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Pouvoir prédictif de la prise de poids précoce sur la prise de poids ultérieure et le syndrome métabolique chez les patients déprimés traités par antidépresseurs : résultats de la cohorte METADAP

Khalil El Asmar

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**Predictive power of early weight-gain on later weight-gain
and metabolic syndrome in depressed patients treated with
antidepressants: findings from the METADAP cohort**

Thèse de doctorat de l'Université Paris-Saclay
préparée à Université Paris-Sud

École doctorale n°570

Spécialité de doctorat: Santé publique - Recherche clinique

Thèse présentée et soutenue à Le Kremlin Bicêtre, le 12 Décembre 2018, par

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Dedications

I would like to dedicate this work to all those who supported me and encouraged me throughout this exciting journey. A special thanks go to my father who has seen the importance of quality education since I was a child. I hope I made you proud.

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Acronyms

AD	Antidepressant
AUC	Area Under the Curve
BP	Blood Pressure
CFA	Confirmatory Factor Analysis
CGI	Clinical Global Impression
CI	Confidence Interval
DALY	Disability Adjusted Life Years
FPG	Fasting Plasma Glucose
GBD	Global Burden of Disease
HDL-C	High Density Lipoprotein Cholesterol
HDRS	Hamilton Depression Rating Scale
IFD	International Federation of Diabetes
IHD	Ischemic Heart Disease
IRR	Incidence Risk Ratio
LDL	Low Density Lipoprotein Cholesterol
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
METS	Metabolic Syndrome
OR	Odds Ratio
ROC	Receiver Operating Characteristic
SEM	Structural equation Modeling
SNRI	Serotonin Norepinepherin Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
WC	Waist Circumference
WHO	World Health Organization
TCA	Tricyclic Antidepressants
TG	Triglycerides

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I. Introduction

1. Motivation for this work

The decision to focus on psychiatric research in general and on major depressive disorders (MDD) in particular had been a major career goal since I completed my graduate studies. From its early onset, my research work was undertaken with the hope of bringing some novelty albeit modest, to the psychiatric research field. Since doctoral studies and academic research offer the optimal environment to experiment novel approaches and challenge existing paradigms, it was decided to study the impact of AD on weight gain and subsequently on metabolic syndrome (MetS) from various statistical and methodological angles. In the following section I will present an overview of the project on which my dissertation work is based, the clinical scope of my research and the 2 different statistical approaches used to address the clinical research question at hand.

Project

METADAP is a 6-month prospective, multi-centric, real-world treatment study, assessing metabolic syndromes before and after antidepressant treatment in MDD patients with a current MDE. Data were collected between November 2008 and March 2013 from six university psychiatry departments which are referral centers for MDE in France. MDE patients were enrolled and assessed at the beginning of an index antidepressant prescription, one, three and six months later for depression and MetS and its five components. METADAP collected a wide array of clinical, genetic as well as metabolomics and proteomics data; however, the dissertation work is only concerned with the clinical component. The study was funded by the Programme Hospitalier de Recherche Clinique from the French Ministry of Health (AOM06022).

Patients

Consecutive in- or out-patients, aged 18 to 65 years, with research-confirmed diagnosis of current MDE in a context of MDD based on the Mini International Neuropsychiatric Interview (MINI), with a minimum depression score of 18 on the 17-item Hamilton Depression Rating Scale (HDRS) (10) and requiring a first or different antidepressant treatment were included. No wash-out period was required. Patients with MDE with psychotic symptoms, bipolar disorders, psychotic disorders,

eating disorders, current substance abuse or dependence (DSM-IV-TR), pregnancy, breast feeding, organic brain syndromes or severe unstable medical conditions were not included. Patients receiving antipsychotics or mood stabilizers during the month preceding inclusion and/or for 4 months or more during the last year preceding inclusion were not included. Antipsychotics, mood stabilizers, stimulants were not permitted during the study because of their metabolic effects. Benzodiazepines at the minimum effective dose and for the minimum duration and psychotherapies were tolerated. After complete description of the study to the subjects, written informed consent was obtained. Interviews and diagnostic assignments were reviewed by a senior psychiatrist, independently from the treating psychiatrist. The index antidepressant treatment had to belong to one of the four following classes: Selective Serotonin Reuptake Inhibitors (SSRI), Serotonin Norepinephrine Reuptake Inhibitors (SNRI), Tricyclic Antidepressants (TCA) and other antidepressant treatments (Others). A monotherapy of antidepressant was required. The drug and its dose were left to the treating psychiatrist, using “real world” treatment options. When antidepressant treatment was changed, patients dropped out from the study. Re-inclusion was permitted by the protocol at any time after drop-out.

Clinical scope

A recent publication in the Lancet Psychiatry (Vigo, et al., 2016) placed mental illness a distant first in global burden of disease (GBD) in terms of years lived with disability (YLDs), and level with cardiovascular diseases in terms of disability-adjusted life-years (DALYs). Major depressive disorder (MDD) ranked second in the 2013 GBD in terms of YLDs. In a context of increasing prescription of antidepressant medication and weight gain induced by antidepressants, the impact of weight gain and specifically early weight gain on subsequent MetS and later weight gain has to be studied. Based on the above, researching the association between the 2 illnesses with highest GBD is of paramount importance from a public health and a clinical perspective. Indeed, there has been no prospective study of reasonable sample size and duration, addressing potential changes in the metabolic profile of MDD patients treated with antidepressants. The dissertation was set out to provide empirical evidence that: (i) MDD treatment increases the risk of MetS; (ii) early weight gain of 3%-5% would significantly increase the risk of MetS incidence; (iii) early weight gain

(3%-5%) would significantly increase the risk of later weight gain (15%-20%). The results of this work aim to impact clinical practice and alert physicians and nurses on the importance of early weight monitoring specially for patients who seem to gain weight during the first 30 days of treatment.

Statistical and methodological approach

Longitudinal data with repeated measures - like METADAP - are best analyzed using mixed models or repeated measures ANOVA. These classical statistical approaches tend to assess only direct associations between variables, but are less robust in assessing and understanding indirect effects such as mediation. Potential causal pathways and multidirectional effects are better unearthed using structural equation modeling (SEM). In conditions such as depression and MetS where the origins of the illness are complex, SEM can deconstruct effects of several variables in relation to one another in terms of indirect, direct and total effects. SEM generates models for evaluating and estimating simultaneous causal relationships between observed and latent variables (Kerkhof et al, 2011; Mi et al, 2011; Nock et al, 2009; Kline et al, 2005). In comparison with classical regression models, SEM is a more theoretically- driven approach that may allow for a more accurate representation of the true variability in MetS. In the dissertation, both, traditional regression methods and SEM were used to answer the same research question of whether early weight gain increases the risk of MetS. While the first approach considered MetS as the outcome and early weight gain as the main risk factor and only estimated direct effects for the association between MetS and weight gain; the latter approach (i.e SEM) investigated whether MetS was mediated by early weight gain or was directly affected by response to treatment, AD treatment and other clinical variables.

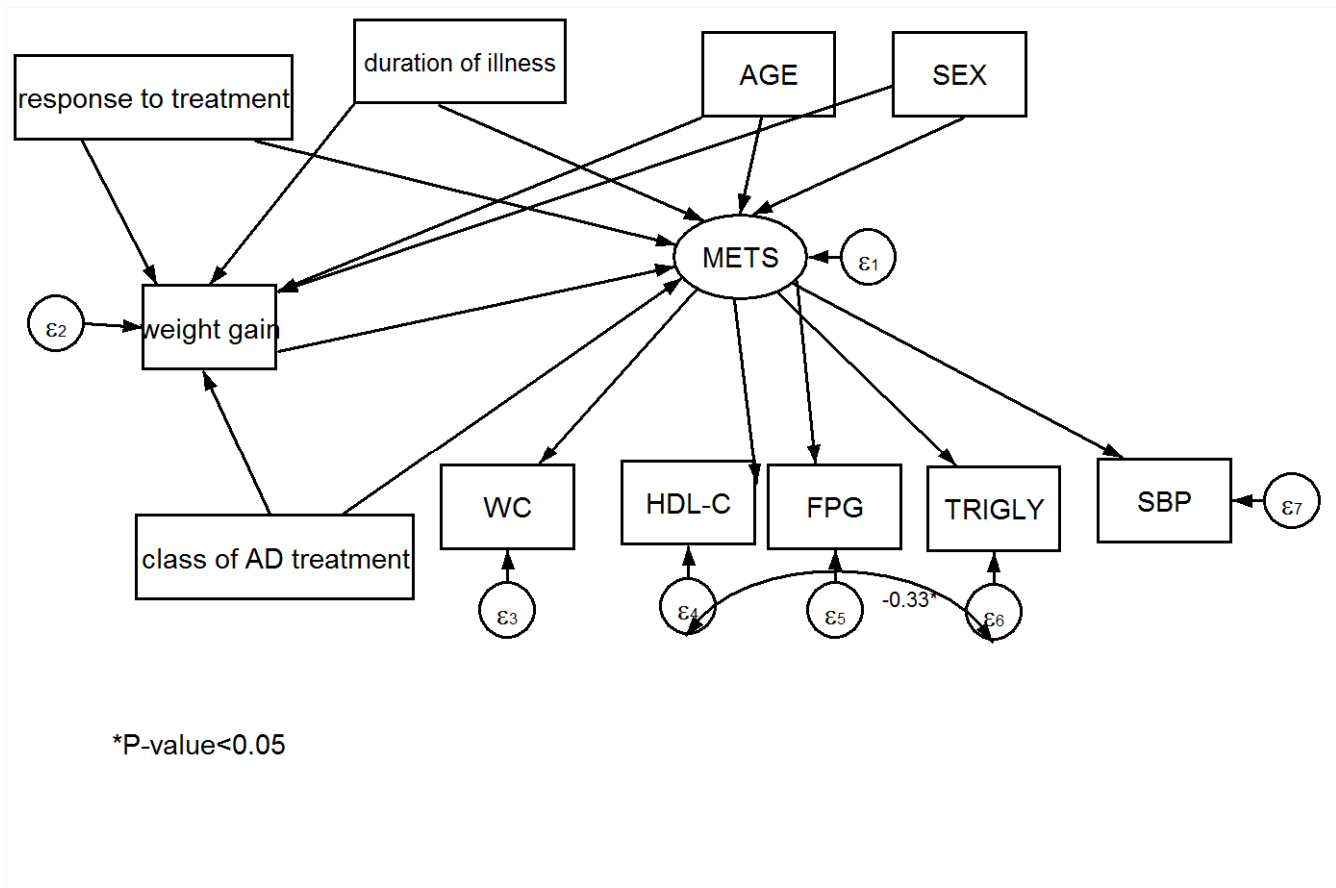


Figure 1: SEM of the relationship between MetS, early weight gain, AD treatment and other clinical variables

2. Major depressive disorders: Public health significance

The World Health Organization (WHO) defines mental health as “the state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community” (WHO, accessed 2018). However, it is estimated that that this “state” is disrupted in one of every three individuals during their lifespan (Ginn et al., 2012; Steel et al., 2014). In a recent publication estimating the true global burden of mental illness, Vigo et al., (2016) have estimated that the global burden for mental illness accounts for 32.4% of YLDs and 13.0% of DALYs. These estimates place mental illness first in GBD in terms of YLDs and at par with CVD in terms of DALYs. The magnitude of mental illness has been emphasized by studies on GBD (Lopez et al., 1998).

However, despite all the evidence about the negative human, social and economical effect of this illness, policy makers have failed to prioritize health care for people living with mental illness (Bloom et al., 2011; Saxena et al., 2007). The epidemiological and demographic transitions have lead to an increase in global population size who will live longer. However, they will do with a greater morbidity and disability (Lozano, et al., 2012; Atun, 2015). Through their direct and indirect effects, mental illnesses are considered as a major cause of the growth of global disability and morbidity (Prince et al., 2007). Among the 5 types of mental illness that rank in the top 20 causes of GBD, major depression disorder ranks second over all. According to the World Health Organization, more than 300 million people globally suffer form depression and is more prevalent among women then men. It is the leading cause of disability world wide, and a major cause of suicide. Suicide is the second leading cause of death in young people, with an estimated figure of 800,000 dying every year from suicide (WHO, accessed 2018). In addition to its direct burden, depression is also a major contributor to cardiovascular disease, which in its turn rank first in terms of GBD. An assessment of the contribution of MDD to the global burden of ischemic heart disease, reported that major depression is responsible for approximately 3% of global IHD DALYs (Charlson et al., 2013)

3. Depression, antidepressants and weight gain

Major Depressive Disorder (MDD) is among the diseases that has the greatest impact worldwide on public health (Vigo et al., 2016). It confers a 50% increased mortality of somatic causes (Vos et al., 2012). Antidepressant drugs are the main treatment for Major Depressive Episodes (MDE) in patients with MDD even though antidepressants (AD) use – even newer generations - can induce weight gain (Carvalho et al., 2016). The literature presents ample evidence about the association between AD treatment and weight gain. A recent cross- sectional survey without control group on 362 psychiatric patients taking AD for a period ranging from 6 to 36 months found that citalopram, escitalopram, sertraline, paroxetine, venlafaxine, duloxetine and mirtazapine, were associated with significant weight gain (Uguz et al. 2015). Blumenthal et al (2014) have also investigated health records of 22,610 adult patients (out of whom 3366 served as control group) to estimate weight gain associated with specific antidepressants over the 12 months following initial

prescription study and concluded that antidepressants differed slightly in their contribution to weight gain (Blumenthal et al., 2014). In their meta-analysis, Serretti et al, evaluated short-term weight change after AD treatment. Mirtazapine, Amitriptyline, and paroxetine were associated with a greater risk of weight gain. Weight loss occurred with fluoxetine and bupropion, with the effect of fluoxetine appears to be limited to the acute phase of treatment (Serretti et al, 2010).

Table 1 summarizes the clinical studies assessing the effects of AD on weight gain. A 4-year prospective cohort by Kivimaki et al (2010) on 5537 working Finnish men and women, reported an average weight gain of 1.4 kg (2.5%) in the control group and 2.5 kg (4.3%) among users of 200 defined daily doses of SSRI and TCA. Another longitudinal study with no control group based on the Canadian National Health Survey, Paten et al., (2009) found that SSRIs and venlafaxine (SNRI) were associated with significant weight gain. During a 1-year placebo controlled trial of fluoxetine treatment, Michelson et al. (1999) reported significant increase in body weight. In a pooled analysis of 9 randomized controlled trials comprising 1485 patients, 4.9% of those with a current MDE in the context of MDD and with an acute treatment with tricyclic drugs significantly gained more than 7% of their initial weight in the first 6 to 8 weeks (Sussman and Bikoff, 2001). Furthermore, a high prevalence of obesity is reported in psychiatric populations, especially those with MDD (De Hert et al., 2009). It has been reported that obesity leads to a reduced life expectancy of psychiatric patients in comparison to the general population, by almost 20 years (Newcomer, 2007).

The Joint Statement of The European Psychiatric Association, The European Society of Cardiology and the European Association for the Study of Diabetes defines a weight gain of 7% or more in the first six weeks of treatment as clinically significant. The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes Guidelines considers a weight gain of >5% a sign to reconsider the treatment, however unlike the latter study, the guideline did not define minimum time duration. Unlike antipsychotics, there are no specific guidelines for antidepressant treatments.

A recent study (Vandenberghe et al., 2015) has shown that early weight gain (>5%), after one month of treatment, with various psychotropic medications, and various diagnoses in a real world setting, is the best predictor for significant weight gain (>15%) in the long term (after one year).

Two other studies (Hoffman et al., 2010; Lipkovich et al., 2008), based on post hoc analyses from clinical trials, have also assessed the predictive value of early weight gain among patients with schizophrenia treated with Olanzapine, Ziprasidone or Aripiprazole. The two studies (Hoffman et al., 2010; Lipkovich et al., 2006) found a 2 kg increase after one month was a good predictor for a 10 kg increase after six months.

Table 1: Clinical studies on the effects of antidepressant treatment on weight gain

Title of the study	Author	Year	Significance	Sample size/ FU period
Major depression, antidepressant medication and the risk of obesity	Patten et al.	2009	SSRI and venlafaxine were significantly associated with obesity. There was no significant association between TCA or antipsychotic medications with obesity	NHPS sample (1994–2004) n=17276
MetS abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use	Van Reedt Dortland, et al.	2010	TCA increased the odds of MetS	n=2981
Long-term weight gain in patients treated with open-label olanzapine in combination with fluoxetine for major depressive disorder	Andersen et al.	2005	Patients were treated with a combination of olanzapine and fluoxetine (OFC). Increases in fluoxetine dose were predictors of weight gain. Long-term (76 weeks) OFC treatment may lead to a large percentage (56%) of patient meeting the criteria for significant weight gain (47%)	n=549
Real-world data on SSRI antidepressant side effects	Cascade et al.	2009	36% of patients experienced side effects associated with SSRI. Forty-nine patients had weight gain	n=700
A naturalistic long-term comparison study of selective serotonin reuptake inhibitors in the treatment of panic disorder	Dannon et al.	2007	Weight gain Paroxetine: 8.2 ± 5.4 kg Fluoxetine: 5.2 ± 4.4 kg Citalopram: 6.9 ± 5.7 kg Fluvoxamine: 6.3 ± 4.2 kg	Duration: 1 year n=200
Changes in weight during a 1-year trial of fluoxetine	Michelson et al.	1999	12-Week treatment: -0.35 kg 50-Week treatment: +3 kg	Duration: 50 weeks n=395

<p>Changes in body weight during treatment with the new antidepressant Nefazodone, three SSRIs Fluoxetine, Setraline, Paroxetine, and the tricyclic Imipramine.</p>	<p>Sussman et al.</p>	<p>2001</p>	<p>Significant weight loss or gain was, respectively, defined as ≤ 7 and $\geq 7\%$ change in body weight from baseline.</p> <p><u>Study 1</u> <i>Acute phase trial</i> SSRI: 4.3% of treated patients lost weight at any point Nefazodone: 1.7% of treated patients lost weight at any point <i>Long-term phase trial</i> SSRI: 17.9% of treated patients had weight gain Nefazodone: 8.3% of treated patients had weight gain</p> <p><u>Study 2</u> <i>Acute phase trial</i> Imipramine: 4.9% of treated patients had weight gain Nefazodone: 0.9% of treated had weight gain <i>Long-term phase trial</i> Imipramine: 24.5% of treated patients had weight gain Nefazodone: 9.5% of treated patients had weight gain</p>	<p>Study 1 Acute phase trial: 6–8 weeks n=1036 Long-term phase trial: 16–46 weeks n=608</p> <p>Study 2 Acute phase trial: 6–8 weeks n=1036 Long-term phase trial: 16–46 weeks n=135</p>
<p>Weight gain: a side effect of TCA</p>	<p>Berken et al.</p>	<p>1984</p>	<p>TCA antidepressants: Amitriptyline, nortriptyline, and imipramine induced weight gain of 1.3 -2.9 lbs per month, and weight increased linearly over time.</p>	<p>n = 40 Average of 6-months treatment</p>
<p>Body weight gain during nortriptyline (TCA) or escitalopram (SSRI) treatment</p>	<p>Uher et al.</p>	<p>2011</p>	<p>Nortriptyline First 12 weeks: +1.22 kg, BMI score increase of 0.44 After 6 months: +1.82 kg, BMI score increase of 0.64 Escitalopram First 12 weeks: +0.14 kg, BMI score increase of 0.05 6 Months: +0.34 kg, BMI score increase of 0.12</p>	<p>n = 630 12 weeks and 6 months of treatment</p>
<p>AD medication use, weight gain, and risk of type 2 diabetes. A population based study.</p>	<p>Kivimäki et al.</p>	<p>2010</p>	<p>Average weight gain of 1.4 kg (2.5%) in the control group and 2.5 kg (4.3%) among users of 200 defined daily doses of antidepressant</p>	<p>n = 5537 4 years</p>

4. Depression, antidepressants and metabolic syndrome

Metabolic syndrome (MetS), a cluster of risk factors for cardio-vascular diseases and type 2 diabetes mellitus, includes increased waist circumference (WC), high blood pressure (BP), hypertriglyceridemia (TG), low HDL-cholesterol (HDL-C), high fasting plasma glucose (FPG) (Eckel et al, 2005) and represents another major burden for public health. Recent convergent papers show that persons with MDD are a high-risk group for MetS and vice-versa (Pan et al, 2012; Vancampfort et al, 2013; Rhee et al, 2014; Rethorst et al, 2014).

In their systematic review of 29 cross sectional studies (n=155 333 subjects), Pan et al found that MetS and depression to be correlated (OR=1.34). In their study of 3000 subjects, Van Reedt et al, were able to detect a correlation and a dose response association between MDD and MetS (Van Reedt et al., 2010). There is a scarcity in prospective studies that assess the association between the two illnesses, but whatever evidence is there does confirm a bidirectional association between the conditions (Pan et al., 2012). The most consistent association remains between depression and obesity related factors (visceral obesity, hypertriglyceridemia and low HDL-C), whereas the association with insulin-resistance (FPG) and hypertension remains less ascertained (Penninx, BW, 2017). The link between depression and MetS being clearly established, the question that one should be asking is: To what extent do AD contribute to an increased cardiovascular risk among MDD patients? Although, several observational studies have shown that the use of AD treatment, would increase or worsen metabolic dysregulations. However, it is important to highlight that observational studies should not be interpreted as causal evidence for cardiovascular inducing effects through pharmaceutical effects of AD. It is very likely that such studies have a strong bias due to confounding-by-indication. With the absence of randomization, subjects using AD treatment can be different from drug-naïve patients, with respect to: depression severity, chronicity of illness or many other reasons leading to the use of AD. Nevertheless, it is possible for observational studies to reduce the confounding-by-indication bias by adjusting for severity of depression, but it won't completely eliminate it.

A consistent body of the literature shows that AD in general and tricyclic antidepressants (TCA) and serotonin and norepinephrine reuptake inhibitors (SNRIs) in particular, increase cardiac vagal

control (Penninx, BW, 2017; Licht et al., 2010), which contributes to an increase in SBP and DBP and therefore hypertension among users (Licht et al., 2009). In their 6 years observational study Hiles et al, (2016) found that AD use was associated with metabolic dysregulations and negatively impacted metabolic health. Compared to non AD users, the use of TCAs, SSRIs and SNRIs was associated with higher WC, triglycerides level, and the number of MetS dysregulations. TCA use was also associated with low HDL-C levels. The reported effect sizes were more important for TCAs as compared to SSRIs and SNRIs, particularly for WC. Depression severity and AD use exerted independent effects on MetS, as drug naïve patients had an increased MetS risk.

In the general population, weight gain is associated with MetS. A 5-year interval observational study of 1384 adult employees at an electronic manufacturing company concluded that weight gain increased the risk of MetS (Lin et al., 2011). Nevertheless, body weight, body mass index (BMI), and WC at baseline were not significant predictors of later weight gain. In this study, individuals experiencing moderate weight gain (between 5 to 10%) were 3 times more likely to develop MetS compared to those who did not gain weight. A linear trend between weight gain and worsening of all MetS components was reported by Hillier et al (2006) among 3770 French adult participants who were followed over a 6-year period (Hillier et al., 2006). Zabetian et al (2009) found a similar trend among 3467 adult Iranian men and women followed for 3 years (Zabetian et al., 2009). He also concluded that weight gain exceeding 4% in men or 1.3% in women would increase the risk of MetS; Lin et al (2011) linked weight gain equal to or higher than 5% to MetS in healthy middle-aged individuals from both genders (Lin et al., 2011).

5. Overview of dissertation

As stated earlier, the literature suggests that abdominal obesity and lipid disturbances - which both are a direct result of weight gain – are the main driving force between depression and MetS. It is under this framework that the presented work was undertaken.

