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50 Shades of Obesity

Obesity & Gender Disparities

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Disclosure

Consulting: *Novo Nordisk, MSD (Merck Sharp & Dohme), BI (Boehringer Ingelheim), Sanofi, AstraZeneca, Pfizer, Teva, Novartis*

Lecture: *Novo Nordisk, MSD, BI, Sanofi, AstraZeneca, Pfizer, Teva, Novartis, Dexon*

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Outline

- Obesity Epidemuology
- Obesity as Dysfunctional fat Disease
- Obesity comorbidities
- Menopause -Related Gain in Visceral Adiposity
- Obesity & Sex Hormones and appetite regulation
- Obesity Treatment

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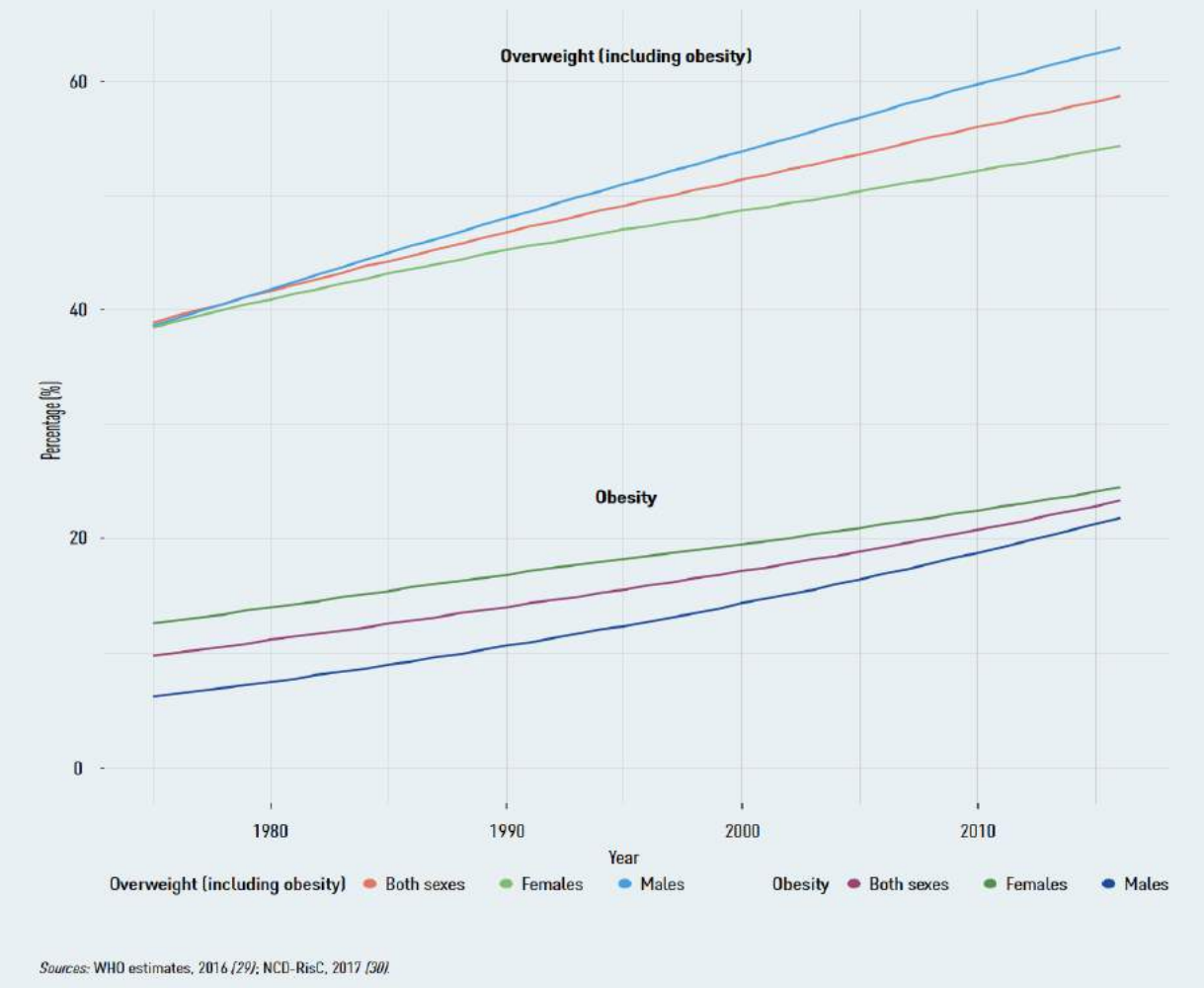
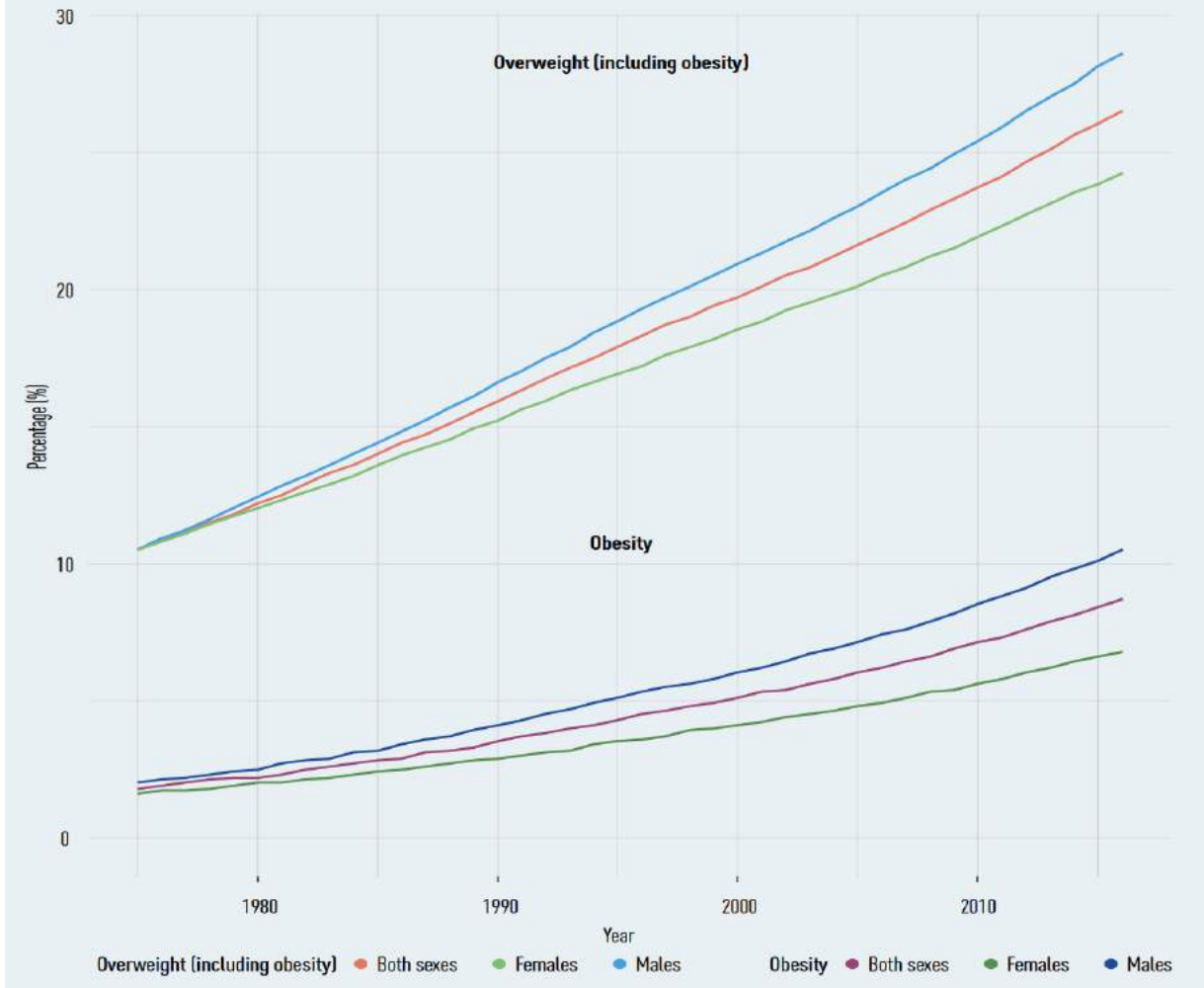
The epidemiology of obesity



Sources: WHO estimates, 2016 *(29)*; NCD-RisC, 2017 *(30)*.



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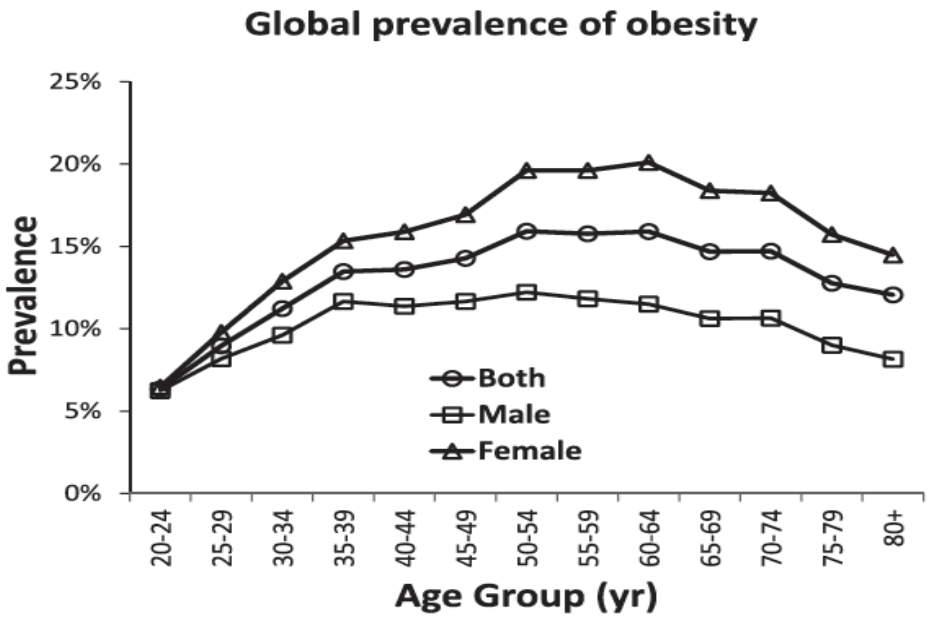
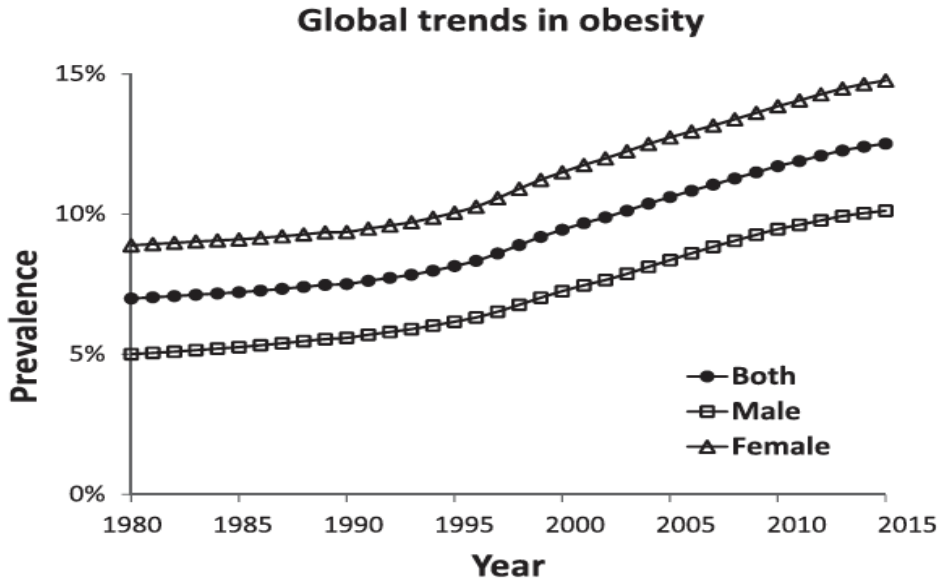
The epidemiology of obesity





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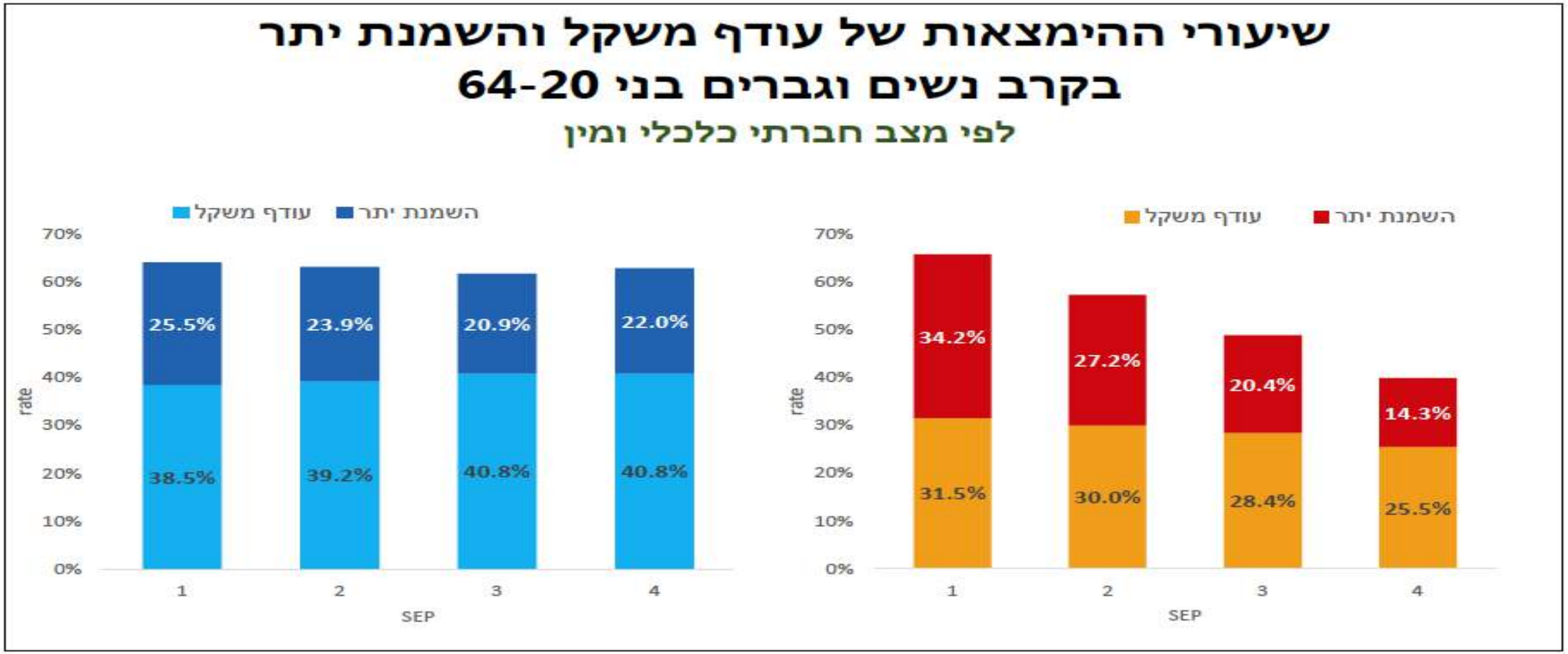
Yu Chung Chooi. Metabolism Clinical and Experimental 92 (2019)

Prevalence of Obesity by Age 20-64



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Obesity is recognised as a disease and a health issue

"obesity is a chronic, relapsing, progressive disease process ….need for immediate action for prevention and control of this global epidemic"

World Obesity Federation[1]

"Obesity is a progressive chronic disease, similar to diabetes or high blood pressure, …"

Obesity Canada[3]

"A progressive disease, impacting severely on individuals and society alike,… obesity is the gateway to many other disease areas…"

European Association for the Study of Obesity[4]

"obesity and overweight as a chronic medical condition (de facto disease state) and urgent public health problem…"

American Medical Association[2]

"It (obesity) is not a lifestyle choice caused by individual greed but a disease caused by health inequalities, genetic influences and social factors.."

Royal College of Physicians UK[5]

"The Treat and Reduce Obesity Act would allow a variety of qualified practitioners, including registered dietitian nutritionists, to more effectively treat this disease, which impacts more than one-third of our nation."

Academy of nutrition and dietetics[6]

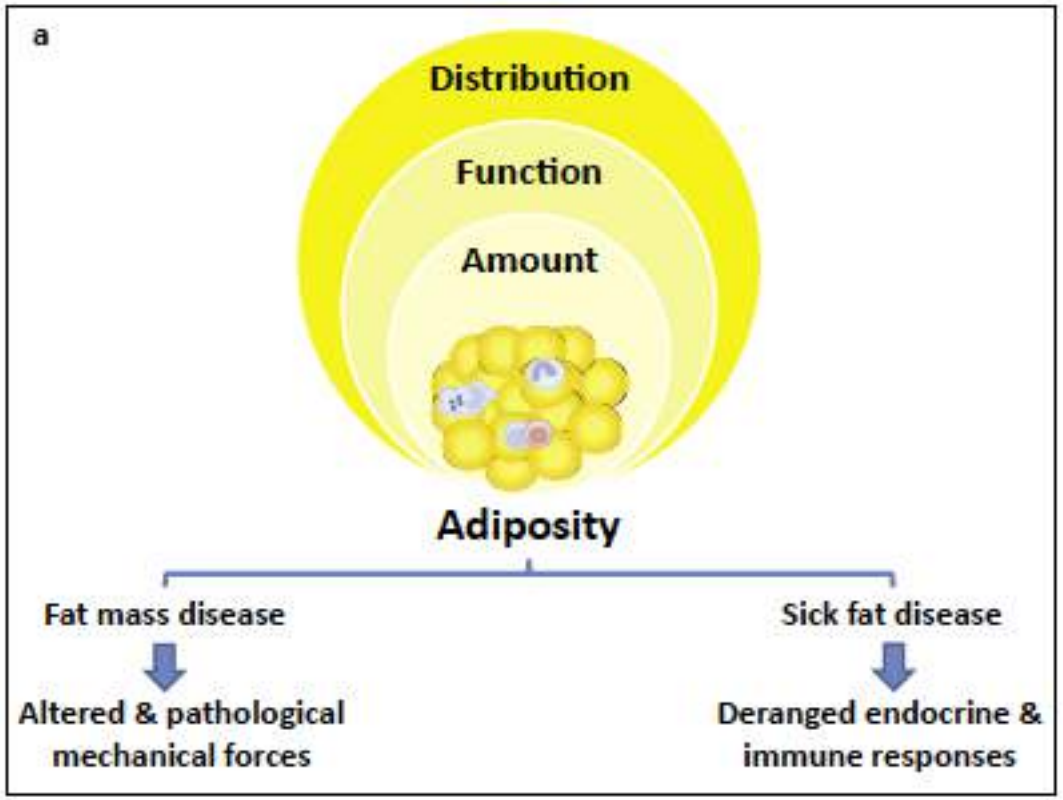
"A pathological state (obesity disease) in which a person suffers health problems caused by or related to obesity thus making weight loss clinically desirable …"

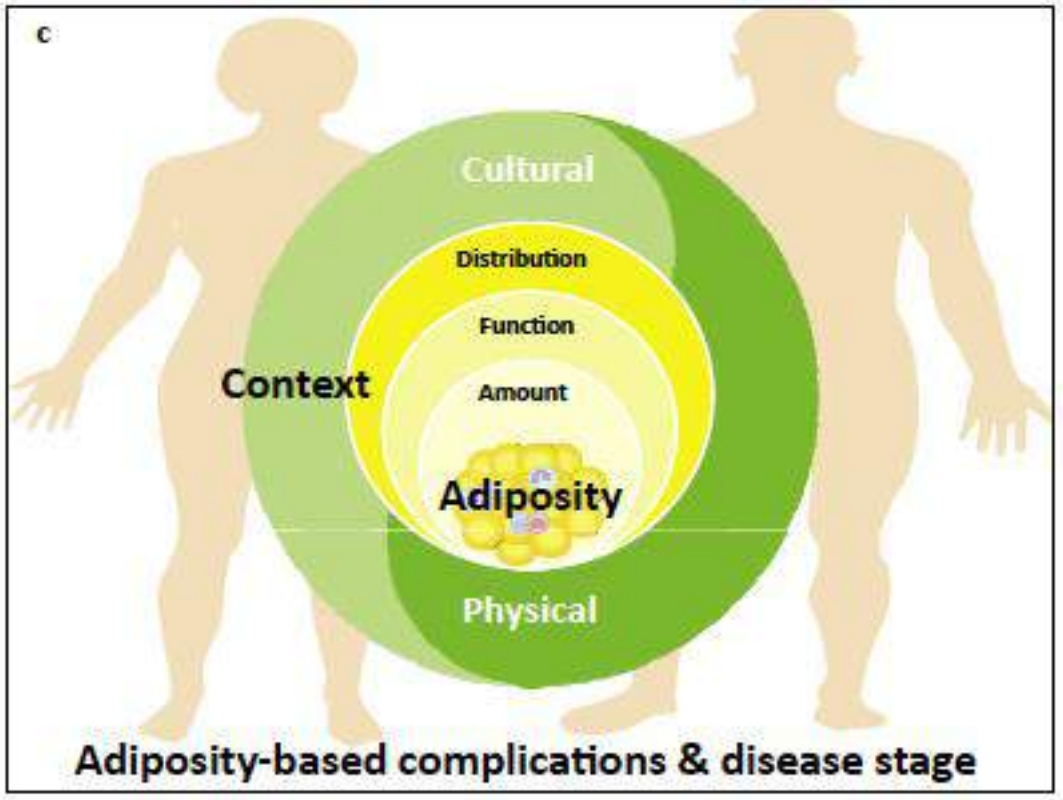
Asia Oceania Association for the Study of Obesity[6]

European Association for the Study of Obesity

1. Bray et al. Obes Rev 2017;18:715–723; 2. AMA resolutions. June 2012. Available here (accessed February 2020); 3. Obesity Canada. Available here; 4. EASO: 2015 Milan Declaration: A Call to Action on Obesity. Available here. Last accessed: June 2019; 5. Royal College of Physicians. Anon. BMJ 2019;364:l45; https://www.rcplondon.ac.uk/news/rcp-calls-obesity-be-recognised-disease; 6. Raynor et al. J Acad Nutr Diet 2016; 116(1): 129-147; 7. AOASO position statement, Nagoya Declaration 2015. Available here

Adiposeopathy - EASO Guidelines





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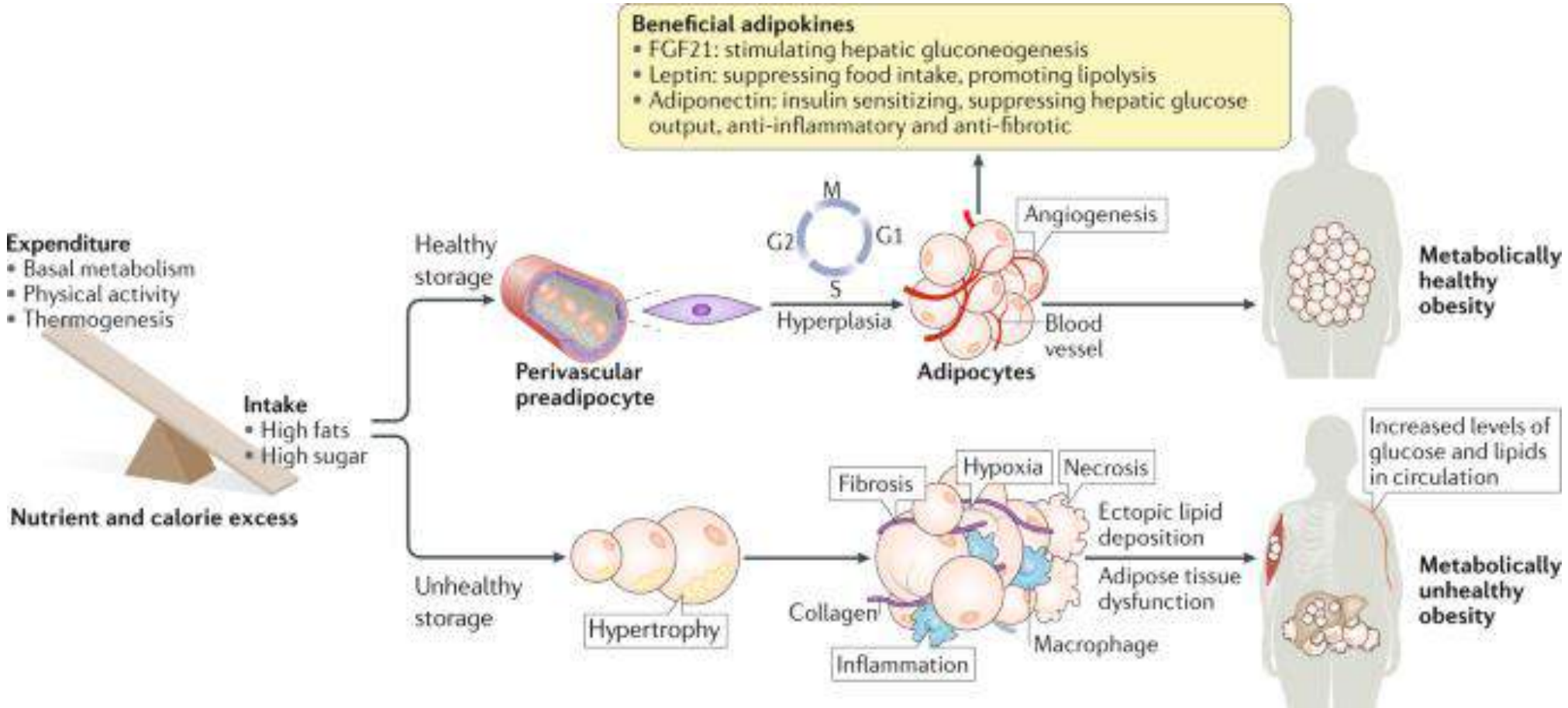
Frunbeck G, Busetto L, Dicker D. et al Obesity Facts 2019

Mechanisms of adipose tissue expansion.



