 1999

Relationship between Referral and Follow-up BMI: 272 Patients

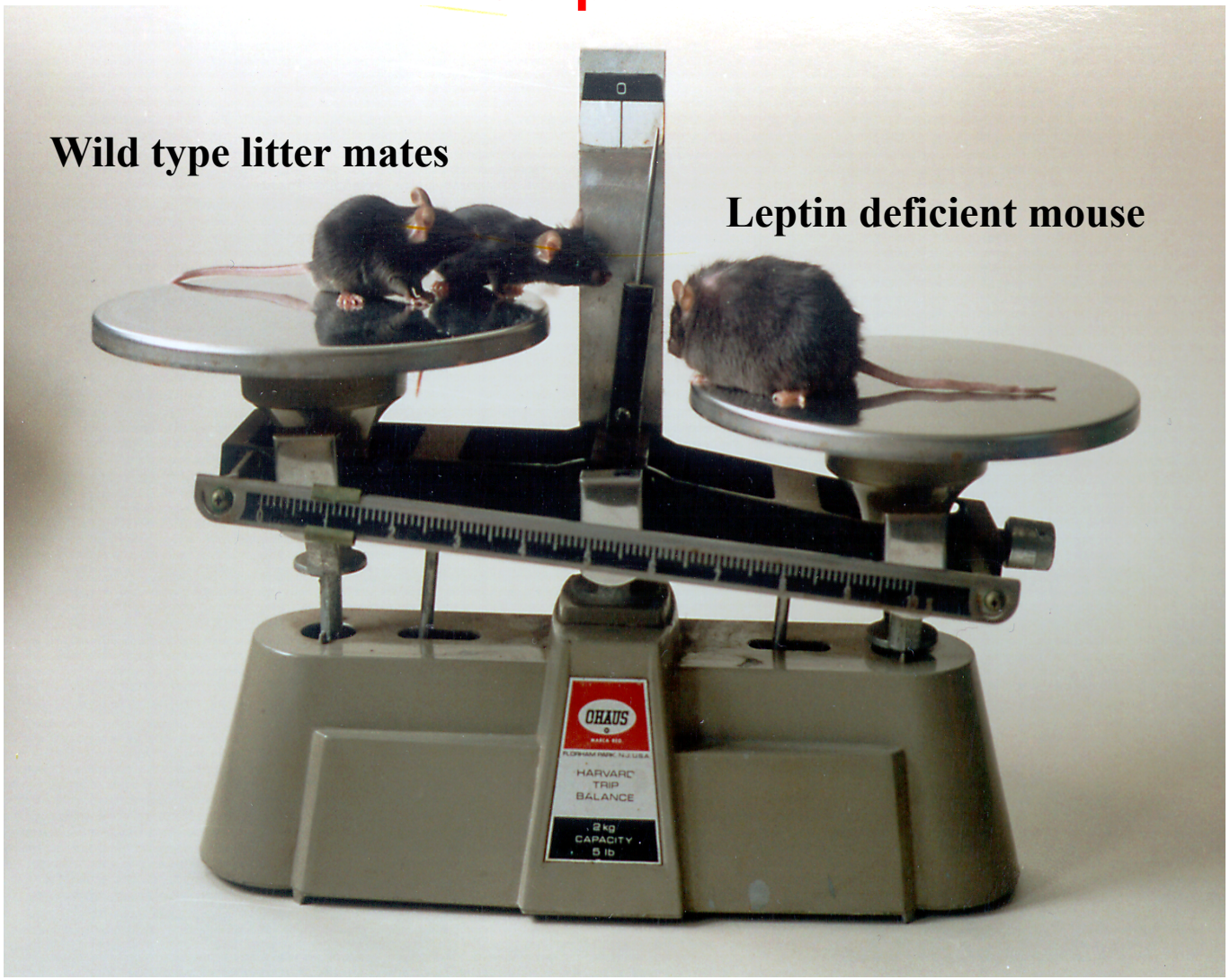
BMI at follow-up (mean: 9.5 years)	Referral-BMI < 13 kg/m² n = 100	Referral-BMI ≥ 13 kg/m² n = 172
≤ 17.5 kg/m²*	35%	12.8%
≤ 5th centile*	44%	19.8%
≤ 10th centile*	56%	29.0%
≥ 25 kg/m²	1%	3.4%
Deceased	11%	0.6%

