Improving prescribing practices in primary care: pharmacological treatment of depression in patients with excess weight

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DEDICATION

I dedicate this dissertation to my husband, Nurlan Dauletbayev, and to our daughter, Denise.

Your love, support, and encouragement made this work possible.

ABSTRACT

Background. Pharmacological treatment of depression needs individualized approaches, with consideration of patients' characteristics amongst other factors. One of the most important factors associated with the differential response to antidepressants (AD) is a patient's body weight. Conversely, obesogenic (weight-increasing) effects of certain AD may put this population at especially high risk for poor response to treatment, and excess-weight-related health problems. Presently, there are no guidelines to individualize the prescribing of AD for patients with excess weight. Moreover, it is not clear whether prescribing of an obesogenic AD is, in fact, associated with increased health risks in this population.

Objectives. The objectives of this thesis are 1) to synthesize the evidence, by groups and types of AD, on the role of excess body weight in response to AD treatment in people with depression; 2a) to describe, in Canadian primary care, the prevalence and patterns of AD prescribing to patients with depression and obesity; 2b) to quantify the differences in prescribing AD with weight-modulating and cardiovascular adverse effects for patients in different weight groups; 3) to estimate the difference in the association between prescribing of obesogenic AD and health care utilization (hospitalizations) in patients with and without excess weight.

Methods. For objective 1, a comprehensive scoping review was conducted. For objective 2a, a cohort of adult patients with depression was extracted from the national Canadian Primary Care Sentinel Surveillance Network (CPCSSN) Electronic Medical Records database for 2011-2016. The association between AD prescribing and weight category was evaluated cross-sectionally. For objective 2b, the CPCSSN cohort was restricted to the incident users of AD. The importance of weight in predicting AD prescribing was examined by the machine learning

algorithm random forest. Associations between obesity and prescribing of AD known for their weight-modulating and cardiovascular adverse effects were examined in logistic and mixed effects regression models. For objective 3, the population-based cohort, "The Care Trajectories - Enriched Data" (TorSaDE), was used. Cox regression analysis and cosine similarity metrics were utilized to examine the role of excess weight in the association between exposure to obesogenic AD and all-cause hospitalizations.

Results. In the scoping review, the evidence on the differential response of people with excess weight to individual AD was synthesized. The analysis for objective 2 showed that, compared with normal weight patients, patients with obesity were more likely to receive an AD prescription (adjusted Odds Ratio [aOR]=1.17; 95% Confidence Interval [CI]: 1.12-1.22). The prevalence of prescribing > 3 AD types was higher in patients with obesity. Prescribing patterns of AD with weight-modulating and cardiovascular effects were different between patients with obesity and normal weight. The adjusted hazard ratio for all-cause hospitalizations was higher in the patients jointly exposed to excess weight and obesogenic AD, compared with patients with only one of these exposures (objective 3). Difference in the cosine similarity between excess weight *vs* no excess weight groups was observed for tricyclic AD.

Conclusion. The data synthesized in the scoping review helped clarifying best practices for antidepressant prescribing for patients with obesity. The positive association between obesity and high prevalence of AD prescribing, and prescribing high number of different AD, including AD with obesogenic and cardiovascular side effects, to patients with obesity is concerning, as well as the trend for the increased risk for hospitalizations in patients with the joint exposure to excess weight and obesogenic AD. The risks and benefits of treatment of the excess weight

patients with individual obesogenic AD need to be further studied using a large longitudinal cohort of patients with depression and repeated BMI measures.

RÉSUMÉ

Contexte. La pharmacologie du traitement de la dépression requiert une approche individualisée ainsi qu'un examen des caractéristiques des patients, entre autres facteurs. Un des éléments les plus importants associés à la réponse différentielle aux antidépresseurs (AD) est le poids du patient. Inversement, les effets obésogènes (augmentation de poids) de certains AD peuvent engendrer chez cette population un taux élevé de risque d'une réponse déficiente au traitement et des problèmes de santé liés à un excès de poids. Actuellement, il n'existe aucune directive pour personnaliser la prescription d'AD aux patients ayant un excès de poids. De plus, il n'est pas clair si la prescription d'AD obésogènes est réellement associée aux risques accrus pour la santé de cette population.

Objectifs. Les objectifs de cette thèse sont 1) faire la synthèse, par groupes et types d'AD, du rôle du surplus de poids en réponse aux AD chez les personnes souffrant de dépression; 2a) décrire la prévalence et les types d'ordonnances d'AD aux patients souffrant de dépression et d'obésité dans les soins primaires canadiens; 2b) dénombrer les variations lors de la prescription d'AD en tenant compte des effets modulateurs de poids et des effets indésirables cardiovasculaires pour les patients de groupes de poids différents; 3) évaluer la variation d'association entre la prescription d'AD obésogènes et l'usage en santé (hospitalisations) chez les patients avec et sans excès de poids.

Méthodologie. Pour l'objectif 1, l'examen approfondi du champ d'application a été réalisé. Pour l'objectif 2a, une cohorte de patients adultes souffrant de dépression a été extraite des archives médicales numérisées de 2011-2016 du Canadian Primary Care Sentinel Surveillance Network (CPCSSN). L'association entre la prescription d'AD et la catégorie de poids a été évaluée de manière transversale. Pour l'objectif 2b, la cohorte du CPCSSN était limitée aux utilisateurs d'incidents d'AD. L'importance du poids dans la prédiction de prescription d'AD

a été examinée par l'algorithme d'apprentissage automatique Radom Forest. Les associations entre l'obésité et la prescription d'AD connus pour leur effet modulateur sur le poids et leurs effets indésirables cardiovasculaires ont été examinées dans des modèles de régression logistique et à effets mixtes. Pour l'objectif 3, la cohorte basée sur la population, « The Care Trajectories – Enriched Data » (TorSaDE) a été utilisée. La régression de Cox et la métrique de similarité du cosinus ont été utilisées pour examiner le rôle de l'excès de poids dans l'association entre l'exposition aux AD obésogènes et les hospitalisations, toutes causes confondues.

Résultats. Dans l'analyse exploratoire, les données probantes sur la réponse différentielle aux AD individuels chez les personnes ayant un excès de poids ont été synthétisées. L'analyse de l'objectif 2 a montré que les patients obèses étaient plus susceptibles de se voir prescrire un AD (rapport de cotes ajusté [aOR]=1,17; intervalle de confiance à 95 % [IC] : 1,12-1,22) par rapport aux patients de poids normal. La prévalence de la prescription de >3 types d'AD était plus élevée chez les patients obèses. Les schémas de prescription d'AD ayant des effets modulateurs de poids et cardiovasculaires étaient différents chez les patients obèses et ceux ayant un poids normal. Le rapport de risque ajusté des hospitalisations était plus élevé chez les patients exposés conjointement à l'excès de poids et aux AD obésogènes, par rapport aux patients n'ayant subi qu'une seule de ces expositions (objectif 3). Une différence dans la similarité du cosinus entre les groupes avec excès *(c.)* sans excès de poids a été observée pour l'AD tricyclique.

Conclusion. Les données synthétisées de l'analyse exploratoire peuvent clarifier les meilleures pratiques en matière de prescription d'AD pour les patients souffrant d'obésité. L'association positive entre l'obésité et la prévalence élevée de la prescription d'AD, ainsi que la prescription d'un nombre élevé d'AD différents, y compris d'AD ayant des effets secondaires obésogènes

et cardiovasculaires, à des patients souffrant d'obésité est préoccupante, tout comme la tendance à l'augmentation du risque d'hospitalisation chez les patients exposés conjointement à un excès de poids et à des AD obésogènes. Les risques et les avantages du traitement des patients présentant un excès de poids par des AD obésogènes individuels doivent faire l'objet d'une étude plus approfondie à l'aide d'une vaste cohorte longitudinale de patients présentant une dépression et des mesures répétées de l'IMC.

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LIST OF ABBREVIATIONS

Abbreviation	Full terminology
AD	Antidepressants
AHFS	American Hospital Formulary Service classification numbers
ATC	Anatomical Therapeutic Chemical codes
BDI	Beck depression inventory
BMI	Body mass index
CADRISQ	Institut de la statistique du Québec
CCHS	Statistics Canada's Canadian Community Health Survey
95% CI	95% Confidence intervals
Covid-19	Coronavirus disease 2019
COPD	Chronic obstructive pulmonary disease
CPCSSN	Canadian Primary Care Sentinel Surveillance Network
DIN	Drug Identification Numbers (DIN)
EMR	Electronic medical records
HAMD-17, HAMD, HDRS	Hamilton depression rating scale
HR	Hazard ratio
ITT	Intention to treat
ISQ	Quebec Institute of Statistics
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
LOCF	Last observation carried forward
MADRS	Montgomery–Asberg depression rating scale
MAOI	Monoamine oxidase inhibitors

MDA	Mean decreased accuracy
MDD	Major depression disorder
MICE	Multiple imputations by chain equations
MI	Multiple imputations
MVR	Multivariable regression
NaSSA	Noradrenergic and specific serotonergic antidepressants
NDRI	Norepinephrine–dopamine reuptake inhibitors
OR	Odds ratio
QIDS-SR	Quick inventory of depressive symptomatology form
RAMQ	Régie de l'assurance maladie du Québec
RCT	Randomized controlled trials
RF	Random forest
SSRI	Selective serotonin reuptake inhibitors
SNRI	Serotonin-norepinephrine reuptake inhibitors
TCA	Tricyclic antidepressants
TRD	Treatment resistant depression
TorSaDE	The Care Trajectories - Enriched Data cohort
TdP	Torsade de Points
PCPs	Primary care providers
WHO	World Health Organization
WSAS	Work and social adjustment scale

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Looking back to the years of my PhD project, I experience an overwhelming feeling of sincere appreciation of fascinating research work and an engaging community of a great many outstanding colleagues and friends. This feeling makes me realize that my project would not have been possible without the continuing help and support from my supervisor, mentors, fellow students, and colleagues. It has been a great privilege for me to work side by side with this community for the past few years!

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during the submission process, which was especially important during the latest steps due to the restrictions associated with the COVID-19 pandemic.

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PREFACE

Format of the thesis and contribution of authors

This is a manuscript-based dissertation comprised of four manuscripts. Two manuscripts have been published. The third manuscript has been accepted for publication in August 2021. The fourth manuscript is in the final steps of preparation for submission. As a doctoral candidate and the first author of all four manuscripts, I am responsible for all the work for this dissertation. I conceptualized the study, formulated the research aim and specific objectives, developed the research design, conducted the analyses, performed data interpretation, and wrote the manuscripts. My research work was guided by my supervisor Dr. Gillian Bartlett and in consultation with my committee members Drs. Tibor Schuster, Christel Renoux, Tracie A. Barnett, Ellen Rosenberg (the first 4 years of my PhD), and Kimberly Munro (the final year of my PhD).

Dr. Bartlett's expertise in and experience with studies in Pharmacoepidemiology and Precision Medicine defined the direction of this work and its methodological aspects. Dr. Bartlett provided the overall guidance on development of the protocol and methodology, conducting the analyses, interpretation of the findings, and presentation of the results, with all committee members contributing to these stages of the project. Dr. Schuster's expertise in Biostatistics and Dr. Renoux's expertise in Pharmacoepidemiology guided my study design, selection of methods of analysis, and interpretation of findings. Drs. Rosenberg and Munro provided clinical expertise on the management of depression and obesity in primary care, and on related clinical problems, and ensured the relevance of this work for the primary care practice. Dr. Barnett's input refined the epidemiological aspects of my research and presentation of results for publishing. All co-authors of the four manuscripts approved their inclusion in this dissertation.

Below is a list of all four manuscripts with a description of specific co-authors' contributions.

Manuscript 1. Puzhko S, Aboushawareb SAE, Kudrina I, Schuster T, Barnett TA, Renoux C, Bartlett G. Excess body weight as a predictor of response to treatment with antidepressants in patients with depressive disorder. Journal of Affective Disorders. 2020 Apr 15;276:153-170. doi: 10.1016/j.jad.2020.01.113.

Svetlana Puzhko performed conceptualization and data curation and wrote the original draft. Gillian Bartlett contributed to conceptualization and supervision of the project, as well as to reviewing and editing. Sarah A.E. Aboushawareb contributed to data curation, reviewing, and editing. Irina Kudrina, Tibor Schuster, Tracie A. Barnett, and Christel Renoux contributed to manuscript reviewing and editing, and to data interpretation.

Manuscript 2. Puzhko S, Schuster T, Barnett TA, Renoux C, Rosenberg E, Barber D, Bartlett G. Evaluating prevalence and patterns of prescribing medications for depression for patients with obesity using large primary care data (Canada Primary Care Sentinel Surveillance Network). Front Nutr. 2020 Mar 17;7:24. doi: 10.3389/fnut. 2020.00024. eCollection 2020.

Svetlana Puzhko designed the methodology and performed data analysis under the supervision of Tibor Schuster and Gillian Bartlett. Christel Renoux and Tracie A. Barnett contributed to the methodology and interpretation of the results. Ellen Rosenberg and David Barber contributed to the interpretation of the results. The text was written by Svetlana Puzhko, with contributions by all co-authors. All co-authors approved the final version of the manuscript.

Manuscript 3. Svetlana Puzhko, Tibor Schuster, Tracie A. Barnett, Christel Renoux, Kimberly Munro, David Barber, Gillian Bartlett. Difference in patterns of prescribing antidepressants known for their weight-modulating and cardiovascular side effects for patients with obesity

compared to patients with normal weight. Accepted for publication in the Journal of Affective Disorders in August 2021.

Svetlana Puzhko conceptualized the research question, designed the methodology, and performed data analysis under the supervision of Tibor Schuster and Gillian Bartlett. Christel Renoux and Tracie A. Barnett contributed to the methodology and interpretation of the results. Kimberly Munro and David Barber contributed to the interpretation of the results. The text was written by Svetlana Puzhko, with contributions by all co-authors. All co-authors approved the final version of the manuscript.

Manuscript 4. Svetlana Puzhko, Tibor Schuster, Christel Renoux, Tracie A. Barnett, Kimberly Munro, Gillian Bartlett. The role of excess weight status in the risk of hospitalizations for patients with depression prescribed obesogenic antidepressants. In the final stages of preparation for submission to the "Pharmacoepidemiology" journal.

Svetlana Puzhko designed the methodology, performed data management, and conducted data analysis under the supervision of Tibor Schuster and Gillian Bartlett. Christel Renoux and Tracie A. Barnett contributed to the methodology and interpretation of the results. Kimberly Munro contributed to the interpretation of the results. The text was written by Svetlana Puzhko, with contributions by all co-authors. All co-authors approved the final version of the manuscript.

Ethics approval

The present study is a modification of the project "Evaluating the Impact of Obesity on Prescribing Practices and Subsequent Health Outcomes", with Dr. Gillian Bartlett as a Principal Investigator. It received ethics approval from the McGill University Institutional Review Board. CPCSSN obtained ethics approval from the research ethics boards of all host

Universities for all participating networks and from the Health Canada Research Ethics Boards. TorSADE received ethics approval from the Research Ethics Committee of the CIUSSS de l'Estrie – CHUS. Please see Appendix A for ethics approvals.

Statement of originality

This dissertation contributed original knowledge to the largely understudied area of antidepressants (AD) prescribing for patients with depression and excess weight in Canada. Recent evidence on the differential response to AD in relation to excess body weight, synthesized in the scoping review included in this dissertation, suggested that patients with excess weight may require individualized approaches to AD selection. In the absence of the obesity-addressing guidelines or clinical recommendations, selection of an effective AD for this population must be challenging for primary care providers. My study was one of the few investigations worldwide and the first study in Canada that recognized the importance of the problem, both for individual patients and public health. It was also the first study to demonstrate a higher prevalence of AD prescribing, prescribing higher number of AD, and higher odds to be prescribed certain obesogenic AD to primary care patients with obesity *vs* normal weight patients, consistent across Canada. These findings highlighted several potential problems with AD prescribing in Canadian primary care that may have a substantial impact on patient's general health and wellbeing and, therefore, need to be addressed by researchers and stakeholders. The lack of obesity-addressing guidelines is one of such problems. Another important concern is the potential presence of a "weight bias" towards patients with obesity in Canadian primary care that could affect prescribers' decision making, potentially making access to all types of treatment less probable for patients with excess weight. Finally, higher odds of prescribing obesogenic AD to patients with obesity, as opposed to the normal weight patients, observed in this study with regard to specific obesogenic AD, can "promote" the

patients to higher obesity classes, as well as contribute to the population-level increase in morbid obesity.

Similarly, my study was the first to demonstrate that patients with obesity and depression who are prescribed obesogenic AD exhibit a trend towards increased risk of hospitalizations during the standard depression treatment course (12 months), compared with the patients with obesity treated with non-obesogenic AD. This trend highlights the importance of considering a patient's weight status upon AD selection. It also suggests that obesogenic AD may not always be the optimal treatment choice for patients with excess weight.

Finally, the scoping review included in this dissertation is one of the two published reviews on the differential response to AD in patients with excess weight, and the first comprehensive review where evidence was synthesized by AD classes and types. In the absence of guidelines and clinical recommendations, this synthesis, presented in a friendly format for knowledge users, may serve as one of the sources facilitating prescribers' decision making.

CHAPTER 1: INTRODUCTION

The prevalence of obesity and depression is high, in Canada and worldwide [1-3]. The economic burden of these two conditions is tremendous [4-7], and it increases when they coexist [8-11]. Moreover, obesity and depression have reciprocal relationships, with each of these conditions increasing the risk for the other [12-33]. What is more, depression and obesity can have synergistic relationships: the combined effect of these two conditions on the quality of life has been shown to exceed the sum of their isolated effects [8]. An increase in the prevalence of both obesity and depression has been observed during the Covid-19 pandemic, with that of depression estimated as approximately 20% in different countries [34-37].

Pharmacological treatment of depression with antidepressant medications (AD) presents many challenges, including resistance to treatment in certain subpopulations. One of these groups comprises people with excess weight [38-42]. The suggested mechanisms of treatment resistance among people with excess weight include increased inflammatory activity, effects on the hypothalamic-pituitary axis, modulating role of comorbidities, pharmacokinetic alterations resulting in reduced bioavailability of medication [43-45], the role of adipokines[46], and polymorphism in some genes[47,48].

In Canada, depression resistant to pharmacological treatment is overrepresented in patients with obesity and overweight patients [49]. The estimated Canada-wide prevalence of treatment-resistant depression (TRD) in primary care was as high as 21.7% in 2014, ranging from 12.8% in Alberta to 28.7% in British Columbia [49]. Compared to non-TRD, TRD is associated with a 40-50% increase in direct and indirect medical care costs [50,51].

In addition to the problem with the effectiveness of AD treatment for people with excess weight suffering from depression, there are concerns about safety. Several AD classes and individual AD were shown to be associated with weight gain [52-54], potentially increasing the number of people with excess weight, who are at risk for a severe course of depression [4] and

other health problems related to excess weight [55,56]. Moreover, weight increase is not the only unwanted effect of AD treatment that patients with obesity or overweight patients may face. Recently published analyses of a cohort of patients with excess weight, extracted from the primary care UK database, show that many commonly prescribed AD classes and individual AD are associated with increased risk for cardiovascular adverse effects, falls/fractures, diabetes, and all causes mortality[57].

The considerable issues with the safety and effectiveness of AD in the population of patients with depression and excess weight point towards the necessity of a tailored approach to prescribing [57]. There is, however, a lack of specific guidelines for treating depression in this population[57]. Tailoring treatment to certain clinical phenotypes and "deep phenotyping" with the use of clinical characteristics, imaging, functional diagnostics, and omics data is swiftly extending nowadays as a rapidly evolving area of medical science, Precision Medicine [58]. Efforts have been made to personalize the choice of AD; however, most algorithms do not include body weight [59,60] even though it is an important and clinically obtainable measure. Moreover, there is a lack of synthesized data on the differential response to AD classes and individual AD that may be useful for physicians in their decision making, with only one literature review on this subject published in 2016 [61]. With the lack of guidelines, clinical recommendations, or even knowledge user-friendly data synthesis, treatment of depression in patients with excess weight may be very challenging for physicians. This may partly explain the overrepresentation of treatment-resistant depression in this population. It may be especially challenging for primary care practitioners (PCPs) who, due to the high prevalence of both conditions in primary care and considering the specifics of our healthcare system (e.g., low access to the specialists) [49,62,63], are largely dealing with managing both obesity and depression in the general population [64]. Presently, it is unknown how Canadian PCPs manage depression in these patients. It is unclear whether they prescribe AD differently for patients with obesity

or patients who are overweight than for patients with normal weight and how these prescribing practices affect depression treatment efficiency and general health. As a first step to improve health outcomes, it is important to evaluate the association between a patient's body weight and AD prescribing by PCPs, with a specific focus on the association between healthcare utilization indicators and prescribing practices. It is also important to synthesize the available data on the differential response of patients with excess weight by AD classes and individual types to assist clinicians in their decision making.

This dissertation addresses these important gaps by synthesizing the available evidence on the differential response to the commonly prescribed AD by AD classes and individual types in a manner that could be easily used by clinicians; describing prevalence and patterns of prescribing AD in Canada and the difference in prescribing certain AD classes and individual medications to treat depression between patients with obesity and normal weight patients, with a focus on AD known for their obesogenic and cardiovascular adverse effects; and examining the role of excess weight in the association between AD prescribing patterns and healthcare utilization indicators in Quebec.

CHAPTER 2: LITERATURE REVIEW

2.1 High prevalence and public health burden of depression and obesity.

According to the World Health Organization, more than 264 million people suffer from depression globally [1]. According to the National Canadian Community Health Survey: Mental Health and Well-Being (CCHS 1.2), the lifetime prevalence of a major depressive episode in Canada was 12.2% (95% confidence intervals [CI] 11.7% to 12.7%) in 2002, with the peak annual prevalence in the 15 to 25 years age group [2], and with an overall annual prevalence of 4.8% (95%CI 4.5% to 5.1%) [2]. The prevalence did not diminish over the years and stayed 4.7% (95%CI 4.3% to 5.1%) [65] in 2012. In line with these numbers, WHO [66] reported an annual depression prevalence of 4.7% in 2015 in Canada; slightly lower than 5.9% [66] in the USA, and comparable to the 3.8% - 6.3% in Europe [66].

The importance of obesity as a global health problem is also growing. During 1975 - 2016, the prevalence of children and adolescents who were overweight or had obesity raised more than four-fold globally, having increased from 4% to 18% [1]. Over 340 million children and adolescents and over 650 million adults were overweight or had obesity in 2016 [1]. The prevalence of obesity is now on the rise even in low-income and middle-income countries, especially in urban populations [1]. Canada is among countries presently facing the obesity epidemic [67]: in 2018, 63.1% of adult Canadians had excess weight, with more than a quarter of the population (26.8%, roughly 7.3 million adults) classified as having obesity and 9.9 million adults (36.3%) as being overweight [3]. The proportion of adults who were classified as with obesity was slightly lower than the national average in British Columbia (23.15%) and Quebec (25%) and was higher than the national average in Newfoundland and Labrador (40.2%), Prince Edward Island (37,8%), Nova Scotia (33.7%), New Brunswick (35.3%), Manitoba (30.8%), Saskatchewan (34.8%) and Alberta (28.8%) [3].

Both depression and obesity are highly comorbid and rank among the leading challenges in public health [4,5]. Both disorders are among the main causes of preventable diseases and disability worldwide, are associated with social stigma and low self-esteem, and are linked to increased healthcare costs placing a substantial financial burden on the healthcare system [6,7]. Obesity increases the risk for many serious health conditions. In 2018, Canadians with obesity had higher prevalence of type 2 diabetes (13.4%), hypertension (29.5%), and heart disease (6.0%) than Canadians with normal weight (2.9%, 9.5%, and 2.7%, respectively) [3]. Obesity is responsible for 0.7% - 3% of total health care expenditures worldwide [68]. In Canada, the estimated annual societal costs related to obesity were 1.0 billion Canadian dollars in 2012 [69].

In turn, depression has been identified as the leading cause of disability worldwide [70] and the major contributor to the overall non-fatal disease-related global health burden [1]. Depression largely affects health-related quality of life, mortality due to intentional injury, functioning, and health care utilization [71]. Depression was reported to raise the risk for coronary heart disease [72], cancer, [73] and stroke [74] and was associated with a 50% to 75% rise in per capita health care costs [75,76]. In Canada, major depressive episode has been identified as the second leading cause of years lived with disability [77].

Even though both obesity and depression are independently associated with substantially higher health care costs [6], the co-occurrence of these conditions may further amplify these associations, leading to an even greater than expected health and economic burden. Obesity and depression share common comorbidities, such as cardiovascular disease and type 2 diabetes. It has been shown that men who had both obesity and depression were at a 7.6 times higher risk of diabetes and a 6.7 higher risk of hypertension, compared to men with obesity who did not suffer from depression [9]. The coexistence of these two conditions was associated with poorer therapeutic response and treatment adherence than either condition

alone [10,78] resulting in higher health care costs [10,11]. Moreover, depression and obesity may act synergistically on patient quality of life as demonstrated by the study of Nigatu et al., 2016, in which the combined effect of the two conditions on physical quality of life exceeded the sum of their separate effects [8].

2.2 Reciprocal relationships between depression and obesity.

Depression and obesity are positively associated [18,79-91], with both conditions sharing several common dysregulated physiological pathways. Heightened inflammation and oxidative stress [92], mitochondrial disturbances and neurotransmitter imbalances [93], dysregulation of the HPA axis, impaired function of glucocorticoid receptors [94-96], disturbances in central serotonin, norepinephrine, and dopamine neurotransmitter systems [97] have been identified in both depression and obesity. Patients with depression and comorbid obesity were found to have high levels of inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6) [92], IL-5, IL-12, and interferon-gamma [98]. A higher level of leptin was shown to have an association with the risk for depressive disorder in men with excess visceral fat [46]. Later, it was suggested that poor leptin signaling plays a more important role as a risk factor for depression than low leptin concentration [99]. It has been suggested that obesity and depression may be different manifestations of the same pathological process when dysregulation of certain common pathways of neurotransmitters can increase an individual persons' vulnerability to both conditions [100,101] (Figure 2.1). One of the suggested upstream mechanisms linking obesity and depression may be dysregulation of Ca2+/cAMP signaling that controls the release of neurotransmitters, as well as hormones and lipogenesis [102].

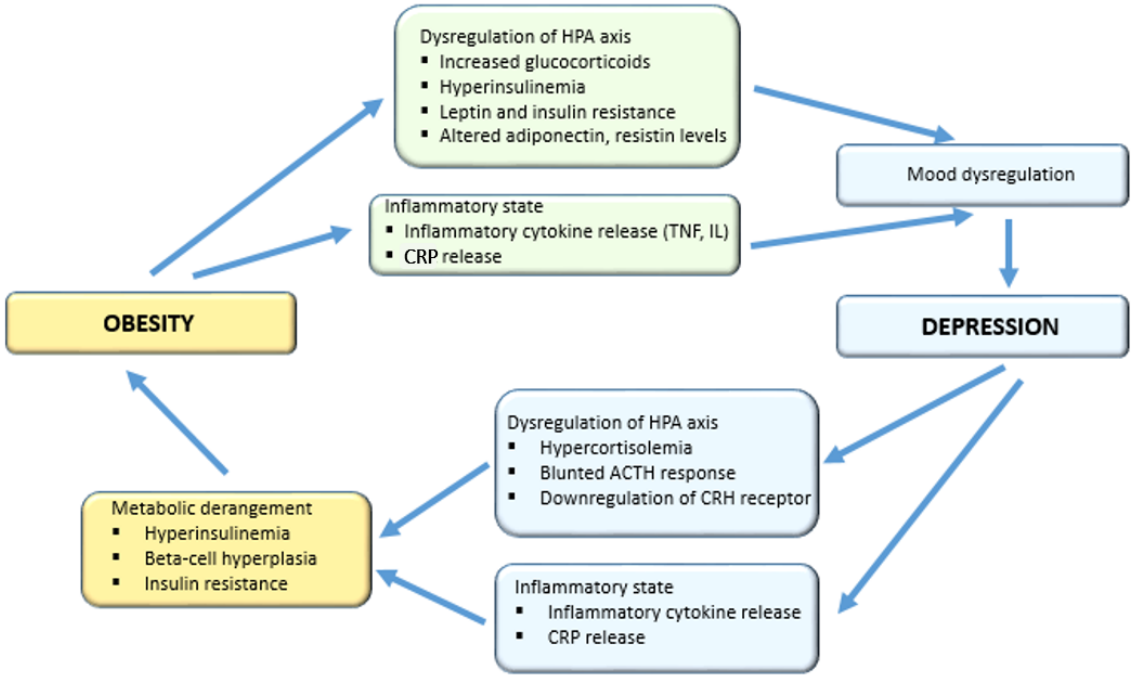
Moreover, obesity and depression may have a causal reciprocal association, with each condition increasing the risk of developing the other. Relationships between these diseases, however, are very complex and do not manifest in all affected patients to the same extent [103].

There is evidence that obesity is prospectively associated with increased depression [12-26], especially in females [18,23,26,31,104-106]. There is slightly less consistent evidence that depression leads to obesity [19,22,27-33], an association that also appears to be more prominent in females than in males [31,32,106]. The potentially causal association between depression and obesity may differ by race [107], ethnicity [108], educational level [109], a subtype of depression, income [107], and cognitive reactivity (ruminative thinking style, satisfaction with appearance) [110,111]. The atypical subtype of major depressive disorder is a strong predictor of obesity [112-115]. These relationships may be even more complex; for example, in a study by Polanka et al., 2019 [113], race/ethnicity was a moderator of the association between subtypes of depression and race: atypical depression was a stronger predictor of obesity in Hispanics/Latinos patients than in non-Hispanic patients.

The obesity-depression putative causal relationship may also vary as a function of sex and genetic polymorphism [47,116-118]. Among genetic polymorphisms associated with both depression and obesity is a polymorphism in the 5-HTT gene that encodes the serotonin transporter engaged in the regulation of both mood and eating habits [119], in GNB3 gene encoding a beta3-subunit of a heterotrimeric guanine-binding protein [47], in a MAOA gene regulating the monoamine system [120]. Recently, significant interactions between body mass index (BMI), depression, and FTO (obesity susceptibility gene) phenotype were reported, with depression increasing the effect of FTO on BMI [121]. A genetic association between specific (atypical) depression phenotype and body weight markers was observed in a study by Milaneschi et al., 2017 [122]: patients with increased appetite and weight, features of atypical depression [112-115], demonstrated a robust positive genetic correlation with BMI.

Figure 2.1. Pathoetiological connection between obesity and depression.

Adapted from Jantaratnotai et al., 2017 [123]



ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; CRP, C-reactive protein; HPA, hypothalamic—pituitary—adrenal; IL, interleukin; TNF, tumour necrosis factor.

2.3 Increased prevalence of obesity and depression during Coronavirus disease 2019 (Covid-19) pandemic

The prevalence of both obesity and depression increased during the Covid-19 pandemic. Researchers from different countries are reporting the prevalence of depression during the pandemic estimated as approximately 20% [34-37]. In a 2020 Canadian study involving 8267 individuals, the prevalence of major depressive disorder was estimated as 44.1% [124]. Fear of acquiring the virus, ambiguity about the future, job loss, financial problems, and pandemic containment measures such as self-isolation and social distancing increased the rates of depression even among people who previously had no psychiatric problems [125,126]. For people

with obesity, who were already at increased risk of social isolation and depression, the enforced quarantine may have especially strong negative impacts on their mental health [127]. Another contributing factor may be weight stigma. In their study, Phul et al., 2020, reported that young adults with pre-pandemic experience of obesity stigma had higher levels of depressive symptoms during the pandemic [128].

Likewise, the Covid-19 pandemic is intensifying the obesity epidemic [129]. Lockdowns introduced by the governments as pandemic containment measures are leading to a worsening of socioeconomic conditions, affecting dietary choices for people with limited resources [129]. In addition, the general lockdown situation and home confinement are having a negative impact on healthy eating behaviours [130-134], with people with obesity affected more [126,133]. In the study by Marchitelli et al., 2020 [125], 60% of patients without a previous night eating habit, reported increased frequency of night eating episodes, placing them at greater risk of developing a night eating syndrome that leads to excess weight gain. Of note, young adults with pre-pandemic experience of obesity stigma had an increased likelihood of eating as a coping strategy and of binge eating [128]. A trend in weight gain during the Covid-19 pandemic has been documented in many different countries [135,136], with patients with obesity showing greater variability of weight than people with normal weight [137,138].

Moreover, in this unprecedented situation, special attention was drawn to the interrelation between depression and obesity. To acknowledge the link between depression related to pandemic factors, including quarantine and other containment measures, and weight gain, the term “depreobesity” was created [138]. For many people, depressive symptoms, triggered by pandemic-related stress, may lead to maladaptive food behaviours and, as a result, substantial body weight changes. In Northern Italy, the direct effect of depression or anxiety on weight, self-reported by the participants of an observational study, was estimated as a 2.07

kg (95% CI 1.07,3.07) gain, with people with obesity gaining weight after one month of the enforced lockdown [139].