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Ghaben, A.L., Scherer, P.E, *Nat Rev Mol Cell Biol*

Cytokine production by PBMC from non-obese and obese individuals

	Non obese (n = 25)		Obese (n = 41)		p value
	range	mean ± SD	range	mean ± SD	
Glucose, mg/dl	72–112	90.1 ± 8.3	69–140	92.4 ± 17.2	NS
Cholesterol, mg/dl	154–252	190.3 ± 30.7	127–289	189.7 ± 31.4	NS
Triglycerides, mg/dl	41–430	91.2 ± 75.7	52.3 ± 460	142.0 ± 77.8	0.0128
HDL, mg/dl	32.2–94.3	63.6 ± 13.9	28.1–66.8	44.1 ± 9.3	<0.0001
LDL, mg/dl	63–174	108.5 ± 29	66–149	117.3 ± 22.6	NS

Cytokines	Non-obese (n = 25)	Obese (n = 41)	p value
Pro-inflammatory			
TNF-α, pg/ml	277 ± 31	505 ± 45	0.0006
IFN-γ, ng/ml	74.0 ± 2.65	93.1 ± 6.0	0.019
IL-1β, ng/ml	3.94 ± 0.34	3.78 ± 0.28	0.7299
IL-6, ng/ml	15.63 ± 2.32	13.53 ± 1.13	0.3648
IL-2, ng/ml	4.92 ± 0.34	6.66 ± 0.38	0.0029
Anti-inflammatory			
IL-10, pg/ml	952 ± 127	651 ± 73	0.04
IL-1ra, pg/ml	930 ± 99	895 ± 52	0.264

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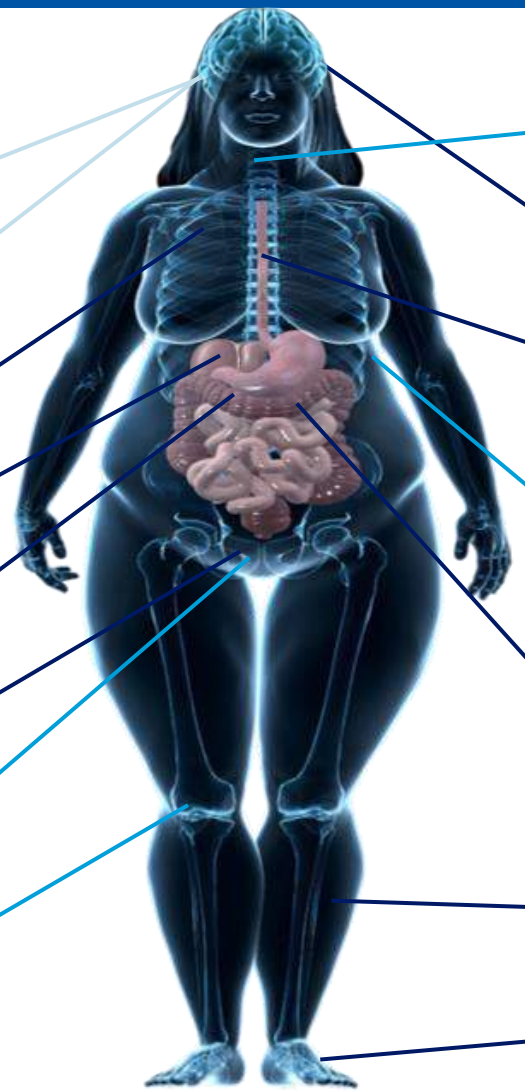
Obesity is associated with multiple comorbidities

Metabolic, Mechanical and Mental

Metabolic

Mechanical

Mental



- Cancers
- Depression
- Anxiety
- Asthma
- NAFLD
- Gallstones
- Infertility
- Incontinence
- Arthrosis
- Physical functioning
- Sleep apnoea
- Cardiovascular diseases
  - Stroke
  - Dyslipidaemia
  - Hypertension
  - Coronary artery disease
  - Coronary heart failure
  - Pulmonary embolism
- Chronic back pain
- Type 2 diabetes
  Prediabetes
- Thrombosis
- Gout

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Adapted from Sharma AM. *Obes Rev* 2010;11:808–9; Guh *et al. BMC Public Health* 2009;9:88; Luppino *et al. Arch Gen Psychiatry* 2010;67:220–9; Simon *et al. Arch Gen Psychiatry* 2006;63:824–30; Church *et al. Gastroenterology* 2006;130:2023–30; Li *et al. Prev Med* 2010;51:18–23; Hosler. *Prev Chronic Dis* 2009;6:A48

Heat map : Prevalence of individuals with multi-body system related morbidity (multi-BSRM) as of 01 January 2014

A - Male

BMI category	25-29	30-39	40-49	50-59	60-69	≥70
Class III obesity	26%	41%	65%	78%	88%	96%
Class II obesity	20%	34%	55%	78%	90%	97%
Class I obesity	14%	25%	46%	69%	85%	96%
Overweight	8%	16%	33%	57%	77%	93%
Healthy weight	5%	10%	23%	45%	67%	89%
	Age group					

Prevalence of multi-BSRM (%)

- ≤20%
- >20%-40%
- >40%-60%
- >60%-80%
- > 80%

B -Female

BMI category	25-29	30-39	40-49	50-59	60-69	≥70
Class III obesity	30%	45%	63%	84%	94%	98%
Class II obesity	25%	36%	57%	79%	92%	98%
Class I obesity	18%	30%	47%	72%	89%	98%
Overweight	13%	22%	36%	63%	83%	96%
Healthy weight	9%	15%	26%	52%	77%	94%
	Age group					

Prevalence of multi-BSRM (%)

- ≤20%
- >20%-40%
- >40%-60%
- >60%-80%
- > 80%

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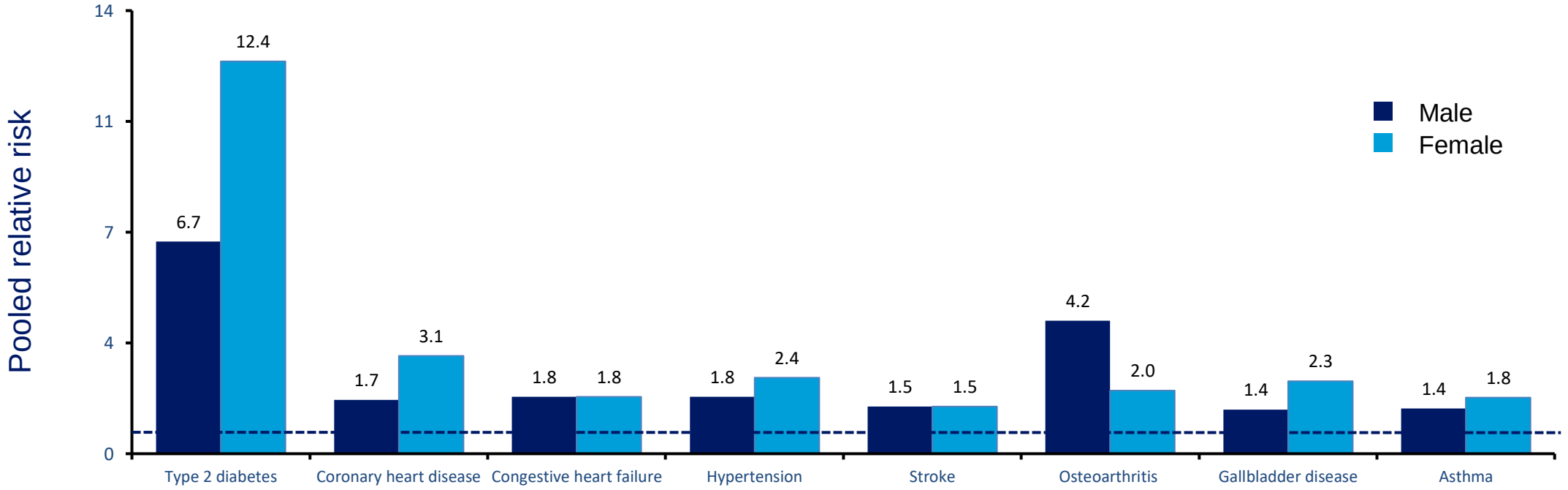
Reges O, Dicker D et al. Israel Journal of Health Policy Research 2020

Obesity increases the risk of multiple comorbidities



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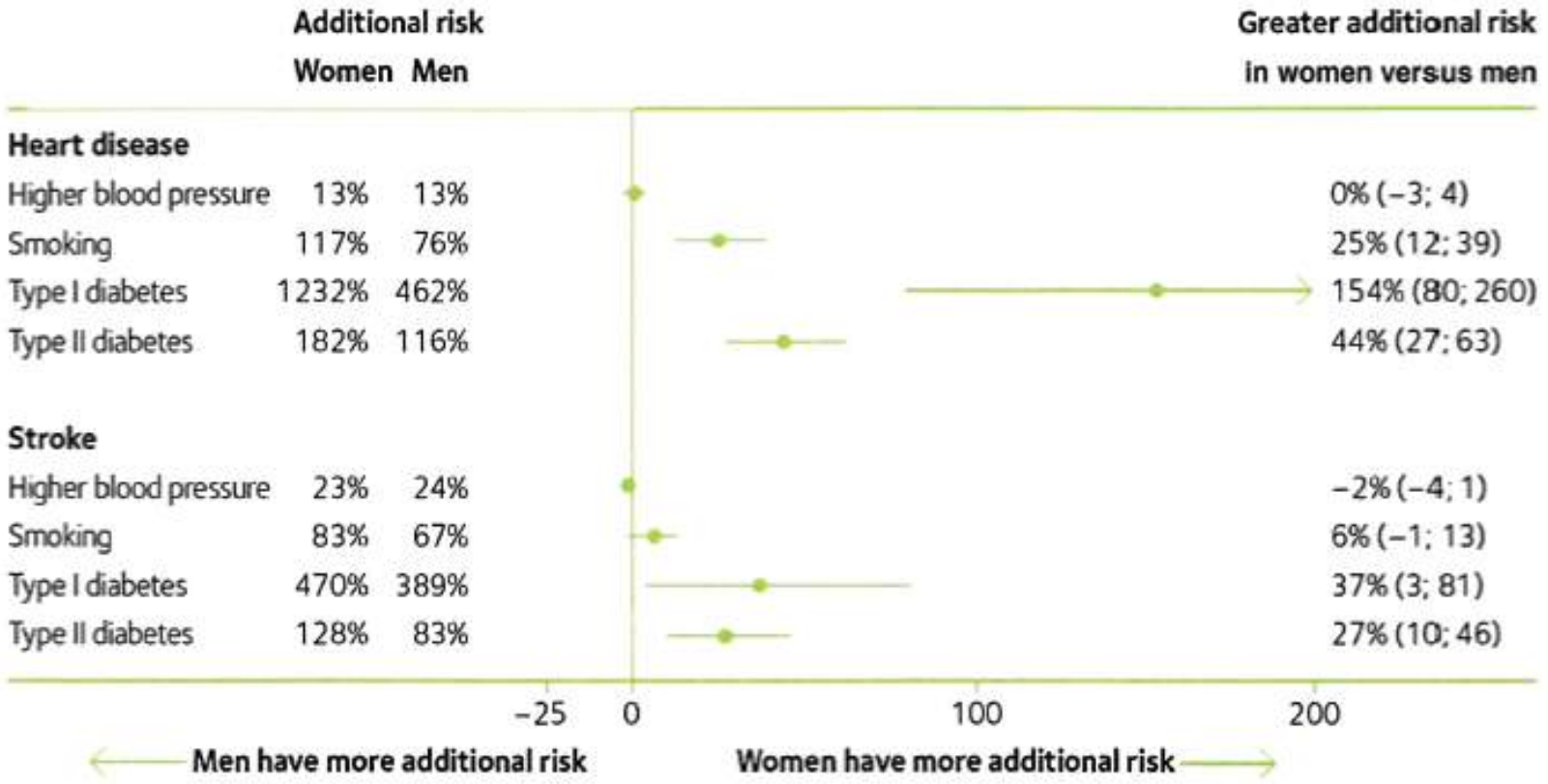
Guh *et al. BMC Public Health* 2009;9:88

Hazards ratios for death according to BMI



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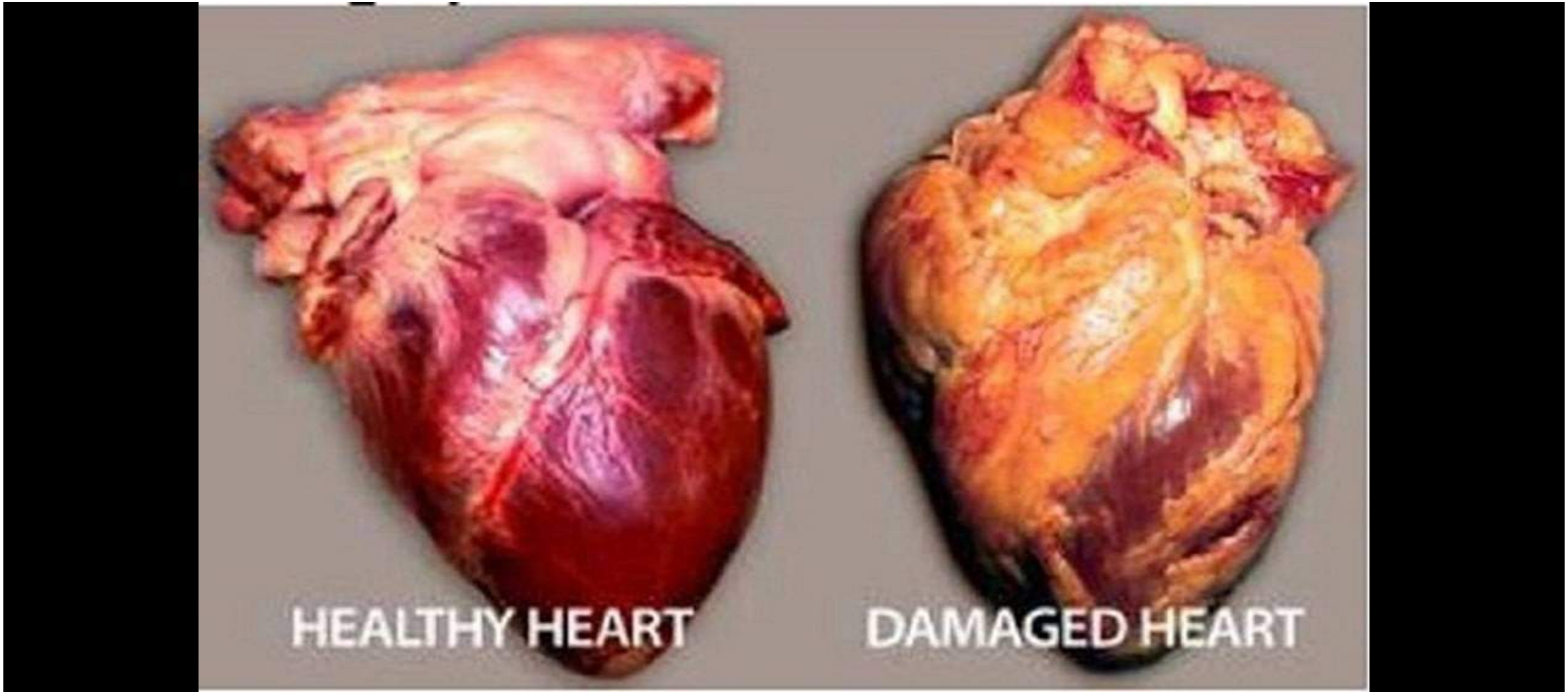
ESHRE Capri Workshop Group, Human Reproduction 2016

Fatty Heart



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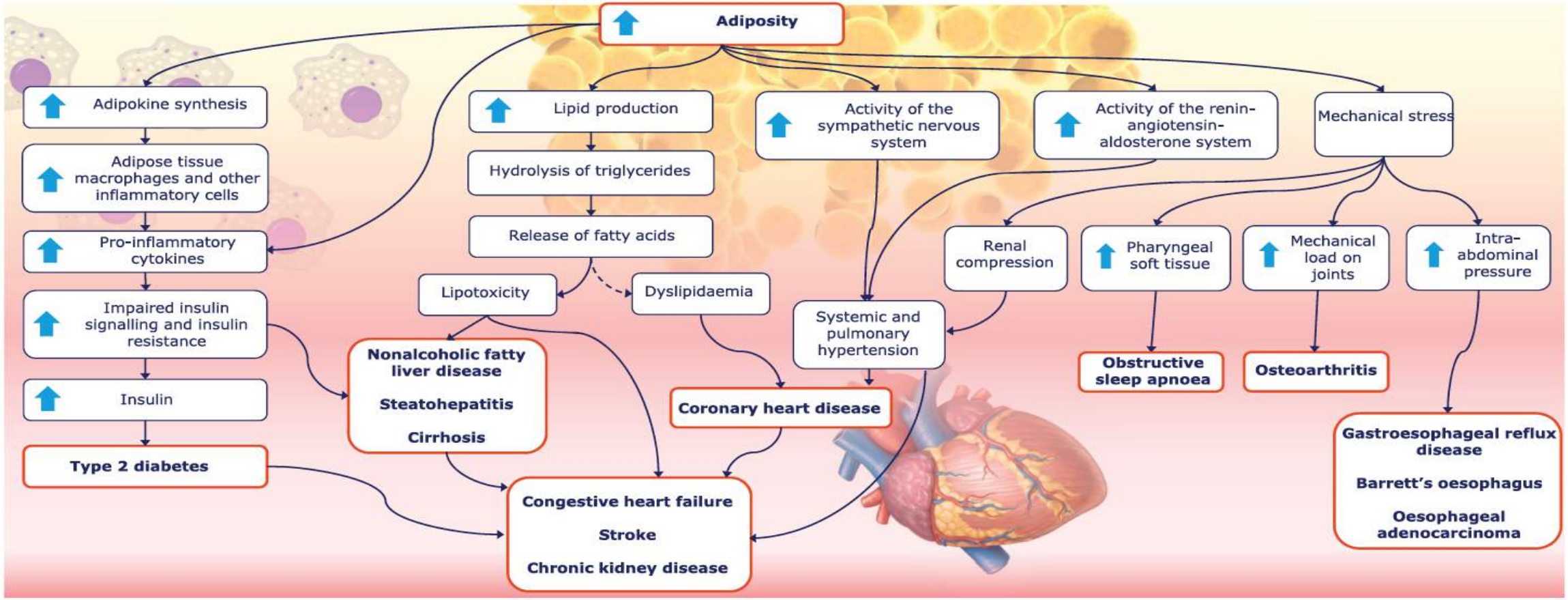
Association of excess adiposity with major risk factors and chronic conditions. Common chronic diseases are shown in red boxes. The dashed arrow denotes an indirect association



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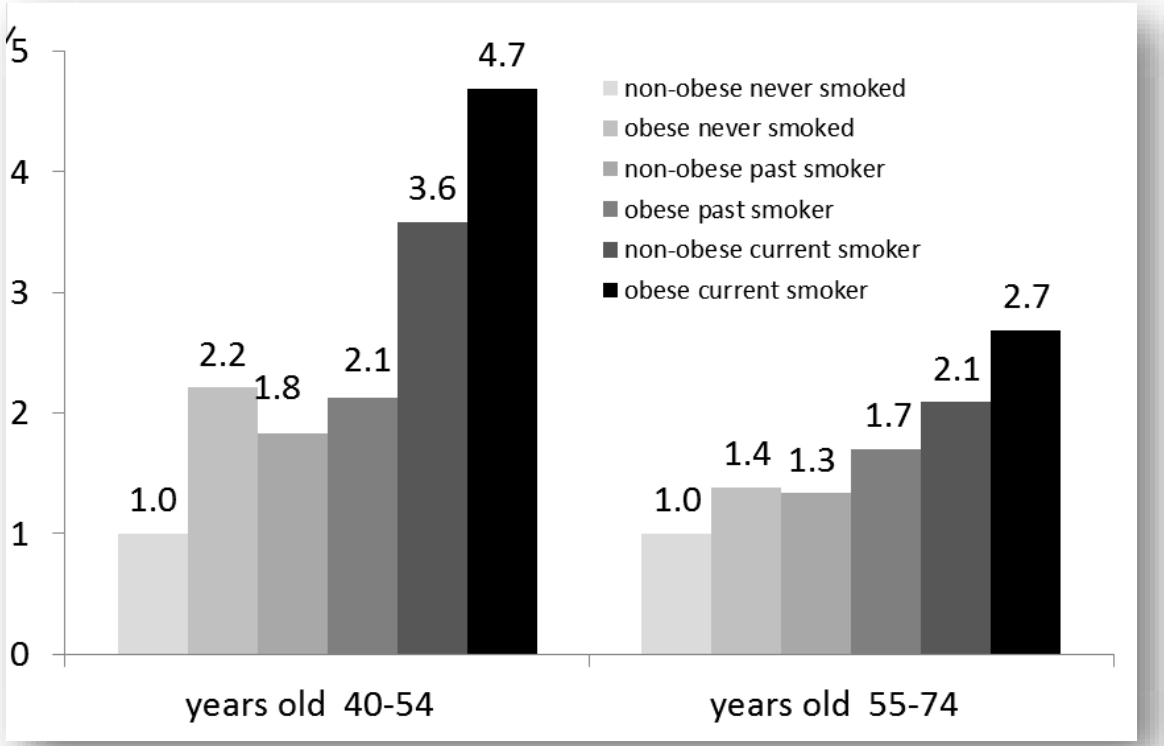
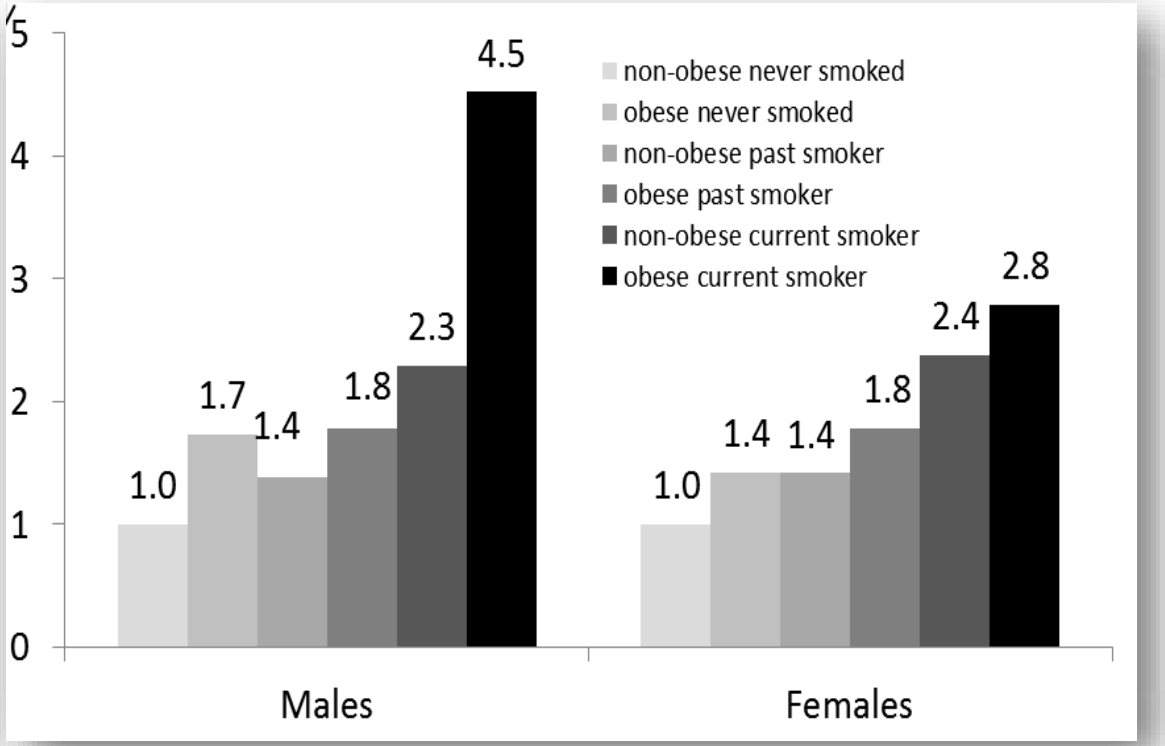
The association between smoking, obesity, combination between them and MI





