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Weight Gain and Lipid Alterations Induced by Psychotropic Drugs

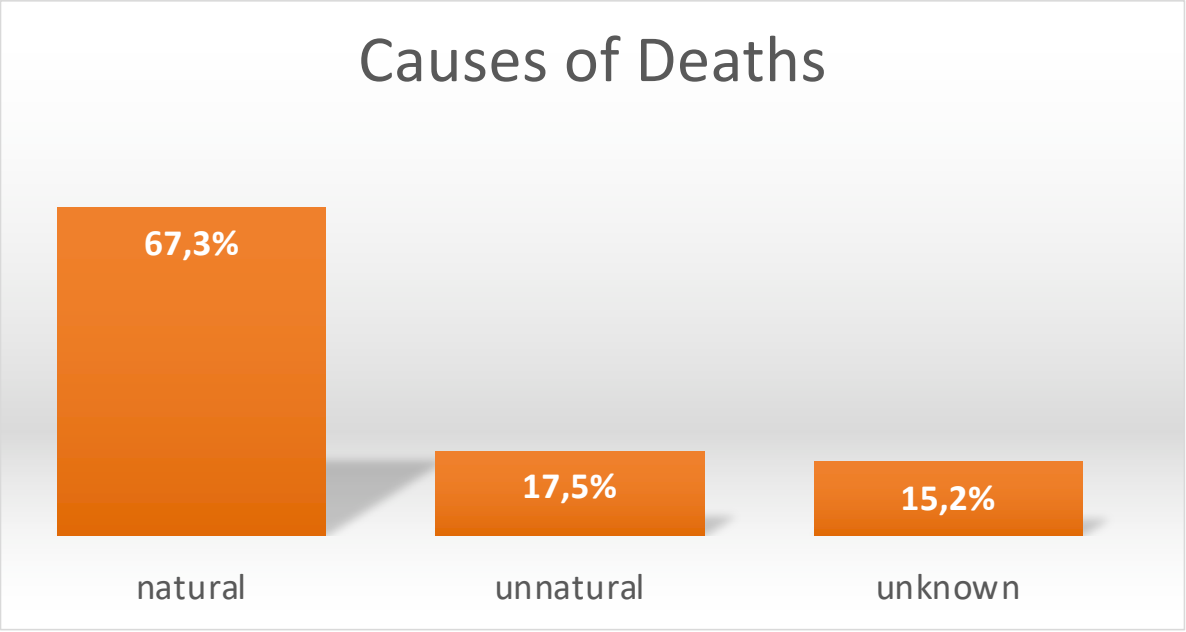
Prof Chin Eap

Lausanne University Hospital, Switzerland

Mortality in mental disorders

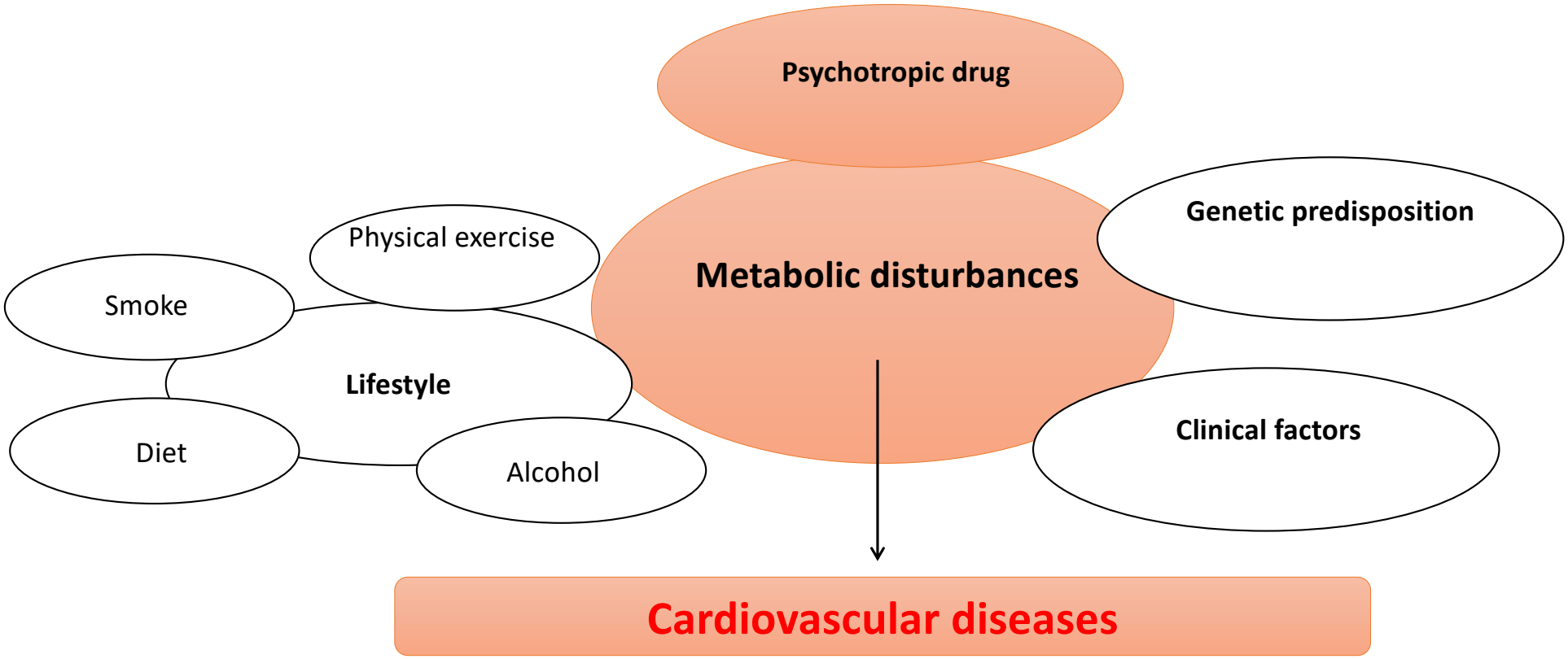
Mortality is higher among people with mental disorders with a reduction in life expectancy of about 10 years or more

Including mainly cardiovascular diseases



Walker ER et al., JAMA Psychiatry 2015

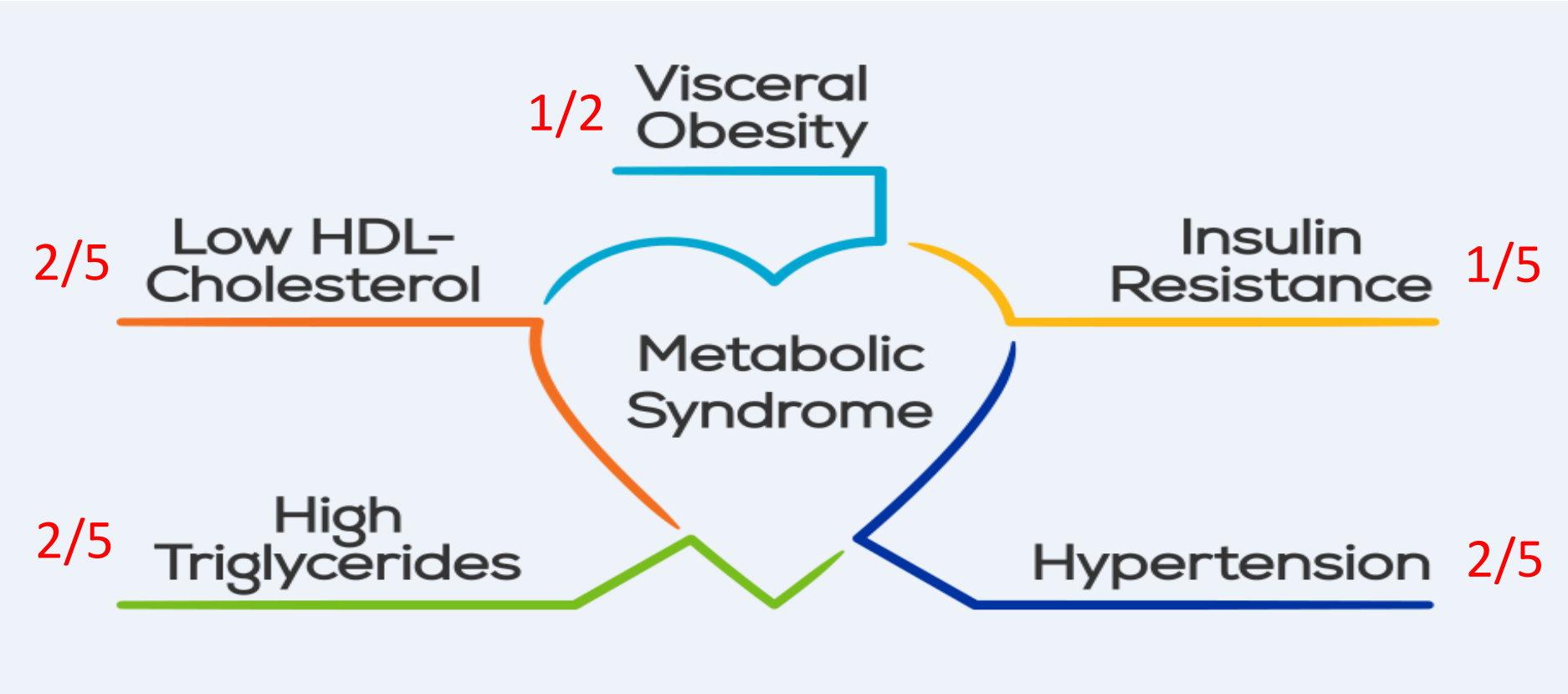
Cardiovascular diseases in mental disorders