*including deceased patients

Hebebrand et al., Am J Psychiatry 154: 566-569; 1997

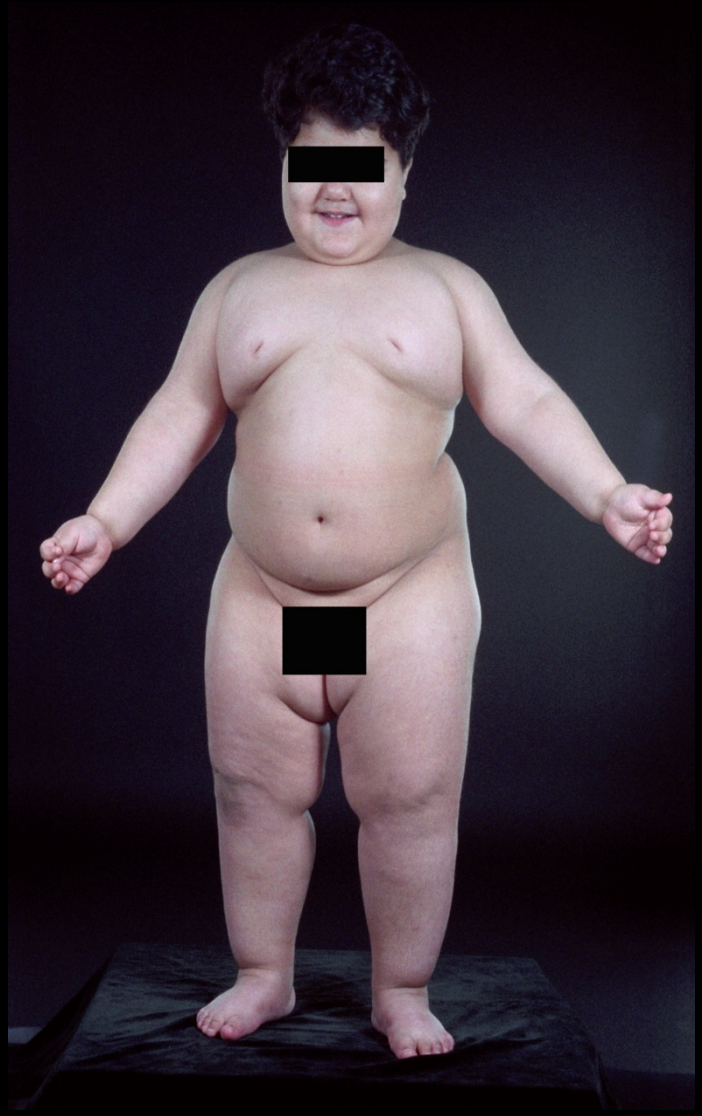
The *ob/ob* mouse

Carpe diem



Zhang et al., Nature 1994

courtesy of Sadaf Farooqi



Child B **before** leptin

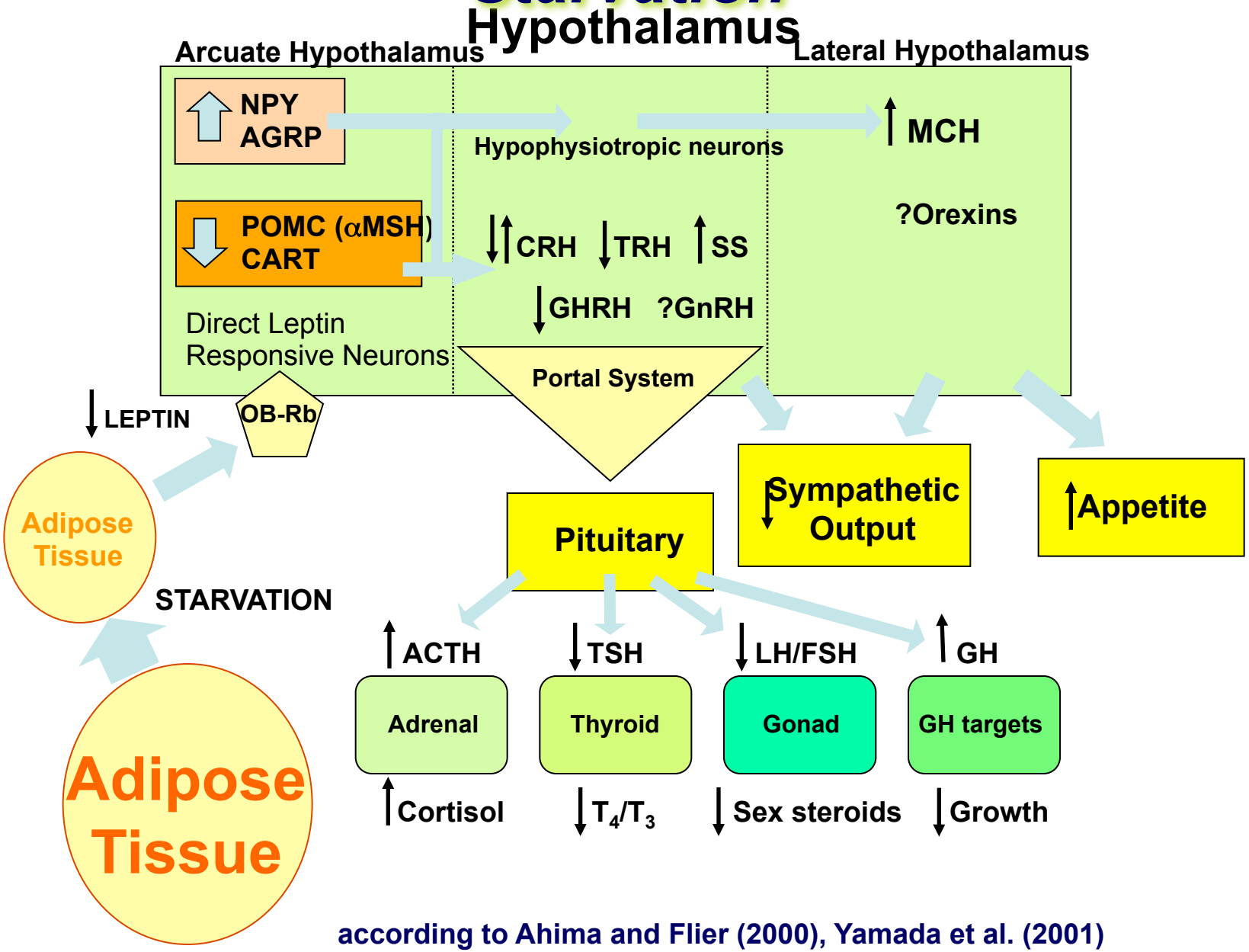
(wt = 42kg at 3yrs)

Child B **after** leptin

(wt = 32kg at 7yrs)

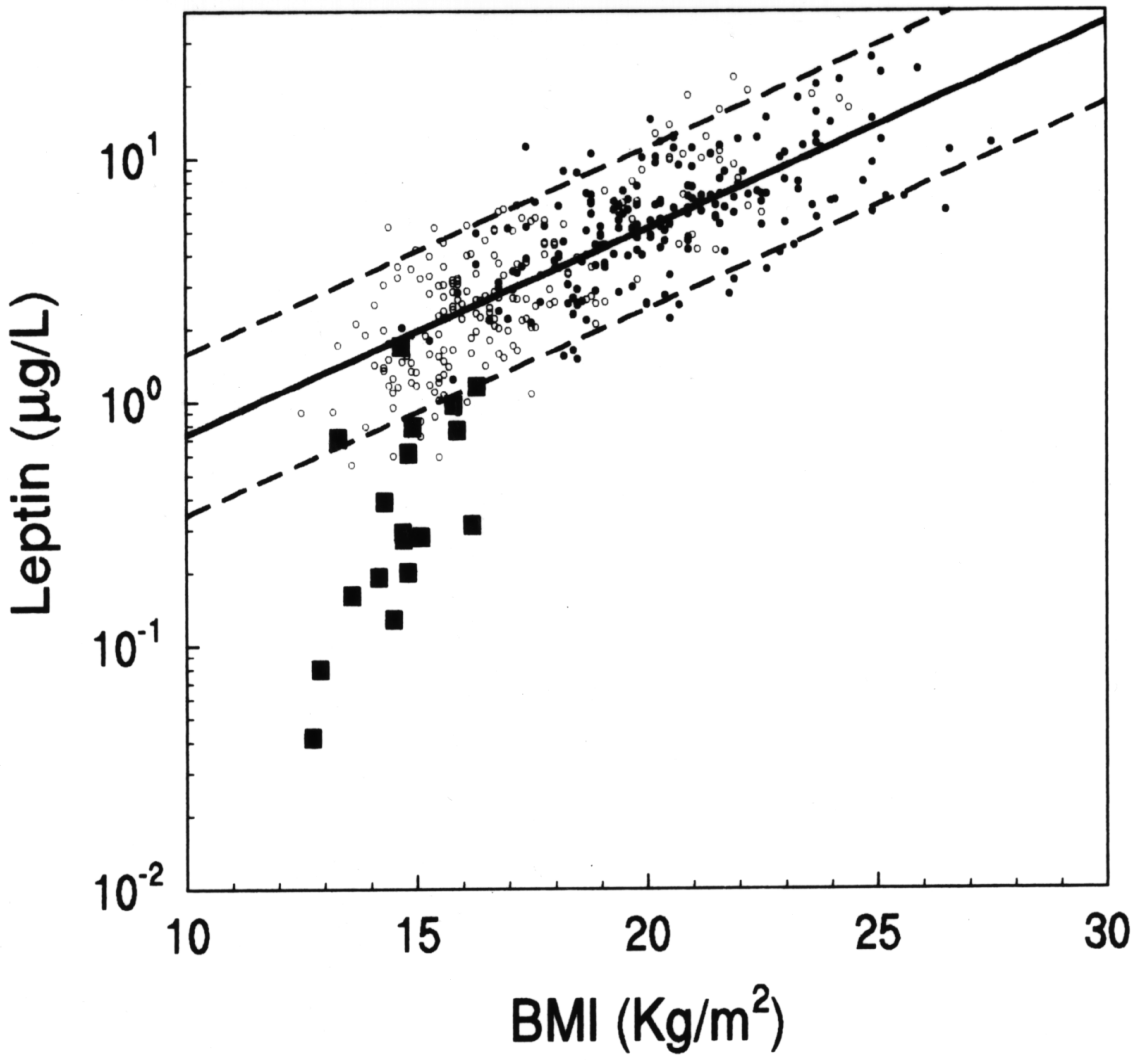
Farooqi et al
1999; NEJM
16;341:879-84

Leptin Signaling: Adaptation to Semi-Starvation



according to Ahima and Flier (2000), Yamada et al. (2001)