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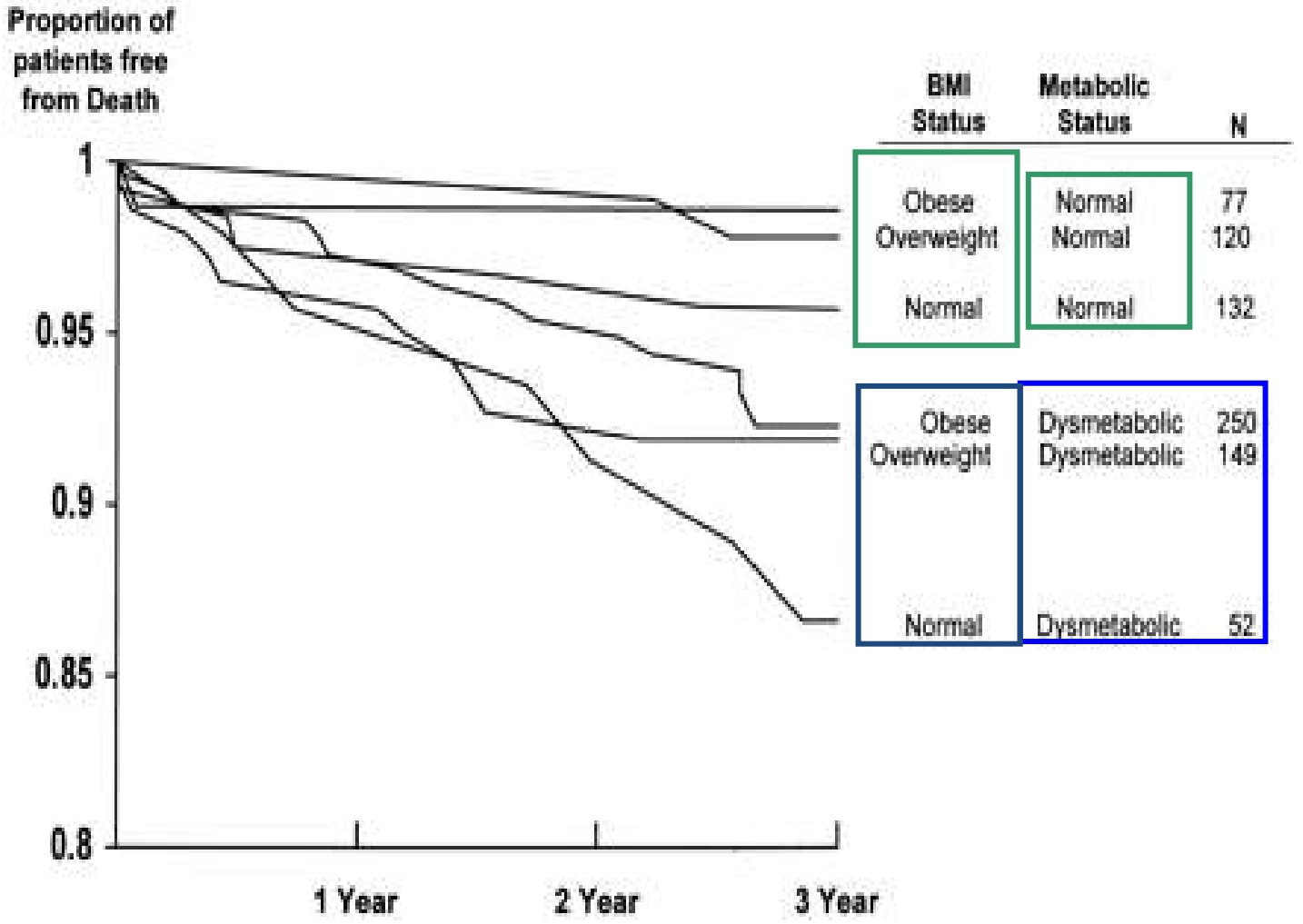
Dicker D, et al EJIM 2016

MetS is more important than obesity alone – effect of visceral versus subcutaneous fat



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Kip et al, Circ.2004;109:706

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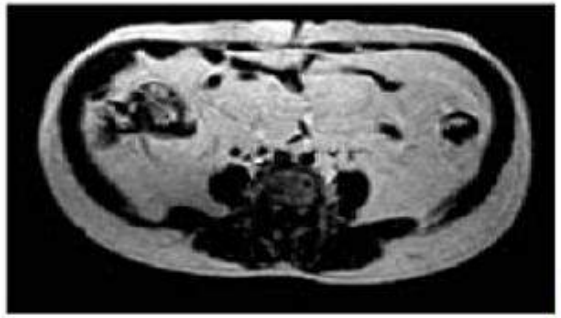
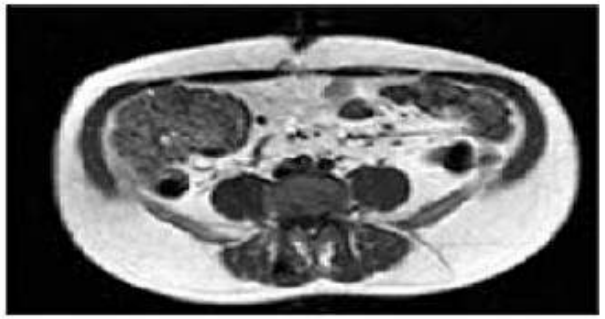
The sexual dimorphism of obesity

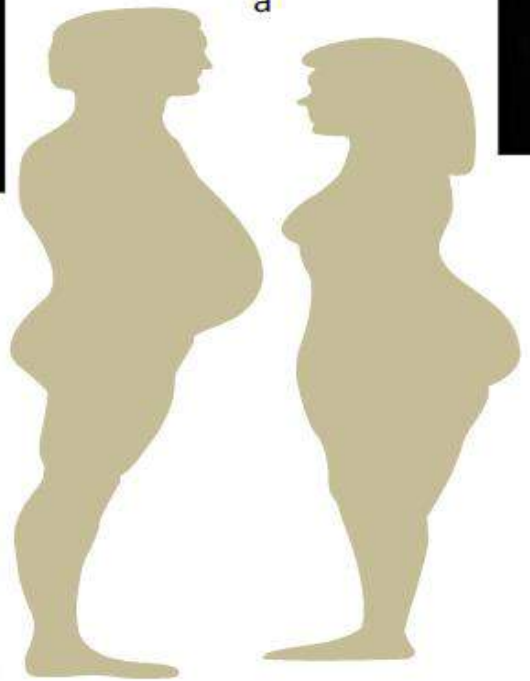
b Visceral



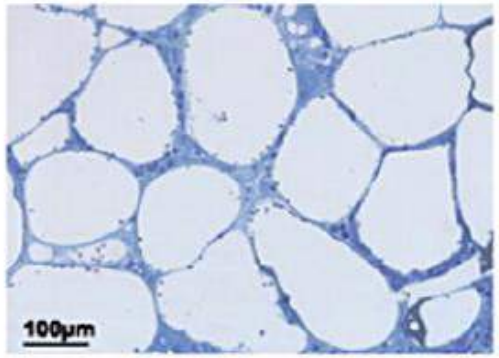
b Subcutaneous fat



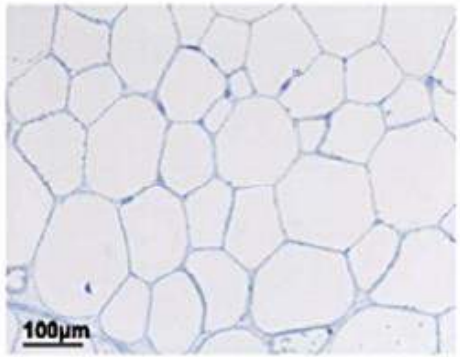
a



c



c



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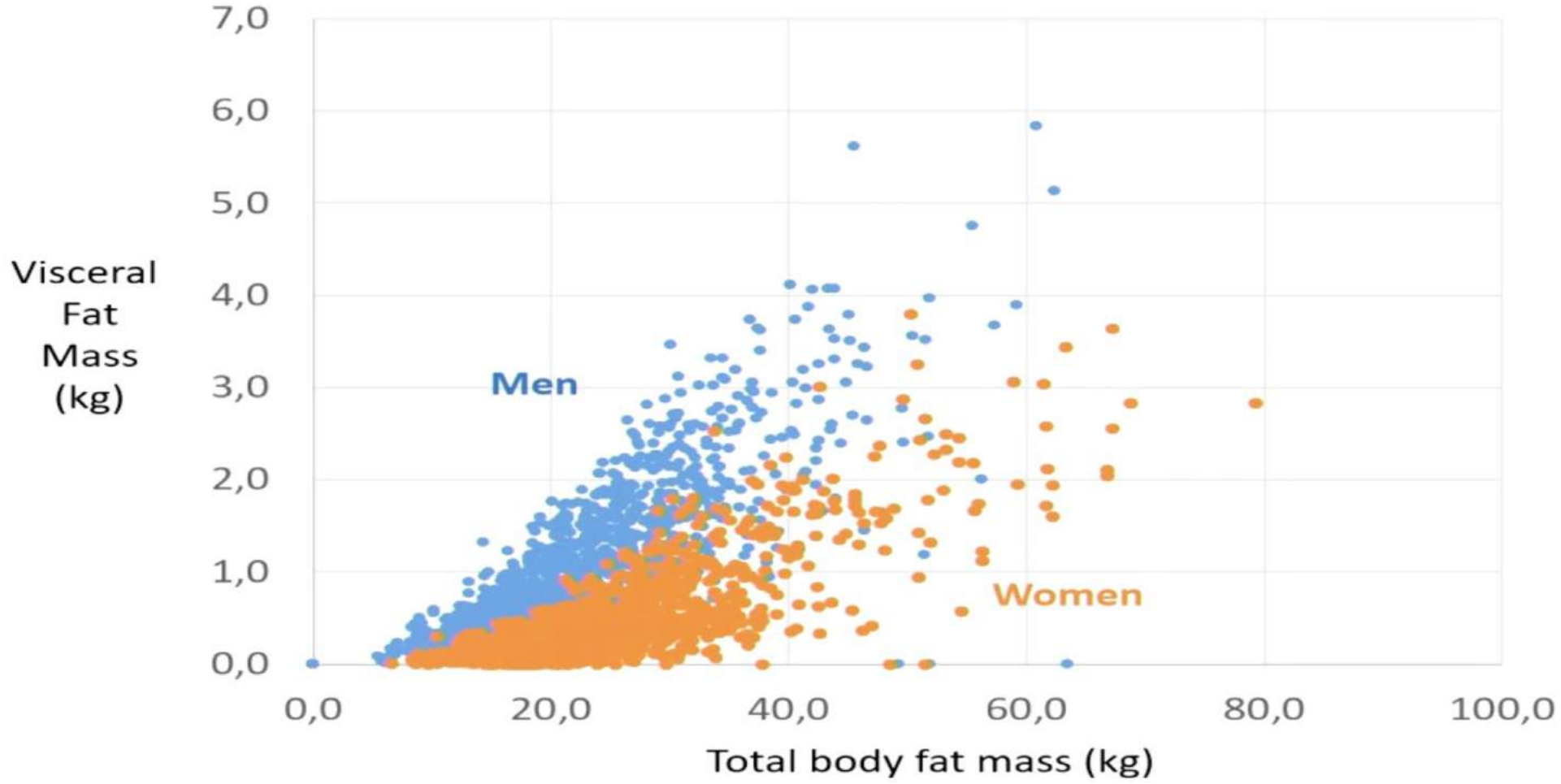
Palmer BF, V *Molecular and Cellular Endocrinology 2015*

The sexual dimorphism of obesity (n=2250)



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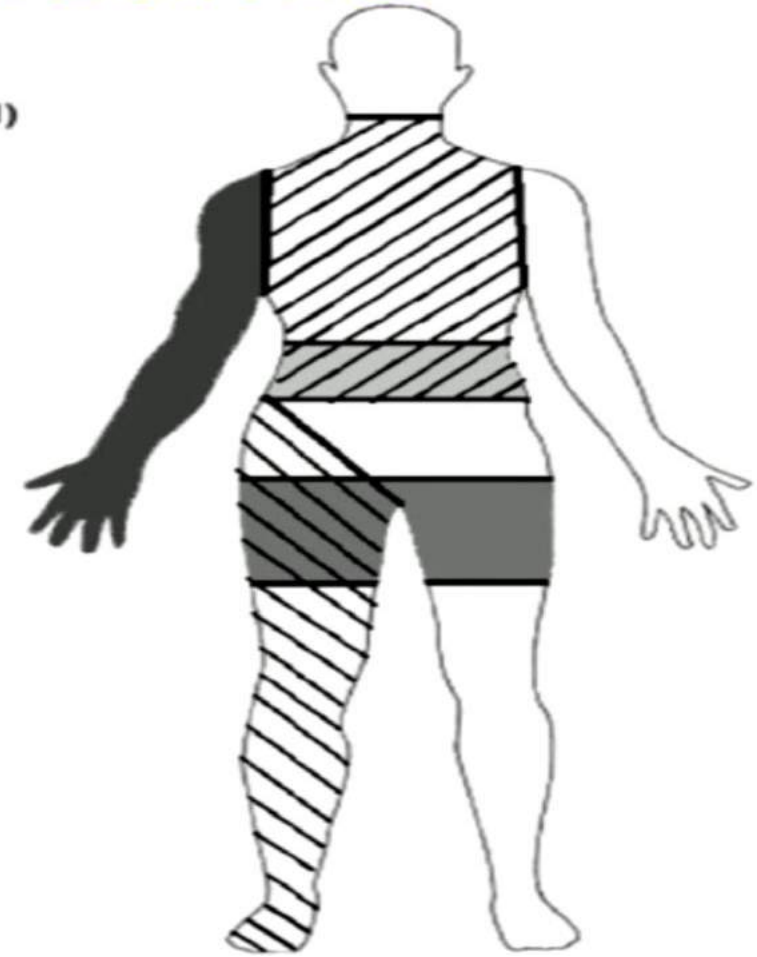
Dexa scan, Oxford BioBank Data

Body Composition Changes Observed after 12 M. Cross-Sex Hormonal Therapy in Transwomen

Mean changes (95% confidence interval)

	Body fat	Lean body mass
Total body	+28% (24;32) +28% (24;31)*	-3% (-4;-2) -3% (-4;-2)*
Arm region	+33% (29;37) +33% (29;37)*	-6% (-7;-5) -6% (-7;-5)*
Trunk region	+21% (16;25) +21% (17;25)*	-2% (-2;-1) -2% (-2;-1)*
Android region	+18% (13;23) +18% (13;22)*	0% (-1;2) 0% (-1;2)*
Gynoid region	+34% (29;38) +34% (30;37)*	-3% (-4;-2) -3% (-4;-2)*
Leg region	+42% (37;46) +42% (37;45)*	-4% (-4;-3) -4% (-4;-3)*



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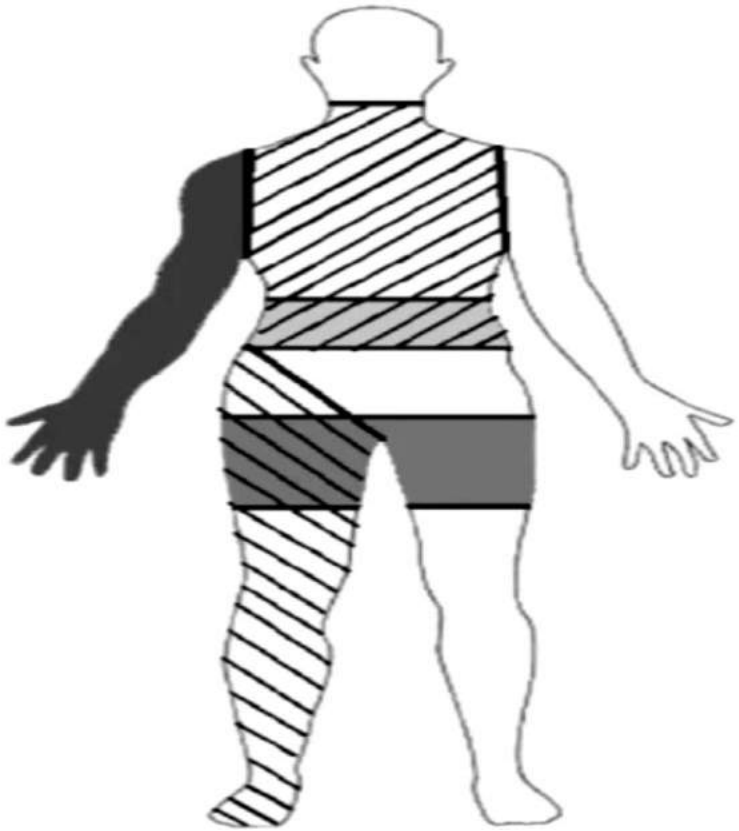
Klaver M EJE 2018

Body Composition Changes Observed after 12 M. Cross-Sex Hormonal Therapy in Transmen

	Mean changes (95% confidence interval)	
	Body fat	Lean body mass
Total body	-10% (-12;-7) -10% (-12;-7)*	+10% (9;11) +10% (9;11)*
Arm region	-10% (-13;-8) -10% (-13;-8)*	+19% (18;21) +19% (18;21)*
Trunk region	-3% (-6;0) -3% (-6;0)*	+9% (8;10) +9% (8;10)*
Android region	+1% (-3;5) +1% (-3;5)*	+10% (8;12) +10% (8;12)*
Gynoid region	-14% (-16;-12) -14% (-16;-12)*	+11% (10;13) +11% (10;13)*
Leg region	-16% (-19;-14) -16% (-19;-14)*	+12% (10;13) +12% (10;13)*



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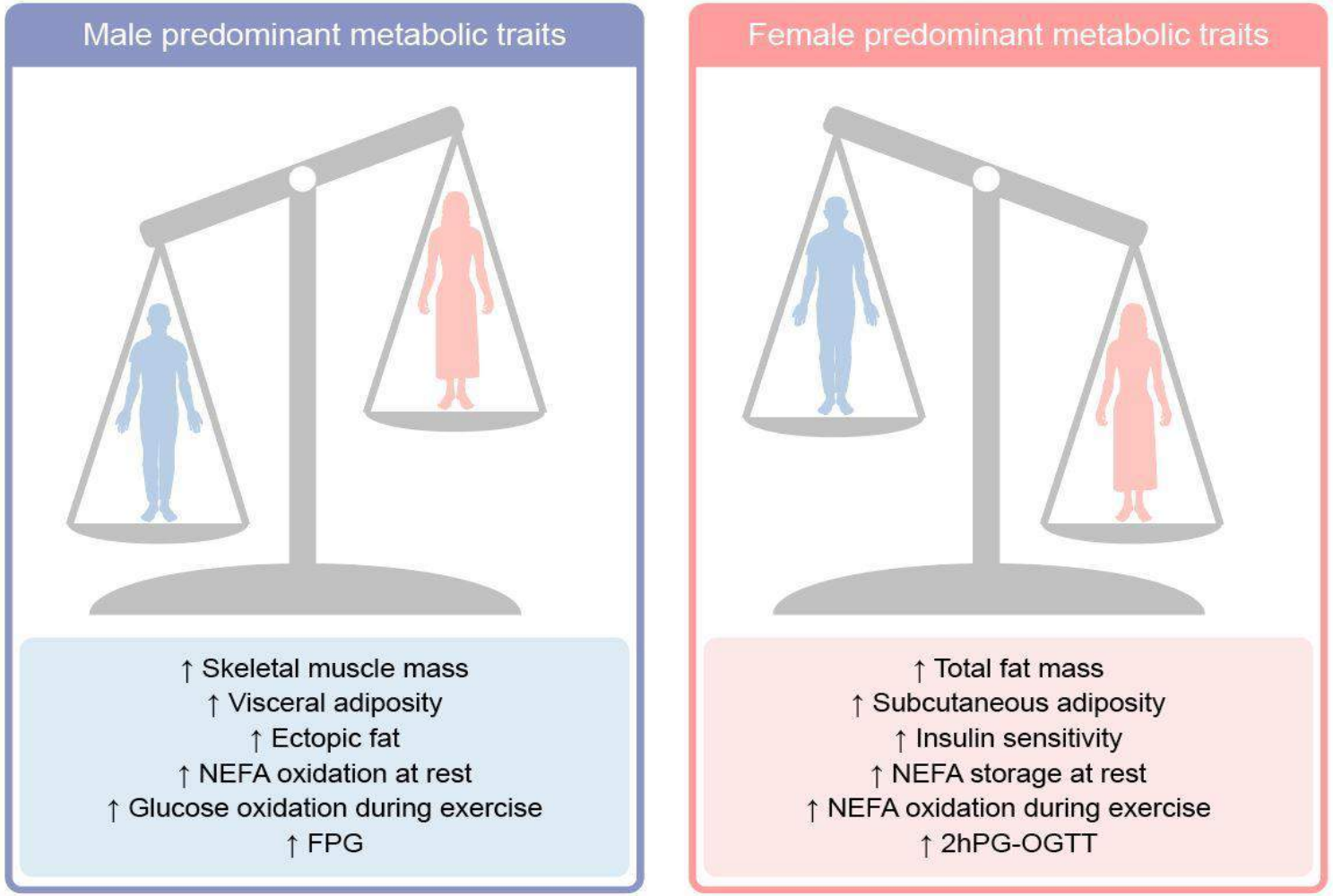
Klaver M EJE 2018

Main sex dimorphisms in body composition and metabolic homeostasis in humans (premenopausal women vs age-matched men)