Reisinger Walker et al., JAMA Psychiatry 2015

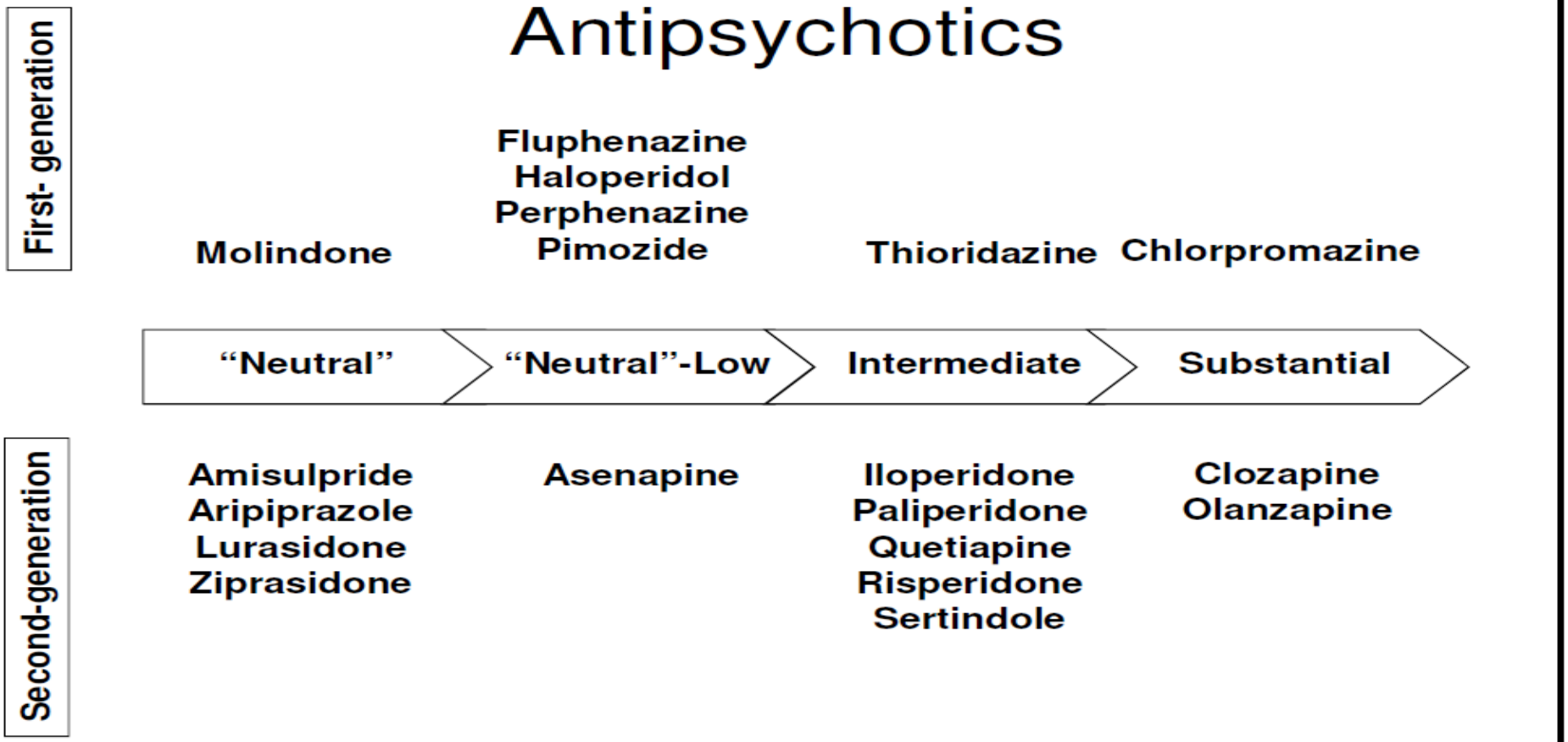
Correll CU et al., World Psychiatry 2015

High prevalence of metabolic syndrome (3 or more metabolic symptoms) in schizophrenic patients



Birkenaes et al. J Clin Psychiatry. 2006; 67(3):425-33
Mitchell et al. Schizophr Bull 2013;39:306-18

Risk of Weight Gain with Antipsychotics



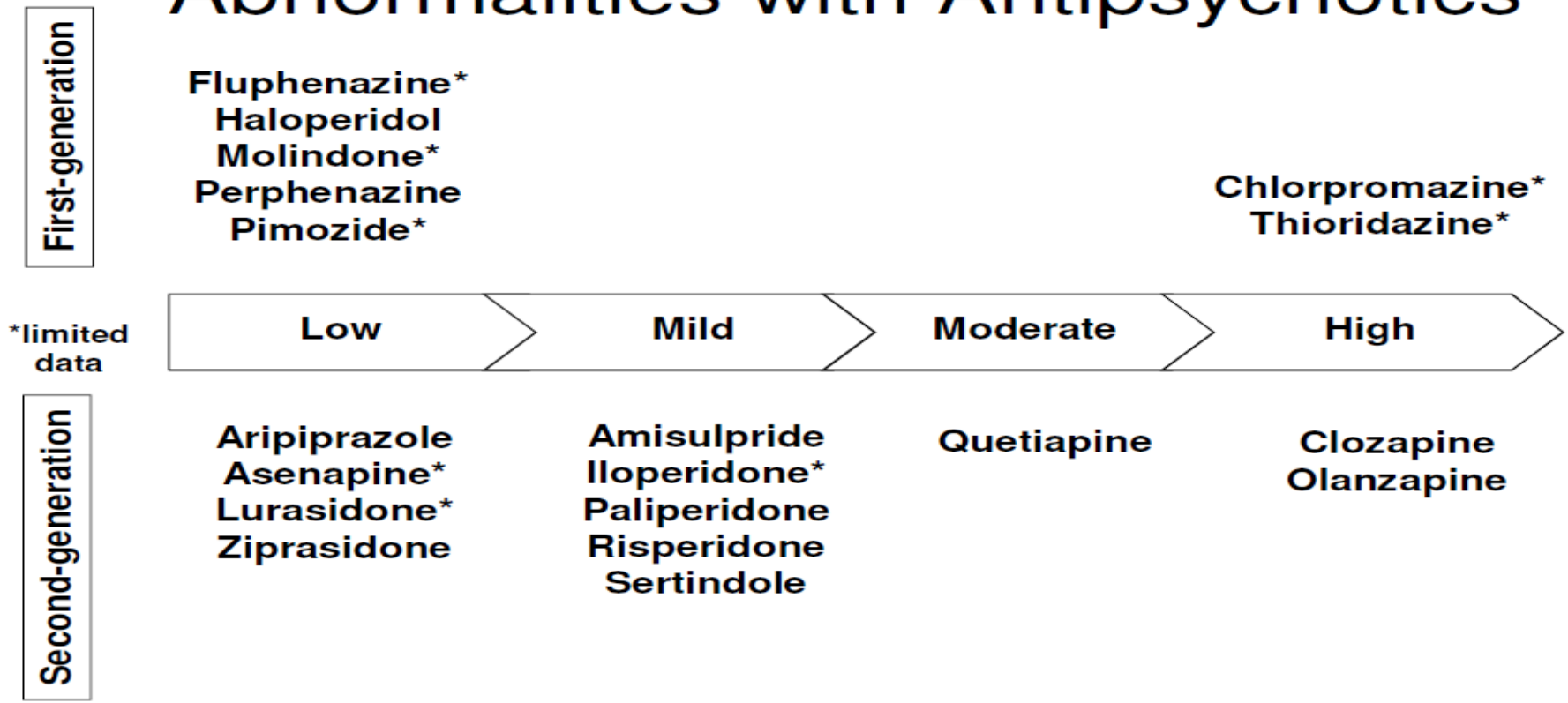
De Hert M, Detraux J, van Winkel R, Correll CU. Nat Rev Endocrinol. 2011;8(2):114-26.

Potential weight gain induced by psychotropics

Potential Weight Change/year (lb)	0-5	0	1-5	6-10	11-15	>15
DRUG CLASS						
Antidepressants SSRI TCA MAOI SNRI Other	Bupropion Fluoxetine	Citalopram Duloxetine Escitalopram Fluvoxamine Nefazodone Selegiline Sertraline Trazodone Venlafaxine	Desipramine Nortriptyline Paroxetine Protriptyline	Amitriptyline Doxepin Imipramine Mirtazapine Phenelzine Tranylcypromine		
Antipsychotics Older Newer	Molindone	Aripiprazole Ziprasidone	Fluphenazine Haloperidol Paliperidone Perphenazine	Quetiapine Risperidone Thioridazine		Clozapine Olanzapine
Mood stabilizers Antiseizure Other	Topiramate	Lamotrigine Oxcarbazepine	Carbamazepine	Gabapentin	Lithium Valproate	

Vieweg VR & al, Am J of Medicine 08;121:647-655

Risk of Lipid and/or Glucose Abnormalities with Antipsychotics



De Hert M, Detraux J, van Winkel R, Correll CU. Nat Rev Endocrinol. 2011;8(2):114-26.