Serum lg10 Leptin Levels in Acute Anorexia Nervosa



- ■ patients aged 12-18 years
- ○ control females aged 6-11 years
- • control females aged 12-18 years

Hebebrand et al 1995, 1997; The Lancet, Mol Psychiatry

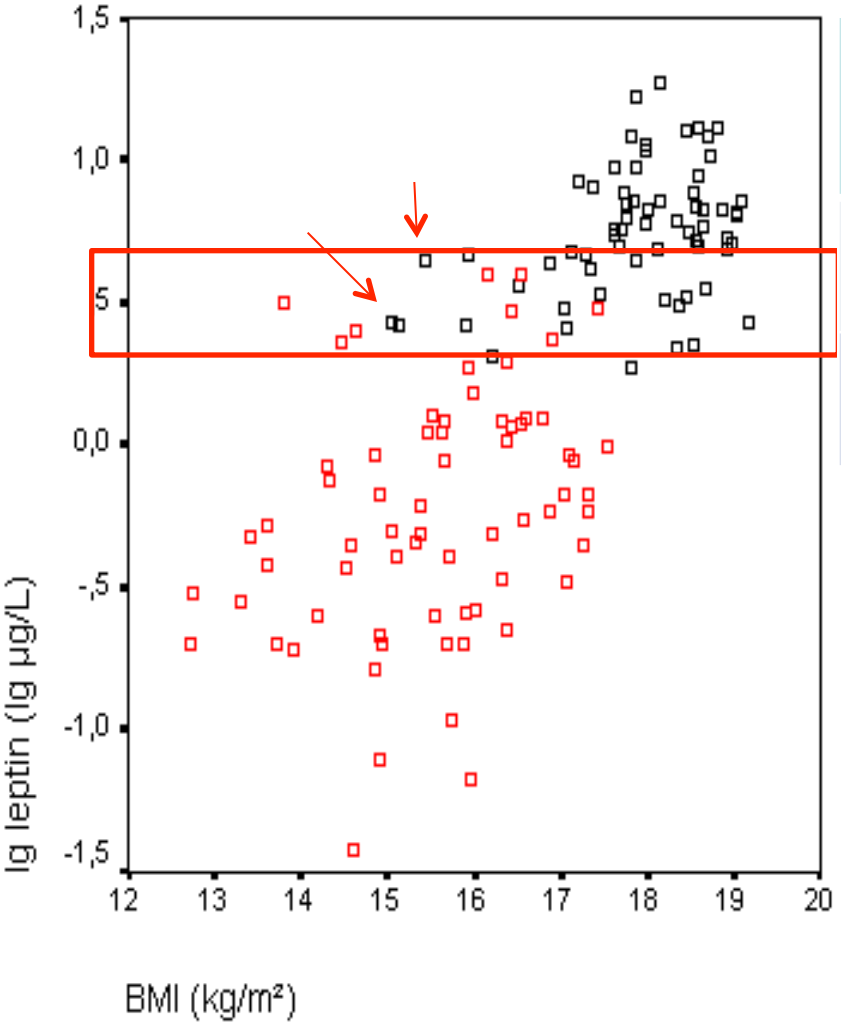
Evidence for a leptin threshold in AN

- **Central hypothesis:**
  Hypoleptinemia in AN patients; healthy underweight females have higher levels

⟹ existence of a **threshold** value/range

- **Background:**
  - hypoleptinemia: a cardinal feature of semistarvation in AN
  - according to most studies leptin levels only infrequently exceed 2 µg/L in patients with AN *(Müller et al. 2009)*
  - threshold of 1.85µg/L separates patients with AN from healthy underweight females (Köpp et al., 1997)

Hypoleptinemia: Sensitivity and Specificity for Diagnosis of Anorexia nervosa



	cut-off (µg/L)	patients		controls	
		true positives	false negatives	true negatives	false positives
100% sensitivity	4.02	74	0	49	16
100% specificity	1.63	64	10	65	0

threshold range 1.6-4 µg/L

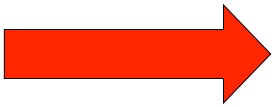
controls
patients
controls with a BMI between 15 and 16 kg/m²

Föcker et al. 2011, J Neural Transmission

Hypoleptinemia: A biological marker for Anorexia nervosa

cut off (µg/L)	sensitivity	specificity	ppV	npV
2.0	0.89	0.97	0.604	0.994
2.5	0.93	0.94	0.444	0.996

