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Potential Mechanisms Underlying the Association Between Obesity and Mental Disorders

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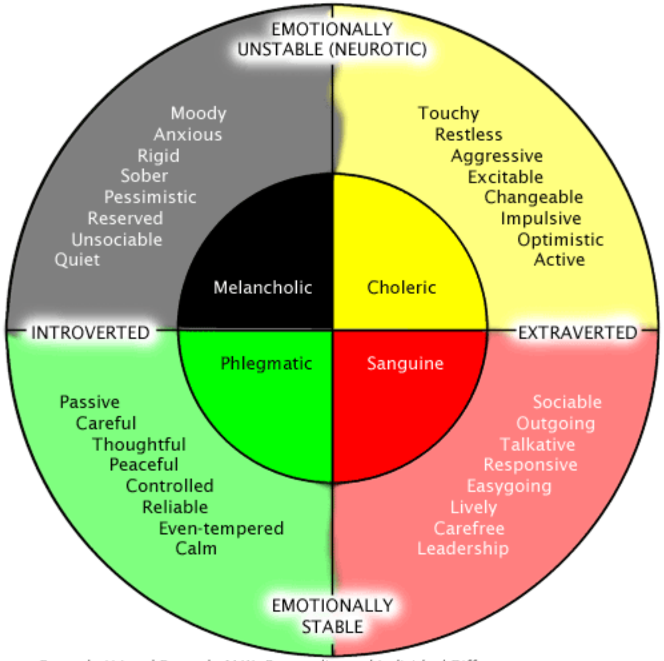
KTQ-Zertifikat

Conflicts of Interest

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

Past Attempts to Associate Somatic Phenotypes with Mental Features



Eysenck, H.J and Eysenck, M.W. *Personality and Individual Differences.* Plenum Publishing, 1958.

Humorism: system of medicine detailing makeup and workings of the human body, adopted by the Indian Ayurveda system of medicine, Ancient Greek and Roman physicians and philosophers

An excess or deficiency of any of 4 distinct bodily fluids (humors/humours) directly influences temperament and health

Hippocratic medicine: black bile, yellow bile, phlegm, and blood; each corresponds to one of the traditional 4 temperaments

Wikipedia

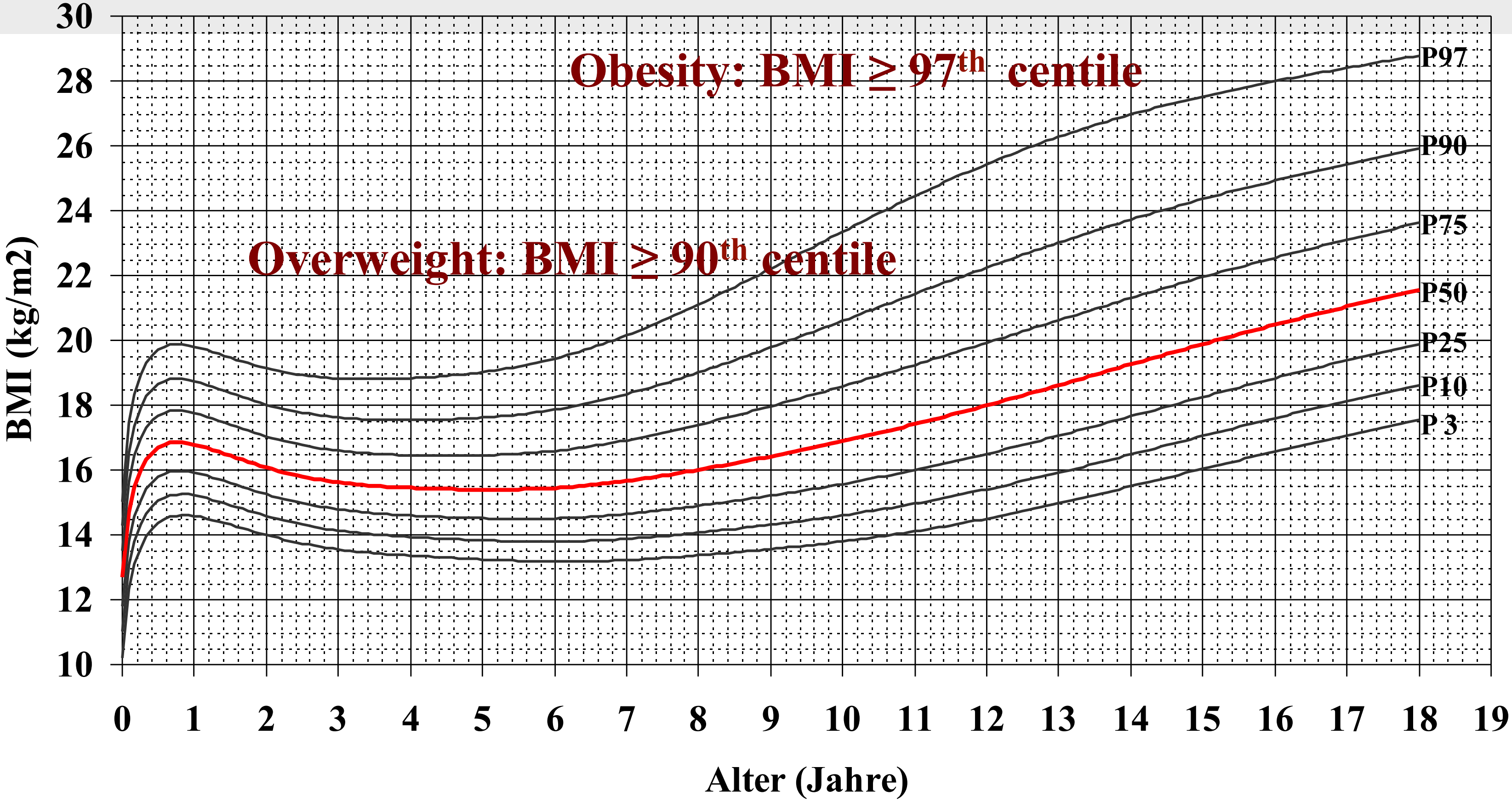
Overview

- Obesity and energy balance
- Association of obesity and mental disorders
  - ADHD, suicide, depression
- Potential *psychological and biological* mechanisms
  - Psychological factors including stress
  - Common genetic factors
  - Inflammation
  - Leptinergic system
- Nutrition, dietary patterns and mental disorders
- Conclusion

Weight Categories based on BMI (WHO, 1998)

Category	BMI (kg/m²)
Underweight	< 18.5
Normalweight	18.5 – 24.9
Overweight	≥ 25
Pre-obesity	25 – 29.9
Obesity Grade I	30 – 34.9
Grade II	35 – 39.9
Grade III	≥ 40

BMI Centiles for Females Aged 0 to 18 Years

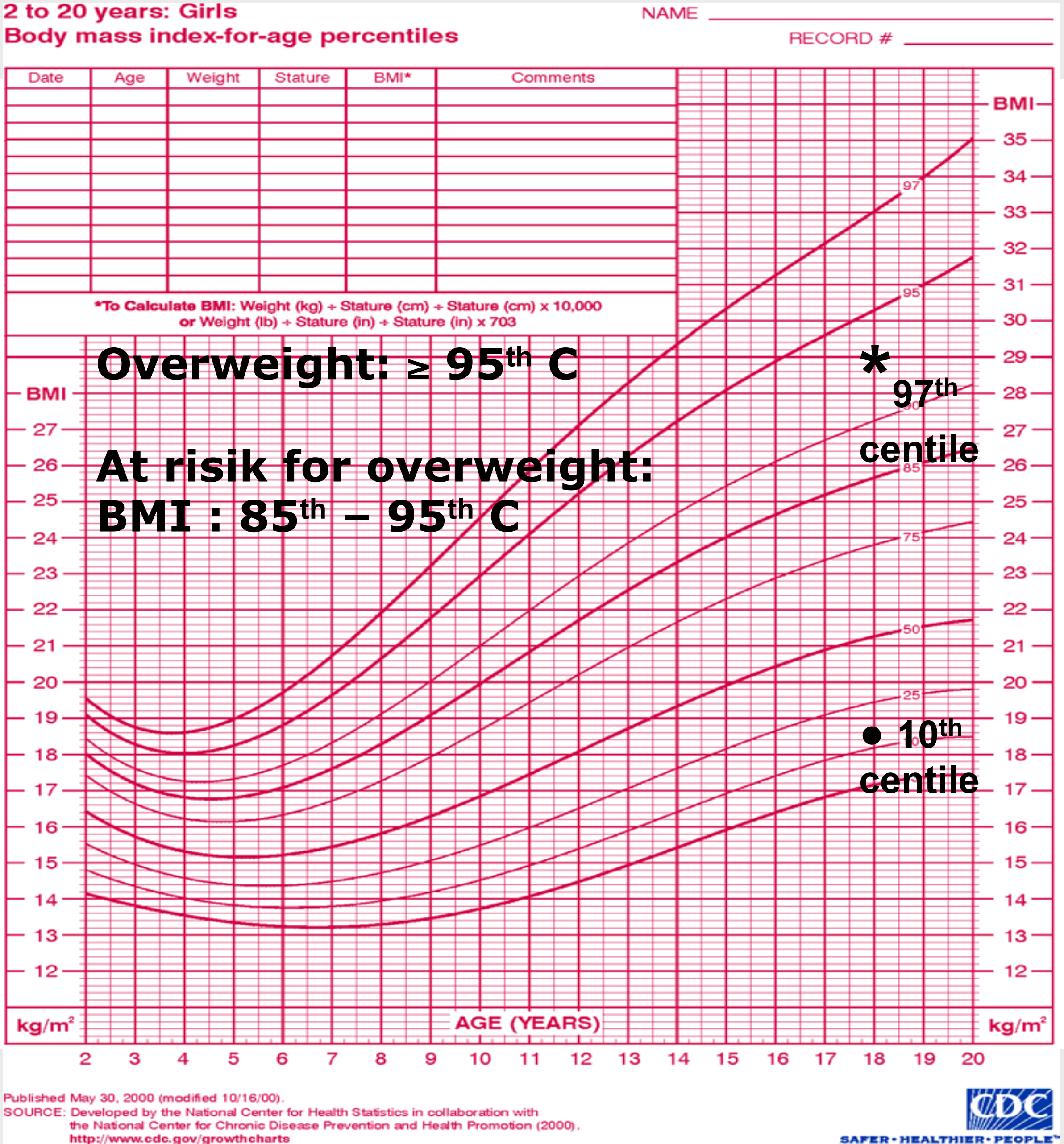


BMI centiles for German children

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

US BMI Centiles (Females)

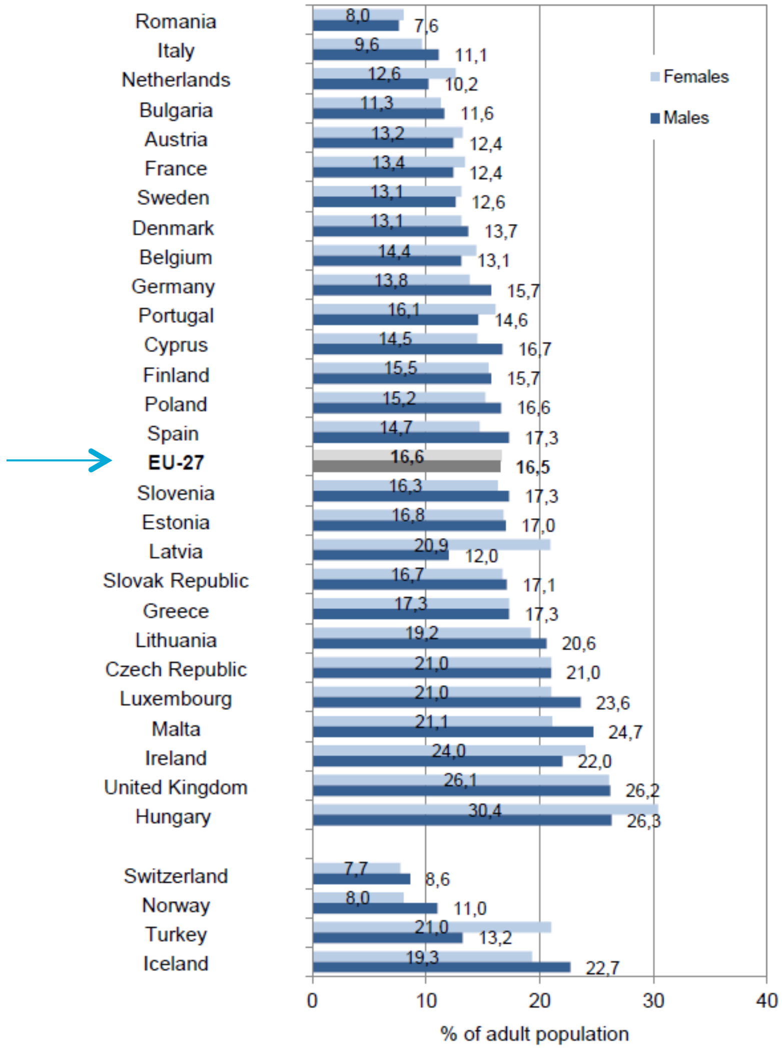
CDC 2000 growth curves



Adult Obesity Cut-off

Adult Overweight Cut-off

The Obesity Challenge for Europe

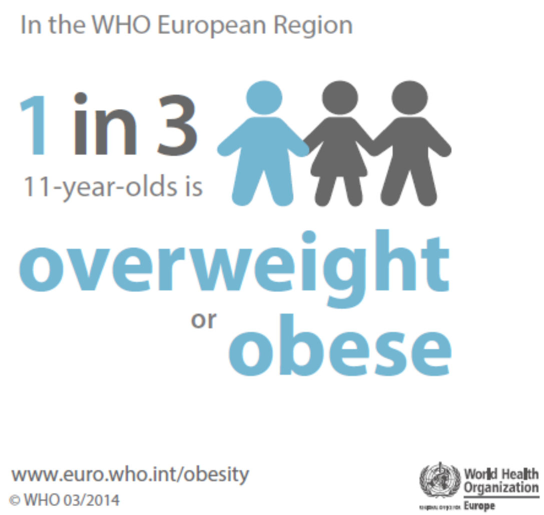


Prevalence of obesity among adults, 2010
(or nearest year)

Obesity Pandemic:

0.86 billion overweight children and adults in 1980

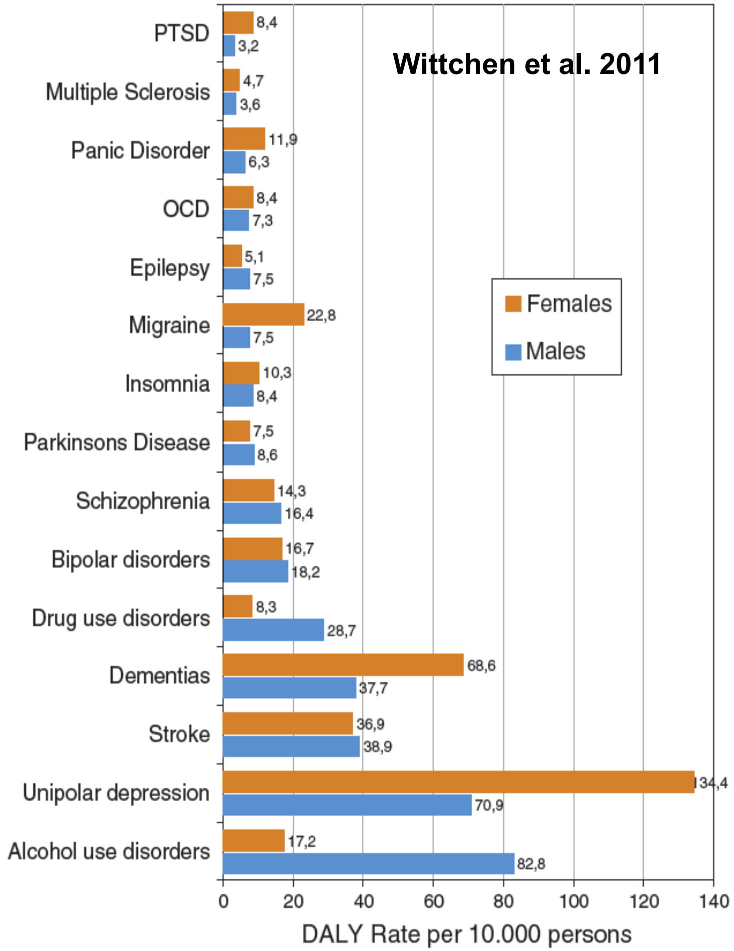
2.1 billion in 2013



OECD Health Data 2012; Eurostat Statistics Database; WHO Global Infobase; Ng et al., Lancet 2014

The Mental Health Challenge for Europe

Disability adjusted life years lost (DALY) for EU



- Example: Major Depressive Disorder
  - High impact in EU
  - Frequent cause for sick leave and early retirement (ER)
    - Increase in ER > 200% during 1992 - 2012

- Associations between obesity / eating behaviour and mental health
- But: Causality/directionality unclear

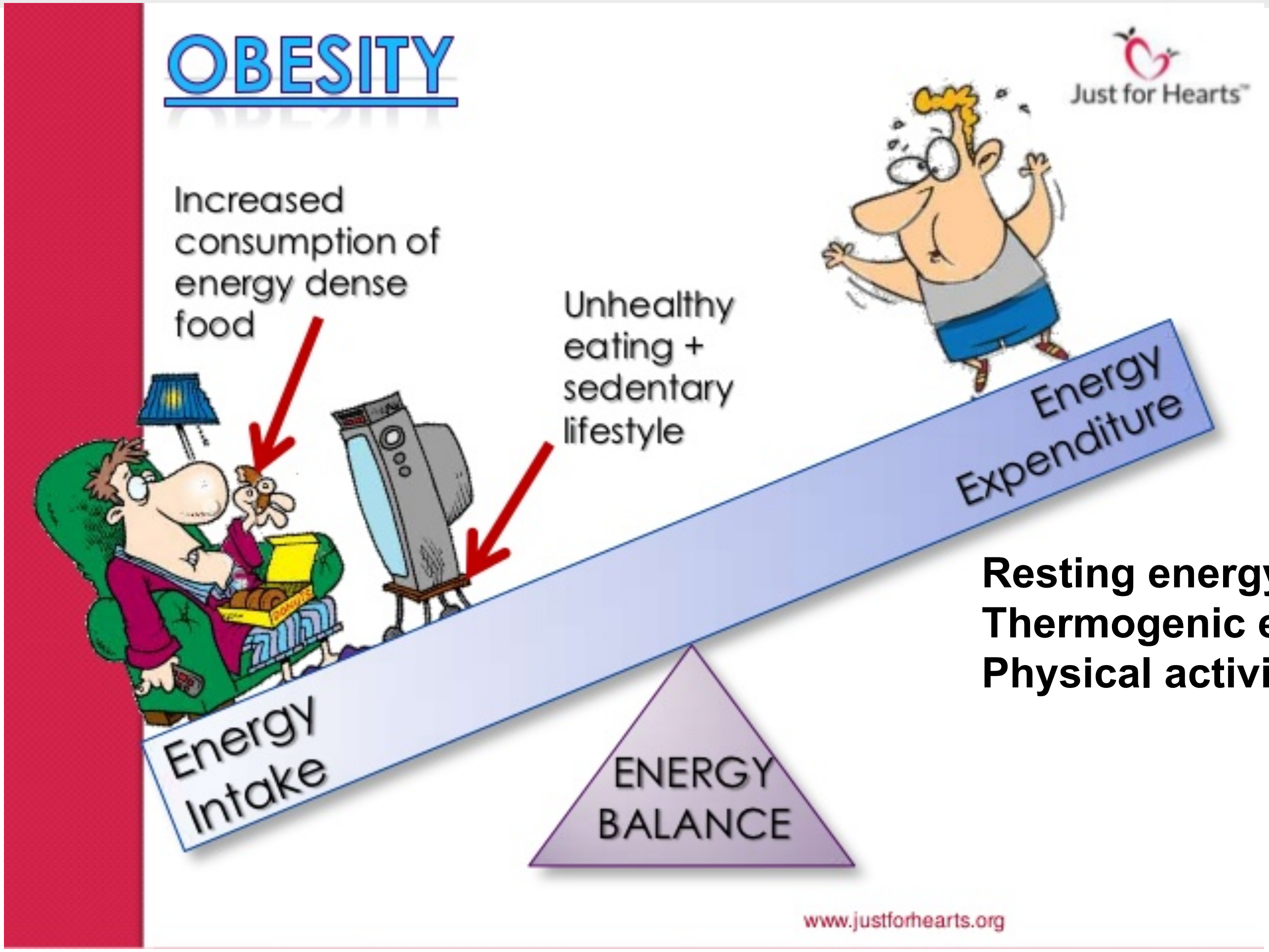
Sources: DAK Health Report 2013; Stewart et al. 2003; Sobocki et al. 2006; Wittchen et al. 2011; Reynolds et al. 2012; Watanabe et al. 2007; Cheung et al. 2013; Gibertini et al. 2012; Vohringer and Ghaemi 2011; wikimedia.org/wikipedia/commons/c/c0/Vincent_van_Gogh_-_Old_Man_in_Sorrow_(On_the_Threshold_of_Eternity).jpg