Clinical factors and interindividual variability of metabolic syndrome induced by antipsychotics

Familial factors

- Family history of obesity
- Parental BMI

Personal factors

- Cannabis use
- Young age (children and adolescents)
- Sex (mixed evidence)
- High levels of negative symptoms (such as alogia, affective flattening, avolition)
- Lack of cognitive restraint in the presence of increased appetite
- Low BMI (<25 kg/m^2)
- Nonsmoking status
- Nonwhite ethnicity

Factors related to psychiatric illness

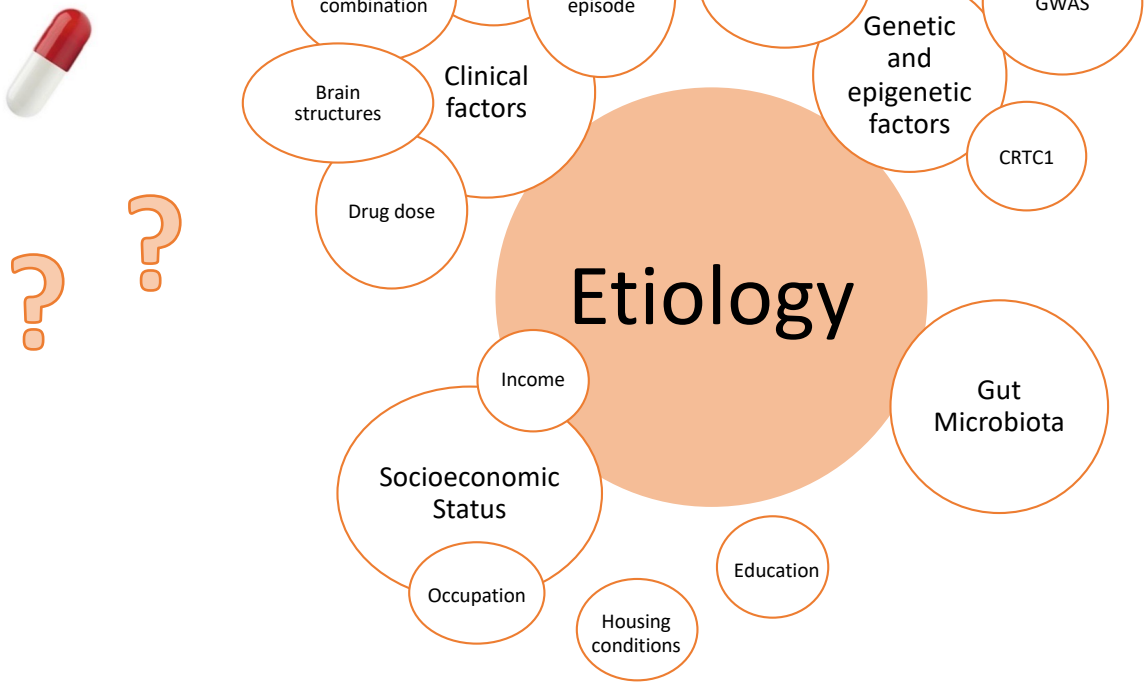
- Improved symptom reduction (limited or inconclusive data)
- First-episode status of psychiatric illness
- Lack of prior antipsychotic treatment

Treatment-related factors

- Early weight gain (within the first 2–4 weeks of antipsychotic treatment)
- Good treatment adherence
- High antipsychotic dose
- Polypharmacy (limited or inconclusive data)
- Long-term treatment
- Specific medications (such as clozapine and olanzapine, which have a high risk of metabolic dysregulation)

De Hert M et a. Nat Rev Endocrinol. 2011

Global approach towards understanding **drug induced cardiometabolic side effects**



De Hert M et al, Nat Rev Endocrinol, 2011

Psy Metab

Started in 2007, continuously supported by SNF
> 3700 patients
Inclusions ongoing
GWAS on all patients
Extensive clinical data

Several ongoing studies on the inflence of genetic factors on response to psychotropic treatment

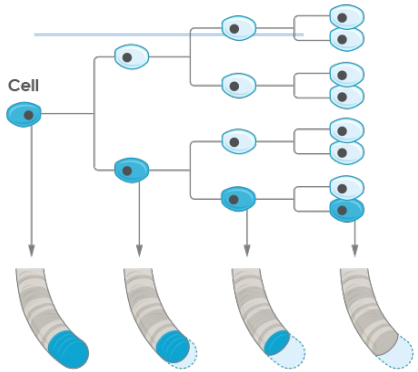
Telomere shortening and psychotropic drugs

Telomere shortening (reversible by telomerase)

Blackburn EH. FEBS letters. 2005

Cellular replications →

Biological environment (oxydation, inflammation) →



Senescence →

Diminished mitochondrial function

Inflammation

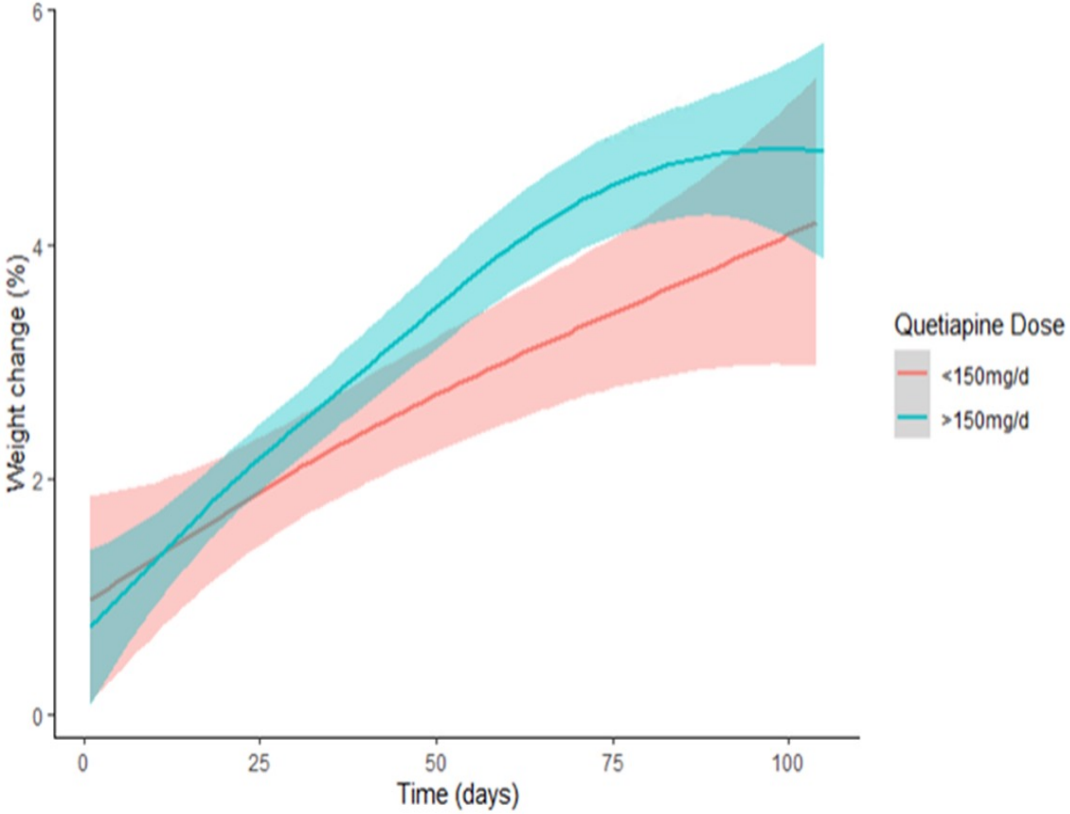
Increased intracellular reactive oxygen species (ROS)

Piras et al. Translational Psychiatry 2024

- 200 patients, telomere length measured before and after one year of psychotropic ttt
- Overall telomere shortening similar to the general population's yearly telomere attrition
- Overall telomere shortening predicted to be increased 4-fold among patients with low baseline weight (i.e., 50 kg) and with clinically relevant weight gain (≥ 7%) after 1 year of ttt
- Mendelian randomization (UKBiobank data) showed a causal effect of BMI on telomere shortening, notably stronger among patients receiving weight-inducing psychotropic treatments (n = 9798) than among psychiatric patients without such drugs (n = 16228) and non-psychiatric controls (n = 252932)

Effects of psychotropic doses on weight gain

Quetiapine



Dubath et al. Pharmacopsychiatry 2021

Overall, dose effect on weight gain is modest to moderate

Studies performed on other psychotropic drugs (clozapine, risperidone, olanzapine, aripiprazole, valproate, mirtazapine…)

Choose the minimally effective dose
Decreasing the dose in an attempt to decrease metabolic effects is not useful

