Is Anorexia Nervosa the opposite of obesity?

Nadia Micali, MD PhD MRCPsych FAED
University of Geneva & Hopitaux Universitaires de Geneve
Switzerland
Nadia.micali@unige.ch

Outline

• Background
• Highlight new findings on the genetics of Anorexia Nervosa
• Do childhood behaviours and growth predict AN?
• Are AN and BMI genetic scores associated with childhood/adolescent ED phenotypes?
• Conclusions
What is Anorexia Nervosa?

A. Food restriction leading to significantly low body weight in the context of age, sex, developmental status

B. Intense fear of gaining weight or becoming fat, or persistent behaviour that interferes with weight gain

C. Disturbance in the way 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.

What is Anorexia Nervosa?

• An uncanny ability to keep one’s own body weight low Irrespective of:
  Environment
  Family and loved ones’ pressure
  Sometimes treatment
Eating Disorders occur across the weight spectrum

AN is different from other ED

- Incidence stable across decades
- Described across cultures
- Diagnosis defined in the 19th century
- Some descriptions date back to 1300-1500
Anorexia Nervosa in the clinic

• Low BMI has traditionally been viewed as the consequence of psychological features of AN (i.e. drive for thinness)
• Sustained weight gain and psychological recovery are tricky
• Best treatment: specific family therapy for AN in adolescents (80% recovery rates)
• Hard to determine prognosis
• NO PHARMACOLOGICAL TREATMENT

Eating Disorders (ED) and related behaviours are cross-sectionally and longitudinally associated with weight and BMI

• BED predicts overweight and obesity (OR 1.90, 95%CI: 1.04–3.48, p<0.001) across US and UK
• BN predicts overweignt and obesity (OR=3. 43, 95%CI: 1.06-11.07, p<0.001)
• AN at age 14 and/or 16 prospectively associated with underweight BMI amongst adolescents (OR=2.43, 95%CI:1.62-3.66, p≤0.0001)

(Field et al, 2014; Micali et al.,2015; Eik-Nes et al, 2015)
Lipid profile in AN vs HC meta-analysis: T cholesterol

Mean difference in AN>HC:

- ApoB
- tryglicerides
- LDL cholesterol
- HDL cholesterol

AFTER PARTIAL WEIGHT RESTORATION AN>HC:

- Cholesterol
- LDL cholesterol
The genetics of AN

Genetic correlation between AN and other traits: latest GWAS (16,992 cases and 55,552 controls)

Watson et al. in press
AN GWAS: genes identified

- 8 independent loci identified
- Genes that are expressed in the brain
- Genes that are associated with metabolic traits (e.g. CADM1)

AN GWAS: what does it tell us about AN?

- Fundamental metabolic dysregulation may explain the exceptional ability that individuals with AN have maintaining a low BMI even in the face of treatment
Do childhood eating and growth predict AN? i.e. can we identify early appetite/metabolic phenotypes related to AN

Background

• Low BMI in adolescent girls and young adults may predict later AN in adulthood (Tyrka et al, 2002; Stice, 2016)

• Childhood under-eating predicts self-reported AN (Nicholls et al, 2009)
Avon Longitudinal Study of Parents and Children (ALSPAC)

• Longitudinal, population-based, prospective study of women and their children
  • All pregnant women living in the geographical area of Avon expected to deliver between 1 Apr 1991 and 31 Dec 1992
  • Children from 14,541 pregnancies (13,988 alive at Year 1)
  • Additional 713 children enrolled later on in childhood

ED data collected at ages 14,16, 18 years -> ED diagnoses derived from objective and Q data

GWAS data available on 17,816 participants

ALSPAC: childhood growth

• Inclusion:
  • Weight and height/length information at three independent time points (birth on)
  • ≥ 1 ED diagnosis OR no ED symptoms
• Exclusion:
  • No diagnosed ED but presence of risk behaviors (e.g., binge eating or purging less than once a month)

1,839 youth from the larger study included in our analysis
Childhood BMI trajectories differ in adolescents who develop AN

Avon Longitudinal Study of Parents and Children (ALSPAC)

- Data on childhood eating behaviours (N=7,837) measured at 8 timepoints between ages 1 -10 years

Latent class growth trajectories to establish longitudinal trajectories of:
- Under-eating
- Fussy eating

Best fitting number of classes using Akaike Information Criterion, Bayesian Information Criterion, entropy and class size
Association between childhood eating behaviours and adolescent AN and BN

Childhood undereating  \rightarrow  Anorexia Nervosa
Childhood fussy eating

Methods
Multivariable logistic regression models

Estimated Risk Difference relative to the reference group, i.e. the change in risk of engaging in outcome for an eating behavior group in comparison to the reference group.

