OBESITY, BRAIN AND MENTAL HEALTH

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Obesity, brain & mental health

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The diversity of obesity- ESPEN 2016
• Obesity, cognitive function & mental health disorders (MHD): what are we talking about?
• Obesity, brain function and structure: what is going on during lifespan?
• Obesity and cognitive function: cause or consequence. Common pathways. A few hypothesis
• Does obesity treatment make our brain fit?
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Obesity is frequent WHO

- Worldwide obesity has more than doubled since 1980.

- In 2014, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 600 million were obese.

- 39% of adults aged 18 years and over were overweight in 2014, and 13% were obese.

- Most of the world's population live in countries where overweight and obesity kills more people than underweight

- Obesity is preventable
• 41 million children under the age of 5 were overweight or obese in 2014
Mental Health Disorders
Mental health disorders

• Anxiety & Panic Disorders
• Bipolar Disorder
• Depression
• Eating Disorders
• Schizophrenia
• Substance Abuse & Addiction
• Tic disorders
• Sleep-related problems
• **Dementia: Alzheimer's disease or type 3 Diabetes**
Mental health disorders are frequent too

- US population
- 25% of adults
- 7% major depressive disorder
- 3% generalized anxiety disorder
- 4% attention deficit/hyperactivity disorder ADHD
- 17% children ADHD or autism spectrum disorders ASD

Cognitive function

• An intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves all aspects of perception, thinking, reasoning, and remembering.

• Neurology Any mental process that involves symbolic operations—eg, perception, memory, creation of imagery, and thinking; CFs encompasses awareness and capacity for judgment.
Do we have the right tools for assessment of obesity & cognitive function?

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• Body Mass index
• Central obesity and waist circumference/waist to hip ratio
Mini Mental State Examination

• MMSE: gold standard +-
• Modified Mini Mental State Examination 3MS
• Spatial and executive function
• Naming
• Memory
• Attention
• Language
• Delayed recall
• Orientation
• Normal >28 out 30 points
• Mild cognitive impairment

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Trail making test
Modified stroop color test

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Digit symbol coding test
Rey Auditory Verbal Learning Test
RAVLT

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• Neither in obesity nor in cognitive assessment, tools are uniform and comparable
• This lack of uniformity may explain some of the conflicting results linking obesity and cognitive function
• Saying that, what do we know of the links between obesity, cognitive function & MHD?
Framingham Heart Study

• Prospective study 18 y follow up
• Male N=551 female N=872
• free from dementia, stroke, and clinically diagnosed cardiovascular disease up to the time of cognitive testing
• cognitive performance (learning, memory, executive functioning, and abstract reasoning) on tests administered 4–6 y later.
Only in men Obesity & HTA are linked to CF

Figure 1  Relation of number of CVD risk factors (0 = none; 1 = either obesity or hypertension present; 2 = both obesity and hypertension present) to cognitive test performance in men.


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Cognitive decline and dementia in diabetes

• 1.2 to 1.5 greater change over time in measures of cognitive function in individuals with diabetes compared to those without diabetes

• Cognitive dysfunction as a chronic complication of diabetes

Diabetologia 2005;48:2460-69

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Cognitive decline in diabetes: is it an early sign?

- TDM 1 & TDM2 age 20-55 years
- Duration of diabetes ≤ 10 years
- Control 20-55 years with no known history of diabetes
- MoCA test

Non published data

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MoCA scores

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![Bar chart showing MoCA scores](image)

**MoCA scores**

- **DM 1 & 2 n=63**
  - Mean: 24.1
  - SD: 4.5

- **Control n=56**
  - Mean: 26.9

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P<0.0001

Non published data
Co-morbidity of obesity/Mets with MHD

• 45% of cases
• Obese mothers: 67% more likely to have a child with Autism Spectrum Disorder


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Obesity, brain function and structure: what is going on during lifespan?
Obesity/Lean and cognitive function across lifespan

- 4-18 years aged group: poorer cognitive indices (executive function)
- 19-65 years age group: negative association between obesity & cognitive function, executive
- 66-95 years: conflicting results (true up to 72 years)

Obesity reviews (2011) 12, 740-755
Maternal obesity & cognitive function in children

• 9/10 studies: association of high maternal BMI with poorer cognitive function in the children
The impact of glucose disorders on cognition and brain volumes in the elderly: the Sydney Memory and Ageing Study

• Longitudinal study in elderly 70–90 years at baseline (n=1,037)
• Community-dwelling elderly cohort with neuropsychological testing (n=880) and brain volumes by magnetic resonance imaging (n=312) measured at baseline and 2 years.
• Primary outcomes were global cognition and total brain volume
MAS cohort at baseline: n = 1037

- Neuropsychometric testing
- Brain MRI

at baseline

- n = 1037
- n = 542

at 2-year follow-up

- 880/1037 (85%)
- 312*/542 (58%)
Degree of glucose intolerance was associated with cognition & brain volume.
• Incident glucose disorders, like diabetes, are associated with accelerated decline in global cognition and brain volumes in non-demented elderly, **whereas stable IFG is not.**

**Trends in glucose disorders and not actual glucose disturbances ?????
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Potential mechanisms linking MetS and MHD


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A short list of the mechanisms linking obesity, brain & MHD

• Genes, obesity and CF
• Low grade inflammation
• Insulin resistance
• Brain-derived neurotrophic factor
Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium N=53949

- Association between general cognitive function and four genes previously associated with Alzheimer’s disease:
  
  TOMM40, APOE, ABCG1 and MEF2C
Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium N=53949

• General cognitive function is heritable and highly polygenic, extending findings of previous studies involving general cognitive function in older individuals.
Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium N=53949