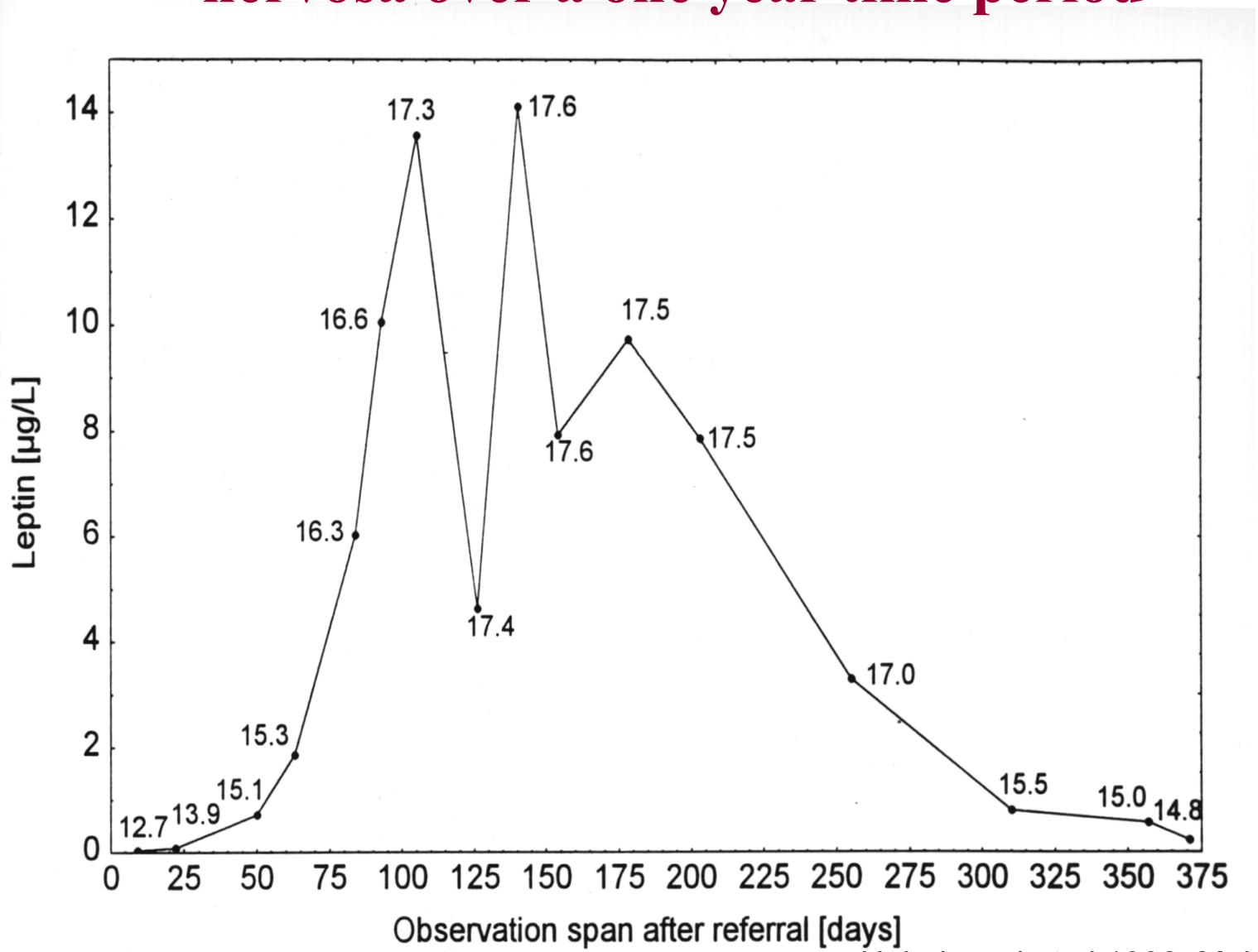
statistical paramter	legend
positive predictive Value	% of individuals with positive test results who are correctly diagnosed as patients
negative predictive Value	% of individuals with negative test results who are correctly diagnosed as healthy
sensitivity	% of actual positives which are correctly identified as such
specificity	% of negatives which are correctly identified



a threshold in the range of 2 µg/L appears appropriate for screening purposes

Föcker et al. 2011, J Neural Transmission

Serum leptin levels in a patient with anorexia nervosa over a one year time period



Hebebrand et al 1998; Mol Psychiatry

Leptin and Anorexia Nervosa

- Assessment of the clinical implications of hypoleptinemia and hyperleptinemia

- Anorexia nervosa is a model disorder to assess the effects of hypoleptinemia and of the rapid transition from hypoleptinemia to hyperleptinemia in humans

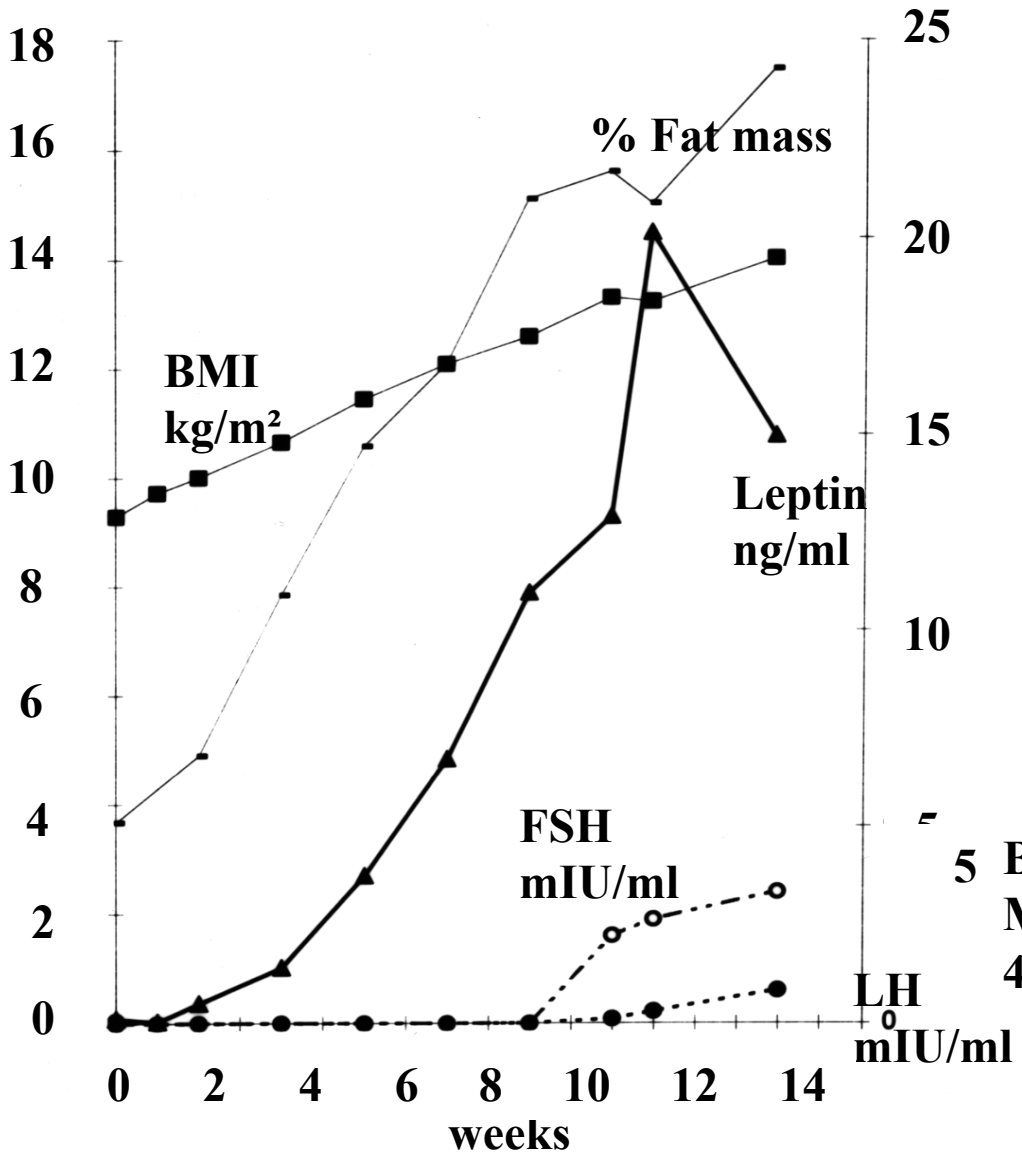
Semi-starvation in humans: selected physical and laboratory findings

amenorrhea
hypothermia
cold intolerance
hypotension
bradycardia
dryness of skin
lanugo
constipation
abdominal pain
increased ventricular -brain ratio

reduced FSH, LH, estrogen
low T3 syndrome
high ghrelin levels
reduced hematopoiesis
hyperadrenocorticism
reduced resting energy
hypoleptinemia