Systematic Review of Prevalence of Anxiety and Major Depressive Disorders

- Bayesian meta-regression approach to estimate point prevalence for 1990, 2005, and 2010
- Point prevalence rates for anxiety disorders/MDD estimated at 3.8%/4.4% in 1990 and 4.0%/4.4% in 2010
  - **crude number of cases increased by 36%**
    - explained by population growth and changing age structures
  - 8/11 GHQ studies: significant **increase in psychological distress** over time
- Other potential factors: greater public awareness, and misuse of terms such as anxiety and depression

Baxter et al. 2014; Depress Anxiety 31:506-16

Physiology: Energy Balance

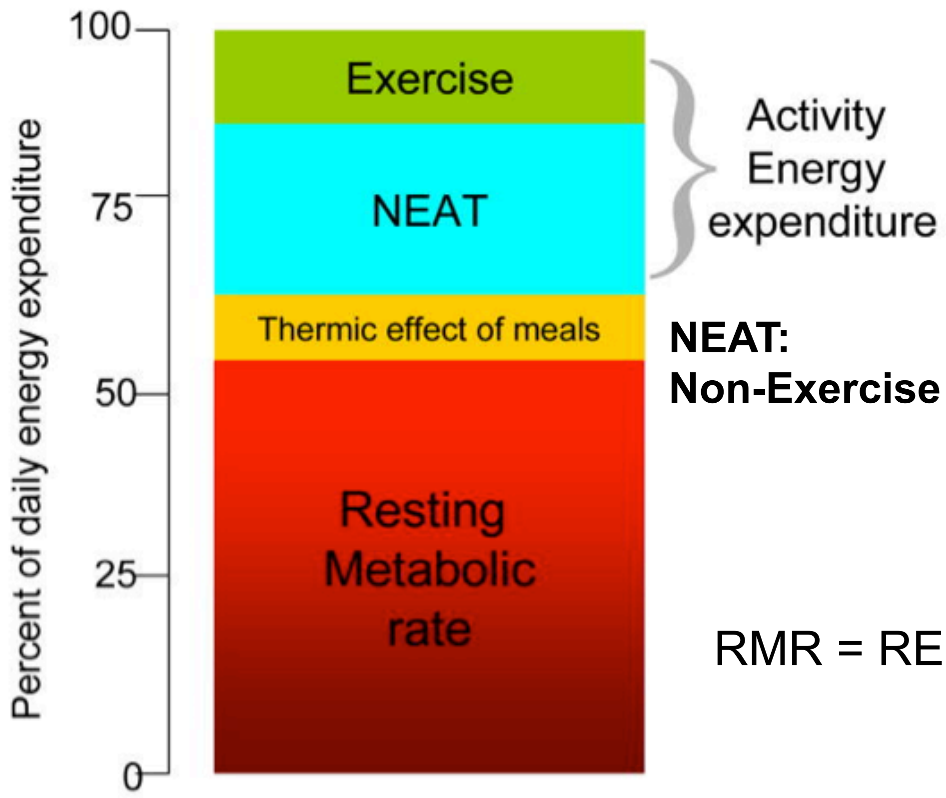


Resting energy expenditure
Thermogenic effect of food
Physical activity

Ageing: Getting heavier during adulthood (US data)

- Dietary Guidelines for Americans (2010) Average daily energy intake (self-reported; national survey):
  - males aged ≥ 19: 2,640 calories
  - females aged ≥ 19: 1,785 calories
  - Actual energy intake much higher!
- Between ages 25 and 44, annual increase in weight:
  - 3.4 % in men and 5.2 % in women
- In men and women, BMI tends to increase until age 50 and 70
- Gain in fat mass up to age 55: 18.5 kg

Energy expenditure



NEAT:
Non-Exercise Activity Thermogenesis

RMR = REE

http://www.teamvic.com/tv/wp-content/uploads/2014/10/percent-of-daily.png

Fat Free Mass and Fat Mass: Energy Requirements

Brain Accounts for 20-25% of Resting Energy Expenditure (REE)

Tissue	REE in kcal/kg/d	Weight
skeletal muscle	14.5	40->50% of TBW*
heart and kidneys	440	384 + 329 g
liver	200	1774 g
brain	**240**	**1609 g**
adipose tissue	4.5	25->50% of TBW

- Adult brain, liver, heart, spleen, and kidneys: 60–70% of REE
  - < 6% of TBW (all organs combined)
- Skeletal muscle: 20–30% of REE
  - 40–50% of TBW
- Inter-individual variation of brain energy expenditure?

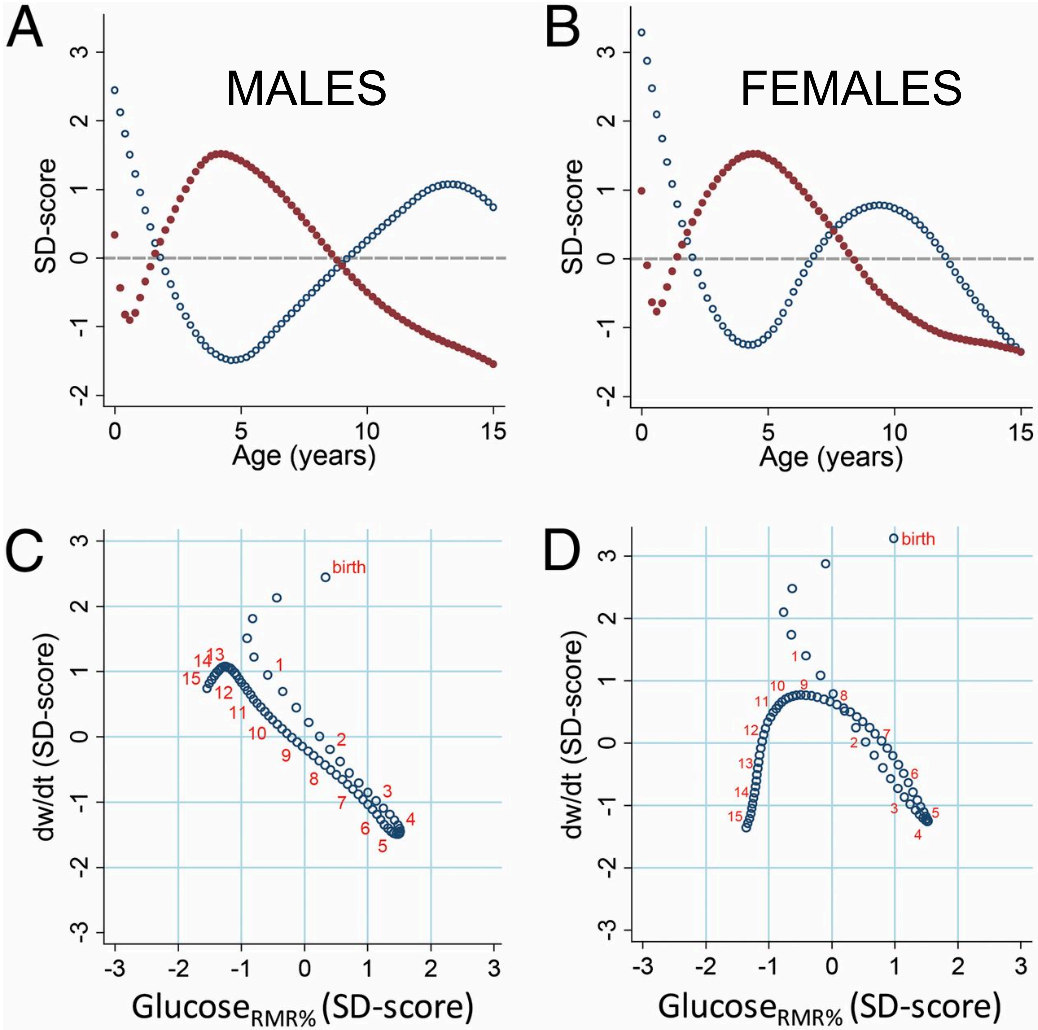
*TBW = Total Body Weight

Javed et al., 2010; Am J Clin Nutr 91:907–12.

Developmental Aspects: Glucose Resting Energy Expenditure% of the Brain and Body Weight Growth Rate during Childhood

Glucose REE %:

ratio between brain glucose uptake and daily glucose-gram equivalent REE or Daily Energy Requirement



Christopher W. Kuzawa et al. PNAS 2014;111:13010-13015

Key messages:

Brain energy requirement (approx. 65% of REE) maximal at age 4.2–4.4 y

Inverse relationship between body growth rate and brain energy requirement

At birth, ages 3 and 5 brain weight 25%, 75%, and 90% of adult weight

PNAS

Short and Long Term Effects of Mental Disorders on Body Weight

Energy intake

Anorexia nervosa

Major depression

ADHD

OCD

Schizophrenia

ASD

Energy expenditure

Anorexia (REE ↓, Activity ↑)

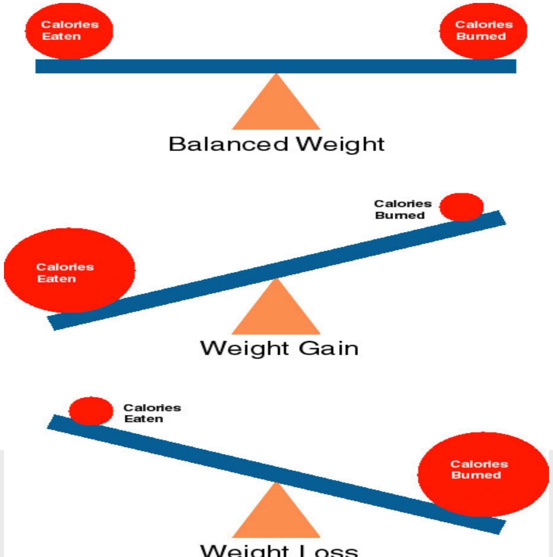
Major depression

ADHD

OCD

Schizophrenia

ASD



Long Lasting Effects of Anorexia Nervosa on Body Weight

	Referral-BMI	
	< 13 kg/m²	≥ 13 kg/m²
	n = 100	n = 172
BMI at follow-up (mean: 9.5 years)		
≤ 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 1997

Differences in Brain Energy Expenditure Adjusted for Fat and Fat Free Mass in Mental Disorders?

- **Intellectual disability: elevated obesity risk**
  - Down Syndrome: REE reduced in childhood
- **Scant systematic investigations in mental disorders**
  - ADHD: REE increased (12 cases, 12 controls; Müller et al. 2010; Eat Weight Disord 15:e144-51)
  - Negative search in PubMed for REE and
    - OCD
    - Anxiety disorders
    - Major depression

Resting Energy Expenditure (kJoule/d), BMI-SDS, Body Fat, Age and Gender in 215 Inpatients in Relationship to Depression Score

	Depression Score ≥ 18 (n=142)	Score <18 (n=71)	Mean difference	T-Test [1], Sig (2-Tailed)
	M (SD)	M (SD)	95% CI	Pearson χ^2
REE kJoule/d	**6565.7** (1412.1)	**7216.8** (1891.0)	651.1 [123.0, 1157.4]	$t(110.2)=2.566, p=0.012$
BMI SDS	0.21 (1.14)	0.28 (1.03)	0.064 [-.28, .37]	$t(211)=0.39, p=0.693$
Body Fat %	27.5 (11.5)	24.0 (11.2)	-3.56 [-7.01, -.25]	$t(211)=-2.15, p=0.032$
Age years	16.1 (1.1)	15.9 (1.2)	-0.15 [-.53, .19]	$t(211)=-0.88, p=0.380$
Female %	72.7	38.4		$\chi^2(81)=24.0, p<0.001$

[1] T-Test BCa Bootstrap 95% CI (1000 samples)

Bod Pod
air displacement plethysmography

calorimetry

Partial correlation between depression score and REE adjusted for gender, age, fat mass, and fat free mass: r=-0.023 [-.16, .12] p=0.744

Föcker, Albayrak, Peters et al, in preparation

EU-NeuroFAST

Association of Obesity and Mental Disorders

- Evidence for positive association with
  - Anxiety disorders
  - Attention deficit-/hyperactivity disorder
  - Binge eating disorder
  - Major depressive disorder

www.drsharma.ca/wp-content/uploads/sharma-obesity-depression.jpg

- Negative association with
  - Conscientiousness
  - Suicide

Halfon et al. 2013 ; Gariepy et al.2010; Luppino et al. 2010; Pott et al. 2010; Pauli-Pott et al. 2010; Cortese 2012; Klinitzke 2013; Jokela et al. 2013;

Association of ADHD and Obesity

Reference	Study group (n)	Age	Association
Spencer et al. (1996)	124 boys, clinical 109 controls	6-17	+
Holtkamp et al. (2004)	97 boys, clinical	Ø 10	+
Faraone et al. (2005)	568 clinical	6-12	+
Hubel et al. (2006)	39 boys, clinical 30 controls	8-14	+
Spencer et al. (2006)	178 clinical	6-13	+
Swanson et al. (2006)	140 clinical	3-5.5	+
Ptacek et al. (2009)	46 boys, clinical	Ø 11.03	+
Anderson et al. (2006)	655 general population	< 16.6	+
Lam et al. (2007)	1429 general population	13-17	+
Pagoto et al. (2009)	6735 general population	18-44	+
Erhart et al. (2011)	2863 general population	11-17	+
Biederman et al. (2003)	140 girls, clinical 122 controls	6-17	-
Curtin et al. (2005)	98 clinical	13.8	-

Upcoming review and meta-analysis: see Cortese et al., 2014; *BMJ Open; 4:e004541*

Adapted from Cortese and Vincenzi Curr Top Behav Neurosci 2012;9:199-218

National Survey of Children´s Health
N=46,707 10-17 y olds

- **Prevalence of obesity (≥ 95th centile) adusted for sociodemographic factors and SES: 14.8% (95% CI: 14.7-15.0)**

	% obese (adj.)	% total
Physical conditions		
Asthma (ever)	19.7	14.9
Severe headache/migraine (past 12 mths)	17.6	8.4
Ear vision problems (ever)	18.4	3.2
Multiple ear infections (past 12 mths)	27.1	2.6
Diabetes (ever)	26.4	0.5
Developmental and behavioral/emotional		
Learning disability (ever)	19.3	13.0
Develop. delay/physical impairment (ever)	22.4	3.5
Speech problems (past 12 mths)	17.7	2.1
Autism (ever)	22.4	0.5
ADHD (ever)	18.9	10.2

Chen et al., 2009; Obesity 18: 210-213

Mothers of ADHD Children: Odds Ratios for Selected Disorders

1869 ADHD children and 5538 non-ADHD children integrated health care delivery system (Kaiser Permanente)

• ADHD	3.23
• Depression	1.88
• Obesity	1.70
• Anxiety neuroses	1.64
• Contusion/abrasions	1.59
• Musculoskeletal symptoms	1.51
• Acute lower respiratory infection	1.47
• Lower back pain	1.45
• Asthma	1.45
• Female genital symptoms	1.43
• Acute sprains	1.41
• Abdominal pain	1.41
• Acne	1.41

Ray et al., Med Care 47: 105-114; 2009

The Protective Role of Obesity for Suicide

Swedish cohort study (males)

- 1.299.177 male conscripts born 1950-1981
  - Followed-up in 1968-1999
  - At baseline: anthropometry, self-reported psychiatric disorders

- **Inverse association between obesity and suicide:**
  - **Suicide risk decreases by 15% for every increment of 5 kg/m²**
  - Results similar upon exclusion of psychiatrically ill males at baseline
  - Association similar for different lengths of follow-up

Magnusson et al., Am J Epidemiol. 2006; 163: 1-8

The Protective Role of Obesity for Suicide

American cohort study (males and females)

- Data sets:
  - National Health Interview Surveys: 1986 - 1994
  - Multiple Cause of Death Data: 1986 - 2002 (National Death Index)

- Survival analyses:
  - **For every BMI increment of 5 kg/m^2 suicide risk decreases by 18% and 24% for males and females**

Kaplan et al., J Nerv Ment Dis 2007; 195: 948-51

Obesity and Suicide - Synopsis

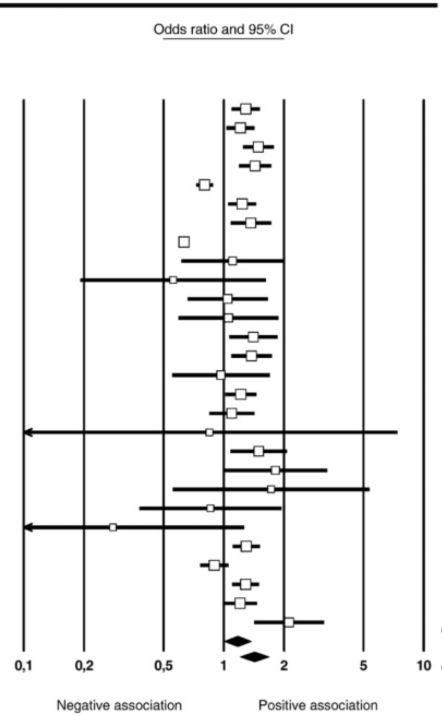
- **Independent confirmations of the association of obesity with reduced suicide rates (data stronger for males than females)**
  - single studies: J-shaped relationship
  - single non-confirmatory studies
- **Several potential mediating or correlative factors:**
  - impulsivity
  - case-fatality in relation to the chosen method of suicide
  - serum levels of cholesterol and its relation to central serotonin
  - leptin and leptin resistance
  - insulin resistance
  - dietary factors such as essential fatty acid intake
  - \`jolly fat´ hypothesis

Perera et al. 2015; Systematic Reviews 4:52

Cross-Sectional Association of Obesity and Depression: Meta-Analysis; 17 studies; N=204,507

- **Significant association** of depression and obesity; OR: 1.2
  - post hoc: significant association in females, non-significant association in males
  - no clear-cut effect of age, continent of residence, year of publication and measurement methods

Name first author	Gender	Odds ratio	Lower limit	Upper limit
John	females	1,29	1,10	1,52
John	males	1,21	1,04	1,42
Haukkala	females	1,49	1,25	1,78
Haukkala	males	1,44	1,20	1,73
Stewart	both	0,80	0,73	0,88
Ross	both	1,24	1,06	1,45
Carpenter	females	1,37	1,09	1,73
Carpenter	males	0,64	0,60	0,67
Hach	females	1,11	0,62	1,99
Hach	males	0,56	0,19	1,63
Herva	females	1,05	0,66	1,66
Herva	males	1,06	0,60	1,88
Johnston	both	1,41	1,07	1,86
Istvan	females	1,38	1,10	1,73
Istvan	males	0,97	0,55	1,70
McIntyre	females	1,22	1,02	1,45
McIntyre	males	1,10	0,85	1,42
Ohayon, 2006	both	0,85	0,10	7,38
Ohayon, 2007	both	1,50	1,09	2,07
Onyke	females	1,82	1,01	3,29
Onyke	males	1,73	0,56	5,36
Palinkas	females	0,86	0,38	1,94
Palinkas	males	0,28	0,06	1,26
Scott	females	1,30	1,11	1,52
Scott	males	0,90	0,77	1,06
Simon	females	1,29	1,11	1,50
Simon	males	1,21	1,00	1,47
Overall random effect size		1.18	1.01	1.37
Outliers excluded		1.26	1.17	1.36



De Wit et al. 2010; Psychiatry Res.178: 230-5

Overall random effect size: 1.2
Outliers excluded: 1.3

Reciprocal Prediction of Obesity and Depression in Longitudinal Studies: Meta-Analysis; 15 studies; N=58,745