Moreover, for people who contracted the virus, both depression and obesity contributed to the Covid-19 related health burden. Obesity was listed among risk factors for severe disease from Covid-19 by the Centers for Disease Control and Prevention [140]. People with obesity who acquired Covid-19 were found to be at increased risk for hospitalization, intensive care, and death [141,142]. According to a recently published systematic review, that included 16 original studies, Covid-19 patients with obesity were 1.78 times more likely to have a poor composite outcome [143]. In addition, many Covid-19 patients develop depression [126,144] that may negatively affect rehabilitation and their return to active life.

Therefore, in the face of a Covid-19 pandemic, management of depression in patients with comorbid obesity has become one of the essential tools to reduce Covid-19 - related health and economic burden.

2.4 Obesogenic adverse effects of AD

The targets of all commonly prescribed AD are monoamines (serotonin, norepinephrine, and dopamine). Monoamines are integrated in the pathways contributing to many biological functions in the human body. Disrupting these pathways may degrade many important adaptive processes. It is understandable, therefore, that AD have many adverse effects, among them, negative cardiometabolic effects and weight gain [52].

Both short-term (after 4 weeks of treatment), medium-term (at 3-6 months of treatment), and long-term (after ≥8 months of treatment) associations between AD treatment and weight gain have been consistently reported [52-54,145-156]. Not all AD have the same effect on weight. Most studies reported an obesogenic effect of a noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine, a tricyclic antidepressant (TCA)

amitriptyline and its metabolite nortriptyline [54,148] [52], and a weight-reducing effect of norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion [53,146,149]. There are also several reports of the gain-modulating effect of selected AD (fluoxetine, paroxetine) from a selective serotonin reuptake inhibitors (SSRI) group [53,146]. The differential effect of AD on weight may be explained by the difference in mechanisms of action for different groups of AD (Figure 2.2).

Figure 2.2. Proposed mechanisms of obesogenic effect for AD classes.

Gill et al., 2020 [52]

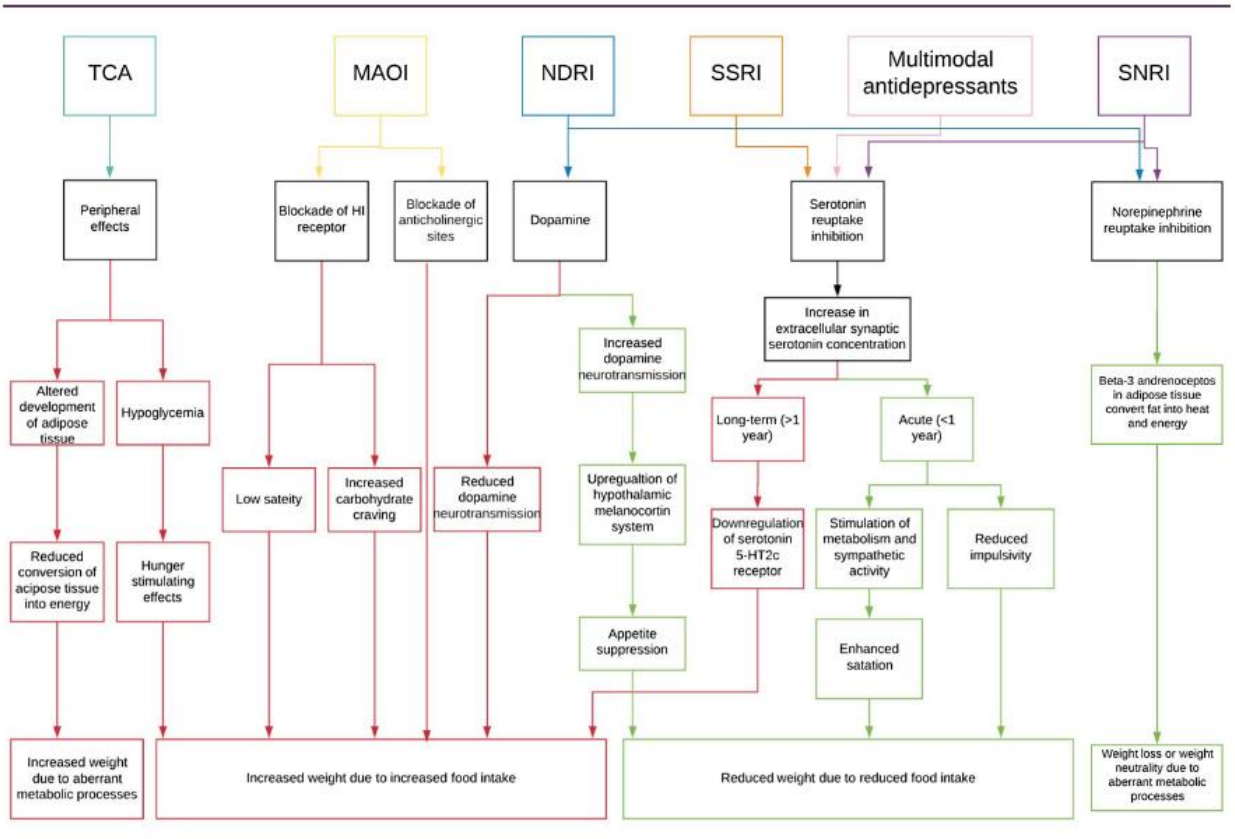


Figure 1 Proposed mechanisms of treatment-emergent weight gain for specific antidepressant classes, where green lines represent weight-loss or weight-neutral processes and red lines indicate processes of weight gain.

TCA: Tricyclic antidepressants
NDRI: Norepinephrine–dopamine reuptake inhibitor
SSRI: Selective serotonin reuptake inhibitors
SNRI: Serotonin and norepinephrine reuptake inhibitors
MAOI: Monoamine oxidase inhibitors

According to the systematic review by Seretti et al, 2009, which included 116 studies, TCA amitriptyline and, to a less extent, nortriptyline, NaSSA mirtazapine, and SSRI paroxetine were consistently associated with a risk of excess weight increase. The average increase in weight associated with the use of these AD ranged from 2.24 to 2.73 kg. In contrast, NDRI bupropion was associated with weight loss. In addition, an association between SSRI fluoxetine and some weight loss during the acute phase of treatment was reported. The pooled estimates for these AD with 95% CI during acute and maintenance treatment are shown in Table 2.1. Only slight effects were observed for the rest of AD that were inconsistent between the studies. The authors also noted that the effect may depend on individual characteristics, such as depression severity, atypical features of depression, patient's premorbid weight, and sex.

Table 2.1. Effect of AD on weight change during acute treatment (4-12 weeks), and medium and long-term treatment (≥4 months).

Adapted from Seretti et al., 2009 [157]

AD	**Acute treatment**		**Maintenance treatment**	
	Mean difference, kg	95% CI	Mean difference, kg	95% CI
		TCA		
Amitriptyline	1.52	1.08, 1.95	2.24	1.82, 2.66
Nortriptyline	2.00	0.74, 3.25	1.24	-0.51, 2.99
		SSRI		
Paroxetine	-0.28	-0.46, -0.09	2.73	0.78, 4.68
Fluoxetine	-0.94	-1.24, -0.65		
Citalopram	-0.64	-0.89, -0.38	1.69	-0.97, 4.34
		NaSSA		

Mirtazapine	1.74	1.28, 2.20	2.59	-0.23, 5.41
		NDRI		
Bupropion	-1.13	-1.31, -0.84	-1.87	-2.37, -1.37

In a recently published review [52], SSRI citalopram was also suggested as AD with a high risk to induce gain (Table 2.2).

Table 2.2. Summary of commonly prescribed AD and the associated risk for adverse weight-modulating effects

Adapted from Gill et al., 2020 [52]

Risk for medication-induced weight gain		
High	**Medium**	**Low**
Amitriptyline Citalopram Mirtazapine Nortriptyline Trimipramine Paroxetine Phenelzine	Duloxetine Escitalopram (acute results demonstrate weight loss/weight neutral) Sertraline (acute results demonstrate weight loss/weight neutral)	Moclobemide Vortioxetine Tranylcypromine Venlafaxine Vilazodone Desvenlafaxine Fluoxetine (acute results demonstrate weight loss/weight neutral) Imipramine Moclobemide Bupropion (associated with weight loss)

In a cohort study that included over 300,000 participants, the long-term risk of weight gain was 11.2 per 100 person-years for patients taking AD (adjusted rate ratio 1.21; 95% CI 1.19, 1.22), compared to the rate of 8.1 per 100 person-years for patients not receiving AD [152]. There may be, however, a way to predict the long-term weight gain in a patient taking AD. It has been shown that >5% weight gain after one month of AD treatment is a good predictor of major long term weight gain after 3 months (>15%) and 12 months (>20%, a mean BMI increase of 3.1 kg/m^2) of treatment [158,159]. Most patients (93%-97%) with a moderate weight gain (≤ 5%) after 1 month of treatment continued to have moderate weight gain after 3 and 12 months (a mean BMI increase of 1.2 kg/m^2 at 12 months). Moreover, analysis of clinical and genetic risk factors may allow for detection of people at risk for > 5% weight gain after 1 month of treatment with psychotropic medications, including AD [158]. It may be, therefore, possible to perform initial screening before prescribing to discern whether a patient may be at risk for major long-term weight gain [158].

2.5 Cardiovascular and other adverse effects of AD

Obesity is an established independent factor for cardiovascular disease [160,161]. This has critical implications for AD that are also associated with increased risks for cardiovascular adverse effects, such as angina, arrhythmia, myocardial infarction, acute coronary heart disease, heart failure, and death, as well as the need for percutaneous coronary intervention and coronary artery bypass graft in cardiac patients [162-167]. There are a few studies that reported no association between AD use and cardiovascular adverse effects [163,166,168,169]; however, mixed results may be explained by the absence of stratification by groups and types of AD [162].

This association appears to be different for different AD classes. In a systematic review published in 2017, that included 22 observational studies, as well as in later studies, use of TCA but not SSRI was associated with an increased risk of acute heart disease (including

coronary heart disease, ischaemic heart disease, myocardial infarction, and sudden death)[170,171]. During recent years, however, the safety of SSRI in cardiac patients was questioned by several authors [162,172]. The mixed findings regarding SSRI may be explained by different associations with cardiovascular events for different individual SSRI. A lower risk of cardiovascular adverse effects was reported for escitalopram, compared to citalopram, sertraline, and paroxetine [173]. Some adverse cardiac effects in geriatric populations taking venlafaxine [174], but not other serotonin and norepinephrine reuptake inhibitors (SNRI), were reported. Increases in blood pressure were observed in patients taking venlafaxine, duloxetine, and TCA [175,176].

Of importance, several AD, among them of TCA and SSRI groups, were associated with a serious adverse effect, prolongation of the QT interval on the electrocardiogram, linked to an increased risk for life-threatening ventricular arrythmia known as "Torsade de Points" (TdP) (Tables 2.3 and 2.4). Prolongation of QT usually occurs due to the inhibition of the cardiac delayed potassium rectifier current, an outward current controlled by potassium channels, by medication [177]. This leads to disrupted ventricular repolarization [177]. With TCA, listed as the highest risk for QT prolongation, disrupted repolarization may occur through the dual mechanism of blockage of sodium and calcium channels; and blockage of the rapidly activating component of the delayed rectifier current. This may explain the greater risk for TCA compared to SSRI which was also reported to cause QT prolongation. Among SSRI, recent studies suggest the highest risk for citalopram and the lesser risk for escitalopram. Other SSRI appear to have no risk[178] or have moderate risk[177,178] for QT prolongation., and there is no sufficient evidence to recommend caution or monitoring during treatment with other SSRIs [179,180]. The greater impact of citalopram on the QT prolongation compared to other SSRI may be partly explained by the effect of its metabolite, didesmethylcitalopram, [181] that is associated with impaired ventricular repolarization [179]. The risk may be higher in people who are genetically predisposed to be ultra-rapid metabolizers of cytochrome P450 2D6 and, therefore,

can have higher concentrations of didesmethylcitalopram [182]. In 2011, the FDA issued recommendations to limit prescribing of citalopram to dosages of ≤40 mg because of the increased risk of QT prolongation at higher doses. Of note, escitalopram, the S-enantiomer of citalopram, in addition to being shown to be more efficient than citalopram in treating depressive symptoms in several studies [183-187], appears to have less effect on QT-interval prolongation than citalopram [179,188]. This may be because single-enantiomers medications commonly have better safety and efficiency profiles than racemic medications. The intrinsic clearance of escitalopram is higher than in citalopram, and, therefore, its steady-state concentration is lower. After discontinuation of the medication, the washout half-life time of escitalopram will be shorter. These characteristics may explain differences in clinical effects between citalopram and escitalopram [189]. Among other AD, mirtazapine was associated with TdP [190]; however, this evidence has been debated [191,192]. Of the SNRI, only venlafaxine is recommended to be used with caution in patients with risk factors for QT-prolongation, even though most studies have failed to find an association between venlafaxine treatment and QT-prolongation [191,192]. Fluoxetine, fluvoxamine, and sertraline were reported to be low risk for QT prolongation, with the lowest risk in paroxetine [193].

Among other adverse effects, abnormal bleeding [194] as well as a small increase in the risk for falls and fractures [195,196] and hyponatremia in elderly [197] were associated with SSRIs. Male sexual disfunction was primarily associated with escitalopram, paroxetine, venlafaxine, sertraline, and duloxetine [198]. TCAs [199], as well as NaSSA mirtazapine and SSRI sertraline [200] were associated with elevated blood glucose levels and the increased risk for type 2 diabetes. Other common adverse effects of AD, that usually do not lead to serious or life-threatening complications, are dry mouth, nausea, constipation, headaches, dizziness, insomnia or somnolence, fatigue, sweating, and tremor [198].

Table 2.3. Antidepressants of most commonly prescribed classes with a higher risk of QT prolongation at therapeutic doses

Adapted from Dietle A., 2015 [192]

AD class	AD type
TCA	Amitriptyline, imipramine, nortriptyline, desipramine, clomipramine, trimipramine
SSRIs	Citalopram, Escitalopram
NaSSA	Mirtazapine (the evidence has been debated)
SNRI	Venlafaxine: use with caution in patients with risk factors (evidence is based on case-reports only)

Table 2.4. Antidepressants of most commonly prescribed classes with a lower risk of QT prolongation at therapeutic doses

Adapted from Dietle A., 2015[192]

AD class	AD type
SSRIs	Paroxetine, fluoxetine, sertraline, fluvoxamine
TCA	Doxepin
SNRI	Duloxetine, desvenlafaxine
NDRI	Bupropion
SARI	Trazodone
Other	Vortioxetine, vilazodone

2.6 Adverse effects of AD in patients with excess weight

Adverse effects of AD specifically in patients with excess weight are understudied. The work of Morris and colleagues published in 2021 [57] is, to our knowledge, the only study that specifically aimed to address this issue. In this study, a retrospective analysis of a cohort of patients with excess weight, extracted from the primary care database, the UK Clinical Practice Research Datalink, linked to health-administrative data, was performed. The five most commonly prescribed AD (amitriptyline, citalopram, sertraline, mirtazapine, fluoxetine) and their AD class (SSRI and TCA) were evaluated separately; other AD were categorized as "other AD classes", with separate groups for "other SSRI" and "other TCA".

Compared to patients with excess weight suffering from depression who did not take AD, patients with excess weight who took TCA and SSRI had an increased risk of cardiovascular disorders (hazard ratio [HR] 1.26; 95%CI 1.01, 1.58 and HR 1.32; 95%CI 1.14, 1.53, respectively). When comparing different AD types, citalopram (HR 1.30; 95%CI 1.07, 1.57), amitriptyline (HR 1.57; 95%CI 1.15, 2.15), sertraline (HR 1.44; 95%CI 1.06, 1.97), and fluoxetine (HR 1.27; 95%CI 0.97, 1.65), were associated with increased risk, as well as combinations of SSRI and TCA (HR 1.86; 95%CI 1.23, 2.82). Mirtazapine was not associated with this adverse effect.

All studied AD, except citalopram, were associated with all-cause mortality in patients with excess weight taking these AD, compared to patients with excess weight not taking AD. The HR ranged from 1.67 (95%CI 1.17, 2.40) for "other SSRI" to 2.99 (95%CI 2.22, 4.02) for the combination of SSRI and TCA with "other AD". Of interest, when citalopram was prescribed in a dosage of 40 mg for 1 year, it was associated with all-cause mortality (HR 1.01; 95% CI: 1.00, 1.02), which is in line with the FDA warning issued in 2011 regarding limiting the dosage of citalopram to ≤40mg to decrease the risk of QT prolongation that may lead to Torsade de Point arrhythmia.

Patients with excess weight who were prescribed citalopram, fluoxetine, mirtazapine, and "other TCA", as well as combinations of TCA, or SSRI+TCA, with "other AD", had an increased risk of diabetes. Patients with excess weight who took fluoxetine and "other TCA" were at increased risk for falls and fractures. Citalopram and sertraline were associated with falls and fractures if prescribed in a dosage of 40 mg or 100 mg, respectively, for 1 year.

The authors disclosed that these results should be considered cautiously due to the possible indication bias and residual confounding. Nevertheless, their findings highlight that treatment of depression in patients with excess weight is a complex problem and requires tailored approaches [57].

2.7 Problems with prescribing medications for people with excess weight. Weight bias.

The association between obesity and medication prescribing has received more attention in the last two decades. Studies showed that prescribing of medications may be different for people with excess weight than for people with normal weight [201-205]. In the UK, obesity increased prescribing for most groups of medications approximately two times in 2005[201]. Moreover, for patients whose BMI exceeded 30 kg/m2, higher levels of obesity were associated with higher prescribing rates, even after adjusting for age, sex, and comorbidities.[201]. For most medications, the increased rates of prescribing were due to both the higher number of patients receiving prescriptions and the volume of prescriptions per patient[201]. In the USA, patients with obesity were more frequently prescribed several classes of medications, including hypertension, lipid-lowering, and diabetes medications, than adults with normal weight in 2005-2008. This was demonstrated in a cross-sectional analysis of a nationally representative sample of the United States that included 9,789 adult participants. Similar to the UK study, a significant trend for greater use of prescribed medications with increased weight was observed for eight of the ten medication classes, including AD [203].

In addition to increased rates of prescribing, people with excess weight may also face an important problem in receiving an adequate standard of medical care due to a phenomenon of "obesity bias", or "weight bias". This originates from beliefs in negative and pejorative stereotypes that people who are overweight and people with obesity are lazy, less intelligent, and willfully non-adherent to physician's recommendations to make changes in their behaviours [206,207]. In addition, some physicians have adopted a policy of refusing certain services to patients with obesity as an incentive to lose weight [208]. Health care providers across all disciplines have been shown to exhibit this bias [209]. Weight bias was associated with shorter time spent in clinical visits, less engagement in discussions, delivering fewer interventions and preventative health screenings in patients with obesity [210,211] and patients with high BMI [212]. For people with mental conditions and comorbid obesity, obesity bias can aggravate already poor physical and mental health outcomes [213].

To summarize, increased rates of prescribing in people with excess weight may be due to a more severe course of disease that requires greater pharmacological treatment, low effectiveness of medications in this population, or differences in the attitudes of prescribers towards prescribing. As a result, people with excess weight may be receiving suboptimal treatment that may negatively affect their health outcomes, especially if patients with obesity have comorbid mental conditions [213]. They can also be at increased risk for adverse effects of medications prescribed in a higher amount, especially if they are prescribed concurrently. In the following section, current evidence on prescribing AD for people with depression and excess weight will be reviewed.

2.8 Prescribing AD for people with excess weight

There are a number of concerns regarding prescribing AD for people with excess weight. First, obesity and being overweight are associated with poor response or non-response to treatment

with different classes and types of AD [38-40,101,214]. Even if patients with excess weight are able to reach the same level of treatment response with an adjusted dose of AD, they may need a longer duration of treatment than patients with normal weight [39]. On the other hand, patients with a certain degree of obesity may have a better response to selected AD types. For example, patients with morbid obesity were shown to respond better to venlafaxine-XR [215]. It is, therefore, possible that the association of excess weight and response to AD treatment is different for different AD classes and even for different AD types belonging to the same class. Several factors have been discussed as potential contributors to a high inter-individual difference in response to antidepressants: increased inflammatory activity and/or neurovegetative symptoms, effects on the hypothalamic-pituitary axis, modulating role of comorbidities, pharmacokinetic alterations resulting in reduced drug bioavailability [43-45,49], the role of adipokines secreted by adipose tissue (leptin) [46] and polymorphisms in some genes (e.g. leptin gene, GNB3) [47,48].

Another concern is that treatment with different AD can affect body weight, including by increasing it. This, in turn, may expand the pool of patients with excess weight suffering from depression [153,155,216] who may be at increased risk for a more complex course of illness and poorer treatment outcomes, compared with patients without obesity [217]. Finally, AD treatment in patients with excess weight is associated with adverse cardiovascular effects [57] that may be especially harmful for the population already at higher risk for cardiovascular diseases [218]. Other adverse effects of AD treatment in patients with depression and excess weight have also been reported [57].

In Canada, a large proportion of patients with life-time depression, namely 85%, are prescribed AD [219]. A substantial part of this population has excess weight. To our knowledge, however, there are no guideline-based protocols tailored to the treatment of depression in patients with obesity. A possible need to increase AD dosage is mentioned in the recent APA

guidelines [220]. This recommendation is based on only one study, and no specific instructions for such dose tailoring were provided. The recent Canadian guidelines, Canadian Network for Mood and Anxiety Treatments (CANMAT) [198], do not address any specific approach to prescribing AD in patients with obesity, and the same is true for the major European guidelines [221,222]. In addition, there are no specific recommendations on prescribing obesogenic AD to patients at risk of obesity (e.g., to patients who are already overweight) in CANMAT 2016 [198]. The British Association of Psychopharmacology (BAP) [221] states that weight is one of the factors to consider when making decisions for AD prescribing, but it does not provide specific recommendations. The National Institute for Health and Care Excellence (NICE) [222] recommends monitoring weight and other AD adverse effects when prescribing. Yet only the American Psychiatric Association (APA) 2010 guidelines [220] recommend consideration of the effect of certain AD on weight, more specifically, the relative tendency to increase weight for mirtazapine and TCA and weight-reducing effect of bupropion, when prescribing AD to patients with excess weight.

Among published research, to our knowledge, only two studies [202,223] aimed to evaluate whether providers are considering patients' body weight when they prescribe AD. The population-based study of Boudreau et al., 2013, conducted in the USA, showed that patients' current BMI or recent changes in BMI may be influencing providers' and patients' choice of AD treatments by considering obesogeneity (the risk to increase patient's weight) of the medication. More specifically, patients with higher BMI had lower odds of initiating mirtazapine, an AD with a documented obesogenic effect. Odds of initiating both mirtazapine and paroxetine (the most obesogenic AD of the SSRI group) were higher among subjects with decreasing BMI compared with patients with stable BMI (odds ratio [OR] 1.87; 95% CI 0.99, 3.50 for mirtazapine; OR 1.31; 95%CI 1.00,1 72 for paroxetine). Of concern, this study observed that patients with obesity might be receiving a lower quality of depression care (e.g.,

shorter duration of depression treatment) when compared with normal weight patients. Researchers observed significantly lower odds of continuous depression treatment with increasing BMI at 180 days after index date [202], meaning that patients with higher BMI were less likely to receive standard of care (AD treatment within 6 months). It is unclear if this was due to prescribers' bias, the low initial response to treatment, or other reasons.

The most recent study related to this topic is the observational study by Tyrer et al., 2020, where the UK primary care database (the Clinical Practice Research Datalink) was used to evaluate first-line AD prescribing in patients with obesity [223]. This study showed that, in the UK, AD were prescribed to two-thirds of patients with obesity. The most common class of AD was SSRIs (90% of all AD prescribed); however, of the other groups, tetracyclic AD mirtazapine, known for its obesogenic effect, and tricyclic AD dosulepin, which was contraindicated as first-line therapy in 2009, were the most commonly prescribed AD in this group of patients. In addition, 0.2% of patients with excess weight were prescribed more than one AD simultaneously, which is also not recommended by guidelines. The authors also expressed a concern that prescribing of fluoxetine, the AD known for its weight-neutral or even weak weight-reducing effect, for the group of patients with obesity, decreased over the years (20.4% [2000]; 8.8% [2018]). Tyrer et al., 2020 [223], concluded that there is uncertainty regarding first-line treatment choice for people with depression and comorbid obesity and highlighted the urgent need for specific guidelines on AD prescribing for patients with excess weight. Of note, Tyrer and colleagues did not compare AD prescribing between the groups of patients with excess and normal weight.

In 2016, a literature review was published on the differential response to AD in patients with excess weight, compared to patients with normal weight [61]. The authors, however, did not aim to synthesize the information by groups and types of AD in a way that would have been clinically actionable. Moreover, in recent years, more studies on the differential response to

AD treatment in patients with excess weight have been published, which were not included in the review by Woo et al. from 2016.

2.9 Relevance for Canadian primary care

In North America, 11%-36% of primary care patients have a mental disorder and more than one-third of mental health patients accessing health care are treated solely by PCPs [64]. Primary care is usually an entry point to depression treatment, due to ease of access to a PCP, lack of specialists in a patient's residential area, or long waiting time to see a specialist [47-49,62,63]. In Canada, about 10% of primary care patients are likely to meet the criteria for major depression disorder [63]. On the other hand, in a typical practice, 60 out of every 100 patients will be overweight, and 25 of these 60 patients will have obesity. Therefore, Canadian PCPs are the ones largely dealing with the treatment of both depression and obesity [224].

Depression treatment rates in Canadian primary care remain low [63]. In 2014, the Canada-wide prevalence of treatment-resistance depression (TRD) in primary care was 21.7% [49], ranging from 12% in Alberta to 28% in British Columbia. In Quebec, the prevalence of TRD in primary care was 13% in 2014. In Canada, a substantial proportion of the population suffering from TRD are patients with excess weight [49]. Considering a possibility of differential response to treatment with different AD classes and individual medications, weight-increasing properties of some commonly prescribed AD, and possible excessive risk of patients with obesity for cardiovascular and other adverse effects of certain AD, patients with depression and comorbid obesity need a specialized approach to treatment. Even though prescribing AD is a common practice for PCPs [63,225], and most AD prescriptions in Canada are issued by them [63], it is unknown how PCPs in Canada manage depression in patients with excess weight, especially with the lack of guidelines and clinical recommendations. It is unclear whether they

prescribe AD differently for patients with excess weight than for patients with normal weight and how these prescribing practices affect treatment efficiency and general health.

Considering the increasing prevalence of both depression and obesity, PCPs in Canada are faced with the challenge of choosing the optimal pharmacological treatment for patients with excess weight suffering from depression. It is important to assess AD prescribing to patients with excess weight in Canadian primary care suffering from depression, and to evaluate the association between prescribing patterns and healthcare utilization indicators.

CHAPTER 3: KNOWLEDGE GAPS AND STUDY OBJECTIVES

3.1. Knowledge gaps

Issues with pharmacological treatment of depression in patients with excess weight is an understudied area. The review of the literature helped identify the following knowledge gaps:

1. Even though several published works suggest that response to certain classes and individual types of AD may be differential in patients with excess weight, there is a lack of comprehensive reviews with the data synthesized by AD classes and types in a knowledge user - friendly manner. Given the lack of existing clinical guidelines, such a review could provide PCPs with a comprehensive picture of the existing data on this subject to assist their decision making.

2. Considering problems with AD prescribing for patients with excess weight described in the literature, one might expect the prevalence of prescribing and the number of AD prescribed to be high in this weight group due to lower efficiency of certain AD and to the lack of available data on tailored prescribing [61]. There are, however, no studies evaluating prevalence and patterns of AD prescribing in Canadian primary care in relation to the obesity status and obesity class. Moreover, whether AD known for their weight increasing and cardiovascular adverse effects are prescribed differently to patients with excess weight in comparison to the patients with normal weight in Canadian primary care has not been examined. In other words, it is unknown whether PCPs in Canada adjust for these adverse effects, which may be especially undesirable in this population, when they select AD. It is especially concerning since a clinically relevant increase in the risks for several serious AD adverse effects was reported for patients with excess weight in the UK [57].

3. Finally, it has not been studied if the association between prescribing of AD with known obesogenic adverse effects and healthcare utilization indicators is different for patients with excess weight, compared to their normal weight counterparts, and whether this prescribing pattern may, in fact, be associated with the higher risks for increased healthcare utilization in this population.

This thesis will address these important knowledge gaps while informing future research directions on tailoring AD prescribing to a specific phenotype of patients: patients with excess weight suffering from depression.

3.2 Study aim and objectives

Study aim: The overarching aim of this study is to examine antidepressants prescribing for people with depression and excess body weight by Canadian primary care providers, with specific attention to antidepressants prescribing patterns, and health outcomes and healthcare utilization.

Objective 1: To synthesize evidence on the role of excess body weight in response to treatment with antidepressant medications in people with depression by classes and individual types of antidepressants.

Objective 2:

a) To describe, in Canadian primary care, the prevalence and patterns of antidepressants prescribing (number of antidepressant types prescribed) to patients with depression and

comorbid obesity in comparison with patients with normal weight, and prescribing differences between patients with obesity classes I-III.

b) To estimate differences in prescribing antidepressants, known for their weight-modulating and cardiovascular adverse effects, for patients of different weight groups, when weight is measured and documented before the first antidepressant prescription.

Objective 3: To estimate differences in the association between prescribing of antidepressants known for their obesogenic (that is, weight-increasing) adverse effects and health care utilization (hospitalizations) in patients with and without excess weight, who suffer from depression.

CHAPTER 4: EXCESS BODY WEIGHT AS A PREDICTOR OF RESPONSE TO TREATMENT WITH ANTIDEPRESSANTS IN PATIENTS WITH DEPRESSIVE DISORDER (MANUSCRIPT 1)

4.1. Preamble

Depression and obesity are both highly prevalent conditions and are, globally, among the major contributors to disability. Treatment of depression is challenging, with many patients not responding or responding poorly to certain AD. Recent studies revealed specific patients' characteristics that are associated with the differential response to AD, depending on AD class and type. Identification of the patient's phenotypes contributing to the differential response to AD will help individualize the depression treatment. One such phenotype is the excess weight. While there is a high prevalence (estimated at 60%) of patients with excess weight in Canadian primary care, presently, no obesity-oriented guidelines or clinical recommendations exist for AD selection. A comprehensive scoping review on the differential response to AD treatment in patients who are overweight or have obesity would emphasize the importance of considering the patient's weight status when prescribing AD.

In my first manuscript, I synthesized the evidence[1] on the differential response to AD treatment in patients with excess weight. The evidence was further structured by AD classes and types to facilitate its usability for prescribers and help them with AD selection. The synthesized evidence highlighted a diminished response to several AD in patients with obesity or high BMI. Conversely, the evidence indicated a stronger response to some AD and AD combinations in patients with severe obesity. The scarcity of data on the response to individual AD types was identified as the knowledge gap.

[1] Please note that the study of Kloiber et al., 2007, was incorrectly cited as an RCT (page 37, Table 4.2.a/4.3).

Title: Excess body weight as a predictor of response to treatment with antidepressants in patients with depressive disorder

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4.2. Abstract

Background: Depression and obesity are debilitating conditions representing an enormous health and economic burden worldwide. Depression is common among patients with excess weight, but more importantly, these patients may be at risk for poor response when treated with antidepressant medications (AD).

Methods: We conducted a comprehensive scoping review to summarize the evidence regarding the difference in response to treatment of depression with AD among patients with excess weight as compared to normal weight patients and to identify knowledge gaps.

Results: The search of the Medline and PsycINFO (2004-2019) identified twelve relevant studies. Tabulation and frequency analysis of the charted data along with a narrative synthesis were performed. Nine studies (75%) reported clinically relevant negative association between patients' high BMI or obesity and treatment response to either nortriptyline, fluoxetine, or various AD; one study (8.3%) reported no difference in response to various AD combinations between BMI groups. One study showed benefits of bupropion and escitalopram combination in patients with morbid obesity (BMI>35 kg/m^2) as compared with escitalopram monotherapy. Another study reported benefits when using venlafaxine-XR in patients with morbid obesity. We also acknowledge the possible role of sex and genetic factors predicting AD treatment response.

Limitations: The search was restricted to two most relevant sources, publications in four languages and adult population.

Conclusion: The synthesized data may be useful to physicians in their decision regarding the choice of AD in patients with excess weight. Researchers need to address causality of association between obesity and treatment response to individual AD types.

4.3. Introduction

Depressive disorder is a disabling condition that results in a substantial economic (Greenberg et al., 2015) and health (Liu et al., 2019) burden. Over 300 million people suffer from depression worldwide (Liu et al., 2019). According to the World Health Organization (WHO), depression is the largest factor contributing to disability globally (Smith, 2014). Treatment of depression is problematic with over 50% non-remitters and 30-50% non-responders to antidepressant medications (AD) (Martin et al., 2018). The reasons for treatment resistance are poorly understood; however, the proportion of obese and overweight patients suffering from treatment resistant depression is reportedly higher than among patients with normal weight (Rizvi et al., 2014).