APA, 1994
Hebebrand et al., 1995, 1997
Otto et al., 2001

Serum leptin and gonadotropin levels during weight gain



Ballauff et al., Mol Psychiatry 4:71-75; 1999

Hypothalamic Amenorrhea: Treatment with Leptin

- 8 females with hypothalamic amenorrhea of ≥ 6 months duration (mean: 5 years)
- 6 untreated controls
- Leptin treatment (r-metHuLeptin) for three months
  - Increment of serum LH levels within 2 weeks
  - Increase of the maximal follicle diameter, size of the ovary and increment of serum estrogen level within 3 months
  - 3 patients ovulated, 2 pre-ovulatory follicles
  - No significant weight loss; no side effects except reduction of appetite in third month of treatment

Welt et al., N Engl J Med 351: 987-97, 2004

Influence of leptin on brain growth

- **Leptin treatment of *ob/ob* mice increases weight of brain**
- **3 adults with leptin deficiency treated with recombinant leptin**
- **MRI at baseline, 3, and 18 months after initiation of treatment**
- **Volume increments of gray matter in frontal gyrus cinguli, inferior parietal lobe and cerebellum**

Matochik et al., JCEM 90: 2851-4, 2005

Semi-starvation in humans: psychological findings

- depressed mood
- social withdrawal
- pre-occupation with food
- rigidity
- hunger
- abnormal eating behavior
- reduced libido
- irritability
- inflexible thinking
- limited spontaneity
- restrained initiative
- restrained emotional expression
- loss of ambition

Keys et al., 1950; APA, 1994

Hyperactivity and Anorexia Nervosa:

different aspects of the phenomenon and clinical terminology

Identify good questions

- **Hyperactivity / elevated activity**
- **Motor restlessness / diffuse or nocturnal restlessness**
- **Excessive or extensive physical activity / intensive engagement in sports**
- **Compulsive physical activity, exaggerated need of physical activity**
- **Behavioral activation, paradoxical liveliness, excessive vitality, surplus of physical energy**

Prevalence rates: 30% - 80%

Hebebrand et al., Phyiol Behav 2003

Factors Associated with „Hyperactivity“ in Anorexia Nervosa

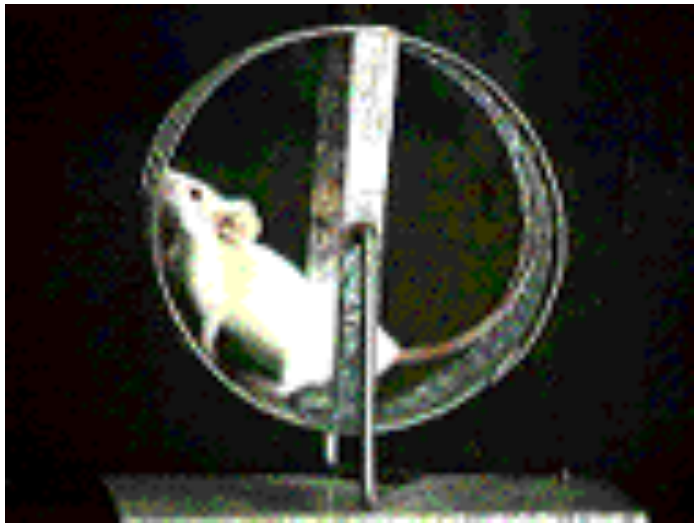
- Early onset
- High physical activity levels during childhood
- Inverse correlation between food intake and level of physical activity during the acute stage of the disorder
- Reduction of the inner restlessness during therapeutically induced weight gain
- Correlation with anxiety, irritability and obsessive-compulsive symptoms
- Worse prognosis

Semi-starvation induced hyperactivity

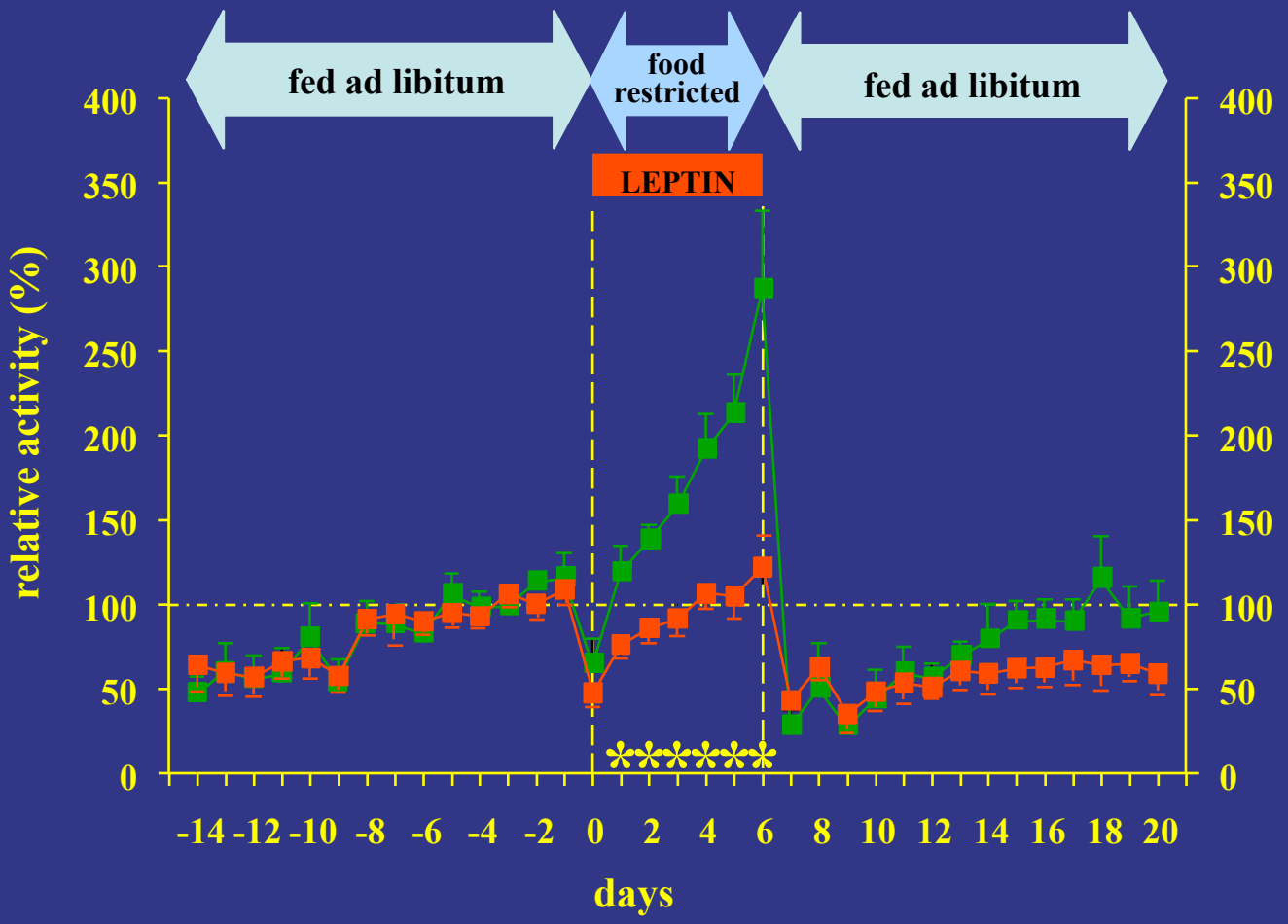
Anorexia based hyperactivity

In rats caloric restriction leads to semi-starvation induced hyperactivity.