- *Pre-obesity* predicted depression at follow-up; **OR: 1.27** (95% CI 1.1-1.5)
  - significant among adults, but not among subjects <20 y
- *Obesity* increased risk of onset of depression at follow-up; **OR: 1.55** (95% CI 1.2-2.0)

- Depression (symptoms and disorder) not predictive of *pre-obesity*; **OR: 1.2** (95% CI 0.9-1.7)
- Depression predictive of *obesity*; **OR: 1.58** (95% CI 1.3-1.9)
  - Most pronounced
    - subjects < 20 y; OR: 1.8 + females > males; OR 2.0 vs.1.4
  - Subgroup analyses: no specific moderators detected

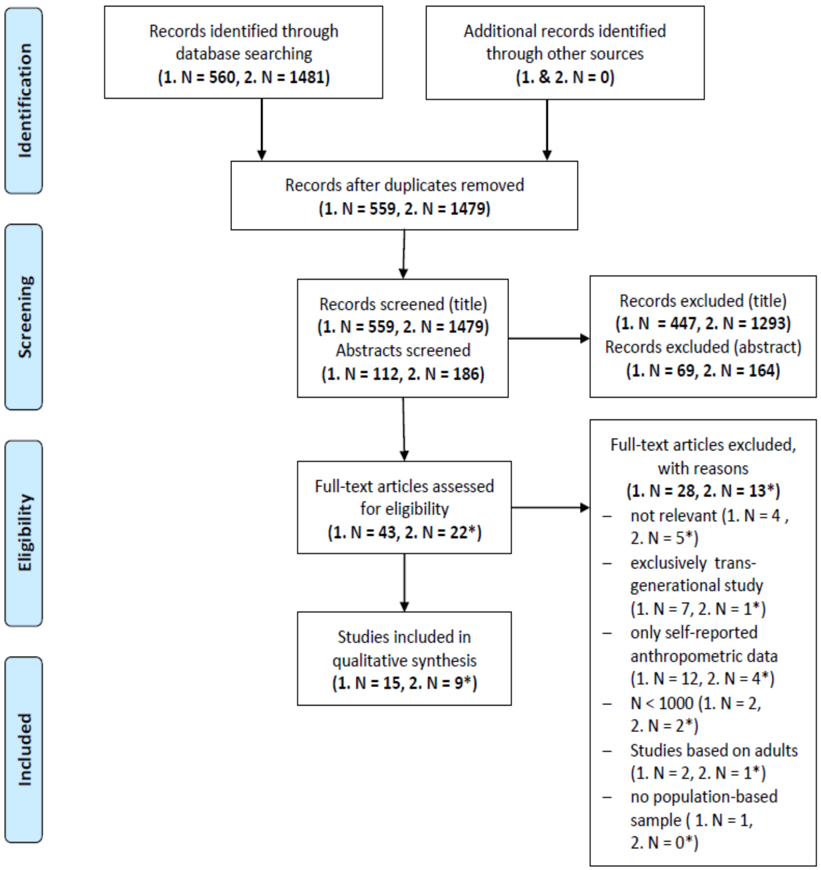
Luppino et al. 2010; Arch Gen Psych 67: 220-9

Depression Predicts Overweight and Obesity: One Year Follow-up of Adolescents

- National Longitudinal Study of Adolescent Health:
  - 9374 adolescents (grades 7-12)
  - Assessment at baseline (1995) and 1 year later
  - Center for Epidemiologic Studies Depression Scale
  - BMI (kg/m^2): self-reported height and weight
  - Obesity: BMI ≥ 95th percentile; overweight: BMI ≥ 85th and <95th percentile; normal weight: BMI <85th percentile
- Baseline obesity not predictive of depression
- Depressed mood at baseline predictive of obesity at follow-up; **OR: 2.1** (95% CI: 1.2-3.6)
  - Persistence after controlling for BMI z score at baseline, age, race, gender, parental obesity, number of parents in home, SES, adolescents' report of smoking, self-esteem, delinquent behavior (conduct disorder), and physical activity

Bidirectionality: Obesity <> Depression?
Search strategy of our systematic review

- Search criteria (Aug. 27, 2014)
  - **1.** (mood OR depress* OR affective disord*) AND obesity AND (child* OR adolesc* OR youth*) AND (longitudinal OR prospective)
  - **2.** (mood OR depress* OR affective disord*) AND obesity AND (child* OR adolesc* OR youth*) AND (epidemiol* OR population)
- Inclusion criteria
  - **Population based (no clinical samples)**
  - **Cases: N ≥ 1000**
  - **Age <18 years at study start**
  - **Measured weight/height**
  - **Validated psychometric instruments**



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

*only additional studies not reported in search No. 1

Longitudinal Studies (search Aug. 27, 2014)

- 4 studies: bidirectional influence of weight status and depression
  - Geoffroy et al., 2014; Marmorstein et al., 2014; Roberts et al., 2013; Frisco et al., 2013
- 4 studies: unidirectional influence of weight status on depression
  - Al Mamun et al., 2007; Clark et al., 2006; Sweeting et al., 2005; Swallen et al., 2005
- 5 studies: unidirectional influence of depression on weight status
  - Larsen et al., 2014; Kubzansky et al., 2012; Bjornelv et al., 2011; Gaysina et al., 2011; Viner et al., 2006

- 3/8 studies: obesity predicts depression
- 3/9 studies: depression predicts obesity

Potential Mechanisms Underlying Associations

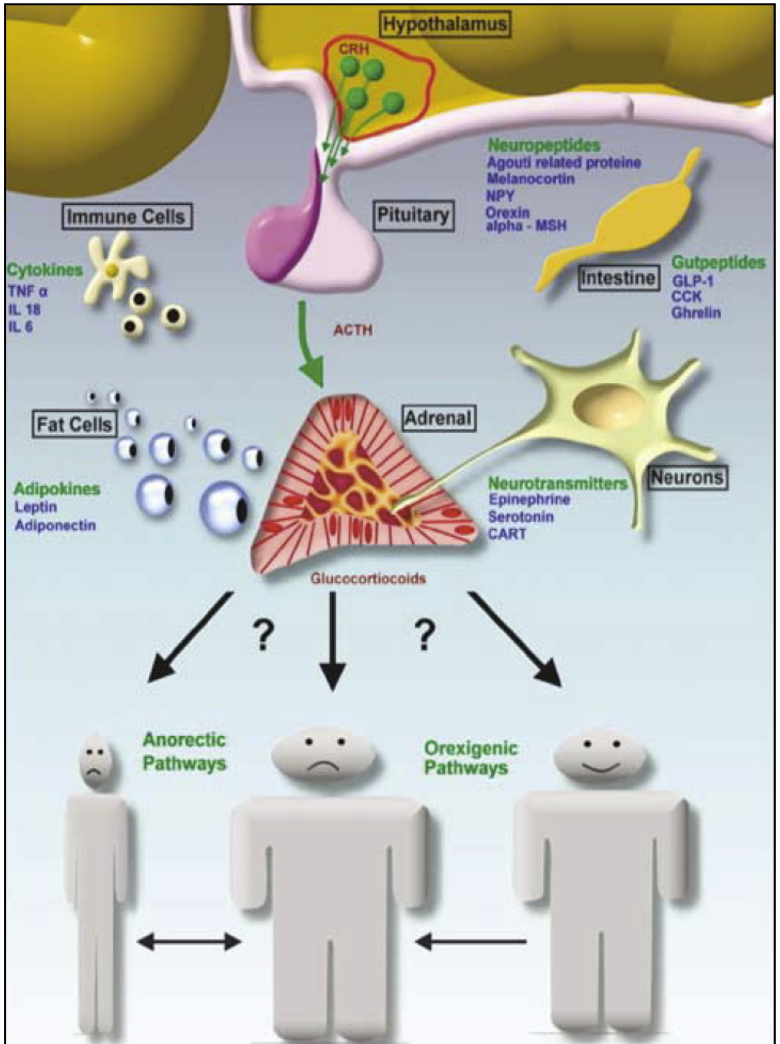
- **Obesity to depression: e.g. weight stigma, body dissatisfaction, body weight concerns, weight related anxiety, failure to lose weight, low self esteem, peer isolation & bullying, functional impairment (reduced mobility)**

- **Depression to obesity: e.g. increased appetite, poor sleep, lethargy, medication side effects, high caloric `comfort´ foods**

- **Common physiological factors in regulation of mood and weight**
- **Common environmental factors**
  - **e.g. poverty entails hopelessness and reduced access to healthy food and safe recreational activities**

Marmorstein et al., 2014; Int J Obesity 38: 906-11;
Yagnik et al., 2014; Int Arch Integrated Med 1: 23-33

Obesity <> Stress/HPA-Axis <> Depression



- Overlapping mechanisms for stress- and weight-regulation
- Stress hormone regulation is impaired in depression
  - e.g. insensitive glucocorticoid receptor

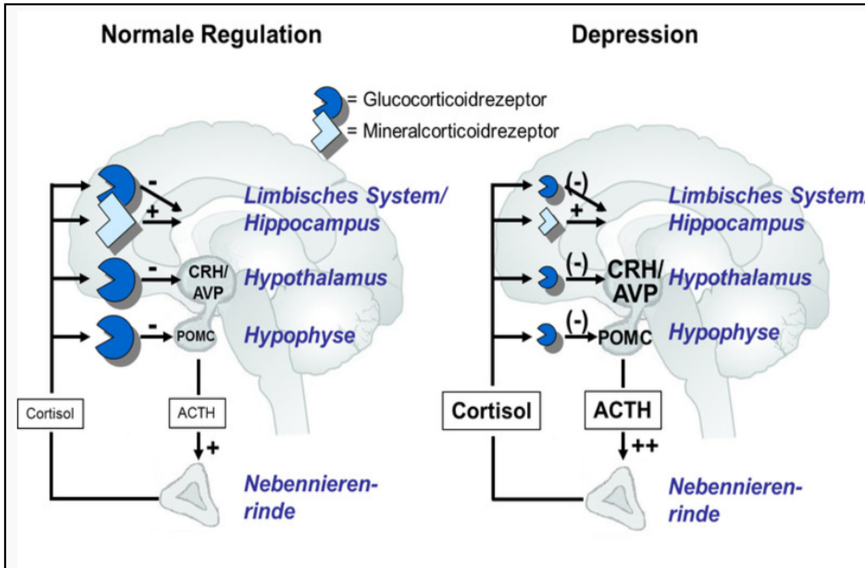


Abb. 1: Die Regulation der Hypothalamus-Hypophysen-Nebennierenrinden-Achse (englisch: hypothalamus-pituitary-adrenocortical, HPA) erfolgt in erster Linie über Glucocorticoidrezeptoren. Bei vielen depressiven Patienten besteht eine Insensitivität dieser Rezeptoren, die zu einer Verstellung des Regulationsgleichgewichts im HPA-System führt.

Bornstein et al. 2006

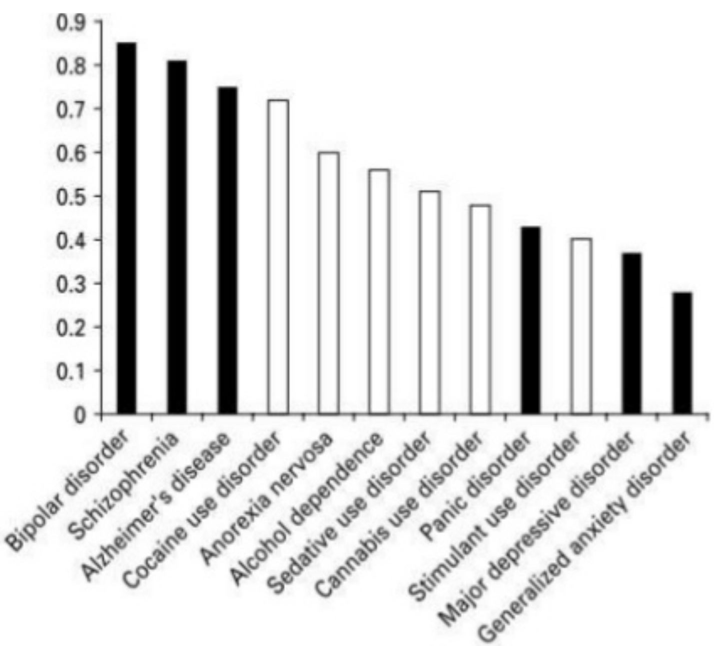
Do genetic risk factors for obesity and mental disorders overlap?

- Complex phenotypes with many genes involved (polygenic)
- Central pathways for the regulation of body weight, mood, and cognition overlap
- Candidate gene studies: unequivocal results are lacking
- Genome wide association studies (GWAS): circumstantial evidence for overlapping SNPs

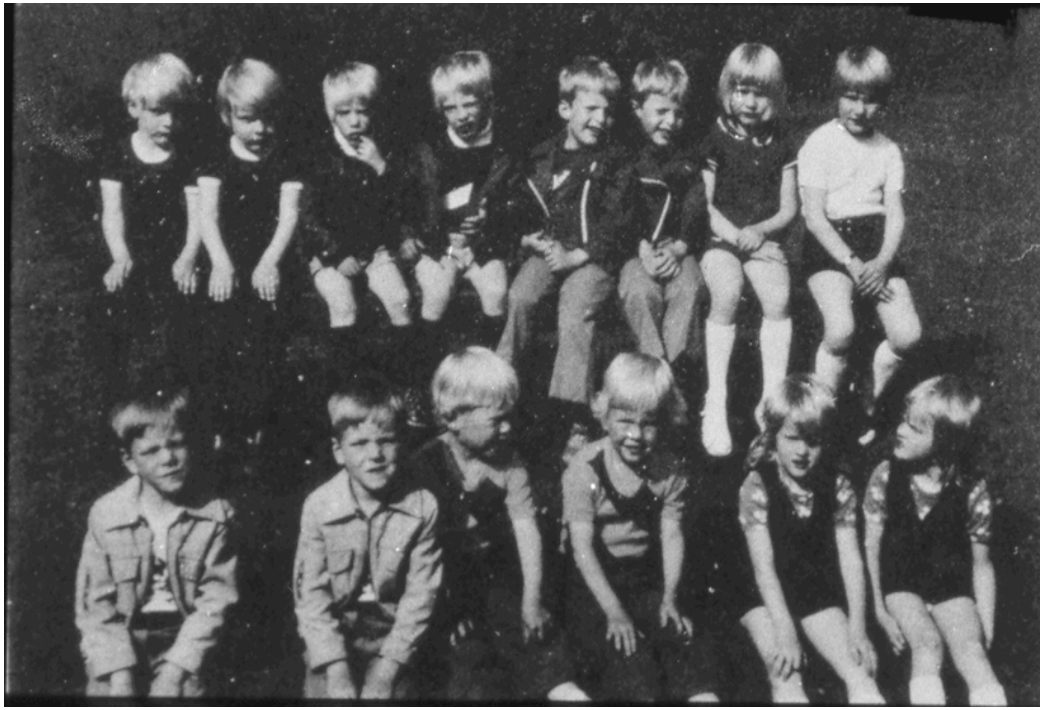
Heritability Estimates

Twin, family, and adoption: substantial heritability

- **BMI: 0.5-0.8**
- **Mental disorders: 0.3-0.9**



Bienvenu et al. Psychiatric 'diseases' versus behavioral disorders and degree of genetic influence. Psychological Medicine 2011;41:33–40.



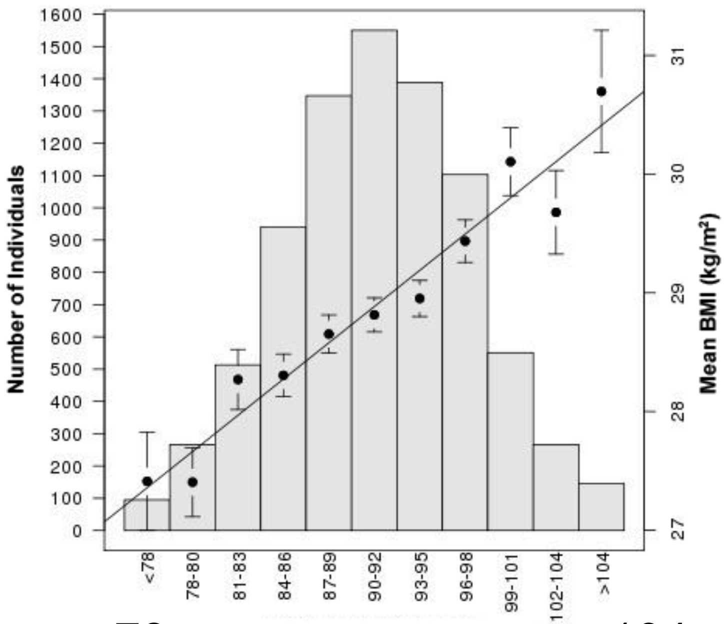
'Identical Twins Reared Apart', Susan L. Farber

Hinney et al. Eur Child Adolesc Psychiatry. 2010;19:297-310
Hinney et al. Prog Mol Biol Transl Sci. 2010;94:241-70

GIANT: BMI

GIANT CONSORTIUM Genetic Investigation of ANthropometric Traits

- **Meta-analysis 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**



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

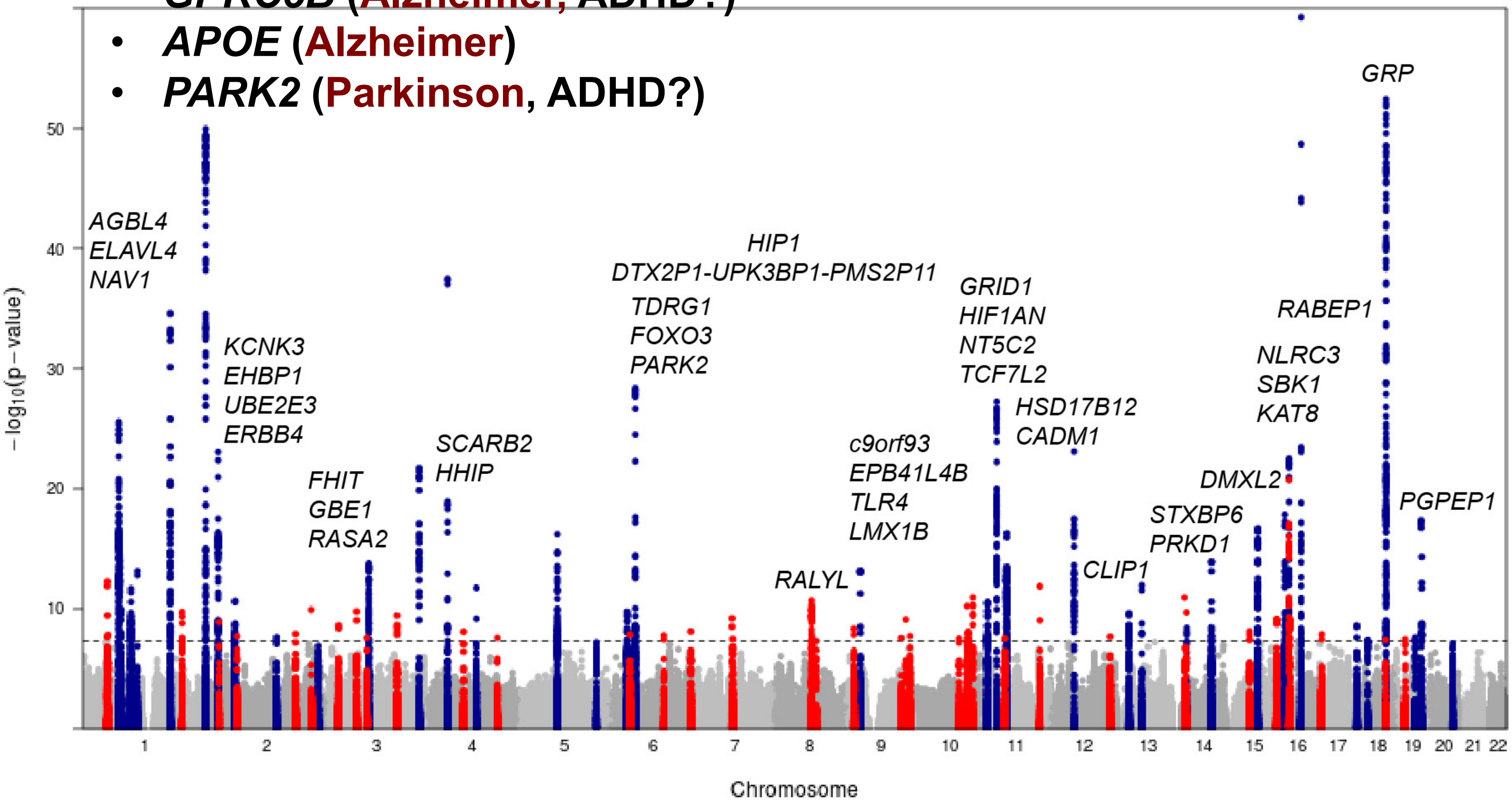
Locke et al. 2015, Nature. 2015 Feb 12;518:197-206