Obesity is one of the most prevalent comorbid conditions of depression (Opel et al., 2015). The relationship between depression and obesity understood to be bidirectional, with excess weight putting patients at risk of developing a depressive episode, and vice versa (Global Burden of Disease Study 2013 Collaborators, 2015). Of interest, obesity and high body mass index (BMI) may negatively impact patient's response to the treatment with AD (Woo, Seo, et al., 2016), contributing to treatment resistance. Some authors propose that there might be a need to adjust or optimize depression treatment strategies according to the patient's weight (Green et al., 2017; Jha, Wakhlu, et al., 2018). In order to make any recommendation for medication optimization, it is important to understand the evidence behind a potential link between excess weight and individual treatment response to AD.

Despite the significance of the problem and high prevalence of depression among patients with high BMI, presently, there is no consensus on how to individualize AD treatment with consideration of the patient's weight. The overarching aim of the present review is to summarize the evidence on whether adult patients with higher than normal weight (obese, overweight, or high BMI) and suffering from depression might have different treatment

outcomes as compared to the adult patients with depression and normal weight, when treated with AD. The authors were specifically interested in understanding the predictive ability of a high BMI and obesity for treatment outcomes with specific AD classes and types as well as identifying knowledge gaps in this area. The role of other important factors in predicting AD treatment response was outside of the scope of this article, however, we briefly discussed them to remind the reader of several important confounders in the association between increased weight and AD treatment response.

4.4. Methods

This study is a comprehensive scoping review. Conducting a scoping review is preferred over a systematic review when the purpose is to scope a body of literature or identify knowledge gaps.

Considering the diversity of design and methods of relevant studies found during our pilot search and high heterogeneity of discussed AD treatment regimens, performing a systematic review would not be appropriate. Scoping review methodology was chosen as more suitable to "summarize findings from the body of knowledge that are heterogeneous in methods" (Tricco et al., 2018). "Scoping reviews do not aim to produce a critically appraised and synthesised result/answer to a particular question, and rather aim to provide an overview …of the evidence" (Munn et al., 2018). Therefore, the evaluation of methodological limitations or assessment of risk of bias of the included evidence is not commonly performed (Peters et al., 2015) and a systematic synthesis of individual studies findings with the generation of summary by meta-analysis is not required (Munn et al., 2018). Scoping reviews, however, still require the use of rigorous and transparent methods to ensure reliability of results. In our scoping review, we used transparent and reproducible search in accordance with PRISMA Extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018) checklist (Appendix,

Table S5), to summarize data on the association between high BMI and obesity with treatment response to distinct AD classes and types and to identify a knowledge gap to be addressed by future research. The review question in PICO format is described in Table 4.1.

4.4.1. Selection of studies

Inclusion criteria

Empirical studies (quantitative studies and quantitative parts of mixed methods studies) were included. The target population comprised adult (18 years old or older) in- and/or outpatients with any ongoing depressive disorder, including major depressive disorder (MDD), who suffered from obesity and/or excess weight, as defined by either WHO classification (WHO, 2000) or the WHO recommendations for populations from Asia (WHO, 2004), and patients with normal weight as a comparator group. Included interventions comprised pharmacological treatment of depression with the most common classes of AD (Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016) (Kennedy et al., 2016): selective serotonin reuptake inhibitors (SSRIs); serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs); tetracyclic antidepressants (TeCA), dual action antidepressants including norepinephrine and dopamine reuptake blocker (NDRI) bupropion, a serotonin antagonist and reuptake inhibitor trazodone (SARI), and monoamine oxidase inhibitors (MAOIs).

Exclusion criteria

Preclinical research was excluded. Non-empirical studies (reviews, commentaries, editorials, methodological papers) and qualitative studies were also excluded. Studies looking at non-pharmacological treatment only or treatment with medications other than AD, and studies with treatment outcomes not measured quantitatively were excluded.

Additional limits

Language: English, French, German, Russian (languages mastered by the first author). Time frame: studies published during the last 15 years (January 2004-January 2019) which would include the first known published researchevaluating the association between excessive weight and response to AD.

4.4.2. Sources of information, search strategy and data extraction

Main sources of information

MEDLINE and PsycINFO, as the two databases most pertinent to this review, were searched through OVID. Backward citation search was also performed.

Search strategy

A detailed search algorithm **(**Appendix, Table S3**)** was developed with a specialized librarian. Keywords and Mesh terms were determined using both advanced search options in OVID and by scanning relevant publications (identified in the test phase). In addition, reference lists of the studies included in the review were searched for relevant articles. SP screened titles and abstracts for eligibility. Full text screening was performed by SP and SA. In case of uncertainty, authors were contacted for additional information.

Charting the data

The following data were extracted from the studies independently by two researchers (SP and SA) using the data charting form developed for this study, disagreements were resolved by consensus as necessary: title, authors, year, country; study design, settings and participants; intervention (treatment with AD, classification and posology); exposure (BMI or weight group, measured or self-reported, measured at baseline or monitored throughout the study); outcomes (the type of depression rating scale, outcome measures used in the studies); data analysis (type of variables representing exposure and outcome (continuous or categorical), methods of

analysis); results (study sample, study groups, effect estimates and uncertainty measures); conclusion.

4.4.3. Data synthesis

Data synthesis was performed according to the PRISMA ScR guidelines (Tricco et al., 2018).

The charted data were tabulated. Using frequency analysis, the counts and percentages of study characteristics (study design, populations, settings, exposure and outcome measures, methods of analysis) and findings were calculated. We further grouped the studies by AD classes and types, and summarized study findings for each group and AD type in a form of a narrative synthesis. In addition, data on individual AD types were summarized in Table 4.5, and a graphical representation of findings (graphical abstract) was created.

4.5. Results

4.5.1. Results of the literature search

The results of the literature search are described in detail with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram in Figure 4.1 and shown in Table S4 of the Appendix 1. The final search produced 443 articles in MEDLINE and 191 articles in PsycINFO. Twelve studies were included in the final analysis.

4.5.2. Studies characteristics. Data synthesis

Study research questions are described in detail in Table 4.2. Each aspect of the retained articles is described in Table 4.2a using frequency analysis. Characteristics of included studies are described in detail in Table 4.3. We found high heterogeneity of intervention types between

the studies (different types of AD evaluated, each type represented by a single study, different dosages and treatment durations) as well as high diversity of analytical approaches. The results of individual studies are shown in detail in Table 4.4.

Of twelve included studies, eleven (91.7%) reported difference in response to AD in patients with excess weight compared with normal weight patients.

4.5.3. Obesity and higher BMI predicted poor response to treatment with different AD

Kloiber et al. (2007) conducted an open-labeled RCT looking at the treatment with individualised AD therapy chosen by the prescribing physicians. The rates of improvement with any AD treatment were slower among overweight and obese patients as compared with normal weight patients, with the slowest rate in the obese group ($p<0.01$, mean scores not reported, presented graphically). Moreover, obese patients were 4.49 times more likely to be non-responders (95%CI: 1.48, 13.64) than normal weight patients.

A negative association of high BMI with a response rate to different AD of SSRI and SNRI groups randomly assigned to patients was reported in the study of Oskooilar et al. (2009). In this post-hoc analysis of three small RCTs, patients with normal BMI showed clinically meaningful greater response to treatment, measured by HRDS and MADRS scales, when compared to obese patients. More specifically, after 8 weeks of treatment, the mean HRDS score for obese patients was 1.65 times higher than for normal patients (7.7 and 12.7 for normal and obese patients, respectively, $p<0.005$, standard deviation or standard error was not reported), and the mean scores on MADRS scale were 1.64 times higher for obese patients than for normal weight patients (10.9 and 17.9 for normal weight and obese patients, respectively, $p<0.005$), whereas the baseline HRDS and MSDRS scores did not differ substantially between the two groups. The gender effect was not accounted for in this analysis. Of note, like in the previous study, AD doses could be titrated if patients were not improving on lower doses. Both studies

did not include underweight patients, and the study of Oskooilar et al. (2009) did not include morbidly obese patients. Neither of studies had a placebo treatment arm. Unlike these two studies, most included works concentrated on a certain AD class or even a certain AD type.

4.5.4. SSRIs

In two quasi-experimental studies (Lin et al., 2014; Papakostas et al., 2005) the response to the 6-8 weeks treatment with 20 mg of an SSRI fluoxetine was evaluated. In a study of Papakostas et al. (2005), greater BMI predicted non-response to fluoxetine after 8 weeks of treatment among outpatients at the Massachusetts General Hospital (369 patients with MDD) while the presence of obesity did not significantly predict outcome. Study of Lin et al. (2014), conducted in Taiwan, used fluoxetine at the same dosage but with a shorter treatment duration (6 weeks) in the Asian population (113 patients with MDD). A weak negative correlation between baseline increased body weight and/or high BMI with the decreased improvement in symptoms and functioning was observed as well as a small statistically significant difference in the BMI between remitters and non-remitters (24.5±4.8 and 22.4±4.2, respectively, p=0.025) (Lin et al., 2014). Therefore, even though these two studies used different measures of fluoxetine treatment effect, both observed an inverse association between higher body weight/BMI and response to treatment with fluoxetine with small but clinically relevant effect sizes.

Several studies compared response to different AD classes in patients with excess weight.

Figure 4.1. PRISMA flow diagram describing literature search for studies examining the association between high BMI/obesity/overweight and treatment response to antidepressants in patients with depression

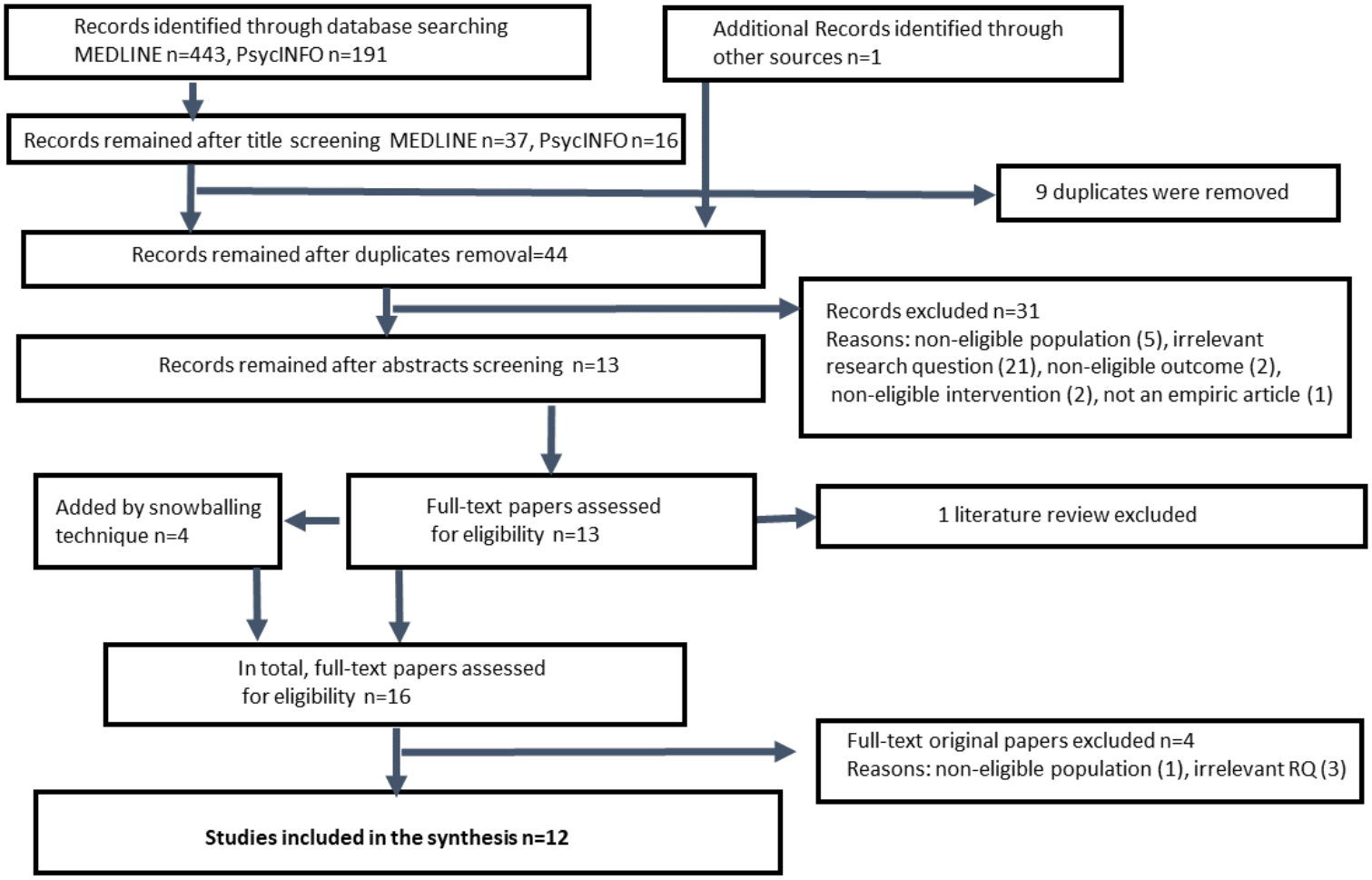

Table 4.1. Review question in PICO format

P	Obese and overweight people >18 years old with depressive disorder (including major depressive disorder)
I	Treatment with antidepressants medications (all groups of antidepressants medications)
C	Normal weight people >18 years old with depressive disorder (including major depressive disorder)
O	Treatment outcomes: clinical outcomes that were quantitatively measured
T	Quantitative studies and quantitative parts of mixed methods studies published within the last 15 years

Table 4.2. Research questions of included studies.

Study ID	First author, year	Study research question
1	Papakostas et al. (2005)	To study excess body weight and obesity in MDD outpatients, with a focus on the treatment of MDD. One of the objectives was to examine the relationship between relative body weight and obesity with clinical response to SSRI fluoxetine
2	Kloiber et al. (2007)	To elucidate the impact of weight status on psychopathology, attention, neuroendocrinology, weight change, and AD treatment response in patients with MDD
3	Khan et al. (2007)	To assess the impact of body mass index (BMI) on response to SSRI or placebo for men and women
4	Uher et al. (2009) (GENDEP project)	Explored the moderation of antidepressant response by body mass index /obesity to establish the specificity to antidepressant mode of action (SSRI and TCA), type of depressive symptoms, and gender.
5	Oskooilar et al. (2009)	Tested the hypothesis that clinically depressed obese patients, when compared with depressed patients with a healthy weight, will be less likely to respond to currently marketed antidepressant medications

6	Toups et al. (2013)	To evaluate differences between obese and normal-weight depressed patients and the moderating effect of obesity on antidepressant treatment outcome
7	Lin et al. (2014)	The aim was to investigate the relationships among body weight, BMI, change in a depression rating scale, and change in a functional scale with fluoxetine treatment for hospitalized patients with MDD.
8	McIntyre et al. (2015)	To assess the effect of baseline BMI on efficacy outcomes in adults with MDD treated with desvenlafaxine or placebo in a pooled, post hoc analysis of RCTS.
9	Woo et al. (2016)	This study examined whether Korean adults with MDD who had one or more metabolic conditions (such as obesity) exhibited differential therapeutic outcomes with antidepressant therapy.
10	Iniesta et al. (2016) (GENDEP project)	To evaluate to what extend can demographic and clinical variables (BMI included) predict outcomes with specific treatments at the level of individual in a study comparing treatment with two different antidepressants, escitalopram or nortriptyline, using a large ethnically homogeneous sample
11	Green et al. (2017)	To investigate the hypothesis that obesity and sex may together be differential predictors of acute remission of specific symptoms for commonly used antidepressant medications.
12	Jha et al. (2018)	To test the hypothesis that pre-treatment BMI differentially predicted antidepressant treatment outcomes. Specifically, it was hypothesized that bupropion-SSRI combination will be more effective than escitalopram monotherapy in depressed patients with BMI≥35 and vice versa in those with normal BMI

Table 4.2a. Description of selected studies

Study characteristics		Count	%	Studies
Study design	RCT	1	8.3	Kloiber et al. (2007)
	Quasi-experimental study	2	16.7	Papakostas et al. (2005), Lin et al. (2014)
	Post hoc analyses of a randomized control trial (RCT)	6	50	Khan et al. (2007), Oskooilar et al. (2009), Toups et al. (2013), McIntyre et al. (2015), Green et al. (2017), Jha et al. (2018)
	Post hoc analysis of a prospective cohort	1	8.3	Woo et al. (2016)
	Partly randomized controlled trial	2	16.7	Iniesta et al. (2016), Uher et al. (2009)
Patients & Settings	Outpatients	9	75	Papakostas et al. (2005), Khan et al. (2007), Uher et al. (2009), Oskooilar et al. (2009), Toups et al. (2013),McIntyre et al. (2015),Iniesta et al. (2016),Green et al. (2017), Jha et al. (2018)
	Inpatients	2	16.7	Kloiber et al. (2007), Lin et al. (2014)
	Both in- & outpatients	1	8.3	Woo et al. (2016)
	MDD diagnosis	8	66.7	Papakostas et al. (2005), Kloiber et al. (2007), Oskooilar et al. (2009), Toups et al. (2013), Lin et al. (2014), McIntyre et al. (2015), Green et al. (2017), Jha et al. (2018)
	Unipolar depression	2	16.7	Khan et al. (2007), Iniesta et al. (2016)
	Unipolar major depression	1	8.3	Uher et al. (2009)
	Depressive disorder: MDD, dysthymic disorder, depressive disorders not otherwise specified	1	8.3	Woo et al. (2016)
Intervention	Monotherapy Fluoxetine	2	16.7	Papakostas et al. (2005), Lin et al. (2014)
	Monotherapy Desvenlafaxine	1	8.3	McIntyre et al. (2015)
	Treatment response to multiple AD	2	16.7	Kloiber et al. (2007), Woo et al. (2016)

	Treatment responses compared between escitalopram (SSRI) and nortriptyline (TCA) using the GENDEP project database	2	16.7	Uher et al. (2009), Iniesta et al. (2016)
	Treatment response compared between bupropion-escitalopram and venlafaxine-mirtazapine combination and escitalopram monotherapy using COMED project database	2	16.7	Toups et al. (2013), Jha et al. (2018)
	Treatment with SSRIs	1	8.3	Khan et al. (2007)
	Treatment with multiple SSRIs and SNRIs	1	8.3	Oskooilar et al. (2009)
	Treatment response to escitalopram, sertraline, and venlafaxine-XR	1	8.3	Green et al. (2017)
	Addition of adjuvant therapy	2	16.7	Uher et al. (2009), Lin et al. (2014)
Exposure	BMI, height and weight measured	11	91.7	Papakostas et al. (2005), Kloiber et al. (2007), Khan et al. (2007), Uher et al. (2009), Toups et al. (2013), Lin et al. (2014), McIntyre et al. (2015), Woo et al. (2016), Iniesta et al. (2016), Green et al. (2017), Jha et al. (2018)
	No report of whether BMI was measured or self-reported	1	8.3	Oskooilar et al. (2009)
	BMI as a continuous variable	9	66.7	Papakostas et al. (2005), Kloiber et al. (2007), Khan et al. (2007), Uher et al. (2009), Lin et al. (2014), McIntyre et al. (2015), Iniesta et al. (2016), Green et al. (2017), Jha et al. (2018)
	Comparing two or more weight groups	4	33.3	Kloiber et al. (2007), Toups et al. (2013), McIntyre et al. (2015), Jha et al. (2018)
	Evaluating the effect of obesity on treatment response	5	41.7	Papakostas et al. (2005), Khan et al. (2007), Uher et al. (2009), Woo et al. (2016), Green et al. (2017)
	Effect of both BMI as a continuous variable and of a weight group on treatment response	7	58	Papakostas et al. (2005), Kloiber et al. (2007), Khan et al. (2007), Uher et al. (2009), McIntyre et al. (2015), Jha et al. (2018), Green et al. (2017)
	Obesity classes	3	25	Toups et al. (2013), Green et al. (2017), Jha et al. (2018)

	BMI categories per the conventional (WHO, 2000) recommendations	10	75	Papakostas et al. (2005), Kloiber et al. (2007), Khan et al. (2007), Uher et al. (2009), Oskooilar et al. (2009), Toups et al. (2013), Lin et al. (2014), McIntyre et al. (2015), Green et al. (2017), Jha et al. (2018)
	BMI categories per recommendations for populations from Asia (WHO, 2004)	1	8.3	Woo et al. (2016)
Outcome Measures	Hamilton Depression Rating Scale (HAM-D, HAMD-31, HAMD-17, HDRS-17) as a primary outcome measure	9	75	Green et al. (2017), Iniesta et al. (2016), Khan et al. (2007), Kloiber et al. (2007), Lin et al. (2014), McIntyre et al. (2015), Oskooilar et al. (2009), Papakostas et al. (2005), Woo et al. (2016)
	Both the Hamilton and the Montgomery-Asberg (MSDRS) depression rating scales	4	33.3	Iniesta et al. (2016), Khan et al. (2007), Oskooilar et al. (2009), Uher et al. (2009)
	Quick Inventory of Depressive Symptomatology Self-Reported Rating Scale (QIDS-SR)	2	16.7	Jha et al. (2018), Toups et al. (2013)
	Changes in scores between baseline and endpoint, or between several time points	7	58.3	Green et al. (2017), Kloiber et al. (2007), Lin et al. (2014), McIntyre et al. (2015), Papakostas et al. (2005), Toups et al. (2013), Woo et al. (2016)
	Dichotomous measures (remitters/nonremitters)	6	50	Green et al. (2017), Lin et al. (2014), McIntyre et al. (2015), Toups et al. (2013), Iniesta et al. (2016), Jha et al. (2018)
	Remission as the end-point total score (HDRS-17) of ≤ 7	2	16.7	Lin et al. (2014), McIntyre et al. (2015)
	Remission as at least one of the last two consecutive scores on the depression scale (QIDS-SR) was <6 and another one <7 or <8 in three studies	2	16.7	Jha et al. (2018), Toups et al. (2013)
	Categorized response to treatment (responders/nonresponders), response to treatment defined as having a 50% or greater reduction in depression score from baseline to endpoint	7	58.3	Green et al. (2017), Kloiber et al. (2007), Lin et al. (2014), McIntyre et al. (2015), Papakostas et al. (2005), Toups et al. (2013), Woo et al. (2016)
	Time to response	1	8.3	McIntyre et al. (2015)
	Self-reported outcome	2	16.7	Jha et al. (2018), Toups et al. (2013)

Data Analysis	Logistic or linear regression	5	41.7	Papakostas et al. (2005), McIntyre et al. (2015), Woo et al. (2016), Green et al. (2017), Jha et al. (2018)
	Cox regression	1	8.3	McIntyre et al. (2015)
	Mixed effects regression model to adjust for clustering	3	25	Kloiber et al. (2007), Uher et al. (2009). Toups et al. (2013)
	Mean changes in depression rating scale scores between groups of different BMI categories or rates of responders/nonresponders and remitters/nonremitters between different BMI groups,	5	41.7	Lin et al. (2014), Woo et al. (2016), Khan et al. (2007), McIntyre et al. (2015), Oskooilar et al. (2009)
	Chi square test to compare results	1	8.3	Woo et al. (2016)
	t-test to compare results	3	25	Khan et al. (2007), Lin et al. (2014), Woo et al. (2016)
	ANCOVA to compare results	2	16.7	Khan et al. (2007), McIntyre et al. (2015)
	Statistical learning approach with application of an Elastic Net Regularized Regression model (ENRR)	1	8.3	Iniesta et al. (2016)

4.5.5. *SSRIs vs. TCAs*

Uher et al. (2009) and Iniesta et al. (2016) used different analytical approaches to evaluate treatment response to SSRIs vs. TCAs in relation to patient characteristics, including weight, based on the data from GENDEP randomised trials.

Uher et al. (2009) used a traditional statistical modeling and found that higher baseline BMI significantly predicted worse outcomes on the MADRS scale in a total sample of patients (797 patients with unipolar major depression) treated with either nortriptyline (TCA) or escitalopram (SSRI), but the effect size was small (β=0.0081, 95%CI 0.0002 to 0.0161, p=0.04). Stratified by the AD class, however, both baseline BMI (continuous) and obesity (categorical) predicted a non-response to treatment (on MADRS scores) with the tricyclic AD but not with the SSRI. More specifically, there was a clinically meaningful and statistically significant negative association between baseline BMI and treatment response among the nortriptyline-treated patients (Table 4.4), and obese patients were at a higher risk (OR=1.31, 95%CI: 1.11, 1.54) for non-response to nortriptyline therapy than those who had normal weight. Moreover, higher BMI was associated with lower blood levels of nortriptyline but not of escitalopram. Study findings were confirmed by subgroup analysis with the sample randomized to treatment with either nortriptyline or escitalopram and after correction for the dose and self-reported compliance. In their work published seven years later, Iniesta et al. (2016) used a different approach, a statistical learning technique, to evaluate different combinations of a large number of covariates (41 to 52), including BMI, in predicting AD treatment outcome. This approach significantly differed from Uher et al. (2009) since it allowed ranking the variables included in the model according to their importance in predicting AD treatment outcome. BMI (continuous variable) was amongst the strongest (according to the effect size) predictors of remission (ranked #6) for the whole sample (escitalopram and nortriptyline), and

the strongest predictor (ranked #1) of non-response to treatment with nortriptyline (ß= -3.82 for reduction in depression symptoms; OR=0.87 and 0.84 for remission for the random- and nonrandomly allocated group, respectively). For patients treated with escitalopram, on the other hand, BMI was a significant predictor for both the reduction of depression symptoms and remission, but it was not among the 10 most important predictors of either outcome. Thus, despite the difference in methodological approaches, the findings from both groups were in line with each other.

4.5.6. SNRIs vs. SSRIs

With regards to SNRIs, the results are mixed. Two studies evaluated the effect of either venlafaxine-XR or desvenlafaxine (active metabolite of venlafaxine) on remission in patients of different weight groups suffering from depression. In both studies, even though an adequate response was observed after treatment with an SNRI for all weight groups, included obese patients, BMI was a significant predictor of remission. The direction of association, however, between a higher BMI and treatment response was different for SNRIs across these studies. In a post hoc analysis of eight RCTs in Canada conducted by McIntyre et al. (2015) (3399 patients with MDD), baseline BMI was a significant predictor of HDRS-17 score changes after treatment with desvenlafaxine and of the treatment response to desvenlafaxine: patients with higher baseline BMI had significantly smaller changes in HDRS-17 score than normal weight patients and were significantly less likely to have a response. The smallest treatment effect was observed in the obese group; however, differences in the HRDS-17 scores between normal weight and obese patients were small (Table 4.4).

By contrast, in an RCT analysis conducted by Green et al. (2017), that examined BMI amongst other predictors of remission when treated with either venlafaxine-XR (SNRI) or an SSRI (escitalopram or sertraline) (659 patients with MDD), an increase in BMI predicted higher odds to have remission in the whole sample. Examination of the interactions between BMI and the treatment arm found that an increase in BMI was associated with greater odds of remission only when treated with venlafaxine-XR compared with escitalopram (OR=1.06; 95% CI 1.001–1.12) and, with marginal significance, when treated with sertraline compared with escitalopram (OR=1.04; 95% CI 0.99 to 1.10), but not when treated with sertraline compared with venlafaxine-XR (OR=0.98; 95% CI 0.93–1.04). Moreover, stratification by obesity class showed that patients with obesity class II and women with obesity class III were more likely to remit on venlafaxine-XR than on escitalopram or sertraline, with the number needed to treat (NNT) equal to 6 and 3, respectively (Green et al., 2017). The response to individual types of AD is described in Table 4.5.

4.5.7. AD combinations

The association between BMI and response to MDD treatment with different AD combinations was studied by two groups who performed a post hoc analysis of the large RCT (COMED) data with a 5-year gap. Toups et al. (2013) reported that the response to AD treatment did not differ between BMI groups. At two time points (at week 12 and 28), there was no differences in response, remission, and percent drop in the self-reported QIDS-SR scale score in patients treated with either escitalopram, bupropion and escitalopram, or venlafaxine and mirtazapine between patients of different weight groups. Repeated effects model failed to show association between treatment outcomes and BMI group in the whole sample; however, only effect sizes and not 95%CI for the odds ratios are reported. More recently, Jha, Wakhlu, et al. (2018)

performed another post hoc analysis of the same COMED data using a logistic regression, but with treatment arm-by-BMI category interaction as an independent variable. Similarly, overall rates of remission did not differ between weight categories for the whole sample, thus confirming findings of Toups et al. (2013); however, Jha, Wakhlu, et al. (2018) found significant treatment arm-by-obesity class interactions. More specifically, patients with obesity classes II and III had significantly higher rates of remission in general and were more likely to remit on the bupropion-escitalopram combination rather than on escitalopram monotherapy or on the combination of venlafaxine with mirtazapine, with moderate clinically relevant effect sizes (OR=2.63, 95% CI=1.20, 5.88). In addition, higher BMI (as a continuous variable) was associated with greater remission likelihood in the bupropion-escitalopram treatment arm.

4.5.8. Effect of sex/gender

In most studies, the analysis was adjusted for sex/gender as the association with the AD treatment response has been established previously (Kornstein et al., 2000; Yang et al., 2011). Khan et al. (2007) reported that obese men, but not obese women showed no or little response to treatment with different SSRIs as compared to control (placebo) group, demonstrating clinically meaningful difference in mean scores on the depression rating scale. In Green et al. (2017), sex did not predict overall remission rate with venlafaxine XR, escitalopram or sertraline. It did, however, modify the association between BMI and changes in cognitive symptoms with higher odds of improvement observed in women with high BMI. In Uher et al. (2009), sex played a role in the improvement of neurovegetative symptoms in obese patients; interestingly, obese women responded poorly to both nortriptyline and escitalopram, while obese men responded poorly to nortriptyline only (Table 4.4)

Table 4.3. Characteristics of included studies

ID #	First author Year Country	Study design Setting Participants	Treatment and special notes	Exposure measures Data collection	Outcome measures Data collection	 Outcome	Data analysis
1	Papakostas et al. (2005), USA	Open-label, non-randomized, non-controlled (quasi experimental) trial 369 outpatients, age 18-65, diagnosed with MDD (DSM-III-R)	Treatment: Fluoxetine 20 mg, fixed-dose, for 8 weeks Control: no control group	Exposure: BMI measures at baseline; weight groups: normal, overweight, obese, according to the NIH (1998) and WHO (1998)	The Hamilton Depression Rating Scale (HAMD)-17 score measured at baseline and every other week for a total of 8 wk.	Responder (≥ 50% reduction in HAMD-17 score from baseline to end-point) /nonresponder.	Logistic regression to evaluate the association between either relative body weight (BMI as a continuous variable), or overweight status, or obesity, and clinical response, controlling for gender and the severity of depression at baseline. ITT analysis with LOCF
2	Kloiber et al. (2007), Germany	RCT; open labeled, 320 inpatients with MDD and 1029 controls for morphometric measures. Mean age=47.73 (SD=14.31).	Treatment: different AD, including SSRI, TCA, mirtazapine, and combinations, according to doctor's choice, doses adjusted to therapeutic ranges using plasma concentrations, for 5 weeks Controls: healthy subjects	BMI measured at admission and in weekly intervals. Weight groups: normal overweight, obese (WHO)	HAM-D at admission and in weekly intervals.	1)Mean HAM-D scores 2)Response: reduction in HAM-D score of >50%	Linear mixed-effects regression model with random intercept, weekly HAM-D scores as within-subjects factor and weight group as fixed factor, adjusted for gender, age, and duration of the index depression episode. The responder rate (%) for different BMI groups.
3	Khan et al. (2007), USA	Post hoc analysis of 29 RCT, double-blinded. 274 outpatients with unipolar depression (DSM-IV). Mean age 42.34 (SD=14.36)	Treatment: one of the SSRIs: citalopram (20mg, fixed), escitalopram (10mg, fixed), fluoxetine (20mg, fixed), paroxetine (20mg), or sertraline (flexible, 50-100mg). The dose of each SSRI equivalent to one another was set using the recommended Physicians Desk Reference (PDR, 2006).	BMI measured at baseline. Weight groups: non-obese (BMI<30) and obese (BMI>30).	17-item HAM-D and Montgomery–Asberg Depression (MADRS) Rating Scale at baseline and the final visit.	Change from baseline in the HAM-D and MADRS total scores.	1.T-tests to compare the mean changes in HAM-D and MADRS for obese and non-obese. 2. ANCOVA with sex, BMI category, and treatment group as the independent variables and the mean change in total HAM-D-17 and MADRS scores as the dependent variables controlling for baseline severity scores.