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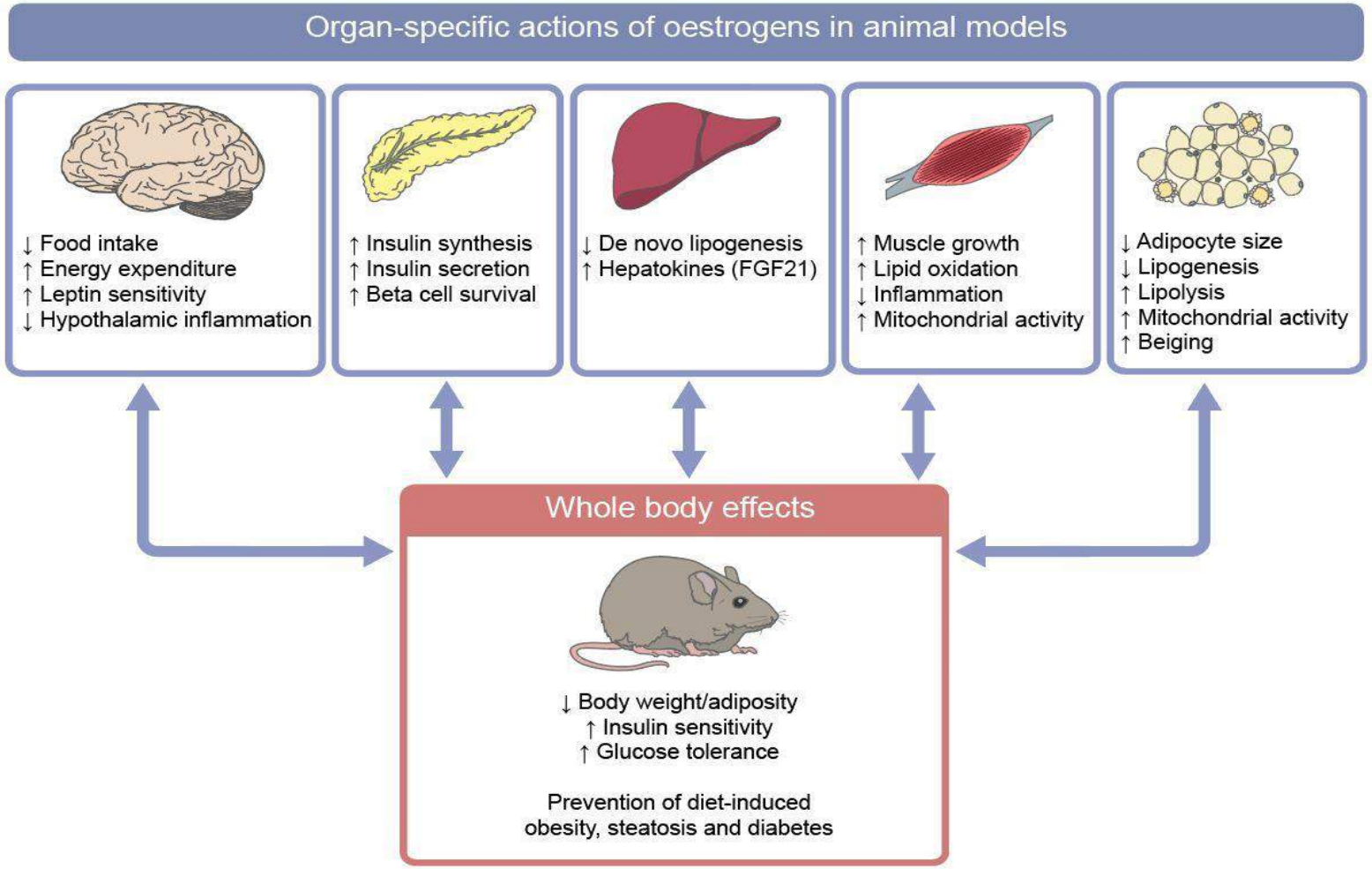
Tramunt et al (2020) Diabetologia

Tissue-specific actions of oestrogens on energy balance and metabolic regulation in rodent models



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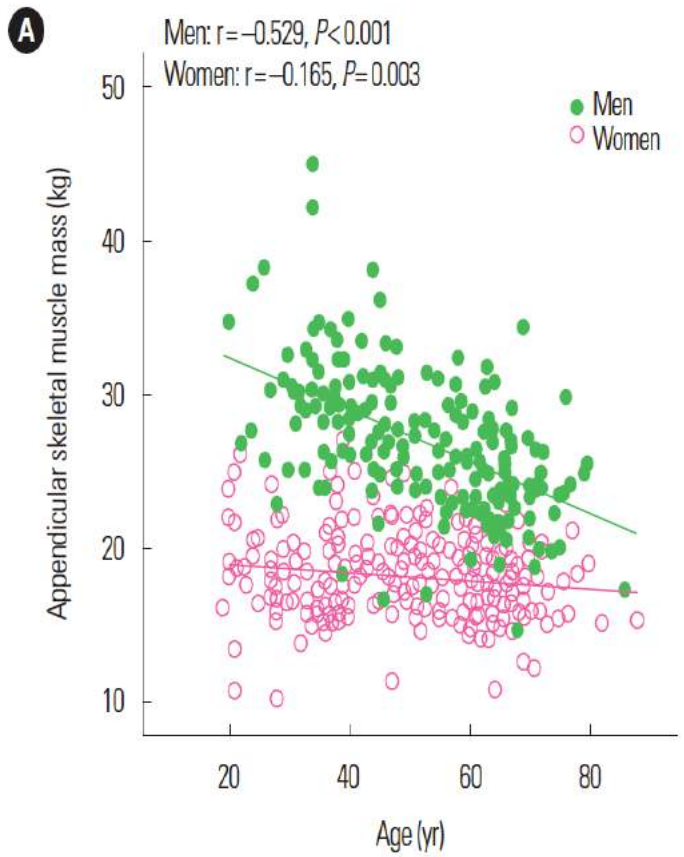
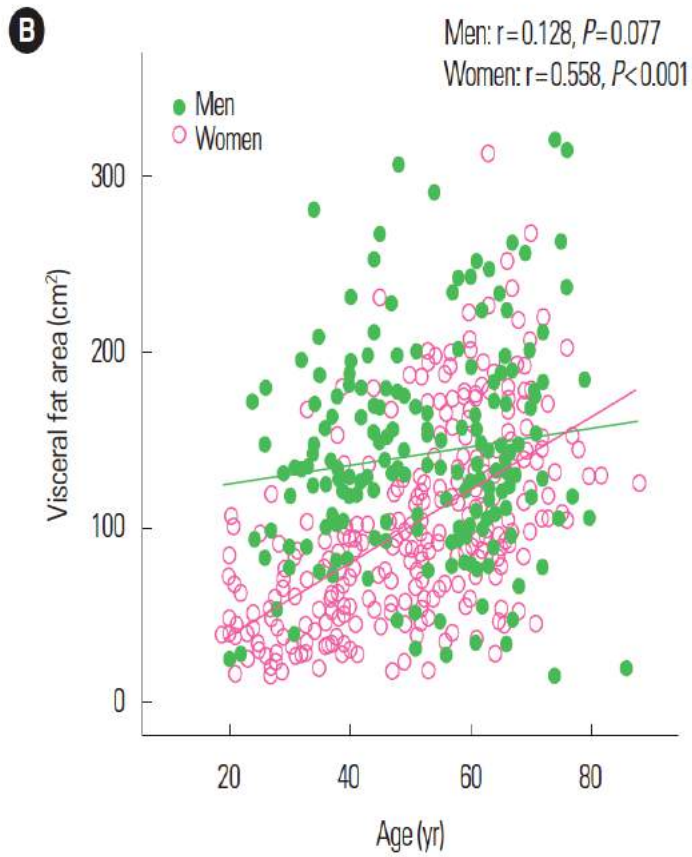
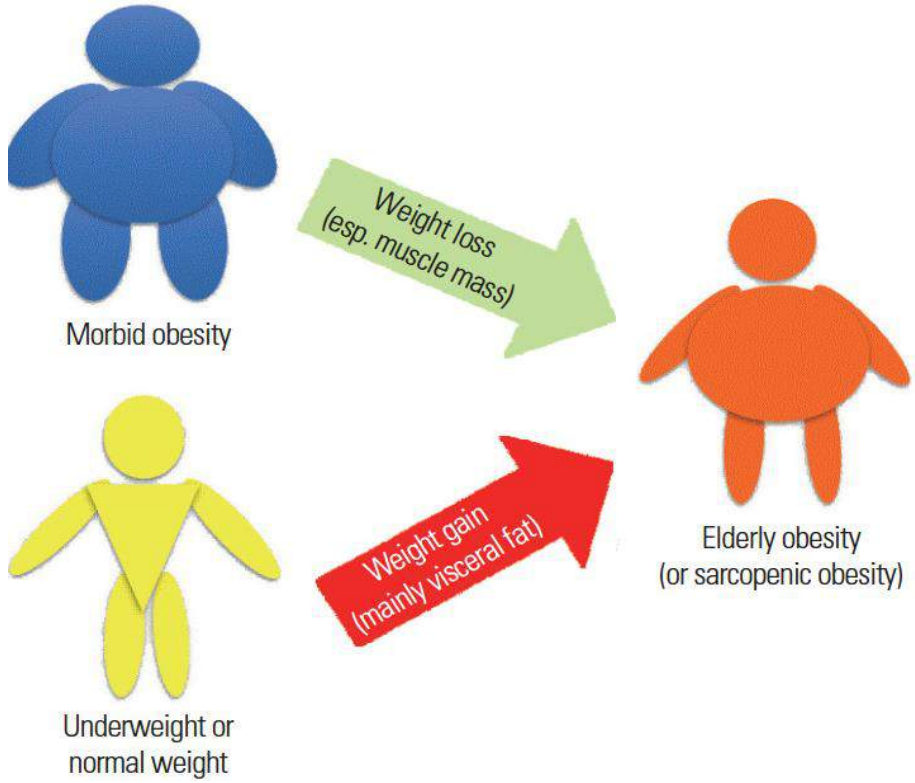
Tramunt et al (2020) Diabetologia

Relationships of age with appendicular skeletal muscle mass (A) and visceral fat area (B)







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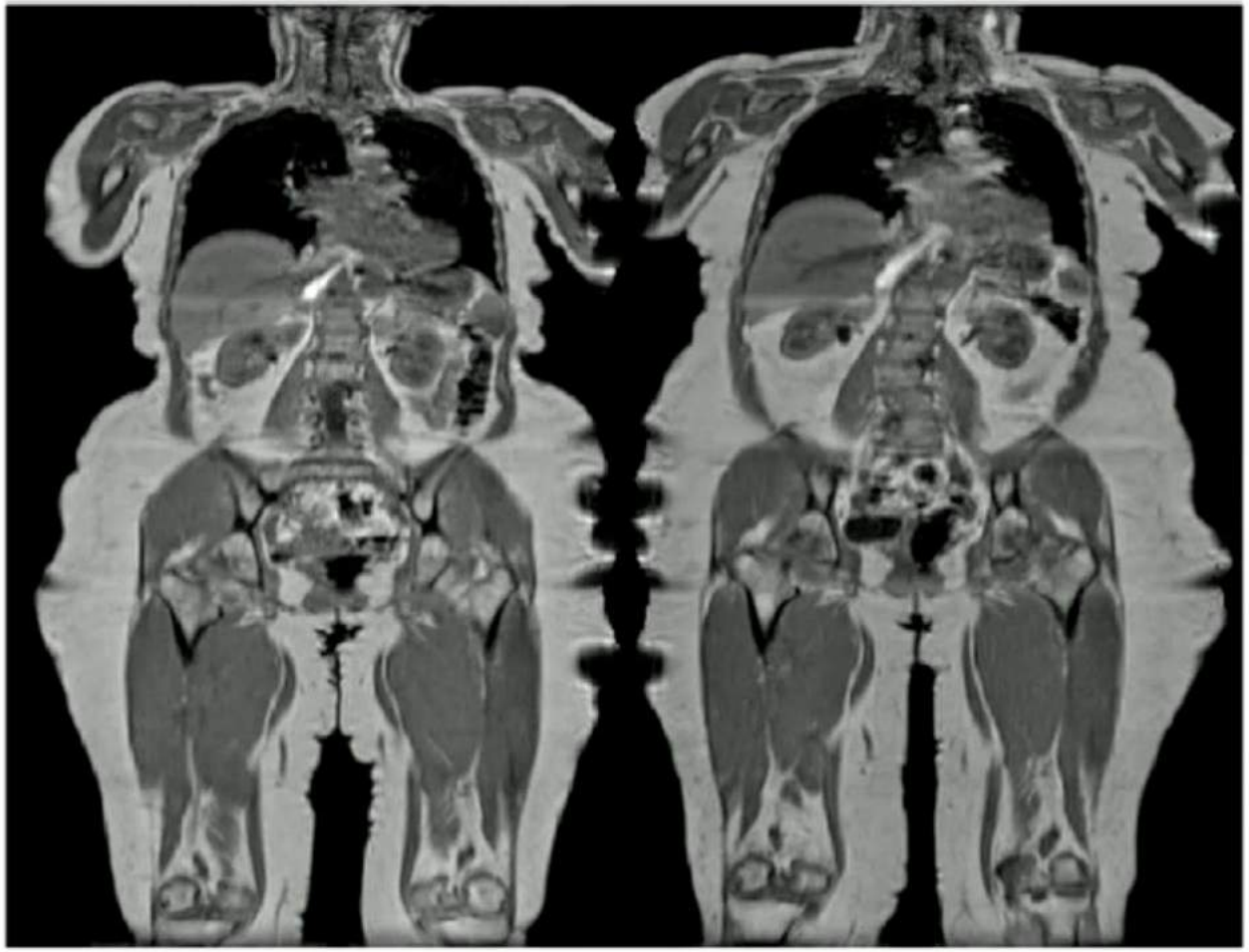
Tae Nyun Kim Journal of Obesity & Metabolic Syndrome 2018

Body Composition Changes Observed after 24 M in Post-Menopausal Women



- UK Biobank
- Longitudinal changes
- N=1,548 women

Age 1	62.35Y	
Age 2	64.62Y	
BMI 1	25.82 kg/m^2	
BMI 2	25.79 kg/m^2	ns
Hip C 1	100.78 cm	
Hip C 2	99.74 cm	p=2 x 10^{-11}
Thigh fat	+0.06%	ns
Thigh mu	- 0.87%	p=9 x 10^{-55}

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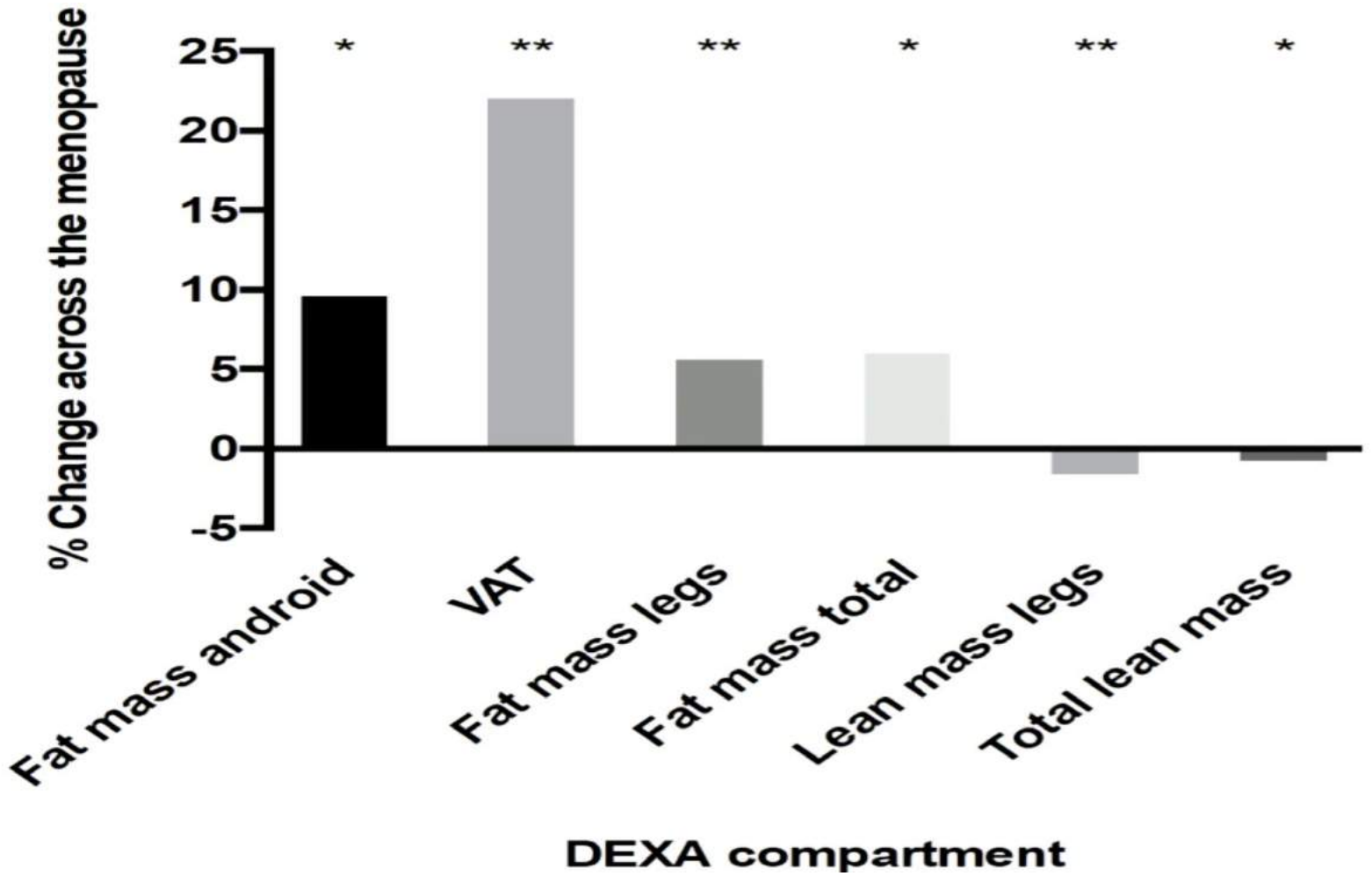
Whitcher B, Sci Rep 2022

Body Composition Changes in Post-Menopausal Women



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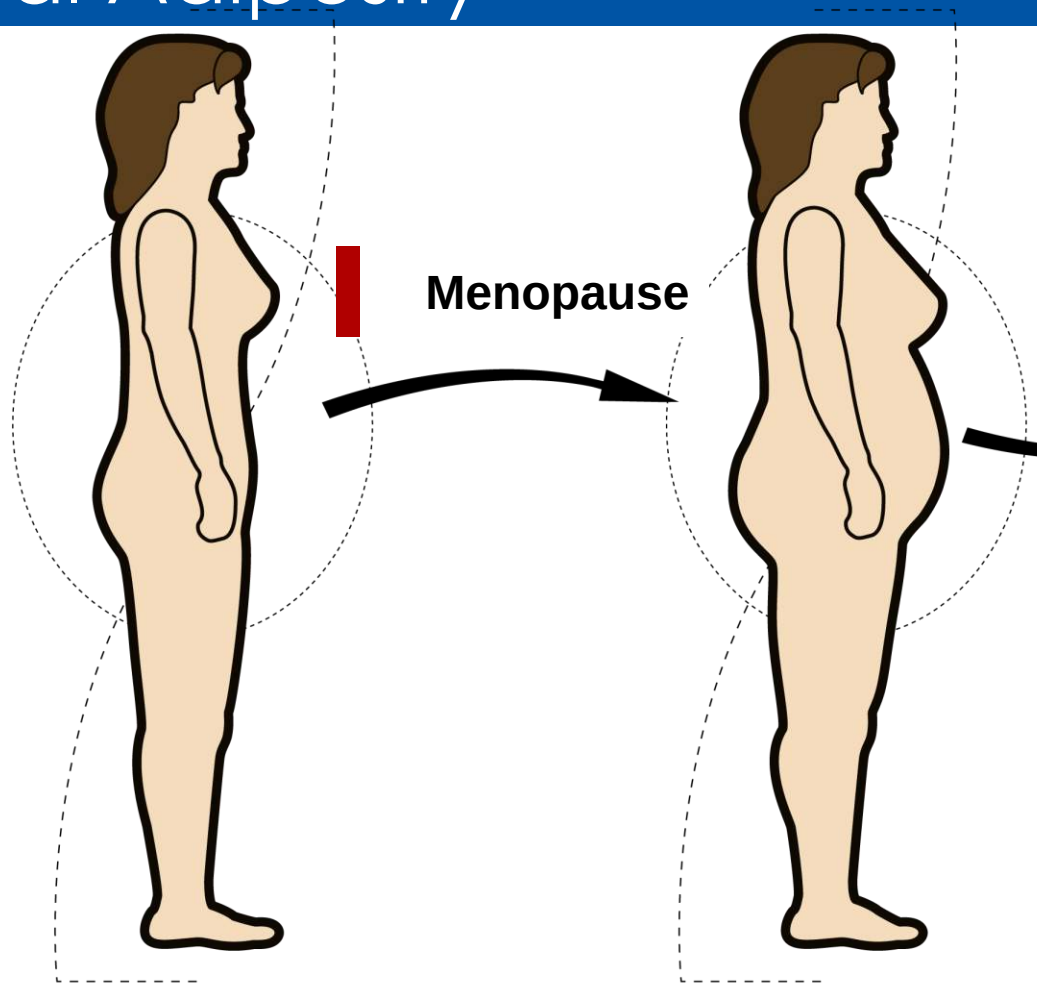
Dehghan A, Menopause 2021