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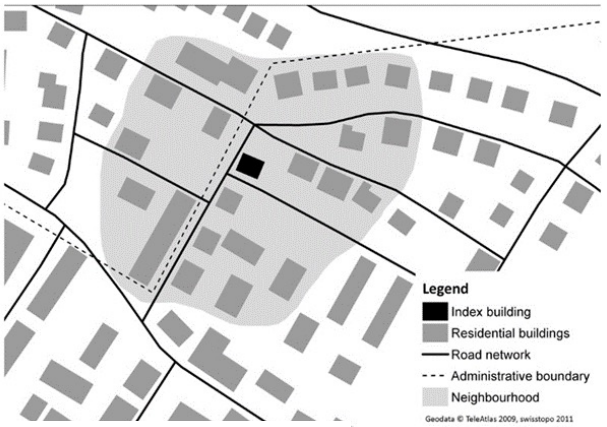
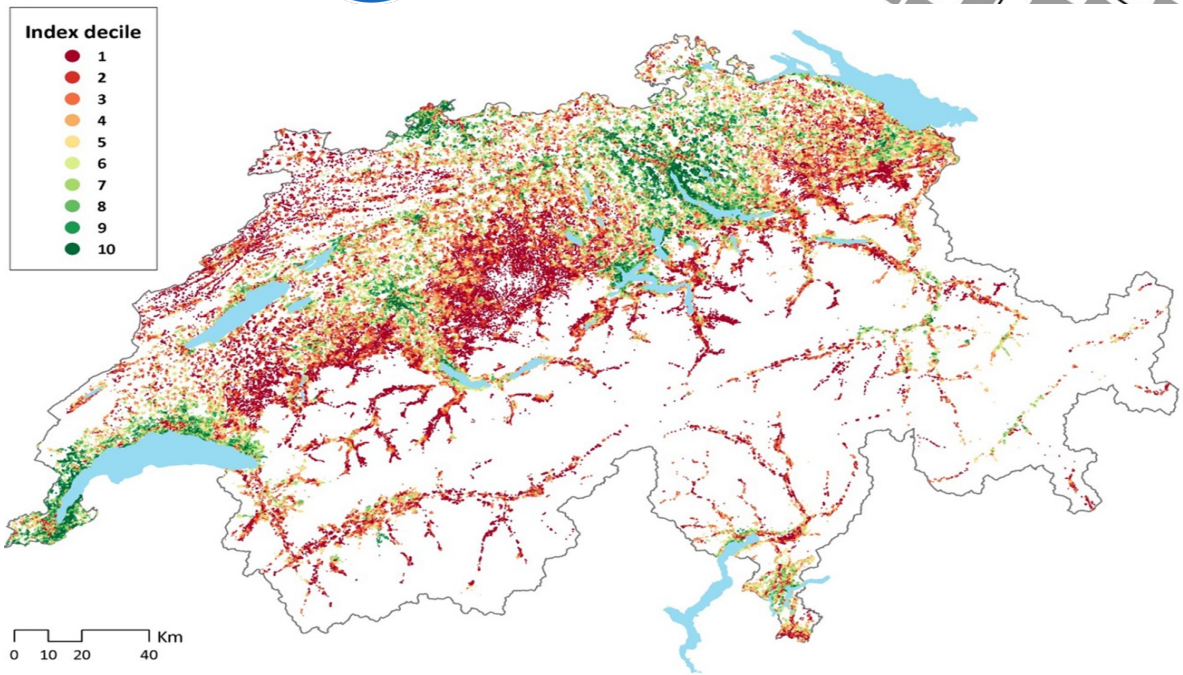
Socio economic positions based on the GPS coordinates in Switzerland

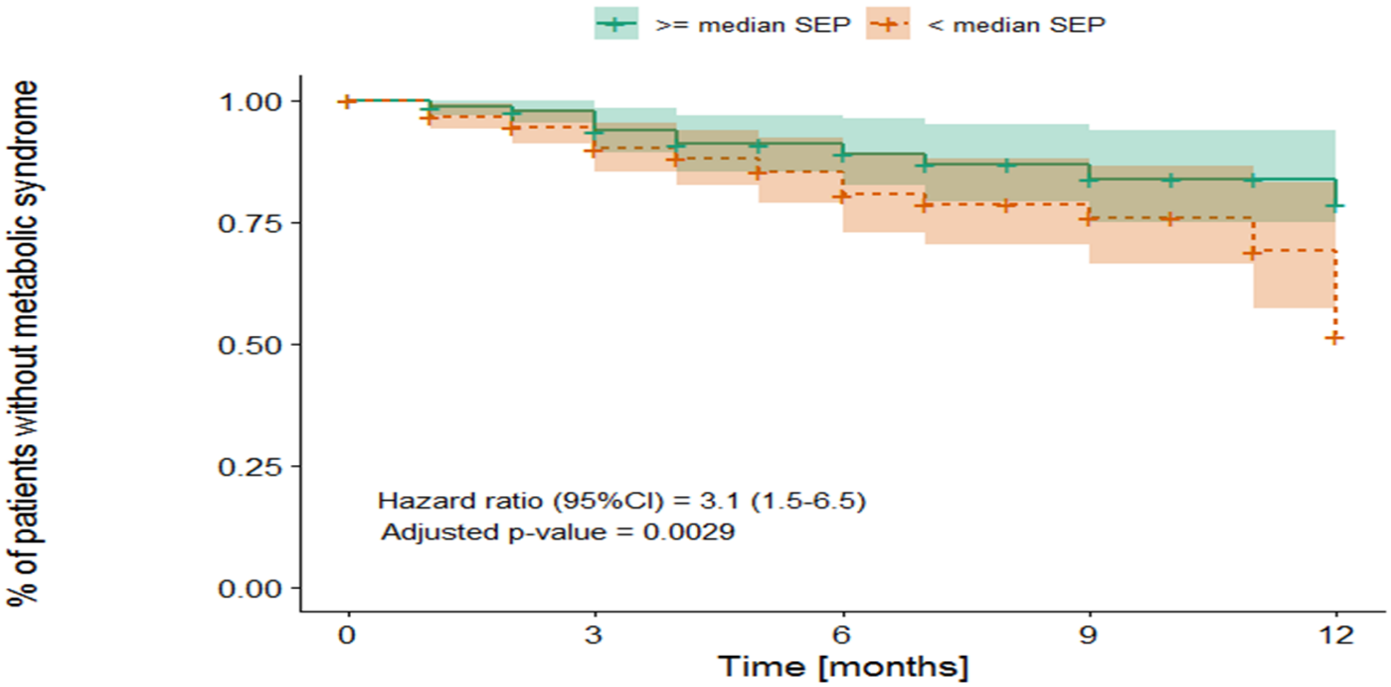




Panczak et al., Plos one, 2014

The SEP is associated with BMI, with all-cause mortality and some cause specific death (lung cancer, cardiovascular disease, traffic accidents, suicide…)

Dubath et al., Translational Psychiatry, 2021



3 fold increased risk of developing metabolic syndrome in patients with lower socio-economic positions

Incidence of new onset metabolic syndrome according to Swiss socio economic position over one year of psychotropic treatment in the adult population

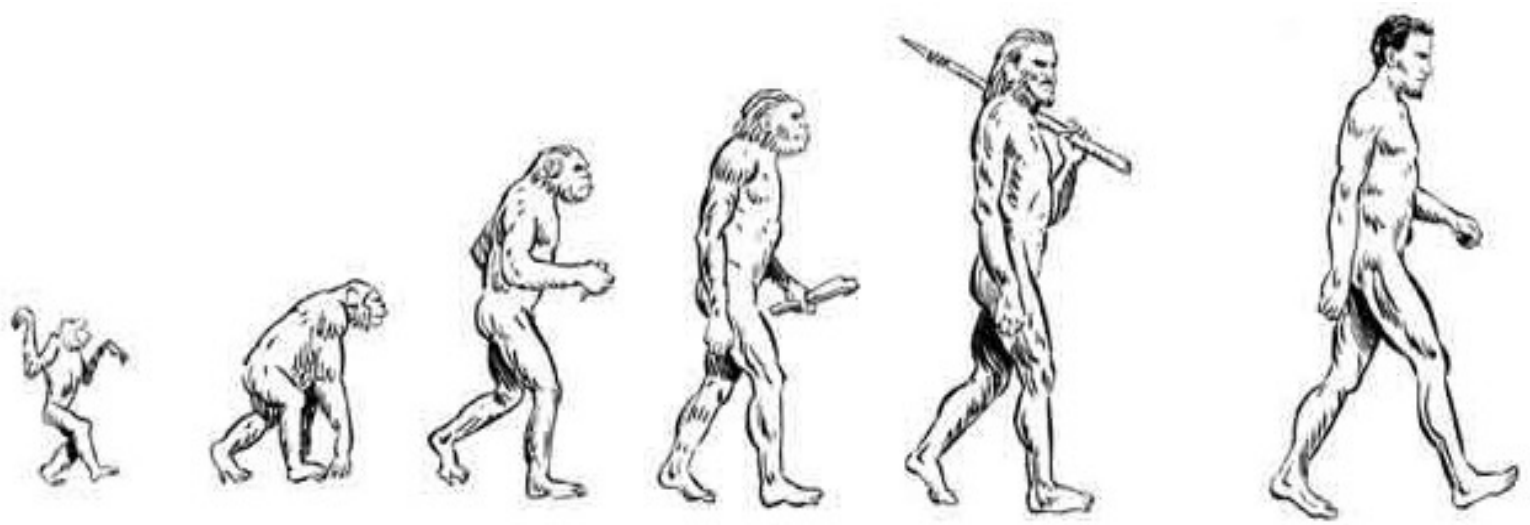
Mandelian Randomization in the UKBB (18,755 controls and 11,314 cases) demonstrated a causality of education on BMI

Weight, genetics and evolution

Multiple genes involved in hunger, satiety and energy homeostasy

After each spontaneous mutation in these genes, pressure of selection to keep these mutations if they lead to weight gain because they offer an advantage in the presence of energy restriction

Our genome inherited from our ancesters has been optimized for situations with calory restrictions !!