			Duration of treatment is unclear. Control: placebo				ITT with LOCF.
4	Uher et al. (2009), UK	Open-labeled part-randomized trials, GENDEP; 797 patients (441 of them randomly allocated) of white European origin from 8 European countries with unipolar major depression (ICD10/DSM-IV) Mean age 42.75±11.70	Two active treatment arms: escitalopram (10-30mg daily) and nortriptyline (50-150 mg daily), for 12 weeks. Clinicians could make appropriate dose adjustments. Control: no control group.	BMI measured at baseline. Weight groups: obese, overweight, normal weight (WHO, 1998)	MADRS as primary outcome measure, HRDS-17, 21-itemBeck Depression Inventory (BDI) as secondary outcome measures, measured weekly.	1)Weekly changes in the total score on MADRS (primary, reported), HRSD-17 and the self-report BDI (not reported).	Linear mixed random intercept random effects model with adjustment for clustering on treatment centers to test the effects of BMI (continuous) and obesity (categorical) on response to AD, controlling for age, sex, drug, baseline depression severity. The interactions tested: between each AD, BMI/obesity, and gender. Analysis for subgroups stratified by variables shown to have significant interactions with main predictor. Sensitivity analysis restricted to randomly allocated subjects.
5	Oskooilar et al. (2009), USA	Post hoc analysis of 3 completed RCT, double-blind, flexible-dose, active-controlled. 56 outpatients with MDD (DSM-IV-TR), age 18-65,	Treatment with one of 4 SSRIs or one of 2 SNRIs for 8 weeks. No placebo arms.	BMI at baseline. Unclear if measured or self-reported. Weight groups: normal weight (BMI=20.0–24.9), overweight (BM= 25.0–29.9), and obese (BMI=30.0–39.9).	HDRS and MADRS at baseline and at the end of treatment.	HRDS and MADRS scores, baseline and at endpoint.	Means of HRDS and MADRS scores, p -values for difference in means.
6	Toups et al. (2013), USA/ Singapore	A post hoc analysis of RCT COMED, open label, single-blinded.	Treatment with escitalopram (plus placebo), bupropion plus escitalopram, or venlafaxine plus mirtazapine for a 12-week	BMI measured at baseline. Weight groups: normal and underweight (BMI <25), over-weight (BMI 25–29), obese I (BMI	Quick Inventory of Depressive Symptomatology QIDS-SR form (self-reported) at baseline and weeks 1, 2, 4, 6, 8,	1)Remission: if one of the last two consecutive scores on QIDS-SR is <6 and another <7;	N (%) of outcomes (remission and response) for different BMI categories. Repeated effects model, adjusted for pulse, BP, treatment, PTSD, substance

		662 outpatients, age 18–75, with MDD (by the Mini International Neuropsychiatric Interview (MINI)).	primary treatment and 16 week follow-up. Clinicians were free to do dose adjustments	30–34) and obese II+ (BMI=35) classes.	10, 12, 16, 20, 24, and 28	2)Response: a drop in QIDS-SR scores of ≥ 50%.	use, clinical settings, number of health problems, and atypical features, to access the association between weight group and outcome.
7	Lin et al. (2014), Taiwan	A post hoc analysis of a nonrandomized clinical trials with no control group (quasi-experimental design). 113 Asian (Han Chinese) inpatients with MDD (DSM-IV (SCID)), age 18-70	Treatment: fixed dose of 20 mg of SSRI fluoxetine daily for 6 weeks, with a possibility of adding adjuvant therapy (anxiolytic and/or sedative-hypnotic medications) Control: no control group	BMI measured at baseline.	HAMD-17 and Work and Social Adjustment Scale (WSAS) at weeks 0, 1, 2, 3, 4, and 6.	1) N(%) of responders; response: a reduction of 50% or more of the HAMD-17 score from the baseline to endpoint. 2)N(%) of remitters; remission: HAMD-17≦7 at end point. 3) changes in HAMD-17 and WSAS from baseline to the endpoint	1)t-test to compare body weight or BMI between remitters/nonremitters and responders/nonresponders 2)Pearson correlation coefficients (r) among body weight, BMI, HAMD-17 and WSAS score changes. ITT with LOCF
8	McIntyre et al. (2015), Canada	A post hoc analysis of data pooled from 8 multicenter, randomized, double-blind, placebo-controlled studies. 3399 adult outpatients with MDD (DSM-IV) Age 18-86.	Treatment: fixed dose of SNRI desvenlafaxine 50 mg daily or 100 mg/daily for 8-12 weeks Control: placebo	BMI measured at baseline and monitored through the follow up at different time points for various RCTs. Weight groups: normal (BMI<=25), overweight (25<BMI<=30), obese (BMI>30). An underweight subgroup (BMI < 18.5) was collapsed into the normal group due to the low group sample sizes	HDRS-17 at baseline, at each week and the end of follow up (8-12 weeks)	1)Change from baseline in HDRS-17 total score at endpoint. 2)Response: first week with ≥50% decrease in HDRS-17 total score; 3)Remission: HDRS-17 total score ≤ 7. 4)Time to response.	1)Analysis of covariance (ANCOVA) to examine change from baseline in HDRS-17 total score for the weight groups 2)Logistic regression to examine baseline BMI as a predictor of change from baseline in total score using with outcome as response or remission 3)Cox regression to examine baseline BMI as a predictor of change from baseline in total

							score using outcome as time to response
9	Woo et al. (2016), Canada/Korea	A post hoc analysis of a prospective cohort study CRESCEN. 541 Korean outpatients and inpatients with depressive disorders (MDD, dysthymic disorder, depressive disorders not otherwise specified [DSM-IV]), age >18	52-weeks treatment under naturalistic conditions: any type, dose, or regimen of the following antidepressants: 1)SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline) 2)Dual reuptake inhibitors and noradrenergic and specific serotonergic antidepressants (bupropion, venlafaxine, and mirtazapine); 3) TCAs and other antidepressants (amitriptyline, clomipramine, imipramine, milnacipran, nortriptyline, tianeptine, and trazodone)	BMI measured at baseline and weeks 1,2, 4, 8, 12, 24 and 52 Weight groups: Obese (BMI≥25) with and without metabolic abnormalities, non-obese (BMI<25), according to WHO for Asian population (WHO EC, 2004)	HDRS-17 score measured at baseline and weeks 1, 2, 4, 8, 12, 24 and 52.	1)Change from baseline in the HDRS-17 total score at several time points 2)N(%) responders. Treatment response: >50% reduction from baseline on at least one evaluation point. 3) Odds (OR with 95%CI) to have insufficient treatment response (ISR) to treatment (no response to at least one AD)	1)Responders and nonresponders were compared using Chi square test, Fisher's exact test, and t-test, and univariate regression analysis. Analysis was done for men and women and for pre- and postmenopausal women 2)Multivariate logistic regression to calculate the risk of insufficient treatment response during follow-up visits in relation to obesity/other metabolic conditions, age, baseline HAMD score, gender, marital and work status
10	Iniesta et al. (2016), UK	Open-labeled part-randomized trials, GENDEP; 793 patients (450 of them randomly allocated) of white European parentage from 8 European countries with unipolar major depression (ICD10/DSM-IV) Mean age 42.8±11.7	Two active treatment arms: escitalopram (10-30mg daily) and nortriptyline (50-150 mg daily), for 12 weeks. Clinicians could make appropriate dose adjustments. Control: no control group.	BMI measured at baseline.	MADRS, HRDS-17, Beck Depression Inventory (BDI) at baseline and weekly.	1) Percentage of improvement in MADRS score at week 12 (continuous) 2) Remission: HRSD-17 score of ≤7 on the last available measurement (categorical)	The statistical learning method, Elastic Net Regularized Regression (ENRR), to determine the contribution of 41-52 covariates, including BMI, to predict reduction of depression symptoms or remission. The analysis was repeated for a subgroup of randomly allocated participants.

11	Green et al. (2017), USA	Secondary analysis of the iSPOT-D RCT data, blinded for outcome assessors only, for 659 outpatients with MDD (DSM-IV), age 18–65 from USA, Europe, New Zealand, Australia, and South Africa	Patients were randomly assigned to 8-weeks of treatment with escitalopram, sertraline or venlafaxine extended release (venlafaxine-XR). Clinicians adjusted medication dosages according to routine clinical practice.	BMI measured at baseline. Weight groups: normal, overweight, obese classes I, II, and III (WHO)	HRDS-17 at baseline and after 8 weeks of treatment.	1)Remitters (HRDS-17 score<=7) / non-remitters 2) HRDS-17 score changes on cognitive and physical/ vegetative symptoms after treatment (continuous)	Logistic and linear regression to evaluate association between BMI and remission, or changes in HRDS-17 score, or cognitive/physical symptoms, and sex as effect modifier in these associations.
12	Jha et al. (2018), USA	A post hoc analysis of RCT COMED, open label, single-blinded 662 outpatients, age 18–75, with MDD (by the Mini International Neuropsychiatric Interview (MINI)).	Treatment with escitalopram (plus placebo), bupropion plus escitalopram, or venlafaxine plus mirtazapine for a 12-week primary treatment and 16 week follow-up. Clinicians were free to do dose adjustments	BMI measured at baseline. Weight groups: normal or underweight (BMI <25.0), over-weight (BMI 25.0–29.9), obese I (BMI 30.0–34.9) and obese II+ (BMI≥35.0) classes.	QIDS-SR form (self-reported) at baseline and weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, and 28	Remission: if one of the last two consecutive scores on QIDS-SR is <6 and another <8;	A logistic regression analysis for the association between remission and baseline BMI category, adjusted for baseline depression severity, gender, treatment arm and treatment-arm-by-weight-category interaction.

Table 4.4. Results of individual studies

ID	First author Year Country	Results	Conclusion
1	Papakostas et al. (2005), USA	In a logistic regression, greater BMI predicted non-response to fluoxetine (p=0.049, x2=3.843, coefficient/S.E.=1.960, 95% CI 1.000–1.076). A trend towards statistical significance for poorer outcome in overweight patients (p=0.067) was found. The presence of obesity did not significantly predict outcome (p=0.16). The mean BMI in responders and non-responders was 25.9±5.2 kg/m2 vs. 27.1±7.0 kg/m2.	Greater BMI, but not obesity, predicted nonresponse to fluoxetine and a greater risk of fluoxetine resistance.
2	Kloiber et al. (2007), Germany	Patients with high BMI (overweight and obese) showed significantly [F (5,275.42) = 3.52, p < .01] slower response (by HAM-D scale scores) to AD treatment and less improvement in attention, with the slowest improvement in the obese patients [F (10,274.21) = 1.92, p <.05]. There was a significant difference in response between obese and normal-BMI patients [F (6,158.93) = 2.66, p =.05, Bonferroni-Holm corrected] and a trend between overweight and normal-weight patients [F (6,228.26) = 2.32, p =.07, Bonferroni-Holm corrected], but no significant difference between overweight and obese patients. The responder (reduction in HAM-D score of >50%) rate after 5 weeks was 50.0% in normal-BMI, 46.5% in overweight, and 17.4% in obese patients The odds to have response for obese relative to normal weight patients: OR=4.49; 95% CI: 1.48–13.64, p < .01	When treated with different AD (SSRI, TCA, mirtazapine, and combinations), both obese and overweight patients showed a significantly slower clinical response to AD treatment and lower odds to have a response than patients with normal weight.
3	Khan et al. (2007), USA	The mean changes ± SD in HAMD rating scale based on BMI category: non-obese: -11.95±7.76 vs. control -7.44±7.61 in men (p<0.01), -15.49±6.74 vs. control -9.96±8.01 in women (p<0.01); obese: -7.35±8.05 vs. control -7.41±7 in men (p>0.05); -13.96±7.58 vs. control -6.90±5.80 in women (p<0.01). The mean changes ± SD in MADRS rating scale based on BMI category: non-obese: -14.62±10.45 vs. control -9.24±9.45 in men (p<0.01), -19.76±9.91 vs. control -13.50±12.34 in women (p<0.05); obese: -9.90±8.16 vs, control –10.85±9.44 in men (p> 0.05); -19.06±10.32 vs. control -7.71±7.72 in women (p<0.01). ANCOVA : Compared to women, men assigned to an antidepressant had a significantly lower mean total change on both the HAM-D-17 [non-obese, F(1,88)=5.292, p=0.024; obese, F(1,39)=7.040; p=0.012] and the MADRS [non-obese, F(1,66)=4.049, p=0.048; obese, F(1,27)=8.631, p=0.007].	Reduced or absent therapeutic response to treatment with different SSRI (citalopram, escitalopram, fluoxetine, paroxetine, or sertraline) for obese men but not obese women was found.

		The difference in the AD mean dose (mg/kg) differed between non-obese and obese patients for males (0.3±0.1 compared with 0.5±0.1, F(1,56)=18.690, p≤0.000) and females (0.6±0.2 compared to 0.4±0.1, F(1,68)=23.882, p≤0.000).	
4	Uher et al. (2009), UK GENDEP project	MADRS total score: BMI as a continuous measure: higher baseline BMI significantly predicted worse outcome (MADRS) in the whole sample, both unadjusted (β=0.0089, 95%CI 0.0011 to 0.0166, p=0.0253) and controlled for sex, age and treatment arm (β=0.0081, 95%CI 0.0002 to 0.0161, p=0.0456). A significant interaction between drug and baseline BMI for nortriptyline (β=0.0174, 95%CI 0.0059 to 0.0289, p=0.0031) but not escitalopram (β=0.0033, 95%CI −0.0075 to 0.0141, p=0.5469). Obesity (categorical) predicted worse outcome (MADRS) in the whole sample (β=0.1257, 95%CI 0.0185 to 0.2330, p=0.0215). For MADRS total score, obesity predicted a worse outcome among nortriptyline-treated patients (β=0.2701, 95%CI 0.1067 to 0.4334, p=0.0012) but not among escitalopram (β=0.0308, 95%CI −0.1122 to 0.1737, p=0.6730) in both men and women. Neurovegetative symptoms (insomnia, poor appetite, weight loss and decreased libido.): Higher BMI and/or obesity at baseline were associated with less improvement in sleep: β=0.0216, 95%CI 0.0110 to 0.0322, p=0.0001 and appetite β=0.0148, 95%CI 0.0046 to 0.0250, p=0.0045 for BMI, for obesity: β =0.2551, 95%CI 0.1373 to 0.3729, p<0.0001 for sleep and appetite. The effect was the strongest in men treated with nortriptyline, intermediate in women treated with either nortriptyline and escitalopram and the weakest among men who were treated with escitalopram. Mood and cognitive symptoms (pessimism, guilt, suicidality): Higher BMI did not predict improvement in mood and cognitive symptoms for both genders. Obesity but not BMI was associated with mood (β=0.1257, 95%CI 0.0104 to 0.2227, p=0.0313) and cognitive symptoms (β =0.1070, 95%CI: -0.0036 to 0.2176, p=0.0578) for both men and women. Study results were confirmed by sensitivity analysis for a subgroup randomized to treatment arms and after correction for the dose and self-reported compliance.	Both high BMI (continuous) and obesity predicted poor response to nortriptyline for men and women. For neurovegetative symptoms, obese men responded less to nortriptyline and obese women responded poorly to both nortriptyline and escitalopram. Obesity but not BMI was associated with mood and cognitive symptoms for both men and women for both AD.
5	Oskooilar et al. (2009), USA	The post-treatment mean scores for HDRS were 7.7, 11.6, and 12.7 and scores for the MADRS were 10.9, 15.4, and 17.9, for patients with normal weight, overweight, and obese groups, respectively. The difference in mean scores at endpoint for HRDS and MADRS scale were statistically significant between normal weight, and overweight or obese patients (p<0.005, effect sizes not reported)	Patients with normal weight had greater response to SSRIs and SNRIs than patients of obese and overweight groups.
6	Toups et al. (2013),	No difference in AD response, remission, and final score on the QIDS-SR was found at weeks 12 and 28.	AD treatment outcomes (response to either escitalopram, or bupropion plus

	USA/ Singapore, COMED project	% drop in QIDS-SR score: Week 12: 43±38.1, 46±32.1, 47±35.9 and 48±31.1 for normal weight, overweight, obesity class I and obesity class II+, respectively. Week 28: 49±37.5, 50±34.3, 47±36.5, and 53±32.5 for normal weight, overweight, obesity class I and obesity class II+, respectively. For the whole sample, for remission, adjusted OR for overweight, obese class I, and obese class II+ respectively are 1.11, 1.30, and 1.05 for week 12, p= 0.79, and 0.89, 0.95, and 1.08 for week 28, p=0.88, 95%CI not reported. For response, adjusted OR for overweight, obese class I, and obese class II+ respectively are 1.07, 1.01, and 1.15 for week 12, p= 0.95, and 0.85, 0.63, and 0.96 for week 28, p=0.31, 95%CI not reported. The model examining BMI category by treatment group effects showed no significant differences in any outcome for any group at week 12 or week 28 (data not shown).	escitalopram, or venlafaxine plus mirtazapine) did not differ across BMI classes.
7	Lin et al. (2014), Taiwan	1)Mean body weight and mean BMI ± SD in responders and remitters: Baseline body weight in responders 61.6±13.8, nonresponders 63.9±13.2 (p=0.343); remission 57.6±12.5 and nonremission 64.5±13.4. (p=0.012). Baseline BMI in responders 23.5±4.7, nonresponders 24.6±4.8 (0.217); remission 22.4±4.2 and nonremission 24.5±4.8, respectively (p=0.025)) 2)Weak negative correlation between BMI or body weight and HAMD 17 or WSAS score changes: r=0.236 and 0.246 for correlation between HAMD-17 with baseline body weight and BMI, respectively, r=0.188 and 0.191 for correlation between WSAS score with baseline body weight and BMI, respectively.	Significant differences in baseline body weight and BMI were found between remitters and nonremitters on fluoxetine treatment: nonremitters had significantly greater baseline body weight and BMI than remitters. Increased body weight and BMI correlated with the decreased improvement in symptoms (HAMD-17 score) and functioning (WSAS score) at end point.
8	McIntyre et al. (2015), Canada	HDRS-17: The adjusted mean difference (95% CI) between the desvenlafaxine and placebo groups at week 8 ranged from –1.99 (–3.29 to –0.69, P = .0027) for the obese group to –2.24 (–3.46 to –1.01, P = .0003) for the normal group at the desvenlafaxine 100 mg/d dose, and from –1.54 (–2.39 to –0.69, P =.0004) for the obese group to –2.02 (–3.02 to –1.03, P < .0001) for the overweight group at the desvenlafaxine 50 mg/d dose. Baseline BMI was a significant predictor of change in HDRS-17 total score (higher baseline BMI, smaller change) for the overall pooled population (P = .0022) and both treatment groups, desvenlafaxine 50 mg/d (P = .048) and 100 mg/d (P =.031) groups, but not for placebo (P = .097). BMI at baseline was a significant predictor of overall treatment response (HDRS-17; P = .0194) and for the desvenlafaxine 50 mg/d group (P = .0397): people with higher BMI were less likely to respond to treatment compared with patients with lower baseline BMI (effect sizes are not reported). Baseline BMI did not predict remission or time to response.	After treatment with desvenlafaxine, there was a statistically significant improvement from baseline compared with placebo for all BMI subgroups. However, baseline BMI predicted change in HDRS17 total score in the whole sample and for both doses of desvenlafaxine, with the smallest effect size in the obese subgroup.

9	Woo et al. (2016), Canada /Korea	In bivariate comparison tests, obesity (p=0.008) and gender (p<0.001) were associated with insufficient treatment response. When stratified by sex, obesity (p<0.005) was the only variable associated with an insufficient treatment response and only in post-menopausal females: n/N (%) reported: 31/156 (19.9%) responders vs. 23/60 (38.3%) nonresponders, p=0.005. In a logistic regression analysis, the significant association of obesity with insufficient treatment response was observed only for post-menopausal females (OR= 2.41, 95%CI: 1.25-4.66 (adjusted for age, HAMD score, marital status and presence of comorbidities)) and males with metabolic disorders (the presence of either hypertension, hyperglycemia, or hypercholesterolemia)): OR=2.32, 95%CI: 1.03–5.20 (adjusted for the same covariates).	Comorbid obesity and other metabolic conditions were considered a predictor of insufficient treatment response in depressive disorders in clinical practice: menopausal women and men with metabolic disorders had poor response to AD treatment.
10	Iniesta et al. (2016), UK GENDEP project	For the whole sample, BMI was one of the significant predictors of non-remission in the whole sample (ranked #4 with OR=0.88 for all participants and ranked #6 with OR=0.82 for randomly allocated participants) and for reduction of depression symptoms (ranked #8 with ß=-2.35). For escitalopram, BMI remained among 46 significant predictors for remission but not among 10 predictors with strongest effect size. For nortriptyline, BMI was one of the most significant predictors (ranked #1, with OR=0.87 for all participants and 0.84 for randomly allocated participants). The statistical significance was confirmed for escitalopram predictive model but nor for the nortriptyline predictive model.	A combination of clinical and demographic variables was predictive of AD treatment outcome. BMI was among the most important variables (ranked according to the effect size) to predict non-response to AD treatment for nortriptyline treatment arm but not for escitalopram treatment arm.
11	Green et al. (2017), USA	Every unit increase of BMI was associated with 6% greater odds of remission for venlafaxine-XR vs. escitalopram (OR=1.06, 95% CI 1.001–1.12). BMI marginally significantly predicted remission for sertraline versus escitalopram (OR=1.04, 95% CI 0.99 to 1.10). BMI did not predict remission for sertraline vs. venlafaxine-XR (OR=0.98, 95% CI 0.93– 1.04). For venlafaxine-XR treatment, predictive probability for remission (presented graphically) in patients with obesity classes I-III was higher than in normal weight patients, with the highest in the obesity classes II and III. For sertraline, predictive probability of remission was higher only in obesity classes II and III than in normal weight group. For escitalopram, probability of remission was lower for obesity classes I and II and not different than in normal patients for obesity class III. Sex effects: BMI was not associated with remission in males, but in females increase in BMI was associated with greater odds of remission (p = 0.019, interaction OR = 1.06 [95% CI 1.01–1.12]). Cognitive symptoms: For every unit increase of BMI, women in all treatment arms showed a 0.13 points greater decrease in cognitive symptoms than males (ß=-0.133, p=0.011).	BMI predicted remission in an AD type-specific and obesity class-specific manner. Morbidly obese patients (obesity classes II and III), compared to patients with normal weight, were more likely to remit and improve physical symptoms (sleep disturbance, somatic anxiety and appetite) on venlafaxine-XR than on sertraline or escitalopram. Women, but not men, with higher BMI were more likely to achieve remission. Women with obesity classes II and III were likely to improve cognitive symptoms (suicidal ideation, guilt, and psychomotor changes) when treated with venlafaxine, sertraline, or escitalopram.

		Physical symptoms: Venlafaxine-XR was associated with a 0.15 points greater decrease in physical symptoms (HRDS) than escitalopram (ß=0.15, p=0.003) for every unit increase in BMI with no sex difference.	
12	Jha et al. (2018), USA/Singapore, COMED project	Greater proportion of obese II+ participants remitted on bupropion-escitalopram (47.4%) than on escitalopram monotherapy (28.6%, NNT = 5.3) or on venlafaxine-mirtazapine combination (37.7%, NNT = 10.3). Greater proportion of normal and underweight patients had remission when treated with bupropion-escitalopram (26.8%) than escitalopram (37.3%, NNT = 9.5) or venlafaxine-mirtazapine combination (44.4%, NNT = 5.7). Participants with obesity II+ were more likely to have a remission with bupropion-escitalopram as compared to escitalopram monotherapy (OR=2.63, 95% CI=1.20, 5.88). Patients with normal weight or underweight were less likely to have a remission when treated with bupropion-escitalopram (OR = 0.40, 95% CI = 0.17, 0.93) than when treated with a venlafaxine-mirtazapine combination. For BMI as continuous variable, a significant treatment arm-by-BMI interaction was found. When stratified by treatment arms, higher BMI was associated with greater remission odds in the bupropion-SSRI arm (OR = 1.037, 95% CI = 1.025, 1.050) but lower odds of remission in SSRI monotherapy group (OR = 0.963, 95% CI = 0.953, 0.974) and in patients treated with venlafaxine-mirtazapine combination (OR=0.985, 95% CI = 0.975, 0.996).	Combination of bupropion with escitalopram was beneficial to obtain remission in morbidly obese patients (BMI≥35). The combination of bupropion with escitalopram was less beneficial for normal or underweight outpatient with depression as compared to escitalopram monotherapy and the combination of venlafaxine with mirtazapine. Higher BMI (as a continuous variable) was associated with greater remission likelihood in the bupropion-escitalopram treatment arm.

4.5.9. Effect of metabolic status

Woo, McIntyre, et al. (2016), evaluated a prospective cohort of 541 Korean community-dwelling patients with depressive disorders treated with different AD under "real world evidence" conditions. They found that association between obesity and response to AD treatment differed not only by sex but also by metabolic status (menopausal status and presence of metabolic disturbances). Age, gender, obesity and other metabolic conditions, and male sex were predictors of insufficient response to treatment with AD. Clinically significant associations between obesity and an insufficient treatment response (HAMD-17) were found in post-menopausal women (adjusted OR= 2.41, 95%CI: 1.25-4.66) but not in pre-menopausal women or in men. For men, other metabolic conditions (hypertension, hyperglycemia, and hypercholesterolemia) but not obesity predicted non-response to AD treatment (adjusted OR= 2.32, 95%CI: 1.03-5.20).

4.6. Discussion

4.6.1. Response to AD classes and types in patients with excess weight.

Eleven of the twelve included studies (91.7%) reported a significant and clinically relevant association between either BMI, weight status, or obesity classes, and AD treatment effectiveness. Only one study (8.3%) (Toups et al., 2013) found no association between treatment response and weight status. Using the same COMED data, another group (Jha, Wakhlu, et al., 2018), however, found a significant treatment arm-by-BMI interaction as well as an association between obesity classes and differences in response to AD. Therefore, the conclusion of Toups et al. (2013) regarding the lack of association between BMI and AD treatment effectiveness should be considered with caution. In two studies (Kloiber et al., 2007; Oskooilar et al., 2009) evaluating treatment with multiple AD classes and types, clinically relevant differences with moderate to large

effect sizes were found (Oskooilar et al., 2009). The diversity between effect sizes and wide confidence intervals can be explained by the wide range of AD classes included in these two studies. In line with this hypothesis, in the ten other studies, the effect size for the treatment outcome differed depending on the AD class, type, or AD combinations. There appears, therefore, to be consistent evidence that response to AD treatment in patients with higher BMI differs from that of patients with normal weight.

These findings are in line with the general consensus that obesity and depression have recognized reciprocal relationships (Jantaratnotai et al., 2017). In recent decades, several RCTs, quasi-experimental studies and cohort studies looked at the association of excess weight and poor response to AD treatment. Woo, Seo, et al. (2016) in their literature review reported that most studies observed differential response to AD in patients with excess weight. Physicians' awareness of this topic, however, remains limited. Moreover, in recent years, more studies on this topic have been published that used certain distinct classes and types of AD for pharmacological treatment of depression. Given the slow uptake of new evidence and newly emerged studies, this review provides a timely synthesis of recent data on the response to certain classes and types of AD in patients with excess weight in a way that may be useful for today's practicing physicians. The results are summarized in Table 4.5 and in the graphical abstract (Supplementary file S2).

Nortriptyline

Poor response to nortriptyline with a relatively large effect size (Uher et al., 2009) and the importance of BMI as a predictor of response to nortriptyline (ranked as #1) (Iniesta et al., 2016) was found in two studies that analysed the same RCT data (GENDEP) using different statistical approaches. A mean difference in depression score changes for obese and normal weight patients (10% of baseline depression scores) (Uher et al., 2009) is an effect size comparable with

differences between active drug and placebo in recently conducted RCTs (Uher et al., 2009; Walsh et al., 2002) and, therefore, is clinically meaningful. Of note, although GENDEP was a partly-randomised study, these results were replicated by repeating analysis for a subgroup of a randomised sample with a random allocation of treatment (Uher et al., 2009) that should have reduced a confounding bias. Since the two studies (Iniesta et al., 2016; Uher et al., 2009) have analysed the same data, more studies on the association between nortriptyline and excess weight are desired to reproduce the results for stronger evidence. Nevertheless, the GENDEP data was a meticulously designed randomised trial involving 8 countries; the data were analysed using a mixed effects regression model (Uher et al., 2009) that allowed for including all available data instead of using the last observation carried forward (LOCF) technique to deal with the lost to follow-up patients (possible source of bias in other trials) and the results were in line with the more recent study where a machine learning technique was used (Iniesta et al., 2016). Poor response to nortriptyline, therefore, may be considered among other factors when making decisions to choose AD for obese/high BMI patients.

Fluoxetine

Further, two quasi-experimental studies conducted in USA (Papakostas et al., 2005) and Taiwan (Lin et al., 2014) found a weak to moderate negative association between higher body weight (Lin et al., 2014) or higher BMI (Lin et al., 2014; Papakostas et al., 2005) and response/remission when treated with a fixed dose (20mg/daily) of fluoxetine. Obesity as a weight category was not significantly associated with the outcome (Papakostas et al., 2005); however, this could be due to the low (lower than national) prevalence of obesity in the sample (20%) leading to the insufficient power to detect significant associations. Of note, patients with severe/unstable medical conditions and/or patients with a history of resistance to AD treatment, including a history

of poor response to fluoxetine, were excluded from these studies. Considering that obese patients are at risk to have comorbidities (Apovian, 2016) and that treatment resistant depression is usually overrepresented by obese and overweight patients (Rizvi et al., 2014), these exclusion criteria may have contributed to underestimating the relative effect of high BMI on poor treatment response to fluoxetine. In addition, no comparison between characteristics of obese and non-obese patients was reported in the study of Lin et al. (2014), meaning that confounding bias cannot be excluded. While this possibility of confounding bias should not be disregarded, the weak to moderate negative association between treatment response to fluoxetine and high BMI or high body weight observed in these two quasi-experimental studies, that could have been underestimated due to the abovementioned reasons, can be considered by clinicians when making decisions of AD choice.

Escitalopram and sertraline

For escitalopram, the absence of a clinically relevant association between high BMI/obesity and treatment response was found (Iniesta et al., 2016; Uher et al., 2009). No study was conducted with response to sertraline as a main outcome. Of note, in a study of Green et al. (2017), sertraline was superior to escitalopram in showing positive effect of high BMI on treatment response, with marginally significant results. However, the comparative efficiency of sertraline compared with escitalopram for morbidly obese patients require further research, especially since response to sertraline was not the main focus of this study.

The difference in the association between high BMI and remission in the studies that used different kinds of SSRIs can be in part explained by the heterogeneity of study designs, settings, and methods of analysis. For example, the association between SSRI and obesity can depend on the obesity class but be masked if an obesity group analysis was not performed. In support of this, high BMI was found not to be a significant predictor of remission in patients treated with escitalopram

in a study of Green et al. (2017); however, the predicted probability to remit on escitalopram was reported to be slightly lower in patients with obesity classes I and II, but not obesity class III, than in normal weight participants. In addition, it can be possible that the association is gender specific for specific depression symptoms (Green et al., 2017; Uher et al., 2009).

Venlafaxine and desvenlafaxine

The diversity of results regarding the association between high BMI and treatment response to SNRIs can be explained by several reasons. First, the differences in depression scale score changes between obese and normal weight patients in a study of McIntyre et al. (2015) were small (0.25 points) and may not be clinically meaningful. In support of this, the minimal clinically meaningful difference in effect size for treatment response calculated for the Hamilton scale in the clinical trials used in McIntyre et al. (2015) study was 3 to 3.5 points (Boyer et al., 2008; DeMartinis et al., 2007). In addition, it may be that the difference in the obesity classes distribution (not reported in the study of McIntyre et al.), as well as different exclusion criteria regarding patients with anxiety disorder could have contributed to the difference in results between these two studies. It is likely that the overall positive association between BMI and treatment response for the whole sample in the study of Green et al. (2017) was mainly due to the effect of venlafaxine-XR. It is also possible that venlafaxine-XR (Green et al., 2017), an extended release formulation, works better for obese patients than desvenlafaxine or other non-extended release AD, assuming that adiposity prolongs the absorption of AD. In addition, it may be that titrating the dose of SNRI for patients with excess weight (Green et al., 2017) compared with using fixed doses (McIntyre et al., 2016) may help achieve the therapeutic effect. In any case, the results of the studies evaluating response to treatment with SNRI in relation to patient's body weight suggest that, while patients of all weight groups

Table 4.5. Evidence regarding differential response to treatment with specific AD types in relation to high BMI/high body weight/obesity

AD type and class	Evidence	Conclusion
Nortriptyline (TCA)	Poor response to nortriptyline in obese/high BMI patients with a relatively large effect size (Uher et al., 2009) and a strong predictive ability of BMI for symptoms reduction and non-remission (Iniesta et al., 2016) were found in two studies that analysed the same RCT data (GENDEP). Uher et al. (2009): Obese patients had 11% to 54% more risk to have non-response to nortriptyline than non-obese patients and higher BMI was associated with lower blood levels of nortriptyline Iniesta et al. (2016): BMI was the most important predictor (ranked #1 according to the effect size) of reduction depression symptoms and non-remission when treated with nortriptyline	The GENDEP data was a meticulously designed randomised trial involving 8 countries, and the results of two independent research groups showed the importance of high BMI/obesity to predict poor response to treatment with nortriptyline. Poor response to nortriptyline may be considered among other factors when making decisions to choose AD for obese or high BMI patients. Since these two studies analysed the same RCT data, more studies are desired to confirm reproducibility of results for stronger evidence
Fluoxetine (SSRI)	There is evidence for moderately lower rates of response/remission when treated with 20mg/day fluoxetine in people with higher body weight/high BMI than in patients with lower BMI or body weight, that was reproduced in two studies conducted in USA and Taiwan. Papakostas et al. (2005): every point of increase in BMI was associated with up to 7.6% increase in the odds of non-response to fluoxetine treatment Lin et al. (2014): a weak to moderate negative association between higher body weight and response/remission when treated with a fixed dose (20mg/daily) of fluoxetine	Clinically relevant negative association with a small effect size between high BMI/high body weight and response/remission when treated with 20mg/daily fluoxetine was reproduced in two studies. This effect may be underestimated due to the exclusion criteria (patients with severe/unstable medical conditions, a history of resistance to AD and/or of poor response to fluoxetine) This negative association can be considered when making decisions to choose AD for patients with high body weight/high BMI.