Model for anorexia nervosa?

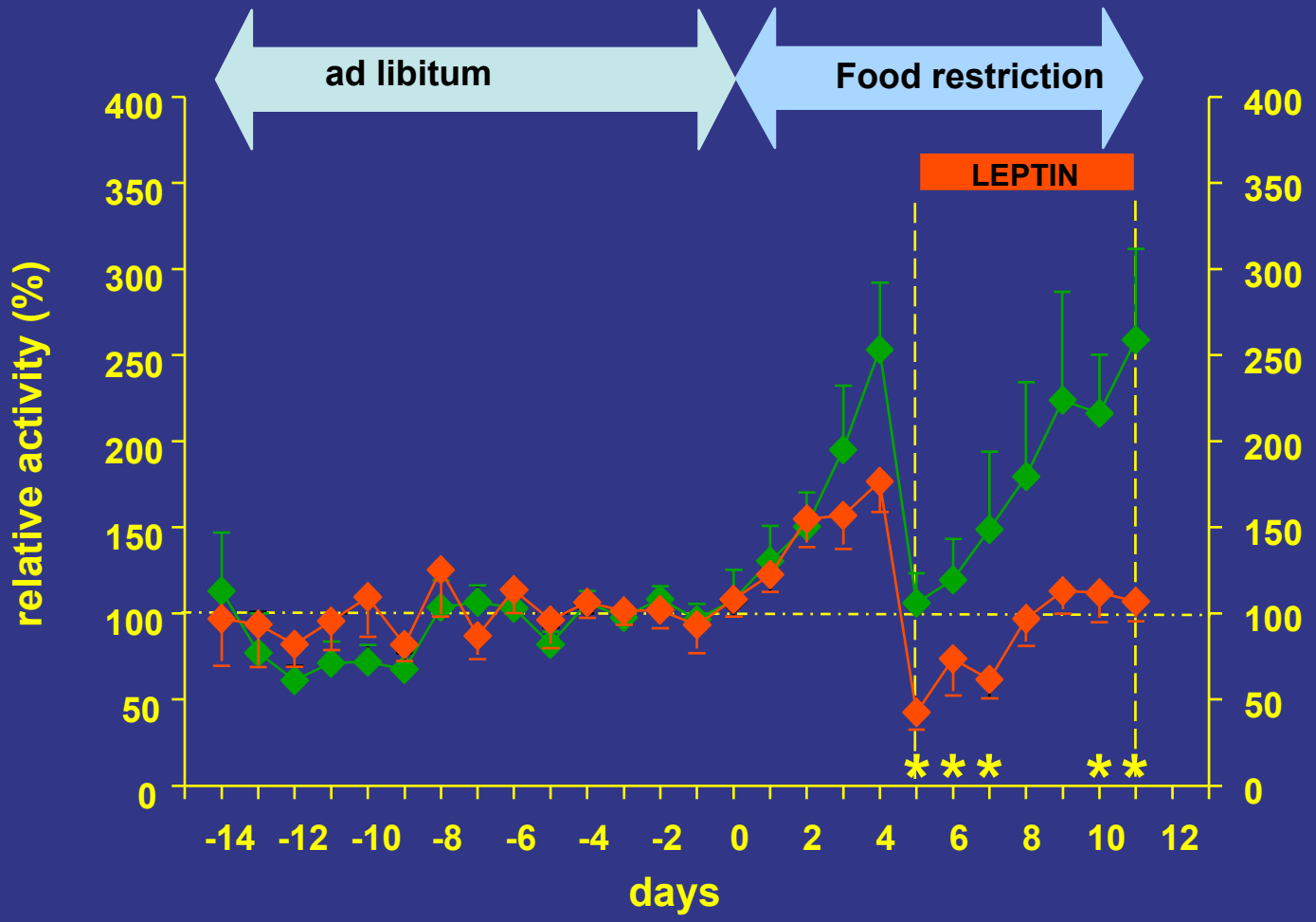


Leptin Suppresses Semi-Starvation Induced Hyperactivity



Exner et al., Mol Psychiatry 5: 476-481, 2000

„Treatment“ of Hyperactivity



Exner et al., 2000

Serum Leptin Levels and Mean Daily Activity in Patients with Anorexia nervosa

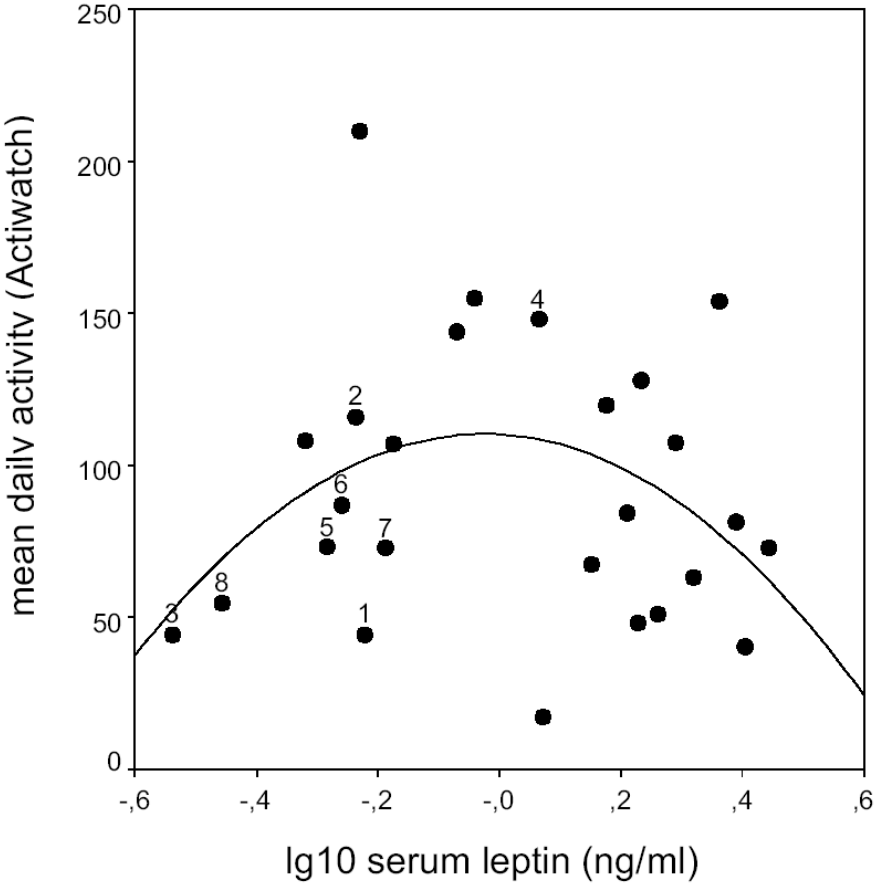


Figure 1: Scatterplot of mean daily physical activity of 72 hours (Actiwatch output) vs. lg10 serum leptin levels of 26 patients with anorexia nervosa. Partial correlation controlled for BMI: r= -.410, p=.042. Numbers 1-8 indicate the patients with lowest BMI within the study sample.