The dissertation is composed of 6 chapters that present and summarize the work undertaken during the last 4 years. The main theme governing this work, is the impact of AD treatment on the weight and cardio-metabolic profile of MDD patients. The first chapter presents the overhauling arch of the METADAP project and investigates the main research question of the METADAP study: Do antidepressants cause metabolic syndrome? Although the initial findings were published as a letter to the editor in *World Psychiatry* (Corruble, El Asmar, et al, 2015), the thesis will present a more elaborate analysis and discussion of the findings. In contrast to the results presented in chapters 2, 3, and 4, and which are focused on a specific subsample of “metabolically healthy” patients, the first one presents findings on the entire sample of 624 patients recruited for the study. The second chapter presents and discusses the impact of early weight gain on MetS incidence. This chapter focusing exclusively on a subsample of 260 non-overweight and MetS free patients, is part of a manuscript that is under review in *Journal of Psychiatric Research*. The third chapter answers a similar research question as chapter 2, but while considering MetS as a single latent variable suggestive of a common pathophysiology of the 5 individual factors. Structural equation modeling (SEM) was used to test the theoretical model that early weight gain precedes the onset of MetS, and whether the relationship between MetS and other clinical factors are mediated by early weight gain. The findings from the structural model were concordant with those obtained in chapter 2, using generalized linear models and generalized linear mixed models. This chapter is part of a research article that is currently in the write up process and is expected to be completed in August 2018. The fourth chapter addresses the issue of early and later weight gain. Specifically, it assesses the impact that early weight gain (3%, 5% and 7% in the first 30 days of treatment) can have on later weight gain (15% and 20% after 6 months of treatment). The analysis also quantifies the power of early weight gain in predicting later weight gain. This chapter is part of an article that has been accepted for publication in *journal of affective disorders* (El Asmar et

al., 2018). The fifth chapter briefly presents all the research papers stemming from the METADAP cohort to which I have contributed in my capacity as a biostatistician; although they do not directly address the research question of whether antidepressants cause metabolic syndrome and weight gain, they have nonetheless contributed to deepening my understanding of various clinical, physiological and genetic factors associated with depression and its treatment. The 6th and final chapter of the dissertation consists of the overall conclusion and wrap up of the presented research work. It draws a conclusion on the major implications this dissertation has on clinical practice in treating major depressive disorders, taking into consideration potential harms on the cardio metabolic profile. It also reflects on and contrasts the different statistical methods used in modeling clinical data issued from prospective cohorts and specifically those containing variables that can be treated as latent constructs such as the MetS.

Chapter 1: Impact of antidepressant treatment on metabolic syndrome

Treating major depressive episodes with antidepressants can induce or worsen metabolic syndrome: results of the METADAP cohort.

Corruble E, El Asmar K, Trabado S, et al. Treating major depressive episodes with antidepressants can induce or worsen metabolic syndrome: results of the METADAP cohort. World Psychiatry. 2015;14(3):366-367. doi:10.1002/wps.20260

Objectives

The first chapter presents the results of the main research question of the METADAP study. Does treating major depressive episodes with antidepressants induce or worsen metabolic syndromes? In a context of increasing prescription of antidepressant medication (Mojtabai, 2013) and weight gain induced by antidepressants (Luppino et al., 2010; Blumenthal, et al., 2014), the impact on MetS of treatment of major depressive episodes (MDE) has to be clarified. Indeed, there has been no prospective study of reasonable sample size and duration, addressing potential changes in metabolic syndromes in MDD patients treated with antidepressants.

Consequently, the first chapter of the dissertation has assessed whether changes in MetS after treatment with AD medication in patients with a current major depressive episode (MDE). It also assessed the relationship of metabolic changes with depression severity, and response to treatment. Based on antidepressant-induced weight gain, it was hypothesized that metabolic dysregulations would worsen after treatment. For this specific chapter, all 624 patients were included in the analysis.

Methods

Assessment of depression

Depression was assessed by clinical psychologists independently from clinicians who treated the patients. Standardized interviews documented the lifetime duration of MDD since the onset of the first MDE, the number of previous MDE, the lifetime duration of prior antidepressant treatment since the onset of MDD, and whether patients were antidepressant-free before inclusion (no antidepressant treatment for at least one year before inclusion (Rubin et al., 2013). Medical records were also examined. In case of discrepancy between interviews and medical records, the

latter were prioritized. The 17-item HDRS and the Clinical Global Impression (CGI) (Guy, 1976) were rated at baseline, one month, three months and six months after initiation of current antidepressant treatment. Response was defined by a decrease of at least 50% of the HDRS total score.

Assessment of metabolic syndromes

MetS was diagnosed based on the International Diabetics Federation definition (Alberti, et al., 2005), which includes high waist circumference (≥ 94 cm in males and ≥ 80 cm in females) (High WC), plus at least any two of the following four criteria: 1) high triglycerides (High TG) (≥ 1.50 g/L or specific treatment); 2) low high-density lipoprotein cholesterol (Low HDL-C) (< 0.40 g/L in males and < 0.5 g/L in females or specific treatment); 3) high blood pressure (High BP) (systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or treatment); 4) high fasting plasma glucose (High FPG) (fasting plasma glucose ≥ 1.0 g/L or treatment). Criteria for MetS were assessed at baseline, three and six months later with standardized procedures. Participants had to have fasted and abstained from strenuous physical activity for 8 hours before examination. TG, HDL-C and FPG levels were assessed using routine standardized laboratory methods. Thereafter, an assistant investigator blind to the major depression assessment measured WC and BP. WC was measured using a steel measuring tape to the nearest 0.1 cm (midway between the lower rib margin and the iliac crest following normal expiration, upon light clothing). BP was measured at rest (at least 5 min) in a supine position on the right arm and averaged over two readings. Information was collected on previous and current medication of MetS, smoking, alcohol consumption through a standardized interview. Weight and Body Mass Index (BMI) were also assessed using standardized procedures. No information about metabolic variables were transmitted to psychiatrists in order to maintain real life conditions. Assessment of MetS were done at baseline before the initiation of antidepressant treatment and after 3 and 6 months after the initiation of antidepressant treatment.

Statistical Analysis

Four metabolic variables were investigated at each time point: the continuous values of MetS components (independently from treatments), the frequency of each altered MetS (based both on

continuous scores thresholds and treatments) as a dichotomy (present/absent), the number of altered components of MetS (range 0–5), and the incidence of MetS. The independent variables of interest were age (years), sex, lifetime duration of MDD (years), lifetime duration of prior antidepressant medication (years) and antidepressant-free duration before inclusion (categorized into >1 year or ≤1 year), severity of depression as measured by HDRS scores at baseline. Analyses were stratified on the presence/absence of MetS at baseline.

Bivariate analyses (t-tests, one-way analyses of variance, chi-square tests) were performed while stratifying by MetS status at baseline.

The continuous values of MetS components over 6 months following initiation of the current antidepressant prescription were assessed using mixed-effects multivariate linear regression models. The change in the number of altered components of MetS (range 0-5) over 6 months was assessed using mixed-effects Poisson regression models. The frequencies of MetS and each MetS component over 6 months were assessed using mixed-effects logistic regression models. In order to assess the role of response to treatment and weight gain on metabolic changes, the previous mixed-effect multivariate models with additional adjustment on response to treatment and weight gain were fitted.

Mixed-effects models represent a well-accepted method for analyzing longitudinal clinical data in which missing or mistimed observations are present (Fitzmaurice et al., 2001). They have been previously applied to examine the association between antidepressants and weight gain (Blumenthal, 2014). All regression models included main effects for time since initiation of current antidepressant treatment, age, sex, reinclusion, HDRS score at baseline (depression severity), lifetime duration of prior MDD, lifetime duration of prior antidepressant medication, antidepressant-free period before inclusion and current antidepressant classes (compared to SSRI as a reference class).

Assumptions for multivariate regression models such as absence of multicollinearity and lack of strongly influential outliers were validated. Additionally, the assumption of number of events (usually 10) per explanatory variable was verified in order to avoid any model overfitting.

We hypothesized an incidence of 15% of MetS in patients without MetS at baseline. To show it with a 80% power, 350 patients without MetS at baseline were required. Assuming 20 % of MetS at baseline and a drop out rate of 25%, the number of patients required at baseline was 630. All analyses used Stata MP v.13. Mixed-effects models were fitted using xtmepoisson, xtmelogit and xtmixed commands. All tests were two-tailed. An alpha level of 5% was used to consider statistical significance.

RESULTS

Study population

A total of 689 patients were pre-included in the study, of whom 643 were included. Nineteen were not taken into account in the analysis because of major deviations to the protocol (Figure 2).

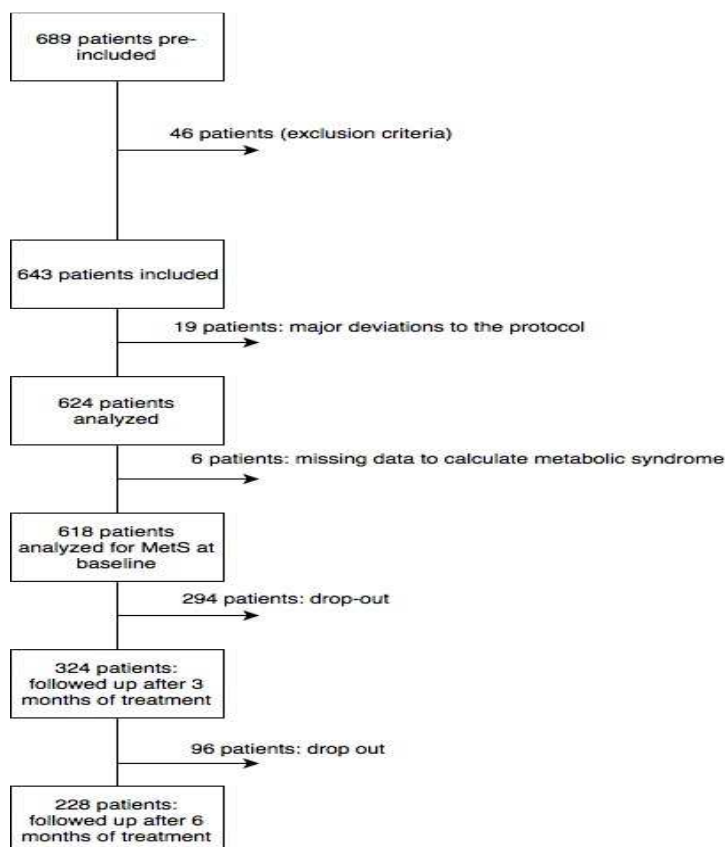


Figure 2: METADAP study flow chart

The sample comprised 624 patients with a mean (\pm SD) age of 45.6 years \pm 13.2, of whom 68.7% were women. 36.8% were current smokers, 46.3% completed high school and 44.9% had a higher

educational level. In total, 87.5% were in-patients at baseline. The mean number of previous MDE was 1.9 ± 2.1 (first MDE: 25.6%). 22.7% were antidepressant naïve at inclusion. The mean lifetime duration of MDD before inclusion was 11.5 years ± 12.2 . The lifetime antidepressant drug duration before inclusion was 2.3 years ± 4.1 . The number of prior antidepressant drugs received before inclusion was 2.1 ± 2.3 . 58% of patients were antidepressant-free at inclusion. The mean duration of follow-up was 4.9 months ± 4.6 . 62% of patients dropped out prematurely: 25.9% before one month, 21.8% between 1 and 3 months, and 14.3% later. The reasons for dropping out were: antidepressant monotherapy change (28.4%), prescription of antipsychotics or mood stabilizers (29.4%), lost to follow up (20.4%), acute somatic condition not compatible with the study (9.9%), withdrawal of consent (6.6%), diagnosis change (mainly from MDD to bipolar disorder) (4.8%), or death (0.5%). Those who dropped out did not differ from completers on age, sex, lifetime duration of MDD, lifetime duration of prior antidepressant medication, HDRS score at baseline, and current antidepressant. The 54 patients who were reincluded did not differ from others on age, gender, lifetime MDD duration, and HDRS score at baseline but had a longer lifetime antidepressant duration ($p < 0.003$) and received SSRI less frequently ($p < 0.001$). 24.7% of patients received benzodiazepines as coprescriptions. The distribution of antidepressant treatment for the overall sample was as follow: SNRI, 239 (38.3%) (venlafaxine 224 [35.9%], duloxetine 14 [2.2%], minalcipran 1 [0.2%]); SSRI, 243 (38.9%) (escitalopram 86 [13.8%], citalopram 48 [7.7%], paroxetine 52 [8.3%], fluoxetine 31 [5%], sertraline 18 [2.9%], fluvoxamine 8 [1.3%]), TCA, 55 (8.8%) (clomipramine: 46 [7.4%], other TCA: 9 [1.4%]), others 87 (13.95%). Patients treated with SSRI were younger ($p < 0.001$) and had a shorter lifetime duration of prior antidepressant drug treatment ($p < 0.001$). Thus, these variables were systematically controlled in multivariate analyses. The mean HDRS score was 24.7 ± 5.0 at baseline and 14.6 ± 7.1 , 12.5 ± 7.6 and 10.6 ± 7.8 after one, three, six months of treatment respectively. After six months of treatment, 67.7% of completers were responders. The *CGI-S* scores were 4.9 ± 0.7 at baseline, and 3.6 ± 1.4 , 3.1 ± 1.5 , 2.6 ± 1.5 after one, three, six months of treatment, respectively.

MetS was calculated for 618 patients due to missing data for 6 patients. The number of altered metabolic components increased with age ($\rho = 0.37$, $p < 0.001$), with the lifetime duration of prior antidepressant treatment before inclusion ($\rho = 0.13$, $p = 0.001$) and was lower in patients who

were antidepressant free at baseline (1.64 ± 0.08 vs 2.07 ± 0.08 ; $p=0.005$). Overall, 176 (28.5%) patients had MetS at baseline. In bivariate analyses, patients with MetS were older, had a higher BMI and a longer lifetime duration of prior antidepressant treatment, but did not differ on any other variable (Table 2). Patients with MetS at baseline qualified either for continuous scores thresholds (High BP: 23.9%, High FPG: 15.6%, Low HDL: 37.6%, High TG: 21.6%) or for the presence of corresponding treatment (High BP: 14.4%, High FPG: 4.5%, Low HDL: 11.1%, High TG: 11.1%) or both (High BP: 6.9%, High FPG: 2.9%, Low LDL: 3.9%, High TG: 3.5%).

Table 2: Comparison of patients with and without metabolic syndrome at baseline

	Metabolic Syndrome at baseline (n= 176)	No Metabolic Syndrome at baseline (n=442)	P
Age (years) (m(sd))	51.8 ± 11.4	43.2 ± 13.1	<0.001
Gender (Females) (%)	66.5	70.4	0.34
Lifetime MDD duration (years) (m±sd)	11.4 ± 12.2	10.0 ± 11.3	0.16
Lifetime number of prior MDE (m±sd)	1.9 ± 2.1	1.6 ± 1.9	0.10
Lifetime duration of prior antidepressant treatment (years) (m±sd)	3.2 ± 4.6	2.1 ± 3.9	0.001
Antidepressant free at baseline (%)	36.2	44.5	0.07
Comedication with benzos at baseline (%)	23.7	27.2	0.36
BMI (kg/m ²) (m±sd)	27.6 ± 5.3	22.9 ± 4.1	<0.001
Drop outs (cumulative) (%)			
M1 (%)	23.9	26.0	0.95
M3 (%)	47.7	47.93	
M6 (%)	59.7	62.24	
HDRS score (m±sd)			
Baseline	24.8 ± 5.2	24.7 ± 4.9	0.85
M1	15.2 ± 7.0	14.42 ± 7.1	0.32
M3	13.3 ± 7.5	12.2 ± 7.6	0.18
M6	11.6 ± 7.5	10.2 ± 7.8	0.20

Number of altered parameters of Metabolic Syndrome	3.6± 0.7	1.2 ± 0.8	<0.0001
High WC (%)	100.0	49.3	<0.001
High BP (%)	61.4	19.7	<0.001
High TG (%)	73.3	11.8	<0.001
Low HDL-C (%)	86.9	27.7	<0.001
High FPG (%)	42.0	7.5	<0.001

Table 2 :

BMI : Body Mass Index ; HDRS : Hamilton Depression Rating Scale ; WC : waist circumference ; BP : blood pressure ; TG : triglyceridemia ; HDL-C : HDL-cholesterol ; FPG : fasting plasma glucose.

HDRS : Hamilton Depression Rating Scale

Baseline: Initiation of current antidepressant treatment

M1 : One month after initiation of current antidepressant treatment

M3 : Three months after initiation of current antidepressant treatment

M6 : Six months after initiation of current antidepressant treatment

Metabolic changes

First, mixed-effect multivariate linear regressions showed that time since initiation of current antidepressant medication was associated with a significant increase of WC ($p < 0.001$), SBP ($p < 0.001$), DBP ($p < 0.001$), HDL-C ($p < 0.001$), and FPG ($p < 0.01$) in the whole sample. Similar results were shown for WC ($p < 0.05$), SBP ($p < 0.001$), DBP ($p < 0.01$), HDL-C ($p < 0.001$), and FPG ($p < 0.05$) in patients without MetS at baseline and for SBP ($p < 0.05$), FPG ($p < 0.01$), and HDL-C ($p < 0.01$) in patients with MetS at baseline (Table 3).

Table 3: Metabolic variables in the whole sample and in patients with and without metabolic syndrome at baseline.

	Whole sample			Patients with MetS at baseline			Patients without MetS at baseline		
	M0 (n=618)	M3 (n=324)	M6 (n=228)	M0 (n=176)	M3 (n=94)	M6 (n=74)	M0 (n=442)	M3 (n=230)	M6 (n=154)
WC (cm) (m±sd)	90.0 ± 14.2	91.8 ± 13.6	92.6 ± 13.4	102.0 ± 13.8	102.6 ± 12.9	102.1 ± 13.0	85.2 ± 11.2	87.5 ± 11.5	88.5 ± 11.4
SBP (mm Hg) (m±sd)	115.9 ± 16.3	118.9 ± 15.0	120.3 ± 14.8	123.2 ± 16.4	124.8 ± 13.9	126.8 ± 15.0	113.0 ± 15.4	116.6 ± 14.9	117.6 ± 13.9
DBP (mm Hg) (m±sd)	73.4 ± 11.7	75.4 ± 10.4	76.3 ± 10.3	77.5 ± 12.7	78.8 ± 9.4	79.4 ± 9.3	71.7 ± 10.9	74.1 ± 10.5	75.0 ± 10.4
TG (g/L) (m±sd)	1.15 ± 0.63	1.18 ± 0.68	1.16 ± 0.62	1.58 ± 0.87	1.56 ± 0.72	1.43 ± 0.65	0.98 ± 0.40	1.03 ± 0.61	1.04 ± 0.57
HDL-C (g/L) (m±sd)	0.53 ± 0.16	0.58 ± 0.2	0.58 ± 0.17	0.45 ± 0.13	0.51 ± 0.15	0.52 ± 0.14	0.56 ± 0.16	0.61 ± 0.16	0.60 ± 0.17
FPG (g/L) (m±sd)	0.89 ± 0.20	0.96 ± 0.38	0.93 ± 0.23	0.98 ± 0.29	1.07 ± 0.48	1.03 ± 0.31	0.86 ± 0.14	0.92 ± 0.32	0.90 ± 0.17
Weight (kg) (m±sd)	67.3 ± 15.3	69.7 ± 15.5	70.7 ± 15.1	77.3 ± 17.3	80.1 ± 17.2	79.3 ± 17.7	63.4 ± 12.5	65.6 ± 12.6	66.9 ± 12.1
BMI (kg/m ²) (m±sd)	24.2 ± 4.9	24.9 ± 4.9	25.3 ± 4.8	27.6 ± 5.2	28.4 ± 5.1	28.0 ± 5.0	22.9 ± 4.1	23.5 ± 4.1	24.1 ± 4.1

WC: waist circumference; SBP: systolic blood pressure ; DBP: diastolic blood pressure ; TG: triglyceridemia; HDL-C: HDL-cholesterol ; FPG: fasting plasma glucose; BMI: body mass index.

Second, mixed-effect multivariate logistic regressions showed that time since initiation of current antidepressant medication was associated with a significant increase in the frequency of High WC, High BP and High FPG in the whole sample (Figure 2, Table 4) and High WC, High BP, High TG and

High FPG, in patients without MetS at baseline (Figure 3, Table 4). This phenomenon was independent from other factors, such as the lifetime duration of prior antidepressant medication, and the presence of an antidepressant-free period at baseline (Table 4). In these models, SNRI had a more deleterious impact than SSRI on High BP and low HDL-C and TCA had a more deleterious impact than SSRI on High BP.

Table 4: Mixed-models multivariate logistic regressions for the presence of each of the five altered parameters of metabolic syndrome over time in the whole sample and in patients without metabolic syndrome at baseline.

		High WC *	High BP *	High TG *	Low HDL-C *	High FPG *
Time since initiation of current antidepressant treatment	Whole sample	1.23 (1.09-1.38) <0.0001	1.17 (1.07-1.27) <0.0001	-	0.83 (0.76-0.91) <0.0001	1.15 (1.05-1.26) 0.01
	Patients without MetS at baseline	1.32 (1.16-1.51) <0.0001	1.23 (1.10-1.37) <0.0001	1.21 (1.06-1.39) 0.05	0.89 (0.81-0.99) 0.03	1.28 (1.12-1.46) <0.0001
Age	Whole sample	1.13 (1.08-1.19) <0.0001	1.11 (1.08-1.14) <0.0001	1.10 (1.06-1.14) <0.0001	1.02 (1.0- 1.05) 0.05	1.09 (1.07-1.13) 0.015
	Patients without MetS at baseline	1.08 (1.03-1.13) <0.0001	1.09 (1.05-1.12) <0.0001	1.10 (1.06-1.14) <0.0001	0.96 (0.93- 0.99) 0.005	1.07 (1.03-1.11) 0.0001
Sex	Whole sample	21.9 (7.1-67.6) <0.0001	0.25 (0.14-0.49) <0.0001	0.08 (0.03-0.20) <0.0001	-	-
	Patients without MetS at baseline	53.03 (13.9-202.1) <0.0001	0.17 (0.08-0.36) <0.0001	0.05 (0.02-0.18) <0.0001	-	0.36 (0.16-0.80) 0.01
Lifetime MDD duration	Whole sample	-	-	-	-	0.96 (0.93-0.99) 0.007
	Patients without MetS at baseline	-	-	-	-	0.94 (0.90-0.98) 0.01
Lifetime duration of prior antidepressant medication	Whole sample	1.15 (1.007-1.32) 0.03	-	-	-	-
	Patients without MetS at baseline	-	-	-	-	-
Antidepressant free at baseline (ref : < 1 year)	Whole sample	-	-	0.29 (0.12-0.71) .007	-	-
	Patients without MetS at baseline	-	-	0.30 (0.10-0.89) .003	-	-
HDRS score at baseline	Whole sample	-	0.92 (0.87- 0.98) 0.01	-	-	-
	Patients without MetS at baseline	-	-	-	-	-
Current antidepressant medication (ref : SSRI)						
SNRI	Whole sample	-	2.28 (1.14-4.56) 0.02	-	2.46 (1.16-5.21) 0.01	-
	Patients without MetS at baseline	-	2.90 (1.31-6.38) 0.008	-	2.74 (1.33-5.65) 0.006	-
TCA	Whole sample	-	3.57 (1.20-10.61) 0.02	-	-	-
	Patients without MetS at baseline	-	4.00 (1.12-14.3) <0.0001	-	-	-

Legend Table 4:

* Mixed-model logistic regression assessing the impact of time since initiation of current antidepressant treatment, age, sex, previous duration of MDD, cumulative lifetime duration of prior antidepressant treatment before inclusion and current antidepressant medication, antidepressant-free at baseline,

re-inclusions and HDRS score at baseline: Odds-Ratios and 95% confidence intervals

Only significant results are shown in this table.

WC : waist circumference; BP : blood pressure ; TG: triglyceridemia; HDL-C: HDL-cholesterol ;

FPG : fasting plasma glucose.