		This should be used with caution considering a possibility of confounding bias in quasi-experimental studies.
Escitalopram (SSRI)	Two studies looked at the treatment response to escitalopram. Uher et al. (2009): No consistent clinically-relevant effect of obesity on treatment response was found and no association between higher BMI with lower blood levels of escitalopram Iniesta et al. (2016): BMI was not among the 10 most predictors for either reduction of depression symptoms or remission for patients treated with escitalopram. No studies comparing treatment response to escitalopram and citalopram in relation to BMI or obesity was conducted.	There is no evidence that points to the different response to escitalopram in patients with obesity compared to normal weight patients.
Sertraline (SSRI)	No study was conducted with response to sertraline as a main outcome. In a study of Green et al. (2017), marginally-significant positive association between BMI and remission with a clinically-meaningful effect size was found when treated with sertraline versus escitalopram (OR=1.04, 95%CI: 0.99-1.10). This means that patients with higher BMI may have more chances to respond to sertraline than escitalopram.	Not enough evidence to consider in clinical decision making
Desvenlafaxine (SNRI)	Evaluated in one study (McIntyre et al., 2015) Patients with higher BMI were less likely to be responders compared with patients with lower BMI (only significance of results but not effect sizes were reported). Small difference (0.25 points) in HDRS-17 depression score in patients with high BMI when treated with desvenlafaxine that may be not clinically meaningful.	Not enough evidence for clinically relevant different response to desvenlafaxine in patients with high BMI/obesity compared with normal weight patients
Venlafaxine-XR (SNRI)	Evaluated in one study (Green et al., 2017). Every unit increase of BMI was associated with 6% greater odds of remission for venlafaxine-XR vs. escitalopram (OR=1.06, 95% CI 1.001–1.12). For venlafaxine-XR treatment, predictive probability for remission in patients with obesity classes I-III was higher than in normal weight patients, with the highest in the obesity classes II and III.	Venlafaxine-XR may be beneficial to treat depression for people with BMI>35 kg/m^2, compared with escitalopram. These results, however, need to be replicated, considering that the study was a secondary analysis of RCT (possibility of confounding bias) and the mixed data for the effect of high BMI on desvenlafaxine (an active metabolite of venlafaxine) and venlafaxine.

respond to SNRI, certain types of SNRIs, such as venlafaxine-XR, may be beneficial to treat depression for people with BMI>35 kg/m^2 (Green et al., 2017). Better response to SNRI venlafaxine-XR by patients with obesity classes II and III than to SSRIs escitalopram and sertraline deserves attention and should be evaluated in further studies to demonstrate consistency.

AD combinations

There are some recent data on the association of high BMI/obesity with response to certain combinations of AD: escitalopram monotherapy, bupropion-escitalopram combination, or venlafaxine-mirtazapine combination. These AD combinations in relation to body weight were researched in two studies where a post hoc analysis of the COMED RCT data was conducted. Of note, even though it is known that bupropion and venlafaxine have a stimulating effect and mirtazapine and escitalopram have a prominent anxiolytic effect, in a COMED study, these treatment options were randomly assigned to the patients with MDD, without stratifying patients by these specific features. No difference in response or remission was found in the first study (Toups et al., 2013) between different BMI groups for the whole sample. Due to higher prevalence of obesity in this sample (higher than in general population (Toups et al., 2013)) and low proportion of normal weight patients, the study may have lacked power to distinguish differences across subgroups. Of note, only effect sizes and not 95%CI for the odds ratios were reported by the authors, reducing the quality of evidence and preventing from judging about clinical relevance of the results. In the later analysis of Jha, Wakhlu, et al. (2018), however, obese II+ participants were more likely to remit with bupropion-escitalopram combination than escitalopram monotherapy or venlafaxine-mirtazapine combination. Therefore, the findings of the lack of overall effect of

obesity on treatment outcomes by Toups et al. (2013) may be partially driven by the fact that the effect of obesity differed for various treatment arms. Jha, Wakhlu, et al. (2018) consider these data in line with the study of Green et al. (2017), since the combination of bupropion and escitalopram has a similar pharmacological profile as venlafaxine (Jha, Wakhlu, et al., 2018). Considering this, findings of Green et al. (2017), that venlafaxine-XR was superior to escitalopram in patients with morbid obesity agree with findings of Jha, Wakhlu, et al. (2018), that the combination of bupropion and escitalopram was superior to escitalopram monotherapy in participants with BMI≥35 kg/m^2. Taking into account the relative reproducibility of these results and the fact that both studies (Green et al., 2017; Jha, Wakhlu, et al., 2018) analysed the data of large pragmatic randomized partly blinded controlled trials involving over 600 patients, prescribing venlafaxine -XR or a combination of bupropion-escitalopram to patients with morbid obesity should be considered (Jha, Wakhlu, et al., 2018) if patients' clinical status does not interfere with stimulating or anxiolytic effects of the AD types included in these combinations.

Of importance, there are other anthropometric measures of adiposity other than BMI and body weight, including waist circumference or hip to waist ratio, and imaging techniques such as dual-energy x-ray absorptiometry (DEXA) or magnetic resonance imaging (MRI). We performed a quick additional search and found no recent studies using these measures to predict response to AD treatment in patients suffering from depression. Only one exploratory study (Tonning et al., 2017) found no association between waist circumference or hip to waist ratio and response to treatment in patients with depression. Lack of power to detect differences in response due to the small number of patients (n=33) as well as high heterogeneity of interventions (pharmacological and non-pharmacological treatment) do not allow to make any conclusions regarding the association between these surrogate markers of visceral fat and AD treatment response.

One relevant paper published more recently and therefore not included in our review (Dreimuller et al., 2019) was brought to our attention during the manuscript review process. The authors performed a post hoc analysis of the Early Medication Change for non-improvers (EMC) RCT where patients with MDD not responding to escitalopram either continued taking escitalopram or were switched to venlafaxine early in the treatment period. The authors found the association between baseline high BMI/ obesity and AD treatment outcome. Of interest, patients with higher initial increase in BMI (weight gain) during treatment had larger decrease in severity of depression during the follow-up. The underlying mechanism of this finding is unclear and require further investigation.

4.6.2. Dose and duration

In two studies (Kloiber et al., 2007; Oskooilar et al., 2009), an inverse association of obesity with treatment response and slower rates of improvement were observed despite physicians could titrate doses of AD. Moreover, scores on the depression scale by the end of treatment did not reach the same level of improvement as in patients with normal weight (Kloiber et al., 2007). It is possible that, for treatment with certain AD, increasing AD dose for patients with excess weight is necessary but it may not be enough to achieve the same therapeutic effect as for normal weight patients. These results suggest that patients with excess weight may need longer duration of treatment than patients with normal weight to reach the same level of treatment response, even with an adjusted dose of AD.

4.6.3. Effect of sex and metabolic status.

Response to AD treatment in patients with excess weight differed by sex (Green et al., 2017; Kloiber et al., 2007; Uher et al., 2009) and related hormonal and metabolic conditions (Woo, McIntyre, et al., 2016). Therefore, these factors likely should be taken in considerations when prescribing AD to patients with excess weight. The moderating activity of sex may depend on the individual type of AD. For example, poor response to SSRIs was reported for obese men but not obese women (Khan et al., 2007). It is possible that the higher levels of circulating female hormones, estrogen and progesterone among women, help prompt indoleamines and catecholamines to respond to treatment (Bies et al., 2003; Harris et al., 1995; Yonkers et al., 1992). Therefore, males lacking these hormones may need higher dose of AD (Khan et al., 2007) to achieve a comparable response. This effect of sex may not hold for all SSRI (Uher et al., 2009) and may be different for certain symptoms of depression (Green et al., 2017). The relationships between excess weight, sex, and AD response can be even more complex and can depend on a metabolic status for each sex. Woo, McIntyre, et al. (2016) found a significant effect of obesity on response to different AD (SSRI, TCA, etc.) only for post-menopausal women and men with metabolic syndrome. One of the explanations for these results may be lower predictive power of BMI for visceral adiposity in men than in women, especially in men of Asian origin (Vogelzangs et al., 2014). Therefore, the effect of high adiposity on treatment response in men may not be fully captured by their BMI group but may become apparent knowing the metabolic condition (Woo, McIntyre, et al., 2016).

In light of the diversity of the groups and types of AD studied in the manuscripts included in our review, our conclusions regarding BMI and BMI categories as predictors of treatment response to individual AD types and AD combinations provide some guidance when choosing the appropriate AD for patients with depression but are not direct clinical recommendations. However,

given that all the abovementioned AD types are currently recommended for use (Kennedy et al., 2016), this review may help personalize choice of AD. Personalization can be based on patient weight group or BMI, as well as obesity class, with considerations for gender and metabolic status, when there are no contraindications and no specific factors (e.g., specific features of depression) favouring prescribing a specific AD type. In addition, other factors, including type of depression, specific features of depression, presence of comorbidities, patients' history of AD response and side effects, as well as clinical experience, are also implicated in decision making regarding AD choice.

4.6.4. Putative mechanisms of treatment resistance

Several mechanisms have been suggested to explain why patients with excess weight differ in their response to AD treatment from normal weight patients. One of the mechanisms may be a large volume of AD distribution in people with excessive adiposity due to the known lipophilicity of these drugs. There is also a hypothesis that, since some AD are more lipophilic than others, and the affinity of each medication for the extra adipose tissue is unique (Hanley et al., 2010), this can lead to variations in plasma concentrations correlated with clinical response (Hiemke, 2008; Ostad Haji et al., 2012). This hypothesis is in line with the results of the study of Uher et al. (2009), where obese patients had poor response to nortriptyline and lower nortriptyline blood concentration while both response to escitalopram and escitalopram blood concentration were normal. Clinical response, however, does not correlate with AD plasma level in patients with depression for all AD (Beasley et al., 1990; Norman et al., 1993; Sparshatt et al., 2011) or throughout the entire course of treatment (Normann et al., 2004; Schwarzenbach et al., 2003) The association between plasma concentrations and clinical response appears much more complex and

depend on many factors affecting drug metabolism. In addition to lipophilic indices of various AD and their correlation with excessive fat in obese and overweight patients, one could take into account linearity of kinetics, substance half-life, liver enzyme inducing and inhibiting properties, and drug-drug interaction concerns. It is especially important in patients with excess weight as they could be at a higher risk for polypharmacy for other co-morbid disorders as well as for a liver disease.

Further, it is known that obesity is a state of systemic low grade inflammation (Forsythe et al., 2008), and that obese patients may have elevated levels of inflammatory biomarkers, such as C-reactive protein (CPR) (Choi et al., 2013; Pavela et al., 2018). Patients with MDD with high levels of inflammation markers (e.g., CRP>1 mg/L) (Jha, Minhajuddin, Gadad, Greer, Grannemann, et al., 2017), associated with high BMI (Jha, Wakhlu, et al., 2018), or even with obesity class (Nguyen et al., 2009) and a relatively increased permeability of a blood brain barrier were found to have better response to dopamine reuptake inhibitors (e.g., bupropion) (Jha, Minhajuddin, Gadad, Greer, Mayes, et al., 2017; Jha, Minhajuddin, Gadad, & Trivedi, 2017; Jha & Trivedi, 2018) or a combination of escitalopram and bupropion (Jha, Wakhlu, et al., 2018) as compared to preponderantly serotonin reuptake inhibitors (escitalopram) (Jha, Minhajuddin, Gadad, Greer, Mayes, et al., 2017; Jha, Minhajuddin, Gadad, & Trivedi, 2017; Jha & Trivedi, 2018). It has been suggested (Jha, Minhajuddin, Gadad, Greer, Grannemann, et al., 2017) that CRP level, with a threshold of 1mg/L, may be helpful to guide selection of AD to improve treatment outcomes. Other inflammatory peptides (IL-6, TNF) were found to be elevated in patients with high adiposity (Forsythe et al., 2008) as well as linked to the altered AD treatment response (Haroon et al., 2018; Lindqvist et al., 2017), providing further evidence of the role of inflammation as one of the mechanisms of AD treatment resistance in obese patients.

The role of adipokines, secreted by adipose tissue, has also been implicated in the mechanism of the relationships between excess weight and treatment response, through the suppression of hypothalamo-pituitary axes and neurotransmitter systems. Levels of circulating leptin correlate positively with body weight and BMI (Maffei et al., 1995; McGregor et al., 1996). Leptin resistance, developed through different mechanisms, that can be specific to AD type, may be one of the putative reasons for a selective treatment resistance in obese patients with depression. For example, it has been suggested that the antihistaminergic activity of several AD, such as amitriptyline and mirtazapine, may contribute to leptin resistance via histamine H1-receptor-mediated dysregulation of hypothalamic nuclei integrating central and peripheral signals relevant to energy balance (Schilling et al., 2013). Another putative mechanism may be deficits in intracellular signaling mechanisms downstream of leptin (Banks, 2012), analogous to the attenuated effect of fluoxetine treatment in mice with the absence of an intact Brain Derived Neurotrophic Factor pathway (Scabia et al., 2018).

Genetic factors may also be implicated. AD response can be influenced by polymorphisms in transporters, neurotransmitter receptors and drug metabolizing enzymes (Kirchheiner et al., 2003). For example, C825T polymorphism in GNB3, a beta-subunit of the heterotrimeric nucleotide-binding G-protein, involved in transduction of downstream signals from cellular receptors, was linked to both to obesity and depression (Klenke et al., 2011) and to the response to AD in an AD-specific manner (Hu et al., 2015; Klenke et al., 2011). Another example is a study of Jin et al, 2010 (Jin et al., 2010), where genotype CYP2C19*2 or *3 for a cytochrome P450 2C19 liver enzyme, CYP2C19, along with age and weight, influenced the clearance of escitalopram, that allegedly could have an impact on the treatment response.

Another explanation for treatment resistance in obese patients is presence of comorbid medical conditions, such as sleep apnea, asthma, and metabolic syndrome all of which can contribute to more severe depression and attenuate response to treatment (Chapman et al., 2005; Moussavi et al., 2007). Finally, decreased physical activity and obesity stigma can also contribute to poor outcomes of AD therapy in patients with excess weight (Uher et al., 2009).

In summary, the exact mechanism linking excess weight and response to AD treatment, which most likely includes a complex interplay between several biological processes, as well as genetic, epigenetic and socio-behavioural factors, remains unclear. Most RCTs included in our review had no control group treated with placebo, that leaves unclear to what degree the association between excess adiposity and treatment response could be mediated through the different response to placebo in patients with high BMI. The cohort studies did not apply methods of causal inference to ensure conditional randomisation and reduce confounding bias. No studies accounted for time-dependent changes in BMI that could be affected by earlier AD treatment and have an impact on the outcome. It is also important to keep in mind that there are other factors shown to have an association with AD treatment response that ideally are needed to be accounted for in the model such as, for example, a history of a childhood trauma (Williams et al., 2016). To evaluate whether there is a causal effect of obesity on AD treatment response, RCTs specifically aiming to evaluate causality of association, or carefully conducted observational studies with the use of causal inference methods, such as marginal structural models, need to be conducted. The strength and even the direction of association may differ across AD groups and even types of AD within the same group, suggesting contribution of different mechanisms depending on the pharmacological action of AD groups and types.

Recently, machine learning approach has become a valid way to build predictive models. The combination of a machine learning and a statistical approach was used in one of the studies included in our review (Iniesta et al., 2016). In this study, BMI was among the 10 most important predictors for nortriptyline treatment response and among significant predictors to escitalopram treatment response (Iniesta et al., 2016). It is possible that a combination of machine learning and statistical modeling will allow to build a universal model predicting response to AD treatment that can be widely used by clinicians. More evidence, however, is needed to evaluate role of different predictors, with stratification by AD type, since evidence points to the possible diversity in treatment response to individual AD types from the same group that may be related to patients' characteristics, such as body weight and sex.

4.6.5. Strength and limitations

Our review has several strengths and limitations. Using a scoping review methodology that allows to summarize data from studies with high diversity in design and methods, we conducted a reproduceable and transparent search on a recently emerging important clinical topic. Among limitations, our search was restricted to only two sources, MEDLINE and PsycINFO, for the period January 2009-January 2019, the population of adult patients, and publications in English, French, German or Russian. Therefore, some of the manuscripts related to our topic might have been missed. Our strategy, however, allowed us to capture manuscripts related to our review question and published in the most reliable sources of high-quality peer-reviewed papers in any of the four abovementioned languages within the period of time when the interest to our research topic started developing. In our research, we concentrated on body weight and BMI as markers of adiposity that are practical and can be easily measured in the doctors office. We did not include more accurate but relatively unavailable measurements of adiposity such as DEXA or MRI, nor did we specifically

search for the surrogate anthropometric markers such as waist circumference and waist-to-hip ratio that are not as routinely used by physicians. Our additional search in MEDLINE and PsycINFO produced only one article where waist circumference and waist-to-hip ratio was evaluated in relation to depression treatment (Tonning et al., 2017) that was mentioned in the discussion. Included studies did not allow for the comparison of treatment response in obese patients with typical and atypical depression since none of the authors stratified depression diagnoses by sub-types. In accordance with our review question, other important predictors of AD treatment response were discussed only as potential confounders of the studied association. Among study strengths, a specialized librarian was engaged to develop the search strategy. Data were charted by two independent researchers. In case of unclarities in the included manuscripts, authors were contacted. Frequency analysis and a narrative synthesis with a discussion of strength and limitations of the included studies and the quality of reported data was performed. Data on different groups and types of AD were systematized and synthesized in a way that may be helpful for practicing physicians to learn the recent evidence on the differential response to AD treatment in patients with high BMI or obesity, suffering from depression. Knowledge gaps to be addressed by future research were identified.

4.7. Conclusion

The data synthesized in this review provide summary of the evidence of a different response to AD in patients with high BMI/high body weight and/or obesity compared with normal weight patients. The magnitude and even the direction of this association may depend on pharmacological class of AD and AD type. Our findings may be useful to physicians in their decision regarding the choice of AD in patients with excess weight. More research is needed to evaluate whether there is

a causal association between obesity and treatment response to individual types of AD; given that RCTs may not be feasible, the use of large healthcare databases combined with methods of causal inference are warranted.

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CRediT authorship contribution statement

Svetlana Puzhko: Conceptualization, Data curation, Writing - original draft. **Sarah A. E. Aboushawareb:** Data curation, Writing – review and editing. **Irina Kudrina:** Writing - review & editing. **Tibor Schuster:** Writing - review & editing. **Tracie A. Barnett:** Writing - review & editing. **Christel Renoux:** Writing - review & editing. **Gillian Bartlett:** Conceptualization, Supervision, Writing -review and editing.

Declaration od Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Yonkers, K. A., Kando, J. C., Cole, J. O., & Blumenthal, S. (1992). Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. *Am J Psychiatry, 149*(5), 587-595. doi:10.1176/ajp.149.5.587

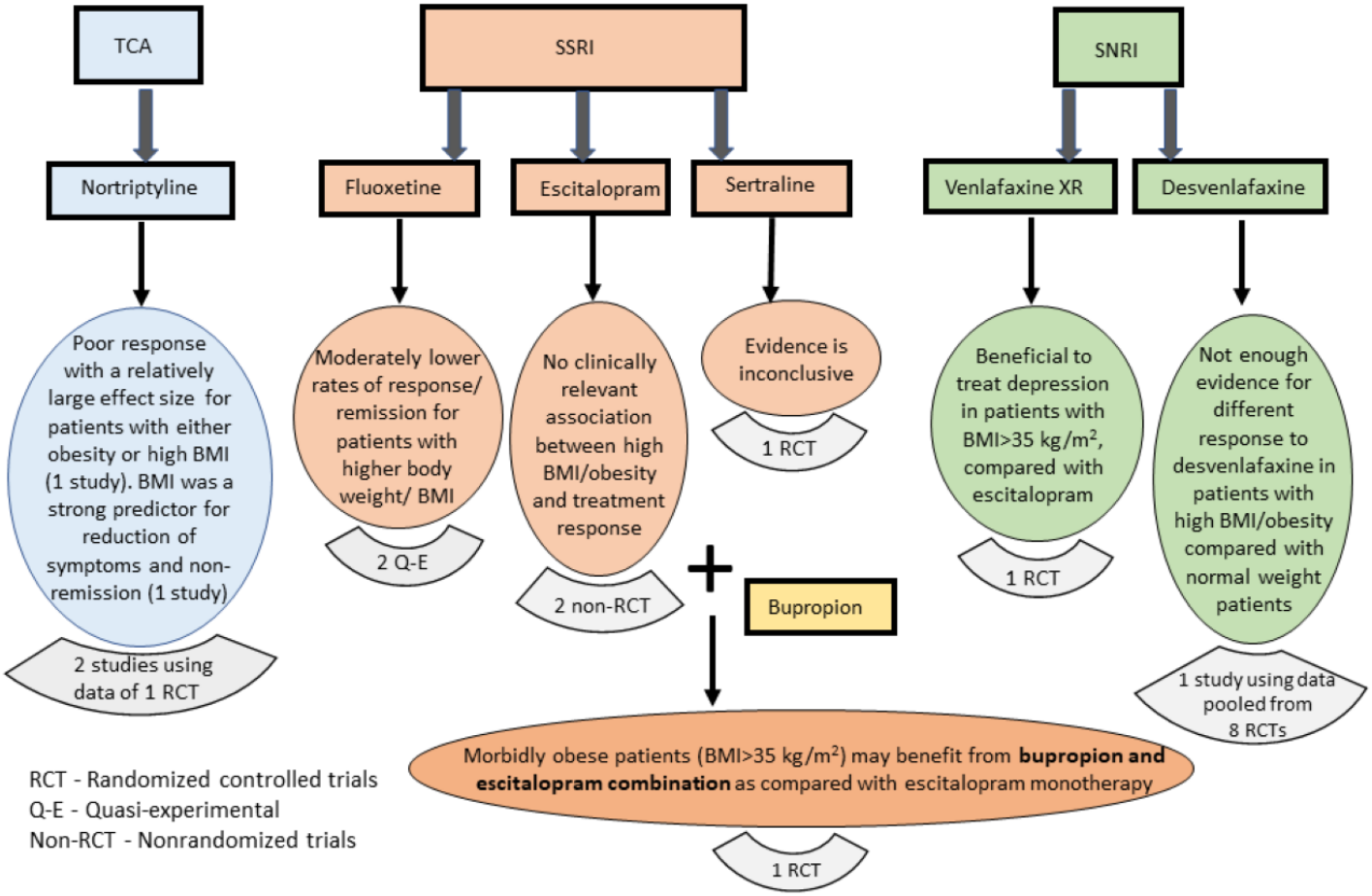
4.10. Supplemental information

4.10.1. Supplementary file S1:

Highlights

- Response to treatment with antidepressants in patients with high BMI and /or obesity may depend on the antidepressant type and on obesity class
- Clinically relevant negative association between either patients' high BMI or obesity and treatment response to either nortriptyline, fluoxetine, or various AD was reported in 75% of included studies.
- Morbidly obese patients may benefit from bupropion and escitalopram combination as compared with escitalopram monotherapy
- More research is needed to evaluate whether there is a causal association between obesity and AD treatment response

4.10.2 Supplementary file S2: Graphical abstract



4.10.3. Appendix:

Table S3. Search strategy

	Concept 1 **Overweight/obese (patients)** **with depression**		**AND Concept 2**	**AND Concept 3**
	Concept 1a	**AND Concept 1b**	Antidepressant treatment	Treatment response/treatment effect/treatment outcomes
	Excessive weight (overweight)/ obesity	Depression		
in MEDLINE or PsycINFO (via OVID)				
Keyword 1	Excess* weight.mp	Depress*.mp	Antidepressant*.mp	Response*.mp
OR Keyword 2	Obese.mp		Antidepressive.mp	Depression rating scale*.mp
OR Keyword 3	Obesity.mp		[All eligible AD groups].mp	Improvement.mp
OR Keyword 4	Overweight.mp		[All eligible AD types].mp	Efficacy.mp
OR Keyword 5	Body mass index.mp			Efficien*.mp
OR Keyword 6				Effect*.mp
OR Keyword 7				Outcome*.mp
OR Subject heading 1		Depressive disorder/	Exp antidepressive Agents/ (Medline)	Treatment outcome/

OR Subject heading 2	Exp Overweight/	Depressive disorder, Major/	Exp Serotonin Uptake Inhibitors/ (Medline) Serotonin Reuptake Inhibitors/ (PsycINFO)	Comparative effectiveness/ (Medline) Treatment Effectiveness Evaluation/ (PsycINFO)
OR Subject heading 3	Body mass index/	Depressive Disorder, treatment-resistant/	Antidepressive agents, Tricyclic/	Psychiatric status Rating Scale/ (Medline) Rating Scales/ (PsycINFO)
OR subject heading 4	Body weight/	Depression/	Antidepressive agents, second-generation/ (Medline)	
OR subject heading 5		Dysthymic disorder/		
Filters:	All adult and (English or French or German or Russian) and humans and last 15 years			

4.10.4. Appendix:

Table S4. Results of MEDLINE and PsycINFO search using OVID

Concept	**Number of publications found**	
	MEDLINE	PsycINFO
Concept 1a	171394	25553
Concept 1b	125765	135813
Concept 2	8138	14607
Concept 3	1829332	607179
Final search: Concept 1 AND Concept 2 AND Concept 3	443	191

4.10.5. Appendix:

Table S5. The PRISMA ScR statement

Table. PRISMA-ScR Checklist

Section	Item	PRISMA-ScR Checklist Item
Title	1	Identify the report as a scoping review.
Abstract		
Structured summary	2	Provide a structured summary that includes (as applicable) background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.
Introduction		
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.
Methods		
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).
Summary measures	13	Not applicable for scoping reviews.
Synthesis of results	14	Describe the methods of handling and summarizing the data that were charted.
Risk of bias across studies	15	Not applicable for scoping reviews.
Additional analyses	16	Not applicable for scoping reviews.
Results		
Selection of sources of evidence	17	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.
Characteristics of sources of evidence	18	For each source of evidence, present characteristics for which data were charted and provide the citations.
Critical appraisal within sources of evidence	19	If done, present data on critical appraisal of included sources of evidence (see item 12).
Results of individual sources of evidence	20	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.
Synthesis of results	21	Summarize and/or present the charting results as they relate to the review questions and objectives.
Risk of bias across studies	22	Not applicable for scoping reviews.
Additional analyses	23	Not applicable for scoping reviews.
Discussion		
Summary of evidence	24	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.
Limitations	25	Discuss the limitations of the scoping review process.
Conclusions	26	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.
Funding	27	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy documents).

CHAPTER 5: EVALUATING PREVALENCE AND PATTERNS OF PRESCRIBING MEDICATIONS FOR DEPRESSION FOR PATIENTS WITH OBESITY USING LARGE PRIMARY CARE DATA (CANADIAN PRIMARY CARE SENTINEL SURVEILLANCE NETWORK) (MANUSCRIPT 2)

5.1 Preamble

Findings of my first manuscript suggest that patients with the obesity-depression phenotype require a tailored approach to AD selection. The "one size fit all" approach may lead to a poor response or even a non-response to treatment. Due to the lack of guidelines addressing this clinical phenotype, selection of the optimal AD medication for patients with excess weight is challenging. As a result, reaching the therapeutic goal may require longer time and high number of switches from one AD to another. This may put the patients with excess weight at an increased risk for adverse effects, including more weight gain when treated with certain AD. Despite the prominence of the possible negative consequences for patients' health and public health, the prevalence and patterns of AD prescribing in patients with excess weight, who suffer from depression, have not been studied in Canada.

In my second manuscript, using a national cohort representative of primary care patients in Canada, I analysed prevalence and patterns of AD prescribing for patients of different weight groups and obesity classes. Evaluation of differences in AD prescribing between patients who are overweight or obese, and patients with normal weight helped identify problems with prescribing and showed directions for further research. The study findings highlighted the importance of weight as a factor associated with AD prescribing and justified the need for longitudinal studies with ensured temporality of associations between excess weight and AD prescribing, that was addressed by my manuscript #3.

Title: Evaluating prevalence and patterns of prescribing medications for depression for patients with obesity using large primary care data
(Canadian Primary Care Sentinel Surveillance Network)

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5.2 Abstract

Introduction: Depression is a serious disorder that brings a tremendous health and economic burden. Many antidepressants (AD) have obesogenic effects, increasing the population of obese patients at increased risk for a more severe disease course and poor treatment response. In addition, obese patients with depression may not be receiving the recommended standard of care due to "obesity bias". It is important to evaluate prescribing pharmacological treatment of depression in patients with obesity.

Objectives: To describe the prevalence and patterns of AD prescribing for patients with depression and comorbid obesity compared with normal weight patients, and to examine the association of prescribing prevalence with obesity class.

Methods: Study sample of adult patients (>18 years old) with depression was extracted from the national Canadian Primary Care Sentinel Surveillance Network (CPCSSN) Electronic Medical Records database for 2011-2016. Measures were prescribing of at least one AD (outcome) and body mass index (BMI) to categorize patients into weight categories (exposure). Data were analyzed cross-sectionally using descriptive statistics and mixed effects logistic regression model with clustering on CPCSSN networks and adjusting for age, sex, and the comorbidities.

Results: Of 120,381 patients with depression, 63,830 patients had complete data on studied variables (complete cases analysis). Compared with normal weight patients, obese patients were more likely to receive an AD prescription (adjusted Odds Ratio [aOR]=1.17; 95% Confidence Interval [CI]: 1.12-1.22). Patients with obesity classes II and III were 8% (95%CI: 1.00, 1.16) and 6% (95%CI: 0,98, 1.16) more likely, respectively, to receive AD. After imputing missing data using Multiple Imputations by Chained Equations, the results remained unchanged. The prevalence of prescribing > 3 AD types was higher in obese category (7.27%, [95%CI: 6.84, 7.73]) than in normal weight category (5.6%; [95%CI: 5.24, 5.99]).

Conclusion: The association between obesity and high prevalence of AD prescribing and prescribing high number of different AD to obese patients, consistent across geographical regions, raises a public health concern. Study results warrant qualitative studies to explore reasons behind the difference in prescribing, and quantitative longitudinal studies evaluating the association of AD prescribing patterns for obese patients with health outcomes.

5.3 Introduction

Depression is a serious medical disorder that brings a tremendous health and economic burden to society. The considerable health burden of depression includes significant morbidity, reduced functioning, poor quality of life and increased mortality, especially from suicide (Wang et al., 2003). Moderate and severe depression has been associated with 50%-75% higher per capita costs of health care (Simon et al., 2011). The overall prevalence of life-time depression in Canada was estimated at 11.3% in 2012 (Pearson et al., 2013). The prevalence of treatment resistant depression in Canadian primary care is 21% (Rizvi et al., 2014); moreover, the individual response to treatment for certain antidepressants (AD) is unknown. One of the clinical markers for ineffective AD treatment may be patient's weight. In Canadian primary care, treatment resistant depression is overrepresented by obese and overweight patients (Rizvi et al., 2014). Several studies reported that obese patients responded poorly to AD medications, with some studies reporting different response to individual AD types in obese patients, especially those with morbid obesity (Green et al., 2017; Rizvi et al., 2014; Woo et al., 2016), compared with normal weight patients. This potential difference in response is, however, not yet reflected in the guidelines (Anderson et al., 2008; Gelenberg et al., 2010; Health & Excellence, 2009; Kennedy et al., 2016). On the other hand, many AD have obesogenic effects, increasing the population of obese patients at elevated risk for poor response to treatment (Kachur et al., 2005; McIntyre et al., 2015; T. L. Schwartz et al., 2004). This negative cycle contributes both to the prevalence of treatment resistant depression and the obesity epidemic.