Holtkamp et al., 2006; Biol Psychiatry 60:311-3

Activity in Semi-Starvation: Minnesota Study

- **The attitude of the men to physical exertion was *ambivalent*. It made them tired and as a rule was avoided. On the other hand, occasionally *some men exercised deliberately*. Thus certain subjects attempted to lose weight by driving themselves through periods of excessive expenditure of energy with the object of either obtaining increased bread rations (when weight loss exceeded the prescribed rate) or avoiding reduction in rations (when weight loss lagged)**
- **subjects moved slowly and cautiously**
- **curtailment of spontaneous activity**
- **coordination was affected**

Franklin, Schiele, Brozek and Keys, J Clin Psychol 4: 28-45, 1948

- **the men rated themselves as ..... *restless*, unable to concentrate, and *markedly „nervous“***

DSM-IV TR Criteria for Anorexia Nervosa

- **A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).**

- **B. Intense fear of gaining weight or becoming fat, even though underweight.**

- **C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.**

- **D. In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)**

Struggle to make your opinions known or don‘t give up

Refusal to Maintain Body Weight at or above a Minimally Normal Weight?

- Refusal evidently implies an active, conscious and willful psychological process
- But: Evidence for underlying regulatory phenomena contributing to both somatic and mental symptoms and the course of disorder
  - Weight course a non-random process
  - Hypoleptinemia underlies amenorrhea
  - Hypoleptinemia contributes to hyperactivity
  - Hyperleptinemia predicts relapse
  - Genetics

J Hebebrand, R Casper , J Treasure, U Schweiger:
J Neural Transmission, 111: 827-4; 2004

Refusal to Maintain Body Weight at or above a Minimally Normal Weight?

- Patients do seek help
- Inferred behavior instead of description of behavior
- Term refusal is not used for any other psychiatric disorder
  - Anxiety, affective, conduct disorders
- Term refusal can be perceived as conveying a paternalistic and prejorative attitude
- No systematic evidence for the term
- Refusal not assessed in standard diagnostic interviews

J Hebebrand, R Casper, J Treasure, U Schweiger:
J Neural Transmission, 111: 827-4; 2004

Hebebrand & Bulik, 2011; Int J Eating Dis 44:665-78

DSM-5 Criteria for Anorexia Nervosa

A. Restriction of energy intake relative to requirements leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low body weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.

B. Intense fear of gaining weight or becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.

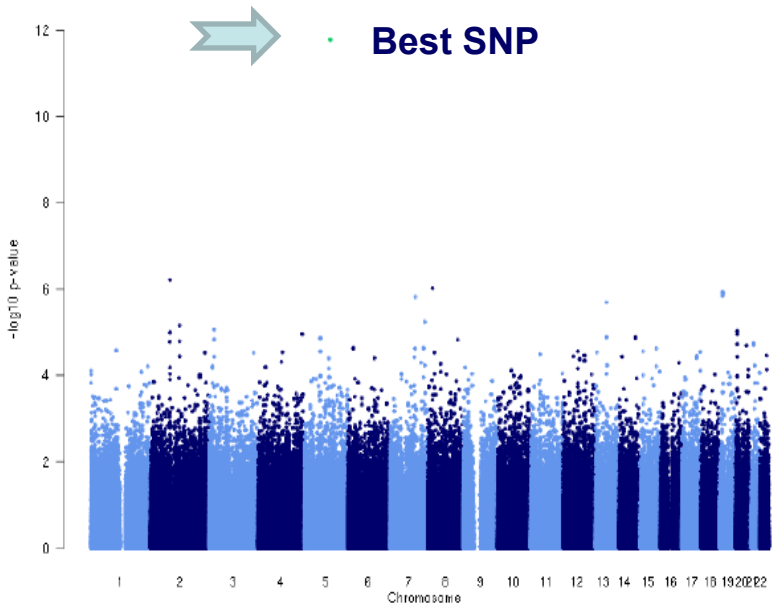
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

GWAS for Anorexia Nervosa

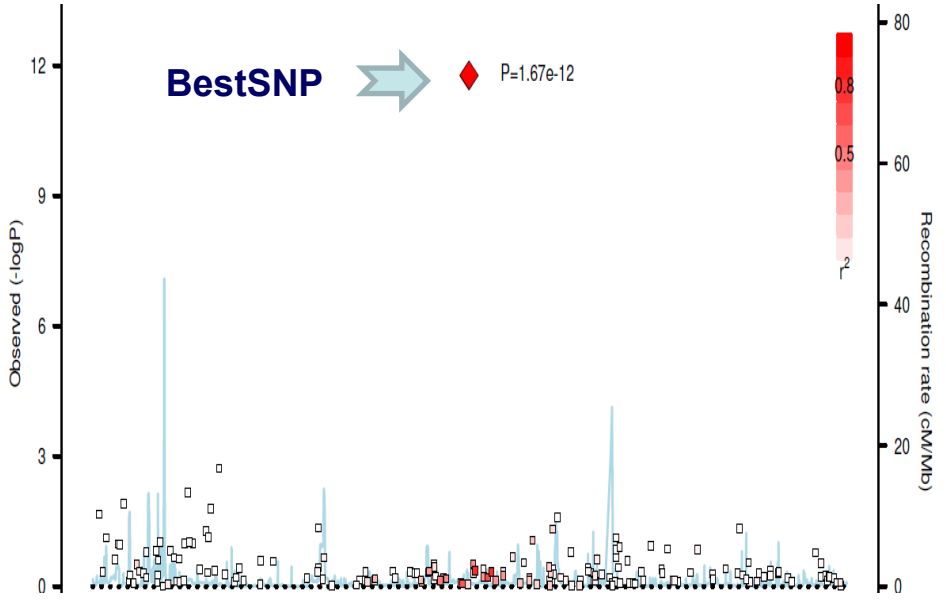
International Multicenter Study funded by ‚Welcome Trust Case Control Consortium' (WTCCC3)

- **Coordinators: C. Bulik (Chapel Hill, USA) and D. Collier (London/UK)**
- **n= 2,907 AN patients (n= 500 from Germany) and 14,860 controls (Illumina 660W-Quad)**