HDRS : Hamilton Depression Rating Scale

SSRI: Selective Serotonin Reuptake Inhibitors

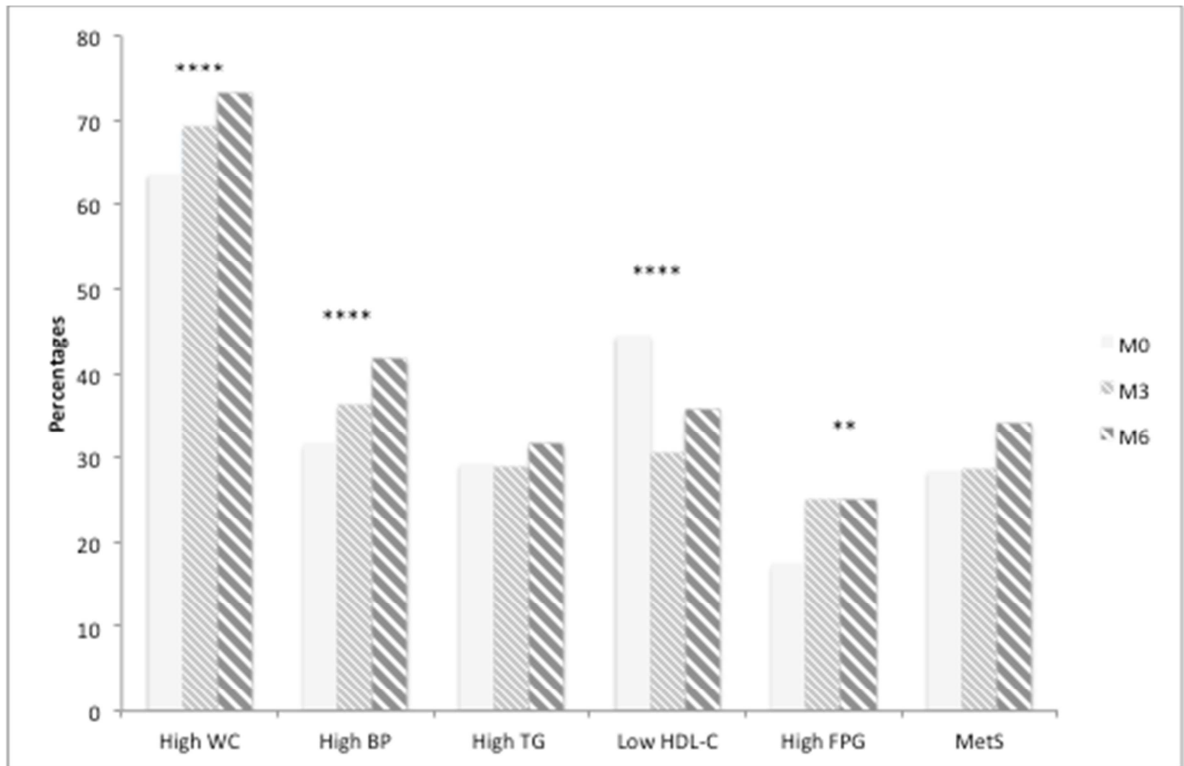
SNRI : Serotonin and Noradrenalin Reuptake Inhibitors

TCA : Tricyclic Antidepressants

Third, the number of altered components of MetS did not change significantly after treatment in the whole sample (M0: 1.9 ± 1.4 ; M3: 1.9 ± 1.4 ; M6: 2.1 ± 1.4). But it significantly increased with time since initiation of current antidepressant medication in patients without MetS at baseline (M0: 1.2 ± 0.9 ; M3: 1.3 ± 1.1 ; M6: 1.5 ± 1.2). The multivariate analyses (Table 5) confirmed this significant increase, which was significantly higher with SNRI than with SSRI, and was significantly lower amongst antidepressant-free patients at baseline. These effects were independent from each other and independent from age. In patients without MetS at baseline, means \pm sd of differences in the number of altered parameters of MetS between baseline and final evaluation were 0.40 ± 0.96 for SSRI ($p=0.001$), 0.35 ± 1.02 for SNRI ($p=0.01$), 0.90 ± 1.28 for TCA ($p=0.007$).

Fourth, no significant change after treatment of the frequency of MetS was shown in the whole sample (Figure 3). In patients without MetS at baseline, the frequency of MetS increased significantly to 11.7% after 3 months and 16.5% after 6 months of treatment (Figure 4, Table 5). This significant increase was evidenced within the SSRI group (0% to 16.2%, $p<0.001$), and the SNRI group (0% to 16.1%, $p=0.001$). Of note, the pattern of metabolic changes was quite similar in patients who dropped out and those who completed the study. And no significant association was shown at any time between MetS and either drop-outs or benzodiazepine co-prescriptions.

Figure 3: Percentages of patients of the whole sample with each altered parameter of metabolic syndrome and with metabolic syndrome, at baseline, and after 3 and 6 months of treatment



M0 : Initiation of current antidepressant treatment

M3 : Three months after initiation of current antidepressant treatment

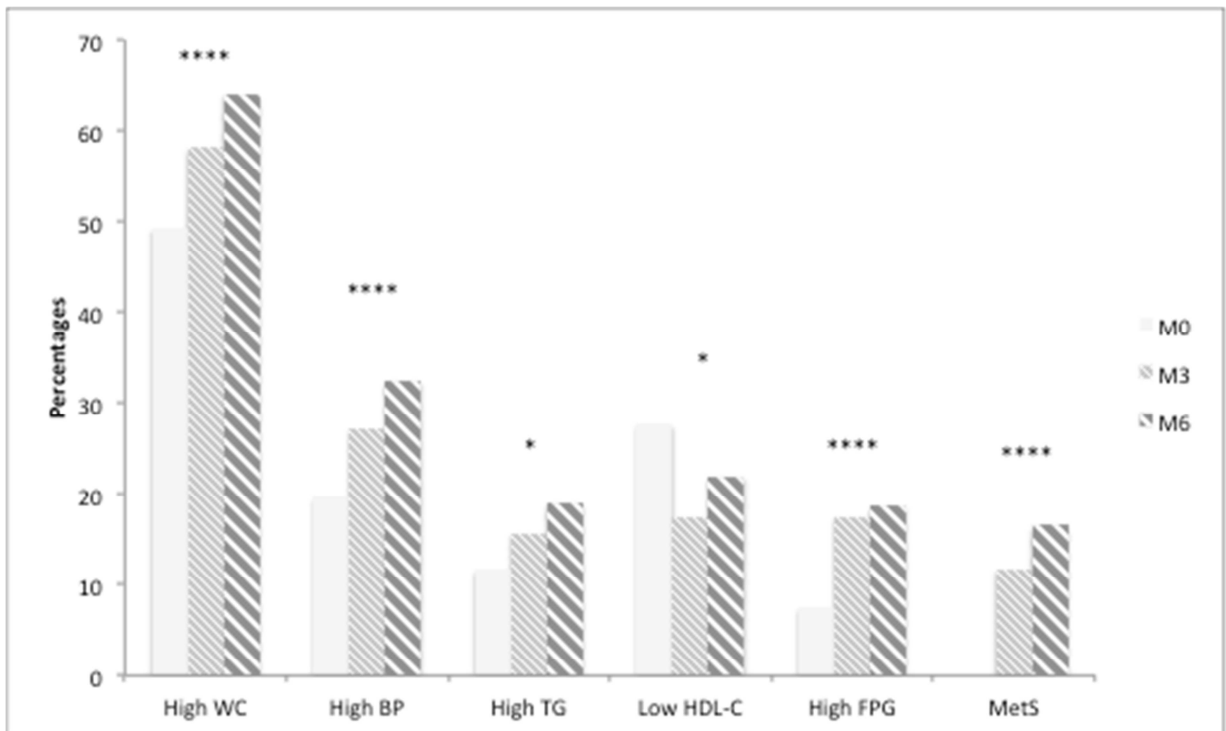
M6 : Six months after initiation of current antidepressant treatment

WC : waist circumference; BP : blood pressure ; TG: triglyceridemia; HDL-C: HDL-cholesterol ; FPG : fasting plasma glucose ; MetS : metabolic syndromes.

P : effect of time since initiation of current antidepressant medication in mixed-effect models adjusted for age, sex, reinclusions, lifetime MDD duration, lifetime duration of prior antidepressant treatment and antidepressant free period before inclusion.

**** : $P < 0.001$ ** : $P < 0.01$.

Figure 4 : Percentages of patients without metabolic syndrome at baseline with each altered parameter of metabolic syndrome and with metabolic syndrome, at baseline, and after 3 and 6 months of treatment.



M0 : Initiation of current antidepressant treatment

M3 : Three months after initiation of current antidepressant treatment

M6 : Six months after initiation of current antidepressant treatment

WC : waist circumference; BP : blood pressure ; TG: triglyceridemia; HDL-C: HDL-cholesterol ; FPG : fasting plasma glucose ; MetS : metabolic syndromes.

P : effect of time since initiation of current antidepressant medication in mixed-effect models adjusted for age, sex, reinclusions, lifetime MDD duration, lifetime duration of prior antidepressant treatment.

**** : $P < 0.001$ * : $P < 0.05$.

Table 5: Mixed-models multivariate regressions for the number of altered parameters of metabolic syndrome over time and the incidence of metabolic syndromes in patients without metabolic syndrome at baseline.

	Number of altered parameters of metabolic syndrome *	Incidence of metabolic syndromes **
Time since initiation of current antidepressant treatment	1.06 (1.02-1.09), p<0.0001	2.29 (1.69-3.10), p<0.0001
Age	1.01 (1.00-1.02), p<0.0001	1.07 (1.006-1.13), p=0.03
Sex	0.57 (0.47-0.70), p<0.0001	-
Antidepressant free at baseline (ref : < 1 year)	0.81 (0.65-0.99), p=0.03	-
Current antidepressant treatment (ref : SSRI)		
SNRI	1.45 (1.16-1.80), p=0.001	-

Only significant results are shown in this table.

* Mixed-model multivariate Poisson regression including the impact of time since initiation of current antidepressant treatment, age, sex, previous duration of MDD, cumulative lifetime duration of prior antidepressant treatment before inclusion and current antidepressant medication, antidepressant-free at baseline, reinclusions and HDRS score at baseline: Incidence Rate Ratios and 95% confidence intervals

** Mixed model multivariate logistic regression including the impact of time since initiation of current antidepressant treatment, age, sex, previous duration of MDD, cumulative lifetime duration of prior antidepressant treatment before inclusion and current antidepressant medication, antidepressant-free at baseline, reinclusions and HDRS score at baseline: Odds Ratios and 95% confidence intervals

SSRI : Selective Serotonin Reuptake Inhibitors

SNRI : Serotonin and Noradrenalin Reuptake Inhibitors

Impact of depression severity and response to treatment on metabolic changes

Metabolic changes were not different in patients with severe depression (HDRS scores at baseline higher than 24) at baseline and the others. Moreover, all multivariate analyses were adjusted on HDRS scores at baseline, showing that metabolic changes were independent from depression severity at baseline.

HDRS score changes were not significantly associated with changes in metabolic variables neither in bivariate analyses nor in mixed-effect multivariate linear regression models. Accordingly, the change in the number of metabolic dysregulations and the incidence of MetS did not differ significantly between responders and non-responders to treatment, neither in bivariate analyses nor in mixed-effects multivariate models including the effect of response to treatment as an explanatory variable (MetS: OR: 0.48, 95%CI (0.12-1.97), $p=0.31$; number of metabolic dysregulations: IRR : 0.79, 95%CI (0.71-1.02), $p=0.06$). Thus, the incidence of MetS and the number of metabolic dysregulations did not depend on response to treatment.

Discussion

This study is the first prospective real life cohort of MDE patients treated with antidepressant monotherapy but without antipsychotics or mood stabilizers, assessing prospectively metabolic syndromes and each of its five components, with a reasonable sample size and follow-up duration, taking into account a range of sociodemographic, clinical and therapeutic features including lifetime MDD duration, lifetime duration of prior antidepressant treatment, antidepressant-free period before inclusion, depression severity at baseline and current antidepressant medication.

The highlight of this study is the early incidence of MetS and its components over time after initiation of antidepressant medication, in patients without MetS at baseline, regardless of depression severity, response to treatment and weight gain. In these patients, the majority of MetS occur in the first three months of treatment. Hence, these results suggest that treating major depression with antidepressants may induce MetS.

The deleterious effects on metabolic syndromes of treating major depression are not limited to patients without MetS at baseline. Significant worsening of MetS is also shown in patients with

MetS at baseline and more generally in the whole sample, although a ceiling effect might have hampered statistically significant changes in MetS prevalence in the whole sample.

In depressed patients treated with antidepressants, WC is the most important MetS component, confirming results in the general population (Ma et al., 2013). At odds with WC and the three other metabolic criteria, the only metabolic parameter which improves after treatment is HDL-C, confirming previous results (Fava et al., 2009; Olusi et al., 1996; Skinner et al., 1989; Cooper et al., 2013), which suggest an inverse correlation between depression severity and HDL-C. Of note, recent studies show that HDL-C is a poor biomarker of cardiovascular risk (Silva et al., 2015).

Interestingly, we show a strong gender effect, women being more prone to WC dysregulation and men to BP and TG dysregulations, as already noted in other populations (Cooper et al., 2013, Hadaegh et al., 2013). Hence, future guidelines for the prevention of MetS in MDD patients receiving antidepressant medication should be gender-specific.

Several reasons may explain such deleterious effects on MetS after treatment of MDE. First, these effects may be due to changes in symptom severity of major depression. Whereas it could have been expected that more severe depression may be associated with higher inflammation, higher insulin-resistance and higher metabolic abnormalities, here we show opposite results, ie more metabolic abnormalities after decrease in depression severity with treatment. In line with this result, we also show that deleterious metabolic changes are not related to response to treatment. Second, we show that detrimental metabolic changes are independent from weight gain. Consequently, weight control strategies are not sufficient to control for metabolic abnormalities in depressed patients treated with antidepressants. Third, our results may argue for an intrinsic metabolic risk due to the pharmacological properties of antidepressants, which share common chemical features and receptorial effects with antipsychotic drugs. Some data in the literature support this view, with documented detrimental effects on BP (Adler et al., 1983; Harrison et al., 2004), TG (Pollock et al., 1994; Kopf et al., 2004), results on FPG being controversial (Ghaeili et al., 2004; Knol et al., 2008; Crucitti et al., 2010; Mojtabai et al., 2014; McIntyre et al., 2006; Hennings et al., 2012; Atlantis et al., 2012; Amsterdam et al., 2006). Accordingly, data in the general population (Cohen et al., 2000; Pyykkönen et al., 2012), in primary care (Hippisley-Cox et al., 2001) and in type 2 diabetes mellitus (Alberti et al., 2005), show that prior or current antidepressant

medication is associated with a higher risk of MetS or cardiovascular disease. However, we prospectively studied MDD patients whereas the impact of MDD was not studied in these previous studies.

There are several caveats in interpreting these results, which have to be underlined. The METADAP attrition rate was relatively high. But it did not differ regarding the presence/absence of MetS at baseline, and was quite similar to the STAR-D attrition rate (Triverdi et al., 2006). We used mixed-effects multivariate models to cope adequately with attrition. And results were similar in patients who dropped out and those who completed the study. Of note, if treatment discontinuation could be a result of metabolic abnormalities, the high attrition rate would have induced an underestimation of MetS. Thus, it can be expected that a lower attrition rate would have increased the magnitude of our positive results. A ceiling effect may have hampered statistically significant changes in the whole sample and in patients with MetS at baseline, especially for MetS prevalence. A source of bias in METADAP is likely to be the adherence to medication, patients with a high level of metabolic dysregulations being more likely to have a lower adherence. However, this could bias the results toward an underestimation of metabolic changes. Whether different antidepressant medications have different metabolic effects is a relevant question for prescribers and patients. We have shown that patients at greatest risk of high number of altered metabolic parameters were those receiving SNRI as compared to SSRI and those who were not antidepressant free at inclusion. This result should be confirmed in a randomized study. Another potential limitation is the confounding-by-indication bias that is due to the observational nature of the METADAP study and the absence of a control group. However, by controlling for depression severity at baseline, lifetime duration of prior MDD, lifetime duration of prior antidepressant medication, and antidepressant-free period before inclusion, the confounding-by-indication bias has been reduced. Taken together, our results suggest that treating major depressive episodes with antidepressants induces or worsens metabolic syndromes. This effect occurs early after initiation of treatment and is independent from weight gain and response to treatment. Hence, initiating and maintaining antidepressant medication should include routine surveillance of MetS. Beyond weight control, specific recommendations for the prevention of MetS in MDD patients receiving antidepressant medication are needed. Further

studies should assess to which extent different antidepressant drugs have different metabolic effects, the underlying mechanisms of this phenomenon, and interventions beyond weight control such as statins, metformin or nutritional programs, to diminish the metabolic risk associated with the treatment of MDE with antidepressant drugs.

Chapter 2: Early weight gain predicts later weight gain

Early weight gain predicts later weight gain in depressed patients treated with antidepressants: findings from the METADAP cohort

Khalil El Asmar, Bruno Fève, Romain Colle, Florence Gressier, Albane Vievard, Séverine Trabado, Céline Verstuyft, Emmanuel Haffen, Mircea Polosan, Florian Ferreri, Bruno Falissard, Philippe Chanson, Laurent Becquemont, Emmanuelle Corruble. (2018) Journal of Affective disorders. DOI:<https://doi.org/10.1016/j.jad.2018.07.059>

Objectives

The objective of this second chapter was to assess whether early weight gain can predict later weight gain in a sample of MDD patients with a current MDE and are initiating a new antidepressant treatment.

Methods

Assessment of early and long term weight gain

Weight was assessed using a standardized procedure; the baseline was in the morning, before breakfast, after one, three and six months of treatment. Early weight gain was defined as equal to, or more than, 3%, 5% and 7% weight gain in the first month of antidepressant treatment, as compared to the patient's weight at enrollment in the study.

The proposed thresholds are in accordance with those proposed for weight gain (Vandenberghe et al., 2015) and by the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes guidelines (Association, 2004) which consider a gain in weight superior to 5% to be an indication to the treating physician to reassess the treatment. Late weight gain was defined as equal to, or more than, (i) 15% after three and six months of treatment and (ii) 20% after six months of treatment.

Measures

The investigated outcome variables were: (i) percent weight gain after six months of treatment assessed as a continuous variable and defined as (weight at M6-weight at baseline)/weight at baseline; (ii) 15% or more weight gain, as compared to baseline values, after three and six months of treatment and (iii) 20% or more weight gain, after six months of treatment. The main exposure

was weight gain after the first month of treatment, as measured by a threshold of 3%, 5% and 7% increase from the baseline.

Statistical analysis

The Pearson's Chi-squared test and the Independent Samples t-test were used to assess statistical differences between the clinical and socio-demographic characteristics of early weight gainers and non-weight gainers. Ordinary Least Squared (OLS) models and their respective R-squared (R^2) were used to assess the adjusted association between % early weight gain and late weight gain. Binary logistic regression models and their corresponding Receiver Operator Curves (ROC), Area Under Curve (AUC), and goodness of fit tests were used to assess the predictive and discriminatory power of early weight gain at 3%, 5% and 7% thresholds. Sensitivity (SEN), specificity (SPE), positive predictive value (PPV), negative predictive value (NPV) and the optimal probability cut-offs were calculated.

All regression models included age (in years), sex, weight status compared to ideal body weight prior to depression, their lifetime duration of MDD (in years), and severity of depression as measured by HDRS scores at baseline. Robust standard errors were used in order to account for the center effect. All analyses used Stata v.13, and all tests were two-tailed. An alpha level of 5% was used to consider statistical significance.

Results

Sample characteristics

The sample consisted of 260 patients at baseline, of whom 82 (31.5%) were having their first major depressive episode. 181 (69.6%) patients were females. Their mean age (\pm SD) was 41.6 years (\pm 13.4), their average lifetime of MDD was 9.5 years (\pm 11.6), and their average HDRS score at baseline was 24.8 (\pm 4.9). The mean duration of follow-up was 4.9 months (\pm 4.6). 124 patients (47% of patients) dropped out prematurely, 89 (34%) dropped out between one and three months and 35 (13%) dropped out later. The reasons for dropping out were: lost to follow-up (43.3%), antidepressant drug change (39.7%), prescription of antipsychotics or mood stabilizers (9.2%), diagnosis change (mainly from MDD to bipolar disorder) (4.3%), withdrawal of consent (2.8%), and death (0.71%).

No significant difference in other socio-demographic variables was found between genders. Before enrollment in the current study, 72.3% of the patients had previously taken antidepressant medications. Out of those who had, 103 (56%), 39 (21.2%) and 17 (9.2%) had taken SNRIs, SSRIs and TCA, respectively. 129 (49.6%) were taking an AD drug at the time of enrollment in the current study but this treatment was withdrawn at inclusion and replaced by another AD treatment.

At baseline, 115 (44.2%), 87 (33.5%), 17 (6.5%) and 41 (15.8%) were beginning a treatment with SSRI, SNRI, TCA, respectively, and other classes of AD; 83 (33.9%), 40 (16.3%), 26 (10.6%), 26 (10.6%) and 14 (5.7%) of patients were taking venlafaxine, escitalopram, citalopram, paroxetine and clomipramine respectively. No significant association was found between early weight gain and class or molecule of AD. Completers and non completers did not differ in age, sex, lifetime duration of MDD, lifetime duration of prior antidepressant medication, HDRS score at baseline, or current antidepressant treatment.

Table 6: (Bivariate) comparisons of early and non early weight gainers

	Total	Weight gain ≤ 3% at M1	Weight gain > 3% at M1	P ^a	Weight gain ≤ 5% at M1	Weight gain > 5% at M1	P ^a
	N=260	N=172	N=88		N=211	N=49	
Overweight^b							
M0, n/N, (%)							
M3, n/N, (%)	21/170 (12.4)	9/113 (8.0)	12/57 (21.1)	0.014	13/141 (9.2)	8/29 (27.6)	0.006
M6, n/N, (%)	26/123 (21.1)	14/86 (16.3)	12/37 (32.4)	0.044	18/107 (16.8)	8/16 (50.0)	0.002
% Weight gain at M3; mean ± S.D	3.1±6.4	0.5±5.0	8.3±6.0	<0.001	1.8±5.6	9.7±6.4	<0.001
% Weight gain at M6; mean ± S.D	6.0±10.1	2.7 ±7.2	13.8±11.6	<0.001	4.3 ±8.3	17.8±12.6	<0.001
Age, mean ± S.D	41.6 ± 13.4	41.3 ± 13.0	42.2 ± 14.2	0.653	42.0 ± 13.4	39.9 ± 13.8	0.322
Sex							
Females, n (%)	181/260 (69.6)	128/172 (74.4)	53/88 (60.2)	0.019	152/211 (72.0)	29/49 (59.2)	0.078
Depression duration (years), mean ± S.D	9.5 ± 11.6	9.7 ± 11.2	9.3 ± 12.2	0.794	10.4 ± 11.7	6.1 ± 10.2	0.021
Smoking, n(%)	109/259 (41.9)	67/172 (38.9)	42/87 (48.3)	0.151	84/211 (39.8)	25/48 (52.1)	0.12
Class of A.D, n(%)							
SSRI	114/260 (44.0)	78/172(45.3)	36/87 (41.4)	0.695	90/211 (42.7)	24/48 (50.0)	0.414
SRNI	87/260 (33.6)	59/172	28/87 (32.2)		70/211 (33.2)	17/48 (35.4)	

		(34.3)					
TCA	17/260 (6.6)	11/172 (6.4)	6/87 (6.9)		16/211 (7.6)	1/48 (2.1)	
Other	41/260 (15.8)	24/172 (14.0)	17/87 (19.5)		35/211 (16.6)	6/48 (12.5)	

^a P-values were calculated using chi2 tests for categorical variables and independent samples t-test for continuous variables

^b defined as those having a body mass index $\geq 25 \text{ kg/m}^2$

Weight gain

The percentage of early weight gain was normally distributed. Its mean (\pm S.D) was 2% (4.1). Out of the 260 patients, 57.2% have lost on average 4.5 kg (± 2.9) compared to their pre-illness weight. Weight gain was greater among these patients compared to those who did not lose weight because of depression (4.6 kg ± 6.9 , vs. 2.6 ± 6.9). As expected, depression induced weight loss was positively but slightly associated with weight gain after 6 months of treatment ($\rho=0.2$, $p=0.02$). Weight gain was independent from response to AD treatment (data not shown). 49 patients (19%) gained at least 5% of their initial body weight during the first month of treatment; 33.6% and 10% gained at least 3% and 7% of their initial body weight, respectively; while 3.9% and 14.6% gained at least 15% of their initial body weight after three and six months of treatment. Only 3 patients (2.4% of completers) became obese after 6 months of treatment. Older patients were at a higher risk of subsequent weight gain; as age increased by 1 year, the average patient's weight increased by 10% after 6 months of treatment (Coeff= 0.10; 95%CI: 0.01- 0.19; $p= 0.03$) (table 7) while the risk of gaining more than 15% of their initial weight increased by 5% (OR:1.05; 95% CI: 1.01-1.08; $p<0.01$) (table 8). Early weight gainers ($>3\%$ and $>5\%$) have gained significantly more weight after six months in comparison to non-early weight gainers (13.8% vs. 2.7%, $p<0.01$ for $>3\%$ group and 17.8% vs. 4.3%, $p<0.01$ for $>5\%$ group). Starting with a sample of non-overweight patients, 12.4% (21/170) of patients became overweight after three months of treatment and 21.1% (26/123) were found to be overweight after six months of treatment, out of which 13 patients were not overweight at the third month of follow up.