In Canada, nearly 60% of adults are overweight and almost one-quarter (23%) are obese (Lau et al., 2007; Rigobon et al., 2015). Both obesity and depression are among the leading causes of preventable diseases and disability worldwide. Obese patients with depression constitute a highly stigmatized population with low self-esteem, poor quality of life, frequent

use of health services, and decreased involvement in the labour force (Barnes et al., 2015; Carey et al., 2014; Simon et al., 2011). Even though several studies suggest that obese patients respond to AD differently compared with normal weight patients and, therefore, may need special approach to treatment, there are no current guidelines on treatment of depression tailored to obese patients, except for those with eating disorders. In addition, the population of obese patients may face an important problem in receiving an adequate standard of medical care due to a phenomenon labelled the "obesity bias" which originates from unsubstantiated beliefs that obese and overweight patients are irresponsible and less likely to be adherent to treatment (Puhl & Heuer, 2009; M. B. Schwartz et al., 2003). Hence, treatment of obese patients with comorbid mental conditions may be suboptimal and may negatively affect their health outcomes (Ferrante et al., 2006). It is imperative, therefore, to evaluate the prevalence and patterns of prescribing pharmacological treatment to patients with depression and comorbid obesity and to examine the association between obesity and AD prescribing. To our knowledge, very few studies (Boudreau et al., 2013; Gafoor et al., 2018) evaluated how health providers prescribe AD to obese and overweight patients with depression; they showed that utilization of AD may be contributing to population-level increases in excess weight ((Gafoor et al., 2018), UK) and that obese patients are less likely to receive recommended standards of care ((Boudreau et al., 2013), USA). To our knowledge, no study evaluated the prevalence and patterns of AD prescribing to patients with obesity in Canada or the association of certain prescribing patterns with the class of obesity. Depression is most commonly diagnosed, managed and treated in primary care in Canada (Craven & Bland, 2013). Primary care is usually an entry point to depression treatment, due to ease of access to a PCP (compared with access to a specialist), lack of specialists in a patient's residential area, or long waiting time to see a specialist (Asarnow et al., 2014; Rizvi et al., 2014). Prescribing AD is a common practice

for many primary care providers (Morkem et al., 2017), and most of AD prescriptions in Canada are issued by PCP (Craven & Bland, 2013).

The goal of the present study is to describe the prevalence and patterns (number of AD types prescribed) of AD prescribing for Canadian primary care patients diagnosed with depression who have comorbid obesity compared with normal weight patients with depression, and to examine the association of prescribing prevalence with obesity status, including obesity class. Study results are expected to generate hypotheses for further longitudinal studies evaluating the association of patterns of AD prescribing for obese patients in Canada with health outcomes. The focus will be on AD known for their risk to increase weight and AD shown to have different treatment outcomes in obese patients.

5.4 Methods.

5.4.1. Data source and study population

For this study, we used Canadian Primary Care Sentinel Surveillance Network **(**CPCSSN), a large pan-Canadian primary care database that combines de-identified patients' electronic medical records (EMRs) data from 12 primary care practice-based research networks across Canada, spanning 8 provinces and 1 territory (Garies et al., 2017; Queenan et al., 2016; Rigobon et al., 2015). CPCSSN extracts primary care data on a regular (quarterly) basis from different EMR products and transforms it into a common database in a central source (Garies et al., 2017; Queenan et al., 2016). By May 2016, nearly 1200 sentinels from over 200 practice sites participated in CPCSSN; the database included demographics, encounter diagnoses, lab results, referrals, procedures, and prescriptions for more than 1.5 million patients (Rigobon et al., 2015). To address problems that may arise from EMR-data related issues, such as unstandardized data entry and free-text documentation, CPCSSN applies extensive cleaning algorithms (Garies et al., 2017).

Although a substantial part of data on patients' BMI is missing in CPCSSN, this database contains more body mass index (BMI) records than the objective BMI measurements collected by Statistics Canada health surveys over the past 20 years (Rigobon et al., 2015). CPCSSN is considered to be representative of the general Canadian population, albeit older adults are over-represented and young adult males are under-represented (Queenan et al., 2016).

The population of adult patients with life-time depression was extracted from the CPCSSN database for the period June 2011 - June 2016. All adult patients (patients who were 18 years of age or older as of June 2011) with depression who had at least one encounter with their primary care provider (PCP) within this period were included. To select patients with life-time depression, a CPCSSN definition of depression and a validated case detection algorithm (Williamson et al., 2014) were applied. The algorithm combines information from patients' problem list (Encounter Diagnosis Codes, used by some providers/sites to record the information on diagnosis (Nicholson et al., 2015)), prescription records, and billing (Billing Diagnosis Codes, used by other providers/sites to record the information on diagnosis (Nicholson et al., 2015)). This algorithm detects life-time depression, including an ongoing depression episode or a history of depression (Williamson et al., 2014). CPCSSN case definition for depression was shown to have a sensitivity of 81.1 (95%CI: 77.2–85.0) and a specificity of 94.8 (95%CI: 93.7–95.9) (Williamson et al., 2014).

5.4.2. Measures

BMI and weight category

BMI was calculated in CPCSSN as body weight in kilograms divided by the square of the height in meters. We used the first record of BMI in CPCSSN for the study period to minimize possible misclassification of exposure (weight groups) due to weight-modulating effects of

certain AD. BMI was used as a continuous exposure variable and was categorized into weight categories using WHO and Health Canada standards: 25 kg/m^2 to 29.99 kg/m^2 = overweight, ≥30 kg/m^2 = obese, 18.5 kg/m^2 to 24.99 kg/m^2 = normal, <18.5kg/m^2 = underweight. Extreme outliers (70 kg/m^2 < BMI <15 kg/m^2) representing values outside plausible ranges were excluded. In addition, patients with obesity were subdivided into three classes. Class I comprises patients with BMI of 30-34.99 kg/m^2, class II contains patients with BMI values between 35 kg/m^2 and 39.99 kg/m^2, and class III includes patients with BMI equal or greater than 40 kg/m^2.

Socio-demographic and health data

Patients' age (continuous variable and categorized into 6 age groups: 18-25 years, 26-35 years, 36-45 years, 46-55 years, 56-65 years, and >65 years of life), sex (dichotomous variable, men/women), and postal code (proxy for rural or urban settings) was applied to characterize patients by weight category. Following Canada Post's procedure for classification, residence in rural or urban areas was determined using the second digit of the first 3 digits practice's postal code (so-called forward sortation areas) assigning "rural" to those who had a value of zero and urban to those with other values. Network identification number (ID) was used to stratify patients attending practices belonging to different networks. The comorbidities measured at baseline included health conditions for which validated case definitions were developed by the CPCSSN: dementia, diabetes, osteoarthritis, hypertension, chronic obstructive pulmonary disease (COPD), Parkinson's disease, and epilepsy. The variable "comorbidities" was further categorized into two categories: 1) no comorbidities; 2) at least one comorbidity. The life-style variable "smoking status" had 66% of missing data and, therefore, was not retained for complete case (CC) analysis. The missing data for this variable

were subsequently imputed, and the analyses were repeated for the whole sample of patients with depression, with and without adjustment for smoking status.

Antidepressant prescription

Medications in the CPCSSN database are assigned World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes. Respectively, AD are assigned ATC NO6A code ("WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment," 2015). The first record of prescription of any of AD recommended by the most recent (2016) Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines (Kennedy et al., 2016) (Supplementary Table S5) during the study period was included in the analysis. There was no washout period for AD use, and our sample was a sample of prevalent users, including both current and new users of AD.

5.4.3. Statistical analysis

Sample description, overall and by weight categories

To characterize participants with life-time depression within each of the four weight categories and to compare their baseline socio-demographic and health characteristics, descriptive statistics were reported. Categorical variables were described using frequencies and percentages. Continuous variables were described using means and standard deviations or medians and interquartile ranges, as appropriate. As the primary purpose was data description, exploration and generation hypothesis, no confirmatory hypothesis tests were conducted. Focus was given on descriptive analysis, with an emphasis on the clinical importance of absolute differences and 95% confidence intervals (95% CI).

Evaluating prevalence of AD prescribing for patients belonging to different weight categories

Period prevalence of AD prescribing was calculated for patients with life-time depression belonging to different weight categories for the 2011-2016 period. The denominator was the number of patients in each of the four weight categories with life-time depression extracted from the CPCSSN database. The numerator comprised patients of the same weight category who were prescribed AD. The presence or absence of exposure to AD was established by evaluating if there was at least one prescription for any of the relevant AD (Supplementary Table S5) in 2011-2016. A subgroup analysis was performed for obese patients (BMI > 30 kg/m^2) according to the degree of obesity (classes I, II and III). Stratification by age groups, sex, and presence of at least one comorbidity was applied. Differences in frequency distributions and proportions were described numerically, including 95% CI, and were illustrated graphically.

Association of obesity status with prevalence of AD prescribing by regression analysis

The association between the obesity status and the prevalence of AD prescribing was examined in a multivariable logistic regression adjusting for age, sex, and comorbidities. The exposure variable "weight" was created with 4 categories: underweight, normal weight, overweight, and obese, with normal weight as a reference category. The outcome was prescribing at least one AD (yes/no). Age, sex, and comorbidities were included as a priori important clinical variables and were retained in the final model. Two types of regression models were applied: 1) logistic regression, without adjustment for network ID, to estimate a marginal national trend in prescribing; 2) mixed effects logistic regression model with random intercept and fixed effects, adjusting for clustering within networks.

Subgroup analysis for patients from different networks

Since different networks belong to different Canadian provinces that may have substantial differences in drug coverage and other factors, we performed a subgroup analysis to evaluate whether there is a consistency of the association between obesity status and AD prescribing prevalence between networks. To ensure consistency of data between network ID and Residence Postal Code, subgroup analysis was conducted for patients without missing data on Residence Postal Code variable (n=62020).

Imputing missing data for weight and smoking status

To evaluate the possible impact of missingness of data on weight and smoking status on the effect estimates, we applied multiple imputation by chain equations (MICE) to the total sample of patients with depression, using the "mice" package for the statistical program "R" version 3.5.2 (R Core Team, 2019). The number of imputed datasets was 5, and the Predictive Mean Matching ("pmm") method was applied to impute missing data for weight and smoking status. The following variables were used in the imputation model: age, sex, comorbidities, network ID. The five imputed datasets were then used to build the regression models for the associations between weight status and AD prescribing, and the obesity classes and AD prescribing. The results were then pooled, and the pooled effect estimates and 95%CI were reported and compared with the CC analysis.

5.5. Results

Data from 120,381 people with life-time depression who had an encounter with their PCP between June 2011 and June 2016 were extracted from the CPCSSN database.

5.5.1. Population characteristics.

Table 5.1. Characteristics of patients with depression belonging to different weight categories

	Weight category				Total N=63,830 n (%)
	Underweight, N=1,685 (2.6%) n (%)	**Normal weight N=23,188 (36.3%) n (%)**	**Overweight N=19,643 (30.8%) n (%)**	**Obese N=19,314 (30.5%) n (%)**	
Age					
mean (SD)	32.9 (17.2)	38.3 (15.9)	43.3 (15.5)	42.1 (14.5)	40.9 (15.6)
median (IQR)	25.4 (22.1)	35.3 (24.4)	42.4 (22.9)	40.9 (21.0)	39.3 (23.5)
Sex					
men	380 (22.6%)	5,569(24.0%)	6,982 (35.5%)	5,791 (30.0%)	18,722 (29.3%)
women	1,305 (77.5%)	17,619 (76.0%)	12,661 (64.5%)	13,523 (70.0%)	45,108 (70.7%)
BMI, first measure					
mean (SD)	17.5 (0.8)	22.2 (1.7)	27.3 (1.4)	36.1 (6.2)	27.8 (6.9)
median (IQR)	17.7 (1.1)	22.4 (2.8)	27.2 (2.4)	34.2 (6.6)	26.5 (8.1)
Comorbidities					
At least one comorbidity	126(7.5%)	1,884(8.1%)	2,451(12.6%)	3,891(20.2%)	8,352(13.1%)
COPD	38 (2.3%)	339 (1.5%)	302 (1.5%)	457 (2.4%)	1,136 (1.8%)
Dementia	19 (1.1%)	199 (0.9%)	235 (1.2%)	212 (1.1%)	665 (1.0%)
Diabetes	14 (0.8%)	314 (1.4%)	564 (2.9%)	1455 (7.5%)	2,347 (3.7%)
Epilepsy	48 (2.9%)	628 (2.7%)	618 (3.2%)	844 (4.4%)	2,138(3.4%)
Hypertension	40 (2.4%)	767 (3.3%)	1,418 (7.2%)	2,372 (12.3%)	4,597 (7.2%)
Osteoarthritis	21 (1.3%)	419 (1.8%)	630 (3.2%)	1,056 (5.5%)	2,126 (3.3%)
Parkinson	2 (0.1%)	38 (0.2%)	40 (0.2%)	33 (0.2%)	113 (0.2%)

BMI: Body mass Index

Of 120,381 patients with depression, 63,830 patients had complete data on BMI, sex, age, comorbidities, and prescribed medications and were included in the CC analysis. Their characteristics are shown in Table 5.1. Among the patients excluded from the CC analysis, 46.8% (56,387 patients) lacked the data on weight, 0.02% (29 patients) on sex, 64.2% (77,296 patients) on smoking, and 3.4% (4,087 patients) on postal codes.

The mean age of participants was 40.9 years (SD=15.6 years); the youngest group was underweight patients (32.9±17.2 (years)) and the oldest were obese (42.1±14,5 (years)) and overweight (43.3±15.5 (years)) patients. The mean age for normal weight group was 38.3±15.9 (years). The majority of the sample (70.7%; (95%CI [70.3, 71.0])) were women; the proportion of women versus men dominated in each weight category (Table 5.1).

The mean BMI for the sample was 27.8 (SD=6.9) kg/m^2, with 36.1 (SD=6.2) kg/m^2 in obese patients and 22.2 (SD=1.7) kg/m^2 in normal weight patients. Obese patients had a substantially higher prevalence of comorbidities (20.2%; (95%CI [19.6, 20.7])) than normal weight patients (8.1%; (95%CI [7.8, 8.5])). For the total sample, the most prevalent comorbidity was hypertension (7.2%; (95%CI [7.0, 7.4])), followed by diabetes (3.68%; (95%CI [3.5, 3.83])), epilepsy (3.4%; (95%CI [3.2, 3.5])) and osteoarthritis (3.3%; (95%CI [3.2, 3.5])). In obese patients, hypertension (12.3%; (95%CI [11.8, 12.8])) and diabetes (7.5%; (95%CI [7.2, 7.9])) were substantially more prevalent than for the whole sample.

5.5.2. Antidepressants prescribing.

Of the 63,830 patients with depression, 41,606 were prescribed at least one AD during the study period. Table 5.2 and Figure 5.1 describe the period prevalence of prescribing at least one AD within 2011-2016 for patients of different weight categories diagnosed with depression. The

prevalence of AD prescribing was higher among obese patients and overweight patients than among normal weight patients (Table 5.2). There was no difference in prescribing for underweight patients.

With regard to differences in sex for patients of different weight categories prescribed AD, the proportion of overweight women receiving AD was slightly higher than the proportion of women with normal weight prescribed AD; however, this difference was not clinically meaningful (Table 5.2). For obese and underweight patients, there was no difference in sex regarding AD prescribing. These patterns are demonstrated by a mosaic plot (Figure 5.2). The plot also shows that the distribution of weight categories (thickness of the bars) is different for men and women: the prevalence of normal weight patients is higher in women and the prevalence of overweight patients is higher in men.

Supplementary Table S6 shows socio-demographic and clinical characteristics for patients with AD prescriptions belonging to different weight categories. The lowest mean value for age was for the category of the underweight patients. The mean age of normal weight patients prescribed AD was 39.0±16.5 (years), and the mean age of obese patients with AD prescriptions was 42.8±14.8 (years). In all weight categories, mean age of those without AD prescriptions was lower than patients with prescriptions (data not shown). Supplementary Table S6 and Figure 5.3 illustrate differences in AD prescribing for patients of different weight categories and age groups. For all age groups, the proportion of obese patients with AD prescription was higher than the proportion of patients without AD prescriptions. This difference, however, is subtler for seniors (patients >65 years of age).

Patients who had at least one comorbidity had a higher prevalence of AD prescribing than patients without any comorbidities for all weight categories. Supplementary Table S6 and

Table 5.2. Prevalence of prescribing at least one AD to patients with depression, according to the weight category and sex

Weight group	Number of patients in the group	Prevalence of AD prescribing for each weight group		
		Number of patients with AD prescriptions	% prevalence	95% CI
Underweight	1,685	1,077	63.9	61.6, 66.2
Men	380	238	62.6	57.5, 67.5
Women	1,305	839	64.3	61.6, 66.9
Normal	23,188	14,476	62.4	61.8, 63.1
Men	5,569	3,535	63.5	62.2, 64.7
Women	17,619	10,941	62.1	61.4, 62.8
Obese	19,314	13,369	69.2	68.6, 69.9
Men	5,791	4,078	70.4	69.2, 71.6
Women	13,523	9,291	68.7	67.9, 69.4
Overweight	19,643	12,684	64.6	63.9, 65.2
Men	6,982	4,522	64.8	63.6, 65.9
Women	12,661	8,162	64.5	63,6, 65.3
Total	63,830	41,606	65.2	64.8, 65.6
Men	18,722	12,373	66.1	65.4, 66.8
Women	45,108	29,233	64.8	64.4, 65.3

AD: antidepressant medications; 95% CI: 95% confidence intervals

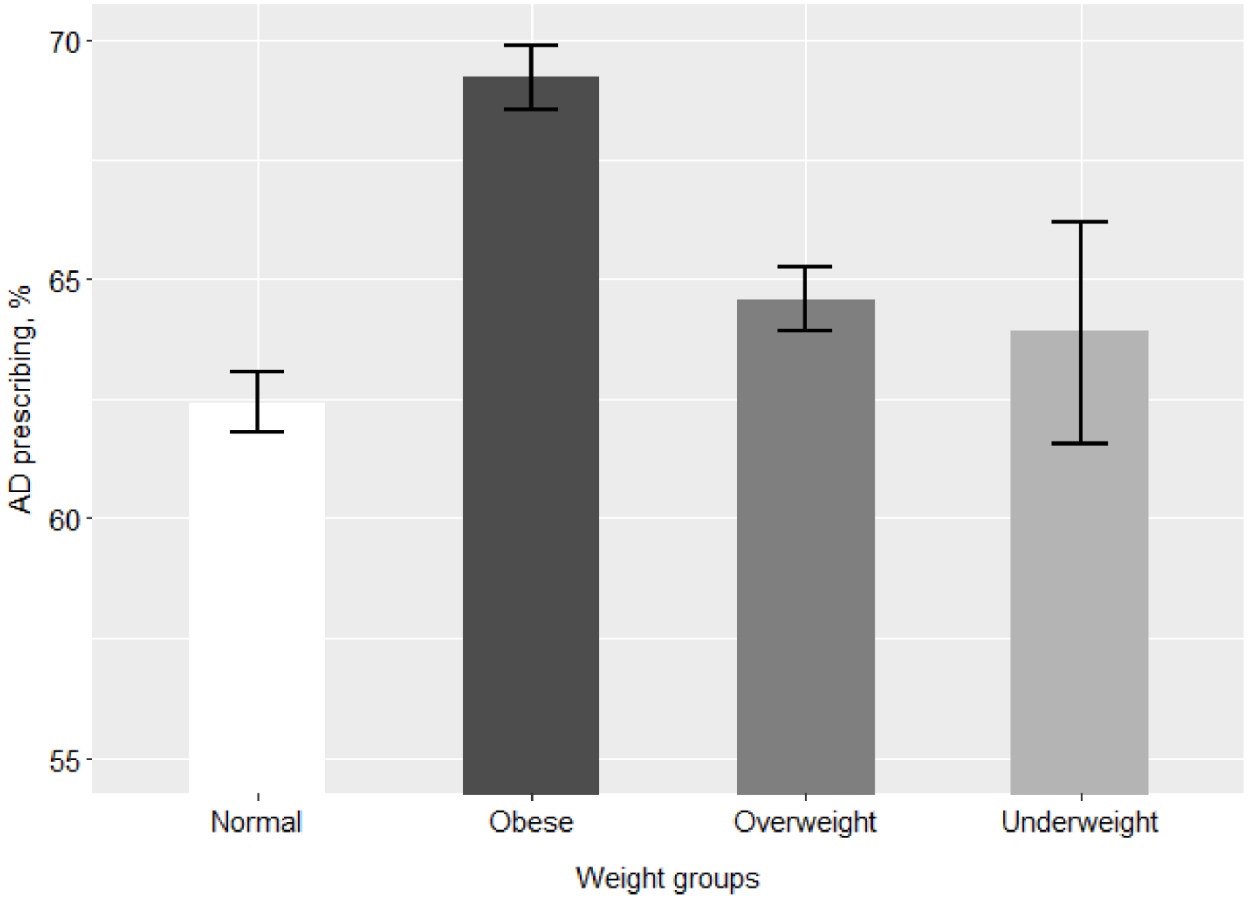

FIGURE 5 1. Prevalence of prescribing at least one AD among patients of different weight groups. AD: antidepressant medications. The bars represent % prevalence and 95% confidence intervals of prescribing at least one AD for patients of each weight group.

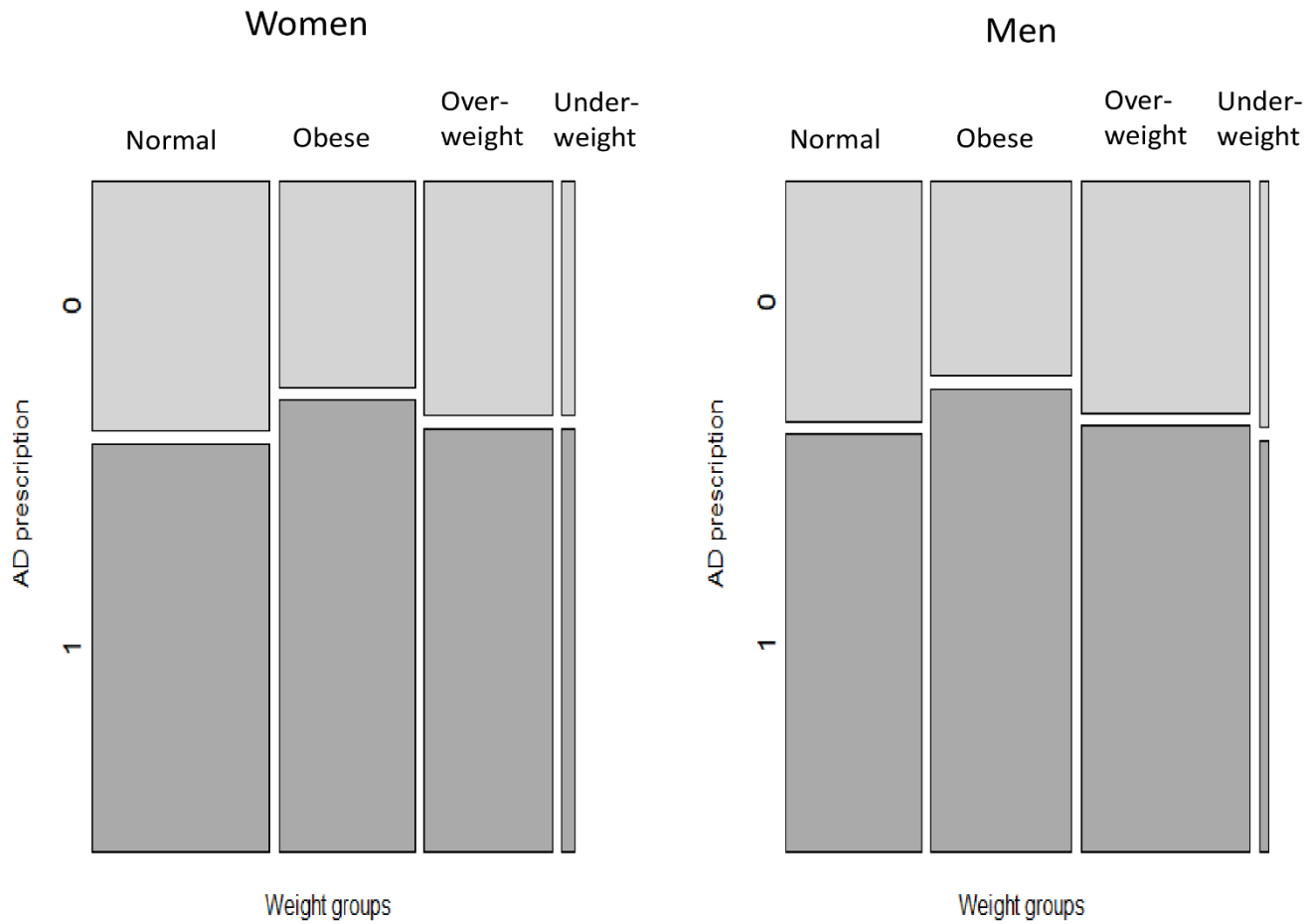

FIGURE 5.2. Prevalence of AD prescribing among patients of different weight categories, according to sex. AD: antidepressant medications. The bars (Normal, Obese, Overweight, Underweight) represent weight categories; thickness of the bars represent a proportion of patients in each weight category. Dark tiles represent proportions of patients with AD prescriptions ("1"), light tiles – proportions of patients without AD prescriptions ("0") in each weight category.

Supplementary Figure S1 also show that the proportion of patients with comorbidities (the thickness of the bars) was the highest in obese patients.

5.5.3. Associations between obesity status and AD prescribing

Table 5.3 shows crude and adjusted odds ratios for the association between the weight category and AD prescribing. After adjusting for covariates and clustering by network, obese patients were 17% more likely (95% CI:1.12, 1.22) and overweight patients were 5% more likely (95%CI: 1.00, 1.09) to receive AD prescriptions compared with normal weight patients. For underweight patients, the results were inconclusive. Seniors (patients > 65 years old) were 16% (95%CI: 1.07, 1.27) more likely to receive AD compared to the youngest patients (18-25 years old). Sex was not a significant predictor of prescribing after adjusting for other factors. Including the variable representing rural versus urban type of residence did not affect the results; therefore, this variable was not retained in the final multivariable model. Receiver operating characteristic (ROC) curve for the model is shown on Supplementary Figure S4 A.

After multiple imputation with MICE (Supplementary Table S7) for the total sample of 120,381 patients, there was not significant or substantial change in results. Likewise, there were no substantial or significant changes in the model after adjusting for smoking status (data not shown).

5.5.4. Subgroup analysis: AD prescribing for obese patients according to the obesity class.

Of 19,314 obese patients in our sample, 55.8% (10,782 patients) belonged to obesity class I, 25.2% (4,869) to obesity class II, and 19% (3,663) to obesity class III. There were fewer patients in obesity class I and more patients in higher obesity classes among women than among men

(Supplementary Figure S2, thickness of the bars). Supplementary Figure S2 show that higher proportions of men and women in higher obesity classes (II and III) received AD than patients in obesity class I.

Table 5.4 shows crude and adjusted odds ratios for the association between obesity class and AD prescribing, with and without adjustment for network clustering. After adjusting for comorbidities and clustering by networks, patients with obesity classes II were 8% more likely (95%CI: 1.00, 1.16) and patients with obesity class III were 6% (95% CI: 0.98, 1.16) more likely to receive AD. Neither sex nor age were important factors in the association between prescribing and obesity class after adjusting for other factors and clustering by networks. ROC curve for the model is shown on Supplementary Figure S4 B.

As compared to the CC analysis, after multiple imputation with MICE, there were no changes in neither effect estimate nor 95%CI for obesity class I, and there were non-substantial and non-significant changes for obesity classes II and III (Supplementary Table S8). No significant or substantial changes after adjusting for smoking status were observed (data not shown).

5.5.5. Prescribing by PCP from different networks

When the analysis was stratified by networks, all networks showed increased odds for patients with obesity, compared to normal weight patients, to receive AD prescriptions, with the exception of one network (Table 5.5, network E) for which the results were inconclusive.

5.5.6. The number of different AD types prescribed

Figure 5.4 shows the difference in prevalence of prescribing either 1, 2-3, or >3 AD types between patients with different weight categories with AD prescriptions. Compared with normal weight

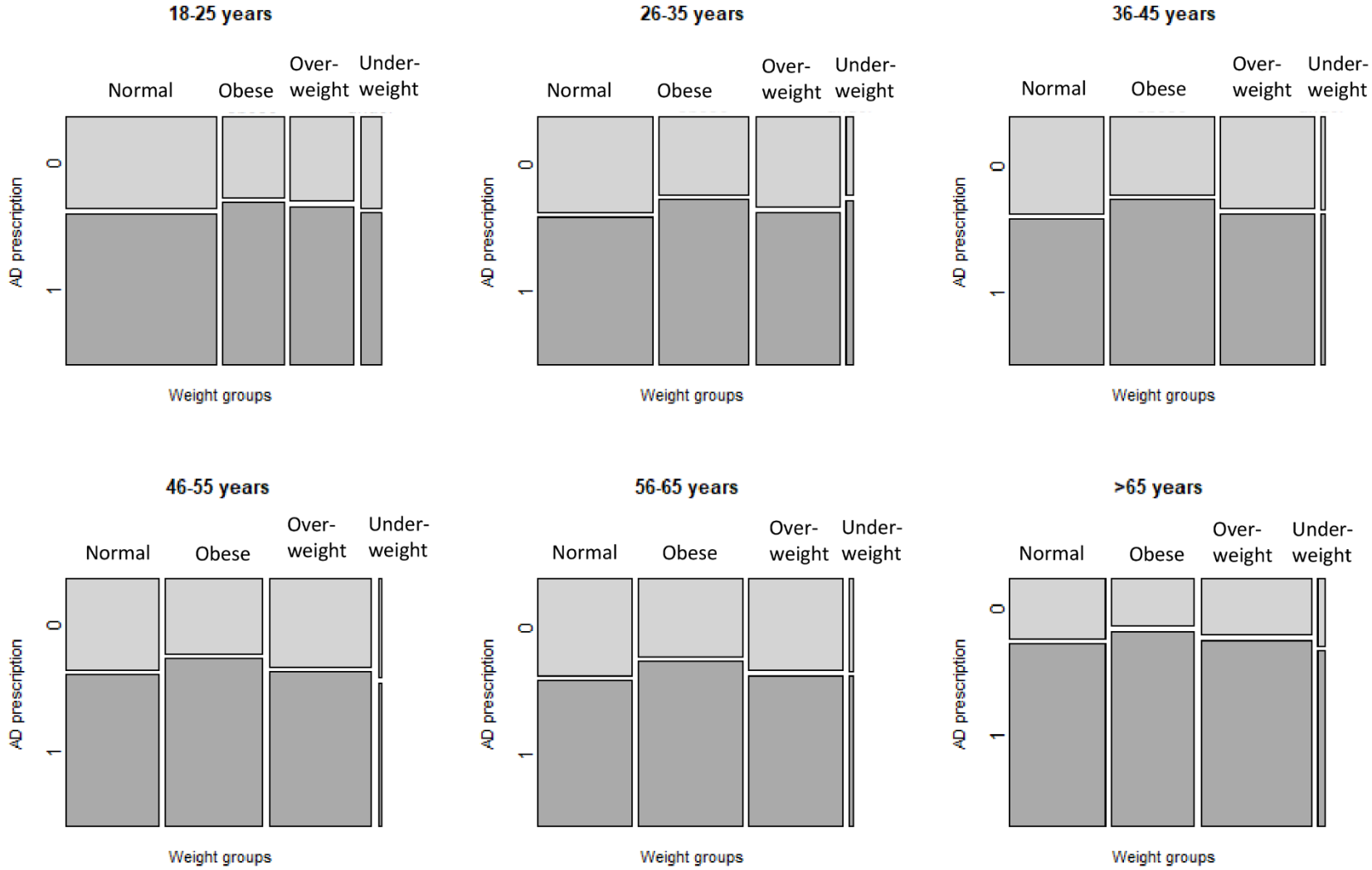

FIGURE 5.3. Prevalence of AD prescribing, according to weight category and age group. AD: antidepressant medications. Each mosaic plot represents an age group. The bars (Normal, Obese, Overweight, Underweight) represent weight categories; thickness of the bars represent a proportion of patients in each weight category. Dark tiles represent proportions of patients with AD prescriptions ("1"), light tiles– proportions of patients without AD prescriptions ("0") in each weight category.

Table 5.3. Univariable and multivariable logistic regression analyses of the association between patient's weight category and AD prescribing among CPCSSN patients with depression, adjusted for clustering by networks.