GIANT: BMI

GIANT CONSORTIUM Genetic Investigation of ANthropometric Traits

Genes with potential relevance for neuropsychiatric disorders:

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



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

GIANT: BMI

GIANT CONSORTIUM

Genetic Investigation of ANthropometric Traits

35/97 SNPs (binomial $P = 0.0019$) in high LD ($r^2 > 0.7$) with ≥ 1 GWAS SNPs of the *National Human Genome Research Institute* (NHGRI) GWAS catalogue ($P < 5x10^{-08}$)

SNPs associated with cardio-metabolic phenotypes and:

- **Alzheimer's disease**
- **Schizophrenia**
- **Nicotine dependence**

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

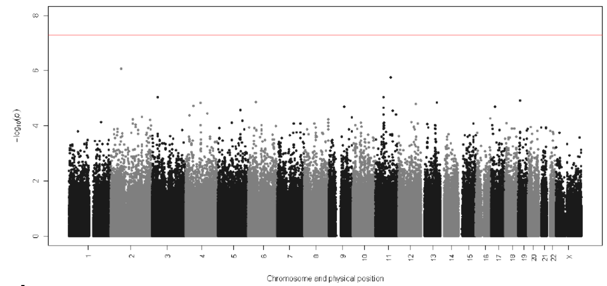
ADHD – Obesity – GWAS Look-up

RAPID PUBLICATION

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

Genome-Wide Association Study in German Patients With Attention Deficit/Hyperactivity Disorder

Anke Hinney,[1]* André Scherag,[2] Ivonne Jarick,[3] Özgür Albayrak,[1] Carolin Pütter,[2] Sonali Pechlivanis,[2] Maria R. Dauvermann,[1,4] Sebastian Beck,[1] Heike Weber,[5] Susann Scherag,[1] Trang T. Nguyen,[3] Anna-Lena Volckmar,[1] Nadja Knoll,[1] Stephen V. Faraone,[6] Benjamin M. Neale,[7,8] Barbara Franke,[9] Sven Cichon,[10,11,12] Per Hoffmann,[11,12] Markus M. Nöthen,[11,12] Stefan Schreiber,[13] Karl-Heinz Jöckel,[2] H.-Erich Wichmann,[14] Christine Freitag,[15] Thomas Lempp,[15] Jobst Meyer,[16] Susanne Gilsbach,[17] Beate Herpertz-Dahlmann,[17] Judith Sinzig,[18,19] Gerd Lehmkuhl,[18] Tobias J. Renner,[5] Andreas Warnke,[5] Marcel Romanos,[20] Klaus-Peter Lesch,[21] Andreas Reif,[21] Benno G. Schimmelmann,[1,4] Johannes Hebebrand[1] and Psychiatric GWAS Consortium: ADHD subgroup



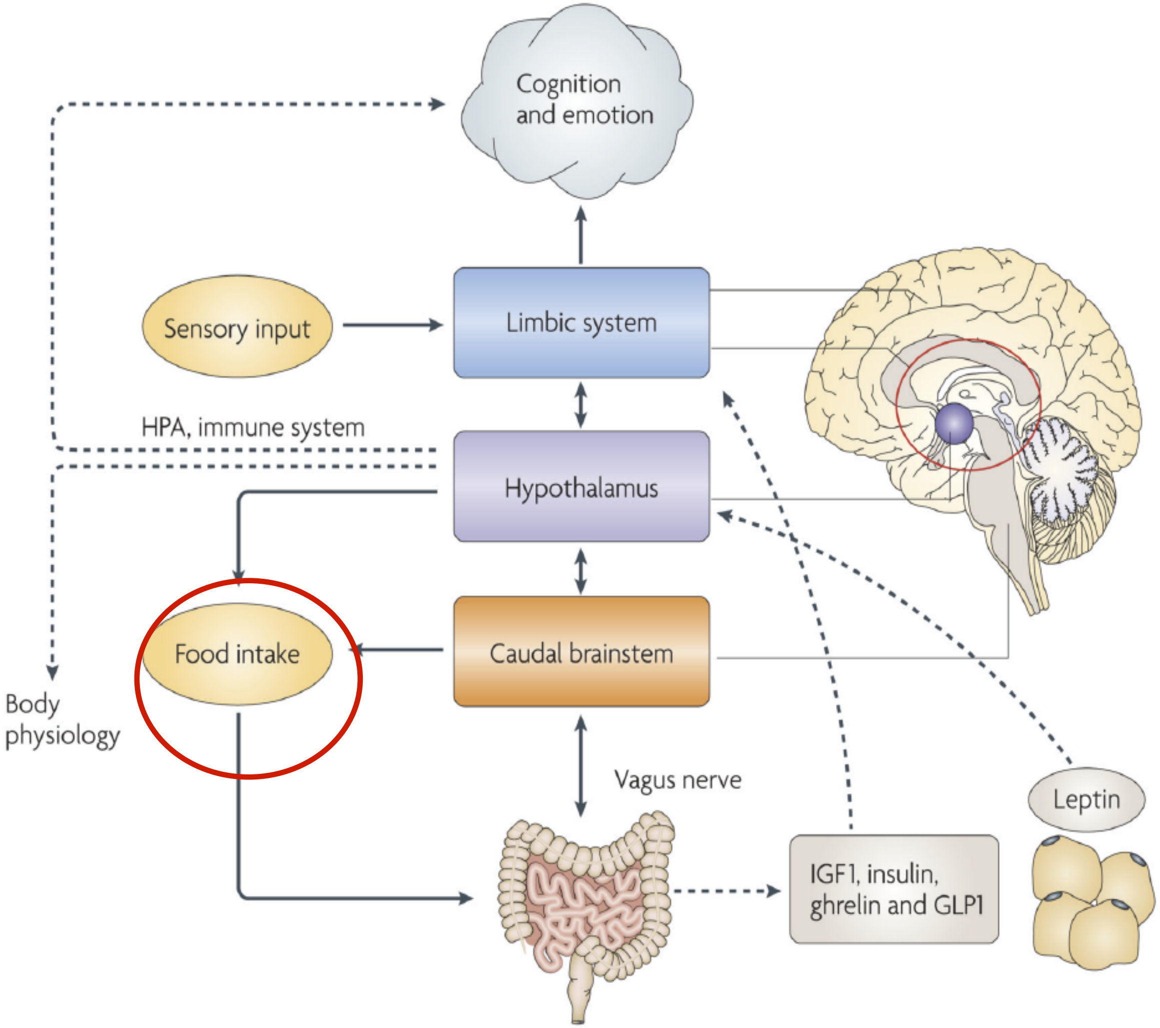
Look-up of 32 obesity polygenes in ADHD GWAS data sets:

- **German GWAS: 495 ADHD cases (6-18 years, Ø age 11 ± 2.7) vs. 1300 controls**
  - **rs206936 in *NUDT3* associated with ADHD risk (OR: 1.39; p_{corr} = 0.01)**
- **Meta-analysis (Psychiatric GWAS Consortium, ADHD subgroup):**
  - **rs6497416 in *GPRC5B* (p_{corr} = 0.02) as a risk allele for ADHD**
  - **more directionally consistent effects than expected by chance**

GPRC5B: Member of metabotropic glutamate receptor family

Hinney et al., 2011, Am J Med Genet Part B ; Albayrak et al., 2013 Am J Med Genet Part B

Food Intake: Impact on Cognition & Emotion



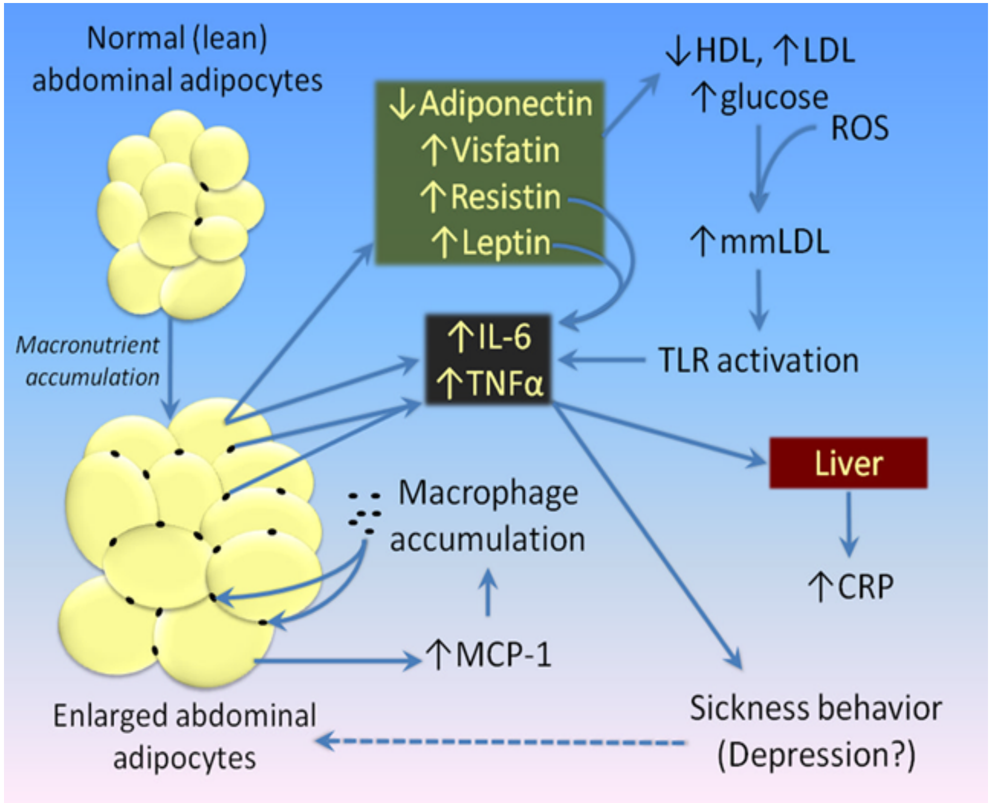
Food intake:

- Vagal stimulation of various brain areas
- Release of hormones and neurotransmitters (gut-brain-axis; adipose tissue)
- Increase of synaptic and cortical plasticity
- Impact on cognition and mood
- Impact on reward system

Gómez-Pinilla F., Nat Rev Neurosci. 2008

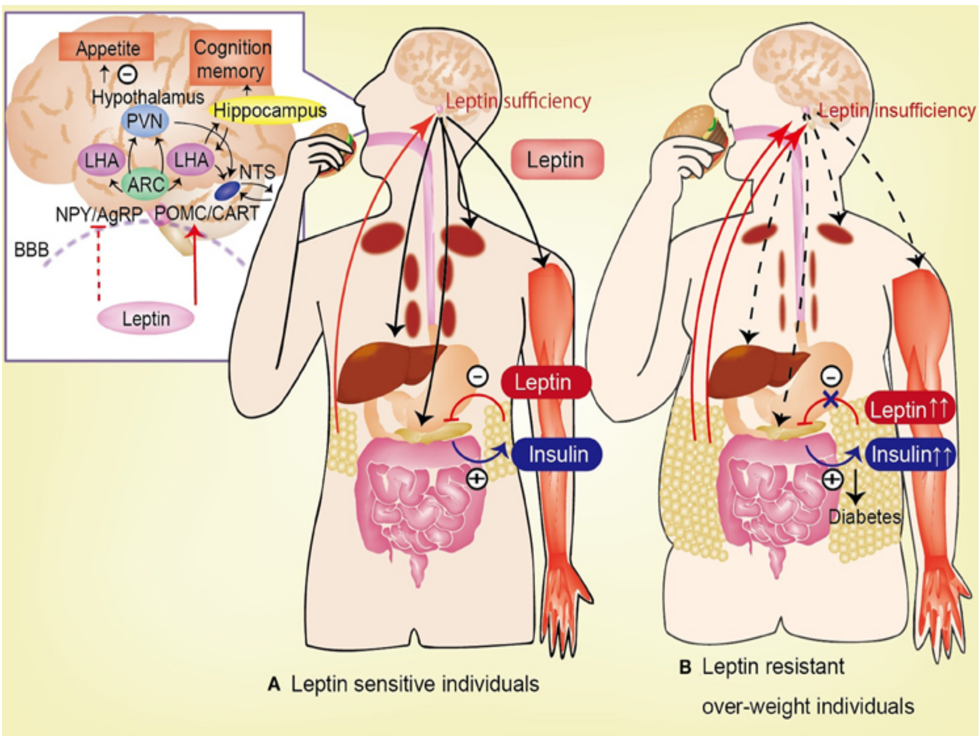
Overlapping Mechanism: Inflammation

Haroon E. 2012



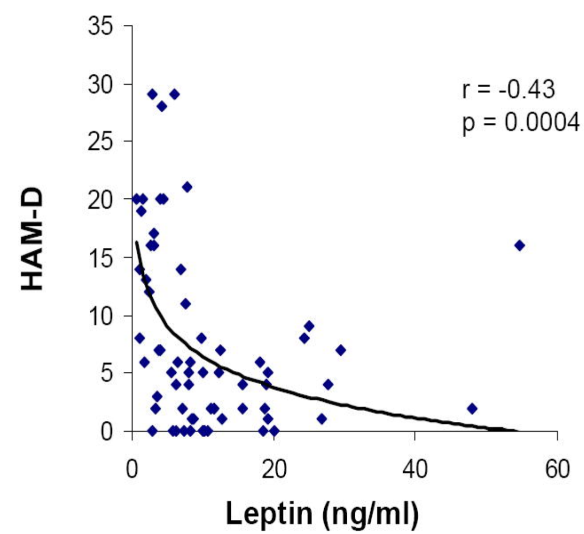
Other potential contributors: Smoking, sleep quantity and quality, Vitamin D deficiency

Important "Player": Leptin
Eating habits, insulin-glucose-axis, cognition, depression



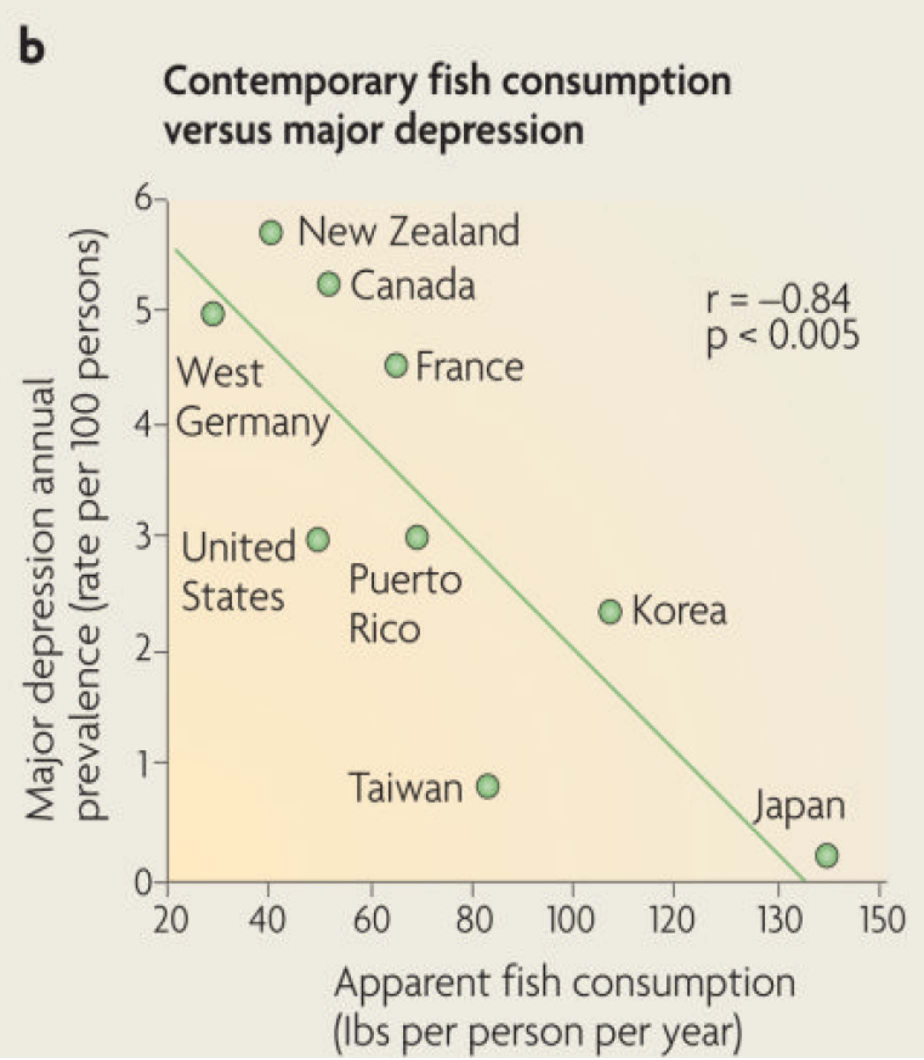
- A balanced leptin level is key
- Increased risk for depression for:
  - Leptin deficiency (Anorexia Nervosa)
  - Leptin resistance (Obesity)
- Leptin-levels show impact on mood irrespective of body-weight

A.



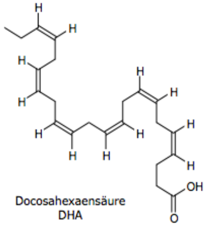
Amitami et al. 2013; Lawson et al. 2012

Single Nutrient & Depression ?