Development of Menopause -Related Gain in Visceral Adiposity



- Insulin resistance
- Apolipoprotein B

CHD risk

- Triglycerides
- HDL cholesterol
- LDL size

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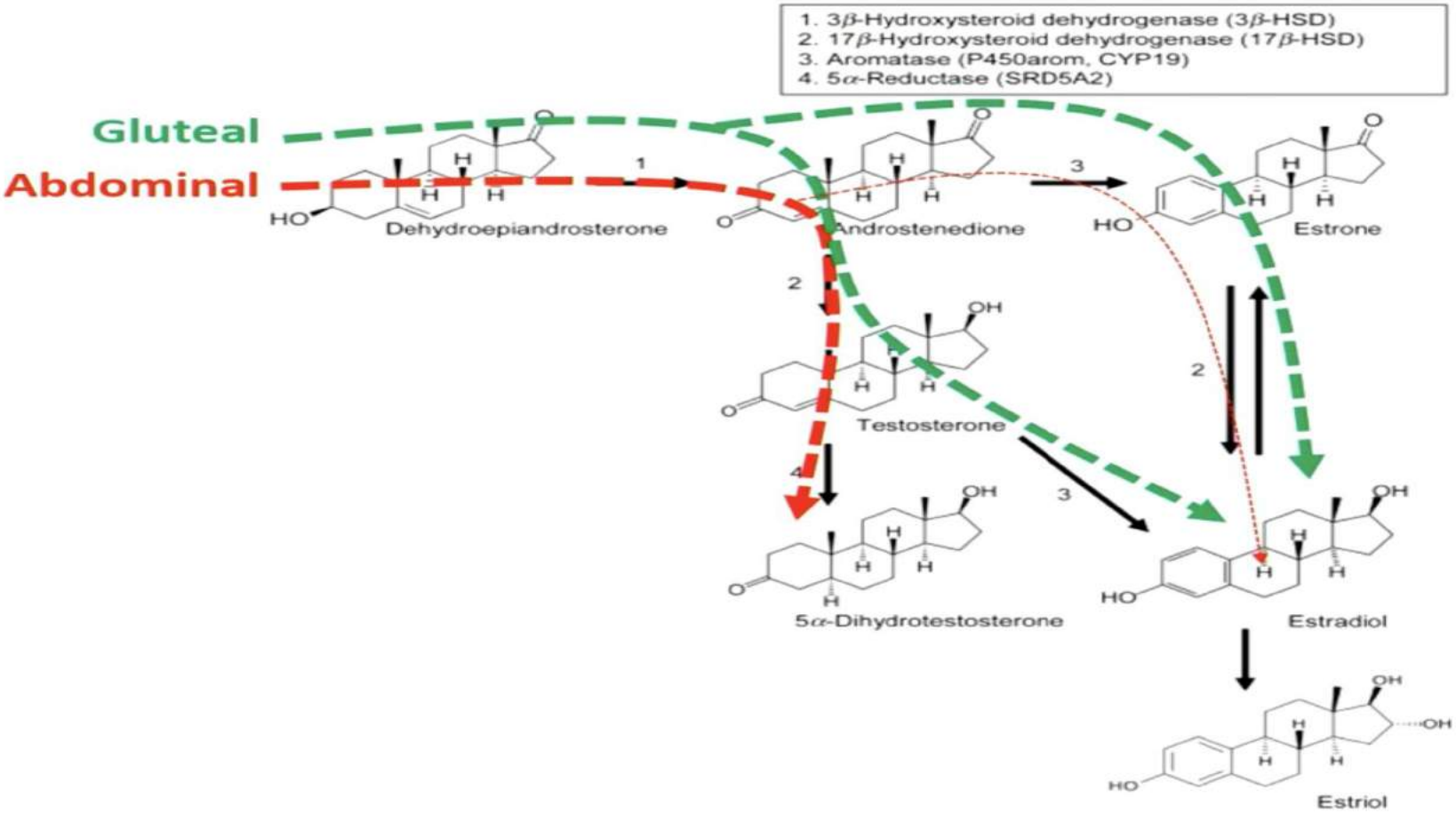
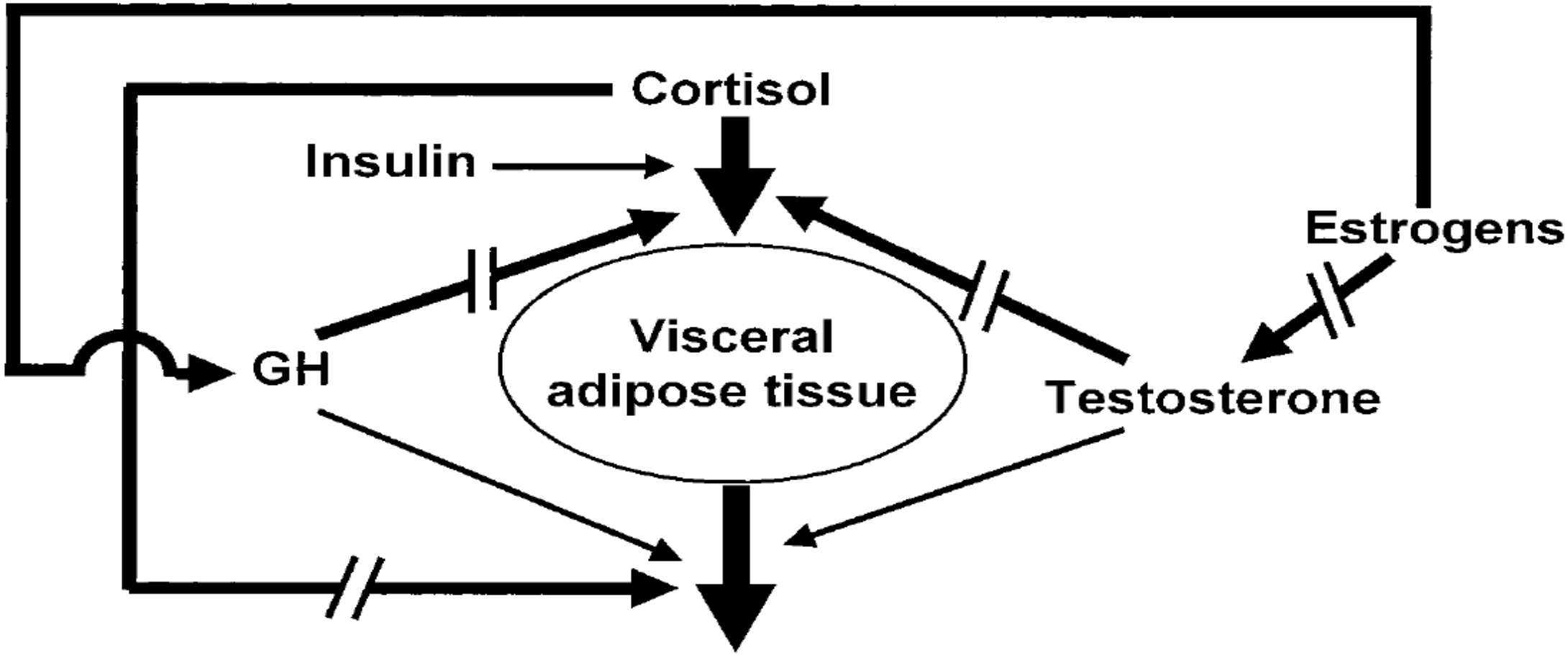
Sex Hormone Conversion in human regional adipose tissues



Karpe F, ECO 2022

Hormonal regulation of abdominal visceral fat



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WAJCHENBERG L. Endocrine Reviews 2000

Main factors contributing to menopausal changes in body compos

Genetic factors	Hormonal factors	Exogenous factors
Genetic predisposition Ethnicity Epigenetic changes	Rapid hypoestrogenemia Relative hyperandrogenemia Low SHBG levels	Unhealthy nutrition Low physical activity Drugs (e.g. steroids, insulin) Diseases
⇩		
Increase in body weight Increase and redistribution of fat mass (from gynoid to abdominal obesity) Decrease in fat-free mass		

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Kozakowski J Menopause Rev 2017

Outline

- Obesity in Israel Gender Implications
- Obesity as Dysfunctional fat Disease
- Obesity comorbidities
- Menopause -Related Gain in Visceral Adiposity
- Obesity & Sex Hormones and appetite regulation
- Obesity Treatment

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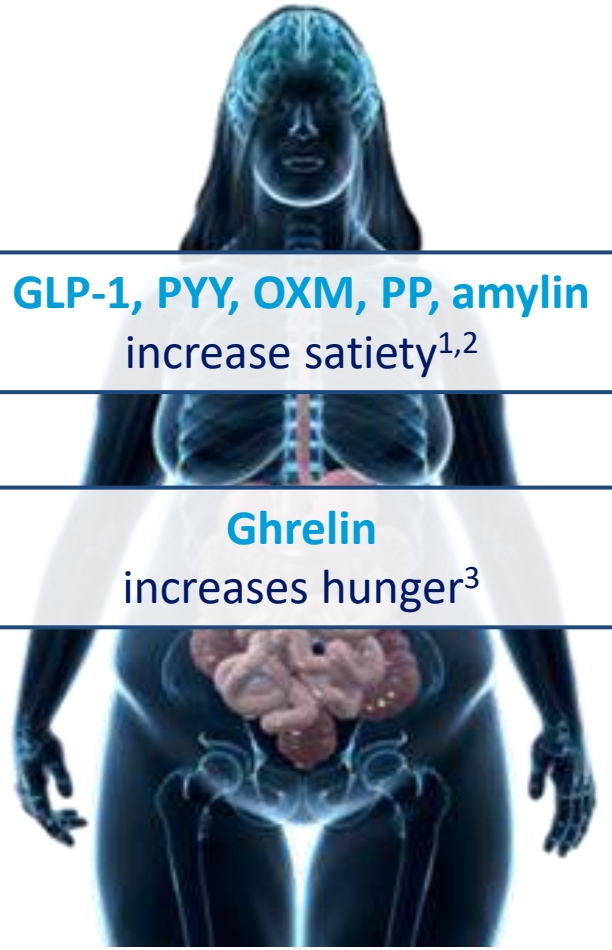
The role of the brain in controlling appetite

Homeostatic eating

'eating for hunger'



GLP-1, PYY, OXM, PP, amylin
increase satiety[1,2]

Ghrelin
increases hunger[3]

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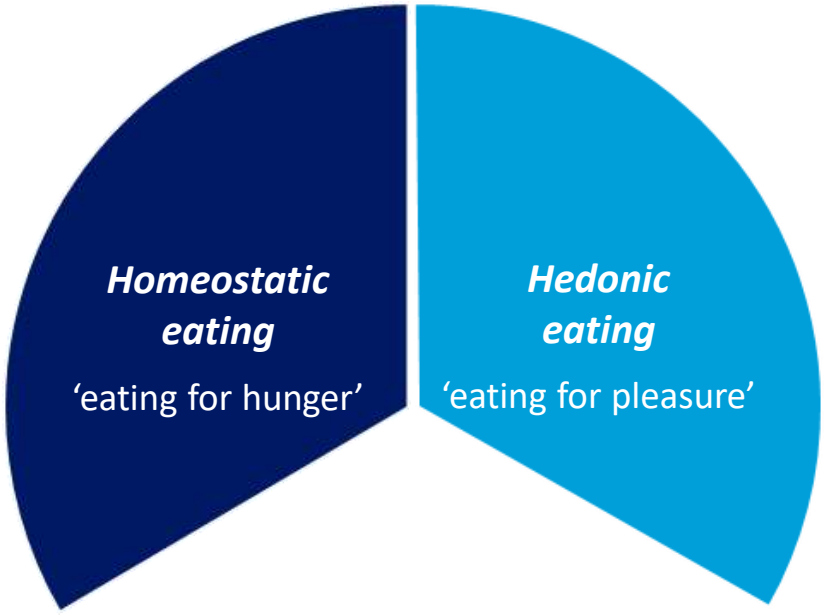
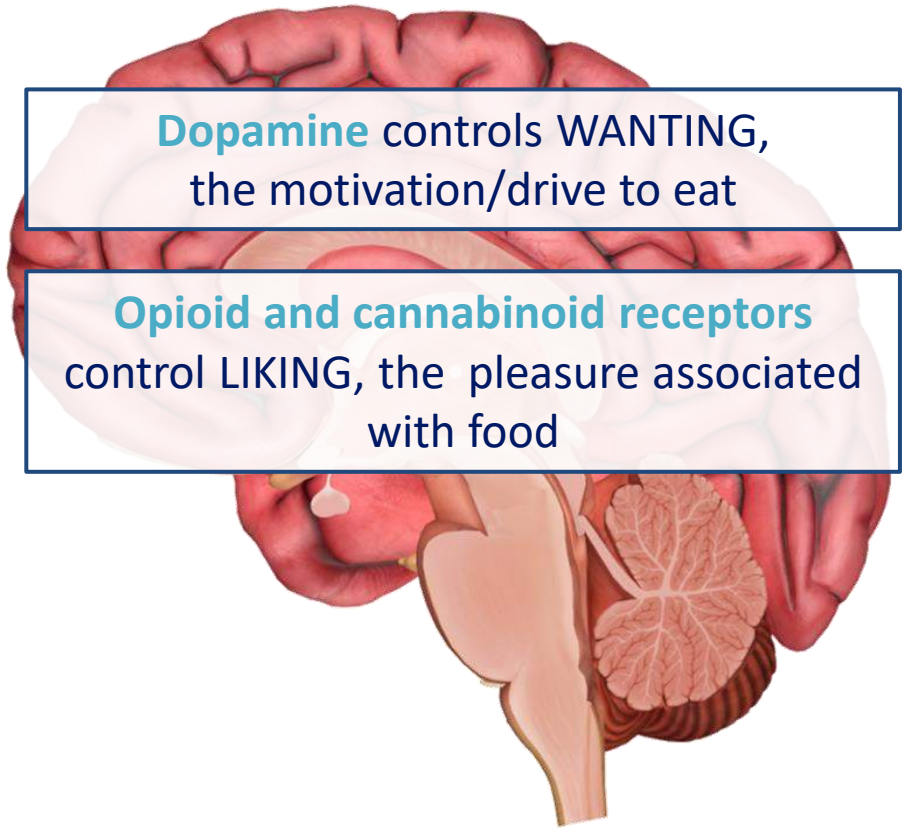
1. Badman MK and Flier JS. Science 2005;307:1909–14; 2. van Bloemendaal L et al. Diabetes 2014;63:4186–96; 3. Klok MD et al. Obes Rev 2007;8:21–34.

The role of the brain in controlling appetite





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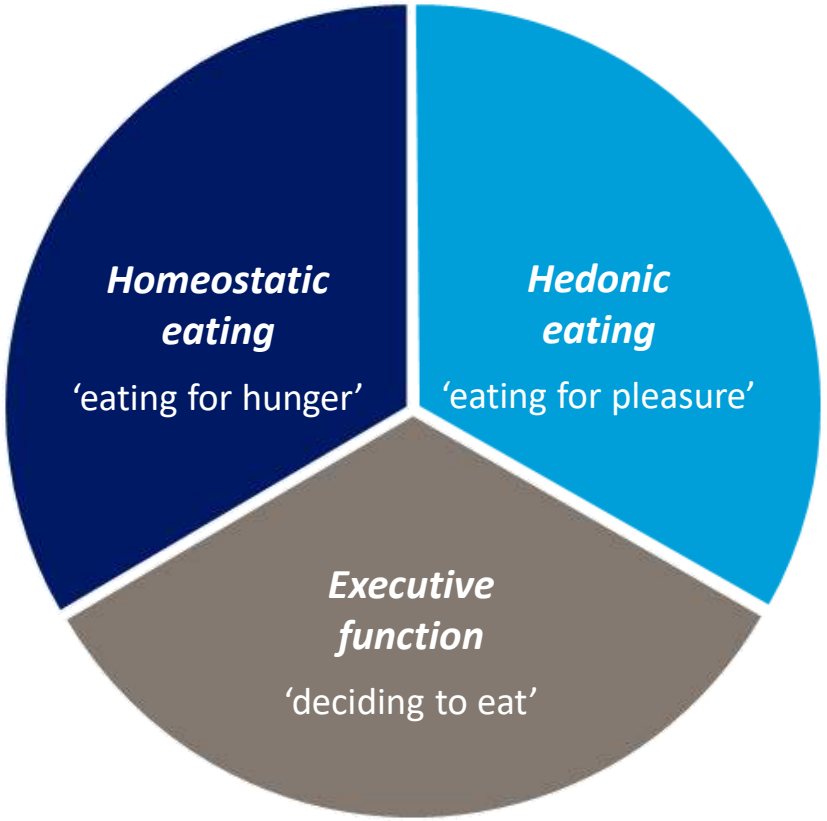
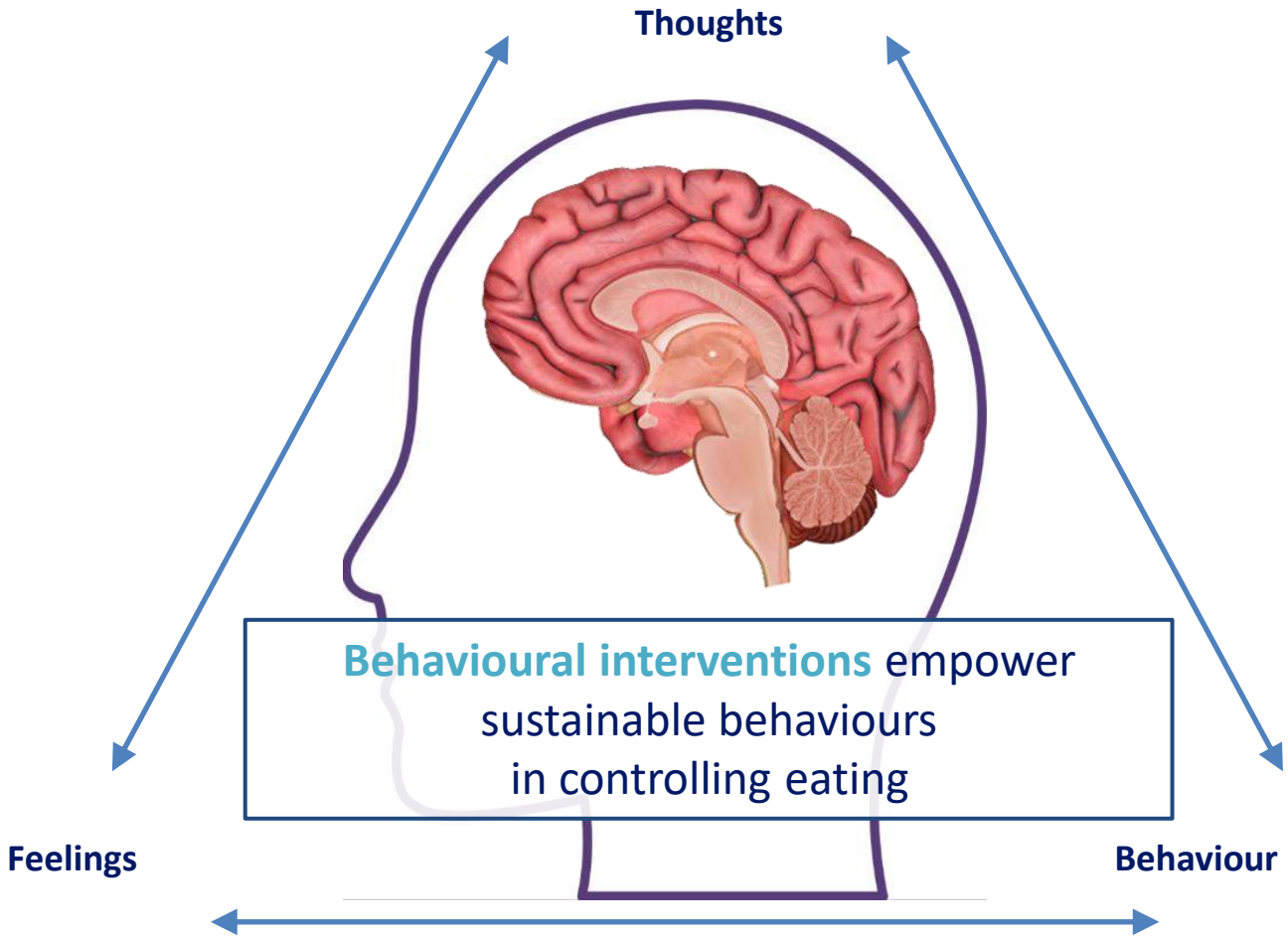
Berridge KC et al. Brain Res 2010;1350:43–64.

The role of the brain in controlling appetite





Vallis M. Clin Obes 2019;9:e12299.

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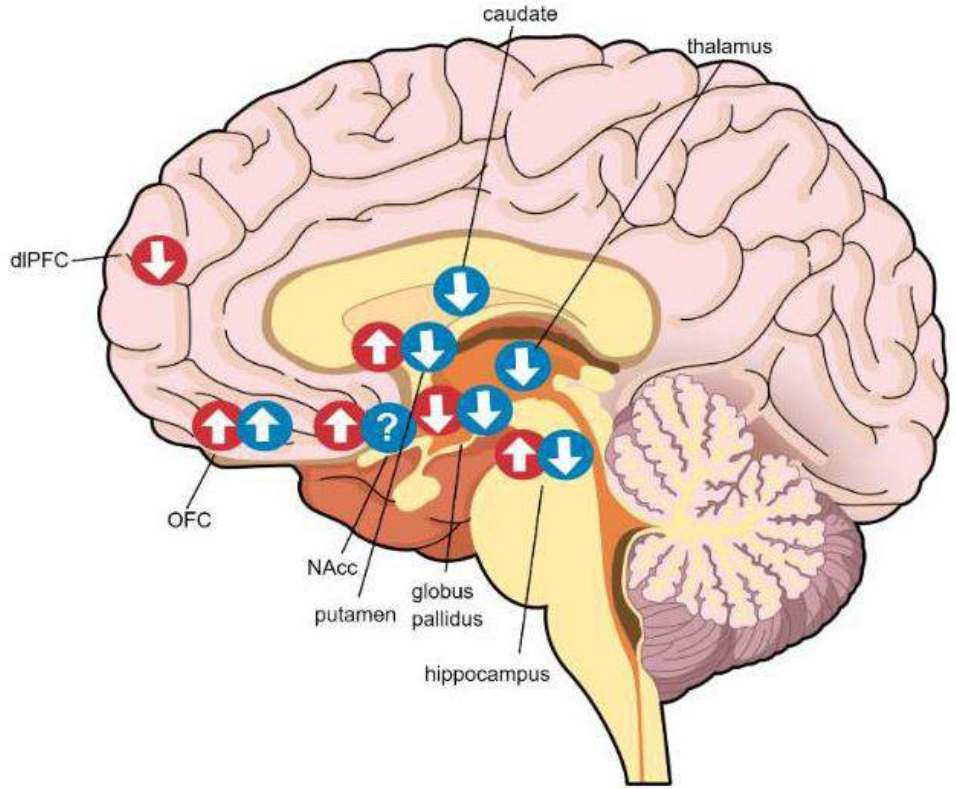
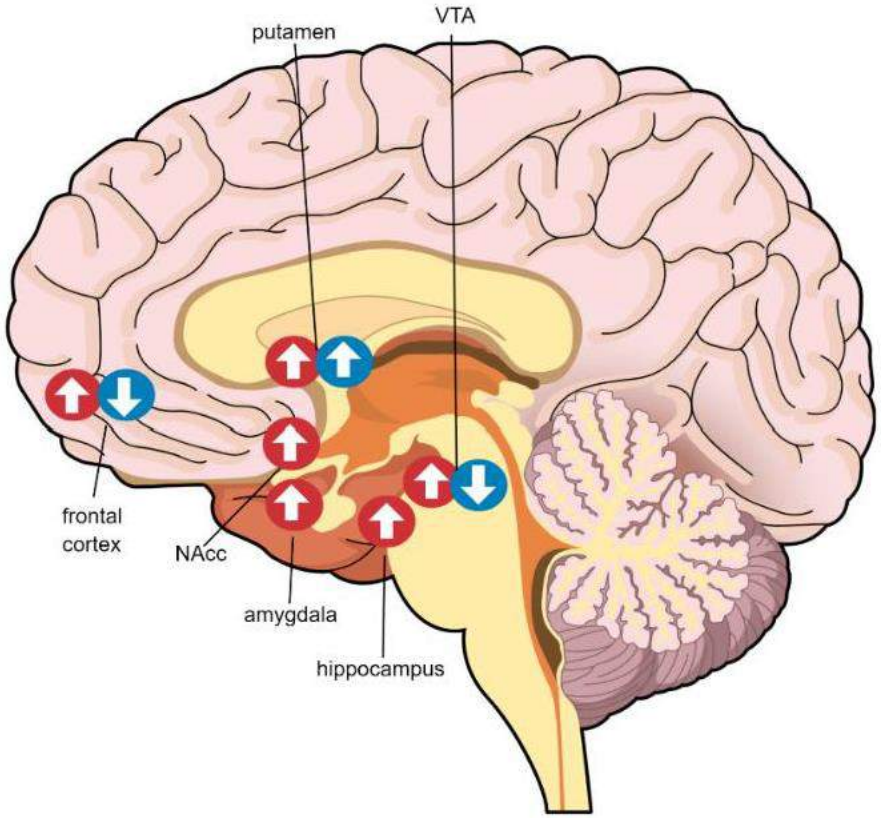
Neuroimaging of Sex/Gender Differences in Obesity: A Review of Structure, Function, and Neurotransmission