- associations within similar genomic regions involved in development of the brain, neurological function, psychiatric disease and educational attainment.
Peripheral inflammation low grade

Disruption of normal feeding

Obesity

Central inflammation

Independent risk factor for Depression, cerebral white matter lesions, Cognitive dysfunction

Both quantity and quality of fat

Direct action on Toll like Receptor 4?
Fat diet/obesity & Cognitive dysfunction: hypothesis

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Insulin resistance

• Connection of METs & Alzheimer disease AD
• AD related to dysfunction of insulin signaling & glucose metabolism: AD as Type 3 Diabetes or Insulin-resistant brain state
Insulin

BBB

Brain Insulin Signaling

Food Intake
Body weight
Reproduction
Learning
Memory

Accelerated aging:
Obesity
• ↑ Insulin resistance
• ↓ Adiponectin
• ↑ Chronic inflammation

Glucose metabolism

Delayed aging:
Longevity
• ↑ Insulin sensitivity
• ↑ Adiponectin
• ↓ Chronic inflammation
Insulin resistance and cognitive impairment
B. Kim and E.L. Feldman

Metabolic Syndrome
T2D, Obesity, Dyslipidemia

Central Insulin Resistance

Dysregulation of insulin signaling
PI3-K/Akt/GSK3α/β

Increased Aβ production

Increased tau Phosphorylation

Senile plaques

NFT

Figure 1 MetS and AD Aβ/tau pathology may act in a feed-forward mechanism to accelerate AD pathology in the presence of IR.
From Mass to individual

genome-wide association studies
GWAS
N=53949

de novo chromosomal inversion
N=1
Brain-derived neurotrophic Factor

• 8-year-old girl with hyperphagia and severe obesity, impaired cognitive function, and hyperactivity who harbored a de novo chromosomal inversion: 46,XX,inv(11)(p13p15.3), a region encompassing the BDNF gene
• Serum concentration of BDNF protein was reduced compared with age- and BMI matched subjects.

• Haplo insufficiency for BDNF was associated with increased ad libitum food intake, severe early-onset obesity, hyper-activity, and cognitive impairment.

• Role of the neurotrophin BDNF in human energy homeostasis, as well as in cognitive function, memory, and behavior.
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Nutrition and cognitive function
Yin and Yang Association or Causality

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Lifestyle & brain structure
The effects of physical activity on functional MRI activation associated with cognitive control in children

Frontiers in Human Neuroscience 2013;7:72

- 8 to 9 year old children
- 60 mn physical activity, 5 days/week for 9 months versus waiting list children
- Functional MRI
- Decrease in fMRI brain activation on pre frontal cortex - improvement in task of attentional & interference control
Physical activity and cardiorespiratory fitness and white matter in older low-fit adults

PloS ONE 2014;9(9):

- Non exercise lifestyle activities: light, moderate physical activity (PA)
- Sedentary behavior
- Moderate to vigorous PA, MV-PA
- Cardiorespiratory fitness: 
  - Oxygen consumption
  - Accelerometer assessment

White matter WM hyperintensities WMH volume at T2 STRUCTURE

Functional anisotropy measured by diffusion tensor imaging (fiber density, axonal diameter, and myelination in white matter, connectivity in the brain communication among cortical networks, particularly those involving executive function, perceptual speed, and memory, fluid cognition)) FUNCTION
• Greater MV-PA related to lower volume of WM lesions
• PA & WM microstructural integrity is region specific: light PA-temporal WM, sedentary behavior-parahippocampal WM

• Both avoiding sedentariness & PA are important in maintaining WM health in older age
Lifestyle & brain structure

Never too late

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Lifestyle and cognition
• One year long lifestyle intervention versus no intervention in 107 elderly (69 years old) obese (BMI 37) improved cognition and QoL

• Intentional weight loss in elderly with MCI associated with improvement in cognitive function

Horie NC et al J Clin Endocrinol Metab 2016;101:1104-12
• Positive Association of dietary glycemic load and cognitive performance in elderly subjects
• Weight loss has neither a positive nor a negative effect on cognitive function and that L-CHO and H-CHO weight-loss diets have similar effects on cognitive performance
• Look AHEAD: Lack of overall intervention effect on CF

Power SE et al Eur J Nutr 2015;54:557-68
Makris A et al Nutrition & Diabetes 2013 ;3, e89

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Lifestyle and cognition

Conflicting results

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Surgery induced weight loss & cognition
Improved Memory Function Two Years After Bariatric Surgery

• 86 individuals (63 bariatric surgery patients, 23 obese controls)

• All participants completed self-report measurements and a computerized cognitive test battery prior to surgery and at 12-week and 24-month follow-up; obese controls completed measures at equivalent time points.
Improved Memory Function Two Years After Bariatric Surgery

- Bariatric surgery patients exhibited high rates of pre-operative cognitive impairments in attention, executive function, memory, and language.

- Relative to obese controls, improvements in memory from baseline to 12-weeks and 24-months post-operatively ($p < .05$).

- Controlling for baseline factors revealed that a lower BMI at 24-months demonstrated a trend toward significance for improved memory ($p = .075$).
Nutrition and cognitive function
Yin and Yang Association or Causality

Association

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Interim conclusions

• Obesity, cognitive function & mental health disorders are frequent & co morbid in a bidirectional way
• Obesity, brain function and structure have a strong correlation during lifespan up to 72 years old
• Genes and environment act with similar pathways on obesity, CF & MHD
• We still have work to know the better way to keep our brain fit?
Age is an issue of mind over matter. If you don't mind, it doesn't matter.
Mark Twain

Thank you

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