Manhatten Plot



Regional Plot



Identify your role

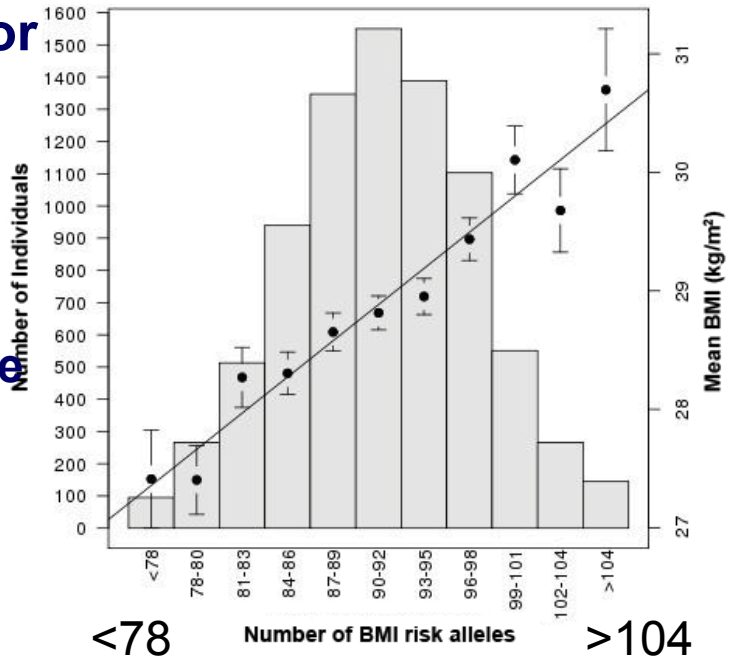
Boraska et al. 2014;
Mol Psychiatry 19:1085-94

GIANT: BMI

GIANT CONSORTIUM

Genetic Investigation of ANthropometric Traits

- Meta-analysis (GWAS and Metabochip) for BMI
- ≤ 339,224 individuals
- 97 BMI loci (56 novel)
- 2.7% of BMI variance explained
  - Frequent alleles explain ≤ 20% of variance
- Role of CNS



Relevant pathways: e.g. synaptic function, glutamate signaling, insulin secretion/ action, energy metabolism, lipid biology

Locke et al. 2015, Nature. 2015 Feb 12;518:197-206

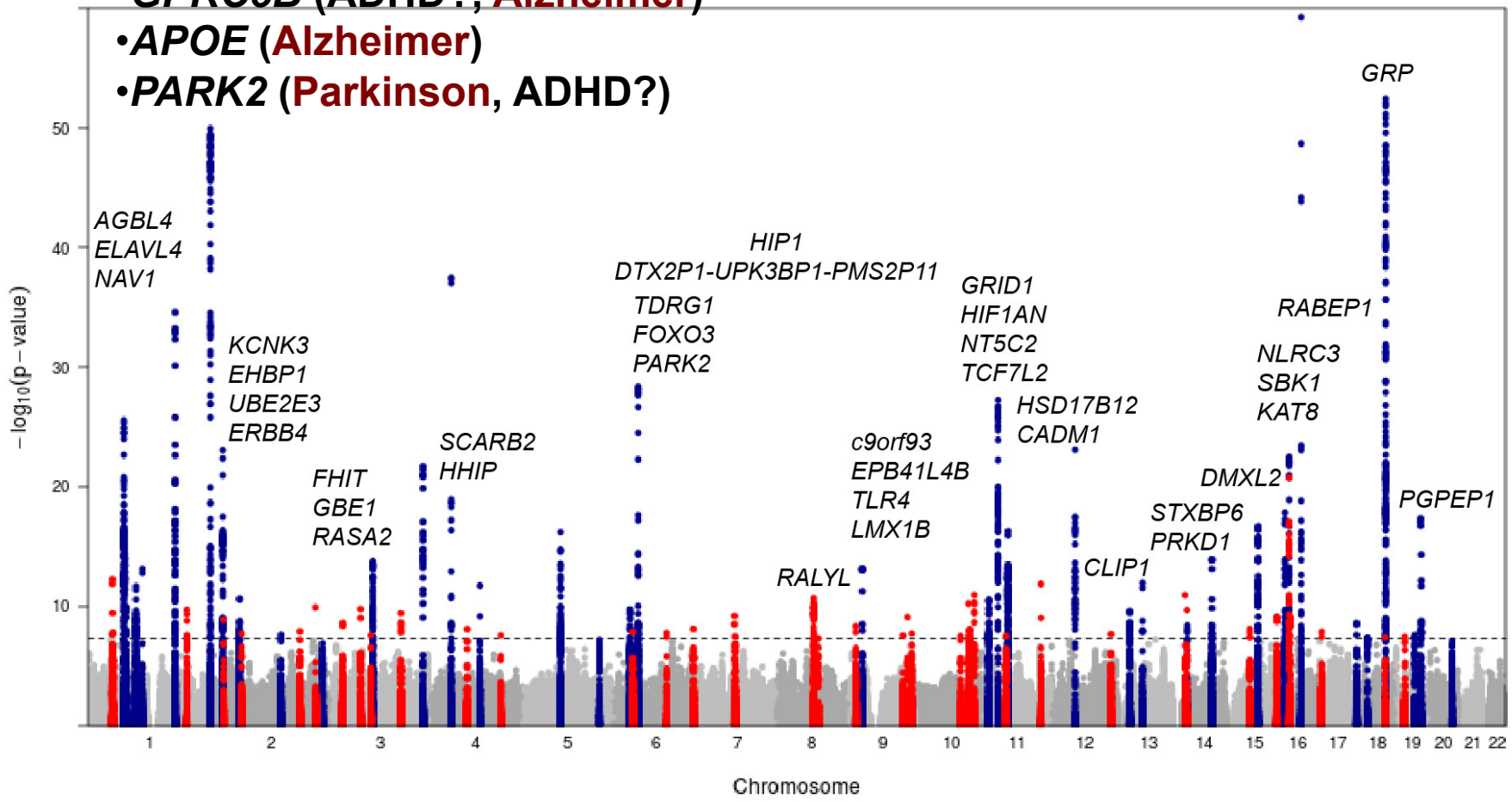
GIANT: BMI

GIANT CONSORTIUM

Genetic Investigation of ANthropometric Traits

Genes with potential relevance for neuropsychiatric disorders:

- ***BDNF*** **(ADHD?, MDD?)**
- ***GPRC5B*** **(ADHD?, Alzheimer)**
- ***APOE*** **(Alzheimer)**
- ***PARK2*** **(Parkinson, ADHD?)**



Locke et al. 2015, Nature. 2015 Feb 12;518:197-206

Three Loci Potentially Involved in both Anorexia Nervosa and Obesity

- Look-up of the 1000 SNPs with lowest p-values of a GWAS for AN (Boraska et al, 2014) in GWAS meta-analysis for BMI variation (Locke et al, 2015)
- Significant association (p-values < $5x10^{-05}$, Bonferroni corrected p < 0.05) for 9 SNPs at 3 independent loci (chr. 2, 10 and 19)
- All risk alleles were directionally consistent for AN and obesity

Hinney et al., in preparation

Acknowledgements

Clinical work: Anne Ballauf, Beate Herpertz-Dahlmann; Anke Hinney, Christian Holtkamp, Helmut Remschmidt,

Rat studies: Cornelia Exner, Martin Klingenspor, Gerhard Heldmaier

Leptin levels: Werner Blum, Manuel Föcker

DSM Criteria: Cindy Bulik, Regina Casper, Ulrich Schweiger, Janet Treasure