- Large differences in prevalence of major depression per country
- Prevalence of depression parallels prevalence of cardiovascular mortality
- Correlation with fish consumption detected
- Hypothesis: Malnutrition with essential fatty acids

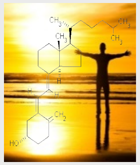
  e.g. docosahexaenacid

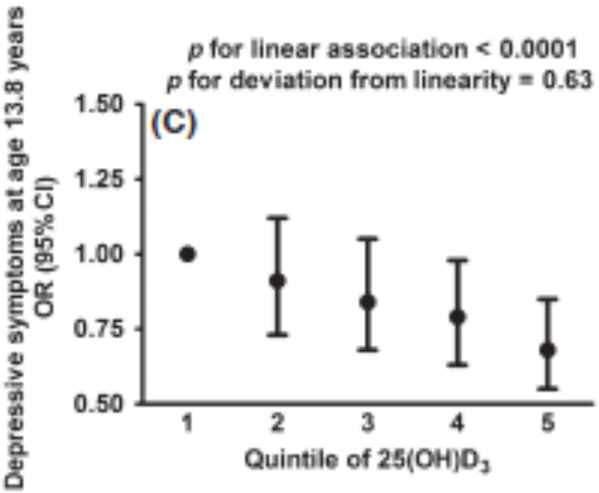


  - Important for nerve membranes
  - Not synthesized by the body

Sources: Gómez-Pinilla F., Nat Rev Neurosci. 2008; Hibbeln JR The Lancet 1998; Weissman MM et al. JAMA 1996

Vitamin D Deficiency & Depression





- Single prospective cohort study (ALSPAC)
- N= 2759; Age: 9.8 -13.8 years
- Association of low 25(OH)D-levels and subsequent depressive symptoms
- Adjusted for: Gender, age, ethnicity, socioeconomic status, BMI, UVB-exposure

Lower 25(OH)D-levels are associated with a higher risk to develop depressive symptoms

Tolppanen et al, J Child Psychol Psychiatry 2012

Vitamin D: KIGGS
Fully adjusted model: Boys

SDQ	VitD+age+SES+migration status+ BMI child +Tanner				
	n	Beta	Sig.	95%CI lower	95%CI upper
Emotional problems	4494	-0,089	0,001	-0,141	-0,037
behavioral problem	4496	-0,005	0,827	-0,052	0,041
hyperactivity	4497	-0,029	0,401	-0,096	0,038
Peer Problems	4496	-0,124	0,000	-0,172	-0,075
Prosocial behavior	4502	0,003	0,905	-0,049	0,055
Total difficulties score	4492	-0,243	0,002	-0,396	-0,091

Nutrition, Eating Patterns and Mental Disorders

- **Associations between dietary patterns and mental health**
  - Jacka et al. 2011a, Jacka et al. 2011b, Quirk et al. 2013, Sanchez-Villegas & Martinez-Gonzalez 2013, Sanchez-Villega et al. 2013, Psaltopoulou et al. 2013b
- **Cross-sectional studies: association between dietary pattern / quality indices and depressive symptoms**
  - Jacka et al. 2010, Kuczmarski et al. 2010, Nanri et al. 2010, Jacka et al. 2011b
  - e.g.: Association between „Western Diet" und reduced scores for „General Health Questionaire" (GHQ-12)
    - Adjusted for age and SES (Jacka et al. 2010)
  - e.g.: „Whole food" dietary pattern decreases, „processed food" dietary pattern increases risk for depressive disorders after 5 years (Akbarly et al. 2009)

Bildquelle: 2014 © FoodnCulture.com,

Recent Reviews: Dietary Patterns and Depression

- **Dietary patterns potentially impact development of depressive symptoms** (Rahe et al. 2014)
  - Systematic review of observational studies (n=16)
    - „Healthy" probands, different dietary patterns, different depression-scales
    - No meta-analysis possible due to heterogeneity (study designs, instruments, etc.)
- **Higher adherence to Mediterranean Diet reduces the risk** to develop a depressive disorder [RR = 0.68, 95% CI = 0.54-0.86] (Psaltopoulou et al 2013)
  - Systematic review und meta-analysis (n=22)
    - Included studies on adherence to MD in stroke, Parkinsons disease, cognition, and depression
- **8/17 RCTs with significant effect on depression** (Opie et al 2014)
  - Systematic review: 17 RCTs
  - **Effective interventions**: single delivery mode, included dietitian, recommendation to reduce red meat intake less likely, selection of leaner meat products, low-cholesterol diet
  - **Only 1 RCT recruited patients with MDD**:
    - 4 hygienic-dietary recommendations improved depression after 6 months (Garcia-Toro M. et al. 2012): MD, exercise, sleeping habits, sunlight-exposure

The Mediterranean Dietary Pattern Reduces Mortality

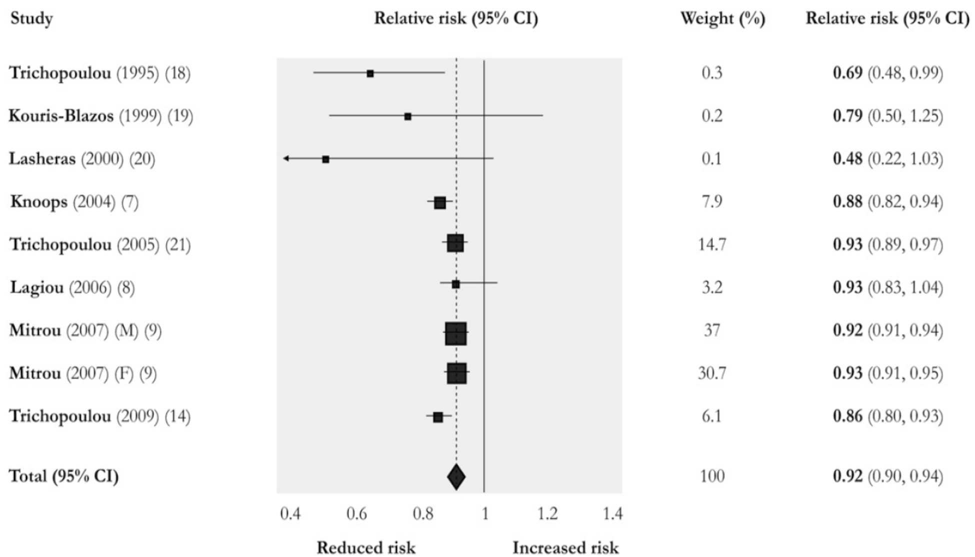
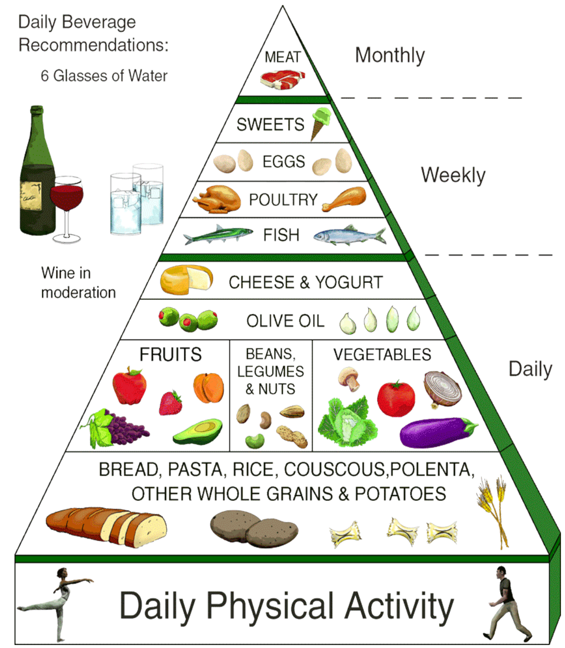
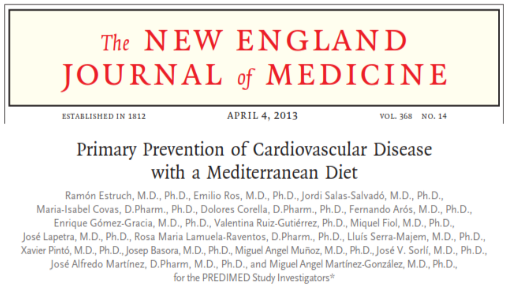


FIGURE 1. Forest plot of the association between a 2-point increase of adherence score to the Mediterranean diet and the risk of all-cause mortality. The center of each square indicates the relative risk of the study, and the horizontal lines indicate 95% CIs. The area of the square is proportional to the amount of information from the study. Diamonds indicate pooled estimates.



http://www.ways2weightloss.com/wp-content/uploads/2012/10/mediterranean-diet-food-wine-pyramid.gif

Simple Advice: Large Effect

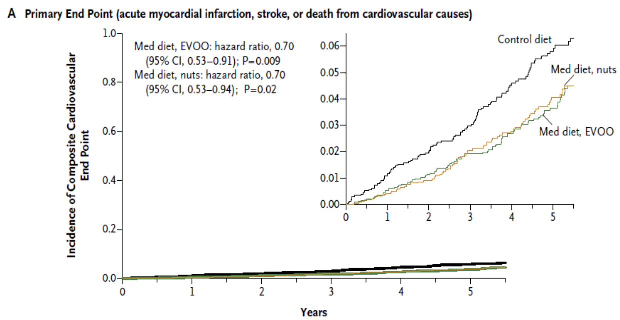


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*



- RCT for primary prevention in cardiovascular (CV) risk patients
- 7447 participants (55-80 years, 57% female)
- Followed-up for 4.8 years
- Risk for CV events significantly decreased:
  - Adj. HR 0.70 ($[CI]_{95\%}$, 0.54-0.92) in „extra-olive-oil“ arm
  - Adj. HR 0.72 ($[CI]_{95\%}$, 0.54-0.96) in „extra-nuts“ arm
- Overlapping mechanismen for development of “metabolic syndrome” and depressive disorder

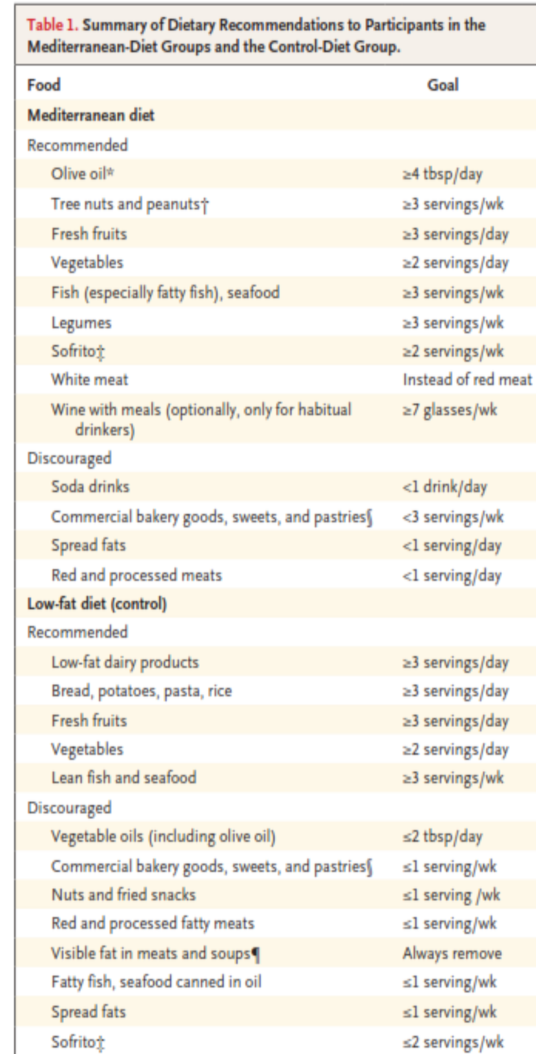


Table 1. Summary of Dietary Recommendations to Participants in the Mediterranean-Diet Groups and the Control-Diet Group.

Food	Goal
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<3 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day
Low-fat diet (control)	
Recommended	
Low-fat dairy products	≥3 servings/day
Bread, potatoes, pasta, rice	≥3 servings/day
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Lean fish and seafood	≥3 servings/wk
Discouraged	
Vegetable oils (including olive oil)	≤2 tbsp/day
Commercial bakery goods, sweets, and pastries§	≤1 serving/wk
Nuts and fried snacks	≤1 serving /wk
Red and processed fatty meats	≤1 serving/wk
Visible fat in meats and soups¶	Always remove
Fatty fish, seafood canned in oil	≤1 serving/wk
Spread fats	≤1 serving/wk
Sofrito‡	≤2 servings/wk

Estruch et al. 2013

Dietary patterns & Depression

Example: Protective Effect of the "Mediterranean Diet"

- **SUN (Seguimiento Universidad de Navarra) study:**
  - **Prospective cohort (10,094 healthy probands)**
  - **Validated 136-item FFQ**
  - **Psychiatric assessments at baseline and follow-up**
- **Results after 4.4 years (median follow-up)**
  - **480 new cases of depression**
  - **Multiple adjusted hazard ratios for an increasing adherence to MD:**
    - **0.74 (0.57-0.98); 0.66 (0.50-0.86); 0.49 (0.36-0.67) und 0.58 (0.44-0,77) (p for trend = 0.001)**
  - **Inverse dose-effect for fruits, nuts, pulses and the ratio of mono-unsaturated to saturated fatty acids**

Sánchez-Villegas A et al. Arch Gen Psychiatry. 2009

Simple Advice: Effects in Patients at Risk
Focus: Type 2 Diabetes (T2DM) & Depression

Sánchez-Villegas *et al. BMC Medicine* 2013, **11**:208
http://www.biomedcentral.com/1741-7015/11/208

BMC Medicine

RESEARCH ARTICLE | Open Access

Mediterranean dietary pattern and depression: the PREDIMED randomized trial

Almudena Sánchez-Villegas[1,2*], Miguel Angel Martínez-González[1,3], Ramón Estruch[1,4], Jordi Salas-Salvadó[1,5], Dolores Corella[1,6], Maria Isabel Covas[1,7], Fernando Arós[1,8], Dora Romaguera[1,9,10], Enrique Gómez-Gracia[1,11], José Lapetra[1,12], Xavier Pintó[1,13], Jose Alfredo Martínez[1,14], Rosa María Lamuela-Raventós[1,15], Emilio Ros[1,16,17], Alfredo Gea[1,3], Julia Wärnberg[1,11] and Lluis Serra-Majem[1,2]

- Addition of nuts (30g/d) to a Mediterranean-Diet decreased the risk to develop a depressive disorder in T2DM patients significantly
  - N = 3923 participants; age (55-80 years) no acute cardiovascular disorder, but high risk population at enrollment (T2DM, smoking, high cholesterol).
  - Adj. HR = 0.59; 95% CI 0.36 to 0.98; median follow-up 3 years
    - Trend, but not significant for the whole study group (adj. HR = 0.78; 95% CI 0.55 to 1.10)

Sanchez-Villegas et al. 2013

Concepts to be pursued

Sanchez-Villegas and Martínez-González *BMC Medicine* 2013, **11**:3
http://www.biomedcentral.com/1741-7015/11/3

BMC Medicine

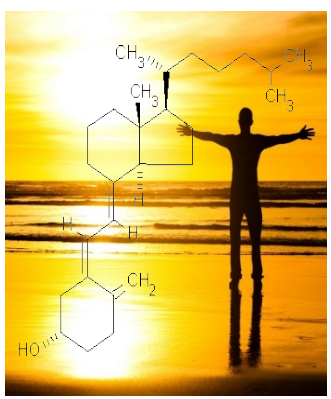
Metabolism, diet and disease

OPINION Open Access

Diet, a new target to prevent depression?

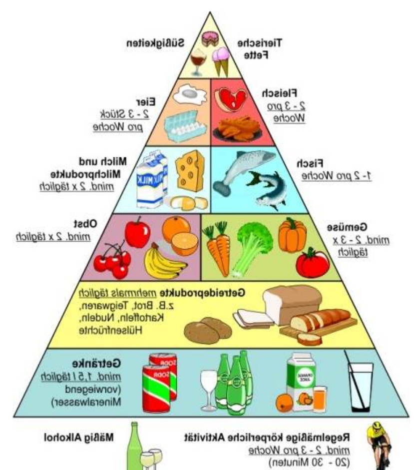
Almudena Sanchez-Villegas[1*] and Miguel A Martínez-González[2]

Mid-term: Vitamin D



http://www.fasten-auf-hiddensee.de/b_fasten/2012-fasten-nach-buchinger.jpg

Long-term: Mediterranean Diet



http://individual-med-publishing.de/infothek-gesundheit.html

Summary

- **Clinical and epidemiological associations between obesity and mental disorders and suicide**
- **Data *not* unequivocal**
- **Specificity of these associations?**
- ***Psychological and biological* mechanisms**
- **Evidence for influence of the diet**
  - **Single nutrients**
  - **Dietary patterns**
  - **Adjunctive treatment**

Mediterranean Diet, as a "treatment" option?

Bidirectionality: Obesity and Depression Systematic Review of Longitudinal Studies

- **Geoffroy et al. 2014** (n= 18,558; 0-50 years)
  - Obesity predicted depression: OR 1.3 (95% CI: 1.1-1.6)
  - Depression not predictive of obesity
- **Frisco et al. 2014** (n=5243; 13-18 years, 19-25 at follow-up)
  - Obesity predicted depressive symptoms: OR 1.3 (95% CI: 1.1-1.6)
  - Depression not predictive of obesity
- **Marmorstein et al. 2014** (n=1512; 11-24 years; twin study)
  - Obesity that developed during late adolescence predicted onset of depression (OR=5.9, confidence interval=2.3-15.0) during early adulthood among females
  - Major Depression by early adolescence predicted onset of obesity; OR=3.8 (95%CI: 1.3-10.6) during late adolescence among females
- **Roberts et al. 2013** (n=4175; 11-17 years, one year follow-up)
  - Obesity did not predict depression
  - Depression predicted obesity: OR 2.9; effect based on males only

From: **Association of the Mediterranean Dietary Pattern With the Incidence of Depression: The Seguimiento Universidad de Navarra/University of Navarra Follow-up (SUN) Cohort**

Arch Gen Psychiatry. 2009;66(10):1090-1098. doi:10.1001/archgenpsychiatry.2009.129

Table 2. Association Between Adherence to the Mediterranean Dietary Pattern and Risk of Depression

	Adherence to the Mediterranean Dietary Pattern Score (Median Score)					
Variable	0-2 (2)	3 (3)	4 (4)	5 (5)	6-9 (6)	*P* Value for Trend
No. of cases per person-years	126/8866	91/8253	97/9240	67/8131	99/9715	
Crude rates per 10^3 (95% CI)[a]	14.2 (11.8-16.9)	11.0 (8.9-13.5)	10.5 (8.5-12.8)	8.2 (6.4-10.5)	10.2 (8.3-12.4)	
Model 1						
HR (95% CI)[b]	1 [Reference]	0.74 (0.57-0.98)	0.66 (0.50-0.86)	0.49 (0.36-0.67)	0.58 (0.44-0.77)	<.001
Model 2						
No. of cases per person-years	67/8748	48/8167	46/9138	32/8061	44/9605	<.001
HR (95% CI)[b]	1 [Reference]	0.73 (0.50-1.06)	0.56 (0.38-0.83)	0.42 (0.27-0.66)	0.50 (0.33-0.74)	
Model 3						
No. of cases per person-years	86/8726	65/8155	61/9116	50/8075	75/9631	.007
HR (95% CI)[b]	1 [Reference]	0.79 (0.57-1.09)	0.67 (0.48-0.93)	0.56 (0.39-0.80)	0.69 (0.50-0.96)	

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] The CIs for rates were calculated with Stata by means of an exact method.
[b] By definition, if the 95% CI of the HR does not include the unity (HR=1.00), the results are statistically significant (2-tailed $P < .05$). For model 1, the HRs were estimated with Cox regression and adjusted for sex, age (years), smoking status (never, current, past smoker), body mass index (calculated as weight in kilograms divided by height in meters squared) and its quadratic term, physical activity during leisure time (metabolic equivalent hours per week), energy intake (kilocalories per day), and employment status (no or yes). Model 2 was the same as model 1 but excludes participants with early depression (those observed only during the first 2 years of follow-up; n=243). Model 3 was the same as model 1 but excludes participants who reported the use of antidepressant medication during follow-up but not a physician-made diagnosis of depression (n=143).

Figure Legend:

Association Between Adherence to the Mediterranean Dietary Pattern and Risk of Depression

Just starting "down-under"

O'Neil *et al. BMC Psychiatry* 2013, **13**:114
http://www.biomedcentral.com/1471-244X/13/114

BMC Psychiatry

STUDY PROTOCOL **Open Access**

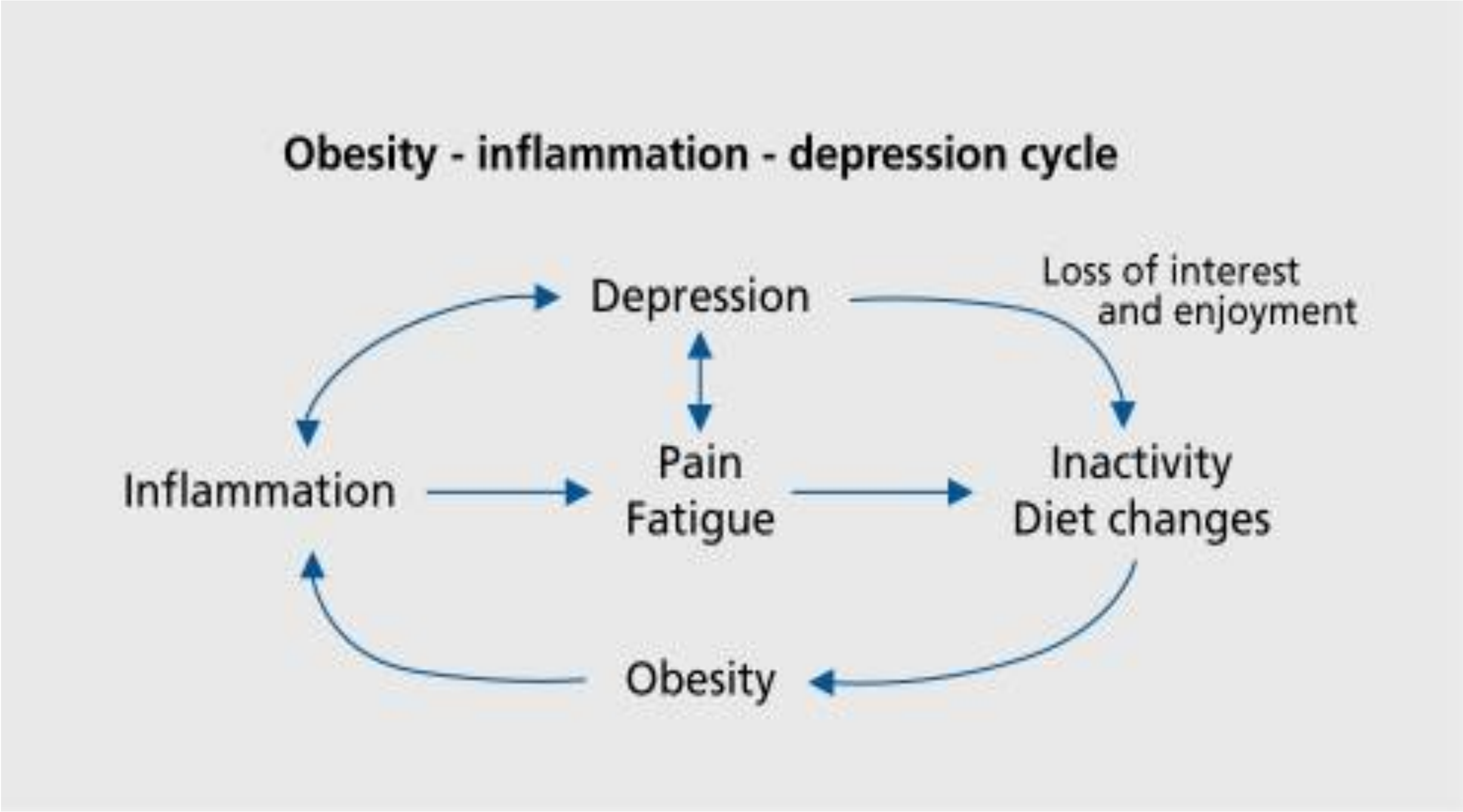
A randomised, controlled trial of a dietary intervention for adults with major depression (the "SMILES" trial): study protocol

Adrienne O'Neil[1,2*], Michael Berk[1,3,4], Catherine Itsiopoulos[5], David Castle[6], Rachelle Opie[5], Josephine Pizzinga[1], Laima Brazionis[7], Allison Hodge[8], Cathrine Mihalopoulos[9], Mary Lou Chatterton[9], Olivia M Dean[1,4,10] and Felice N Jacka[1,4]

Content

- The challenges
- Overlapping genetic factors
- Nutrition, eating patterns and mental disorders
- Overlapping mechanisms, common denominators?
- Drawing consequences
- Conclusion and outlook

Inflammation in Depression: is Adiposity a Cause?