Gray matter volume differences in obesity by sex/gender



Resting state connectivity differences in obesity by sex/gender



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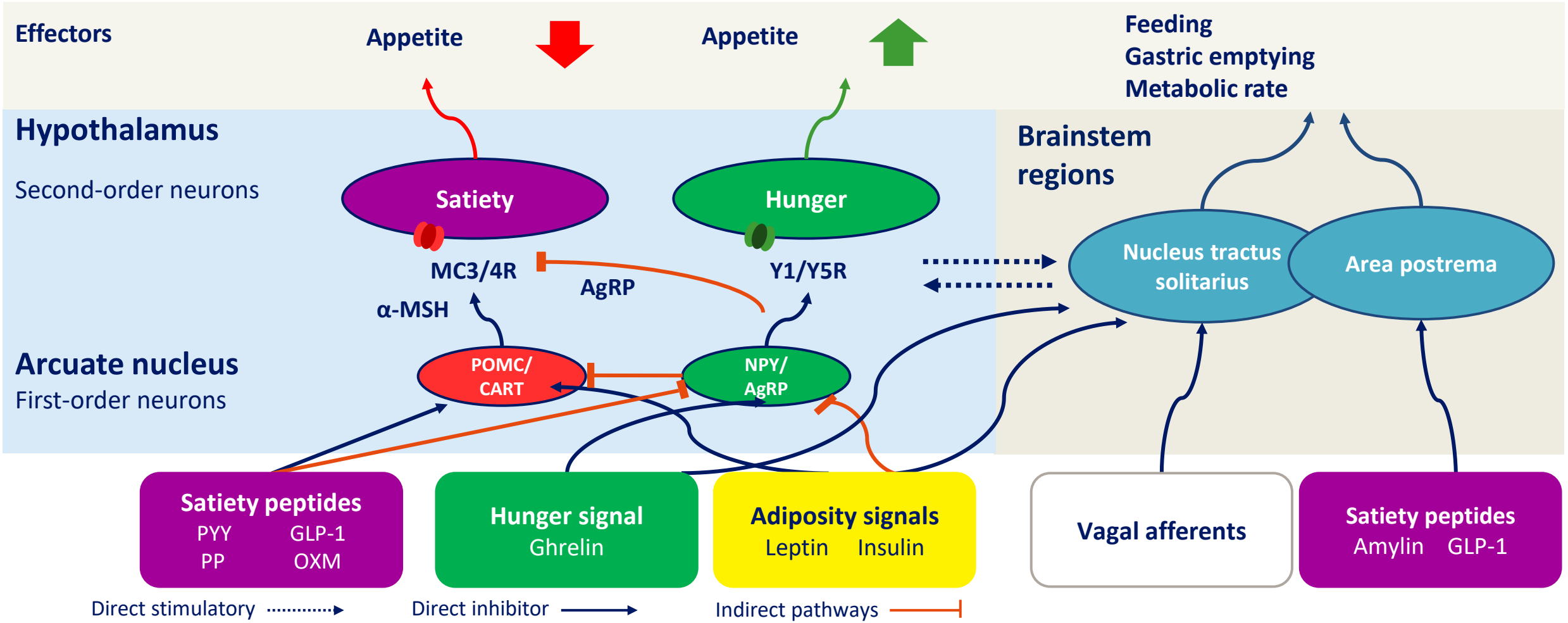
Women Men

Kroll DS. Nutrients 2020

Homeostatic regulation of appetite



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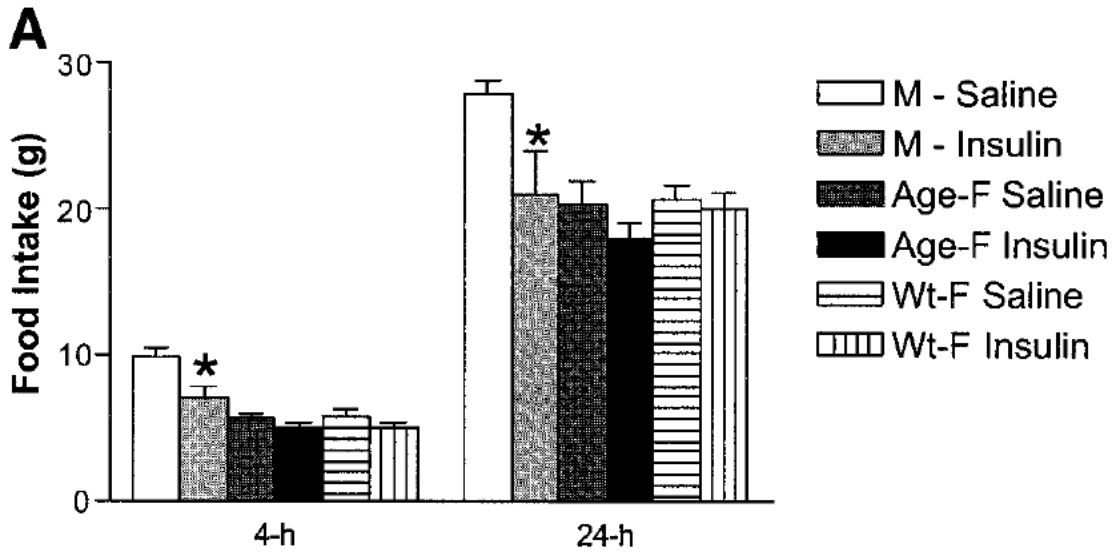
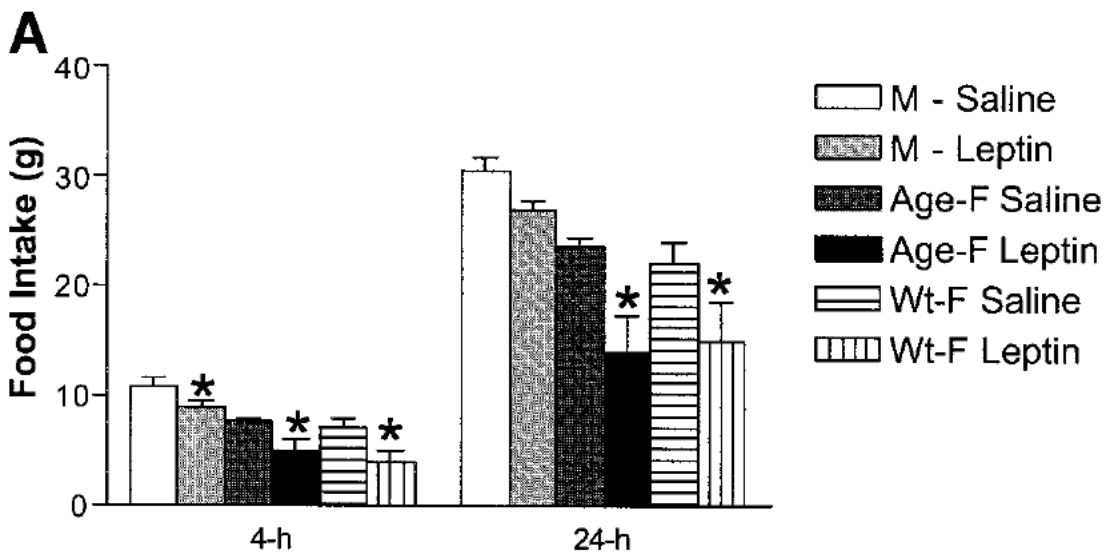
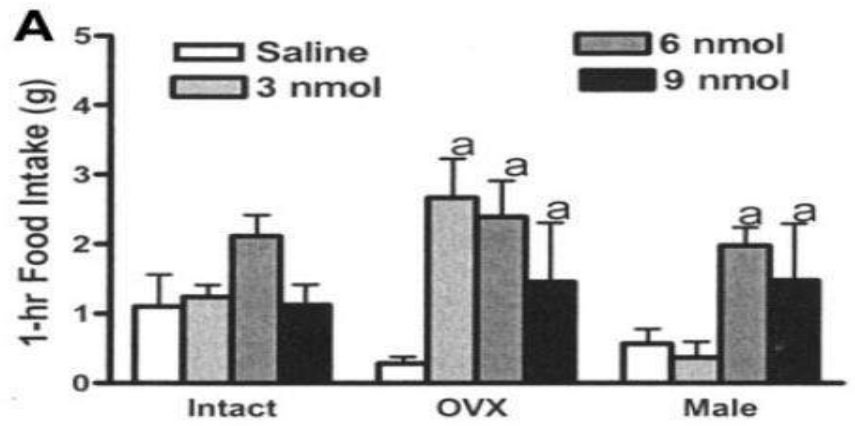
Differential Sensitivity to Central Leptin and Insulin in Male and Female Rats

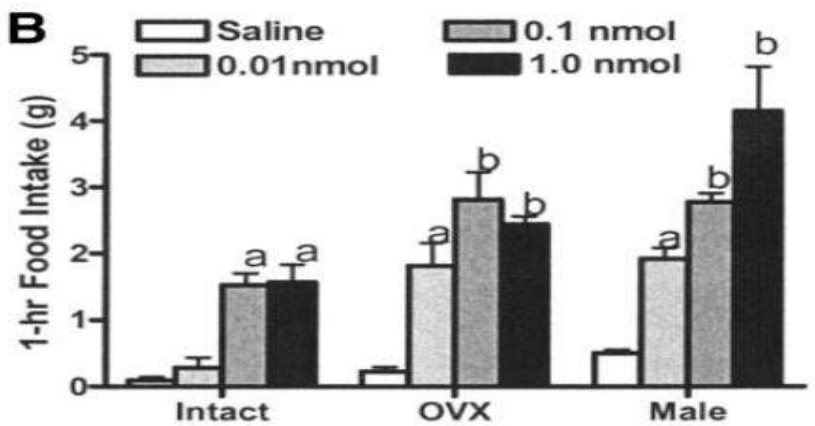


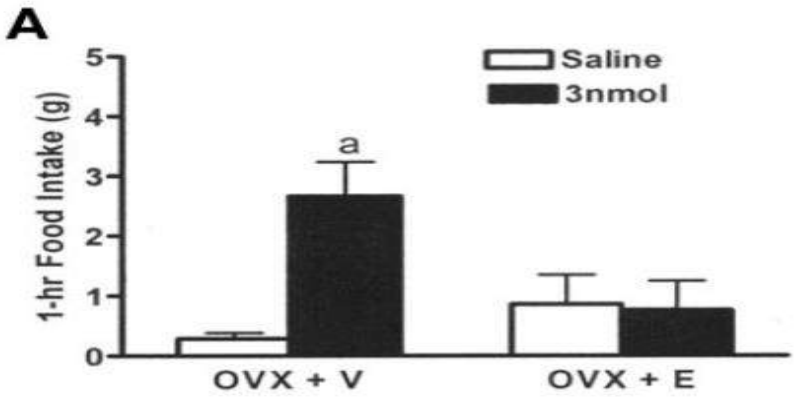


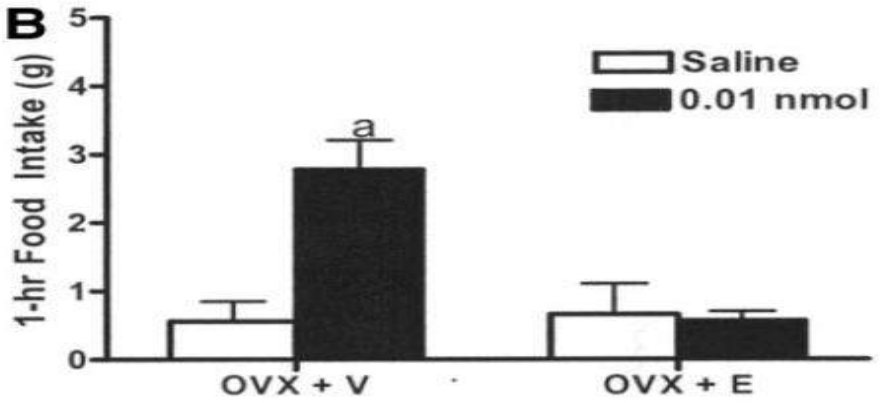
Clegg DR. DIABETES, 2003

Estradiol-Dependent Decrease in the Orexigenic Potency of Ghrelin in Female Rats









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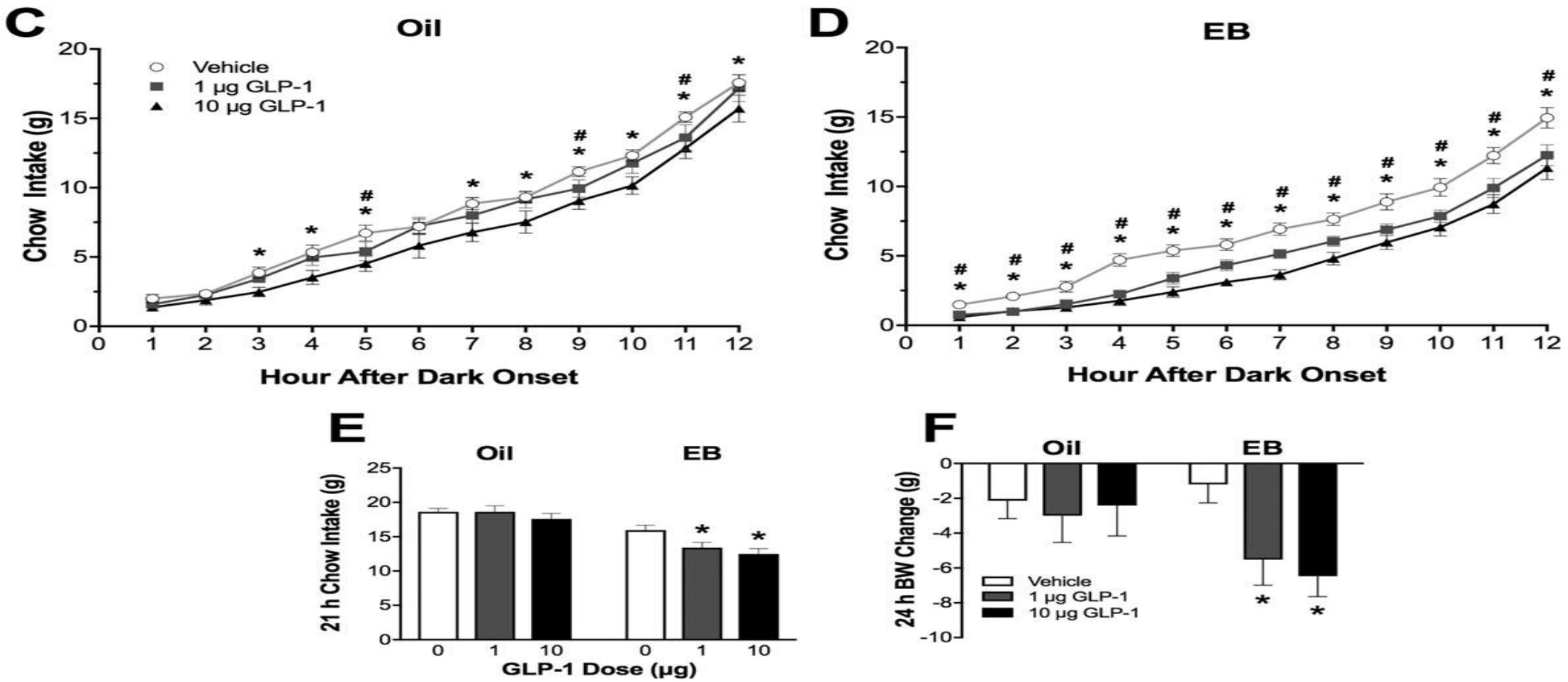
Clegg DR. DIABETES, 2007

Estradiol modulates the anorexic response to central glucagon-like peptide 1



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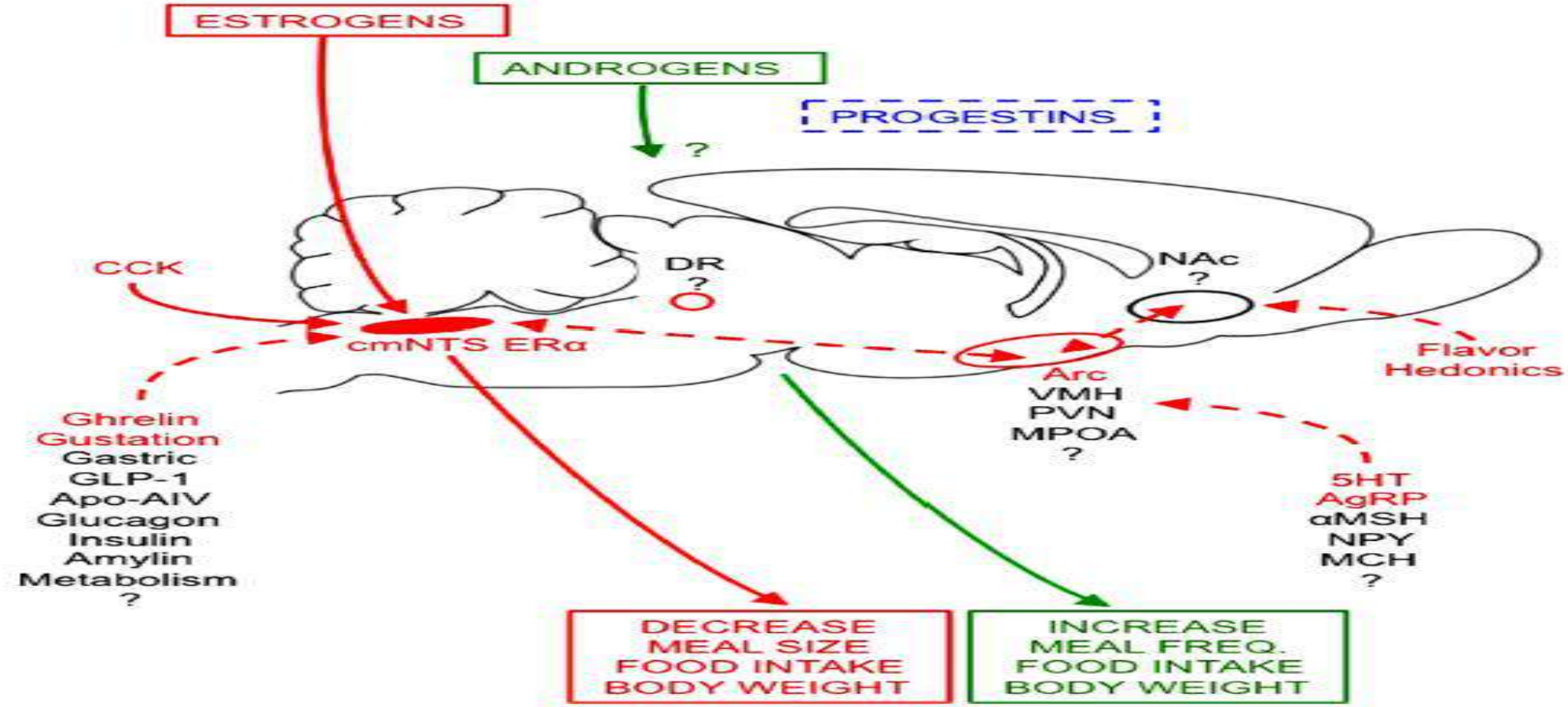
Maske CB. Hormones and Behavior 93 (2017)

Schematic summary of the activational effects of gonadal steroid hormones on eating.



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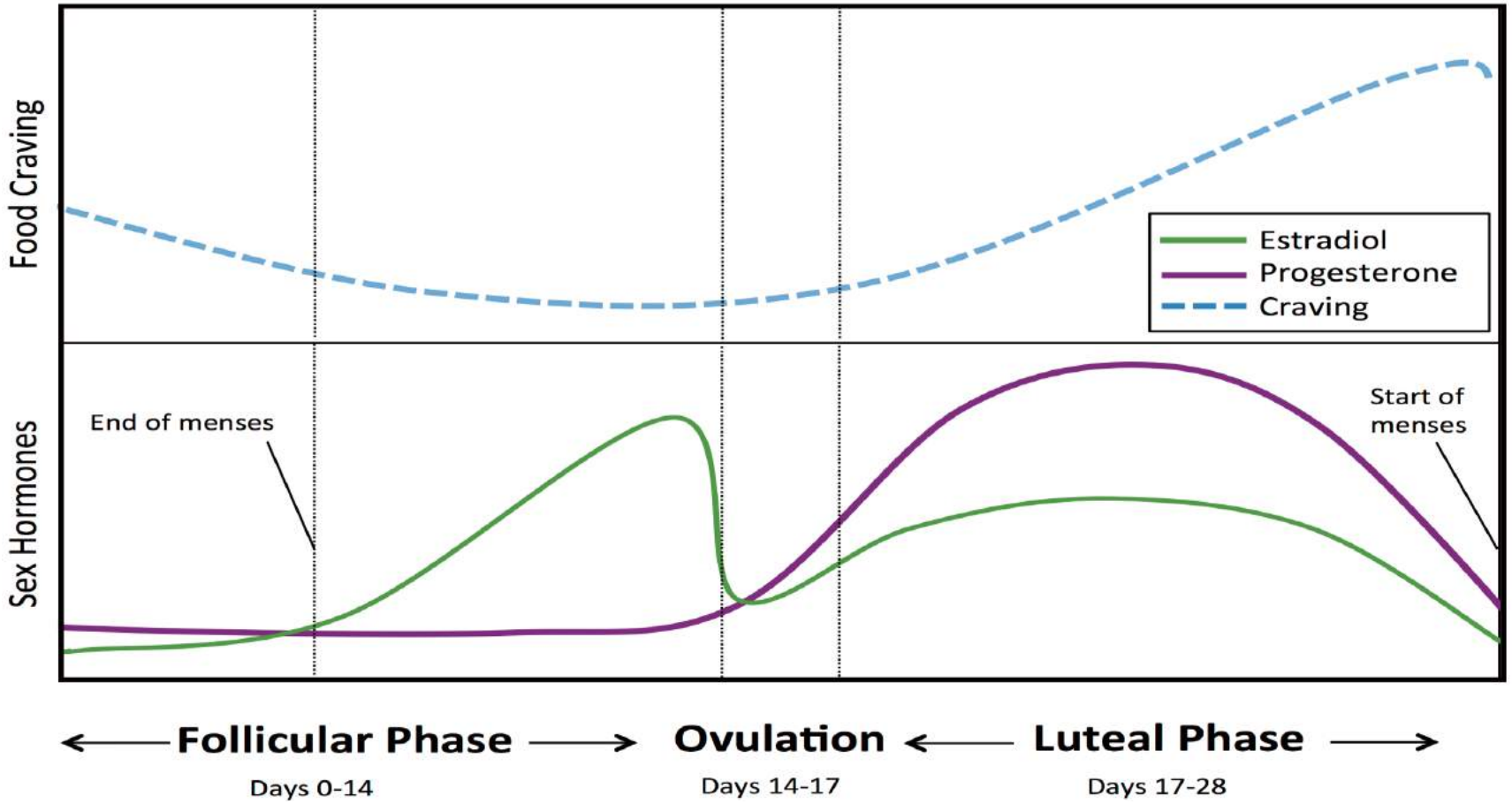
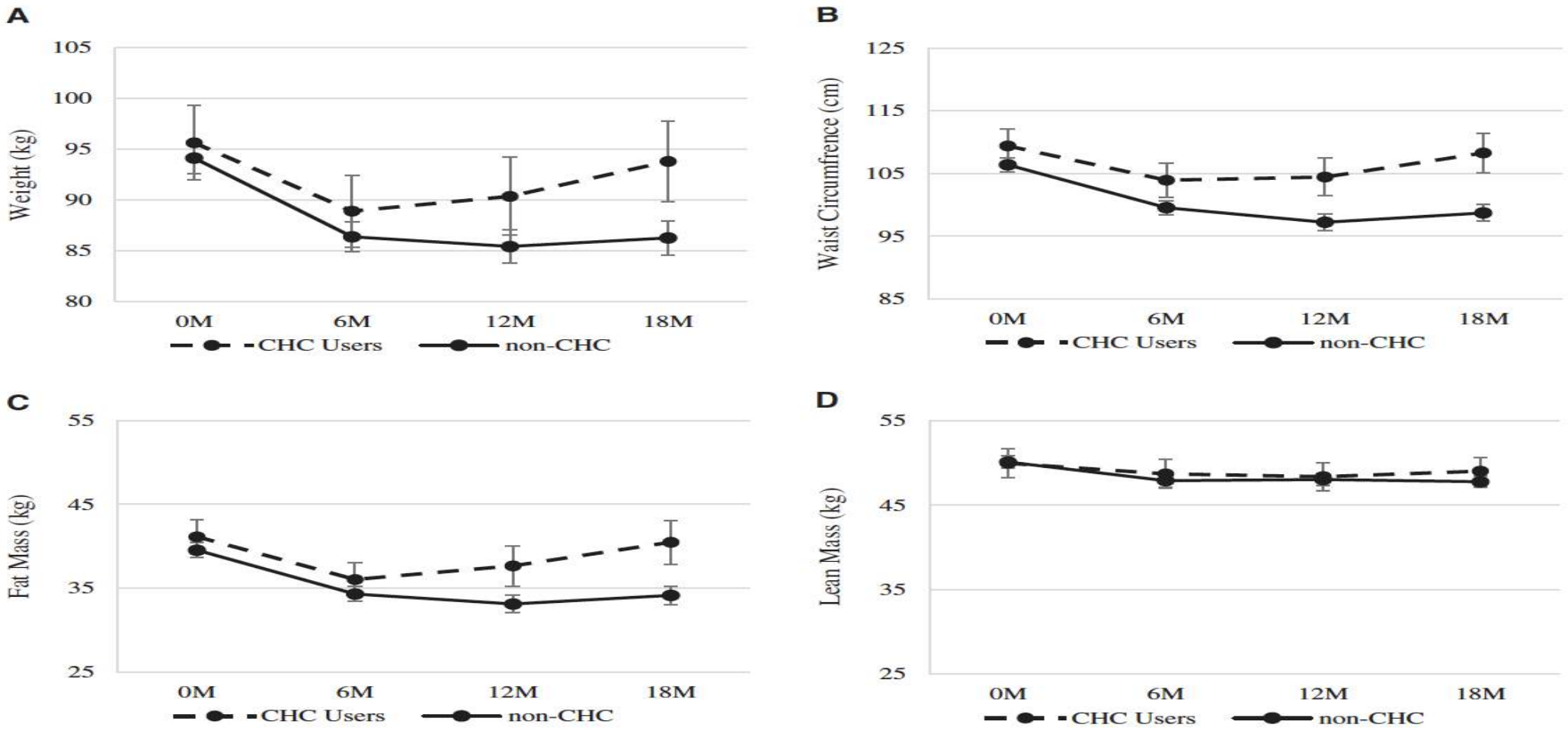
Asarian L, Am J Physiol Regul Integr Comp Physiol 2013