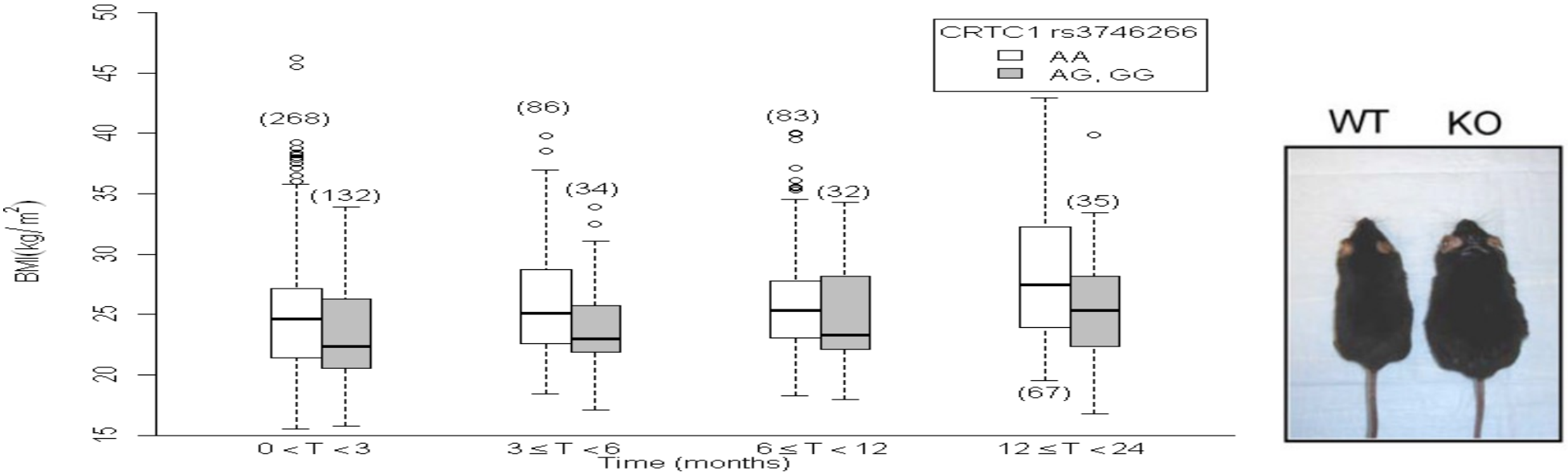
Problems of excess weight not limited to humans…

Time, June 2017

Original Investigation

Influence of *CRTC1* Polymorphisms on Body Mass Index and Fat Mass in Psychiatric Patients and the General Adult Population

Chong et al. JAMA Psychiatry 2013

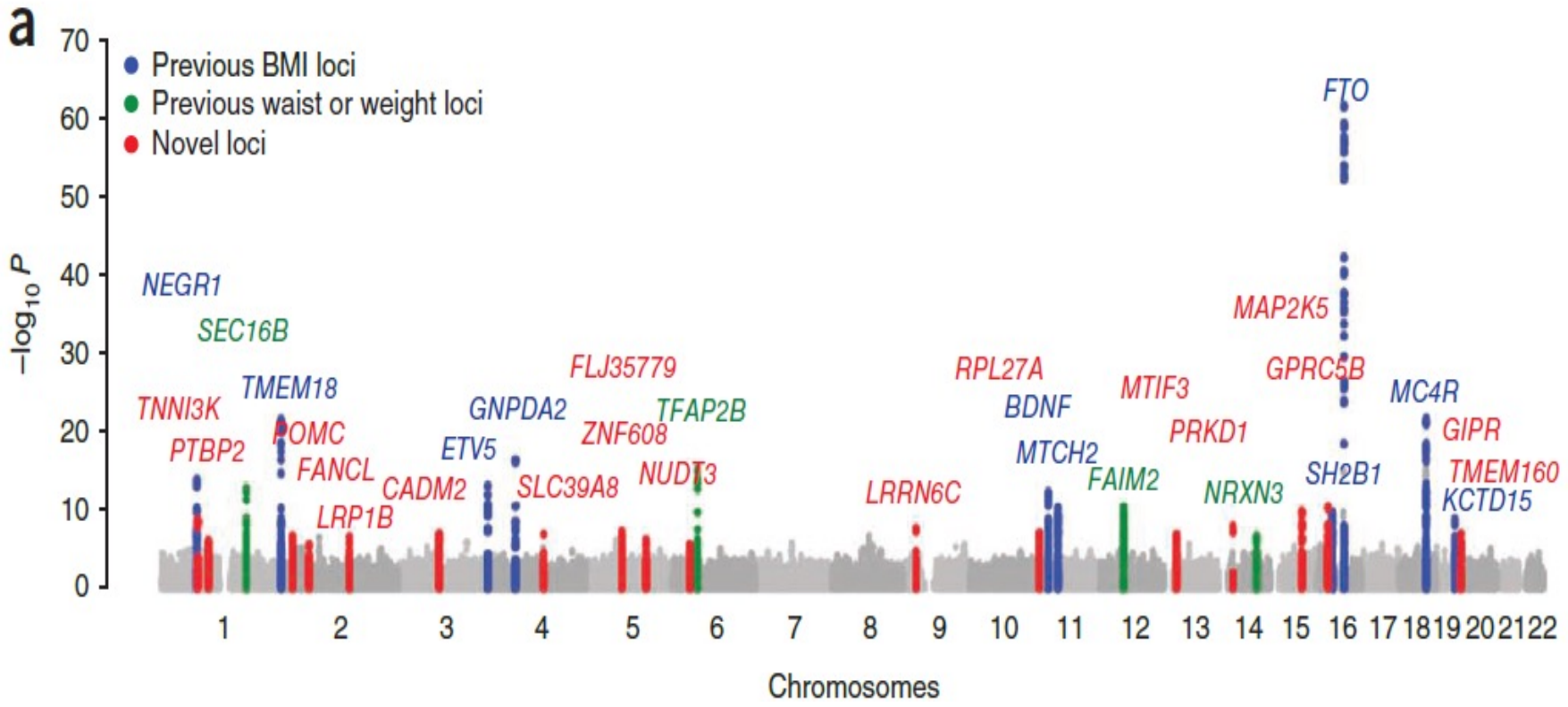


CRTC1: CREB regulated transcription co-activator 1: Transcriptional regulation factor involved in energy balance, obesity and comportment modifications in animal

CRTC1 knock – out mice has a depressive phenotype and is obese

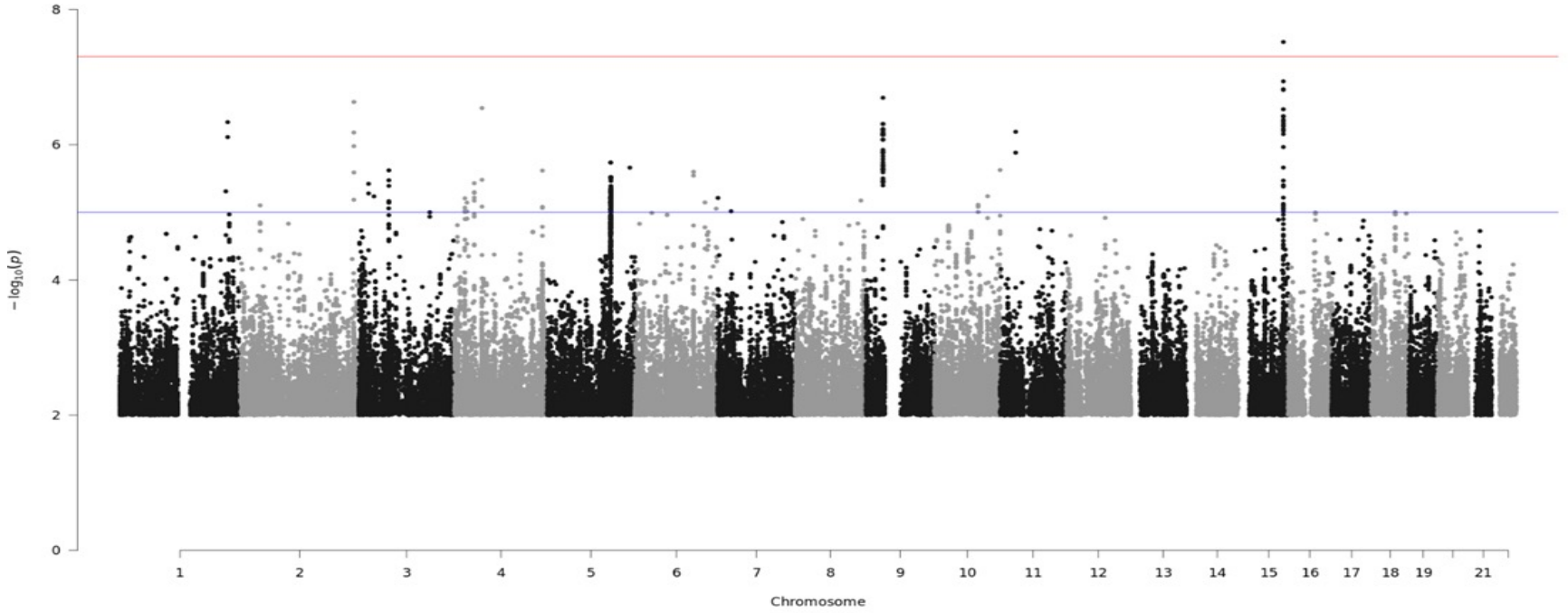
In humans treated with WG inducing drugs: strongest effect in premenopausal women: 3.9 BMI unit difference

Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index



Received 13 May; accepted 15 September; published online 10 October 2010; doi:10.1038/ng.686

GWAS with BMI slope (6 months) during treatment (n= 1135)



Identification of four novel loci associated with psychotropic drug-induced weight gain in a Swiss psychiatric longitudinal study: a GWAS analysis

- Association with proteins involved in the immune system, the transport of many molecules including glucose and sugar, associations with BMI, fasting glucose, T2D, hypertension in population based cohorts cohorts

J Sjaarda et al Molecular Psychiatry 2022

Psychotropic drug-induced **lipid disturbances:** a genome-wide association study in a Swiss psychiatric cohort (M Jan et al., in preparation)

Total N=824 with GWAS significant results with large size effects for specific drugs in small groups of patients (N<100)