Table 7: Adjusted linear models showing the associations between early and late weight gain at 3 and 6 months

	weight change after 3 months of treatment*		weight change after 6 months of treatment**	
	Coef (95%CI)	P ^a >z	Coef (95%CI)	P ^a >z
% early weight gain	1.02 (0.98; 1.07)	<0.01	1.29 (0.75; 1.83)	<0.01
Sex (ref: male)	0.24 (-2.33; 2.80)	0.811	1.41 (-4.17; 6.99)	0.52
Age (years)	0.00 (-0.03; 0.03)	0.918	0.10 (0.01; 0.19)	0.03
MDD^b duration in years	-0.01 (-0.08; 0.06)	0.789	-0.06 (-0.23; 0.12)	0.42
HDRS^c at baseline	0.10 (-0.11; 0.32)	0.25	0.29 (-0.33; 0.91)	0.26

* R-squared for model: 0.48

**R-squared for model: 0.35

^a results were obtained by fitting a linear regression model controlling for class of AD treatment at baseline

^b MDD: Major Depression Duration

^c Hamilton Depression Rating Scale

Patients who had a weight gain less than or equal to 3%, after one month, continued to have a moderate weight gain over a course of three and six months. Over a period of six months, these patients had a mean weight increase of 2.7 kg, which was significantly lower than the 13.8 kg increase in the high early weight gain group.

An early weight gain (>5%) was significantly associated with a higher rate of premature drop out as compared to the absence of early weight gain (67% vs 47%, $p= 0.02$). Over the six months follow up period, the mean BMI of both male and female patients increased significantly ($p<0.01$) by 1.4 kg/m^2 and 1.6 kg/m^2 respectively. Among those who completed, the prevalence of patients with normal weight dropped significantly ($p=0.03$) from 86.9% at baseline to 73.9% after six months; while the percentage of overweight patients increased significantly ($p<0.01$) to 11.9% and 18.5% after three and six months, respectively.

Table 8: Adjusted logistic regression models predicting 15% weight gain after 6 months of AD treatment with different levels of early weight gain (3%, 5%, 7%)

	Model 1 [*]		Model 2 ^{**}		Model 3 ^{***}	
	OR (95%CI)	P ^a	OR (95%CI)	P ^a	OR (95%CI)	P ^a
% early weight gain (3%[*], 5%^{**}, 7%^{***})	11.25 (4.59;27.59)	<0.01	9.88 (3.63;26.85)	<0.01	17.83 (6.43; 49.43)	<0.01
Sex (ref: male)	1.86 (0.91; 3.79)	0.09	1.82 (0.70;4.74)	0.22	1.67 (0.85;3.27)	0.14
Age (years)	1.03 (1.01; 1.06)	0.04	1.05 (1.01;1.08)	0.01	1.06 (1.02; 1.10)	0.01
MDD^b (years)	0.97 (0.92; 1.02)	0.24	0.99 (0.95;1.04)	0.69	0.98 (0.94;1.01)	0.19
HDRS^c at baseline	1.13 (0.97; 1.32)	0.13	1.13 (1.02; 1.25)	0.02	1.13 (1.01; 1.27)	0.04

* model with 3% early weight gain as main exposure variable

** model with 5% early weight gain as main exposure variable

*** model with 7% early weight gain as main exposure variable

^a results were obtained by fitting logistic regression models controlling for class of AD treatment at baseline

^b MDD: Major Depression Duration

^c Hamilton Depression Rating Scale

Early weight gain as predictor of mid to long term weight gain

Results from linear models (see table 7) show that % weight gain after 1 month of AD treatment is positively associated with % weight gain at three (Coeff=1.02; 95% CI: 0.98-1.07; $p<0.01$) and six months (Coeff=1.29; 95% CI: 0.75-1.83; $p<0.01$) respectively, and this association is independent from class of AD treatment, sex, age, severity of depression and duration of MDD. With respective R-squared of 48% and 35%, the two linear models show that the percent of early change in weight is a strong predictor of the percent of later change in weight.

The 3%, 5% and 7% early weight gain thresholds were strongly associated with 15% weight gain after six months of treatment; with patients who gained more than 3% or more than 5% of their initial weight being 11 times (OR:11.3; 95% CI: 4.6-27.6; $p<0.01$) and 10 times (OR:9.9; 95% CI: 3.6-26.9; $p<0.01$) more at risk of a weight gain (>15%) after six months of treatment. The odds ratio increases to 17.8 (OR: 17.8; 95% CI: 6.4-49.4; $p<0.01$) for patients who have gained >7% of their initial weight in the first month of treatment. Older patients and those with a higher HDRS score at baseline were also more likely to experience long term weight gain (table 8).

The 3% threshold was found to be the best predictor of early weight gain with the highest area under the curve (AUC=0.87) (figure 5) for predicting a weight gain of 15% or more after three months of treatment. The threshold had sensitivity (SENS) of 86%, specificity (SPEC) of 81%, a positive predictive value (PPV) of 17% and a negative predictive value (NPV) of 99%. The 5% thresholds had a close predictive power to that of the 3% threshold (AUC=0.86, SENS=71%, SPEC=83%, PPV=17%, NPV=98% (table 9).

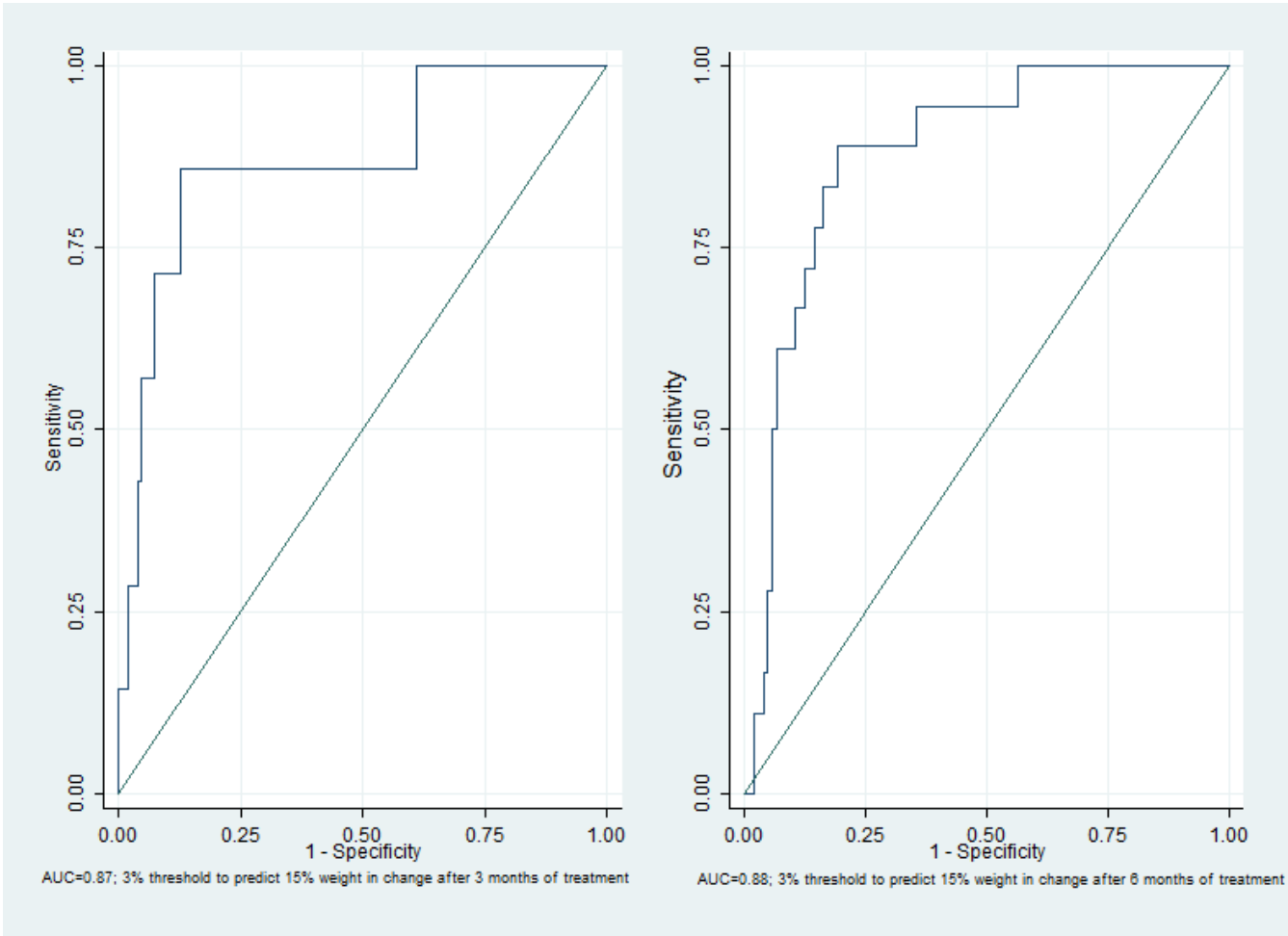


Figure 5: ROC curves for models predicting 15% weight change after 3 and 6 months of treatment

Table 9: Receiver operating parameters for a 1 month weight change predicting a weight gain of 15% or more after 6 months of treatment

	AUC ^a	Sensitivity	Specificity	PPV ^b	NPV ^c
3% weight change	88	83	82	44	97
5% weight change	83	67	77	33	93
7% weight change	82	72	77	35	94

^a Area Under the Curve

^b Positive Predictive Value

^c Negative Predictive Value

The 3% threshold was also found to be the best predictor for a weight gain of 15% after six months of treatment (table 5) (AUC=0.88, SENS=83%, SPEC=82%, PPV=44%, NPV=97%). Patients who gained more than 3% of their initial weight after one month but have not reached a 15% weight gain at three months still had a higher weight gain than those with less than 3% weight gain (4.5 kg vs. 0.4 kg, p<0.01). The difference remains significant after six months (3.9 kg vs. 1.0 kg, p=0.002). The 3% threshold was also found to be the best predictor of 20% weight gain after six months (AUC=0.90, SENS=90%, SPEC=78%, PPV=27.2%, NPV=99%) (table 10).

Table 10: Receiver operating parameters for a 1 month weight change predicting a weight gain of 20% or more after 6 months of treatment

	AUC^a	Sensitivity	Specificity	PPV^b	NPV^c
3% weight change	90	90	79	27	99
5% weight change	75	60	80	21	96
7% weight change	78	60	74	17	95

^a Area Under the Curve

^b Positive Predictive Value

^c Negative Predictive Value

Discussion

Our study found depressed patients with a normal weight who were treated with AD had an increase in likelihood of becoming overweight. The prevalence of patients who went from normal weight to overweight increased to 12.4% in the first three months of treatment and to 21.1% after six months of treatment. These results are in accordance with findings from psychiatric literature that demonstrates that acute SSRI and TCA treatment was found to be associated with significant weight gain (4.9%), while the rate increased to 24.5% for long term treatment (Sussman et al., 2001). Recent literature has shown that even newer generations of AD, such as SNRI, can also induce weight gain (De Hert et al., 2009); however, our study did not find any relationship between a particular class of AD and weight gain.

Our results were also comparable to those from two Swiss cohorts on patients treated with various psychotropic drugs including antipsychotics. Notably, the two cohorts had a higher rate of overweight patients due to the longer treatment duration and the fact of having overweight patients at baseline, while our baseline sample included only non-overweight patients (Vandenberghe et al., 2015; Choong et al., 2012). An early weight gain of 3% was found to be the best predictor for a weight gain of $\geq 15\%$ after three (AUC=87%) and six (AUC=88%) months of treatment and that of $\geq 20\%$ after six months (AUC=90%). Our defined threshold is lower than the one identified (Vandenberghe et al., 2015) who found that the 5% threshold is a better predictor of a weight gain of $\geq 15\%$ after three months and of $\geq 20\%$ after one year. In order to validate whether the difference between the optimal threshold that was identified in our study and the one from Vandenberghe et al, was due to the exclusion of overweight patients at baseline, we have considered looking at the overall sample including patients who were overweight or had metabolic syndrome at baseline. The results (not shown) from the ROC analysis still showed a better predictive power of the 3% threshold as compared to the 5% threshold. This consistently lower threshold could be specific to clinically depressed patients treated with AD, as opposed to a sample with diagnosis heterogeneity from the Swiss cohort.

However, the predictive power (AUC) of the identified thresholds in our study were higher than those reported in the Swiss cohort that reported an AUC=79% for a one month weight change of

≥5% predicting a weight gain of ≥15% after three months of treatment and an AUC=68% of ≥20% after 12 months.

The difference between the two studies could be explained by: (i) the longer follow up duration (six months in our cohort vs. 12 months in the Swiss one) which would impact the predictive power of early weight gain, since events that would occur in a 12 month period are more difficult to predict than those occurring in a six month period; and (ii) the fact that the results from the Swiss cohort all pertain to psychiatric patients, while our results are derived from a specific and more homogenous group of normal weight and clinically depressed patients with MDD and a current MDE. The high negative predictive value of the 3% threshold indicates that this cutoff will correctly predict the future weight gain status of 99% of patients at three months and 97% of patients at six months.

Other studies have reported similar NPV and PPV values for the predictive power of early weight gain (Hoffman et al., 2010; Lipkovich et al., 2008) of 2 kg. However, these studies have reported an absolute threshold expressed in kilograms, which does not take into consideration the variability of weight at baseline, a relative threshold expressed in percentage change is considered to be more accurate. The three thresholds that were investigated (3%, 5% and 7%) of early weight gained remained significant after adjusting for several clinical variables, which indicate the robustness of these predictors, independently from age, sex, MDD duration, depression severity at baseline, as well as the class of AD. Our results have shown that weight gain was positively correlated with age, which is in agreement with the overall consensus that older patients treated with psychopharmacological drugs are more likely to develop adverse drug reactions (Alexopoulos, 2004). However, more recent research suggested that increase in weight arising from psychotropic medication decreases with the age of patients (Greil, 2013; Vandenberghe et al., 2015). Our sample consisted of patients who were not overweight at baseline which could be a reason why older patients have put on more weight as compared to younger ones.

No significant association between class of AD and later weight gain was observed. These results suggest that the 3% threshold should be used to monitor weight gain independent of the class of treatment used. Although some studies have associated the use of venlafaxine, citalopram, and escitalopram with weight gain (Uguz et al., 2015), however no conclusive evidence has been found

about the impact of these drugs on weight gain. Given that these drugs were administered to the majority of our sample, weight gain can either be attributed to the drug or to the improvement of depression. A separate analysis (not shown) has shown no association between response to treatment after 1 and 3 months on weight gain. However, the absence of such an association could be the result of a loss of statistical power due to the relatively high attrition rate in the cohort.

Several strengths could be highlighted in the present study. To the best of our knowledge, no previous study has assessed the predictive power of early weight gain thresholds (3%, 5% and 7%) on long term weight gain in a prospective cohort of non-overweight MDE patients treated with antidepressant mono-therapy but without antipsychotics or mood stabilizers. Furthermore, this study is based on a homogenous group of normal weight, clinically depressed patients, with MDD and a current MDE, without any psychiatric co-morbidities or concomitant treatment such as antipsychotics, mood stabilizers, and stimulants. The homogeneity of the studied sample minimizes any confounding and interactive effect that is due to other psychiatric conditions. It also takes into account a range of socio-demographic, clinical, and therapeutic features including lifetime MDD duration, depression severity at baseline, and current antidepressant medication. Furthermore, our results about weight gain with antidepressants are close to those of the literature (Dannon et al., 2007; Kivimaki et al., 2010; Michelson et al., 2010; Sussman et al., 2001) suggesting their generalizability.

However, there are several limitations in interpreting our results. First, given that our baseline sample consisted of strictly non-overweight patients, only the 3% threshold should be considered for clinical recommendations. Second, the study sample cannot be considered representative of the general population of patients with MDD in real world clinical practice, but only of patients treated in psychiatric settings. Third, because treatment selection was not randomly assigned, clinicians may have taken potential for weight gain into account for specific patients which could introduce a confounding effect by medications. Fourth, the attrition rate of this sample was relatively high, but quite similar to the STAR-D attrition rate (Warden et al., 2009; Warden et al., 2008). Furthermore, we do not know whether change of treatment or treatment discontinuation is due to weight gain; nonetheless, the effect of early weight gain has to be taken into

consideration while looking at study discontinuation. Weight gain is a main side effect of AD treatment and a main reason for treatment termination during the first eight weeks of treatment initiation (Goethe et al., 2007; Uher et al., 2011). Compared to non-early weight gainers, patients with early weight gain (>3%) in the first month of antidepressant treatment are at an 11 times higher risk of crucial weight gain during the six months of antidepressant treatment. The 3% threshold for weight gain after one month should be used as an indicator to initiate early weight monitoring in non-overweighed depressed patients with long term antidepressants treatment.

Chapter 3: Early weight gain predicts later metabolic syndrome

Early weight gain predicts later metabolic syndrome in depressed patients treated with antidepressants: findings from the METADAP cohort. *Khalil El Asmar, Bruno Fève, Romain Colle, Séverine Trabado, Céline Verstuyft, PharmD PhD, Florence Gressier, Albane Vievard, Emmanuel Haffen, Mircea Polosan, Florian Ferreri, Bruno Falissard, Philippe Chanson, Laurent Becquemont, Emmanuelle Corruble. (2018) Journal of psychiatric research*

Objectives

The objective of this second chapter was to assess whether early weight gain can predict later MetS in a sample of MDD patients with a current MDE and are initiating a new antidepressant treatment.

Methods

Assessment of early weight gain

Weight was assessed using a standardized procedure in the morning before breakfast while the patient was still fasting, at baseline, and after one month of treatment. Early weight gain was defined as more than 5% weight gain in the first month of treatment, as compared to weight at enrollment in the study. The proposed threshold is in accordance with the one proposed for weight gain by Vandenberghe et al. (2015) (Vandenberghe et al., 2015) and by the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes guidelines (Association et al., 2004) which consider a gain in weight superior to 5% to be an indication to the treating physician to reassess the treatment.

Assessment of metabolic syndrome

Metabolic syndrome was assessed after 3 and 6 months of antidepressant treatment.

The main outcome of interest was MetS as a binary variable as defined by the International Federation of Diabetes (IFD) (Alberti et al., 2006).

Secondary outcomes included the number of metabolic dysregulations and the individual metabolic dysregulations of MetS. They were measured as continuous variables: WC, TG, HDL-C, FPG, Diastolic Blood Pressure (DBP), and Systolic Blood Pressure (SBP). They were also assessed as

individual criteria of MetS: High WC: ≥ 94 cm in males and ≥ 80 cm in females; High TG: ≥ 1.50 g/L or specific treatment; Low HDL-C : < 0.40 g/L in males and < 0.5 g/L in females or specific treatment; High BP : SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or specific treatment; High FPG ≥ 1.0 g/L or specific treatment. Baseline metabolic measures for all patients were assessed prior to the initiation of the treatment. Training and quality control was done to ensure that all measures were collected identically at all visits.

Statistical analysis

The main independent variable was weight gain after the first month of treatment, as measured by a threshold of 5% increase from baseline. The main dependent metabolic variable was the incidence of MetS after 3 and 6 months of antidepressant treatment. The secondary dependent metabolic variables were the number of altered MetS criteria (range 0–5) and the 6 (including SBP and DBP as components of BP) quantitative criteria defining MetS.

Pearson Chi-squared tests and independent samples t-tests were used to assess statistical differences of clinical and socio-demographic characteristics as well as metabolic parameters between early weight gainers and non-weight gainers.

The longitudinal association between early weight gain and metabolic variables was assessed using: (i) mixed-effects logit models for MetS incidence and each of the 5 MetS criteria and (ii) mixed-effects Poisson models for the number of altered MetS criteria. Fixed effect linear models were used to test the association between early weight gain and levels of WC, TG, HDL-C, FPG, DBP, and SBP after 6 months of treatment. Stratified subgroup analyses using mixed effect models was conducted to assess the risk of developing metabolic syndrome separately for patients with more than 2% weight gain and those with no significant weight gain ($\leq 2\%$).

Mixed-effects models represent a well-accepted method for analyzing longitudinal clinical data in which missing or mistimed observations are present (Fitzmaurice et al., 2001). They have been previously applied to examine the association between antidepressants and weight gain (Blumenthal et al., 2014). All fixed and random effect regression models included main effects for age (years), sex, weight status compared to ideal body weight prior to depression, lifetime duration of MDD (years), and severity of depression as measured by HDRS scores at baseline.

Robust standard errors were used in order to account for the center effect. Secondary analyses were performed to control for TG levels on top of the aforementioned adjustment variables in order to assess whether the relationship between early weight gain and MetS was confounded by baseline TG levels.

Binary logistic regression models and their corresponding Receiver Operator Curves (ROC), Area Under Curve (AUC), and goodness of fit tests were used to assess the predictive and discriminatory power of early weight gain. Sensitivity (SEN), specificity (SPE), positive predictive value (PPV), negative predictive value (NPV) and the optimal probability cut-offs were calculated.

All analyses used Stata v.13. All tests were two-tailed. An alpha level of 5% was used to consider statistical significance.

Results

Sample characteristics

The sample consisted of 260 patients (227 in-patients and 33 out-patients) at baseline, of whom 181 (69.6%) were females. The patients' mean age (\pm SD) was 41.6 years (\pm 13.4), and their mean weight and BMI were 59.6 kg (\pm 9.3) and 21.3 kg/m² (\pm 2.4) respectively. Their average lifetime MDD duration was 9.5 years (\pm 11.6), and their average HDRS score at baseline was 24.8 (\pm 4.9); 129 (49.6%) were taking an AD drug before enrollment in the current study but this treatment was withdrawn at inclusion and replaced by another AD treatment, 72.3% of patients had previously taken antidepressant medications. Out of those who had, 103 (56%), 39 (21.2%) and 17 (9.2%) had respectively taken SNRIs, SSRIs and TCA. At baseline, 115 (44.2%), 87 (33.5%), 17 (6.5%) and 41 (15.8%) were respectively on SSRI, SNRI, TCA and other classes of AD; 83 (33.9%), 40 (16.3%), 26 (10.6%), 26 (10.6%) and 14 (5.7%) of patients were respectively taking venlafaxine, escitalopram, Citalopram, paroxetine and clomipramine (table 11). Average daily doses per AD molecule is also described in table 6. No significant association was found between early weight gain and class nor molecule of AD.

Table 11: Distribution of patients treated with each individual antidepressant along with its average dose and the mean/SD/median weight gain with that antidepressant

		Average dose (mg/day)	Percent Weight gain				
			N	%	Mean	S.D	Median
Effexor	Venlafaxine	118	83	33.9	0.9	5	0.6
Séroplex	Escitalopram	12.9	40	16.3	2.1	5.2	1
Deroxat	Paroxétine (chlorydrate)	22.7	26	10.6	2.1	5.3	1.6
Séropram	Citalopram	21.2	26	10.6	2	3.9	2.1
Anafranil	Clomipramine	71.5	14	5.7	0.7	4.2	0.01
Norset	Mirtazapine	21	14	5.7	3	3.8	2.7
Prozac	Fluoxétine	22.7	11	4.5	0.8	2.7	0
Zoloft	Sertraline	50	10	4.1	0.7	5	0.5
Other		25	6	2.5	0.3	4	1
Cymbalta	Duloxétine	60	5	2	0.7	3	0.4
Marsilid	Iproniazide	50	4	1.6	2	2	1.7
Laroxyl	Amitriptyline	100	2	0.8	3.5	0.6	3.5
Floxyfral	Fluvoxamine	175	2	0.8	-3.1	4.4	-3.1
Moclamine	Moclobémide	300	1	0.5	0.8		0.8
Ludiomil	Maprotiline	25	1	0.4	1.4		1.4

The mean duration of follow-up was 4.9 months \pm 4.6. 124 patients (47% of patients) dropped out prematurely— 89 (34%) between 1 and 3 months and 35 (13%) later. The reasons for dropping out were: lost to follow-up (43.3%), antidepressant drug change (39.7%), prescription of antipsychotics or mood stabilizers (9.2%), diagnosis change (mainly from MDD to bipolar disorder) (4.3%), withdrawal of consent (2.8%), and death (0.71%). Completers and non completers did not differ in age, sex, lifetime duration of MDD, lifetime duration of prior antidepressant medication, HDRS score at baseline, or current antidepressant treatment. Among the 127 patients completing the study, we were able to calculate MetS status after 6 months for 120 patients, as the remaining 7 had missing data on at least 1 of the 5 MetS criteria.