Ovarian hormone level sand proposed variation in food craving for each cycle phase



Hallam J, YALE JOURNAL OF BIOLOGY AND MEDICINE 2016

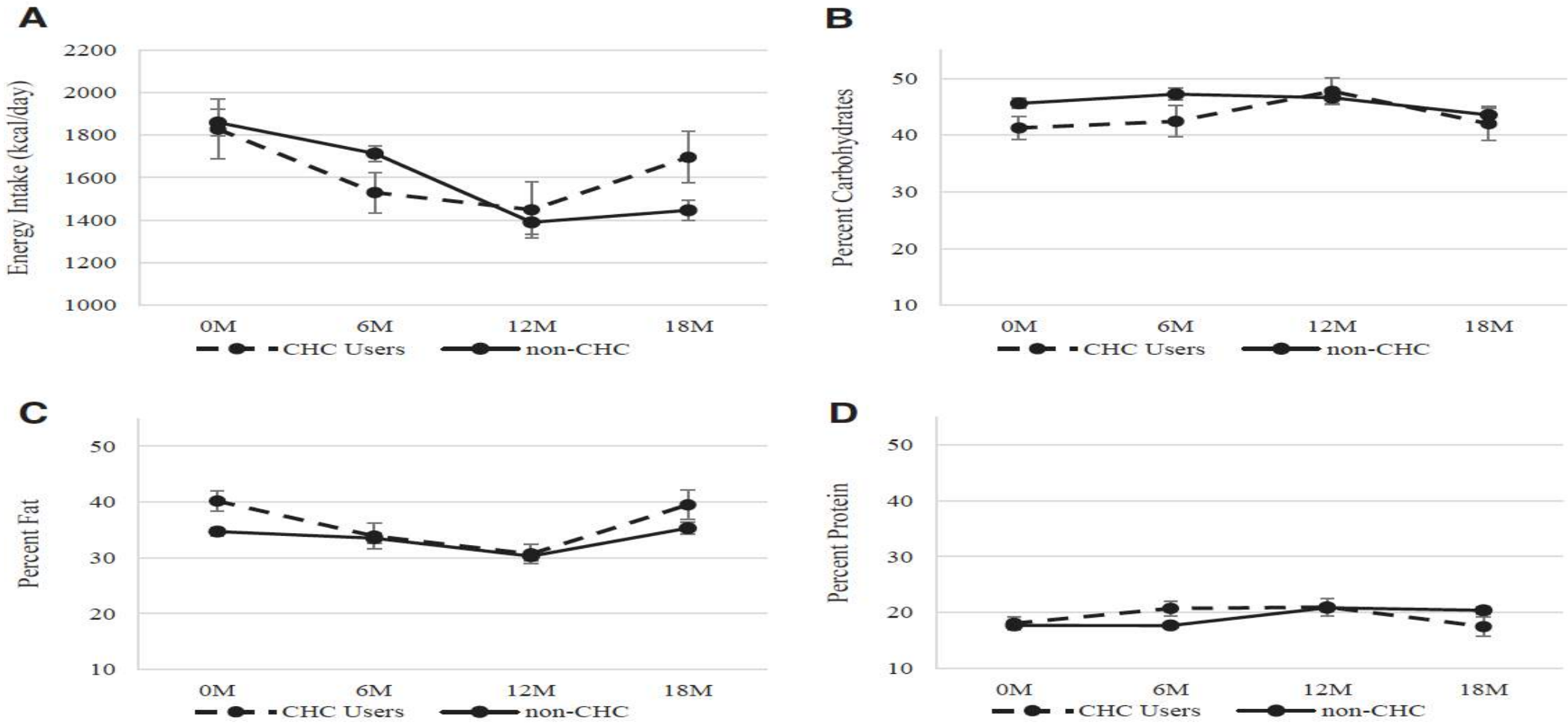
Impact of Combined Hormonal Contraceptive Use on Weight Loss



European Association for the Study of Obesity

Caldwell AE. OBESITY 2020

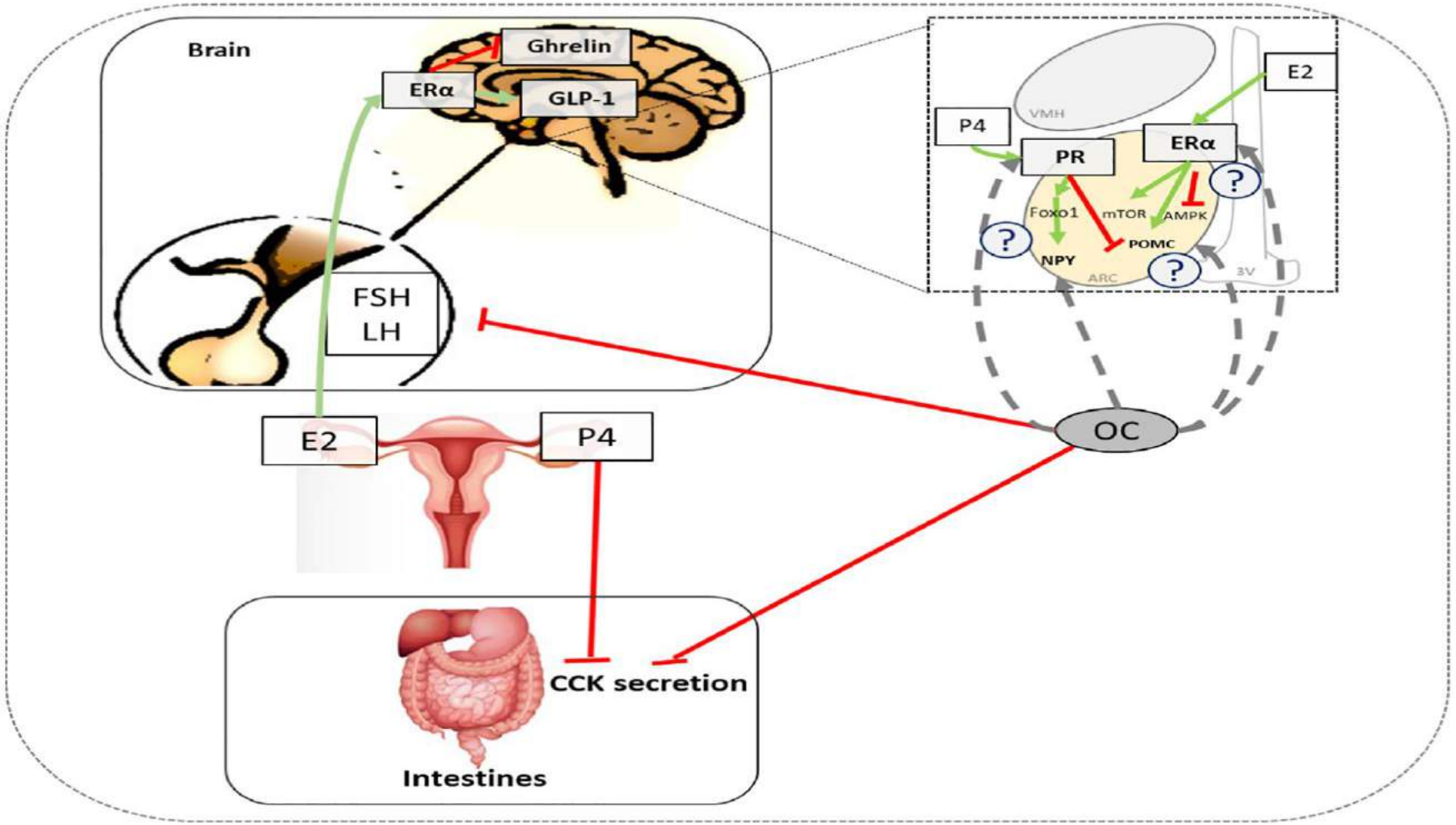
Impact of Combined Hormonal Contraceptive Use on Weight Loss



European Association for the Study of Obesity

Caldwell AE. OBESITY 2020

Schematic representation of mechanisms of E2 and P4 and potential mechanisms of OC action on energy intake



L. Metz, L. Isacco, Metabolism Clinical and Experimental (2022)

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Outline

- Obesity in Israel Gender Implications
- Obesity as Dysfunctional fat Disease
- Obesity comorbidities
- Menopause -Related Gain in Visceral Adiposity
- Obesity & Sex Hormones and appetite regulation
- Obesity Treatment

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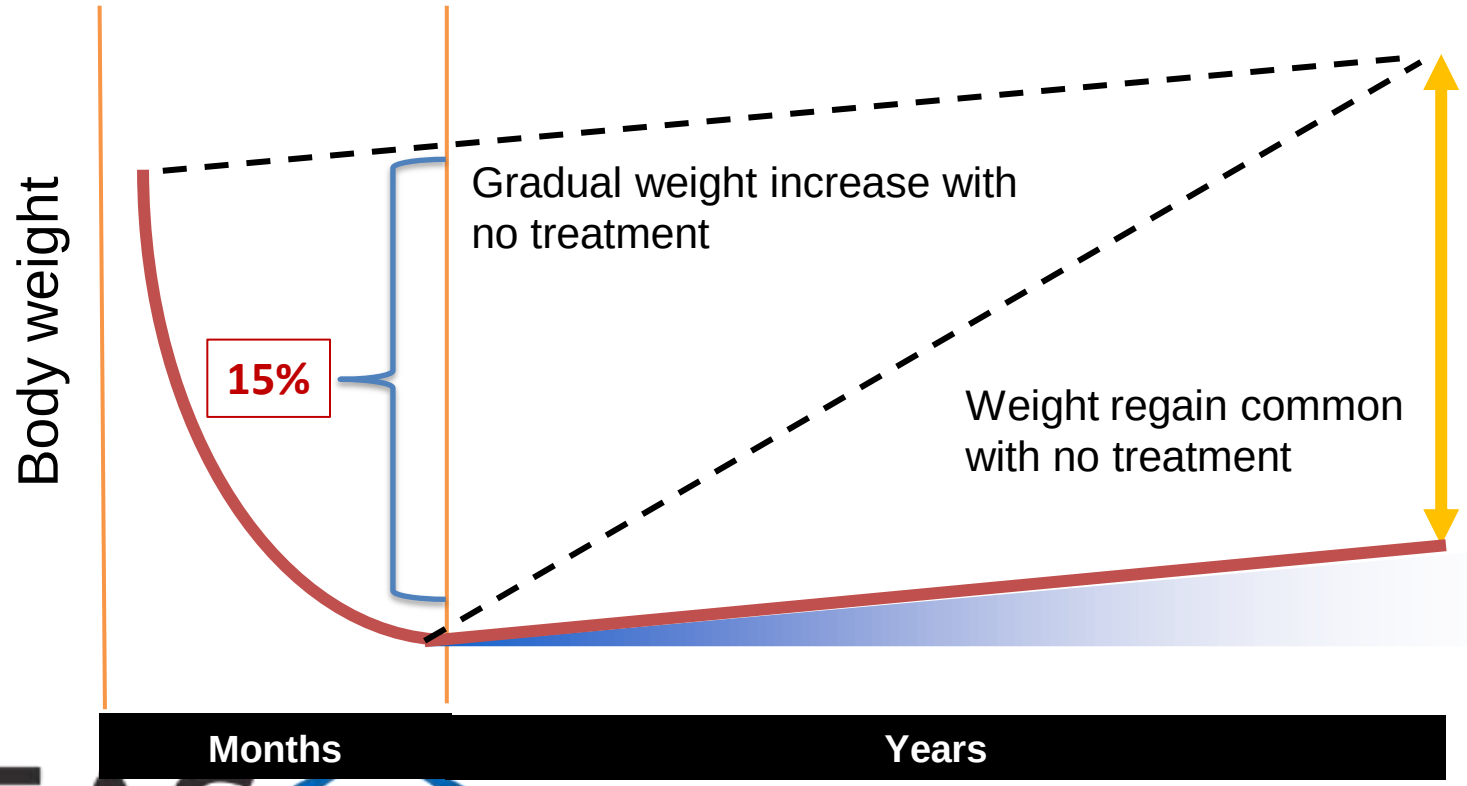
Obesity Treatment targets

1. Achieve weight loss

2. Maintain weight loss and prevent weight regain

3. Provide clinically meaningful benefits



- Reduce diabetes risk & help manage diabetes
- Reduce cardiovascular risk
- Reduce functional impairment
- Improve quality of life

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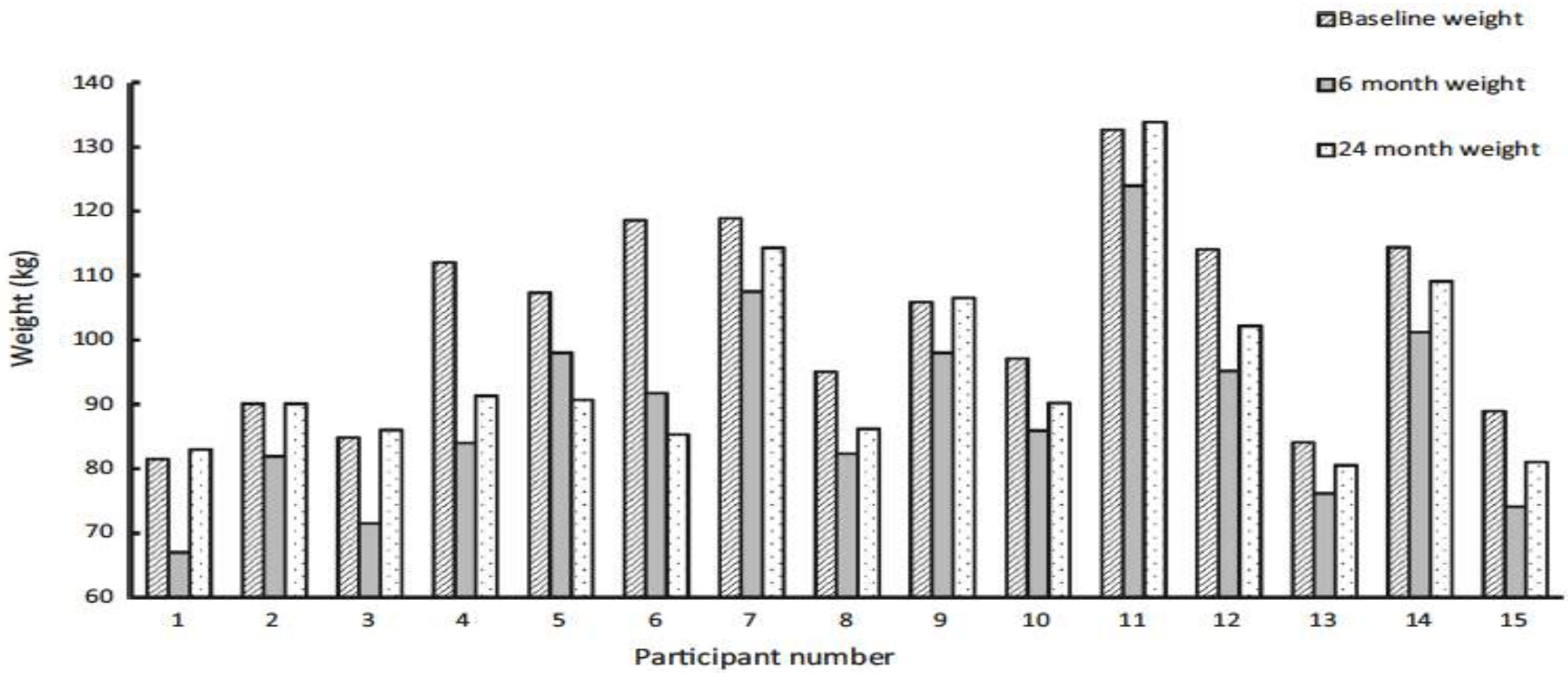
1. Wadden et al. *Circulation* 2012;125:1157–70; 2. Jensen et al. *J Am Coll Cardiol* 2014;63(25 Pt B):2985–3023; 3. Purcell et al. *Lancet Diabetes Endocrinol* 2014;2:954–62; 4. Villareal et al. *Am J Clin Nutr* 2005;82:923–34.

Weight Loss and maintenance



George Thom, European Journal of Clinical Nutrition (2020)

Weight Loss and maintenance

Participant characteristics	Baseline	6 months	*P* value
Weight (kg)	103.0 ± 15.5	89.2 ± 15.2	<0.001
BMI (kg/m^2)	39.4 ± 4.3	34.1 ± 4.8	<0.001
Total adipose tissue mass (kg)	54.6 ± 12.7	43.1 ± 13.2	<0.001
Skeletal muscle mass (kg)	28.8 ± 4.0	28.4 ± 3.8	0.121
RMR (kcal/day)	1788 ± 349	1497 ± 225	<0.001
Measured–predicted RMR (kcal/day)	n/a	−150 ± 162	0.003
Leptin (ng/mL)	64.0 ± 12.2	39.5 ± 21.6	<0.001
Total Ghrelin (pg/mL)	573.8 ± 232.0	814.5 ± 337.0	0.001
Total GLP-1 (pmol/L)	45.1 ± 21.9	32.1 ± 12.4	0.015
PYY (pg/mL)	70.7 ± 34.5	88.1 ± 26.1	0.157
GDF-15 (pg/mL)	573.7 ± 235.4	568.4 ± 184.2	0.861
Insulin (μU/mL)	12.9 ± 6.6	10.5 ± 6.1	0.110
Glucose (mmol/L)	6.4 ± 1.7	5.8 ± 1.4	0.861

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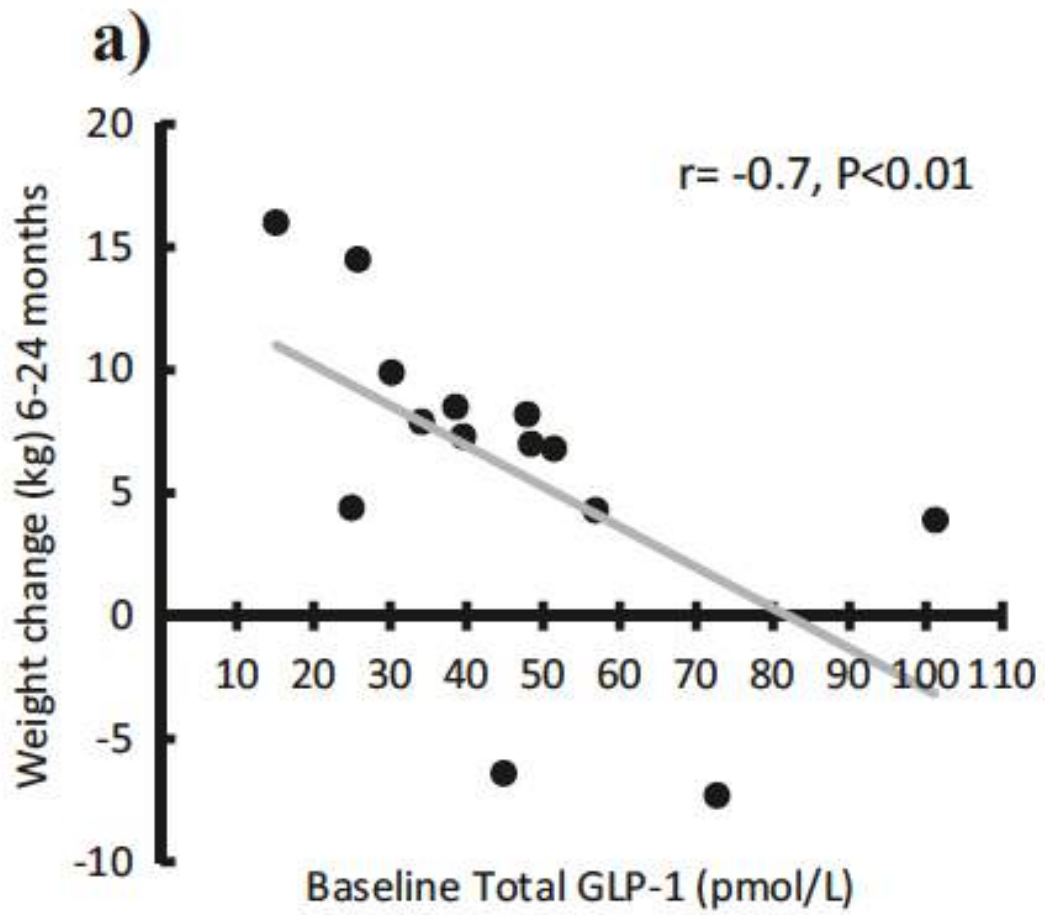
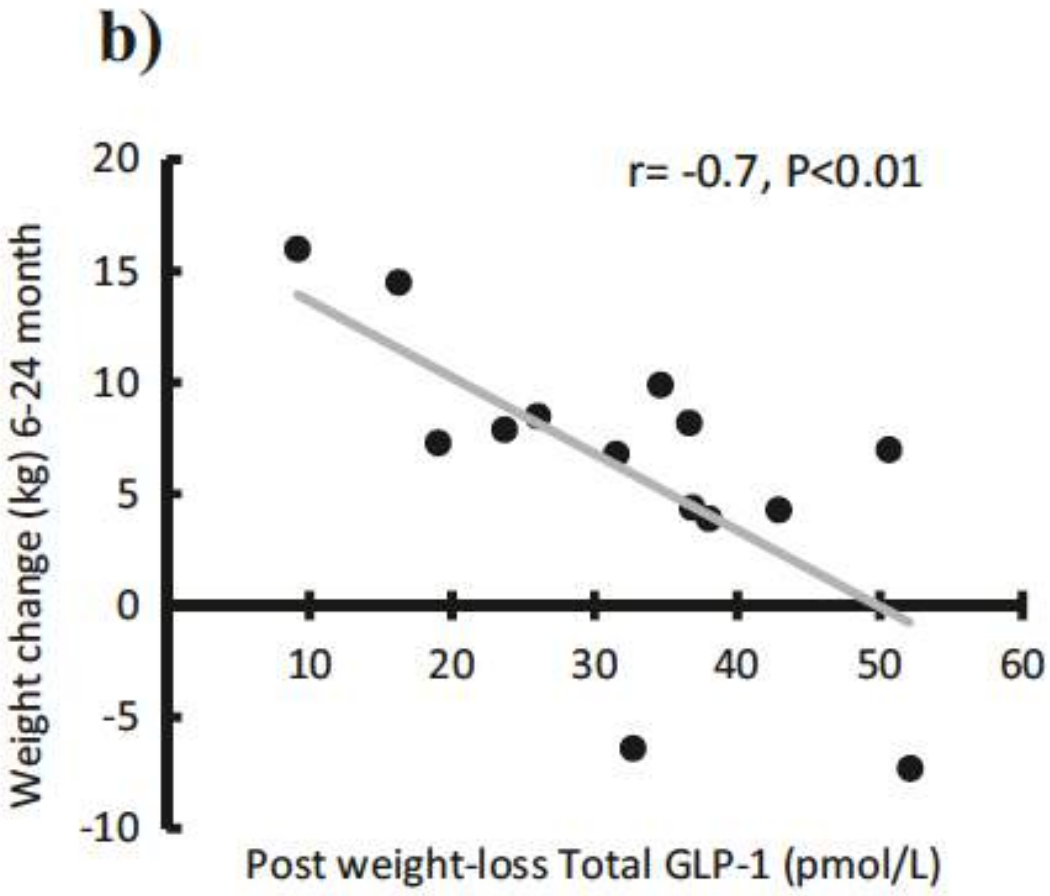
George Thom, European Journal of Clinical Nutrition (2020)