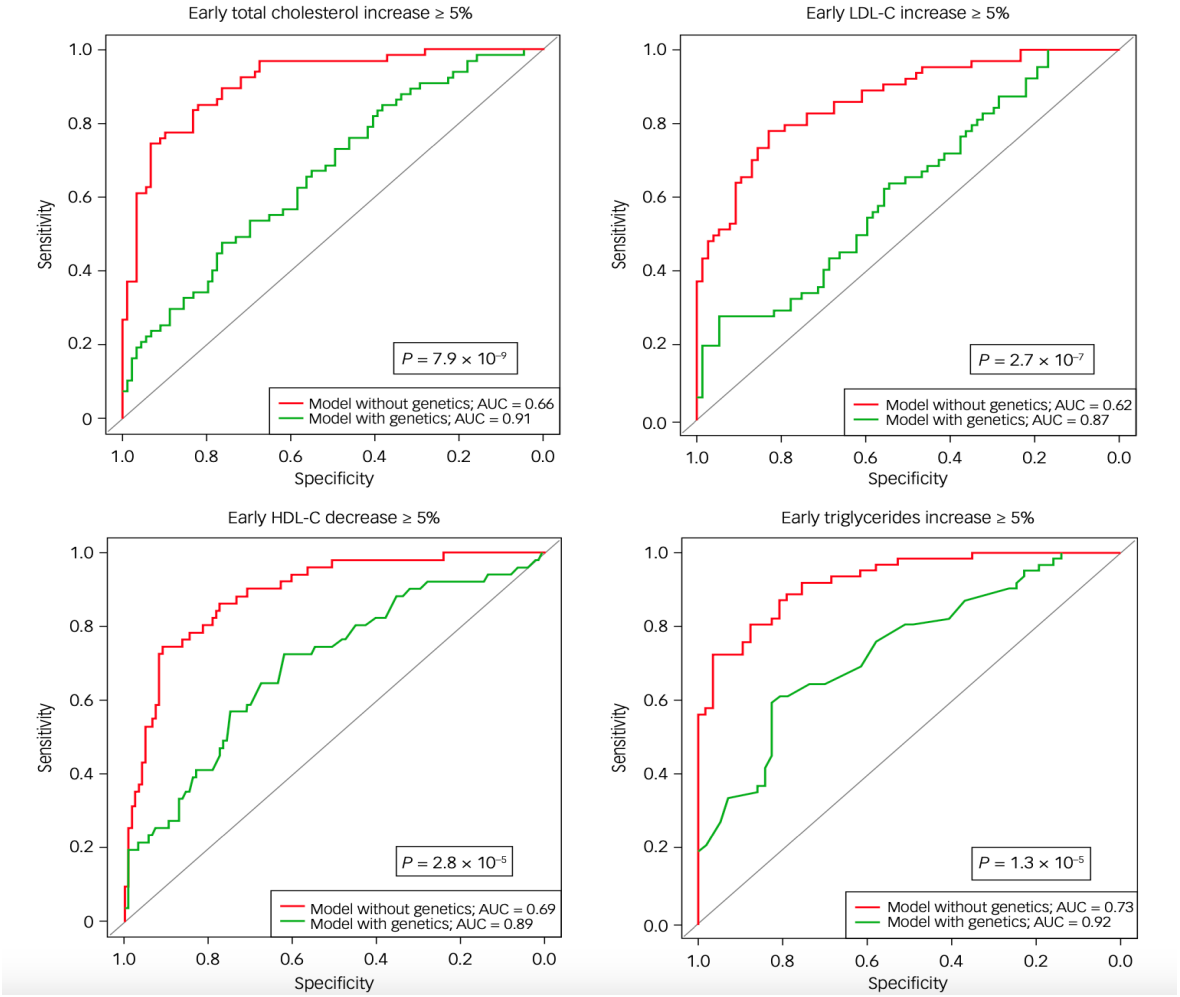


Fig. 1 Receiver operating characteristic curves for early worsening of lipid levels Delacretaz et al., Br J Psychiatry Open 2024.

RESEARCH Open Access

Psychotropic drug-induced genetic-epigenetic modulation of *CRTC1* gene is associated with early weight gain in a prospective study of psychiatric patients

Aurélie Delacrétaz[1], Anaïs Glatard[1], Céline Dubath[1], Mehdi Gholam-Rezaee[2], Jose Vicente Sanchez-Mut[3], Johannes Gräff[3], Armin von Gunten[4], Philippe Conus[5] and Chin B. Eap[1,6*]

Delacretaz et al., Clinical Epigenetics 2018

78 patients receiving psychotropic drugs that induce metabolic disturbances, with weight and other metabolic parameters monitored regularly. Methylation levels in 76 CRTC1 methylation sites were assessed before and after 1 month of psychotropic treatment in blood samples.

Significant methylation changes were observed in three CRTC1 CpG sites in patients with early and important weight gain (>=5% after 1 month; FDR corrected p value = 0.02).

Combining genetic and methylation data showed that cg12034943 was significantly associated with early weight gain in patients carrying the G allele of rs4808844A>G (p = 0.03), a SNP associated with this methylation site (p = 0.03).

RESEARCH Open Access

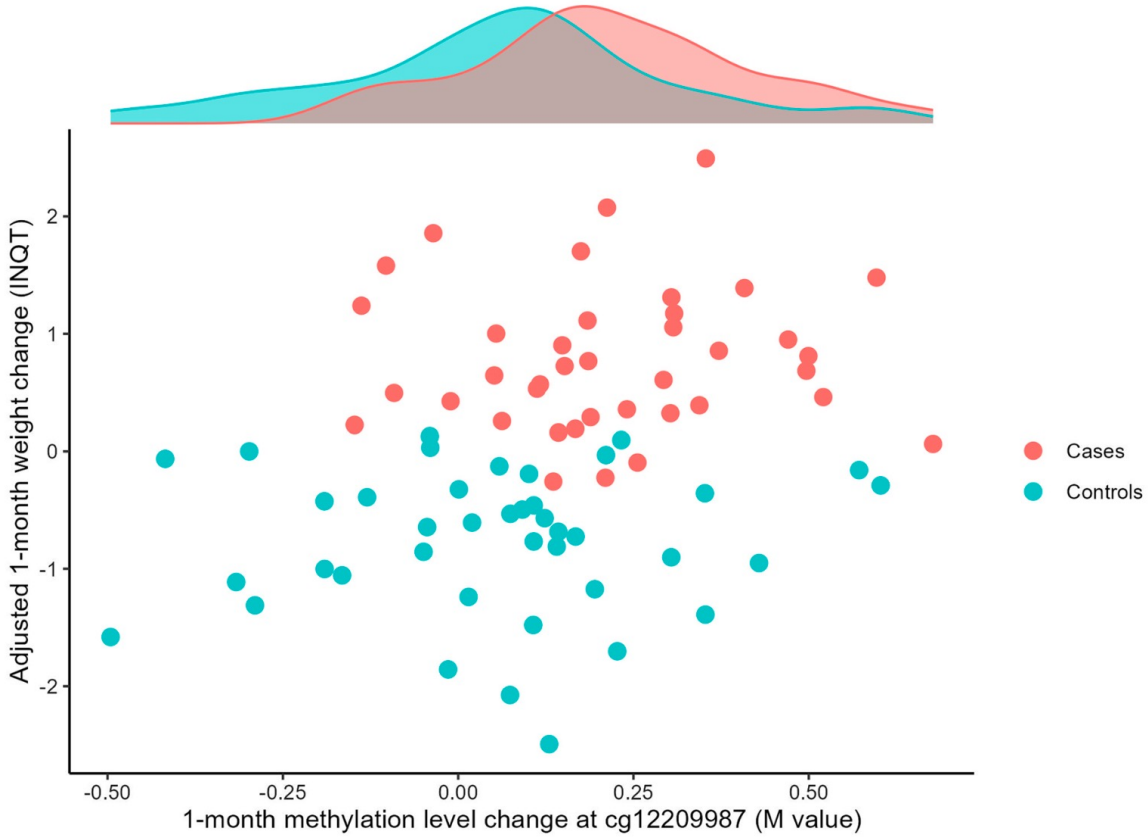
DNA methylation may partly explain psychotropic drug-induced metabolic side effects: results from a prospective 1-month observational study

Céline Dubath[1*], Eleonora Porcu[2,3,7], Aurélie Delacrétaz[1], Claire Grosu[1], Nermine Laaboub[1], Maria
Armin von Gunten[4], Philippe Conus[5], Kerstin Jessica Plessen[6], Zoltán Kutalik[2,7,8] and Chin Bin Eap

Epigenome-wide significant methylation changes ($p < 9 \times 10^{-8}$) at 52 loci.

In patients with important early weight gain cg12209987 showed a significant increase in methylation levels ($p= 3.8 \times 10^{-8}$), which was also associated with increased weight gain in the whole cohort.

Epigenome-wide DNA methylation measured at baseline and after 1 month of treatment in 79 patients (Dubath et al., Clin Epigenetics, 2024)



PLOS ONE

RESEARCH ARTICLE

Psychological trauma occurring during adolescence is associated with an increased risk of greater waist circumference in Early Psychosis patients treated with psychotropic medication

Luis Alameda[1,2,3,4¤a]*, Axel Levier[5¤b], Mehdi Gholam-Rezaee[6], Philippe Golay[2,7,8], Frederik Vandenberghe[5], Aurélie Delacretaz[5], Philipp Baumann[9], Anaïs Glatard[5], Céline Dubath[5], Andres Herane-Vives[10,11,12], Victoria Rodriguez[1], Alessandra Solida[2], Kim Q. Do[9], Chin B. Eap[5,13], Philippe Conus[2]

Body Mass Index, Weight Gain and Waist Circumference measured prospectively at baseline and after 1, 2, 3, 6 and 12 months of weight gain inducing psychotropic treatment.

