How to Bridge the Gap between Research and Clinical Practice
Examples from Anorexia Nervosa Research

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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**

<table>
<thead>
<tr>
<th></th>
<th>10-12</th>
<th>13-14</th>
<th>15-16</th>
<th>18-20</th>
<th>21-23</th>
<th>24-26</th>
<th>27-29</th>
<th>33-35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td>15.6</td>
<td>16.6</td>
<td>17.4</td>
<td>18.4</td>
<td>18.5</td>
<td>18.5</td>
<td>18.7</td>
<td>19.4</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>15.3</td>
<td>16.6</td>
<td>17.8</td>
<td>19.7</td>
<td>20.0</td>
<td>20.2</td>
<td>20.5</td>
<td>21.3</td>
</tr>
</tbody>
</table>

Hebebrand et al., Int J Eat Dis 1996
German BMI Percentiles (Females)

Overweight: BMI ≥ 90. P

Obesity: BMI ≥ 97. P

Anorexia nervosa: BMI < 10. P

Kromeyer-Hauschild et al. (2001); Monatsschrift Kinderheilkunde 149: 807
US BMI Percentiles (Females)

2 to 20 years: Girls
Body mass index-for-age percentiles

<table>
<thead>
<tr>
<th>Date</th>
<th>Age</th>
<th>Weight</th>
<th>Stature</th>
<th>BMI*</th>
<th>Comments</th>
</tr>
</thead>
</table>

*To Calculate BMI: Weight (kg) + Stature (cm) + Stature (cm) x 10,000
or Weight (lb) + Stature (in) + Stature (in) x 703

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CDC 2000 growth curves

10th Percentile

Published May 30, 2000 (modified 13/16/30).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). http://www.cdc.gov/growthcharts
### 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

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

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

r = 0.63

Make use of the spin-off
Referral-BMI and Weight Loss

Weight loss in kg/m²

Premorbid BMI Percentile

r = 0.66

Coners et al., Int J Eat Dis 1999
Relationship between Referral and Follow-up BMI: 272 Patients

<table>
<thead>
<tr>
<th>Referral-BMI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 13 kg/m²</td>
<td>≥ 13 kg/m²</td>
</tr>
<tr>
<td>n = 100</td>
<td>n = 172</td>
</tr>
</tbody>
</table>

BMI at follow-up (mean: 9.5 years)

<table>
<thead>
<tr>
<th>BMI at follow-up</th>
<th>35%</th>
<th>12.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 17.5 kg/m²*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5th centile*</td>
<td>44%</td>
<td>19.8%</td>
</tr>
<tr>
<td>≤ 10th centile*</td>
<td>56%</td>
<td>29.0%</td>
</tr>
<tr>
<td>≥ 25 kg/m²</td>
<td>1%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Deceased</td>
<td>11%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

*including deceased patients

Hebebrand et al., Am J Psychiatry 154: 566-569; 1997
The \( \textit{ob/ob} \) mouse

Carpe diem

Wild type litter mates

Leptin deficient mouse

Zhang et al., Nature 1994
Child B before leptin
(wt = 42kg at 3yrs)

Child B after leptin
(wt = 32kg at 7yrs)
courtesy of Sadaf Farooqi
Leptin Signaling: Adaptation to Semi-Starvation

Hypothalamus

- Arcuate Hypothalamus
- Lateral Hypothalamus

NPY
AGRP

POMC (αMSH)
CART

Hypophysiotropic neurons

CRH
TRH
SS
GHR
GnRH

Portal System

Pituitary

ACTH
TSH
LH/FSH
GH

Adrenal
Thyroid
Gonad

Cortisol
T4/T3
Sex steroids
Growth

Sympathetic Output

Appetite

Adipose Tissue

LEPTIN

according to Ahima and Flier (2000), Yamada et al. (2001)
Serum lg10 Leptin Levels in Acute Anorexia Nervosa

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

<table>
<thead>
<tr>
<th>cut-off (µg/L)</th>
<th>patients</th>
<th>controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>true positives</td>
<td>false negatives</td>
</tr>
<tr>
<td>100% sensitivity</td>
<td>4.02</td>
<td>74</td>
</tr>
<tr>
<td>100% specificity</td>
<td>1.63</td>
<td>64</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>cut off (µg/L)</th>
<th>sensitivity</th>
<th>specificity</th>
<th>ppV</th>
<th>npV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>0.89</td>
<td>0.97</td>
<td>0.604</td>
<td>0.994</td>
</tr>
<tr>
<td>2.5</td>
<td>0.93</td>
<td>0.94</td>
<td>0.444</td>
<td>0.996</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>statistical parameter</th>
<th>legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive predictive Value</td>
<td>% of individuals with positive test results who are correctly diagnosed as patients</td>
</tr>
<tr>
<td>negative predictive Value</td>
<td>% of individuals with negative test results who are correctly diagnosed as healthy</td>
</tr>
<tr>
<td>sensitivity</td>
<td>% of actual positives which are correctly identified as such</td>
</tr>
<tr>
<td>specificity</td>
<td>% of negatives which are correctly identified</td>
</tr>
</tbody>
</table>

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  reduced FSH, LH, estrogen
hypothermia  low T3 syndrome
cold intolerance  high ghrelin levels
hypotension  reduced hematopoiesis
bradycardia  hyperadrenocorticicism
dryness of skin  reduced resting energy
lanugo  hypoleptinemia
constipation
abdominal pain
increased ventricular -brain ratio

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

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., Physiol 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
• 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

• 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 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
1. 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.

2. Intense fear of gaining weight or becoming fat, even though underweight.

3. 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.
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)

Manhattan Plot

Regional Plot

Identify your role
GIANT: BMI

- 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
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., submitted
Leptin hebt inhibitorischen Effekt einer Futterrestriktion auf das Längenwachstum auf

- Das Längenwachstum von jungen futterrestrikierten Mäusen ist beeinträchtigt
- Leptin unterdrückt den wachstumshemmenden Effekt einer Futterrestriktion (Tibia)
  - Leptin wirkt über Leptinrezeptoren in Wachstumsfugen

Gat-Yablonski et al., Endocrinology 145: 343-350, 2005
Acknowledgements

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

Rat studies: Cornelia Exner, Martin Klingenspor, Gerhard Heldmaier

Leptin levels: Werner Blum

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