GLP-1 as a predictor of Weight Loss and maintenance





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George Thom,European Journal of Clinical Nutrition (2020)

Semaglutide is not approved in the Europe for weight management

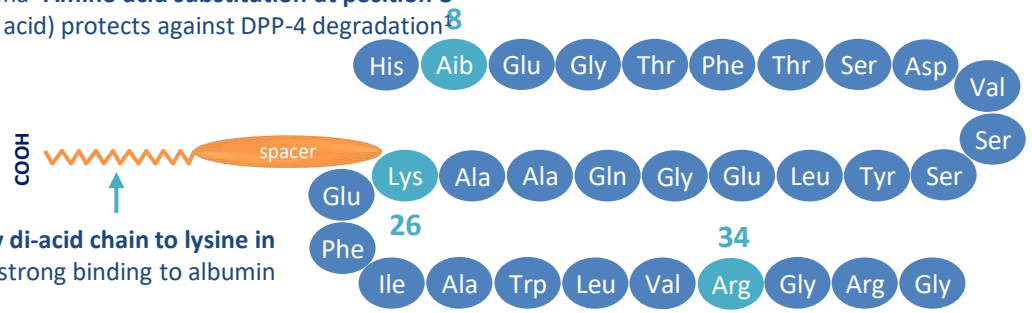
Mechanism of action of semaglutide

Semaglutide is a human GLP-1 analogue

- 94% homology to human GLP-1
- $t_{½}$ of approximately 1 week

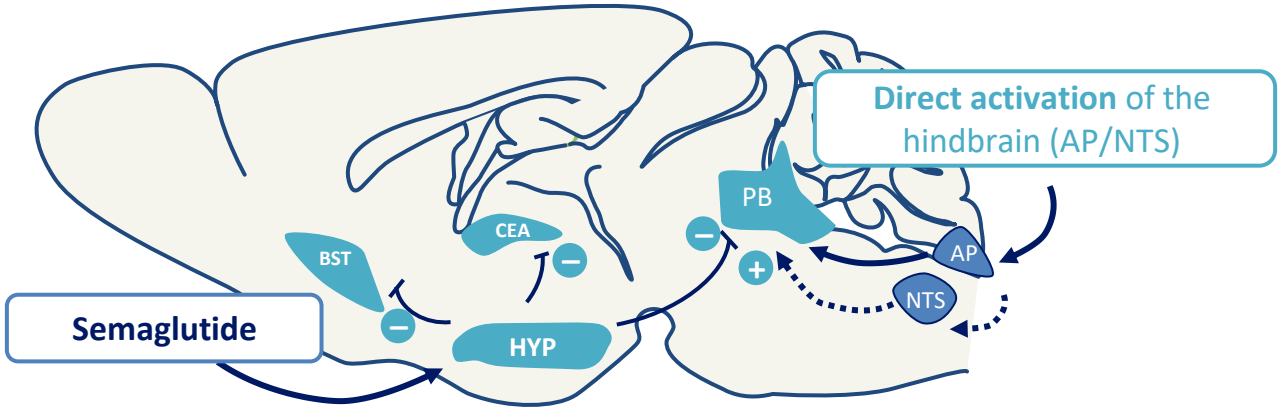
(alanine to alpha-aminoisobutyric acid) protects against DPP-4 degradation

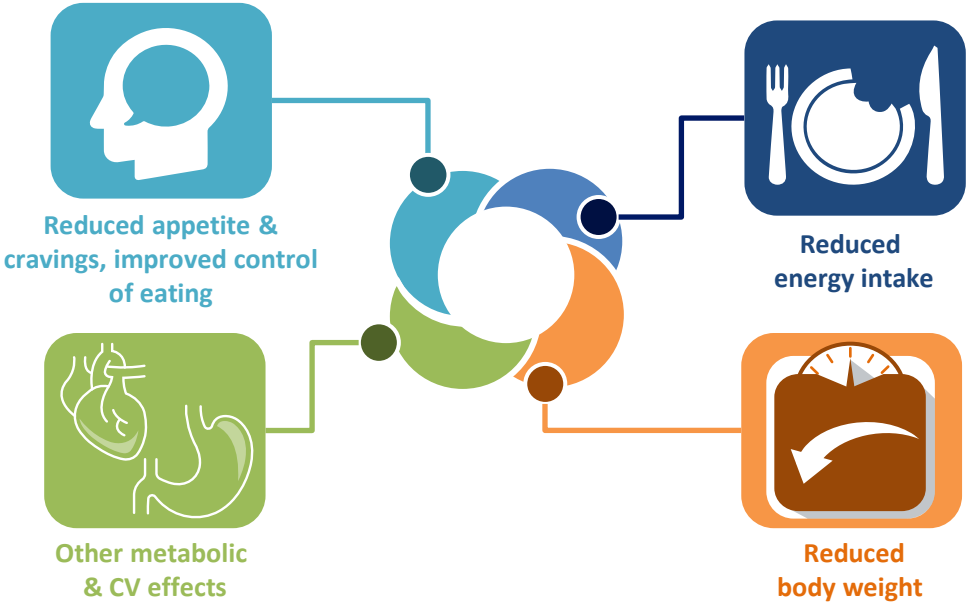
Amino acid substitution at position 8



Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin

Amino acid substitution at position 34 (lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site





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STEP 2 population
Demographics and baseline characteristics

Characteristic	Semaglutide 1.0 mg (N=403)	Semaglutide 2.4 mg (N=404)	Placebo (N=403)	Total (N=1,210)
Age – years	56 ± 10	55 ± 11	55 ± 11	55 ± 11
Female sex – n (%)	203 (50.4)	223 (55.2)	190 (47.1)	616 (50.9)
Body weight – kg	99.0 ± 21.1	99.9 ± 22.5	100.5 ± 20.9	99.8 ± 21.5
BMI, mean – kg/m^2	35.3 ± 5.9	35.9 ± 6.4	35.9 ± 6.5	35.7 ± 6.3
Waist circumference – cm	113.9 ± 14.0	114.5 ± 14.3	115.5 ± 13.9	114.6 ± 14.1
HbA_{1c} – %	8.1 ± 0.8	8.1 ± 0.8	8.1 ± 0.8	8.1 ± 0.8
Duration of diabetes – years	7.7 ± 5.9	8.2 ± 6.2	8.2 ± 6.2	8.0 ± 6.1
Systolic blood pressure – mmHg	130 ± 14	130 ± 13	130 ± 13	130 ± 14
Diastolic blood pressure – mmHg	80 ± 9	80 ± 9	80 ± 9	80 ± 9
Glucose-lowering drug class – n (%)				
Biguanides	379 (94.0)	370 (91.6)	362 (89.8)	1,111 (91.8)
Sulfonylureas	99 (24.6)	110 (27.2)	99 (24.6)	308 (25.5)
SGLT2 inhibitors	96 (23.8)	99 (245)	105 (26.1)	300 (24.8)
Thiazolidinediones	16 (4.0)	19 (4.7)	19 (4.7)	54 (4.5)

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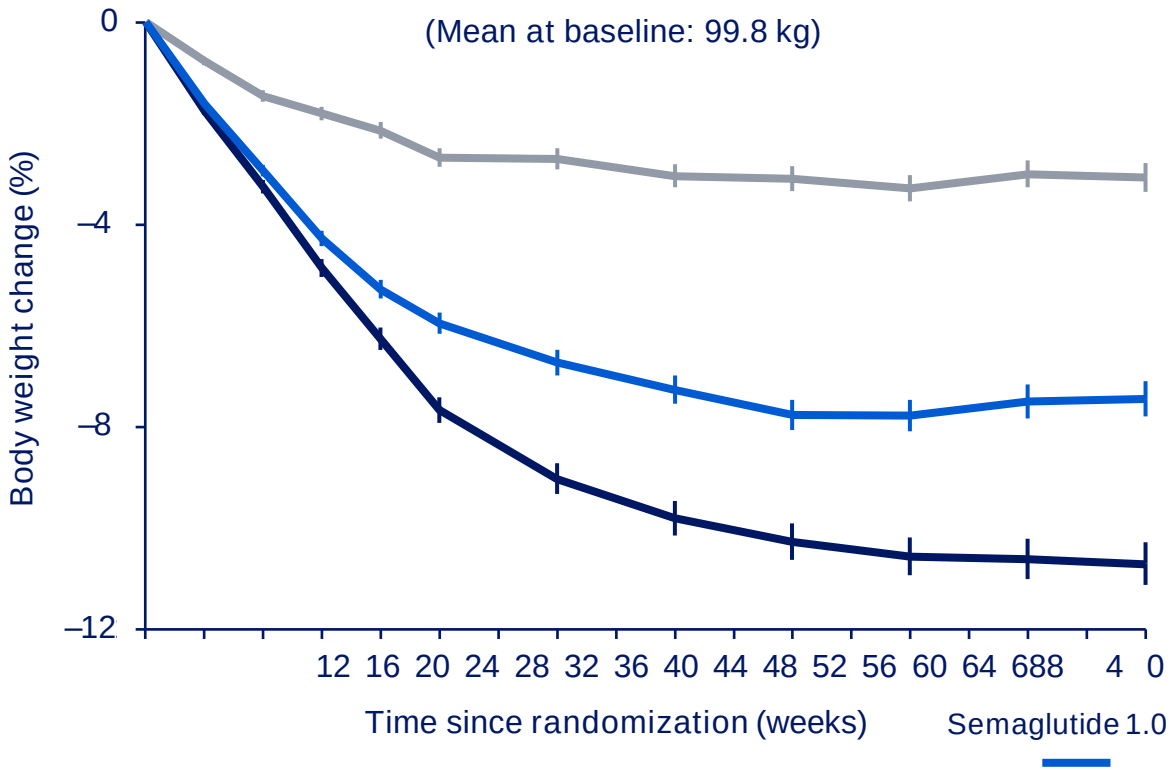
Data are mean ± standard deviation unless otherwise indicated.
BMI, body mass index; HbA_{1c}, glycated hemoglobin; SGLT2, sodium–glucose co-transporter-2.

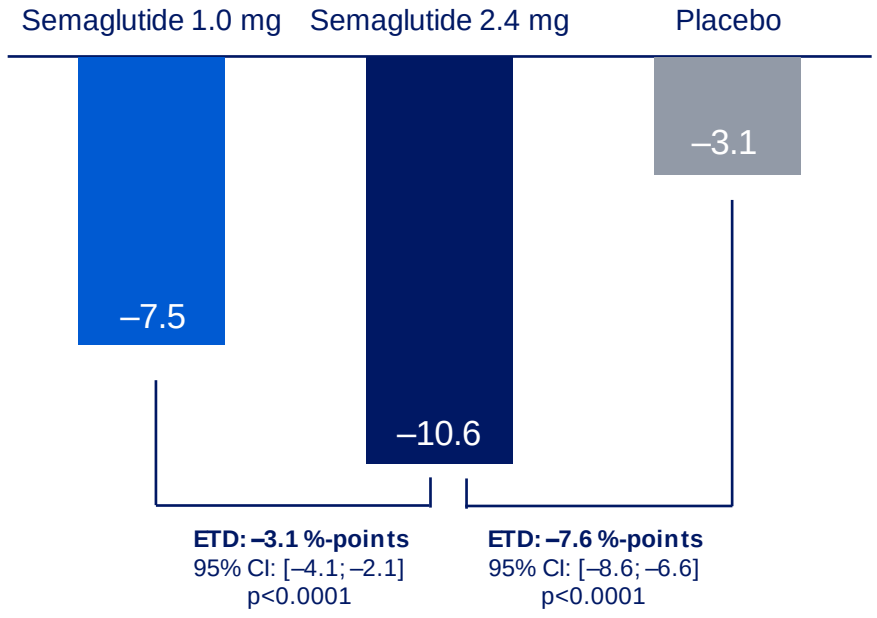
Lingvay I, et al. Presented at the American Diabetes Association (ADA) virtual meeting, June 25–29, 2021.

STEP 2 key results
Body weight change (%) from baseline to week 68

On treatment – observed change over time



Trial product estimand
Estimated change from baseline to week 68*

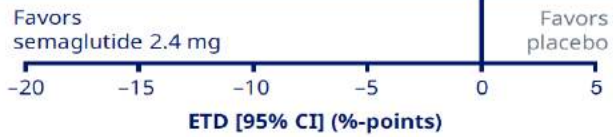


Observed data for the on-treatment period (during treatment with trial product [any dose of trial medication administered within the previous 2 weeks]).
Error bars are ± standard error of the mean. P values are not controlled for multiplicity.
**Trial product estimand (assesses treatment effect if trial product was taken as intended).*
CI, confidence interval; ETD, estimated treatment difference.
Davies M, et al. Lancet. 2021;397:971–84.

Lingvay I, et al. Presented at the American Diabetes Association (ADA) virtual meeting, June 25–29, 2021.

Change from baseline in body weight at week 68 by baseline characteristics

Subgroup		Patients, n		Mean change, %		ETD	Interaction p value
		Semaglutide 2.4 mg	Placebo	Semaglutide 2.4 mg	Placebo		
Primary analysis		**404**	**403**	**–10.6**	**–3.1**		
By age, years	18–<65	316	317	–10.4	–3.1		0.6105
	65–<75	78	78	–11.3	–2.8		
	75–<85	10	8	–14.1	–4.4		
By sex	Female	223	190	–12.0	–3.2		0.0038
	Male	181	213	–8.9	–2.9		
By race	White	237	242	–11.8	–3.4		0.0733
	Asian	112	108	–8.3	–2.6		
	Other	55	53	–10.2	–2.3		



Interaction p value not controlled for multiplicity. Analyses assumed all participants were treatment adherent and not using other anti-obesity therapies (the trial product estimand). Mixed model for repeated measurements, with percent weight loss as dependent variable and treatment, subgroup and their interaction, stratification groups (diabetes therapy and HbA_{1c} category) and the interaction between stratification groups as factors and baseline body weight as covariate, all nested within visit.
CI, confidence interval; ETD, estimated treatment difference.

Lingvay I, et al. Presented at the American Diabetes Association (ADA) virtual meeting, June 25–29, 2021.

Exploration of treatment effect in females
Adjusted analysis

	Original analysis				Adjusted analysis			
	Mean change in BW, %				Mean change in BW, %			
	Semaglutide 2.4 mg	Placebo	ETD [95% CI]	Interaction p value	Semaglutide 2.4 mg	Placebo	ETD [95% CI]	Interaction p value
Female	–12.0	–3.2	–8.8 [–10.2; –7.5]	0.0038	–12.0	–3.1	–8.8 [–10.2; –7.5]	0.0046
Male	–8.9	–2.9	–5.9 [–7.3; –4.5]		–9.0	–3.0	–6.0 [–7.4; –4.6]	

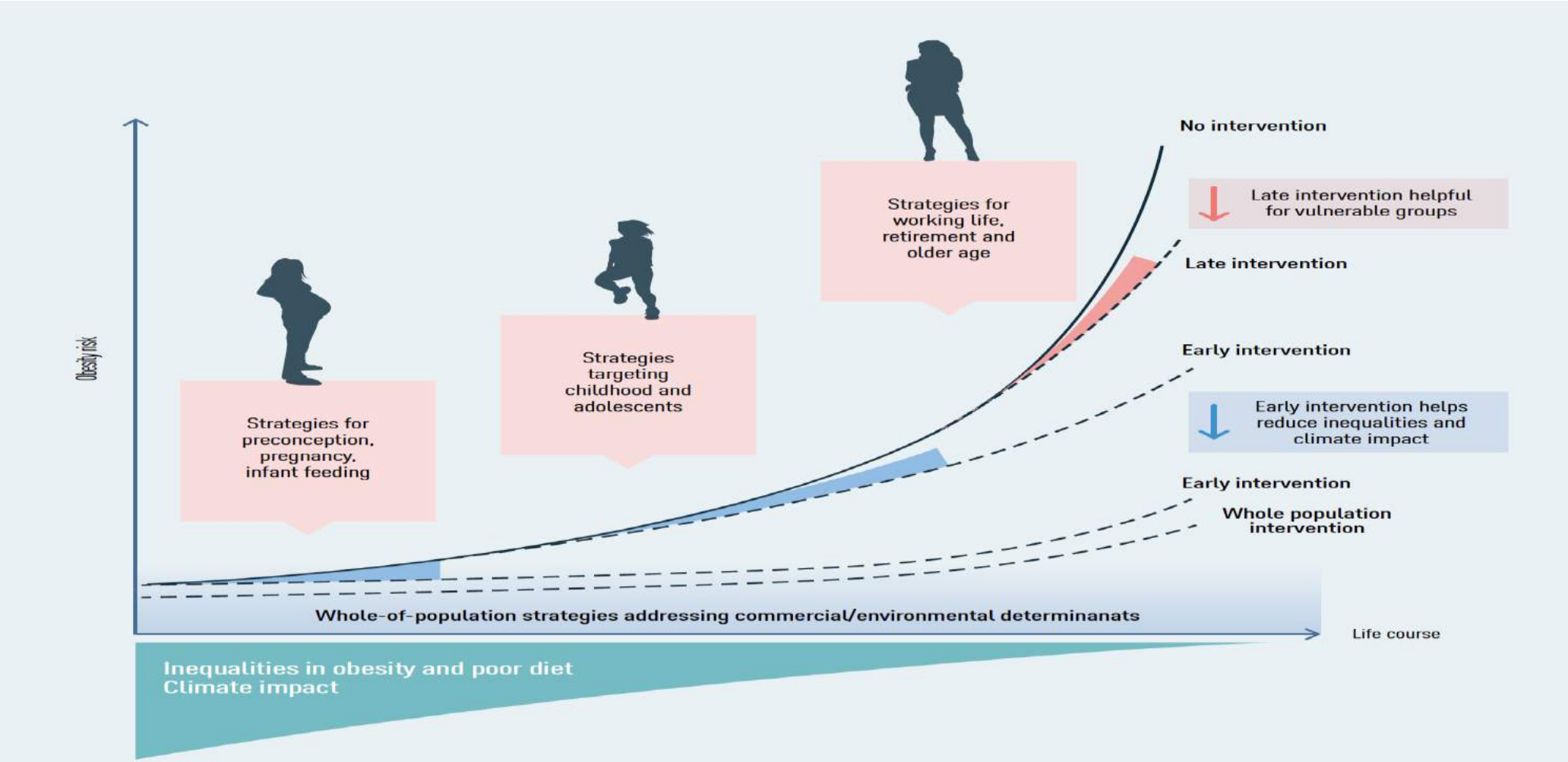
Baseline variables included in model

- Treatment
- Sex
- Interaction between treatment and sex
- Baseline BW (continuous)
- Diabetes therapy
- HbA_{1c} group
- Interaction between stratification groups (diabetes therapy and HbA_{1c} group)
- Treatment
- Sex
- Interaction between treatment and sex
- Baseline BW (continuous)
- Diabetes therapy
- HbA_{1c} group
- Interaction between stratification groups (diabetes therapy and HbA_{1c} group)
- **BW group**
- **Ethnicity**
- **Race***

**Age group omitted due to convergence issue.*
BW, body weight; CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated hemoglobin.

Lingvay I, et al. Presented at the American Diabetes Association (ADA) virtual meeting, June 25–29, 2021.

Whole-of-population policy interventions to address obesity, supported by targeted strategies across the life course



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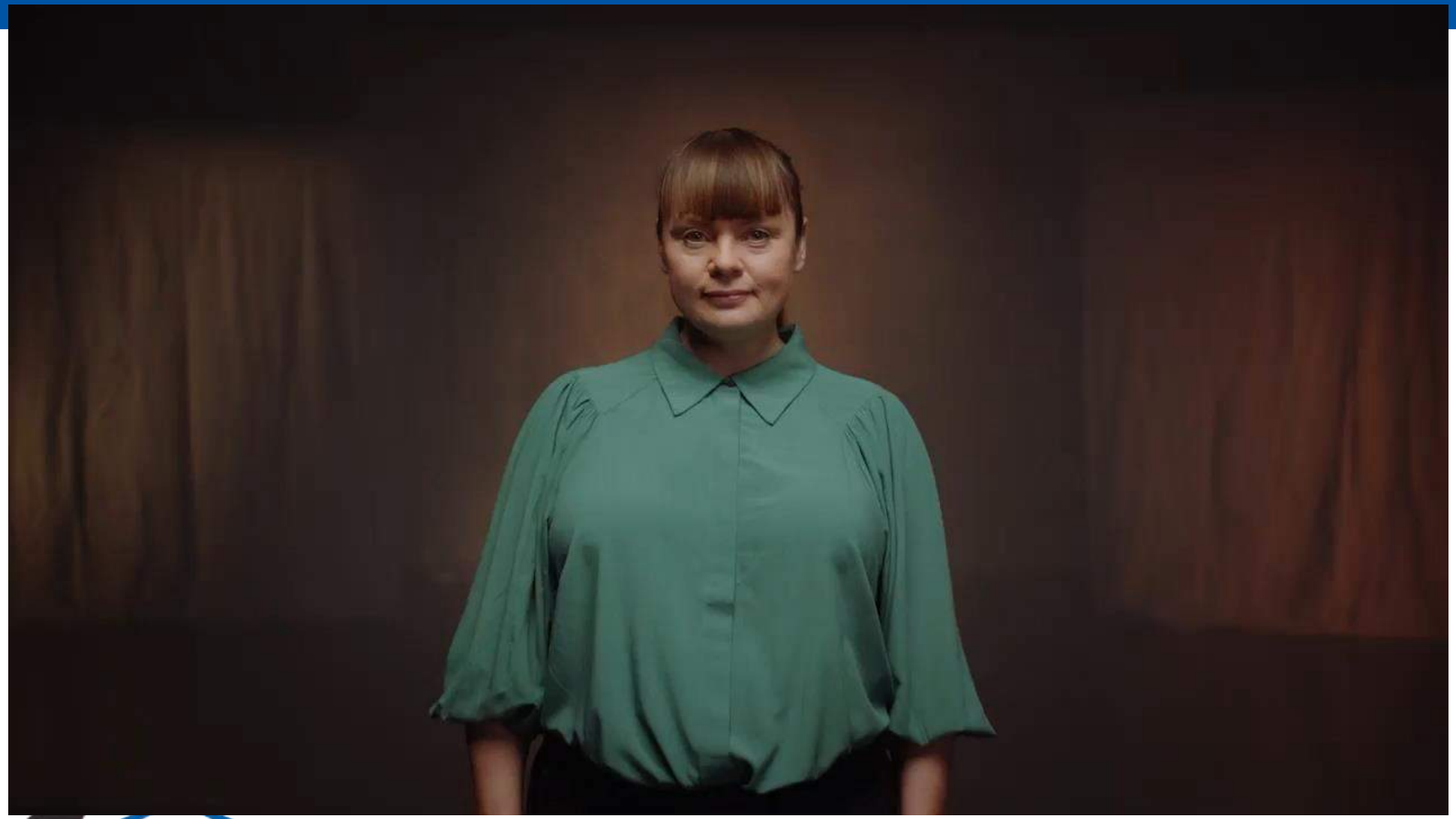
Adapted from Godfrey et al. (2010). Reproduced with permission of Elsevier under Creative Commons CC-BY-NC-ND license (119).



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Thank You