Variables	Weight category	Logistic regression, unadjusted to network ID				Mixed effects model with adjustment for clustering**	
		cOR	95%CI	aOR*	95%CI	aOR*	95%CI
Weight group	Normal weight (Ref)	1	-	1	-	1	-
	Underweight	1.07	0.96, 1.18	1.05	0.95, 1.16	1.02	0.91, 1.13
	Overweight	1.10	1.05, 1.14	1.06	1.02, 1.11	1.05	1.00, 1.09
	Obese	1.35	1.30, 1.41	1.23	1.18, 1.28	1.17	1.12, 1.22
Sex	Women (Ref)	1	-	1	-	1	-
	Men	1.06	1.02, 1.10	1.00	0.96, 1.04	0.98	0.95, 1.02
Age (years)	18-25 (Ref)	1	-	1	-	1	-
	25-35	0.99	0.94, 1.04	0.95	0.90, 1.00	1.00	0.95, 1.06
	35-45	0.99	0.94, 1.04	0.91	0.86, 0.96	0.98	0.93, 1.04
	45-55	1.06	1.00, 1.12	0.92	0.87, 0.97	0.98	0.93, 1.03
	55-65	1.18	1.11, 1.26	0.91	0.85, 0.97	0.94	0.88, 1.00
	>65	1.91	1.76, 2.06	1.13	1.04, 1.23	1.16	1.07, 1.27

Complete cases analysis.
AD: antidepressant medications; cOR: crude odds ratio; aOR: adjusted odds ratio.
*Adjusted also for the following comorbidities: hypertension, diabetes, epilepsy, osteoarthritis, COPD, Parkinson's disease, and dementia.
**Adjusted for clustering by networks.

Table 5.4. Univariable and multivariable regression analyses of the association between obesity class and AD prescribing among CPCSSN patients with depression and obesity.

Variables	Obesity class	Logistic regression, unadjusted to network ID				Mixed effects model with adjustment for clustering**	
		cOR	95%CI	aOR*	95%CI	aOR*	95%CI
Weight group	Class I (Ref)	1	-	1	-	-	-
	Class II	1.13	1.05, 1.22	1.10	1.02, 1.19	1.08	1.00, 1.16
	Class III	1.17	1.08, 1.28	1.10	1.01, 1.19	1.06	0.98, 1.16
Sex	Women (Ref)	1	-	1	-	-	-
	Men	1.08	1.01, 1.16	1.03	0.96, 1.10	1.01	0.95, 1.09
Age (years)	18-25 (Ref)	1	-	1	-	1	-
	25-35	1.06	0.95, 1.18	1.03	0.93, 1.14	1.07	0.96, 1.20
	35-45	1.06	0.96, 1.18	0.99	0.89, 1.10	1.05	0.95, 1.17
	45-55	1.13	1.01, 1.25	0.95	0.85, 1.06	1.00	0.89, 1.12
	55-65	1.33	1.18, 1.55	0.94	0.83, 1.07	0.97	0.85, 1.11
	>65	2.04	1.74, 2.40	1.09	0.92, 1.30	1.14	0.95, 1.36

Complete cases analyses.
AD: antidepressant medications; cOR: crude odds ratio; aOR: adjusted odds ratio.
*Also adjusted for comorbidities.
**Adjustment for clustering with networks as clusters.

Table 5.5. Multivariable logistic regression analyses of the association between patient's weight category and AD prescribing among CPCSSN patients with depression, according to networks

Network ID	***A***	***B***	***C***	***D***	***E***	***F***	***G***	***H***	***I***	***J***	***K***	***L***
aOR*;	1.08;	1.14;	1.14;	1.21;	0.69;	1.33;	1.15;	1.31;	1.26;	1.64;	1.26;	1.42;
95%CI	0.99,1.18	1.00,1.30	0.99,1.31	1.06,1.38	0.23,2.03	0.86,2.05	1.05,1.27	1.06,1.63	1.02,1.55	1.13,2.38	1.01,1.53	1.08,1.86

AD: antidepressant medications; aOR: adjusted odds ratio; 95% CI: 95% confidence intervals
*Adjusted to age, sex, and all comorbidities

patients, the prevalence of prescribing > 3 AD was higher in the obese category (7.3% (95%CI [6.8, 7.7]) than in the normal weight category (5.6% (95%CI [5.2, 6.0])). Likewise, the prevalence of prescribing 2-3 AD was higher in the obese category (36.6% (95%CI [35.8, 37.5]) than in the normal weight category (32.7% (95%CI [31.9, 33.5]). Conversely, prevalence of prescribing only one AD was lower in obese patients (56.1% (95%CI [55.3, 56.9]) than in normal weight patients (61.7% (95%CI [60.9, 62.5]). This pattern seems to be more prominent in women than in men as demonstrated by the mosaic plots on Supplementary Figure S3.

The smooth surface plot on Figure 5.5 shows how the number of AD types prescribed changes between different BMIs in relation to age. Each horizontal line on the plot corresponds to an age group. As the figure shows, the number of different AD types increases with an increase in BMI for young patients. For middle aged patients, this relationship is less prominent. For old patients with a very high BMI, the number of AD types prescribed to a patient decreases.

5.6. Discussion

In our study, we evaluated the prevalence of AD prescribing among primary care patients with depression in Canada belonging to different weight categories in eight Canadian provinces and one territory, and we examined the association of prescribing prevalence with obesity status and with obesity class. We observed that primary care patients with obesity were more likely to receive pharmacological treatment for depression than normal weight patients, with the highest odds for morbidly obese patients (classes II and III), and that a greater proportion of obese patients received prescriptions for a high number (more than three) of different AD types than did normal weight patients. These relationships are not modified by sex but may depend on patient's age.

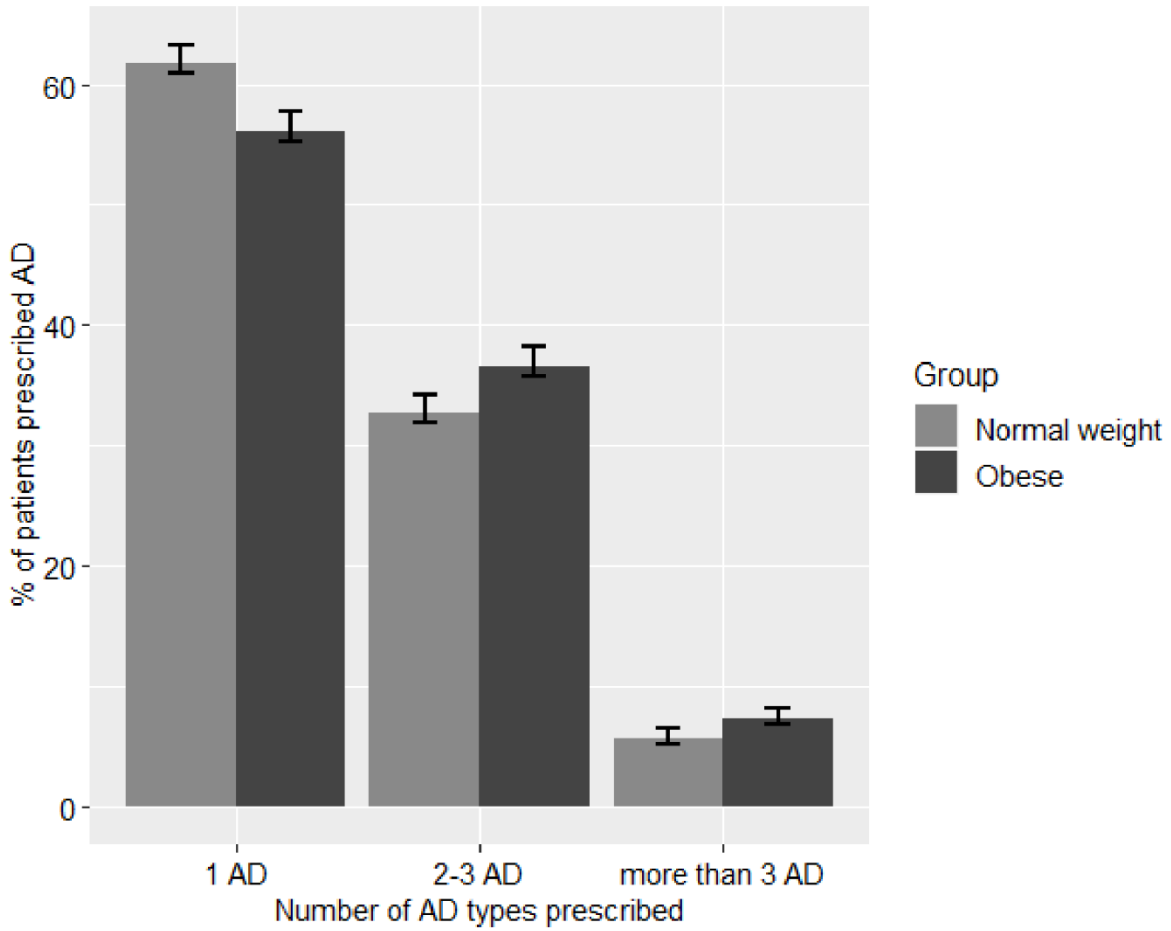

FIGURE 5.4. Number of different AD types prescribed to patients with obesity and normal weight patients. AD: antidepressants medications. The bars represent % prevalence and 95% confidence intervals of prescribing 1, 2, or >3 different types of AD for either obese or normal weight categories.

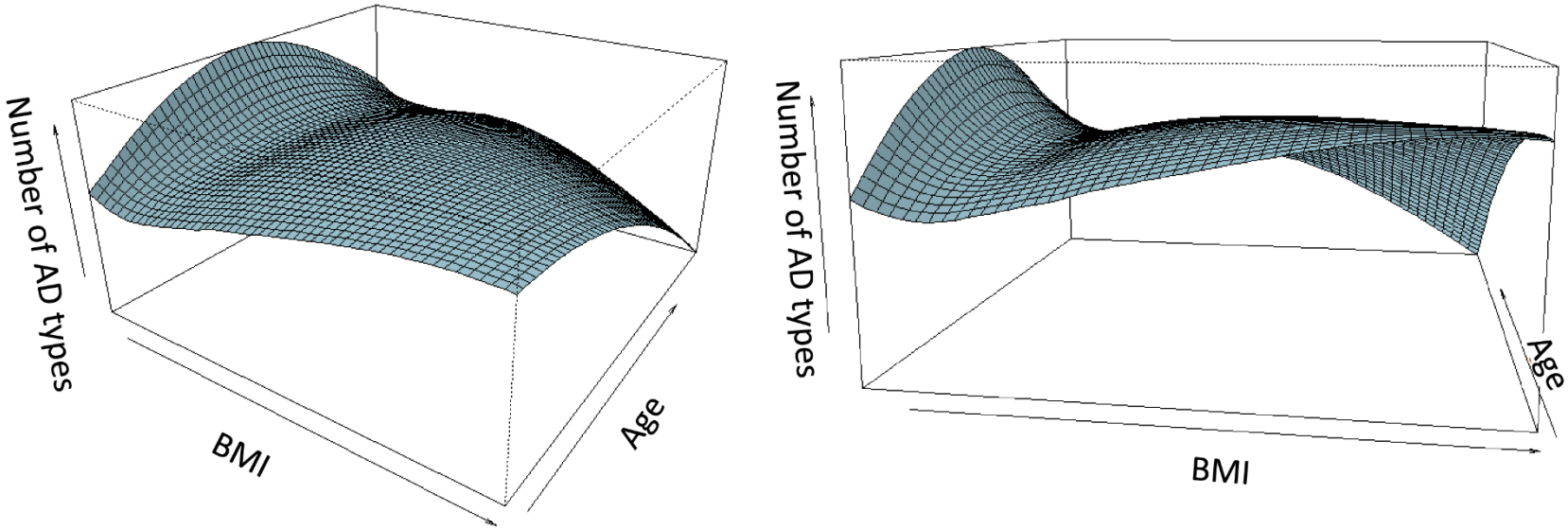

FIGURE 5.5. Number of different AD types prescribed to a patient, in relation to BMI and age. AD: antidepressant medications; BMI: body mass index. Two different views (at different angles) of the same smooth surface plot are presented. The plot represents relationships between the number of different AD types prescribed to a patient, patient's BMI, and patient's age. Each horizontal line represents an age group. For young patients, the number of different AD increases with increasing BMI. For middle aged patients, the relationship is close to U-shaped. For old patients, the number of AD types prescribed decreases with an increase in BMI.

Our results are in line with the studies conducted in the UK and the USA ("The impact of obesity on drug prescribing in primary care," 2005; Kit et al., 2012) which also reported high prevalence of AD prescribing in obese patients with depression. One of our main findings was that, after adjusting for covariates and clustering by networks, people with depression and comorbid obesity were 17% (95% CI [1.12,1.22]) more likely than normal weight patients to receive pharmacological treatment with AD. Despite differences between the networks, possibly related to the socio-demographic characteristics and beliefs of patients and doctors between provinces, as well as to the differences in drug insurance coverage and access to medical help, nationwide in Canada, obese patients with depression were more likely to be prescribed pharmacological treatment using AD. For only one network, the results were inconclusive, probably due to the small number of patients.

It is still unclear whether these findings reflect more severe form of depression in patients with obesity that requires pharmacological treatment, or the attitudes and beliefs of PCP that lead them to prescribe pharmacological treatment to people with obesity more often than to normal weight patients. In support of the former, obesity was associated with more severe depression (McElroy, 2015; Opel et al., 2015; Pratt & Brody, 2014), especially in extremely obese patients (Noh et al., 2015). Patients with obesity may need dose adjustment and a longer treatment duration to reach the same level of response as non-obese patients (Kloiber et al., 2007; Oskooilar et al., 2009; Papakostas et al., 2005; Puzhko et al., in press 2020). Since our population is a population of prevalent users and our analysis is cross-sectional, longer treatment duration for obese patients may have contributed to the prevalence of both obesity and AD prescribing in this group.

It is possible, however, that obesity bias contributes to this pattern of treatment: obese patients may be considered by some PCP as unmotivated and non-adherent to recommendations

for behavioral changes (Forhan & Salas, 2013) and, therefore, less likely to respond to psychotherapy. Therefore, they prescribe medications. In support of this hypothesis, it has been previously reported that obese patients in the USA were less likely to receive psychotherapy as a treatment for a new depression episode (Boudreau et al., 2013), possibly due to the health providers and/or patients' bias on the efficacy of counseling in obese patients (Boudreau et al., 2013). It is known that negative attitudes towards obese patients can influence decision-making by medical professionals and impact the care they provide (Phelan et al., 2015; M. B. Schwartz et al., 2003). Rejection of certain treatments for obese patients in different countries worldwide has become a problem highlighted by several studies (Eyal, 2013; Goldberg, 2013). Moreover, it has been recently shown in a qualitative study (Seymour et al., 2018) that health professionals who had weight bias "used less teaching discourse" for obese patients and started them on pharmaceutical therapies sooner. Qualitative studies are needed to find out whether health professionals often go straight to prescribing pharmacological therapy to obese patients, bypassing the psychotherapy option. Such behavior is particularly important to combat because of the obesogenic properties of AD which can increase the risk for patients with class I to be "promoted" to higher obesity classes.

Of importance, patients with high obesity classes are more likely to have multiple comorbidities (Lebenbaum et al., 2018) and higher mortality rates (Flegal et al., 2013). In addition, they are more likely to suffer from the obesity stigma leading to low self-esteem (Wu & Berry, 2017) and are at increased risk for depressed mood (Chen et al., 2007; Fettich & Chen, 2012; Mooney & El-Sayed, 2016). In our study, patients with morbid obesity had higher odds of receiving AD. This may be attributed to their elevated risk for more severe depression that needed pharmacological treatment. On the other hand, it can be attributed to the higher prevalence of obesity bias towards morbidly obese patients (Green et al., 2017; Jha et al., 2018).

These reasonings, however, should be considered with caution: the cross-sectional nature of our study (our study design was limited by the database restrictions) does not allow us to account for the temporality of findings. We cannot state with certainty whether AD were initially prescribed to obese patients or if prescribing AD contributed to a greater proportion of obese patients with AD prescriptions. The latter possibility, however, is of equal concern, since utilization of AD may contribute to increasing the risk of a long-term weight gain at the population level, moving normal weight and overweight patients to the obesity group (Gafoor et al., 2018). It has been reported that at least 1.5% of the obesity rate increase among young adults in the USA during the last two decades can be explained by the increase in the prevalence of depression and AD use (Wehby & Yang, 2012). Of note, even though the receiver operating (ROC) curves did only show moderate predictive capability for our model (Supplementary Figure S4), our purpose was not to predict prescribing. The statistical models were employed to establish direction and magnitudes of associations between obesity (and other important patient's characteristics), and prescribing. The relatively low model prediction accuracy indicates that other important predictors (e.g., type and severity of depression, physicians' preferences etc.) need to be included for better predictive capacity, this will require further research.

Another important finding was an increased prevalence of prescribing a high number of different AD types by PCP to obese patients compared with normal weight patients. It is possible that patients with obesity have more complex disease with a number of specific features that require concurrent prescribing of more than one AD. It may also be explained by a greater prevalence of treatment resistant depression in this population (Rizvi et al., 2014) requiring a high number of switches from one AD to another. Resistance to treatment with AD in obese patients with depression may be caused by an interplay of multiple factors. One of them may be the reduced

bioavailability of AD, the drugs with a relatively high lipophilicity, due to excess of adipose tissue in obese patients (Hiemke, 2008; Ostad Haji et al., 2012). This may lead to lower plasma concentrations and, potentially, an attenuated therapeutic effect. In addition, contributing roles of inflammatory cytokines (Forsythe et al., 2008; Haroon et al., 2018; Jha et al., 2017; Jha et al., 2018; Lindqvist et al., 2017) and adipokines (Banks, 2012; Scabia et al., 2018; Schilling et al., 2013), as well as genetic factors (Hu et al., 2015; Jin et al., 2010; Kirchheiner et al., 2003; Klenke et al., 2011) were proposed. These players may have an impact on drug metabolism and dysregulation of hypothalamic pituitary axes and cell signalling pathways which modifies the response to therapy. Different response to certain groups and types of AD in patients with excess weight, as compared to normal weight patients, was reported in several studies and described in two recent reviews (Puzhko et al., in press 2020; Woo et al., 2016). Our findings, therefore, may reflect physicians' difficulties with selection of an effective AD medication for obese patients with depression.

Of note, the relationships between the number of different AD types prescribed and patient's BMI may depend on age, as illustrated by the smooth surface plot on Figure 5.5. For very young patients, in general, the number of prescribed AD types increases with the increase of BMI. This may reflect particular difficulties with a choice of AD to treat depression requiring a high number of switches in people with excess weight at a young age. This observation deserves further evaluation since certain types of AD were shown to be associated with the increased risk of suicides in this particular age group (Barbui et al., 2009; Dragioti et al., 2019; Fazel et al., 2007); therefore, choosing the most effective AD without a high number of switches may help decrease this risk. For middle aged patients, the relationship between AD number and BMI is less prominent. Moreover, for this age group, the relationship is close to U-shaped, with higher number

of AD types prescribed to people with a very low and a very high BMI. This observation may reflect difficulties with the choice of appropriate medication not only in the obese but also in the underweight group that warrants corresponding investigation. Contrary to the youngest group, for older participants, the number of prescribed AD types decreases with the increase of BMI. Old patients with obesity may have higher number of comorbidities and receive higher number of different medications, compared with their younger counterparts. Therefore, PCP may try to avoid concurrent prescribing of more than one AD type to the elderly to decrease the probability of side effects of drug-drug interactions due to polypharmacy, which is in line with the guidelines on AD prescribing in older population (Gelenberg et al., 2010). Of note, patients of the oldest group (>65 years old) were more likely to receive at least one AD prescription, compared with the youngest group of patients, even when the odds ratio for age was adjusted for the obesity status. Considering that our sample includes prevalent users, these results, at least in part, can be related to the fact that older patients are more likely to have relapses and may be less likely to reach an adequate response to treatment than their young counterparts (Gelenberg et al., 2010).

Our results suggest that obesity may be one of the important factors that require an individualized approach to pharmacological treatment of depression in all age groups. Recent evidence on different responses to certain AD in obese patients compared with normal weight patients (Green et al., 2017; Jha et al., 2018; Khan et al., 2007; Kloiber et al., 2007; Oskooilar et al., 2009; Uher et al., 2009; Woo et al., 2016) can not be disregarded. Currently, there are no guidelines but there are several recent studies and reviews that contain clinically relevant information on the difference in response to certain AD in patients with obesity and with certain obesity classes (Green et al., 2017; Iniesta et al., 2016; Jha et al., 2018; Uher et al., 2009). There are also published detailed recommendations on how to avoid the weight-increasing effect of AD

(Aronne & Segal, 2003; Blumenthal et al., 2014; Chiwanda et al., 2016; Gafoor et al., 2018; Hasnain & Vieweg, 2013; Kachur et al., 2005; Lee et al., 2016; Thomas L Schwartz et al., 2007; Serretti & Mandelli, 2010; Wehby & Yang, 2012). Of note, it has been shown in a recent RCT that patients with morbid obesity may benefit from certain AD and AD combinations (Green et al., 2017; Jha et al., 2018) and, therefore, require individualized approach to treatment. These recommendations, however, are not included in the guidelines, and, therefore, may be unknown to a wide community of primary care physicians. All this evidence needs to be synthetized and appraised so that experts can consider whether its quality and strength allows the addition of obesity-specific recommendations to the guidelines. Our results show that the risk of adverse effects due to drug-drug interactions in obese patients at increased risk for polypharmacy seems to be accounted for only when prescribing different AD types for older patients but not in the young or the middle-aged group. Better guidelines on the individualized selection of AD for patients with depression and comorbid obesity would help optimize AD treatment in obese patients with depression and may help decrease the number of adverse effects due to drug-drug interactions.

Our study has certain strength and limitations. First, the CPCSSN depression detection algorithm detects life-time depression, precluding one from distinguishing between prevalent or incident cases. In line with this limitation, our study has a cross-sectional design, and we discussed our findings in the light of the limitations of a cross-sectional study. Second, the information on socioeconomic status (SES) is not recorded in the CPCSSN database; therefore, we were not able to adjust our models for it. We, however, were able to adjust for the urban/rural residency as a proxy of SES, using postal codes. One of the limitations is that the information on type and severity of depression, as well as a number of important lifestyle variables, such as diet and exercising, are not recorded in the database making it impossible to adjust for these salient variables. Another

potential confounder which we could not adjust for due to the lack of reliable information in our database is the diagnosis of an eating disorder in a patient with depression. Certain eating disorders are indications for AD prescribing. Including patients with eating disorders who maintained normal weight in our reference (i.e., normal weight) group could lead to underestimation of the association between obesity and prescribing AD for depression. If a substantial proportion of patients with eating disorders (e.g., bulimia nervosa, binge eating or night eating) were obese or overweight, this could lead to overestimating the association between excess weight and prescribing AD for depression. Most often, however, people with eating disorders are either underweight or have normal weight (Hay, 2020). In addition, prevalence of eating disorders among adult primary care patients is low in Canada (Langlois et al., 2011), and we do not expect a substantial proportion of patients with this diagnosis in our sample. Therefore, the confounding effect of this variable is not likely to have a substantial impact on our results. In addition, pregnant women or patients with cancer who can experience substantial weight changes, were not excluded as identifying them in the CPCSSN database was not feasible. This could also have confounded our results. Finally, one of the serious limitations of our study was a high proportion of missing data on weight in our database, as well as on smoking status. To deal with this problem, we used the MICE technique to impute missing data and re-evaluated associations between excess weight and AD prescribing, and the obesity classes and AD prescribing, to compare with the CC analysis. This sensitivity analysis showed that the size of effect estimates became slightly smaller for the dataset with the imputed data for weight and did not change substantially after adjusting for the smoking status, but the associations kept the same directions and the level of significance.

5.7. Conclusion

In summary, this was the first study to evaluate differences in prevalence and patterns of prescribing AD between obese and normal weight patients, and between patients with different classes of obesity in Canadian primary care. We also describe the association between AD prescribing and obesity, using a large national primary care dataset. It is also the first study to demonstrate consistency in the direction of this association between different networks participating in CPCSSN, showing uniformity of the association across Canadian provinces. In terms of methodology, this was, to our knowledge, the first study where the MICE technique was applied to deal with the substantial proportion of missing data on important clinical variables, such as weight and smoking status, in the national CPCSSN database. Higher prevalence of AD prescribing and prescribing high number of AD to obese patients compared with normal weight patients in all provinces of Canada raises a public health concern. Longitudinal studies are required to evaluate how AD prescribing patterns, including prescribing individual AD groups and types, can be related to obese patient's general health and subsequent heath care utilization. Focus should be on the AD types known for their risk of weight gain and the types that were shown non-effective or less effective for patients with obesity in recent publications. Stakeholders and experts may want to revise the evidence to add recommendations on a different approach to AD selection for patients with obesity, especially for patients with obesity II and III classes. To obtain stronger evidence, more studies should be conducted to evaluate the response to individual AD drugs in obese patients.

5.8. Acknowledgements

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

The datasets generated for this study are available on request to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by The Institutional Review Board of McGill University. Written informed consent for participants was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SP was primary investigator and conducted the research under the supervision of TS and GB. All authors contributed on the methods and interpretation of results. The text was written by SP and revised by the other authors.

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5.9. References

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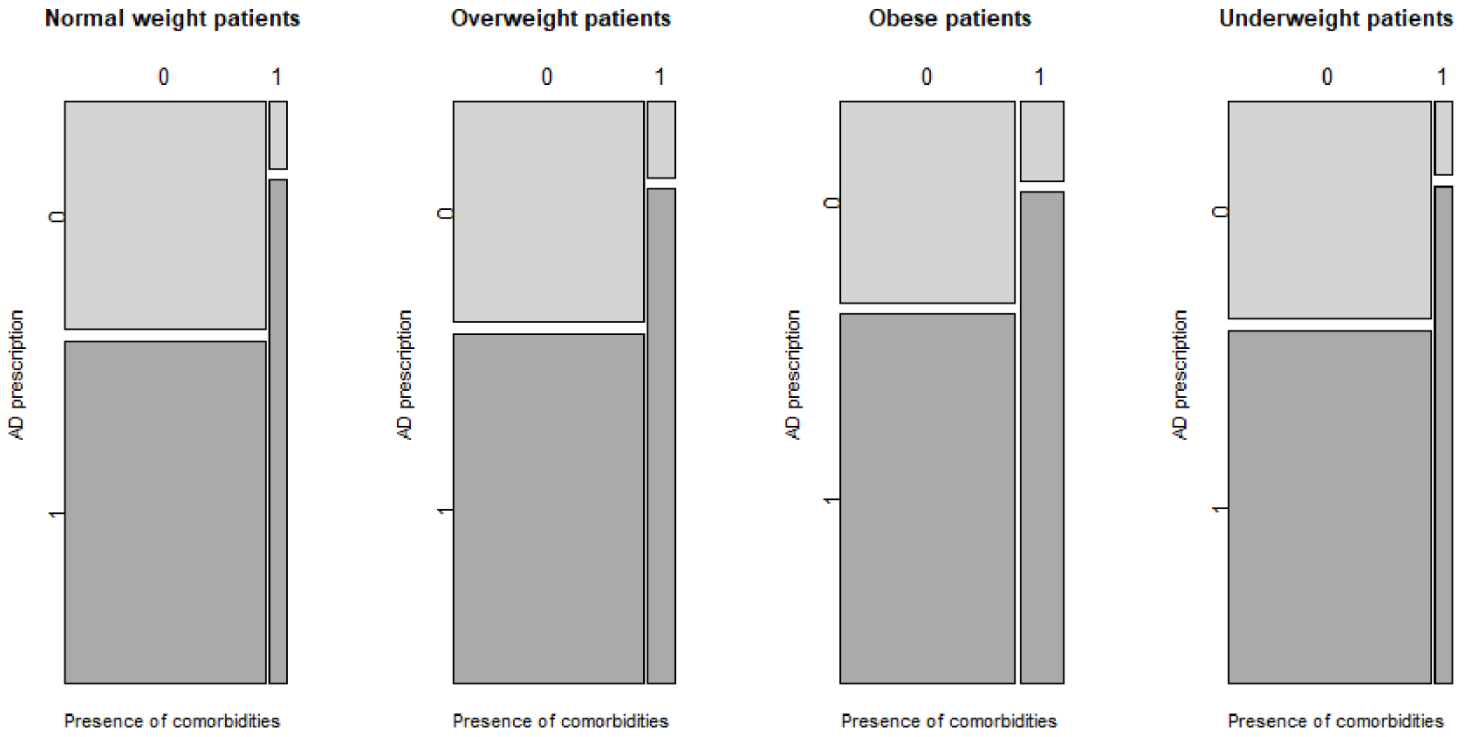
5.10. Supplemental material

5.10.1

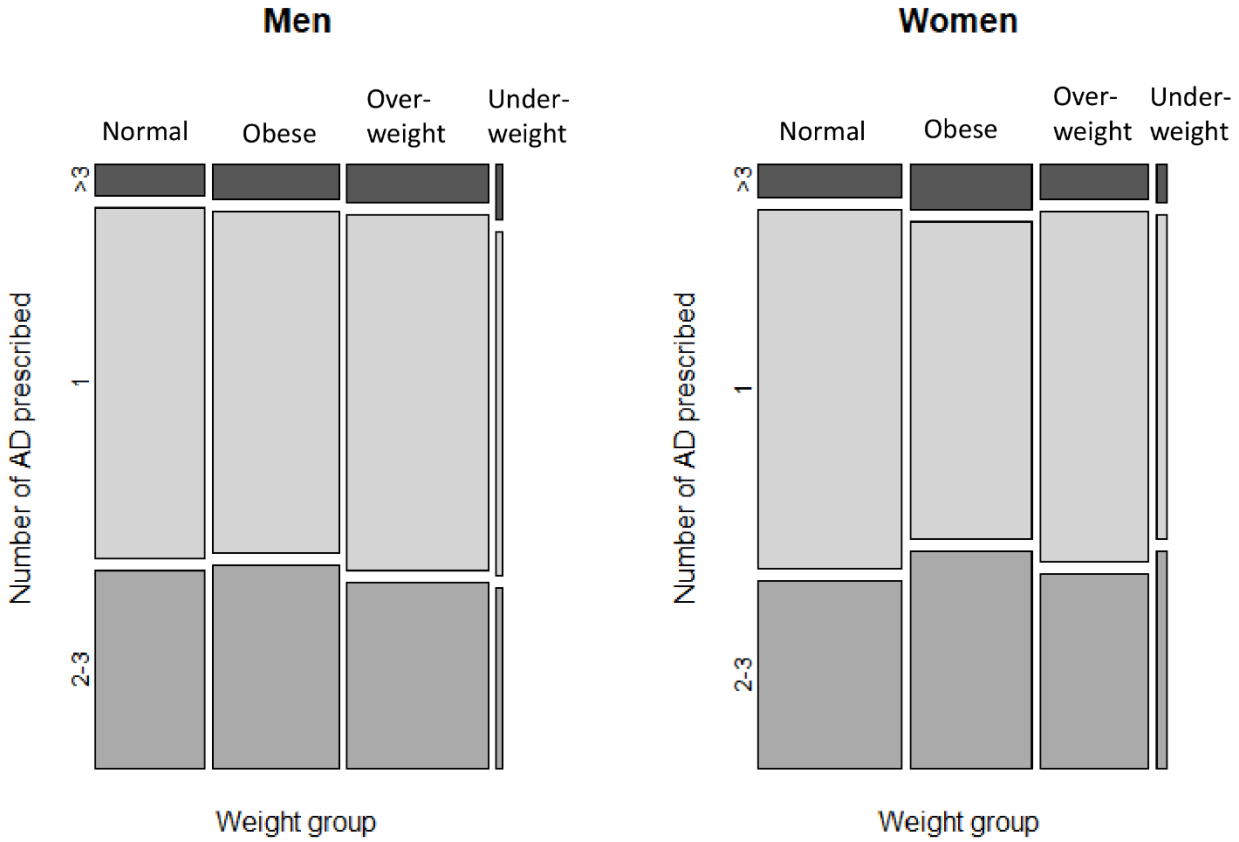


Supplementary Figure S1 Prevalence of AD prescribing for patients of different weight categories, with and without comorbidities. AD: antidepressant medications. Four mosaic plots represent four weight categories. Vertical bars represent proportion of patients with ("1") and without ("0") a comorbidity; thickness of the bars represent a proportion of patients in each category. Dark tiles represent proportions of patients with AD prescriptions ("1"), light tiles – proportions of patients without AD prescriptions ("0") for each category according to the presence or absence of comorbidities.