Shelton & Miller ; Dialogues Clin Neurosci. 2011; 13(1): 41–53

In Planung/Ausführung in Australien: RCT zur diätetische Intervention bei Depression

O'Neil et al. BMC Psychiatry 2013, 13:114
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BMC Psychiatry

STUDY PROTOCOL Open Access

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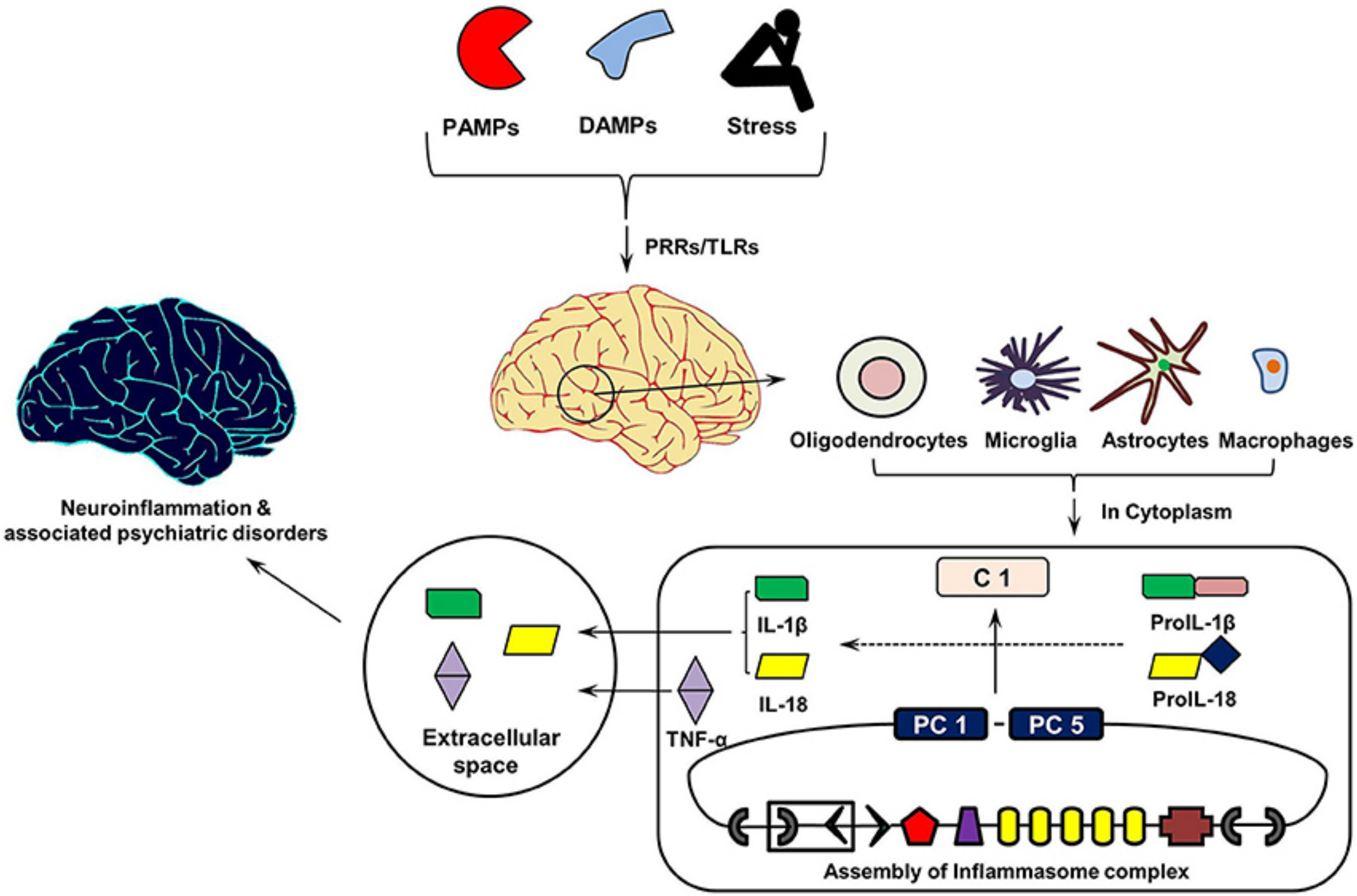
- 12-Wochen, paralleles Gruppendesign (Kontrolle: neutrale Lebensberatung), einfach blind.
- 3 Beratungssitzungen/Woche
  - Speisepläne
  - Ausgabe Nüssen/Öl etc.

- 1°: Verbesserung gemäß MADRS (Montgomery Asberg depression rating scale)
- 2°: Schweregrad und Verbesserung nach CGI (clinical global impression)
- Weitere 2°: HADS, QoL-SF36, …FFQs, DST … Blutparameter, BMI, …, H-Ök.
- Inklusion:
  - Erwachsene mit MDD nach DSM-IV und MADRS >18
  - Und: "Problematisches Ernährungsmuster" gemäß "Dietary Screening Test" (DST <60)

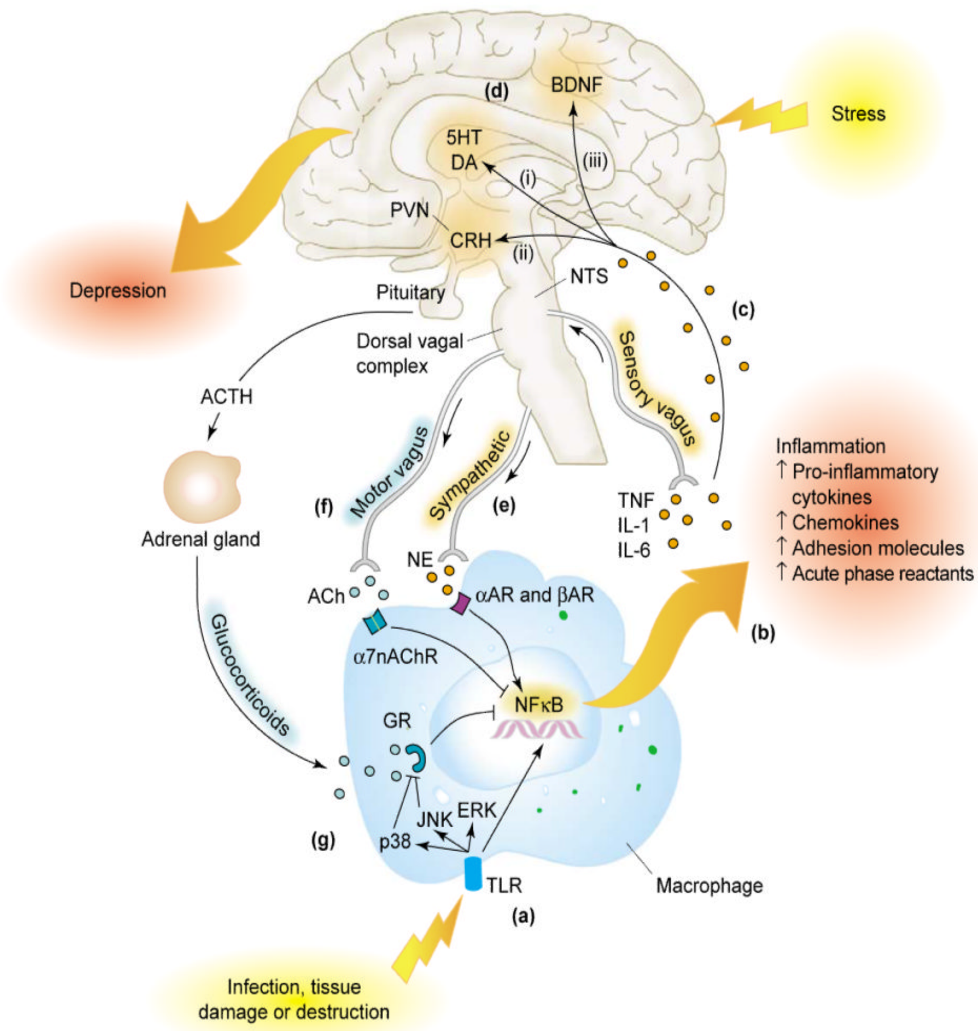
Content

Inflammasomes cascade in brain, consequences for mental health



Singhal et al., Frontiers in Neuroscience 2014

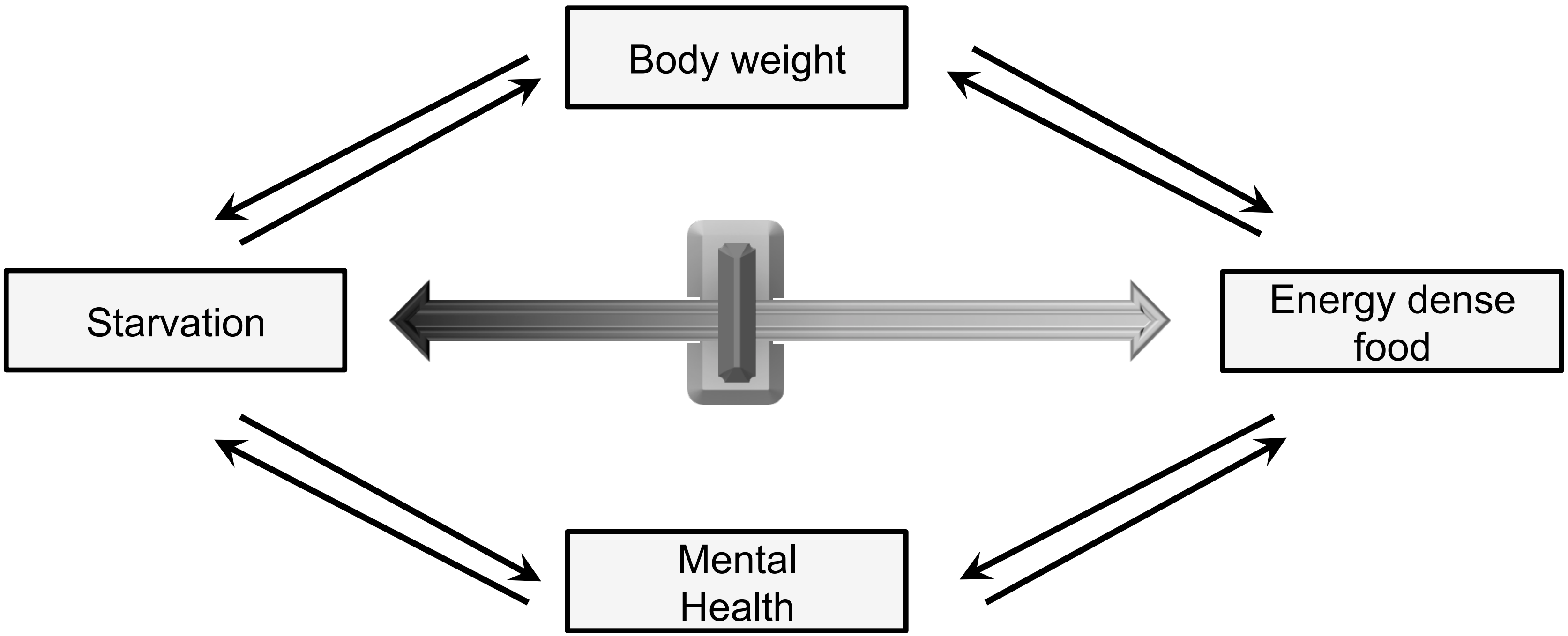
Infections, inflammation, stress & depression



- Infections, tissue damage, and chemokines from hypertrophe adipocytens may lead to macrophage accumulation:
  - Initiation of pro-inflammatory processes
  - Downstream effects on neurobiological pathways and neurotransmitters involved in mental health (e.g. BDNF, serotonin etc.)

Raison et al. 2006

Our Vision: An adequate balance is possible



Summary and Conclusion

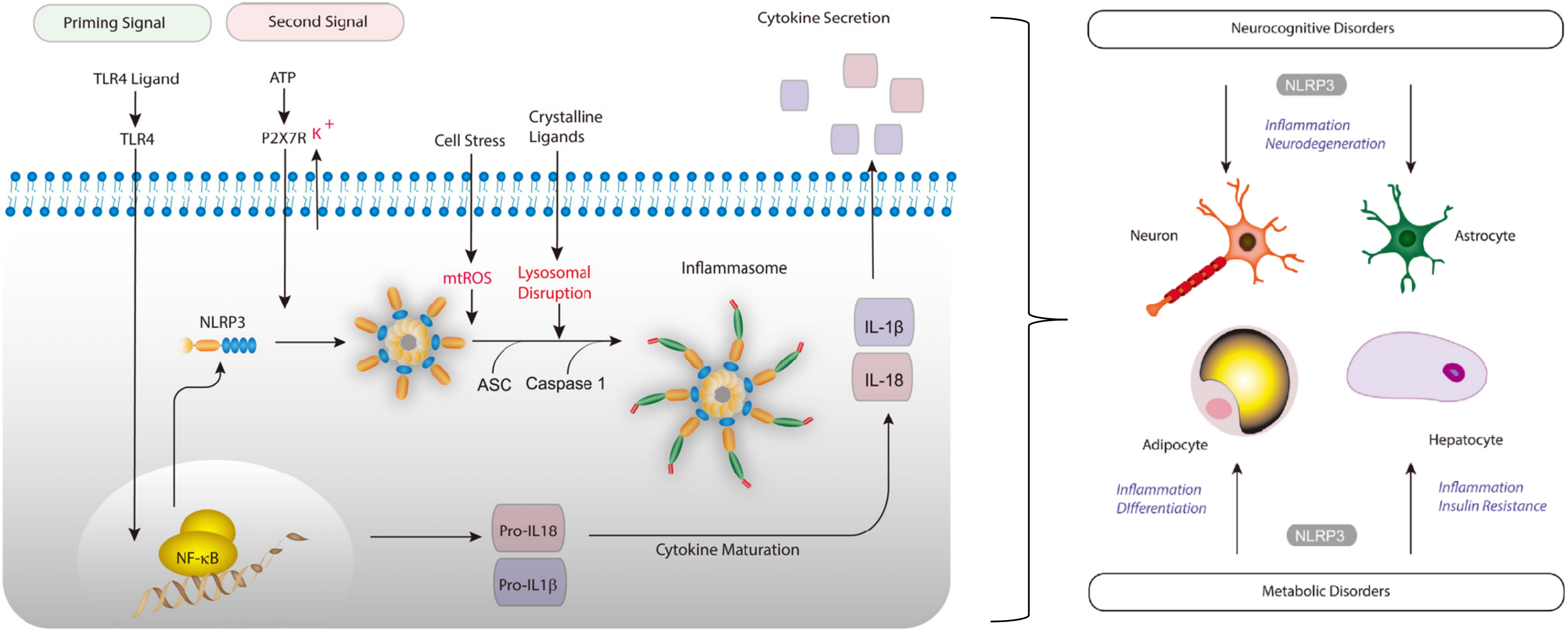
- „Bad eating habits" may precipitate psychiatric disorders
- Certain food components can contribute
- Most important: Eating pattern / whole life style
- Mediators: Genetic predisposition
- Potential mechanisms
  - Subchronic inflammation
  - Interaction with:
    - Leptin-elatonergic system
    - HPA-axis
    - Serotonergic-Dopaminergic system

Complex interaction s with potential for

innovative therapies and preventive measures

Back-ups … werden bei Bedarf übersetzt ☺

Innate immune system, inflammasome & health



Choi AJS et al. Mol. Cells 2014

Content

- The challenges
- Genetic background
- Nutrition, eating patterns and mental disorders
- Overlapping mechanisms, common denominators?
- Drawing consequences
- Conclusion and outlook

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 < 5×10^{-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

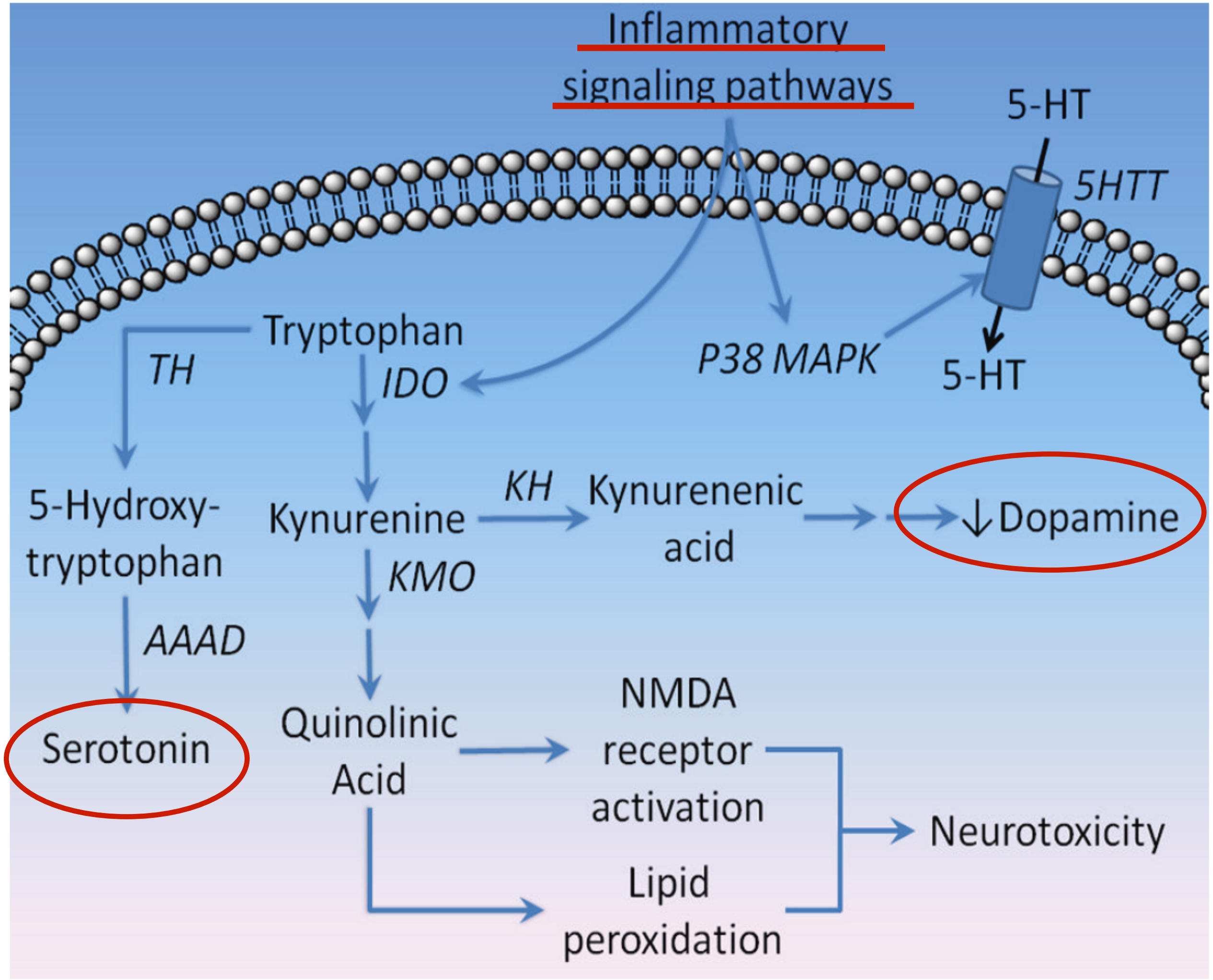
Results: U-shaped

- In longitudinal analyses
  - Underweight predicted subsequent depression in both sexes [odds ratio (OR) 1.25, 95% confidence interval (CI) 1.11–1.40]
  - Depression predicted subsequent underweight in males only (OR 1.84, 95% CI 1.52–2.23).
  - Obesity predicted subsequent depressive symptoms in females only (OR 1.34, 95% CI 1.14–1.56)
  - But depression did not predict obesity.