Table 12: Comparison between early and non-early weight gainers for socio-demographic and metabolic variables

	Total		Early weight gain		No Early weight gain		p	p*
	N=260	%	N=64	%	N=196	%		
Age, m (sd)	41.6	13.4	41.5	14	41.7	13.3	0.95	
Sex								
Females (%)	181	69.6	37	57.8	144	73.5	0.02	
MDD duration (years), m(sd)	9.5	11.6	8.5	12.7	9.9	11.2	0.41	
HDRS score at baseline m(sd)	24.8	4.9	26.2	5.3	24.4	4.7	0.01	
Smoking, n (%)	109	41.9	32	50	77	39.3	0.31	
BMI (M0), m(sd)	21.1	2.3	20.9	2.5	21.1	2.2	0.52	
Class of A.D, n (%)								
SSRI	114	43.8	27	42.2	87	44.4	0.41	
SRNI	88	33.9	22	34.4	66	33.7		
TCA	17	6.5	3	4.7	14	7.1		
Other	41	15.8	12	18.8	29	14.8		
MetS								
M0, n/N, (%)	0/260	0	0/64	0	0/196	0	-	0.2
M3, n/N, (%)	15/167	9.0	6/36	16.7	9/131	6.9	0.07	
M6, n/N, (%)	12/120	10.0	5/21	23.8	7/99	7.1	0.02	
# of MetS dysregulations								
M0 m(sd)	1	0.8	1	0.9	1	0.8	0.9	0.05
M3 m(sd)	1.2	1.0	1.6	1.1	1.1	0.9	0.01	
M6 m(sd)	1.3	1.1	2.1	1.3	1.2	1.0	0.01	
High WC								
M0, n/N, (%)	94/260	36.1	21/64	32.8	73/196	37.2	0.52	0.76
M3, n/N, (%)	80/170	47.1	21/37	56.8	59/134	44.4	0.18	
M6, n/N, (%)	69/123	56.1	15/21	71.4	54/102	59.9	0.12	
High FPG								
M0, n/N, (%)	22/259	8.5	6/63	9.5	16/196	8.2	0.73	0.79
M3, n/N, (%)	27/170	15.9	8/37	22.2	19/134	14.2	0.24	
M6, n/N, (%)	19/122	15.6	6/21	28.6	13/102	12.9	0.07	
High BP								
M0, n/N, (%)	51/260	19.6	13/64	20.3	38/196	19.4	0.81	0.51
M3, n/N, (%)	43/171	25.2	12/37	32.4	31/134	23.1	0.20	
M6, n/N, (%)	36/123	29.3	7/21	33.3	29/102	28.4	0.65	
High TG								

M0, n/N, (%)	27/260	10.4	12/64	18.8	15/196	7.7	0.01	0.03
M3, n/N, (%)	22/171	12.9	7/37	18.9	15/134	11.2	0.21	
M6, n/N, (%)	20/123	16.3	8/21	38.1	12/102	11.8	0.01	
Low HDL-C								
M0, n/N, (%)	67/260	25.8	13/64	20.3	54/196	27.8	0.25	0.51
M3, n/N, (%)	24/170	14.1	9/37	24.1	15/134	11.3	0.04	
M6, n/N, (%)	23/123	18.7	7/21	33.3	16/102	15.7	0.06	

P:* P-value reported from logistic regression mixed models accounting for the repeated measures of the metabolic parameters

Early weight gain

Percentage of early weight gain was normally distributed. Its mean (\pm S.D) was 2% (4.1). 49 patients (18.8%) gained at least 5% of their initial body weight. 33.6% and 10% gained at least 3% and 7% of their initial body weight, respectively. An early weight gain $>5\%$ was significantly associated with a higher rate of premature drop out as compared to the absence of early weight gain (67% vs 47%, $p= 0.03$).

Mets and metabolic parameters

In the whole sample (Table 12), 15/167 patients (9%), and 12/120 (10%) had developed MetS after 3 and 6 months respectively. The average number of MetS criteria increased from 1.0 ± 0.8 at baseline to 1.3 ± 1.1 at 6 months.

For completers (Table 13), the MetS incidence was 13/127 (10.2%) in the first 3 months and 12/120 (10%) after 6 months. During the follow-up period, the prevalence of high TG levels and high WC increased significantly from 10.5% to 16.3% and 40.3% to 56.1%, respectively. The prevalence of the remaining three criteria increased, though not significantly during the 6 months follow-up period (Table 13).

Table 13: Comparison between early and non-early weight gainers for socio-demographic and metabolic variables in the subgroup of completers

	Total		Early weight gain		No Early weight gain		p	p*
	N=124	%	N=21	%	N=103	%		
Age, m (sd)	42.2	12.8	44.1	13.5	41.9	12.8	0.46	
Sex								
Females (%)	86	69.4	12	57.1	74	71.8	0.18	
MDD duration (years), m(sd)	9.5	11.5	7.2	11.5	10.0	11.5	0.33	
HDRS score at baseline m(sd)	25.0	4.8	27.0	6.5	24.8	4.8	0.06	
Smoking, n (%)	54	43.6	11	52.4	43	41.8	0.62	
BMI (M0), m(sd)	21.3	2.1	20.1	2.1	21.4	2.1	0.36	
Class of A.D, n (%)								
SSRI	56	45.2	9	42.8	47	45.6	0.96	
SRNI	44	35.5	7	33.3	37	35.9		
TCA	10	8.1	2	9.5	8	7.8		
Other	14	11.3	3	14.3	11	10.7		
MetS								
M0, n/N, (%)								0.03
M3, n/N, (%)	13/124	10.4	5/21	23.8	6/100	6.0	0.07	
M6, n/N, (%)	12/120	10.0	5/21	23.8	7/99	7.1	0.02	
# of MetS dysregulations								
M0 m(sd)	1.0	0.8	1.0	0.8	1.0	0.8	0.81	0.01
M3 m(sd)	1.1	1.0	1.8	1.2	1.1	1.0	0.01	
M6 m(sd)	1.3	1.1	2.1	1.3	1.2	1.0	0.01	
High WC								
M0, n/N, (%)	50/124	40.3	8/21	38.1	42/103	40.8	0.48	0.04
M3, n/N, (%)	57/121	47.1	13/21	61.9	44/100	44.0	0.13	
M6, n/N, (%)	69/123	56.1	15/21	71.4	54/102	52.9	0.12	
High FPG								
M0, n/N, (%)	10/124	8.1	3/21	15.0	7/103	6.8	0.21	0.09
M3, n/N, (%)	20/121	16.5	7/21	33.3	13/100	13.0	0.02	
M6, n/N, (%)	19/122	15.6	7/21	33.3	13/101	12.9	0.07	
High BP								
M0, n/N, (%)	18/124	14.5	2/21	9.5	16/103	15.5	0.463	0.62
M3, n/N, (%)	33/121	27.3	8/21	38.1	25/100	25.0	0.22	
M6, n/N, (%)	36/123	29.3	8/21	38.1	29/102	28.4	0.65	
High TG								

M0, n/N, (%)	13/124	10.5	5/21	23.8	8/103	7.8	0.02	<0.01
M3, n/N, (%)	15/121	12.4	5/21	23.8	10/100	10.0	0.08	
M6, n/N, (%)	20/123	16.3	8/21	38.1	12/102	11.8	0.01	
Low HDL-C								
M0, n/N, (%)	35/124	28.2	5/21	23.8	30/103	29.1	0.65	0.79
M3, n/N, (%)	14/120	11.7	4/21	19.5	10/99	10.1	0.24	
M6, n/N, (%)	23/123	18.7	7/21	33.3	16/102	15.7	0.167	

P:* P-value reported from logistic regression mixed models accounting for the repeated measures of the metabolic parameters

Early weight gain as predictor of metabolic parameters

Early weight gainers had a higher prevalence of MetS that was borderline significant after 3 months (16.7% [6/36] vs. 6.9% [9/131], $p=0.07$) and significant after 6 months (23.8% [5/21] vs. 7.1% [7/99], $p=0.02$) of treatment (Table 7). Furthermore, the average number of metabolic parameters increased significantly for early weight gainers as compared to non-weight gainers after 3 months (1.6 vs. 1.1, $p=0.01$) and 6 months (2.1 vs. 1.2, $p=0.01$) (Table 7). In the completers' subgroup (Table 8), early weight gainers had a higher prevalence of MetS after 3 months (23.8% [5/21] vs. 6.0% [6/100], $p=0.01$) and 6 months (23.8% [5/21] vs. 7.1% [7/99], $p=0.02$) of treatment. The average number of metabolic parameters increased significantly for early weight gainers after 3 months (1.8 vs. 1.1, $p=0.01$) and after 6 months (2.1 vs. 1.2, $p=0.01$). Moreover, the adjusted mixed models, showed that the 6 months' increase in both incidence of MetS ($p=0.04$) and the number of metabolic parameters ($p=0.03$) were statistically significant. The fixed effect regression models (Table 3) showed that early weight gainers have a 7.3 ($p<0.01$) and 5.5 ($p<0.01$) higher risk of developing MetS and are at 1.8 ($p<0.01$) and 1.7 ($p<0.01$) higher risk of developing an additional metabolic dysregulation after 3 and 6 months of treatment respectively. No significant association was found between classes of antidepressants and MetS. The logistic regression model exhibited high discriminatory and predictive power of MetS (AUC=0.8, SENS= 67%, SPE=85%, NPV=95%). In a separate analysis (data not shown) controlling for response to treatment, the association between weight gain and MetS after 3 and 6 months did not differ in direction nor magnitude, showing that the relation between weight gain and MetS is also independent from response to treatment.

The average number of metabolic parameters was not different at baseline for the 2 weight groups in the whole sample and for completers. However, the gap between the 2 groups increased significantly at 3 and 6 months (Table 13). Fixed effect regression models also showed that early weight gainers had a three-fold higher risk of having high TG levels ($p=0.03$), were 3 times more at risk of low HDL-C levels ($p=0.002$), and were 7 times more at risk of high WC ($p=0.009$) after 3 months of treatment. The risk of having high WC and high TG levels after 6 months also increased 2 folds as compared to the 3 months measure. In addition, the risk of high

FPG, which was not significant after 3 months of treatment, becomes 2.5 times higher after 6 months ($p < 0.001$) among early weight gainers as compared to non-weight gainers (Table 14).

Table 14: Early weight gain > 5% as a predictor of later incident metabolic syndrome, number of altered MetS parameters, and each parameter in multivariate logistic and Poisson regression models

	After 3 months			After 6 months		
	Risk Measure OR/IRR	95% CI	P	Risk Measure OR/IRR	95% CI	P
MetS	7.3	(5.5 – 9.6)	<0.01	5.5	(3.4 – 8.8)	<0.01
Nb of altered MetS parameters	1.8	(1.4 – 2.3)	<0.01	1.7	(1.6 – 1.9)	<0.01
High WC	7.1	(3.7 – 13.5)	<0.01	15.5	(9.3 – 25.8)	<0.01
High TG	3	(1.3 – 7.0)	0.01	6.2	(2.7 – 14.5)	<0.01
Low HDL-C	3.2	(1.9- 5.6)	<0.01	2.2	(1.2- 4.1)	0.01
High FPG	2.9	(1.0 – 8.5)	0.52	2.5	(1.6 – 3.9)	0.01
High BP	1.7	(0.8 – 3.8)	0.18	0.9	(0.5 – 1.6)	0.71

Legend: Reference group: patients with early weight gain ≤5%.

The predictive power of all fixed effect logistic models was robust with an Area Under the Receiver Operating Curve averaging 0.8 for all models— with the exception of the Low HDL-C -indicating good fit for the data (Figure 6).

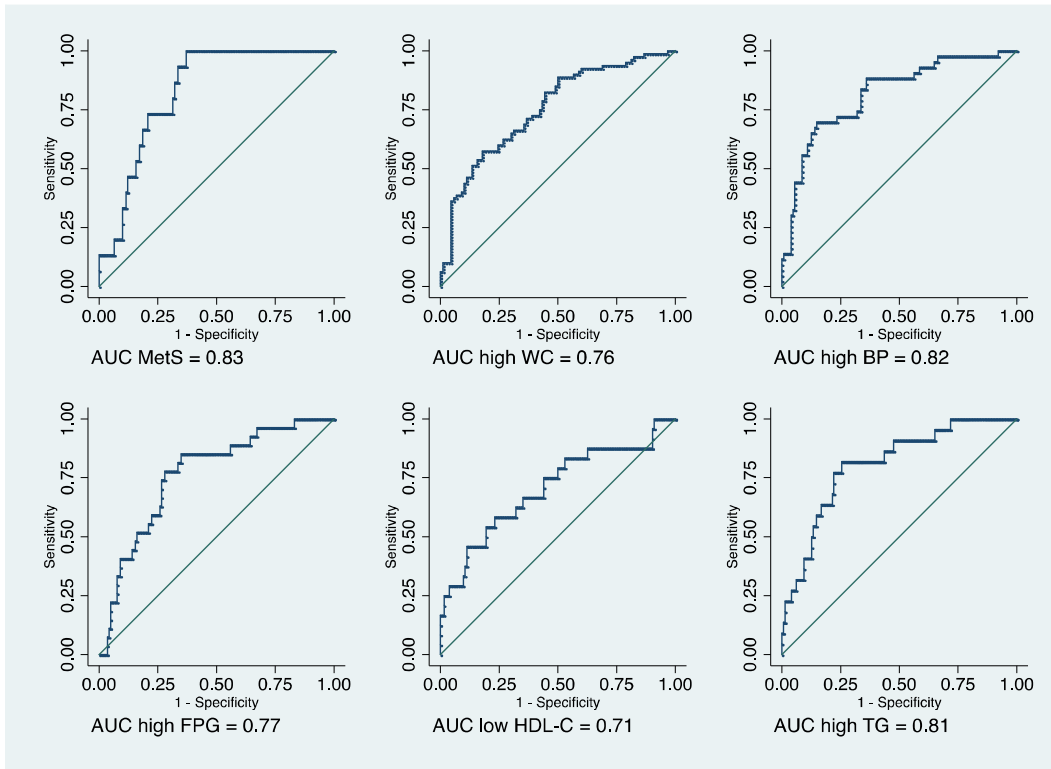


Figure 6: Receiver Operating Curve (ROC) of early weight gain (>5%) for MetS and each of its dysregulation

Analyzing the data longitudinally, linear mixed models showed that independently from sex, age, duration of depression, severity of depression, and classes of antidepressants, percent of early weight gain was found to be a positive predictor of WC [$\beta=6.29$, 95%CI (1.65, 10.94), $p=0.01$], TG levels [$\beta=0.41$, 95%CI (0.13, 0.69), $p=0.01$], and FPG [$\beta=0.13$, 95%CI (0.03, 0.23), $p=0.01$] over a 6-month follow-up period. Although HDL showed a negative trend, the prediction of early weight

gain was not statistically significant [$\beta=-0.05$, 95%CI (-0.15, 0.03), $p=0.21$]. It is worth noting that no association between classes of antidepressants and MetS or metabolic criteria could be observed in any of our multivariate models.

The secondary analyses controlling for high TG levels showed the absence of any significant association between high TG and MetS, while the association between early weight gain and MetS remained significant with a similar OR magnitude.

Weight gain of more than 5% after 1 month of antidepressant treatment was the best predictor of MetS and parameters. The ROC analyses showed that, as compared to models with 3% and 7% cutoffs, the 5% threshold yielded the highest discriminatory power. Indeed, in predicting MetS after 6 months of treatment, the models with early weight gain of $\geq 3\%$ and $\geq 7\%$ had an AUC of 0.7, while the model with an early weight gain $\geq 5\%$ had an AUC of 0.8. More importantly, only the 5% weight gain threshold significantly predicted MetS after 6 months of follow up (SPE= 85%, SEN=67%, NPV=95%) while the 3% and 7% thresholds were not found to be significant predictors of MetS after 6 months. Compared to the 5% threshold, the AUCs of the models containing the 3% and the 7% thresholds were consistently lower for the 5 metabolic parameters (Table 15).

Table 15: AUC for models reporting measures of morbidity (OR) for patients having a $> 3\%$ and $>7\%$ weight gain versus $\leq 3\%$ and $\leq 7\%$ respectively

	AUC for models with 3% weight gain cut-off	AUC for models with 7% weight gain cut-off
MetS	0.7	0.7
High WC	0.7	0.7
High TG	0.7	0.7
Low HDL-C	0.7	0.7
High FPG	0.7	0.7

High BP	0.8	0.8
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Subgroup analysis

A subgroup analysis stratifying patients into 3 distinct sub-groups: (i) those with weight loss, (ii) those with no significant weight gain ($\leq 2\%$) and those who gained weight ($> 2\%$), showed that only patients who have gained weight were at a higher MetS incidence risk [OR=1.64, 95%CI (1.19;2.27, p=0.002)] and at higher risk of increased number of altered MetS parameters [IRR=1.07, 95%CI (1.02;1.13, p=0.006)] (Table 16).

Table 16: Subgroup analysis for incident of metabolic syndrome and number of altered MetS parameters, stratified by weight change status.

	Weight loss N=82			No significant weight gain ($\leq 2\%$) N=75			Weight gain ($>2\%$) N=103		
	Risk Measure OR/IRR	95% CI	P	Risk Measure OR/IRR	95% CI	P	Risk Measure OR/IRR	95% CI	P
MetS	6.27	(0.39 - 99.4)	0.192	1.41	(0.91-2.17)	0.118	1.64	(1.19-2.27)	0.002
Nb of altered MetS parameters	1.05	(0.98 - 1.11)	0.103	1.01	(0.95-1.07)	0.673	1.07	(1.02-1.13)	0.006

Mixed effect Logit models (for MetS incidence) and mixed effect Poisson models (for nb of altered MetS parameters) controlling for age (years), sex, weight status compared to ideal body weight prior to depression, lifetime duration of MDD (years), and severity of depression as measured by HDRS scores at baseline

Discussion

Among depressed patients, early weight gain (>5%) after initiation of antidepressant treatment predicts the later incidence of MetS and an increased number of MetS criteria. The incidence risk remains significantly high over time with an OR of developing MetS of 7.3 after 3 months and 5.5 after 6 months of treatment. The number of MetS criteria maintains similar incidence rate ratio (IRR) of 1.8 and 1.7 after 3 and 6 months respectively.

This effect is related to some specific criteria of MetS, namely high WC, high TG levels, and low HDL-C levels after 3 months of treatment, in addition to high FPG after 6 months of treatment.

The association between the 5% weight gain threshold with MetS and its metabolic parameters (namely WC, TG, and FPG) increased from 3 to 6 months after the beginning of antidepressant treatment, suggesting an increased risk of developing metabolic abnormalities over a more prolonged period of time. Our analyses do control for whether or not patients lost weight as part of their depression by controlling for weight status compared to ideal body weight prior to depression, therefore the adverse association between weight gain and MetS is independent from the fact that some patients had lost weight as a result of their depression.

We show that the threshold of 5% for early weight gain is the best predictor of MetS and its metabolic parameters as compared to a 3% or 7% threshold. While the 3% cut-off lacked predictive power due to its small effect size, the 7% cut-off lacked statistical power due to a limited sample size.

To the best of our knowledge, no previous study has assessed the incremental risk of early weight gain on later MetS incidence among non-overweight depressed patients. However, a study by Vandenberghe (2015) did show that a weight gain >5% in the first month of psychotropic drugs treatment was significantly associated with prevalence of MetS after 1 year of treatment (Vandenberghe et al., 2015). Our results go beyond the findings of the recent Swiss cohort (Vandenberghe et al., 2015) that has found that a weight gain of more than 5% during the first 30 days of treatment was associated with an increase of TG levels and a decrease in HDL. The results from the Swiss cohort pertain to all psychiatric patients, while our results are derived from a specific group of metabolically healthy (MetS-free and not-overweight at baseline) and clinically depressed patients with MDD and a current MDE.

Our results are comparable to findings from antipsychotics literature that show antipsychotics have been associated with early and regular weight gain as well as increased prevalence of MetS and MetS dysregulations (Lambert and Newcomer, 2009, Martínez-Ortega et al., 2013, Mitchell et al., 2013, Vandenberghe et al., 2015).

Several strengths could be highlighted in the present study. It is the first prospective real life cohort of non-overweight MDE patients, without MetS, treated prospectively with antidepressant monotherapy but without antipsychotics or mood stabilizers, and that assesses prospectively MetS and each of its five components, with a reasonable sample size and follow-up duration. It also takes into account a range of socio-demographic, clinical, and therapeutic features including lifetime MDD duration, depression severity at baseline, and current antidepressant medication. Our results about weight gain with antidepressants are close to those of the literature (Dannon et al., 2007, Kivimäki et al., 2010, Michelson et al., 1999, Sussman and Bikoff, 2001) suggesting their generalizability. Another strength lies in the multivariate models, which showed that the associations between early weight gain on the one hand and MetS and number of metabolic parameters on the other remain significant after adjusting for several clinical and demographic confounding variables. The results from the stratified subgroup analysis, further validate the association between weight gain and MetS incidence, by showing that only the group of patients who have gained weight had an increased risk of MetS incidence and number of altered MetS parameters.

Our results focus on a particularly pure sample of patients with MDD and current MDE who are normal weight with no MetS. With no studies published on this specific sub-group, our results are considered highly relevant as they provide insight about the pathway connecting AD monotherapy with subsequent weight gain and developing MetS. Furthermore, our definition of early weight gain (in the first 30 days of treatment) is more conservative than other studies. In fact none of the identified studies that have assessed the effects of antidepressants on weight gain did so in using the definition that is shorter than 6 weeks' time.

There are several caveats in interpreting these results. First, the study sample cannot be considered as a representative sample of the general French population of patients with MDD in ordinary clinical practice, as it only collected data from 6 university psychiatric departments and

didn't aim to generalize prevalence of MDD. Second, because medication selection was not randomly assigned, physicians may have taken potential for weight gain into account for specific patients which could introduce a confounding by medications effect. Third, the attrition rate of this sample was relatively high, and the results from the multivariate analysis were based on 120 out of the 260 recruited patients; nonetheless the attrition rate in our study was quite similar to that of STAR-D (Warden et al., 2009a, Warden et al., 2009b). A comparative analysis was done, and results were similar for patients who dropped out and those who have completed the study. Furthermore, study discontinuation has to be looked at, taking the effect of early weight gain into consideration. In fact, weight gain is a main undesired effect of AD treatment and a major reason for treatment discontinuation during the first 8 weeks of treatment initiation (Goethe et al., 2007, Uher et al., 2011). In the present study, 67% of early weight gainers have discontinued the study as opposed to 47% of non-early weight gainers, further supporting the common hypothesis from the literature.

Finally, our results did not find any association between MetS, number of altered MetS parameters, or individual MetS dysregulations on the one hand and classes of antidepressant on the other. These results are coherent with those of Martínez-Ortega (2013) with other psychotropic treatments but have to be taken cautiously because the absence of randomization of the cohort (Martínez-Ortega et al., 2013).

An early weight gain of more than 5% in the first month of antidepressant treatment predicts later metabolic syndrome in non-overweight depressed patients treated with antidepressants in psychiatric settings. It should therefore raise psychiatrists' concerns about the patients' cardio-metabolic profile.

Chapter 4: A structural equation model to explore the relationship between early weight gain and MetS incidence

This chapter will be published as an article as part of the post-doc objectives

Objectives

In this chapter we use structural equation modeling to test the theoretical model that early weight gain precedes the onset of MetS, and whether the relationship between MetS and other clinical variables (response to treatment, depression severity, duration of illness at time of enrollment, class of AD treatment, age and sex) is mediated by early weight gain. We consider MetS as a single latent variable suggestive of a common pathophysiology of the 5 individual factors. This chapter focuses on the same subsample of 260 non-overweight and “metabolically healthy” MDD patients.

Methods

Metabolic Syndrome

The assessment of MetS is identical to that described in the methods section of chapter 3.

Assessment of Weight gain

The assessment of weight gain is identical to that described in the methods section of chapter 3.

Statistical analysis

An exploratory factor analysis (EFA) with varimax rotation was conducted in order to identify the underlying structure of MetS. A screeplot was generated in order to visualize the different eigenvalues to be retained. This approach also called parallel analysis was described by Horn (1965), and it suggests that eigenvalues larger than 1 should be retained. A confirmatory factor analysis (CFA) was then performed in order to determine if the emergent factors believed to compose MetS conform to what is expected based on the findings from the literature (Brown, 2006).

The constituents of MetS were chosen based on the IFD definition and these were: waist circumference, fasting glucose, HDL cholesterol, fasting triglyceride levels, and systolic blood pressure (Eckel et al, 2005).

Given that latent variables do not have units of measurement, the variance of the factor with the highest factor loading in the exploratory factor analysis was constrained to 1.0 and was designated as the metric for the CFA. Structural equation modeling (SEM) was used to test the theoretical model against the observed dataset that early weight gain precedes the onset of MetS. The goodness of fit of the hypothesized factor structure was tested using the Chi-square (χ^2) statistic, root mean squared error of approximation (RMSEA), the standardized root mean square residual (SRMR), and the Comparative Fit Index (CFI) (Kline, 2005; Hu et al, 1999). Pearson Chi-squared tests and independent samples t-tests were used to assess statistical differences of clinical and socio-demographic characteristics as well as metabolic parameters between early weight gainers and non-weight gainers.