Models adjusted for covariates:
Maternal education at birth, maternal age at birth, birthweight and gestational age

Childhood Undereating predicts AN in girls

Risk Differences (RD)
In comparison to the Low persistent group.

6% risk increase in AN – girls only
RD: 6%. 95%CI: 0, 12
(N = 54)
Childhood Fussy eating predicts AN

Risk Differences (RD)
In comparison to the Low persistent group
2% risk increase in AN
RD: 2%, 95%CI: 0, 4

2% risk increase in AN
RD: 2%, 95%CI: 1, 4

Are AN and BMI genetic scores associated with childhood/adolescent ED phenotypes?
Methods: polygenic score calculation

- Polygenic score (PGS) was based on summary statistics of the BMI GWAS in the GIANT consortium and UKBiobank (N ~ 789,224) and AN latest GWAS
- Calculation, application, and evaluation of the PGS was carried out with PRSice Target cohort: The Avon Longitudinal Study of Parents and Children (ALSPAC)
- Association with best-fit PGS (corrected for multiple testing and overfitting) is reported
Methods: Data analyses

Childhood Eating behaviours & ED behaviours / cognitions

- Multinomial, linear or logistic regressions were applied using the BMI-PGS & AN-PGS to predict outcomes

Covariates for all analyses: sex

PGS-BMI and PGS AN are associated with childhood eating behaviour

Mean polygenic score-BMI, polygenic score-AN (PGS), and SE per child eating behavior group (N= 7,825)

Herle et al, in prep
**Undereating trajectories**

One standard deviation (SD) increase in BMI-PGS

 Undereating

20% decrease (RRR=0.80, 95%CI: 0.68-0.95) in odds of belonging to the high and stable trajectory

**Fussy eating trajectories**

One standard deviation (SD) increase in BMI-PGS

15% decrease (RRR=0.85, 95%CI: 0.78-0.93) in the odds of being in the high and stable trajectory

One standard deviation (SD) increase in AN-PGS

8% increase (RRR=1.08, 95%CI: 0.99, 1.18) in the odds of being in the high and stable trajectory
Results: BMI-PGS predicts ED behaviours/cognitions

Results: causal mediation analysis with BMI age 11 years as mediator

• BMI at age 11 significantly mediates the effect of the BMI-PGS
Is AN best explained as a single or multi-polygenic disorder?

Methods: Data analyses II
Single and multi-PGS models in predicting AN diagnosis

AN diagnosis
• Logistic regressions were applied using PGS derived from 26 GWAS including the BMI-PGS from the GIANT consortium
Covariates for all analyses: sex
Single-PGS approach in predicting AN: tested

- BMI-PGS and overweight-PGS are significant after correcting for multiple testing
- Direction of effect BMI-PGS, overweight-PGS, and AN-PGS are in line with what we expected

Results: multi-PGS approach in predicting AN

A multi-PGS model containing 16 PGS outperforms a single-PGS model in AN prediction!
Conclusions

• AN likely to be due to metabolic and psychiatric genes
• Complex disorder
• Our patients difficulties in reaching a ‘normal’ BMI might be real and driven by their metabolism rather than psychologically-driven
• This is confirmed by the association between childhood growth and eating behaviours and the association between the AN-PGS and these phenotypes
• Other ED are different and maybe more driven genetically by high BMI-PGS

CAVEATS

• Genetic risk likely to interact with environment

• GWAS only available in AN, but efforts to collect samples of BN and BED
• Need to increase AN GWAS sample size to obtain better prediction
• Need to replicate findings in other samples
• Still a simplistic view of complex behaviours and disorders
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- Great quality of life
- Great work opportunities
Thank you!

Nadia.micali@unige.ch