113 early psychosis Patients classified as Early-Trauma and Late-Trauma if the exposure had occurred before age 12 or between ages 12 and 16 respectively

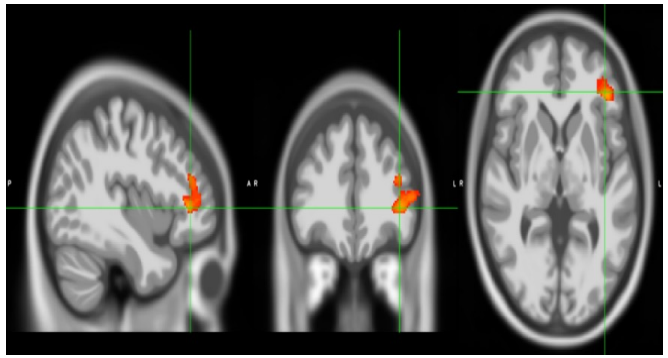
Late-Trauma patients, when compared to Non-Trauma patients showed greater WCs during the follow-up [p = 0.013].

Hypothesis: trauma occurring during adolescence may induce elevated levels of glucocorticoids which, combined with inhibition of sex steroids, would lead to increased fat accumulation in visceral adipose tissue, contributing to a greater waist circumference

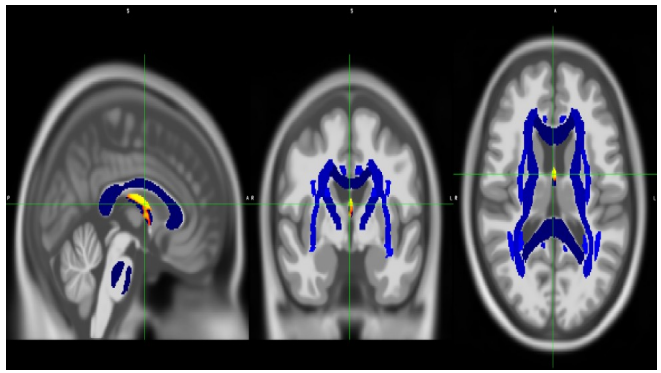
Brain regions are associated with weight gain variation induced by psychotropic drugs (Grosu et al., Translational Psychiatry 2024)

Study of structural and white matter microstructures in patients with weight-gain (> 5%, N=19) the first month of treatment and in patients with stable weight (N=22).

Grey Matter Volume : Frontal Lobe



Generalized Fractional Anisotropy : Fornix



Frontal lobe: part of the reward system and part of the fronto-striatal network linked to impulsivity.

Fornix: connection to structures involved in homeostatic and reward system, related to food intake.

In the weight-gain group, reduction of:

Cluster of grey matter in the frontal lobe (p-corrected=0.007)

Cluster of generalized fractional anisotropy in the fornix (p-corrected=0.004)

Weight gain is associated with a poorer control of impulsivity (PANSS G14 score, p=0.02).

Weight gain variation in psychiatric patients after the introduction of psychotropic drugs is associated with impulsivity and with structural and white matter microstructures differences in the brain.

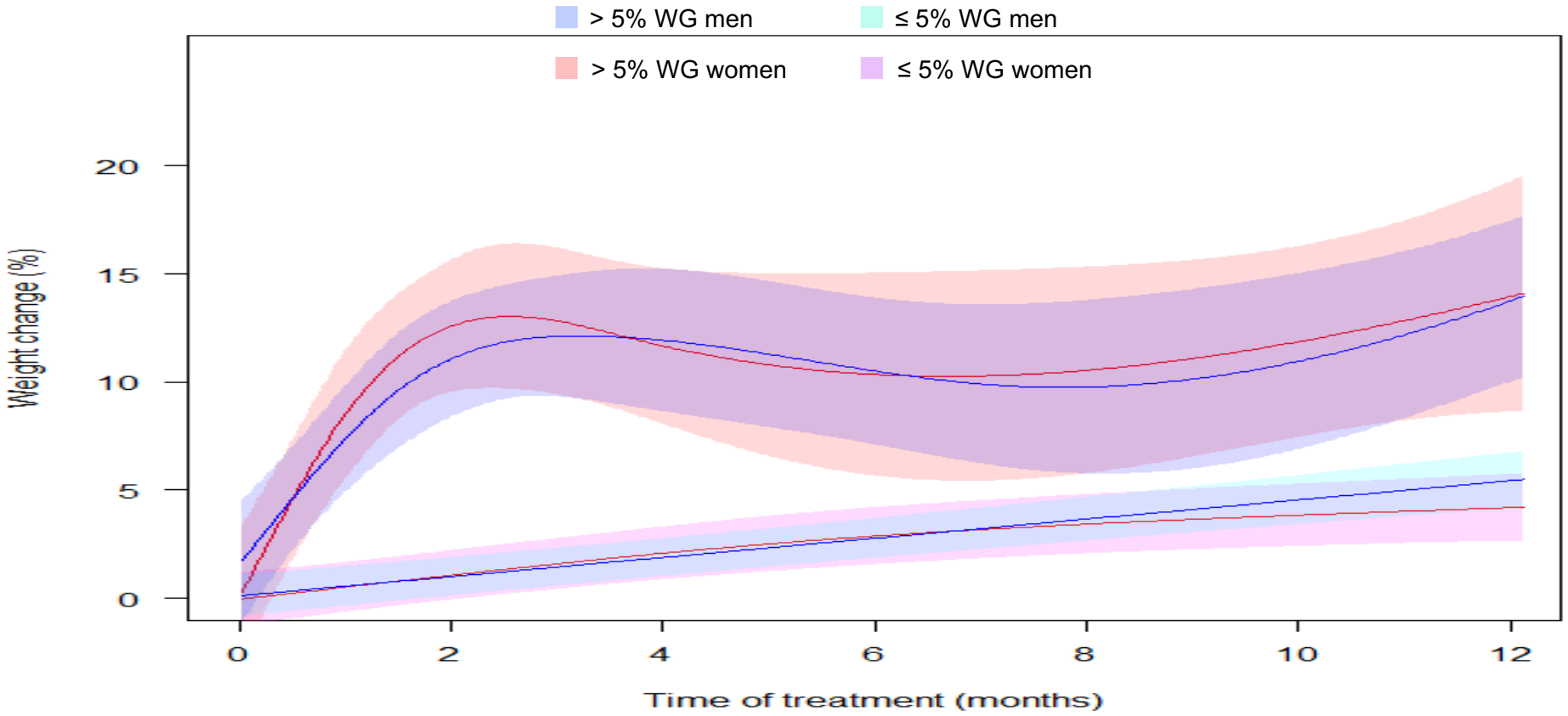
Gut microbiome as a mediator of antipsychotics metabolic side effects

Ridaura, V. K., et al. (2013). Science.
Stenman, L. K., et al. (2016). Benef Microbes.
Tang, W. H., et al. (2017). Circ Res.

Dubath et al., paper in preparation

>5% weight gain at one month (Vandenberghe et al., J Clin Psy 2015)

Best predictor for an important weight gain (>15% at 3 months, >20% at one year)



Increase of lipids >5% as a predictive marker for the development of dyslipidemia (n = 181)

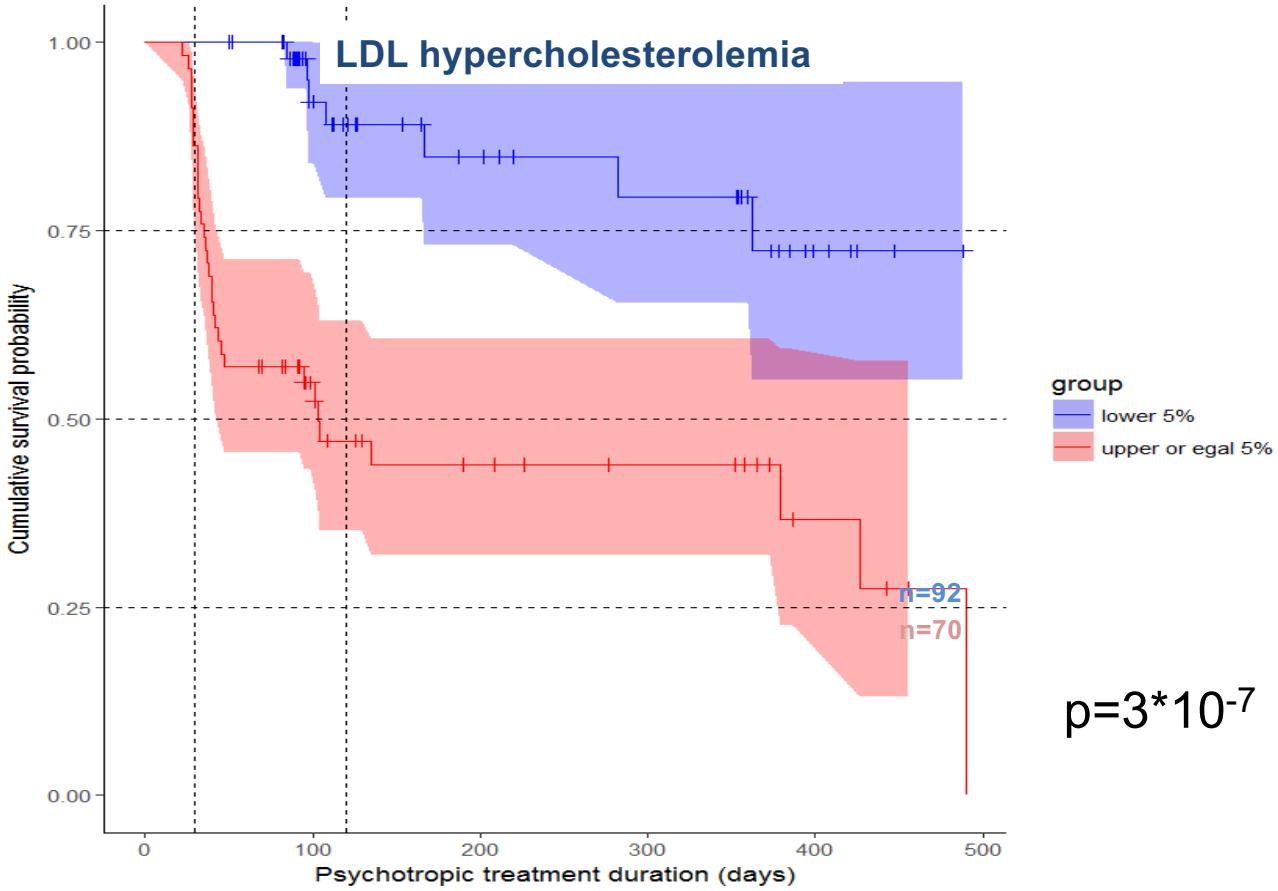
Thresholds at 1 month

Increase >=5%:
TC, LDL-C, TG
Non-HDL-C

Decrease >=5%
HDL-C

For predicting dyslipidemia at 3 months or at a later stage

Sensitivity: 70%–100%
Specificity 53%–72%



$p=3*10^{-7}$

Delacretaz et al, J Clin Lipidology, 2018

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Monitoring during treatment with psychotropic drugs at risks