Results

Sample profile

For details about the sample profile, please refer to chapters 2 and 3.

Metabolic Syndrome factor analysis

The confirmatory factor analysis for the latent construct of MetS contained five observed variables as derived from the IFD definition, and these were: Waist circumference, HDL-C level, triglycerides level, SBP, and FPG. The performance of the one factor model was tested using Stata 13. Previous studies have identified a strong association between HDL-C and triglycerides (Shen et al, 2003). Therefore, a correlated residual between HDL and triglycerides was introduced into the model. A one factor model was constructed where each of the 5 observed variables were fitted to load onto the single factor. A correlation between the error terms of HDL-C and triglyceride was designated (Figure 7). Four of the five components (with the exception of MetS) loaded significantly on the latent MetS construct. The error term (residuals) correlation between triglycerides and HDL-C was also statistically significant (standardized coefficient=-0.164, P-value=0.009). The one factor CFA had a comparative fit index (CFI) of 0.9, a root mean squared error of approximation (RMSEA) of

0.08 and a standardized root mean square residual (SRMR) of 0.04. These results suggest that the latent MetS construct had a moderate to good fit.

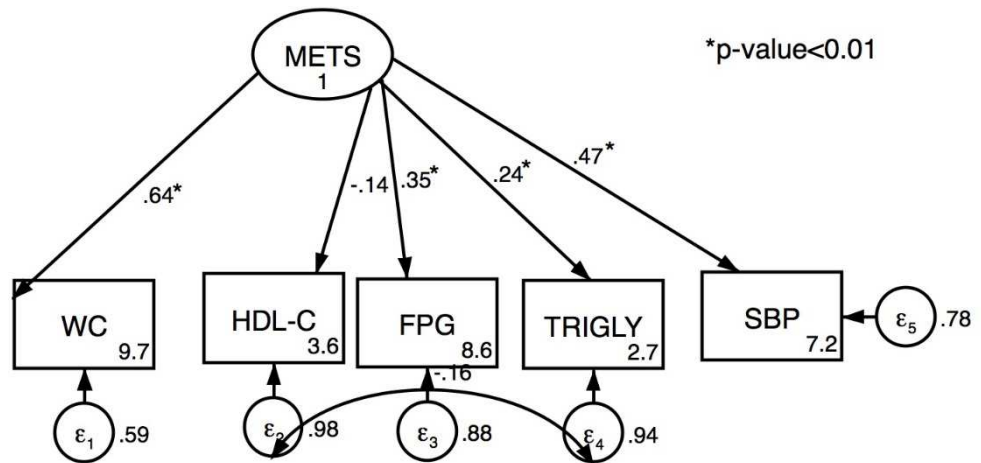
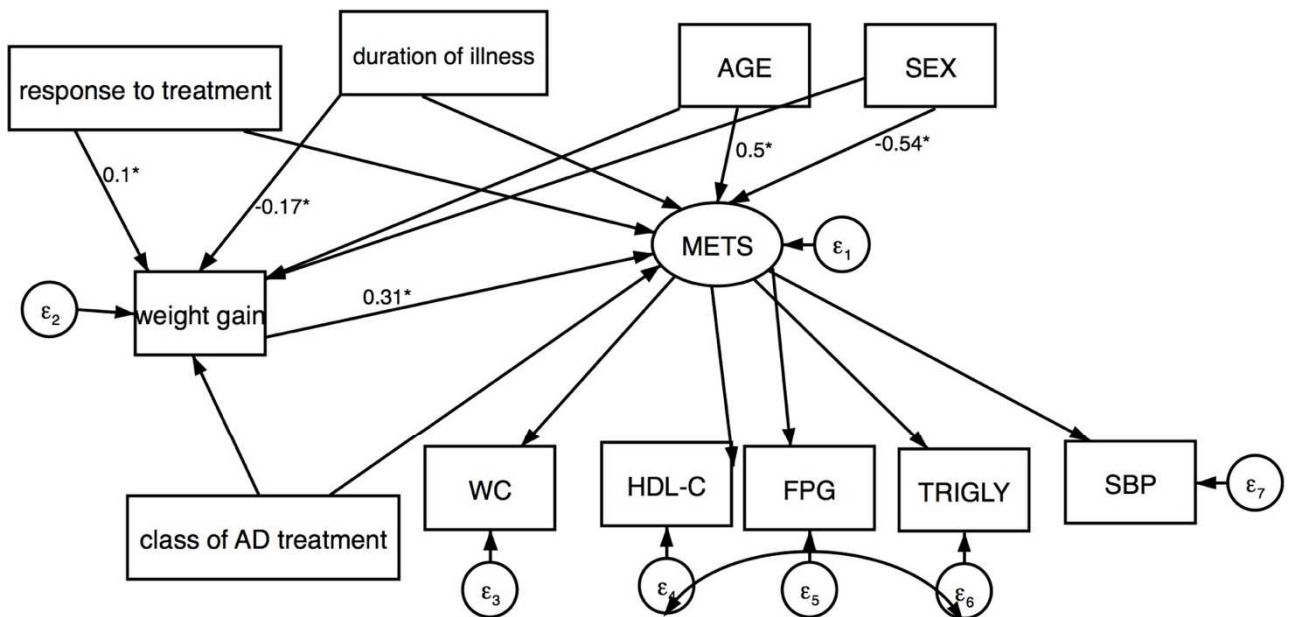


Figure 7: CFA One-Factor standardized solution for the metabolic syndrome

Structural equation modeling

The structural equation model was fit to model the relationship between the clinical variables and early weight gain on one hand, and between early weight gain and MetS on the other. The model also helped in assessing whether weight gain had a moderating effect on the relationship between the clinical variables (class of AD treatment, age, sex, severity of depression and duration of illness) and MetS. Figure 8 displays the path coefficients between the observed variables and the latent MetS construct. Early weight gain was positively and significantly correlated with MetS (Standardized coeff: 0.1, p-value < 0.001) and response to treatment (Standardized coeff: 0.5, p-value < 0.001), but negatively correlated with duration of the depression illness (Standardized coeff: -0.17), p-value < 0.001). The absence of a direct effect between duration of illness and response to

treatment on one hand and MetS on the other, infer that the relationship between these two variables and MetS is totally mediated by early weight gain. Age and sex were significantly associated with MetS where the male sex (Standardized coeff: 0.5, p-value<0.001) and older age (Standardized coeff: -0.5, p-value<0.001) being risk factors for MetS. In the fitted model, the 5 constituents of MetS loaded significantly on the latent MetS construct, indicating that the measurement model (the model examining the relationship between MetS and its measures) performs well within the overall structural model. With a CFI of 0.8, a RMSEA of 0.09 and a SRMR of 0.06, the structural equation model exhibited an average fit to the data.



*P-value<0.05

Figure 8: Structural Equation Model of the relationship between the latent MetS construct and early weight gain

Discussion

Although the literature remains inconclusive about the presence of a single pathophysiological mechanism that accounts for the clustering of the 5 MetS dysregulations, principle component analysis (PCA) have suggested that 2 or 3 dysregulations were needed to account for the majority

of the variance in MetS. Four variables (WC, FPG, HDL-C and triglycerides) consistently loaded together on the first component, which is in agreement with a metabolic syndrome factor. These results were independent of age, ethnicity or race (Alberti et al., 2005; Ford, 2003). An other study utilizing CFA to model the structure of MetS has demonstrated that the proposed one factor overarching structure was well supported across younger and older participants and across individuals with and without cardiovascular disease (Shen et al 2003). Controversy remains as whether MetS should be considered as a single latent factor predicted by 5 discrete factors or whether it really is a compilation of 5 dysregulations and should therefore be treated as an observed variable. Indeed, these controversies remain of relevant theoretical and clinical significance. In fact, our CFA and SEM showed a satisfactory but not an exceptional model fit, which could be due to the particularities of our sample (non overweight MDD patients). While the factor structure of MetS has been previously tested (Shen et al 2003; Ford, 2013; Stevenson et al, 2012), it was never tested on a population of MDD patients. As discussed in previous chapters, SEM offers some advantages over traditional statistical models in terms of being able to estimate, total, direct and indirect effects among various exposure and outcome variables. In our case, SEM was used to test whether early weight gain mediated the relationship between response to treatment, AD treatment, duration of illness, age, and sex on one hand and MetS on the other. The results showed that weight gain fully mediated the relationship between response to treatment and duration of depression on one hand and MetS on the other. The results also suggest that weight gain affects MetS independently from age and gender. These results are concordant with the results from the previous chapter using logistic regression models, which have shown that early weight gain predicts later MetS incidence. Our findings highlight the robustness of our hypothesis that a weight gain as small as 5% is a significant predictor of later MetS incident. The results of this study strongly highlight the importance of early weight screening and detection of early weight gain in identifying individuals at a risk for MetS.

Several studies have suggested early weight gain was a predictor of MetS. A 5-year interval observational study of 1384 adult employees at an electronic manufacturing company concluded that individuals experiencing moderate weight gain (between 5 to 10%) were 3 times more likely to develop MetS compared to those who did not gain weight (Lin et al., 2011). A linear trend

between weight gain and worsening of all MetS components was reported over a 6-year follow up period (Hillier et al., 2006). A similar trend was among 3467 adult Iranian men and women followed for 3 years. Zabetian et al (2009) concluded that weight gain exceeding 4% in men or 1.3% in women would increase the risk of MetS (Zabetian et al., 2009). The findings of this chapter add to the body of literature and reveal a statistically significant association between early weight gain and MetS. To our knowledge, no other study has investigated the relationship between early weight gain and MetS using both structural path components and measurement models. The results go beyond those of the previous chapter, where the logistic regression models (which only allow to assess a direct effect) showed an absence of a significant association between response to treatment and MetS.

The results of the SEM were able to detect an indirect effect between response to treatment and MetS that is mediated by weight gain. The absence of a direct association between treatment response and MetS, is in agreement with findings from a recent pooled post hoc analysis of 4279 patients randomized to receive either desvenlafaxine or a placebo, that showed that response to Desvenlafaxine was independent from MetS status (McIntyre et al., 2016). However, our results show that if response to treatment is accompanied by weight gain, then the patient is likely to develop MetS; suggesting an indirect effect of response to treatment on MetS.

The study has several strengths. To our knowledge, this is the first study that uses CFA and SEM in order to investigate the multi-directional relationship between weight gain, response to AD treatment and MetS, among a population of non-overweight MDD patients. The prospective nature of the METADAP study, allowed the SEM to faithfully represent the clinical trajectories leading to MetS. The results from the SEM are concordant with those from the standard regression analysis (presented in the previous chapter) indicating their robustness. They even go beyond the previous ones, by presenting a trajectory for the association between the clinical factors and MetS.

Nevertheless, the study has some limitations that should be highlighted. First, although the CFA showed satisfactory fit, however it was no ideal. Compared to other published studies from the literature (Shen et al 2003; Ford, 2013; Stevenson et al, 2012), our CFA for the one factor structure of MetS exhibited a relatively poorer fit. The reason could be attributed to the fact that the 1

factor MetS was never tested in a population of non-overweight MDD patients. Second, the study sample cannot be considered as a representative sample of the general French population of patients with MDD in ordinary clinical practice, as it only collected data from 6 university psychiatric departments and didn't aim to generalize prevalence of MDD. Finally, our results did not find any association between MetS and classes of antidepressant. These results are coherent with those of Martínez-Ortega (2013) with other psychotropic treatments but have to be taken cautiously because the absence of randomization of the cohort (Martínez-Ortega et al., 2013).

Chapter 5: Other publications

The following chapter presents additional collaborations to research articles stemming from the METADAP cohort, in which I contributed as my capacity as a statistician, during my doctoral studies. Specifically I have contributed to the drafting of the analysis plan, validation of the statistical analysis in cases where the main author was capable of running the analysis independently, and leading on the statistical analysis whenever the main author faced challenges in running the analysis independently. I have also contributed to the revision of the manuscripts after receiving peer reviews

Article 1

Severe insomnia is associated with hypertriglyceridemia in women with major depression treated in psychiatry settings: *Costemale-Lacoste JF, Trabado S, Verstuyft C, El Asmar K, Butlen-Ducuing F, Colle R, Ferreri F, Polosan M, Haffen E, Balkau B, Falissard B, Feve B, Becquemont L, Corruble E. J Affect Disord. 2017 Aug 1;217:159-162. doi: 10.1016/j.jad.2017.04.011. Epub 2017 Apr 9.*

background

Hypertriglyceridemia (HTG) is a cardiovascular risk factor. In the general population, elevated fasting triglyceridemia (TG) is associated with insomnia. Since insomnia is a core symptom of Major Depressive Episodes (MDE), we studied the association of severe insomnia with HTG in major depression.

methods

We used the baseline data of the METADAP cohort, comprising 624 patients with a current MDE in a context of Major Depressive Disorder treated in psychiatry settings, without current alcohol use disorders. Patients were screened for severe insomnia, defined by a score of four or more on the three Hamilton Depression Rating Scale (HDRS) sleep items, and for HTG characterised by $TG \geq 200 \text{mg/dL}$.

results

Severe insomnia was observed in 335(54%) patients with a current MDE, of whom 234(70%) were women; 49(8%) patients had HTG, of whom 25(51%) were women. 69(11%) patients were treated

with lipid-lowering drugs. Severe insomnia was associated with a higher frequency of HTG in the whole sample (9.9% vs 5.6%, $p=0.046$) and in the subgroup of women (9.0% vs 2.0%, $p=0.002$). Multivariate logistic regression analyses adjusted for age, education levels, BMI and total HDRS scores confirmed the association between severe insomnia and HTG in the whole sample (OR=2.02, 95%CI [1.00-4.08], $p=0.05$) as well as in the subgroup of women (OR=4.82, 95%CI [1.5-15.5], $p=0.008$). No association was shown in men.

perspectives

HTG should be systematically investigated in depressed patients with severe insomnia and particularly in women. Further studies are needed to explain the association we observed between severe insomnia and HTG.

Article 2

Should a routine genotyping of CYP2D6 and CYP2C19 genetic polymorphisms be recommended to predict venlafaxine efficacy in depressed patients treated in psychiatric settings? *Taranu A, Colle R, Gressier F, El Asmar K, Becquemont L, Corruble E, Verstuyft C. Pharmacogenomics. 2017 May;18(7):639-650. doi: 10.2217/pgs-2017-0003. Epub 2017 May 8.*

Objectives

The antidepressant venlafaxine (VEN) is metabolized by CYP2D6 and CYP2C19. The aim of this study was to assess the relevance of generalizing to daily practice the genotyping of CYP2D6 and CYP2C19 to predict VEN efficacy in depressed patients treated in psychiatric settings.

Methods

This study was nested in a naturalistic cohort, with 206 patients requiring a new antidepressant treatment and genotyped for CYP2D6 *3, *4, *5 del, *6, *2xN, *10, *41 and CYP2C19 *2, *3, *4, *5, *17 alleles.

Results

CYP2D6 and CYP2C19 phenotypes were associated neither with the Hamilton depression rating scale score improvement, nor with response and remission.

Conclusion

Routine CYP2D6 and CYP2C19 genotyping cannot be recommended to predict VEN efficacy in depressed patients treated in psychiatry settings.

Article 3

The Catechol-O-methyltransferase Val(108/158)Met Genetic Polymorphism cannot be Recommended as a Biomarker for the Prediction of Venlafaxine Efficacy in Patients Treated in Psychiatric Settings. *Taranu A, Asmar KE, Colle R, Ferreri F, Polosan M, David D, Becquemont L, Corruble E, Verstuyft C.*

Basic Clin Pharmacol Toxicol. 2017 Nov;121(5):435-441. doi: 10.1111/bcpt.12827. Epub 2017 Aug 6.

Background

The antidepressant venlafaxine is known to increase the turnover of cerebral monoamines, which are catabolized by the catechol-O-methyltransferase (COMT). The COMT (Val(108/158)Met, rs4680) genetic polymorphism affects the cerebral COMT activity. But whether this genetic polymorphism is associated with response to venlafaxine remains unclear.

Objectives

We assessed the impact of the COMT Val(108/158)Met, rs4680 genetic polymorphism on the efficacy of venlafaxine in depressed patients. This study was nested in the METADAP cohort, a real-world naturalistic treatment study in psychiatric settings. A total of 206 Caucasian patients with a unipolar major depressive episode (DSM-IVTR) treated with venlafaxine and evaluated with the Hamilton Depression Rating Scale (HDRS) were studied.

Results

One hundred and eighty patients were genotyped for the COMT Val(108/158)Met, rs4680 genetic polymorphism and classified into three genotype subgroups: Val/Val, Val/Met and Met/Met. The COMT genotype was the explanatory variable, and the variables to be explained were HDRS score, HDRS score improvement over time, response rate and remission rate. Venlafaxine had a trend to higher efficacy in the Val/Val patients as compared to Met/Met carriers, as shown by the HDRS

score improvement after 3 months of treatment, but this result was not significant in mixed models [Val/Val: 59.78% (± 22.4); Val/Met: 51.64% (± 26.3); Met/Met: 39.52% (± 27.6)]. The percentage of responders and remitters after 3 months of treatment was not significantly different in the three genotype groups, although coherent trends were shown.

Conclusion

The COMT Val(108/158)Met, rs4680 genetic polymorphism cannot be recommended as a biomarker for the prediction of venlafaxine efficacy in patients treated in psychiatric settings.

Article 4

The association of β -arrestin2 polymorphisms with response to antidepressant treatment in depressed patients. *Petit AC, El Asmar K, David DJ, Gardier AM, Becquemont L, Fève B, Verstuyft C, Corruble E.*

Prog Neuropsychopharmacol Biol Psychiatry. 2018 Feb 2;81:74-79. doi: 10.1016/j.pnpbp.2017.10.006. Epub 2017 Oct 12.

Background

The study of genetic polymorphisms involved in antidepressants (AD) response is essential to provide a personalized medicine approach in the field of depression. β -arrestin 2 (ARRB2) is a candidate gene in the pharmacogenetics of AD as it is involved in the signaling cascade downstream of numerous neurotransmitter receptors.

Methods

We investigated the association between five ARRB2 single nucleotide polymorphisms (SNPs): rs1045280, rs2036657, rs4790694, rs3786047 and rs452246, and response to AD treatment in a sample of 569 patients with a major depressive episode treated for 6 months.

Results

We show that GG/GT patients for rs4522461 (n=534) and AA/AC patients for rs4790694 (n=244) have a lower response to AD than other genotype groups (HDRS score of 10.9 vs 8.0 after 6 months, multivariate analysis: p=0.03; 12.2 vs 9.6, p=0.02, respectively).

Conclusion

These data provide additional evidence that β -arrestin 2 is a regulator of intracellular signal transduction processes involved in AD treatment.

Article 5

Framingham coronary score in individuals with symptoms or diagnoses of mental disorders: A review and meta-analysis. *Rigal A, Colle R, El Asmar K, Elie-Lefebvre C, Falissard B, Becquemont L, Verstuyft C, Corruble E. Psychiatry Res. 2018 May;263:41-47. doi: 10.1016/j.psychres.2018.02.035. Epub 2018 Feb 19. Review.*

Background

Patients with mental disorders have a higher coronary morbidity and mortality as compared to the general population. However, it remains unclear whether their coronary risk scores are higher than those of the general population.

Methods

We reviewed studies and meta-analyze case-control studies about coronary risk scores in individuals with symptoms or diagnoses of mental disorders. Search was performed in Pubmed and clinical trial registration databases. Four case-control studies were identified, comprising 963 individuals with symptoms or diagnoses of mental disorders and 1681 controls. They focused on the most validated coronary risk score, the Framingham Risk Score 1998 (FRS 1998).

Results

The mean FRS 1998 was significantly higher in individuals with symptoms or diagnoses of mental disorders than in the general population $7.9 (\pm 6.9)$ vs. $5.0 (\pm 4.8)$. FRS 1998 differs between individuals with symptoms or diagnoses of mental disorders and controls (Mean difference:1.84 [95% CI:0.57-3.11], $p = 0.005$); high heterogeneity was observed ($I^2 = 78\%$; $p < 0.003$). The difference was driven by three FRS 1998 criteria: smoking, diabetes and HDL cholesterolemia. The mean FRS 1998 was significantly higher in men, and to a trend in women. In conclusion, individuals with symptoms or diagnoses of mental disorders have a higher coronary risk score than controls.

Conclusion

The FRS 1998 should be used as a simple and objective way of monitoring coronary risk in order to improve prevention of coronary events in psychiatric settings.

Article 6

Glycogen Synthase Kinase-3 β genetic polymorphisms and insomnia in depressed patients: a prospective study. Jean-Francois Costemale-Lacoste , Romain Colle , Severine Martin , [Khalil El Asmar](#) , Emanuel Loeb , Bruno Feve , Celine Verstuyft , S ´ everine Trabado , Florian Ferreri , Emmanuel Haffen , Mircea Polosan , Laurent Becquemont , Emmanuelle Corruble. 2018. Journal of Affective Disorders. DOI: 10.1016/j.jad.2018.07.062

Background

80-90% of patients with Major Depressive Episode (MDE) experience insomnia and up-to 50% severe insomnia. Glycogen Synthase Kinase-3 β (GSK3B) is involved both in mood regulation and circadian rhythm. Since GSK3B polymorphisms could affect protein levels or functionality, we investigated the association of GSK3B polymorphisms with insomnia in a sample of depressed patients treated with antidepressants. [Methods](#)

In this 6-month prospective real-world treatment study in psychiatric settings (METADAP), 492 Caucasian patients requiring a new antidepressant treatment were included and genotyped for five GSK3B Single Nucleotide Polymorphisms (SNPs) (rs6808874, rs6782799, rs2319398, rs13321783, rs334558). Insomnia and MDE severity were rated using the Hamilton Depression Rating Scale (HDRS). Bi and multivariate analyses were performed to assess the association between GSK3B SNPs and insomnia (main objective). We also assessed their association with MDE severity and HDRS response/remission after antidepressant treatment.

Results

At baseline severe insomnia was associated with the GSK3B rs334558 minor allele (C+) [OR=1.81, CI95%(1.17-2.80), p=0.008]. GSK3B rs334558 C+ had greater insomnia improvement after 6 months of antidepressant treatment (p=0.007, β =0.17, t=2.736). No association was found between GSK3B SNPs and MDE baseline severity or 6-month response/remission.

Conclusion

GSK3B rs334558 was associated with insomnia but not with MDE severity in depressed patients. Targeting GSK3B in patients with MDE and a severe insomnia could be a way to improve their symptoms with greater efficiency. And it should be further studied whether the GSK3B-insomnia association may fit into the larger picture of mood disorders.

Chapter 6

Clinical implications

While the bidirectional relationship between depression and MetS has been well established in the literature, the impact of AD treatment on cardio-vascular health in general and MetS in particular remains to be cemented. The results from the first chapter show that treating major depressive episodes with antidepressants induces or worsens metabolic syndromes. This effect occurs early after initiation of treatment and is independent from weight gain and response to treatment. In the second and third chapters we focused on weight gain among non-overweight patients as the driving force behind the relationship between AD treatment and the metabolic syndrome. The results showed that early weight gain of more than 5% in the first month of antidepressant treatment predicts later metabolic syndrome in non-overweight depressed patients treated with antidepressants in psychiatric settings, with a considerable effect size of 5.5. The results also showed correlation between weight gain and number of MetS dysregulations, high WC, and low HDL-C. These findings were also consistent with evidence from the literature that depression is mostly correlated with obesity-related components (abdominal obesity, low HDL-C, hypertriglyceridemia), whereas associations with hyperglycemia and hypertension are confirmed less frequently (Penninx, 2017). Using structural equation modeling, we were able to look beyond the direct effect of early weight gain on MetS incidence. SEM allowed us to test for the mediation effect of early weight gain on the association between response to AD treatment and MetS. Results have shown that weight gain, fully mediated the association between response to treatment and MetS. In other words, unless response to treatment is accompanied with weight gain, the patients is not likely to develop MetS. The fourth chapter assessing the impact of early weight gain on later weight gain showed that compared to non-early weight gainers, patients with early weight gain (>3%) in the first month of antidepressant treatment were at significant higher risk of crucial weight gain (>15%) during the six months of antidepressant treatment. Compared to 5% and 7% early weight gain, the 3% threshold was found to be the best predictor of later weight gain.