Nur zur Info, Folie ausgeblendet

Geoffroy 2014

Innate immune defense & serotonin metabolism

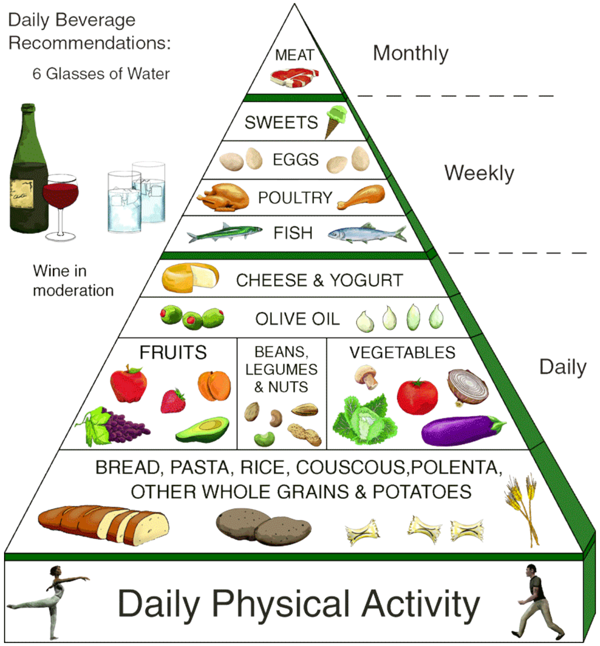


Shelton RC, Miller AH. 2010, Prog Neurobiol.,91(4):275-99.

Neu: Direkte Evidenzen aus großen Studien

- Ca. 35% Risiko-Reduktion für kardiovaskuläre Erkrankungen bei den "stärksten Nutzern" von nativem Olivenöl
- Ca. 37% Reduktion der Sterblichkeitrate beim Vergleich höchstes zu niedrigstes Quintile bzgl. Aufnahme von "Polyphenolen"

- Beispiel: EPIC –Greece
  - (Trichopoulou A et al. Adherence to the Mediterranean diet and survival in a Greek population. NEJM 2003)
  - Relative Beiträge
    - Wein (moderat!) 23,5%
    - Wenig "rotes" Fleisch 16,6%
    - Hoher Gemüse-Anteil 16,2%
    - Früchte&Nüsse 11,2%
    - Hülsenfrüchte 9,7%
    - Hohes MUFA/SFA Verhältnis 10,6%



Kontroverse: Olivenöl oder MUFA; Bedeutung der Polyphenole

In Planung:
Pilotstudie zum "Heilfasten" bei Depression

Studiendesign (Ausschnitt!)

- Prospektive, einarmige, interventionelle Beobachtungsstudie
- 14-tägiges modifiziertes Heilfasten (nach Buchinger)

- 6 Erwachsene und 6 männliche Jugendliche mit mittelschwerer, depressiver Symptomatik (BDI-II Score > 19)

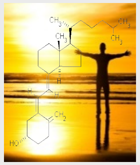
LVR Qualität für Menschen + UKM Universitätsklinikum Münster

Universitätsklinikum Essen

Hypothesen (Ausschnitt!)

- Die Kernsymptomatik schwächt sich im Verlauf der kurzen Intervention merklich ab
  - Stimmungsverbesserung (gemessen durch Clinical Depression Scales [CDS-R], Beck Depression Inventory II [BDI-II] und zusätzlich Expertenrating mit Hamilton Rating Scale for Depression [HRS-D]
- Intensive Betreuung = große Adhärenz?
- Nach 2-4 Tagen wird kein Hungergefühl?
- Effekt noch nach 8 Wochen beobachtbar?
- Akzeptanz, Adhärenz?

In Planung:
Pilotstudie zur Vitamin D Substitution



Konsekutive teil-/stationäre Aufnahmen
vom 01.11.2015 bis zum 30.04.2017

- Untersuchungsgruppe:
  - Alter: 11-18,9 Jahre
  - BDI-II Score > 13
  - 25(OH)D-Spiegel ≤ 30nmol/L
- Design/Zeit/Dosis
  - RCT, doppleblind, 2 Arme
  - Vitamin D 880I.E.*und Placebo*
    - Studie nicht AMG pflichtig
  - Supplementation über 28 Tage
    - Entspricht mittlerer stationärer Aufenthaltsdauer
- Annahme
  - Der 25(OH)D-Spiegel wird innerhalb von 4 Wochen auf das Zielniveau angehoben.
- Endpunkte
  - Primär: BDI-II Score
  - Sekundär: 25(OH)D-Spiegel
  - Safety: Routinelabor
- Offene Forschungsfrage:
  - Reicht der Zeitraum eines erhöhten Spiegels für positive Effekte auf den BDI-II

Osman et al. 2004; Dolle et al. 2012; Straub et al. 2014; Aloia 2011; *Dr. B. Scheffler Nachf. GmbH & Co.KG

In Planung/Ausführung in Australien: RCT zur diätetische Intervention bei Depression

O'Neil *et al. BMC Psychiatry* 2013, **13**:114
http://www.biomedcentral.com/1471-244X/13/114

BMC Psychiatry

STUDY PROTOCOL **Open Access**

A randomised, controlled trial of a dietary intervention for adults with major depression (the "SMILES" trial): study protocol

Adrienne O'Neil[1,2*], Michael Berk[1,3,4], Catherine Itsiopoulos[5], David Castle[6], Rachelle Opie[5], Josephine Pizzinga[1], Laima Brazionis[7], Allison Hodge[8], Cathrine Mihalopoulos[9], Mary Lou Chatterton[9], Olivia M Dean[1,4,10] and Felice N Jacka[1,4]

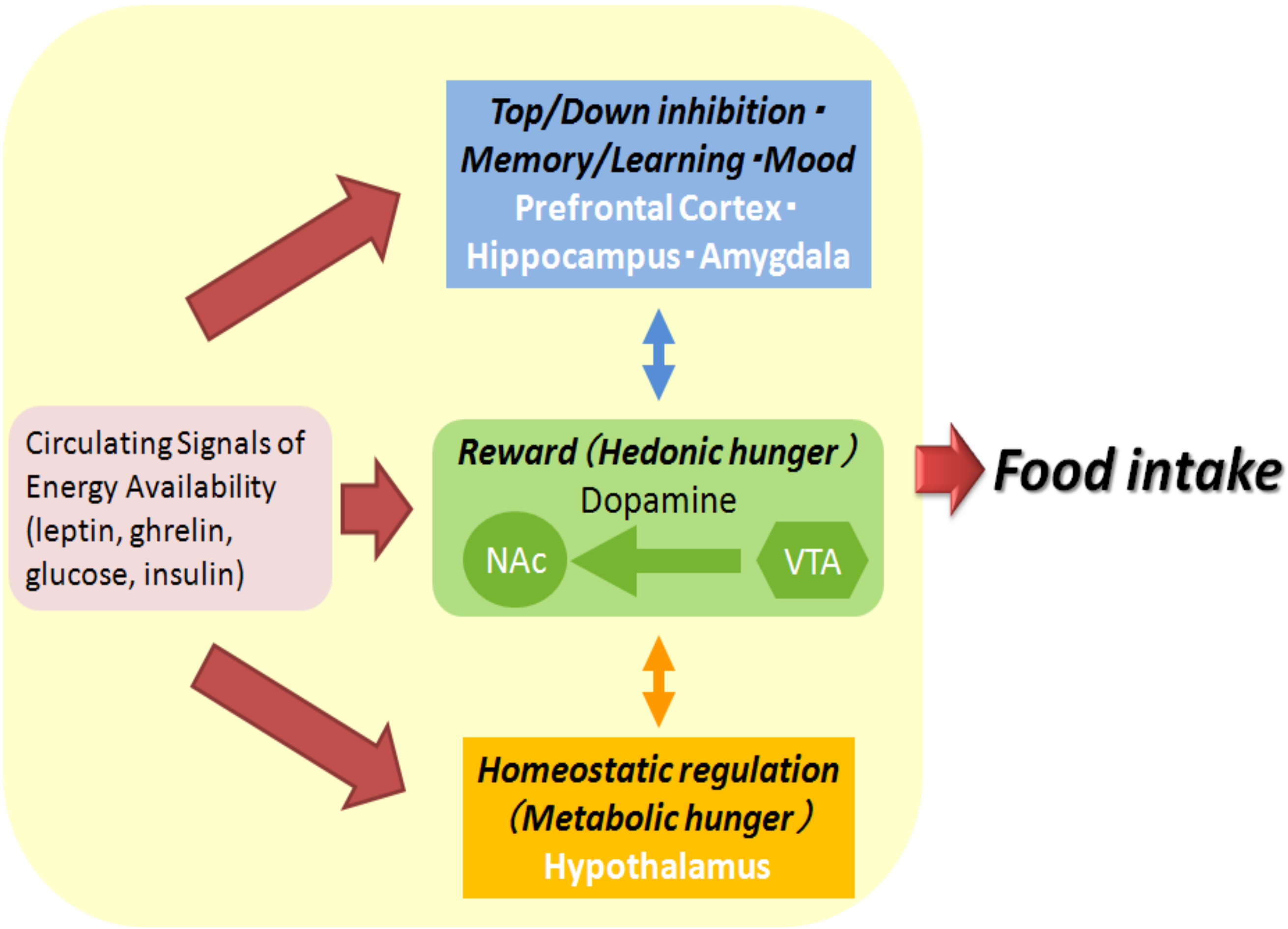
- 12-Wochen, paralleles Gruppendesign (Kontrolle: neutrale Lebensberatung), einfach blind.
- 3 Beratungssitzungen/Woche
  - Speisepläne
  - Ausgabe Nüssen/Öl etc.

- 1°: Verbesserung gemäß MADRS (Montgomery Asberg depression rating scale)
- 2°: Schweregrad und Verbesserung nach CGI (clinical global impression)
- Weitere 2°: HADS, QoL-SF36, …FFQs, DST … Blutparameter, BMI, …, H-Ök.
- Inklusion:
  - Erwachsene mit MDD nach DSM-IV und MADRS >18
  - Und: "Problematisches Ernährungsmuster" gemäß "Dietary Screening Test" (DST <60)

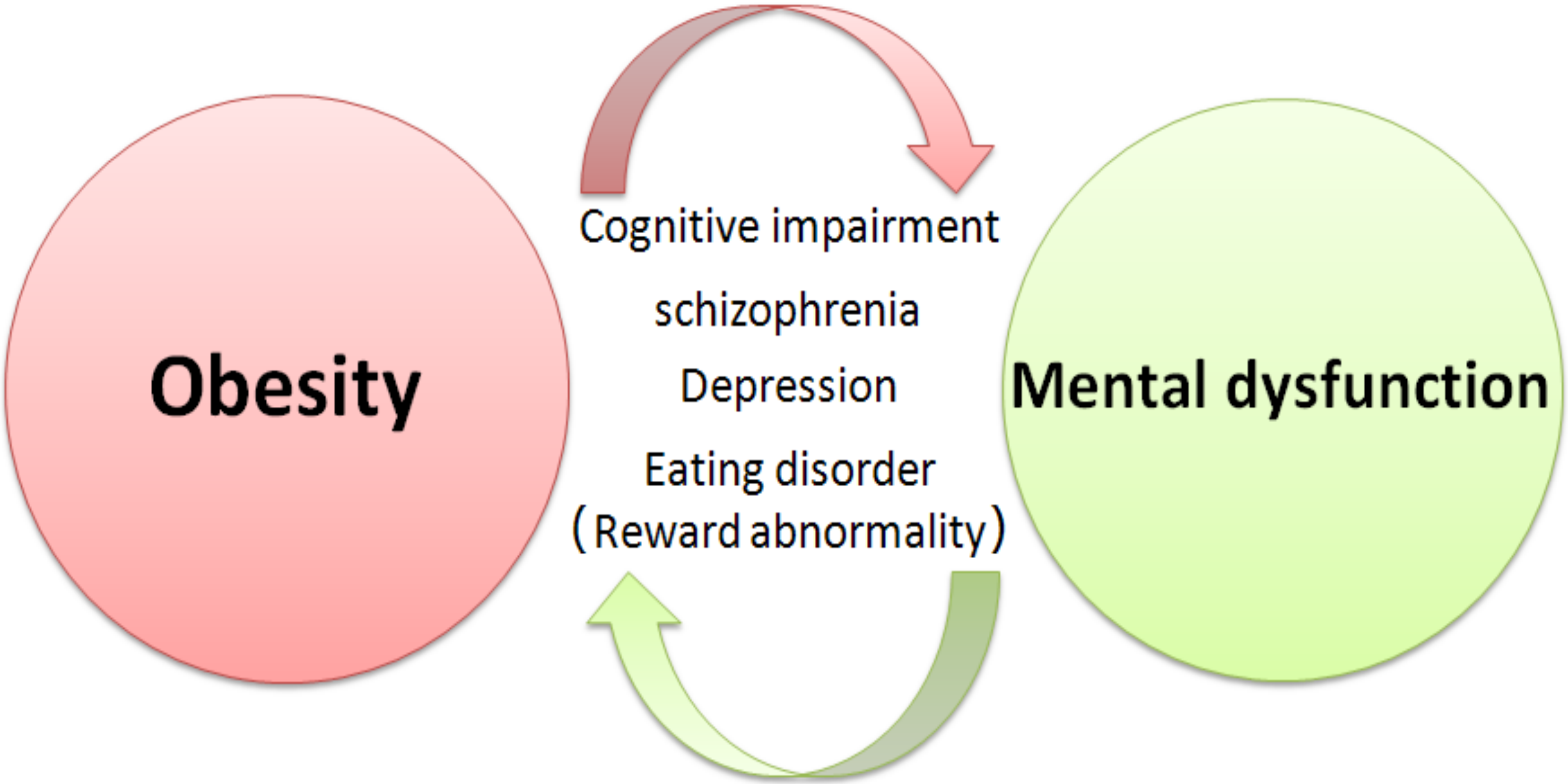
In Planung:
Beobachtungsstudie “adaptierte Mediterrane Diät”

- Einführung eines adaptierten, mediterranen Menus als ein Auswahlmenu im Speiseplan einer LVR Klinik für eine Testzeitraum (1/2 Jahr).

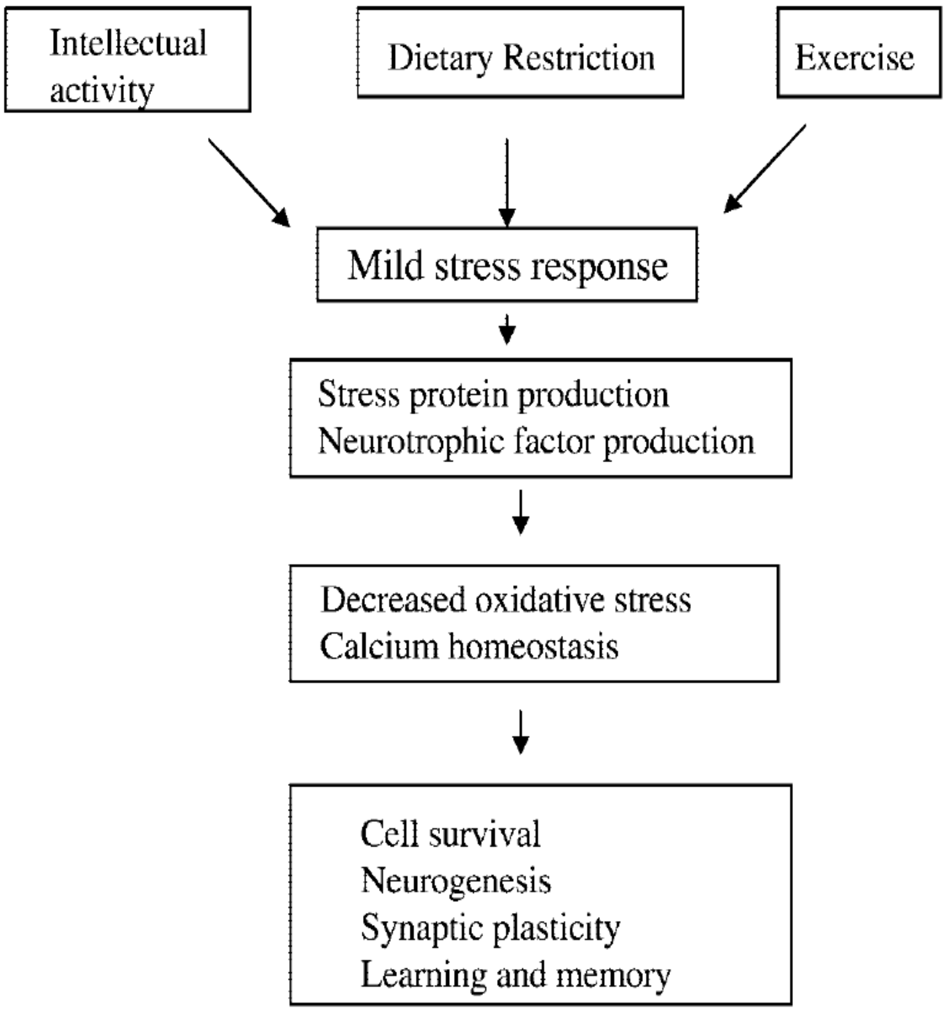
- **Wissenschaftlich:** Begleitung und Auswertung
  - Adhärenz, Effektschätzung in Abhängigkeit vom Störungsbild, etc.
- **Wirtschaftlichkeit:** Evaluation, Kosten-Nutzen-Analyse
  - Mehr-Kosten der Diät, Aufenthaltstage, etc.
- **Patienten & Pflegepersonal:** Befragung zur Zufriedenheit



Yamada-Goto N, 2013



Yamada-Goto N, 2013



Mattson MP 2002

Back-ups … Anorexia Nervosa

Subchronic inflammation & Anorexia Nervosa?

- Although inflammation is increasingly implicated in psychiatric disorders, less is known about its role in anorexia nervosa (AN), an illness with low body mass index (BMI).
- Despite abnormally low BMI, AN seems to be associated with increased inflammatory cytokines. Whether specific elevated cytokines represent trait or state markers of AN, and whether they could be treatment targets requires further study.

Solmi M et al. 2015

Dysfunctional reward system common grounds for obesity and anorexia nervosa?