CHUV

		Personal / Family history (a)	Weight (BMI)	Waist circumference	Blood Pressure	Fasting plasma glucose	Fasting Lipid profile (b)
1st year	Baseline	X	X	X	X	X	X
	1 month		X				X
	3 months		X		X	X	X
Quarterly			X				
Annually		X		X	X	X	X

(a) Obesity, diabetes, dyslipidemia, hypertension or cardiovascular problems, smoking

(d): Total cholesterol, HDL, LDL, triglycerides

1) De Hert et al., European Psychiatry 24 (2009) 412–424.
2) Diabetes Care, Vol 27/2 : 596-601, February 2004

Development and external validation of the Psychosis Metabolic Risk Calculator (PsyMetRiC): a cardiometabolic risk prediction algorithm for young people with psychosis

Benjamin I Perry, Emanuele F Osimo, Rachel Upthegrove, Pavan K Mallikarjun, Jessica Yorke, Jan Stochl, Jesus Perez, Stan Zammit, Oliver Howes, Peter B Jones, Golam M Khandaker

The Lancet Psychiatry 2021

The Psychosis Metabolic Risk Calculator (PsyMetRiC) developed to predict up to 6-year risk of incident metabolic syndrome in young people (aged 16–35 years) with psychosis from commonly recorded information at baseline (age, sex, ethnicity, body-mass index, smoking status, prescription of a metabolically active antipsychotic medication, HDL concentration, and triglyceride concentration)

The psychosis metabolic risk calculator (PsyMetRiC) for young people with psychosis: International external validation and site-specific recalibration in two independent European samples

Benjamin I. Perry,[a,b,1]* Frederik Vandenberghe,[c,1]*** Nathalia Garrido-Torres,[d,1] Emanuele F. Osimo,[a,b,e] Marianna Piras,[c] Javier Vazquez-Bourgon,[d,f]** Rachel Upthegrove,[g,h] Claire Grosu,[c] Victor Ortiz-Garcia De La Foz,[f] Peter B. Jones,[a,b] Nermine Laaboub,[c] Miguel Ruiz-Veguilla,[d] Jan Stochl,[a] Celine Dubath,[c] Manuel Canal-Rivero,[d] Pavan Mallikarjun,[g] Aurélie Reymond-Delacrétaz,[c] Nicolas Ansermot,[c] Emilio Fernandez-Egea,[a,b] Severine Crettol,[c] Franziska Gamma,[i] Kerstin J. Plessen,[j] Philippe Conus,[k] Golam M. Khandaker,[a,l,m,1] Graham K. Murray,[a,b,1] Chin B. Eap,[c,n,o,p,1] and Benedicto Crespo-Facorro [d,1]

The Lancet Regional Health – Europe 2022

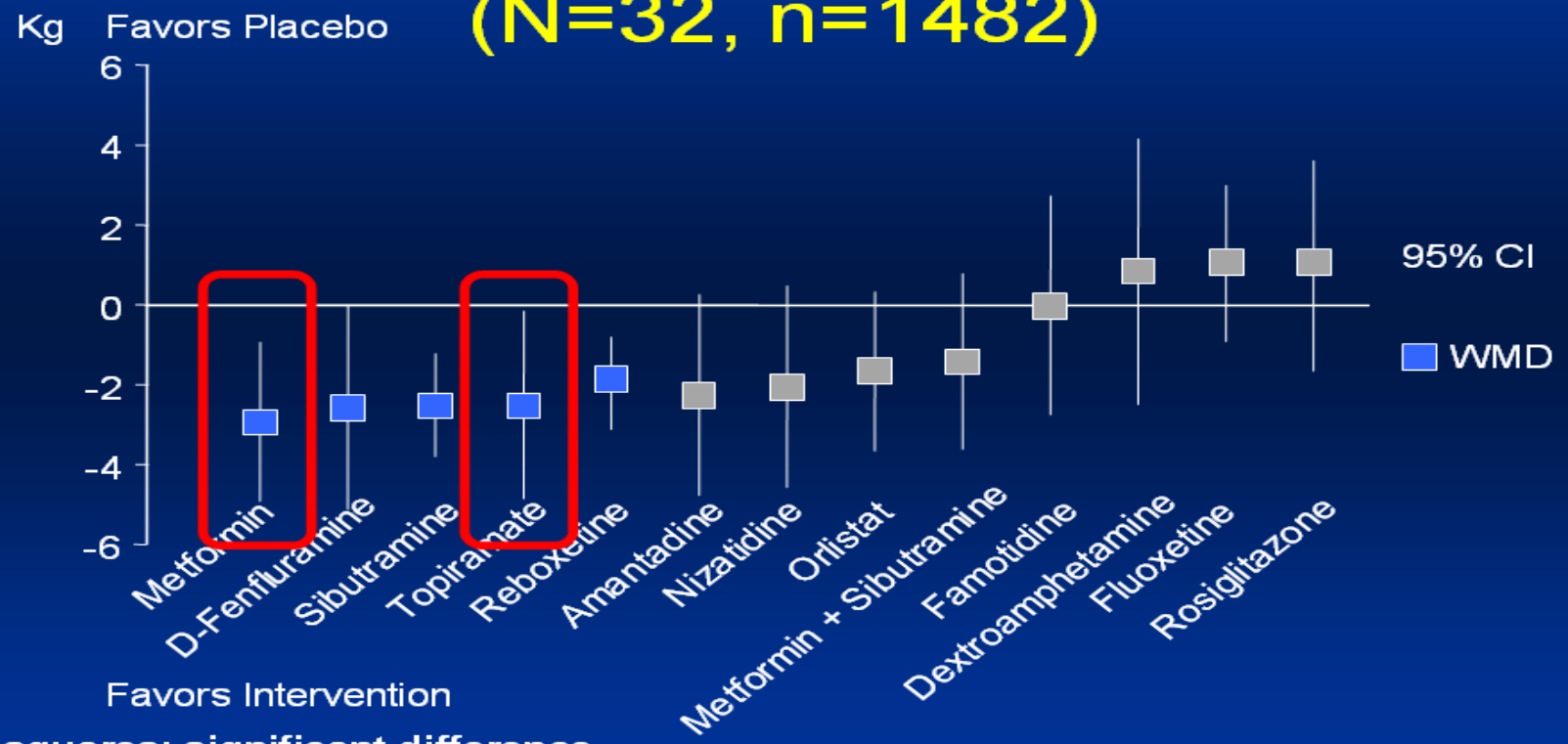
CLINICAL TAKE HOME MESSAGES (1)

- Metabolic risk to take into account, especially for the choice of the drug
- Identification of patients at risk (young patients, low BMI, non-Caucasian, first episode …)
- Web-applications to identify patients at risks helpful
- Need to monitor metabolic parameters
- Life-style intervention (diet, physical activity), necessary but not very effective if prescription of high risk drugs
- Thresholds at one month indicating higher risks of important WG and dyslipidemia:
  - **>5%** of weight gain
  - **>5%** of lipid increases (TC, LDL, non-HDL, triglycerides)
  - **>5%** decreases (HDL)

CLINICAL TAKE HOME MESSAGES (2)

- If threshold > 5%, evaluate the risk/benefit ratio of maintaining or switching the drug
- Act rapidly (less difficult not to gain weight than to lose weight, less difficult not to increase lipid levels than to decrease lipid levels)
- If necessary, combine with other drugs to reduce the metabolic risk
- Future: genetics factors useful for prediction of dyslipidemia induced by psychotropic drugs ?? (not for weight gain)

Pharmacologic Weight Loss (kg) Compared to Placebo in Antipsychotic-treated Patients (N=32, n=1482)



Blue squares: significant difference

Maayan L, Vakhrusheva J, Correll CU. Neuropsychopharmacology. 2010 Jun;35:1520-30.

With the collaboration of:

Profs P Conus, A von Gunten, J Plessen

MD: F Gamma

Post-docs: Drs F Vandenberghe, A Glatard, A Delacretaz, C Dubath, E Choong, J Sjaarda and many others

Statisticians: Dr M Gholam-Rezaee, Dr S Ranjbar

PhD students M Piras, C Grosu, N Laaboub and many others

The staff of the UPPC, the medical staff who participated in the inclusion process and participants of PsyMetab and PsyClin