The above findings are of high clinical implications. They indicate the necessity of early weight and lipid profile monitoring of patients on AD treatment, especially those who with a “healthier” metabolic profile. Consequently, to avoid excess weight gain and subsequently MetS among depressed patients treated with AD, psychiatrists have to closely monitor these patients for weight change in the first month of treatment and to routinely check for all MetS criteria, with particular attention to WC, HDL and TG in the first 6 months of AD treatment. In case of weight gain of more than 3% in the first month of treatment, psychiatrists and nurses should systematically look at metabolic abnormalities (high Waist Circumference, high Blood Pressure, high triglyceridemia, low HDL-Cholesterolemia, and high Fasting Plasma Glucose) 3 and 6 months later, and refer their patients to general practitioners in case of abnormal values.

Statistical considerations

The multi-directional relationships between depression, the use of AD treatment, weight gain and MetS require the use of flexible statistical models that allow a faithful representation of these associations. While the bi-directional association between depression and cardiovascular illness has been well established, the association between the use of AD treatment and MetS remains less ascertained. As discussed earlier, the literature does provide evidence that MDD patients treated with AD are at an increased risk of weight gain. However, it can also be argued that weight gain could be the result of the recovery from depression. Structural equation modeling has the capacity to disentangle the complex mechanism that links these variables together. In fact, SEM is the only statistical approach that would allow us to identify, test and estimate direct and indirect effects that clinical variables can have on MetS. Furthermore, given the prospective nature of the METADAP study, SEM has enabled us to faithfully represent the sequential clinical trajectories leading to MetS, i.e: initiation of AD treatment at baseline, followed by weight gain after 1 months, which in its turn is followed by MetS incidence after 6 months. However, the use of SEM remained contingent on our ability to present MetS as single latent variable suggestive of a common pathophysiology of the 5 individual MetS factors. While the single factor structure of

MetS has been validated in several studies, to our knowledge it was never tested in a population of non-overweight MDD patients.

Mixed effect models are an alternative (though a less flexible one) for structural equation modeling in analyzing longitudinal and repeated measures data. The main advantage of linear mixed models (LMM) and generalized linear mixed models (GLMM) (McCullagh et al, 1989; Agresti, 2013; Breslow et al, 1993) is that they represent a well-accepted method for analyzing longitudinal clinical data in which missing or mistimed observations are present (Fitzmaurice et al, 2001). With an important attrition rate and the absence of data imputation, linear mixed models (LMM) and generalized linear mixed models (GLMM) remain a better alternative in analyzing longitudinal data than repeated measures ANOVA, because the latter will deal with the missing data through list-wise deletion. Which means that we would only be able to analyze the final sample of completers, which would tremendously reduce our statistical power.

Perspectives

In this dissertation we have studied the relationship between AD treatment, weight gain and MetS on a sample of MDD patients. Clinical findings have suggested that early weight gain due to AD treatment would increase the risk of both later weight gain and later MetS incidence. The relationship between AD use, response to treatment and weight gain remain complex. Despite the simultaneous increase in AD use and obesity trends in Western societies, additional prospective cohorts are needed to fully test the hypothesis that weight gain among AD users is indeed an iatrogenic effect. Although impact of AD on cardiovascular morbidity still cannot be ascertained, the results from the first chapter showed that AD use – irrespective of the class - does impact and worsen metabolic dysregulations, which would require specific clinical attention. A long term cohort study is required to confirm whether discontinuation and re-initiation of AD treatment would be linked to fluctuation in MetS dysregulations. There has been similar studies in which Licht et al (2010) have shown that stoppers and starters of AD were the only groups of subjects with significant (and opposite) change in autonomic activity. However, to the best of our knowledge there hasn't been a study that specifically monitors metabolic dysregulations among a cohort of MDD patients treated with AD.

Although the presented results are based on analyses from a longitudinal cohort (observational study) and not an experimental design, they remain of valuable nature in the absence of a large scale RCT. In fact, in order to effectively ascertain whether AD medication contribute to cardiovascular risk, a long term placebo controlled RCT would be required. However, such a trial might not be financially or ethically feasible, and future psychiatric research about the impact of AD treatment on cardiovascular health will have to rely on prospective studies and meta-analysis of such studies.

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List of publications from dissertation

First publication:

Early weight gain predicts later weight gain in depressed patients treated with antidepressants: Findings from the METADAP cohort.

Asmar KE, Fève B, Colle R, Gressier F, Vievard A, Trabado S, Verstuyft C, Haffen E, Polosan M, Ferreri F, Falissard B, Chanson P, Becquemont L, Corruble E.
J Affect Disord. 2018 Dec 1;241:22-28. doi: 10.1016/j.jad.2018.07.059. Epub 2018 Jul 26

Second publication

Early weight gain predicts later metabolic syndrome in depressed patients treated with antidepressants: Findings from the METADAP cohort.

Asmar KE, Fève B, Colle R, Gressier F, Vievard A, Trabado S, Verstuyft C, Haffen E, Polosan M, Ferreri F, Falissard B, Chanson P, Becquemont L, Corruble E.
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Third publication

Treating major depressive episodes with antidepressants can induce or worsen metabolic syndrome: results of the METADAP cohort.

Corruble E, El Asmar K, Trabado S, Verstuyft C, Falissard B, Colle R, Petit AC, Gressier F, Brailly-Tabard S, Ferreri F, Lépine JP, Haffen E, Polosan M, Bourrier C, Perlemuter G, Chanson P, Fève B, Becquemont L.
World Psychiatry. 2015 Oct;14(3):366-7. doi: 10.1002/wps.20260. No abstract available.

Annex 1 : Executive summary in French

Motivation de ce Travail

Après avoir terminé mes études supérieures, le majeur objectif de ma carrière était de me concentrer sur la recherche psychiatrique et en particulier les troubles dépressifs majeurs (TDM). Dès le début, mes travaux de recherche avaient comme but d'apporter une nouveauté même-si modeste au domaine de la recherche en psychiatrie.

Bien que les études doctorales et les recherches universitaires offrent un environnement optimal pour expérimenter de nouvelles approches et défier les paradigmes existants, j'ai décidé d'étudier l'impact des antidépresseurs sur la prise de poids en premier lieu et par la suite leurs effets sur le syndrome métabolique de divers points de vue statistiques et méthodologiques.

Dans la section qui suit, je présenterai un aperçu du projet sur lequel mon travail de thèse est basé, l'objectif de ma recherche et les deux différentes approches statistiques utilisées dans le but de répondre à cette question de recherche clinique.

Le type de l'Etude

Les données de l'étude proposées proviennent de METADAP, une étude prospective multicentrique de 6 mois, une cohorte d'observation du traitement dans le monde réel de patients diagnostiqués avec un trouble dépressif majeur, en plein épisode dépressif majeur dans laquelle une évaluation du syndrome métabolique a été faite avant et après un traitement antidépresseur chez ces patients. La collecte de données s'est étalée entre Novembre 2008 et Mars 2013 auprès de six départements de psychiatrie universitaire. Ces derniers sont des centres de référence pour le traitement des épisodes dépressifs majeurs en France.

Ces patients ont été évalué sur la dépression, le syndrome métabolique et ses cinq composantes au début du traitement antidépresseur de l'index (M0), après 1 mois (M1), après 3 mois (M3) et au sixième mois plus tard (M6).

METADAP a recueilli un large éventail de données cliniques, génétiques ainsi que métabolomiques et protéomiques, cependant, le travail de thèse ne concerne que les composantes cliniques.

METADAP a été financée par le Programme Hospitalier de Recherche Clinique du Ministère de la Santé français (AOM06022).

Les Participants

L'échantillon est constitué de patients hospitalisés fixes ou ambulatoires réguliers, âgés de 18 à 65 ans en pleine crise dépressive dans un contexte de trouble dépressif majeur confirmé à l'aide de Mini Interview Internationale Neuropsychiatrique (MINI) et en précisant le seuil du score de dépression à 18 sur l'Échelle d'Évaluation de la dépression de Hamilton (HDRS-17 items ou HDRS), nécessitant la prescription d'un traitement antidépresseur ou un changement de l'antidépresseur déjà utilisé. Aucune période de sevrage n'était nécessaire.

Les patients ayant TDM présentant des troubles ou des symptômes psychotiques, bipolaires, du comportement alimentaire (TCA), une toxicomanie ou une dépendance (DSM-IV-TR), des syndromes cérébraux organiques ou des conditions médicales sévères instables ainsi que les femmes enceintes ou allaitantes n'ont pas été inclus.

De même, les patients recevant des antipsychotiques ou des stabilisateurs de l'humeur au cours du mois précédent l'inclusion et/ou pendant 4 mois ou plus au cours de l'année précédant l'inclusion n'ont pas été inclus. Les antipsychotiques, les stabilisateurs de l'humeur et les stimulants n'ont pas été autorisés pendant l'étude en raison de leurs effets métaboliques. Les benzodiazépines à une dose minimale efficace et pour une durée minimale et les psychothérapies ont été tolérées. Après une description exhaustive et détaillée de l'étude, tous les participants ont fourni leur consentement éclairé par écrit.

Il faut mentionner que les interviews et les diagnostics ont été examinés par un psychiatre expert indépendamment du psychiatre traitant.

Le traitement antidépresseur de l'index prescrit ou changé devrait appartenir à l'une des quatre classes suivantes : les inhibiteurs sélectifs de la recapture de la sérotonine (ISRS), les inhibiteurs de la recapture de la sérotonine-noradrénaline (IRSN), les antidépresseurs tricycliques (ATC) et autres traitements antidépresseurs.

Une monothérapie d'antidépresseur était nécessaire. Le médicament et sa dose ont été laissés au psychiatre traitant, en utilisant des options de traitement « monde réel ». Lorsque le traitement antidépresseur a été modifié, les patients ont abandonné l'étude. La réintégration était permise par le protocole à tout moment après l'arrêt.

Etendue Clinique du Travail

Une publication récente faite par Vigo, et al, en 2016 publiée par "The Lancet Psychiatry", a classifié la maladie mentale au premier plan de la charge mondiale de morbidité en termes d'années de vie en bonne santé perdues en raison d'une incapacité ou de la maladie (YLD), et au niveau des maladies cardiovasculaires en termes d'années de vie ajustées sur l'incapacité (DALY).

Selon le GBD en 2013, le trouble dépressif majeur est classé en deuxième rang en termes de YLD. Dans un contexte de prescription croissante de médicaments antidépresseurs et de prise de poids induite par ces derniers, l'impact de la prise de poids, spécifiquement la prise de poids précoce et son effet sur le syndrome métabolique devrait être étudiée, de même son influence sur la prise de poids ultérieur.

En se basant de ce qui précède, la recherche de l'association entre ces deux maladies ayant un GBD élevé a une importance primordiale du point de vue clinique et de la santé publique. En effet, il n'y a pas eu d'études prospectives faites sur des échantillons faibles et raisonnables en termes de taille des participants et la durée de l'étude, traitant les changements potentiels dans le profil métabolique des patients atteints de TDM sous la prescription des antidépresseurs.

Cette thèse a été établie pour fournir des preuves empiriques sur 3 niveaux. En premier lieu, le traitement du TDM augmente le risque du syndrome métabolique. En deuxième lieu, une prise de poids précoce de 3% à 5% peut augmenter significativement le risque d'incidence du syndrome métabolique et enfin une prise de poids précoce (3% -5%) qui, par conséquent, peut mener à l'augmentation significative du risque d'une prise du poids ultérieure (15% -20%). Les résultats de ce travail visent à influencer la pratique clinique et alerter les médecins et les infirmières sur

l'importance du suivi précoce du poids, en particulier chez les patients qui gagnent du poids au cours des 30 premiers jours de traitement.

Approche Statistique et Méthodologique

METADAP représentent des données longitudinales avec des mesures répétées, qui sont mieux analysées en utilisant des modèles mixtes ou des mesures répétées ANOVA.

Ces approches statistiques classiques ont tendance à évaluer uniquement les associations directes entre les variables, mais sont moins robustes pour évaluer et comprendre les effets indirects tels que la médiation.

Les voies de causalité potentielles et les effets multidirectionnels sont mieux mis en évidence en utilisant les modèles structuraux ou connus sous le nom de "Structural Equation Modeling (SEM)".

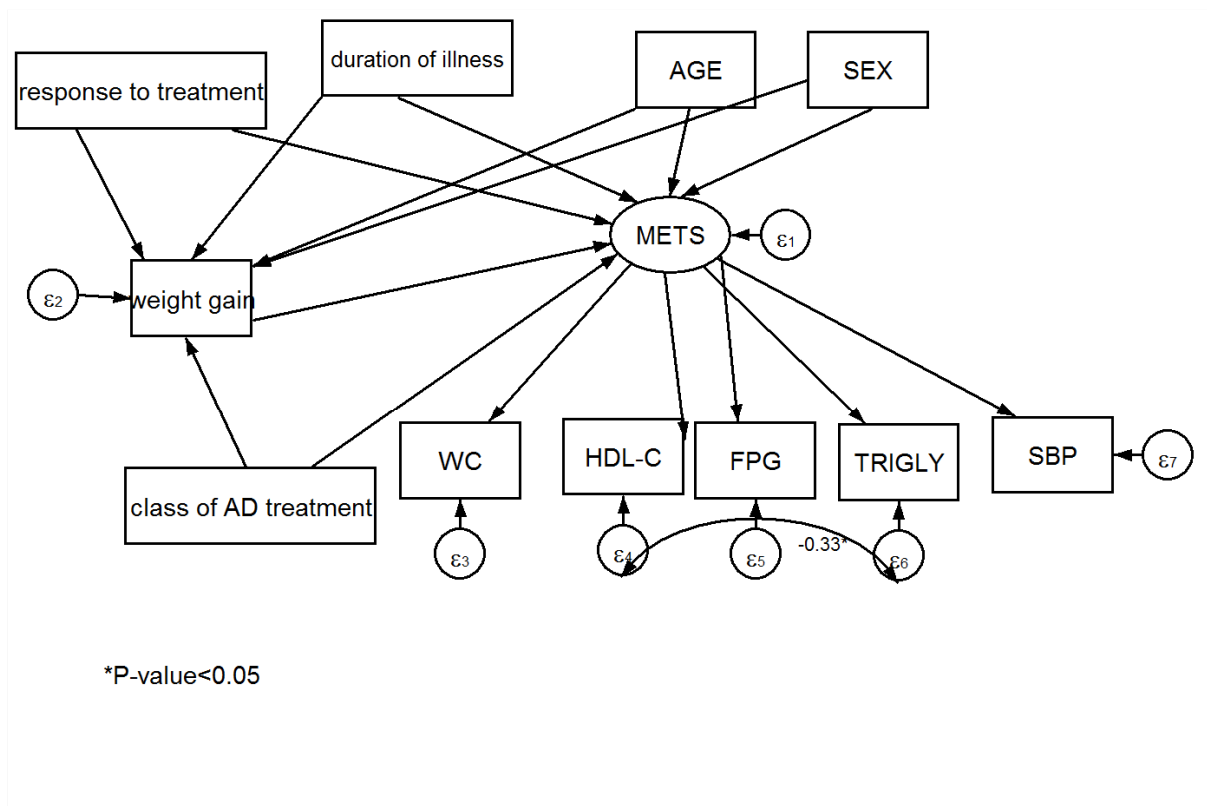
Concernant notre étude où l'origine de la dépression et du syndrome métabolique sont complexes, la modélisation par équations structurelles peut démolir les effets de plusieurs variables les unes par rapport aux autres en termes d'effets indirects, directs et totaux.

Kerkhof et al., (en 2011), Mi et al., (en 2011), Nock et al., (en 2009) et Kline et all., (en 2005) ont montré que le SEM génère des modèles pour évaluer et estimer les relations causales simultanées entre les variables observées et les variables latentes.

En comparaison avec les modèles de régression classiques, le SEM est une approche plus théorique qui permet d'acquiescer une représentation plus précise de la variabilité réelle du syndrome métabolique.

Dans notre thèse, deux méthodes statistiques : la régression traditionnelles et SEM ont été utilisés pour répondre à la même question de recherche, si la prise de poids précoce augmente le risque du syndrome métabolique. Bien que la première approche considère que le syndrome métabolique comme étant le résultat, que la prise du poids précoce est un facteur de risque principal et estimant uniquement les effets directs sur l'association entre le syndrome métabolique et la prise du poids; La deuxième approche examine si le syndrome métabolique a été médié par une prise de poids

précoce ou a été directement affectée par la réponse au traitement, le traitement par antidépresseurs et d'autres variables cliniques.



SEM de la relation entre le syndrome métabolique, prise de poids précoce, traitement AD et autres variables cliniques

Aperçu de la Thèse

La littérature suggère que l'obésité abdominale et les perturbations lipidiques, qui toutes les deux résultent directement de la prise de poids, sont la principale force motrice entre la dépression et le syndrome métabolique. C'est dans ce cadre que le travail présenté a été débuté. La thèse est composée de six chapitres qui présentent et résumant le travail mené au cours des quatre dernières années. Le thème principal de ce travail est l'impact du traitement par des antidépresseurs sur le poids et le profil cardiométabolique des patients atteints de Troubles Dépressifs Majeurs (TDM).

Le premier chapitre présente l'arche de révision du projet METADAP et étudie la principale question de recherche de l'étude METADAP : est-ce que les antidépresseurs sont-ils à l'origine du syndrome métabolique ? Bien que les rapports initiaux aient été publiés sous forme d'une lettre à l'éditeur dans *World Psychiatry* (Corruble, El Asmar, et al, 2015), la thèse présentera une analyse et une discussion plus élaborées des résultats. Contrairement aux résultats présentés dans les chapitres 2, 3 et 4, qui se concentrent sur un sous-échantillon spécifique de patients « métaboliquement sains », le premier chapitre présente des résultats sur l'échantillon complet de 624 patients recrutés pour l'étude.

Le deuxième chapitre aborde la question de la prise du poids précoce et ultérieure. Plus précisément, il évalue l'impact de la prise du poids précoce (3%, 5% et 7%) dans les 30 premiers jours de traitement sur la prise du poids ultérieure (15% et 20%) après 6 mois de traitement. L'analyse permet également de quantifier la puissance de la prise du poids précoce dans la prédiction de la prise du poids ultérieure. Ce chapitre fait partie d'un article accepté pour publication dans le journal des troubles affectifs (El Asmar et al., 2018).

Le troisième chapitre présente et discute l'impact de la prise de poids précoce sur l'incidence d'un syndrome métabolique. Ce chapitre est consacré exclusivement à un sous-échantillon de 260 patients ayant un poids normal et n'ayant pas un syndrome métabolique. Ce dernier fait partie d'un manuscrit en cours de révision dans le *Journal of "Psychiatric Research"*.

Le quatrième chapitre répond à la même question de recherche traitée dans le chapitre 2, mais en considérant le syndrome métabolique comme étant une variable latente unique suggestive d'une physiopathologie commune des 5 facteurs individuels. La modélisation par équation structurelle (SEM) a été utilisée pour tester le modèle théorique selon lequel la prise du poids précoce précède l'apparition du syndrome métabolique, et si la relation entre le syndrome métabolique et d'autres facteurs cliniques sont liée à une prise de poids précoce. Les résultats du modèle structurel sont en accord avec ceux obtenus dans le chapitre 2, en utilisant des modèles linéaires généralisés et des modèles mixtes linéaires généralisés. Ce chapitre fait partie d'un article de recherche en cours de rédaction et devrait être achevé en août 2018.

Le cinquième chapitre présente brièvement tous les documents de recherche issus de la cohorte METADAP à laquelle j'ai contribué en tant que biostatisticien, bien qu'ils ne traitent pas directement la question portant sur le fait que les antidépresseurs causent le syndrome métabolique et la prise du poids, ce dernier m'a aidé à approfondir ma compréhension des divers facteurs cliniques, physiologiques et génétiques associées à la dépression et à son traitement.

Le sixième et le dernier chapitre de la thèse consiste la conclusion globale et la synthèse des travaux de recherche présentés préalablement. Une conclusion sur les principales implications de cette thèse sur la pratique clinique du traitement des troubles dépressifs majeurs, en tenant compte des risques potentiels pour le profil métabolique cardiovasculaire qui ont été tirée. Ces deux conclusions exposent et opposent les différentes méthodes statistiques utilisées pour modéliser les données cliniques issues des cohortes prospectives et en particulier celles contenant des variables qui peuvent être traitées comme des constructions latentes telles que le syndrome métabolique.

Chapitre 1 : L'impact du traitement par des antidépresseur sur le syndrome métabolique

Objective : Évaluer les changements concernant le syndrome métabolique après un traitement par des antidépresseur chez les patients ayant un TDM.

L'hypothèse proposée : le traitement du TDM aggrave le syndrome métabolique.

Méthode : Dans la cohorte prospective de six mois (METADAP), 624 patients adultes nécessitant l'initiation d'une monothérapie antidépressive pour un EDM actuel, ont été évalués concernant le syndrome métabolique et ses cinq composantes (tour de taille, pression artérielle, triglycéridémie, Cholestérolémie, glycémie à jeun), au départ de l'étude, après trois et six mois du traitement.

Résultats : Quatre composantes du syndrome métaboliques sont altérées après le traitement. Le tour de taille, les pressions artérielles systolique et diastolique, le taux du cholestérol, la glycémie à jeun ont subi une augmentation après le traitement. Chez les patients sains ne présentant pas un syndrome métabolique au départ, le nombre de composantes altérées et l'incidence de syndrome ont augmentés avec le temps depuis le début du traitement (IRR respectivement : 1,05, IC à 95% (1,02-1,08), $p < 0,0001$ et OR : 2,29, IC à 95% (1,69-3,10), $p < 0,0001$), indépendamment de la réponse au traitement et de la prise du poids. Le risque du syndrome métabolique était inférieur chez les patients non traités par des antidépresseurs au départ (OR : 0,84, IC à 95% (0,72-0,96), $p < 0,02$) et avec les inhibiteur de la recapture de la sérotonine- noradrénaline (IRSN) qu'avec les inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) (OR : 1,18, IC à 95% (1,01-1,38), $p = 0,03$).

Conclusion : le traitement du trouble dépressif majeur avec des antidépresseurs induit ou aggrave le syndrome métabolique, indépendamment de la réponse au traitement et de la prise de poids. Une surveillance systématique du syndrome métabolique est essentielle chez les patients déprimés traités par des antidépresseurs.

Chapitre 2 : La prise du poids précoce prédit un gain du poids ultérieur.

Contexte : Le gain du poids est un des effets secondaires majeurs du traitement antidépresseur. Nous avons évalué si la prise du poids précoce est un facteur prédictif de la prise de poids à long terme chez les patients déprimés traités par des antidépresseurs.

Méthode : Dans la cohorte prospective de six mois METADAP, 260 patients en poids normal présentant un trouble dépressif majeur et ayant nouvellement subi un épisode dépressif majeur ont été évalués pour un gain de poids précoce ($> 3\%$, $> 5\%$ et $> 7\%$) après un mois de traitement et après trois et six mois. De même, ces patients ont été évalués pour un gain du poids à long terme ($> 15\%$ et $> 20\%$). L'analyse ROC a été utilisée pour déterminer le pouvoir prédictif de la prise de poids précoce.

Résultats : 12,4% (21/170) des patients étaient en surpoids après trois mois du traitement et 21,1% (26/123) étaient en surpoids après six mois. En comparant avec les patients qui n'ont pas gagné du poids à un stade précoce, les patients présentant un gain du poids précoce ($> 3\%$, $> 5\%$ et $> 7\%$) étaient de 11,3 (OR = 11,3, IC 95%: 4,6-27,6), 9,9 (OR = 9,9, 95 % IC: 3,6-26,9) et 17,8 (OR = 17,8, IC 95%: 6,4-49,4), plus à risque de prise de poids tardive ($> 15\%$). L'analyse ROC a montré que la prise de poids précoce ($> 3\%$) après un mois de traitement était le meilleur facteur prédictif de gain du poids à long terme ($\geq 15\%$) après trois mois [surface sous la courbe (ASC) = 87%] et six mois de traitement (ASC = 88%).

Perspectives : Vu que notre échantillon était composé de patients ayant un IMC normal, le seuil de prise du poids de 3% après un mois devrait être utilisé comme indicateur pour initier une surveillance précoce du poids chez les patients déprimés traités par des antidépresseurs. Malheureusement, un taux d'attrition élevé demeure une limite dans cette cohorte et dans d'autres cohortes en milieu psychiatrique.

Chapitre 3 : Un gain du poids précoce prédit un syndrome métabolique ultérieur.

Contexte : Le syndrome métabolique est un problème majeur de santé publique. Nous avons évalué si la prise du poids précoce permettait de prédire un métabolisme ultérieur chez les patients déprimés traités par des antidépresseurs.