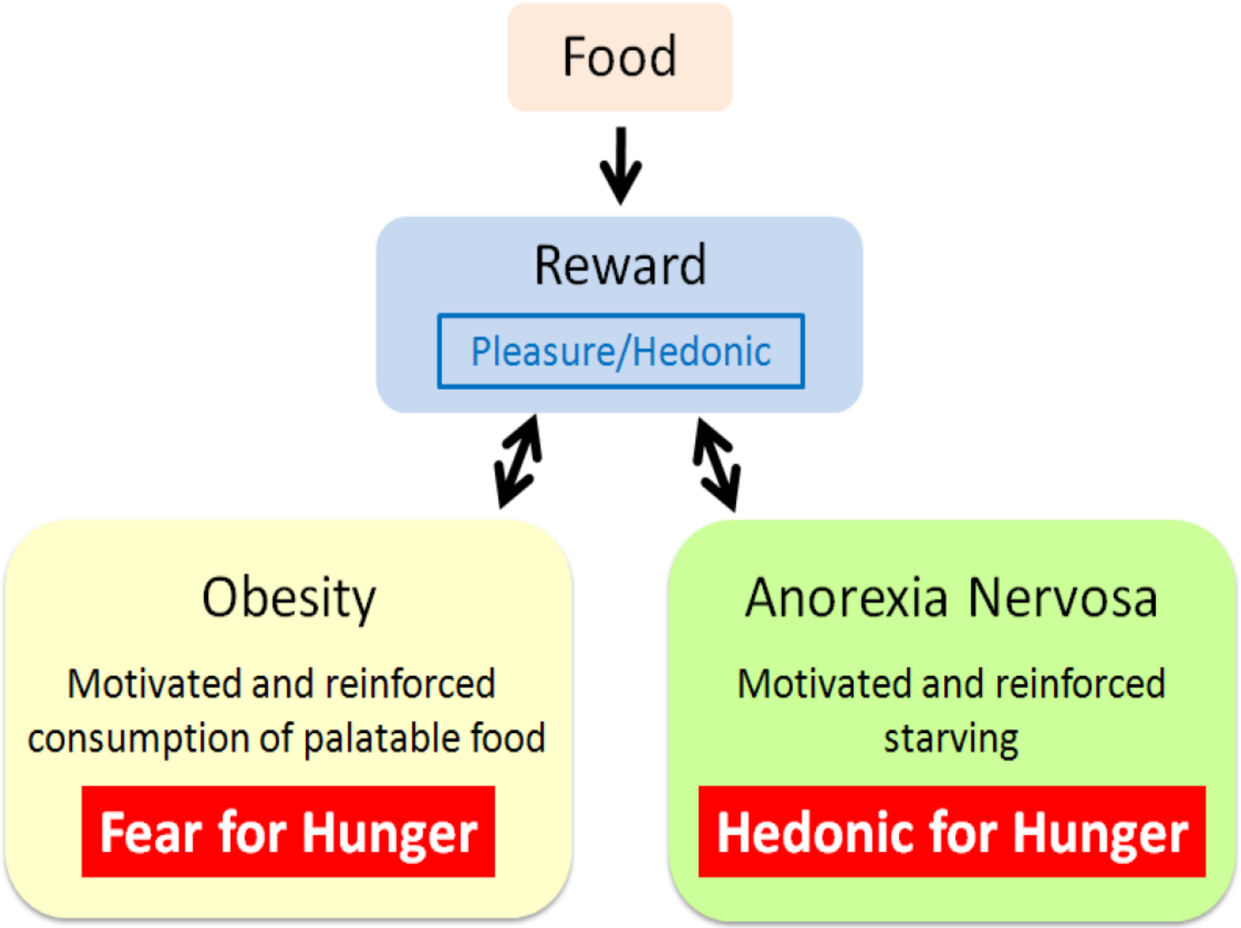
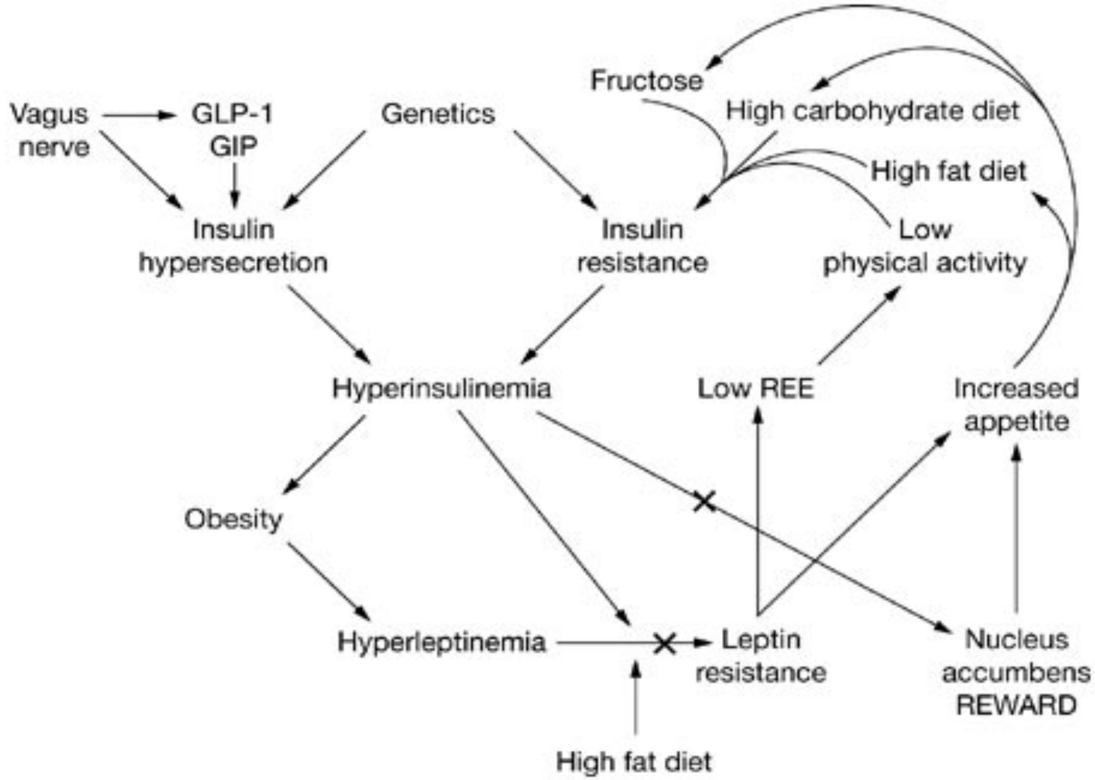


Figure 1. Postulated shared mechanisms related to reward circuits of anorexia nervosa and obesity. The sense of hunger regulated by reward circuits might be the key component of obesity and anorexia nervosa.

Yamada-Goto N, 2013

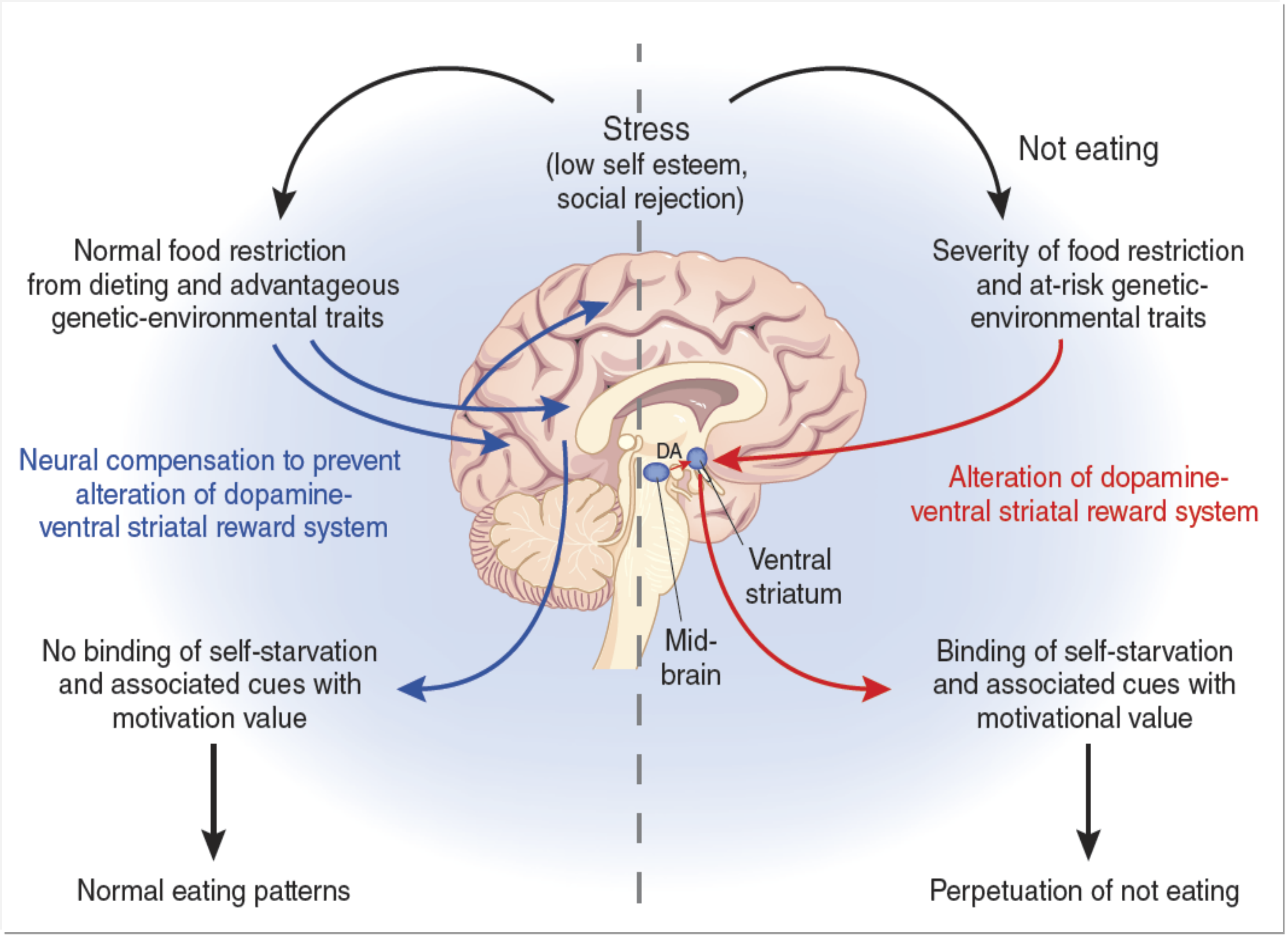
Figure 4 Insulin, leptin, reward and obesity



Lustig RH (2006) Childhood obesity: behavioral aberration or biochemical drive? reinterpreting the first law of thermodynamics *Nat Clin Pract Endocrino Metabol* **2:** 447–458 doi:10.1038/ncpendmet0220

nature CLINICAL PRACTICE ENDOCRINOLOGY & METABOLISM

Modified dopaminergic reward system in anorexia nervosa?



Zink CF, Weinberger DR; Cracking the moody brain: the rewards of self starvation. Nat Med. 2010 Dec;16(12): 1382-3.

Mediterranean Diet an option for eating disorders

© California Walnut Commission

Adherence towards MD ameliorates binge eating

S. Bertoli et al. / Clinical Nutrition 34 (2015) 107–114

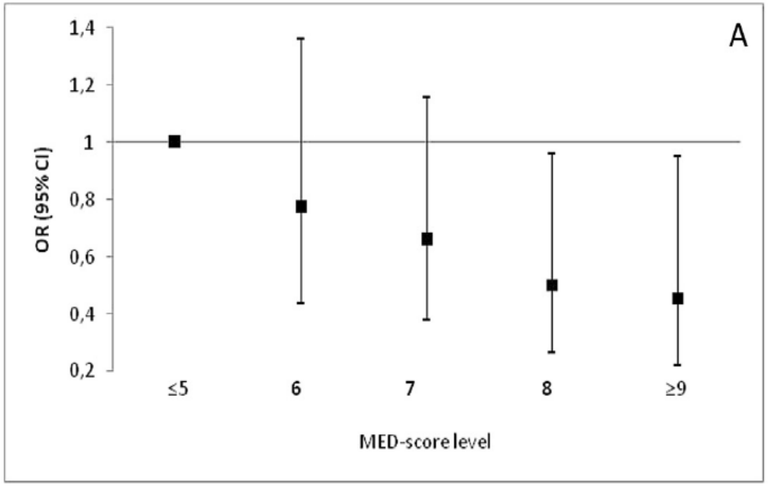
Table 2
Nutritional status, eating behaviour and depressive and anxiety status of the sample according to MED-score level.

Variable	Value	Total Mean (SD)	MED-score level					
			≤5 (*N* = 410) Mean (SD)	6 (*N* = 330) Mean (SD)	7 (*N* = 328) Mean (SD)	8 (*N* = 225) Mean (SD)	≥9 (*N* = 167) Mean (SD)	*p*
Nutritional status	BMI kg/m^2	29.7 (5.3)	29.4 (5.2)	28.8 (5.2)	29.4 (5.4)	29.7 (5.7)	29.1 (5.4)	*0.387*
	% Above cut-off of obesity	39.9	42.1	35.8	40.6	42.9	37.5	*0.342*
	Body fat mass%							
	Female	39.1 (4.9)	38.2 (4.7)	38.6 (4.8)	39.2 (4.7)	40.4.9 (5.1)	40.4 (4.9)	***0.011***
	Male	32.3 (5.7)	32.1 (5.7)	31.7 (6.1)	32.6 (5.5)	33.6 (4.7)	31.8 (6.2)	*0.333*
	Waist circumference cm							
	Female	91.6 (12.7)	90.8 (12.8)	89.8 (12.5)	91.9 (12.6)	93.7 (13.5)	93.5 (11.8)	***0.015***
	Male	106.5 (12.4)	106.6 (10.9)	105.4 (13.0)	108.8 (13.4)	108.5 (11.1)	103.3 (13.2)	*0.136*
Binge eating	BES score	12.0 (7.5)	12.8 (7.2)	11.2 (7.4)	12.1 (7.6)	12.1 (8.0)	10.7 (7.5)	***0.011***
	% Above cut-off	25.5	26.9	21.5	27.0	28.8	23.2	*0.255*
Depression	QD percentiles	47.6 (28.4)	49.6 (28.1)	46.7 (27.9)	48.4 (29.2)	47.5 (28.5)	43.1 (27.6)	*0.153*
	% Above cut-off	3.2	2.2	2.7	4.5	4.0	3.0	*0.395*
Anxiety	STAI X II percentiles	46.0 (28.5)	45.8 (29.3)	44.6 (28.1)	44.3 (28.8)	49.5 (28.3)	47.6 (26.9)	*0.216*
	% Above cut-off	3.8	4.4	3.6	3.0	4.4	3.6	*0.879*

All associations and means comparison were examined with $\chi 2$ analyses and *one-way ANOVA*, respectively.
p-Value is reported in italics. Significance ($p<0.05$) is reported in bold.

MED-Score: Validiertes 14-Item Instrument zur Messung der Adhärenz zur Mediterranen Diät (Martinez-Gonzalez MA, 2012)

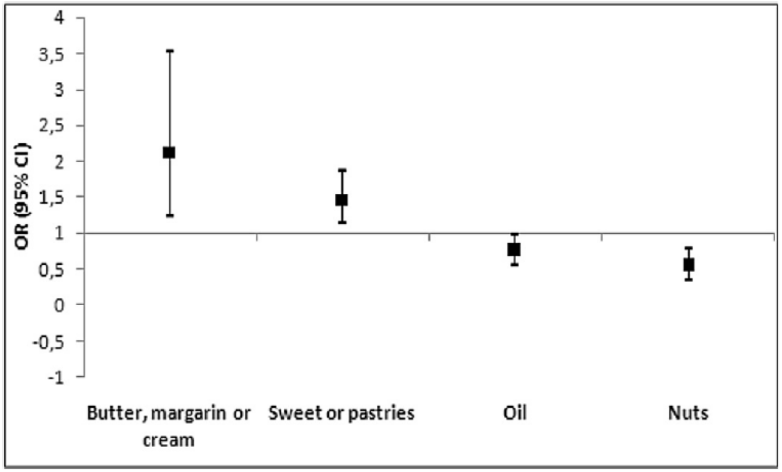
Adherence towards MD ameliorates binge eating



Multivariate OR (95%) für Binge Eating versus MED-Score Level als Maß für Adhärenz.

(adjustiert für Alter, Geschlecht, BMI, Rauchen, Ehestand, körperliche Aktivität)

MED-Score: Validiertes 14-Item Instrument zur Messung der Adhärenz zur Mediterranen Diät (Martinez-Gonzalez MA, 2012)



Multivariate OR (95%) für Binge Eating versus ausgewählte Bestandteile des MED-Score.

(adjustiert für Alter, Geschlecht, BMI, Rauchen, Ehestand, körperliche Aktivität)

Früchte, Gemüse, Hülsenfrüchte und Wein zeigten keine signifikante, unabhängige Assoziation.

Bertoli S, 2015

RESULTS:

Greater numbers of stressors were associated with lower postmeal REE (p = .0
lower fat oxidation (p = .04), and higher insulin (p = .01), with nonsignificant eff
for cortisol and glucose. Women with prior MDD had higher cortisol (p = .008) a
higher fat oxidation (p = .004), without significant effects for REE, insulin, and glucose. Women with a depression history who also had more stressors had a higher peak triglyceride response than other participants (p = .01). The only difference between meals was higher postprandial glucose following sunflower
compared with saturated fat (p = .03).

CONCLUSIONS:

The cumulative 6-hour difference between one prior day stressor and no stress
translates into 435 kJ, a difference that could add almost 11 pounds per year. These findings illustrate how stress and depression alter metabolic responses t
high-fat meals in ways that promote obesity.

Weight alterations in mental disorders

Disorder	Body weight		Reference
	Prämorbid	Acute	
Bipolar Disorder		↑	Bernstein et al. 2015
Depression (MDD) **typical** **atypical**		 ↓ ↑	 Byrne et al. 2015 Gold et al. 2002
ADHD		↑	Albayrak et al. 2013
Schizophrenia		↑	Theisen et al. 2001
Autism		↑	Broder-Fingert et al. 2014
Eating disorders **AN** **BN**	 ↔ ↑	 ↓ ↑	 Coners et al. 1999 Müller et al. 2012
Alzheimer‵s disease	↓	↓	Hinney et al. 2014

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Alzheimer`s disease	↓	↓	Hinney et al. 2014

PGC: 'Cross-Disorder' Analysis
Psychiatric Genomics Consortium

Hypothesis: specific gene variants predispose to 5 disorders: autism spectrum disorders, ADHD, bipolar disorder, MDD, and schizophrenia

33,332 cases (5 disorders) and 27,888 controls of European descent

SNPs at 4 loci genome-wide significant (p<5×10−8) in the primary analysis:

- 3p21
- 10q24
- 12p: *CACNA1C*
- 10p: *CACNB2*

CACNA1C and CACNB2: L-type voltage-gated calcium channel subunits 1 and 2

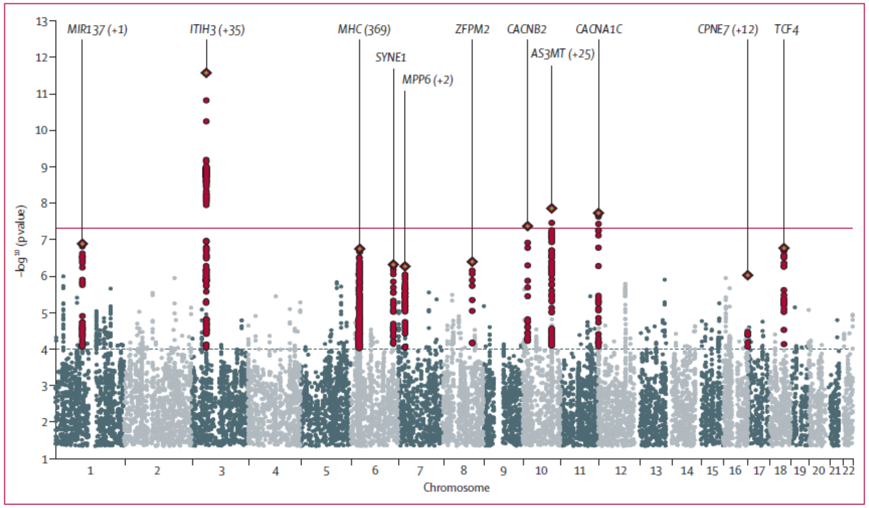

Figure 1: Manhattan plot of primary fixed-effects meta-analysis
Horizontal line shows threshold for genome-wide significance ($p<5\times10^{-8}$).