Methods : Dans la cohorte prospective METADAP de six mois, 260 patients ayant un poids normal présentant un trouble dépressif majeur et ayant nouvellement subi un épisode dépressif majeur, ont été évalués pour une prise de poids précoce (> 5%) après un mois de traitement, pour l'incidence tardive du syndrome métabolique après trois et six mois de traitement. Les variables étudiées étaient le syndrome métabolique et le nombre de composantes du syndrome et chaque critère a part (tour de taille élevé, tension artérielle élevée, triglycéridémie élevée, HDL basse et glycémie à jeun élevée). Les modèles multivariés ont été ajustés en fonction de l'âge, du sexe, de la durée du TDM précédente, de la gravité de l'EDM actuelle et des antidépresseurs.

Résultats : 24,6% des patients présentaient un gain de poids précoce. En comparant avec les participants qui n'ont pas gagnés du poids, l'incidence du syndrome métabolique était plus élevée chez les patients ayant un gain de poids précoce : 16,7% contre 6,9% après 3 mois ($p = 0,07$) et 23,8% contre 7,1% après 6 mois ($p = 0,02$). Parmi les finissants ($n = 120$), la prise de poids précoce était significativement associée à une incidence plus tardive du syndrome métabolique (OR : 5,5) et à un nombre plus élevé de composantes du syndrome (IRR : 1,7). Cet effet était dû aux composantes tel que le tour de taille, triglycéridémie et cholestérolémie.

Conclusion : En comparant avec les participants qui n'ont pas gagnés du poids à un stade précoce, les patients présentant un gain du poids précoce au cours du premier mois de traitement par des antidépresseurs présentent un risque significativement plus élevé de développer un syndrome métabolique au cours des 6 mois après le début du traitement. Une surveillance précoce du poids est recommandée afin de définir des mesures préventives pour éviter de nouveaux syndromes métaboliques chez les patients déprimés traités par des antidépresseurs.

Chapitre 4 : Un modèle d'équation structurelle pour explorer la relation entre la prise du poids précoce et l'incidence du syndrome métabolique.

Objective : Dans ce chapitre, nous avons utilisé la modélisation des équations structurelles pour tester le modèle théorique selon lequel la prise du poids précoce précède l'apparition du syndrome métabolique et si la relation entre le syndrome métabolique et d'autres variables cliniques (réponse au traitement, gravité de la dépression, durée du traitement AD, l'âge et le sexe) est médiée par la prise du poids précoce.

Méthode : La modélisation par équation structurelle (SEM) a été utilisée pour tester le modèle théorique selon lequel la prise du poids précoce précède l'apparition du syndrome métabolique. La validité de l'ajustement ou "the goodness of fit " de la structure factorielle hypothétique a été testée à l'aide du test statistique Chi-square (χ^2), de l'erreur quadratique moyenne approximation (RMSEA), du résidu quadratique moyen normalisé (SRMR) et de l'indice d'ajustement comparatif (CFI).

Résultats : La prise du poids précoce était corrélée positivement et significativement avec le syndrome métabolique et la réponse au traitement, alors qu'elle est corrélée négativement avec la durée de la maladie dépressive. Aucun effet direct entre la durée de la maladie et la réponse au traitement d'une part, et le syndrome métabolique d'autre part a été trouvée, en déduire que la relation entre ces deux variables et le syndrome métabolique est totalement liée à la prise de poids précoce.

Conclusion : Nos résultats mettent en évidence la robustesse de notre hypothèse selon laquelle un gain de poids aussi faible que 5% est un facteur prédictif significatif de survenue d'un syndrome métabolique ultérieur. Les résultats de cette étude soulignent fortement l'importance du dépistage et de la détection précoce de la prise de poids lors de l'identification des individus à risque de syndrome métabolique.

Les Implications Cliniques

Bien que la relation bidirectionnelle entre la dépression et le syndrome métabolique est bien établie dans la littérature, l'impact du traitement par médicaments antidépresseurs sur la santé cardiovasculaire en général et sur le syndrome métabolique en particulier reste peu documenté.

Les résultats du premier chapitre montrent que le traitement des épisodes dépressifs caractérisés par antidépresseurs induit ou aggrave le syndrome métabolique. Cet effet survient précocément après le début du traitement, indépendamment de la prise du poids et de la réponse au traitement.

Dans le deuxième et troisième chapitre, nous avons mis l'accent sur la prise de poids chez les patients ayant un poids normal. Les résultats ont montré que la prise de poids précoce de plus de 5% au cours du premier mois de traitement antidépresseur prédit la survenue ultérieure d'un syndrome métabolique chez les patients déprimés ayant un poids normal et traités par antidépresseurs par des psychiatres. Les résultats ont également montré une corrélation entre la prise de poids et le nombre de critères du syndrome métabolique, un tour de taille élevé et un taux d'HDL bas. Ces résultats sont en accord avec les données de la littérature selon lesquelles la dépression est principalement corrélée aux composantes liées à l'obésité (obésité abdominale, taux bas de HDL, hypertriglycémie), alors que les associations avec l'hyperglycémie et l'hypertension sont moins fréquentes (Penninx, 2017). Le SEM nous a permis de tester l'effet de médiation de la prise du poids précoce sur l'association entre la réponse au traitement par des antidépresseurs et le syndrome métabolique. Les résultats ont montré que la prise du poids dépendait totalement de l'association entre la réponse au traitement et le syndrome métabolique. En d'autres termes, à moins que la réponse au traitement ne s'accompagne pas d'une prise du poids, il est peu probable que les patients développent un syndrome métabolique.

Le chapitre, évaluant l'impact de la prise du poids précoce sur la prise de poids ultérieure, a montré qu'en comparaison avec les patients qui n'ont pas subi de changement pondéral, les patients présentant une prise de poids précoce ($> 3\%$) durant le premier mois du traitement par des antidépresseurs ont eu un risque plus élevé de prise de poids majeure ($> 15\%$) ultérieure au cours des six mois du traitement. En comparant la prise de poids précoce entre 5% et 7%, le seuil de 3% s'est révélé être le meilleur seuil pour prédire la prise de poids ultérieure.

Les résultats ci-dessus ont des implications cliniques élevées. Ils indiquent la nécessité d'un suivi précoce du poids et du profil lipidique chez les patients déprimés ayant un poids normal et débutant un traitement par antidépresseurs, en particulier chez ceux qui ont un profil métabolique « plus sain ». Par conséquent, pour éviter les prises de poids sous traitement, et par la suite, un syndrome métabolique chez les patients déprimés traités par antidépresseurs, les psychiatres et les infirmières doivent surveiller les changements pondéraux de près pour ces patients pendant le premier mois de traitement et vérifier systématiquement toutes les composantes du syndrome métabolique, en portant une attention particulière au tour de taille, la cholestérolémie et la triglycéridémie durant les 6 premiers mois du traitement antidépresseur. En cas de gain de poids de plus de 3% au cours du premier mois de traitement, les psychiatres et les infirmières doivent systématiquement examiner les anomalies métaboliques (tour de taille élevé, hypertension artérielle élevée, triglycéridémie élevée, faible cholestérolémie HDL et glycémie à jeun élevée) après 3 et 6 mois, en orientant leurs patients vers des médecins généralistes en cas de valeurs anormales.

Les Considérations Statistiques

Les relations multidirectionnelles entre la dépression, l'utilisation d'un traitement antidépresseur, la prise du poids et le syndrome métabolique nécessitent l'utilisation de modèles statistiques flexibles permettant une représentation précise et fiable de ces associations. Bien que l'association bidirectionnelle entre la dépression et les maladies cardiovasculaires soit bien établie, l'association entre l'utilisation du traitement antidépresseur et le traitement du syndrome métabolique reste moins établie. Comme discuté précédemment, la littérature fournit des éléments en faveur du fait que les patients atteints de TDM traités avec des antidépresseurs présentent un risque accru de prise du poids. Cependant, on peut également affirmer que la prise du poids peut résulter de la dépression. La modélisation des équations structurelles a la capacité de démêler le mécanisme complexe qui relie ces variables. En fait, le SEM est la seule approche statistique qui permettrait d'identifier, de tester et d'estimer les effets directs et indirects que les variables cliniques peuvent avoir sur le syndrome métabolique. De plus, compte tenu du caractère prospectif de l'étude METADAP, le SEM nous a permis de représenter fidèlement les trajectoires cliniques séquentielles conduisant au syndrome métabolique, c'est-à-dire que le début du traitement par antidépresseurs suivi d'un gain du poids après 1 mois, suivi ensuite par une incidence du syndrome métabolique après 6 mois. Cependant, l'utilisation de la SEM est restée contingente sur notre capacité à présenter le syndrome métabolique en tant que variable latente unique suggérant une physiopathologie commune aux cinq facteurs individuels de syndrome. En effet, la structure à un facteur de syndrome métabolique a été validée dans plusieurs études, à notre connaissance, elle n'a jamais été testée sur une population de patients atteints de TDM avec un poids normal.

Les modèles à effets mixtes constituent une alternative pour la modélisation des équations structurelles dans l'analyse des données de mesures longitudinales et répétées. Le principal avantage des modèles linéaires mixtes (LMM) et des modèles mixtes linéaires généralisés (GLMM) selon McCullagh et al en 1989, Breslow et al, 1993 et Agresti en 2013 est qu'ils représentent une méthode bien acceptée pour analyser les données cliniques longitudinales dans lesquelles des observations manquantes ou erronées sont présentes (Fitzmaurice et al, 2001). Avec un taux d'attrition important et l'absence d'imputation des données, les modèles linéaires mixtes (LMM) et les modèles mixtes linéaires généralisés (GLMM) restent de meilleures alternatives pour analyser

les données longitudinales que les ANOVA à mesures répétées, parce que ces dernières traiteront les données manquantes grâce à une suppression par liste, ce qui signifie que nous ne pourrions analyser que l'échantillon final des patients qui terminent l'étude, ce qui réduirait considérablement la puissance statistique et la pertinence des résultats.

Perspectives

Dans cette thèse, nous avons étudié la relation entre le traitement antidépresseur, la prise de poids et le syndrome métabolique sur un échantillon de patients déprimés. Les résultats cliniques ont montré que la prise du poids précoce associée à l'initiation du traitement antidépresseur augmentera le risque de prise du poids ultérieure et d'incidence ultérieure du syndrome métabolique. Mais la relation entre l'utilisation des antidépresseurs, la réponse au traitement et la prise du poids reste complexe. Malgré l'augmentation simultanée de la consommation d'antidépresseurs et la tendance à l'obésité dans les sociétés occidentales, des études supplémentaires sont nécessaires pour évaluer si la prise du poids chez les déprimés traités par antidépresseurs est un effet iatrogène. Bien que l'impact des antidépresseurs sur la morbidité cardiovasculaire reste mal connu, les résultats du premier chapitre ont montré que l'utilisation d'antidépresseurs, indépendamment de leurs classes, avait un impact sur les dérèglements métaboliques, nécessitant une attention clinique spécifique. Une étude de cohorte à long terme est nécessaire pour confirmer si l'interruption et la réinstauration du traitement par des antidépresseurs seraient liées à la fluctuation des dysrégulations métaboliques.

Bien que les résultats présentés soient basés sur des analyses d'une cohorte longitudinale (étude observationnelle) et non sur un plan expérimental de type essai randomisé contrôlé versus placebo en double aveugle, ils sont utiles en l'absence des essais randomisés contrôlés à grande échelle. En fait, afin de déterminer efficacement si les médicaments antidépresseurs contribuent au risque cardiovasculaire, un essai randomisé contrôlé à long terme serait nécessaire. Cependant, un tel essai pourrait ne pas être financièrement ou éthiquement réalisable, et donner des résultats dans un sous-groupe de patients uniquement, et les futurs travaux de recherche sur l'impact du traitement par antidépresseurs sur la santé cardiovasculaire devront s'appuyer sur des études prospectives de grande ampleur.

Treating major depressive episodes with antidepressants can induce or worsen metabolic syndrome: results of the METADAP cohort

Recent data (1-4) show a high comorbidity between major depressive disorder and metabolic syndrome (MetS) (5), a cluster of risk factors for cardiovascular diseases and type 2 diabetes including high waist circumference, high blood pressure, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and high fasting glucose.

In a context of increasing prescription of antidepressant medication (6) and evidence of weight gain induced by antidepressants (7), the impact of antidepressant treatment on MetS has to be clarified. Indeed, there has been no prospective study of reasonable sample size and duration addressing the incidence of MetS in patients with major depressive episode treated with antidepressants.

This question was addressed in the METADAP, a 6-month prospective, multicentric, real-world treatment observational cohort study of 624 patients with a diagnosis of major depressive disorder and a current major depressive episode. Data were collected from November 2009 to March 2013 in six university psychiatry departments in France.

Consecutive in- or out-patients, aged 18 to 65 years, with a current major depressive episode in a context of major depressive disorder (with a minimum score of 18 at the Hamilton Depression Rating Scale-17, HDRS-17) were assessed for MetS at the start of the index antidepressant treatment (M0), and one (M1), three (M3) and six (M6) months later. All of them provided their written informed consent.

Patients with psychotic symptoms, bipolar disorders, psychotic disorders, eating disorders, current substance abuse or dependence, pregnancy, organic brain syndromes or severe unstable medical conditions were not included. Patients receiving antipsychotics or mood stabilizers before inclusion and/or for 4 months or more during the last year were also excluded. Antipsychotics, mood stabilizers and stimulants were not permitted during the study, because of their metabolic effects. Benzodiazepines at the minimum effective dose and for the minimum time period and psychotherapies were allowed. The index antidepressant treatment had to be a monotherapy. The drug and its dose were left to the treating psychiatrist, using "real world" treatment options.

MetS was diagnosed according to the International Diabetes Federation definition (8). Participants had to have fasted and abstained from strenuous physical activity for 8 hours before examination. Triglycerides, HDL cholesterol and fasting plasma glucose levels were assessed using

routine standardized laboratory methods. Thereafter, an assistant investigator blind to the major depression assessment measured waist circumference and blood pressure.

Mixed-effects multivariate models were used, because they are a well-accepted method for analyzing longitudinal clinical data in which missing or mistimed observations are present (9). All regression models included main effects for time since initiation of current antidepressant treatment, age, gender, HDRS-17 score at baseline, lifetime duration of prior major depressive disorder, lifetime duration of prior antidepressant medication, antidepressant-free period before inclusion, and current antidepressant classes.

Of 689 pre-included patients, 643 were included, of whom 19 had major deviations to the protocol. Thus, 624 patients were analyzed. Six had missing data for MetS at baseline.

Patients' mean age was 45.6613.2 years; 68.7% were women, 87.5% were inpatients at baseline. Their mean HDRS-17 score at baseline was 24.765.0. Their mean number of previous major depressive episodes was 1.962.1. The average lifetime duration of major depressive disorder before inclusion was 11.5612.2 years. The lifetime duration of antidepressant drug treatment before inclusion was 2.364.1 years.

Upon inclusion, 22.7% of patients were antidepressant naïve. The administered antidepressant was a selective serotonin reuptake inhibitor (SSRI) in 38.9% of cases, a serotonin norepinephrine reuptake inhibitor (SNRI) in 38.3%, a tricyclic antidepressant (TCA) in 8.8%, and another one in 14.0%. The mean duration of follow-up was 4.964.6 months. The drop-out rate was 25.9% before M1, 21.8% between M1 and M3, and 14.3% later. The main reasons for drop-out were antidepressant change (28.4%), prescription of antipsychotics or mood stabilizers (29.4%), and lost to follow-up (20.4%).

In patients without MetS at baseline (N5442, 70.8%), the incidence of MetS was 11.7% at M3 and 16.5% at M6. This increase was significant (mixed-effect multivariate logistic regression: OR52.29, 95% CI: 1.69-3.10, $p < 0.0001$). It was observed within both the SSRI (0% to 16.2%, $p < 0.001$) and the SNRI group (0% to 16.1%, $p < 0.001$). This increase was independent from other factors, such as age, lifetime duration of prior antidepressant medication, and presence of an antidepressant-free period at baseline.

The number of altered components of MetS significantly increased with time (M0: 1.260.9, M3: 1.361.1, M6: 1.561.2; mixed-model multivariate Poisson regression: incident risk ratio, IRR51.06, 95% CI: 1.02-1.09, $p < 0.0001$). It

was significantly higher in patients treated with SNRIs than in those treated with SSRIs (IRR=1.45, 95% CI: 1.16-1.80, p<0.001), and it was lower amongst patients who were antidepressant-free at baseline (IRR=0.81, 95% CI: 0.65-0.99, p<0.03). These effects were independent from each other, from age and gender.

In patients with MetS at baseline, mixed-effect multivariate linear regressions showed significant increases over time of supine blood pressure (M0: 123.26±16.4 mmHg, M3: 124.86±13.9 mmHg, M6: 126.86±15.0 mmHg, p<0.05) and fasting plasma glucose (M0: 0.986±0.29 g/l, M3: 1.076±0.48 g/l, M6: 1.036±0.31 g/l, p<0.01), which were independent from other factors.

The highlight of this study is the early and significant incidence of MetS after initiation of treatment with antidepressants. The majority of cases occurred in the first three months of treatment. A significant worsening of MetS was also observed in patients who already had the syndrome at baseline.

Taken together, these results suggest that treating major depressive episodes with antidepressants can induce or worsen MetS. Specific recommendations for the prevention of MetS in patients with major depressive disorder receiving antidepressant medication are needed. Further studies assessing the underlying mechanisms of this phenomenon are warranted.

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Title: Predictive power of early weight-gain on later weight-gain and metabolic syndrome in depressed patients treated with antidepressants: findings from the METADAP cohort

Abdominal obesity and lipid disturbances - which both are a direct result of weight gain – are the main driving force between depression, antidepressants and MetS. In a context of increasing prescription of antidepressant medication and weight gain induced by antidepressants, the impact of weight gain and specifically early weight gain on subsequent MetS and later weight gain has to be studied. It is under this framework that the presented work was undertaken. The dissertation aimed at answering 3 research questions: (i) Do antidepressants cause metabolic syndrome? (ii) What is the impact of early weight gain on MetS incidence? and (iii) what is the impact of early weight gain on later weight gain?

METADAP is a 6-month prospective, multi-centric, real-world treatment study, assessing metabolic syndromes before and after antidepressant treatment in MDD patients with a current MDE. Data were collected between November 2008 and March 2013 from six university psychiatry departments which are referral centers for MDE in France. MDE patients were enrolled and assessed at the beginning of an index antidepressant prescription, one, three and six months later for depression and MetS and its five components.

Generalized linear models, generalized linear mixed models and structural equation modeling were used to answer the above research questions.

The results show that treating major depressive episodes with antidepressants induces or worsens metabolic syndromes. This effect occurs early after initiation of treatment and is independent from weight gain and response to treatment. They also showed that early weight gain of more than 5% in the first month of antidepressant treatment predicts later metabolic syndrome in non-overweight depressed patients treated with antidepressants in psychiatric settings, with a considerable effect size of 5.5. The results also showed correlation between weight gain and number of MetS dysregulations, high WC, and low HDL-C. Using structural equation modeling, we were able to look beyond the direct effect of early weight gain on MetS incidence. Using structural equation modeling, we have shown that weight gain, fully mediated the association between response to treatment and MetS. In other words, unless response to treatment is accompanied with weight gain, the patients is not likely to develop MetS. Finally, assessing the impact of early weight gain on later weight gain showed that compared to non-early weight gainers, patients with early weight gain (>3%) in the first month of antidepressant treatment were at significant higher risk of crucial weight gain (>15%) during the six months of antidepressant treatment. Compared to 5% and 7% early weight gain, the 3% threshold was found to be the best predictor of later weight gain.

In this dissertation we have studied the relationship between AD treatment, weight gain and MetS on a sample of MDD patients. Clinical findings have suggested that early weight gain due to AD treatment would increase the risk of both later weight gain and later MetS incidence. The relationship between AD use, response to treatment and weight gain remain complex. Despite the simultaneous increase in AD use and obesity trends in Western societies, additional prospective cohorts are needed to fully test the hypothesis that weight gain among AD users is indeed an iatrogenic effect. Although impact of AD on cardiovascular morbidity still cannot be ascertained, the results from the first chapter showed that AD use – irrespective of the class - does impact and worsen metabolic dysregulations, which would require specific clinical attention. A long term cohort study is required to confirm whether discontinuation and re-initiation of AD treatment would be linked to fluctuation in MetS dysregulations.

Keywords : Depression, antidepressants, metabolic syndrome, weight gain, cohort.

Titre : Pouvoir prédictif de la prise de poids précoce sur la prise de poids ultérieure et le syndrome métabolique chez les patients déprimés traités par antidépresseurs: résultats de la cohorte METADAP

L'obésité abdominale et les perturbations lipidiques, qui toutes les deux résultent directement de la prise de poids, sont la principale force motrice entre la dépression, les antidépresseurs et le syndrome métabolique. Dans un contexte de prescription croissante de médicaments antidépresseurs et de prise de poids induite par ces derniers, l'impact de la prise de poids, spécifiquement la prise de poids précoce et son effet sur le syndrome métabolique devrait être étudiée, de même son influence sur la prise de poids ultérieure. C'est dans ce cadre que le travail présenté a été débuté. Cette thèse a pour but de répondre à 3 questions de recherches. La première question est : si le traitement par antidépresseurs induit un syndrome métabolique. La deuxième question est : quel est l'impact du gain de poids précoce sur l'incidence du syndrome métabolique et la dernière question : quel est l'impact de la prise de poids précoce sur la prise de poids ultérieure?

Les données de l'étude proposées proviennent de METADAP, une étude prospective multicentrique de 6 mois, une cohorte d'observation du traitement dans le monde réel de patients diagnostiqués avec un trouble dépressif majeur, en plein épisode dépressif majeur.

Des modèles linéaires généralisés, des modèles mixtes linéaires généralisés et une modélisation des équations structurelles ont été utilisés pour répondre aux questions de recherche ci-dessus.

Les résultats montrent que le traitement des épisodes dépressifs majeurs par des antidépresseurs induit ou aggrave le syndrome métabolique. Cet effet survient tôt après le début du traitement, indépendamment de la prise du poids et de la réponse au traitement. Les résultats ont montré que le gain du poids précoce de plus de 5% au cours du premier mois de traitement antidépresseur prédit plus tard le syndrome métabolique chez les patients déprimés ayant un poids normal traités par antidépresseurs en milieu psychiatrique, avec une taille d'effet considérable de 5,5. Les résultats ont également montré une corrélation entre le gain du poids et le nombre de dysrégulations du syndrome métabolique, un tour de taille élevé et un taux d'HDL bas. En utilisant la modélisation des équations structurelles, nous avons pu voir au-delà du fait de l'effet direct de la prise du poids précoce sur l'incidence du syndrome métabolique. Les résultats ont montré que la prise du poids dépendait totalement de l'association entre la réponse au traitement et le syndrome métabolique. En d'autres termes, à moins que la réponse au traitement ne s'accompagne pas d'une prise du poids, il est peu probable que les patients développent un syndrome métabolique. Finalement, l'évaluation de l'impact de la prise du poids précoce sur la prise de poids ultérieure, a montré qu'en comparaison avec les patients qui n'ont pas subi un changement pondéral, les patients présentant un gain du poids précoce (> 3%) durant le premier mois du traitement par des antidépresseurs ont eu un risque plus élevé de gain du poids crucial (> 15%) au cours des six mois du traitement. En comparant la prise du poids précoce entre 5% et 7%, le seuil de 3% s'est révélé être le meilleur prédicteur de la prise du poids ultérieure.

Dans cette thèse, nous avons étudié la relation entre le traitement par antidépresseurs, la prise du poids et le syndrome métabolique sur un échantillon de patients atteints de TDM. Les résultats cliniques ont suggéré que la prise du poids précoce due au traitement par antidépresseurs augmenterait le risque de prise de poids ultérieure et d'incidence ultérieure du syndrome métabolique. Ainsi que la relation entre l'utilisation des antidépresseurs, la réponse au traitement et la prise de poids reste complexe. Malgré l'augmentation simultanée de la consommation d'antidépresseurs et la tendance à l'obésité dans les sociétés occidentales, des cohortes prospectives supplémentaires sont nécessaires pour tester pleinement l'hypothèse traitant que la prise de poids chez les utilisateurs des antidépresseurs est un effet iatrogène. Bien que l'impact des antidépresseurs sur la morbidité cardiovasculaire ne puisse toujours pas être déterminé, les résultats du premier chapitre ont montré que l'utilisation des antidépresseurs, indépendamment de leurs classes, avait un impact sur les dérèglements métaboliques, nécessitant une attention clinique spécifique. Une étude de cohorte à long terme est nécessaire pour confirmer si l'interruption et la réinstauration du traitement par des antidépresseurs seraient liées à la fluctuation des dysrégulations du syndrome métabolique.

Mots clés : Dépression, antidépresseurs, syndrome métabolique, gain du poids, cohorte.