5.10.2

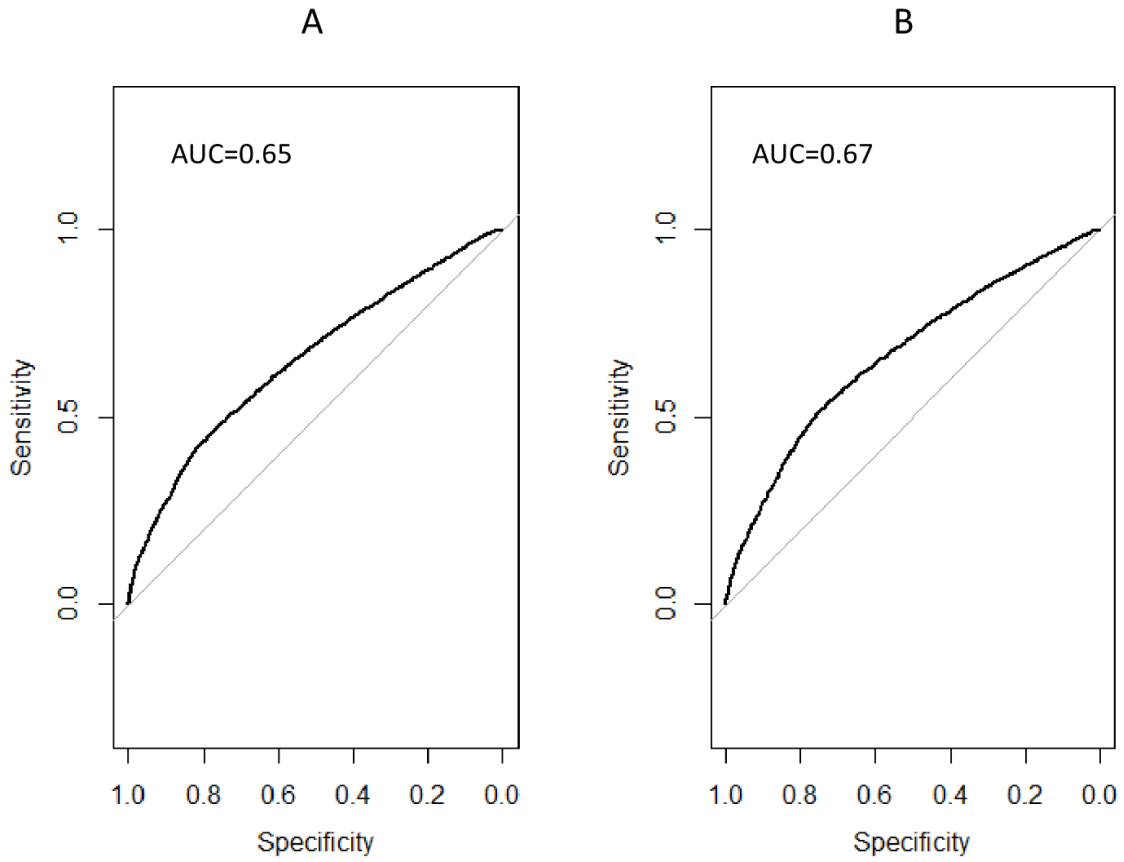
Supplementary Figure S2 Prevalence of AD prescribing among patients of different obesity classes, according to sex. AD: antidepressant medications. The bars (I, II, and III) represent obesity classes I, II, and III; thickness of the bars represent a proportion of patients in the obesity class. Dark tiles represent proportions of patients with AD prescriptions ("1"), light tiles – proportions of patients without AD prescriptions ("0") in each obesity class.

5.10.3



Supplementary Figure S3 Proportions of patients with prescriptions for 1, 2-3, and more than 3 different types of AD, according to weight and sex. AD: antidepressant medications. The bars (Normal, Obese, Overweight, Underweight) represent weight categories; thickness of the bars represent a proportion of patients in each weight category. Black tiles represent proportions of patients with prescriptions of >3 AD types; dark grey tiles – proportions of patients with prescriptions of 2-3 AD types, light grey tiles represent proportions of patients with prescriptions of only one AD type.

5.10.4



Supplementary Figure S4 Receiver Operating Characteristic (ROC) curves for the mixed effects logistic regression models, adjusted for clustering by network. A. Mixed model for the association between patient's weight category and AD prescribing among patients with depression. B. Mixed model for the association between obesity class and AD prescribing among patients with depression and obesity. AD: antidepressant medications. AUC: Area Under the Curve

5.10.5. Supplementary Table S5. Antidepressant medications included in the analysis.

Medications for depression	
Class	**Type**
Selective Serotonin Reuptake Inhibitors (SSRI)	Escitalopram, citalopram, sertraline, fluoxetine, paroxetine, fluvoxamine
Serotonin-norepinephrine reuptake inhibitors (SNRI)	Venlafaxine, duloxetine, desvenlafaxine
Tricyclic antidepressants (TCA)	Amitriptyline, nortriptyline, doxepin, imipramine, clomipramine, desipramine, trimipramine, amoxapine,
Tetracyclic antidepressant	Maprotiline
Norepinephrine and specific serotonergic antidepressants (NaSSA)	Mirtazapine
Norepinephrine-dopamine reuptake inhibitors (NDRI)	Bupropion
Serotonin antagonist reuptake inhibitors (SARI)	Trazodone, nefazodone, vilazodone, vortioxetine
Second-generation “atypical” antipsychotic	Quetiapine
Irreversible Monoamine oxidase (MAO) inhibitors	Phenelzine, tranylcypromine
Reversible inhibitor of MAO-A	Moclobemide

5.10.6. Supplementary Table S6. Characteristics of patients prescribed AD, according to weight categories

Characteristics	**Weight category**				**Total N=63,830 n (%)**
	Underweight, N=1,685 (2.6%)	**Normal weight N=23,188 (36.3%)**	**Overweight N=19,643 (30.8%)**	**Obese N=19,314 (30.3%)**	
	AD+ N=1,077 (63.9%) n (%)	**AD+ N=14,476 (62.4%) n (%)**	**AD+ N=12,684 (64.6%) n (%)**	**AD+ N=13,369 (69.2%) n (%)**	**AD+ N=41,606 (65,2%) n (%)**
Age					
mean (SD)	33.4 (17.5)	39.0(16.5)	44.0 (16.0)	42.8 (14.8)	41.6(16.0)
median (IQR)	26.0 (22.1)	35.7 (25.4)	43.0 (23.5)	41.6 (21.6)	39.9(24.2)
Gender					
Men	238 (22.1)	3535 (24.4)	4,522 (35.7)	4,078 (30.5)	12,373(29.7)
Women	839 (77.9)	10,941 (75.6)	8,162 (64.4)	9,291 (69.5)	29,233(70.3)
BMI, first measure					
mean (SD)	17.4 (0.8)	22.2 (1.7)	27.3 (1.4)	36.2 (6.2)	28.1(7.1)
median (IQR)	17.6 (1.2)	22.4 (2.8)	27.2 (2.5)	34.3 (6.7)	26.8(8.4)
Comorbidities					
At least one comorbidity	110(10.2)	1,665(11.5)	2,129(16.8%)	3,353(25.08)	7257(17.4)
COPD	31 (2.9)	306 (2.1)	279 (2.2)	407 (3.0)	1023(2.5)
Dementia	17 (1.6)	177 (1.2)	214 (1.7)	188 (1.4)	596(1.4)
Diabetes	14 (1.3)	273 (1.9)	496 (3.9)	1247 (9.3)	2030(4.9)
Epilepsy	45 (4.2)	582 (4.0)	577 (4.6)	769 (5.8)	1973(4.7)
Hypertension	34 (3.2)	672 (4.6)	1,220 (9.6)	2,041 (15.3)	3967(9.5)
Osteoarthritis	17 (1.6)	372 (2.6)	538 (424)	903 (6.8)	1830(4.4)
Parkinson	2 (0.2)	35 (0.2)	37 (0.3)	29 (0.2)	103(0.25)3

AD: antidepressant medications; BMI: Body mass Index

5.10.7. Supplementary Table S7. Univariable and multivariable regression analyses of the association between patient's weight category and AD prescribing among CPCSSN patients with depression, adjusted for clustering with Networks as clusters. MICE analysis

Variables	**Weight Category**	**Logistic regression, unadjusted to network ID**				**Mixed effects model with adjustment for clustering****	
		cOR	**95% CI**	**aOR***	**95% CI**	**aOR***	**95% CI**
Weight group	Normal weight (Ref)	1	-	1	-	1	-
	Obese	1.20	1.14, 1.26	1.14	1.08, 1.21	1.13	1.07, 1.19
	Overweight	1.07	1.03, 1.11	1.04	1.00, 1.08	1.03	0.99, 1.08
	Underweight	1.04	0.93, 1.15	1.05	0.94, 1.16	1.03	0.93, 1.15
Sex	Women (Ref)	1	-	1	-	1	-
	Men	1.02	0.99, 1.04	0.98	0.95, 1.00	0.98	0.95, 1.00
Age (years)	18-25 (Ref)	1	-	1	-	1	-
	25-35	1.07	1.03, 1.11	1.04	1.00, 1.08	1.06	1.02, 1.10
	35-45	1.09	1.05, 1.13	1.02	0.98, 1.06	1.05	1.01, 1.09
	45-55	1.14	1.10, 1.19	1.02	0.98, 1.07	1.04	1.00, 1.08
	55-65	1.24	1.18, 1.30	0.98	0.95,1.05	1.01	0.96, 1.06
	>65	1.71	1.63, 1.81	1.11	1.05, 1.18	1.09	1.03, 1.16

AD: antidepressant medications; cOR: crude odds ratio; aOR: adjusted odds ratio; 95% CI: 95% confidence intervals; MICE: multiple imputations by chained equations

*Adjusted also for the following comorbidities: hypertension, diabetes, epilepsy, osteoarthritis, COPD, Parkinson disease, and dementia;

**adjusted for clustering by networks

5.10.8. Supplementary Table S8. Univariable and multivariable regression analyses of the association between obesity class and prescribing of AD among CPCSSN patients with depression and obesity. MICE analysis

Variables	Obesity class	Logistic regression, unadjusted to network ID				Mixed effects model with adjustment for clustering**	
		cOR	95%CI	aOR*	95%CI	aOR*	95%CI
Weight group	Class I (Ref)	1	-	1	-	-	-
	Class II	1.12	1.04, 1.19	1.09	1.02, 1.17	1.08	1.01, 1.16
	Class III	1.11	1.02, 1.21	1.05	0.95, 1.16	1.03	0.93, 1.13
Sex	Women (Ref)	1	-	1	-	-	-
	Men	1.01	0.95, 1.07	0.98	0.92, 1.03	0.98	0.93, 1.03
Age (years)	18-25 (Ref)	1	-	1	-	1	-
	25-35	1.13	1.00, 1.27	1.10	0.98, 1.23	1.11	0.99, 1.24
	35-45	1.12	1.00, 1.26	1.06	0.94, 1.19	1.08	0.96, 1.22
	45-55	1.19	1.07, 1.32	1.04	0.93, 1.16	1.05	0.94, 1.17
	55-65	1.32	1.16, 1.49	1.02	0.94, 1.22	1.02	0.89, 1.17
	>65	1.71	1.52, 1.93	1.07	0.92, 1.04	1.05	0.92, 1.19

AD: antidepressants; cOR: crude odds ratio; aOR: adjusted odds ratio; 95% CI: 95% confidence intervals; MICE: multiple imputations by chained equations

*Also adjusted to comorbidities; **adjustment for clustering by networks

CHAPTER 6: DIFFERENCE IN PATTERNS OF PRESCRIBING ANTIDEPRESSANTS KNOWN FOR THEIR WEIGHT-MODULATING AND CARDIOVASCULAR ADVERSE EFFECTS FOR PATIENTS WITH OBESITY COMPARED TO PATIENTS WITH NORMAL WEIGHT (MANUSCRIPT 3)

6.1. Preamble

In my second manuscript, I demonstrated the differences in prescribing AD to patients of different weight groups who suffer from depression. I also showed a higher prevalence of AD prescribing to people with obesity as compared to their normal weight counterparts. It remained, however, unclear whether PCPs prescribed AD more often to patients with excess weight or the patients' weight status changed to "obesity" during the treatment due to obesogenic adverse effects of certain AD. Up to the moment of my study's initiation, prescribing of obesogenic AD to patients with excess weight had not been studied in Canada. It was particularly important to investigate this topic since some obesogenic AD also exert cardiovascular adverse effects. These adverse effects can especially be detrimental in patients with excess weight, who already are at risk for cardiovascular complications.

In my third manuscript, I addressed the above-mentioned problems by examining the associations between the obesity status and prescribing of AD, which are known for their obesogenic and cardiovascular adverse effects. The temporality of associations was insured by including only the patients from the national primary care cohort who had had their BMI measured before the first AD prescription. I have also applied the machine learning algorithm, random forest, to evaluate the importance of weight as a variable in predicting the prescription of individual AD types across Canadian provinces. My results suggest that while PCPs appear to consider the patient's weight when selecting an AD for depression treatment, patients with obesity are still more likely to be prescribed certain AD with obesogenic and cardiovascular

adverse effects than patients with normal weight. My study highlighted the need for quantitative longitudinal studies to examine whether the excess weight, in fact, modifies the association between prescribing obesogenic AD and health outcomes.

Title: Difference in patterns of prescribing antidepressants known for their weight-modulating and cardiovascular adverse effects for patients with obesity compared to patients with normal weight

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6.2. Abstract

Background: Patients with depression and comorbid obesity may be more prone to weight modulating and cardiovascular adverse effects of selected antidepressants (AD). It is important to ascertain whether these AD prescriptions differ by patient weight status.

Methods: Canadian Primary Care Sentinel Surveillance Network **(**CPCSSN) electronic medical records were used. Participants were adults with depression prescribed an AD in 2000-

2016, with weight categories established before the first prescription. Logistic regression and mixed effects models were applied to examine associations between obesity and AD prescribing, adjusted for sex, age, and comorbidities. Machine learning algorithm random forest (RF) was used to evaluate the importance of weight in predicting prescribing patterns.

Results: Of 26,571 participants, 72.4% were women, mean age was 38.9 years (standard deviation (SD)=14.2) and mean BMI 27.0 kg/m^2 (SD=6.5); 9.5% had ≥ 1 comorbidity. Patients with obesity, compared to normal weight patients, were more likely to receive bupropion (adjusted odds ratio (aOR) 1.24, 95%CI: 1.09,1.42), fluoxetine (aOR 1.14, 95%CI : 0.97,1.34), and amitriptyline (aOR 1.13, 95%CI : 0.93,1.36), and less likely to receive mirtazapine (aOR 0.55, 95%CI : 0.44,0.68) and escitalopram (aOR 0.88, 95%CI : 0.80, 0.97). RF analysis showed that weight was among the most important predictors of prescribing patterns, equivalent to age and more important than sex.

Conclusions: AD prescribing patterns for patients with obesity appear to be different for selected AD types, including AD known for their weight-modulating and cardiovascular adverse effects. Longitudinal studies are needed to examine whether these prescribing patterns are associated with significant health outcomes.

6.3. Introduction

Depression and obesity are both serious medical conditions that bring a substantial health and economic burden (Druss et al., 2000; Jantaratnotai et al., 2017). This includes significant morbidity, reduced functioning, poor quality of life, and increased mortality (Wang et al., 2003). The overall prevalence of life-time depression in Canada was estimated at 11.3% (Pearson et al., 2013) and obesity at 26% (Roberts et al., 2012) in 2012, with a higher prevalence of depression in patients with obesity (Jantaratnotai et al., 2017). According to the data from the Canadian Community Health Survey (2005), obesity was associated with an approximately 30% increase in depression prevalence (Chen et al., 2009). Moreover, the ongoing global Covid-19 pandemic has contributed to further increases (Dozois, 2020). Even though patients with obesity constitute a substantial proportion of patients with depression, they are often excluded from Randomized Controlled Trials (RCTs) due to comorbidities associated with obesity (Martin-Rodriguez et al., 2015). Therefore, it is unclear whether depression treatment guidelines, which are largely based on these RCTs, can be generalized to patients with obesity. In recent decades, efforts have been made to personalize treatment of depression (Iniesta et al., 2016; Perlis, 2013) but most algorithms do not include body weight. It is unclear if standard treatment approaches are applicable to patients with depression and comorbid obesity as they may respond in an unpredictable fashion to certain AD medications (Puzhko, Aboushawareb, et al., 2020; Woo et al., 2016), with either attenuated or heightened response to individual ADs, especially in situations of severe obesity. This may be due, among several possible reasons, to changes in the distribution of lipophilic AD in people with excessive adipose tissue; low-grade inflammation associated with obesity; leptin resistance, developed through various mechanisms, that can be specific to AD type; genetic polymorphism in transporters, drug metabolizing enzymes, and/or neurotransmitter receptors; or the presence of comorbid medical conditions (Puzhko, Aboushawareb, et al., 2020). Another consideration

is that certain ADs have obesogenic (weight-increasing) (McIntyre et al., 2015) and/or cardiovascular adverse effects (Beach et al., 2014) and may be less suitable for this population.

In the absence of specific guidelines on AD prescribing for patients with depression and comorbid obesity, the extent to which patient weight status is considered in prescribers' decision making is unclear. Worldwide, very few studies have investigated physician's decisions on AD prescribing for patients with depression and excess weight (Boudreau et al., 2013; Gafoor et al., 2018; Tyrer et al., 2020). A US study (Boudreau et al., 2013) reported that mirtazapine (an obesogenic AD) was less likely to be prescribed to patients with high BMI than to normal weight patients. A UK study suggested, however, that utilization of AD may be contributing to population-level increases in excess weight (Gafoor et al., 2018). In a more recent study using primary care data in the UK, fluoxetine (a non-obesogenic AD with a slight weight-reducing effect) and mirtazapine were amongst the ADs most commonly prescribed to patients with obesity and depression (Tyrer et al., 2020). To our knowledge, no studies using Canadian data have been published, therefore it is not clear which trend might be predominant. Most AD prescriptions in Canada are issued by primary care physicians (PCP) who usually diagnose and manage depression (Craven et al., 2013). In a recent study (Puzhko, Schuster, et al., 2020) that used national electronic medical records (EMR) data, it was demonstrated that the prevalence of AD prescribing was higher for patients with depression and comorbid obesity in Canadian primary care, compared with their normal weight counterparts, and that patients with obesity received a higher number of different AD types. The authors were unable, however, to make any conclusions on the temporality of this association. In the present study, we used national primary care data to evaluate whether prescribing of AD differs by patient weight category, when weight is measured and documented before the first AD prescription. We focused on ADs known for their weight-modulating (weight gain or weight loss) (Gill et al., 2020; Serretti et al., 2010) and cardiovascular (changes in heart rate, coronary heart disease,

arrythmia, myocardial infarction) (Almog et al., 2018; Biffi et al., 2017; Dietle, 2015; Nezafati et al., 2015) adverse effects, specified in Table 1.

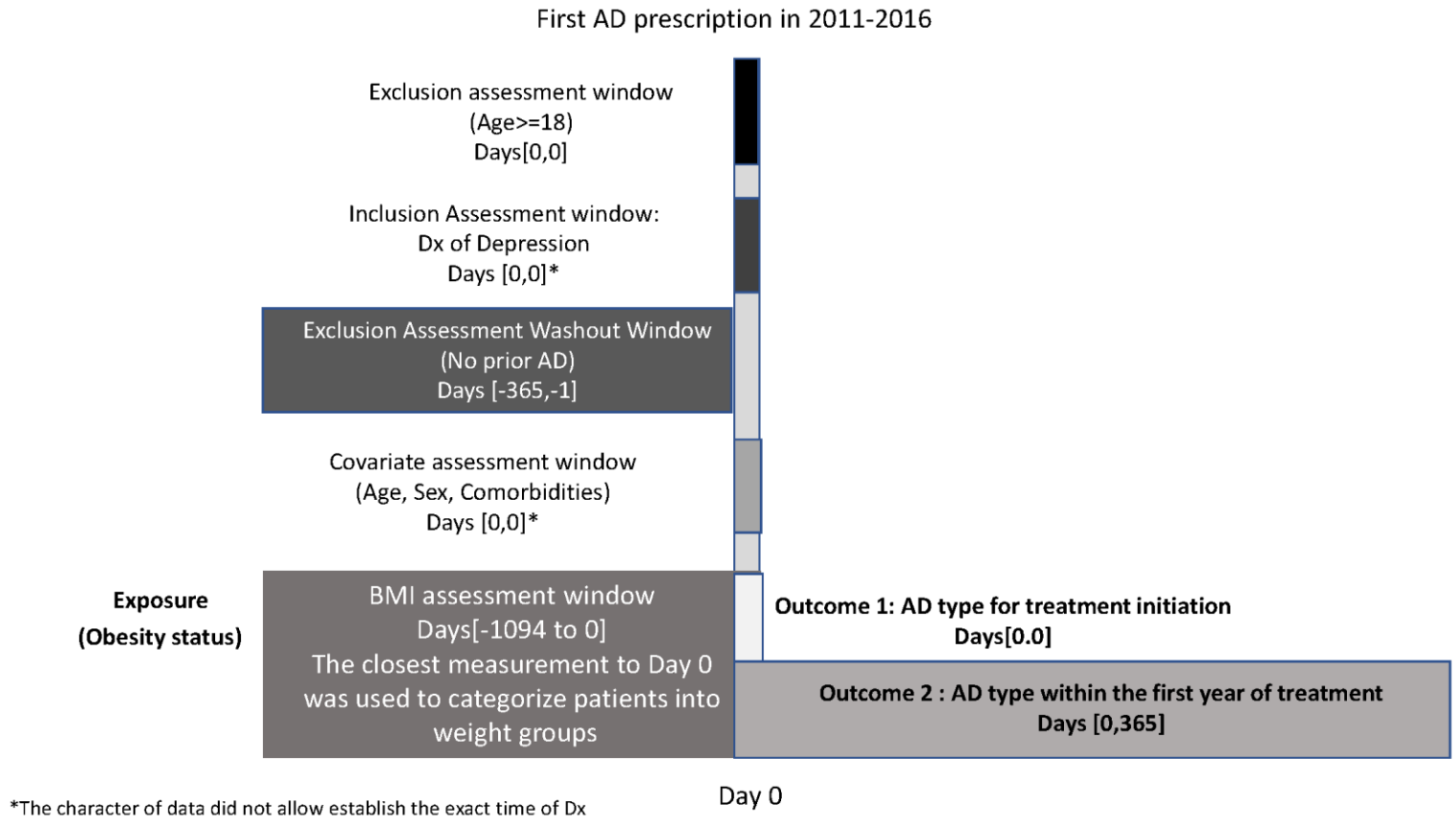
6.4. Methods.

6.4.1. Data source and study population

The Canadian Primary Care Sentinel Surveillance Network **(**CPCSSN) is a large pan-Canadian multi-disease electronic medical records' surveillance system for primary care. It combines de-identified primary care patients' EMR data from 12 primary care practice-based research networks across Canada, including 8 provinces and 1 territory (Queenan et al., 2016; Rigobon et al., 2015). By May 2016, approximately 1200 sentinels from more than 200 practices contributed their records to CPCSSN for over 1.5 million patients. CPCSSN contains reliable data for patients' weight and height (Rigobon et al., 2015) measured by health professionals. This database over-represents older adults and under-represents young adult males (Queenan et al., 2016); however, it is representative of the general care-seeking Canadian population.

For this study, a sample of adult new AD users with prescriptions issued in 2000-2016 was extracted (Figure 6.1). First, patients with depression who received any AD prescription during July 1, 2000-June 30, 2016 were identified. To select patients with depression, a CPCSSN definition of depression and a validated case detection algorithm (Williamson et al., 2014) were applied. The algorithm combines information from patients' problem list (Encounter Diagnosis Codes, used by some providers/sites to record the information on diagnosis, prescription records, and billing [Billing Diagnosis Codes, used by other providers/sites to record the information on diagnosis]). This algorithm detects life-time depression (Williamson et al., 2014), including acute depression episode and a history of depression, with a sensitivity of 81.1% (95%CI: 77.2–85.0) and a specificity of 94.8%

Figure 6.1. Sample extraction: primary care patients with depression registered with CPCSSN receiving antidepressants in 2000-2016



(95%CI: 93.7–95.9) (Williamson et al., 2014). Next, the first AD prescription during the study period was identified, and a washout period of 1 year (no AD prescriptions during 365 days before the first prescription) was applied. This approach aimed to exclude patients without an acute depressive episode. The sample was then restricted to adult patients (≥18 years on the day of the first prescription) who had valid data on height and weight measured ≤3 years prior to the first prescription.

6.4.2. Measures

BMI and weight category

BMI was calculated as body weight in kilograms divided by the square of the height in meters. When multiple BMI measures were available, we used the record closest to the first prescription of an AD. Patients' weight was categorized using WHO and Health Canada standards: <18.5kg/m^2 = underweight, 18.5 kg/m^2 to 24.99 kg/m^2 = normal, 25 kg/m^2 to 29.99 kg/m^2 = overweight, ≥30 kg/m^2 = obese. Extreme outliers (70 kg/m^2 < BMI <15 kg/m^2) representing values outside plausible ranges were excluded.

Socio-demographic and health data

Patients' age at the time of the first prescription (continuous variable), sex (men/women), and postal code (a proxy for rural or urban settings) were used to characterize patients. Comorbidities measured at baseline included health conditions for which validated case definitions were developed by the CPCSSN: dementia, diabetes, osteoarthritis, hypertension, chronic obstructive pulmonary disease (COPD), Parkinson's disease, and epilepsy. The variable "comorbidities" was categorized as none versus ≥ 1 comorbidity.

Antidepressant prescription

Medications in the CPCSSN database are assigned World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes. ADs were assigned the corresponding ATC NO6A code ("WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment," 2015). The prescription of any of the ADs recommended by the most recent (2016) Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines (Kennedy et al., 2016) during the study period was included in the descriptive analysis and random forest models. For seven ADs, known either for their weight-modulating or cardiovascular adverse effects (Table 1), the association with obesity status was examined.

6.4.3. Statistical analysis

Association of obesity status with a type of AD prescribing

The association between weight category and prescribing of certain AD types was examined in a multivariable (MVR) regression analysis adjusting for age, sex, and presence of at least one comorbidity. Two outcomes were examined: 1) prescribing a specific type of AD (yes/no) for treatment initiation; 2) prescribing a specific type of AD (yes/no) within 12 months from the time of the first prescription, including the first prescription. The 12-month period corresponds to the average duration of acute (3 months) and maintenance (9 months) treatment as recommended in the Canadian guidelines (Kennedy et al., 2016). Two types of conditional regression models were applied: 1) logistic regression; and 2) mixed effects logistic regression with random intercept and fixed effects, adjusting for clustering within networks. A series of models were built for seven different types of ADs, most known for their weight-modulating and/or cardiovascular adverse

effects: amitriptyline, mirtazapine, bupropion, fluoxetine, paroxetine, citalopram, and escitalopram. The reported confidence intervals were adjusted for multiple testing by Bonferroni correction (Weisstein, 2004).

Table 6.1. Obesogenic and cardiovascular adverse effects of antidepressants

AD class	AD	Weight changes*	Cardiovascular complications**
TCA	Amitriptyline	Substantial weight gain	Arrhythmia (high risk), myocardial infarction, coronary heart disease, ischemic heart disease, sudden death (Almog et al., 2018; Biffi et al., 2017)
SSRI	Citalopram	Weight neutral or weight gain	Arrythmia (high risk)
	Escitalopram	Weight neutral or weight loss	Arrythmia (high risk, debated to be lower risk than citalopram)
	Fluoxetine	Weight neutral or weight loss	Arrythmia (low risk)
	Paroxetine	Substantial long-term weight gain	Arrythmia (low risk)
NaSSA	Mirtazapine	Substantial weight gain	Arrythmia (debated to be high risk), changes in heart rate (Nezafati et al., 2015)
NDRI	Bupropion	Weight loss	-

AD: antidepressants; TCA: Tricyclic antidepressants; SSRI: *Selective serotonin reuptake inhibitors;* NaSSA: *Noradrenergic and specific serotonergic antidepressants;* NDRI: Norepinephrine–dopamine reuptake inhibitors.
*Risk for weight changes based on (Gill et al., 2020; Serretti et al., 2010)
**Risk for arrythmia (QT prolongation) based on (Dietle, 2015)

Evaluating the importance of weight group, age, sex, and comorbidities in predicting prescribing AD type using random forest

The importance of the variable "weight category" among other potential predictors of prescribing AD type was evaluated using a machine learning approach, random forest (RF) (Breiman, 2001). Importance of a certain variable in the model was determined by computation of the mean decreased accuracy (MDA) of a variable. MDA shows the difference in prediction accuracy before and after removing the variable from the model (Strobl et al., 2007). Using the R package "Random Forest", the number of trees was set to 1000 and the number of variables considered at each split ("mtry") was 2. MDA was illustrated graphically.

All data manipulations were conducted using SAS 9.4; further analyses were done in R, version 3.5.2 (Team et al., 2019).

6.5. Results

6.5.1. Population characteristics

The final cohort included 26,571 patients suffering from depression who were new users of AD, had their BMI measured within 3 years before the date of the first AD prescription, and had complete data on BMI, age, comorbidities, and prescribed medications (Figure 6.2, Table 6.2).

6.5.2. Prevalence of AD prescribing

The prevalence of AD prescribing is illustrated in Supplementary Figure S3. The most prescribed AD medications for patients of all weight groups (prescribed to more than 20% of patients) were selective serotonin reuptake inhibitors (SSRI) citalopram and escitalopram (Supplementary Figure S3).

6.5.3. Association of AD prescribing with weight category

Figure 6.3 shows associations of AD types prescribed within the first year after initiation of treatment by weight category for patients with obesity, compared to normal weight patients. Associations for choice of AD to initiate treatment with weight category for obese patients were similar in magnitude and direction (Supplementary Table S1). *Positive associations:* Bupropion and fluoxetine were substantially more likely to be prescribed to patients with obesity in both regression models. The associations of amitriptyline prescribing with obesity status were also substantial, even though confidence intervals were consistent with the null value in both models. *Negative associations:* Patients with obesity were substantially less likely to receive mirtazapine in both models.

Regarding escitalopram, a strong negative association between obesity status and escitalopram prescribing was observed in MVR (aOR 0.88, 95%CI: 0.0.80, 0.97) model. This association became less prominent in the mixed effects model, with confidence intervals consistent with the null value (OR 0.95, 95%CI: 0.86, 1.05). For all seven ADs, the effect estimates and confidence intervals were consistent between the unadjusted (data not shown) and MVR models for all ADs, except escitalopram, after taking clustering on networks into account. No difference in prescribing patterns between patients with obesity and normal weight patients was observed for citalopram and paroxetine.

6.5.4. Post-hoc analysis for escitalopram prescribing

Analysis of prevalence stratified by provinces. Of all seven ADs, only escitalopram had a substantial difference in the aOR between MVR and mixed effects models (Figure 6.3). Therefore, further analysis for this AD was undertaken. The descriptive analysis of prescribing prevalence

Figure 6.2. Flow chart of patient population

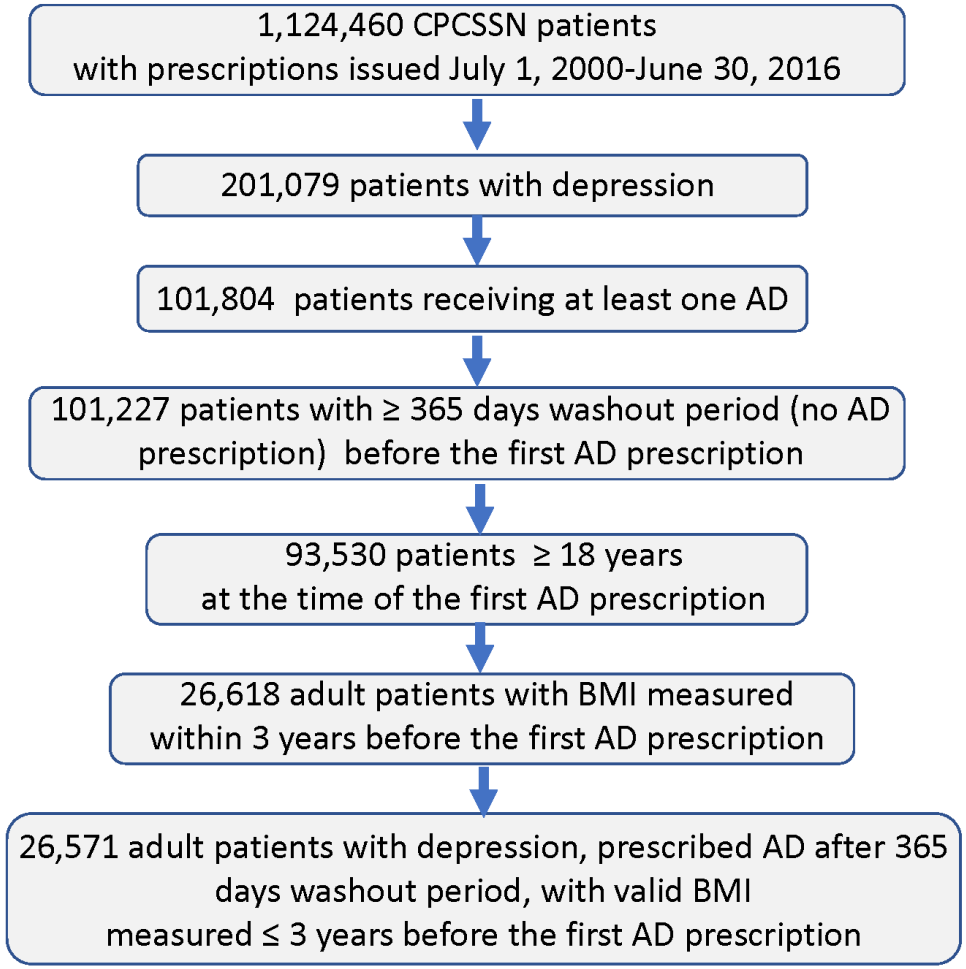
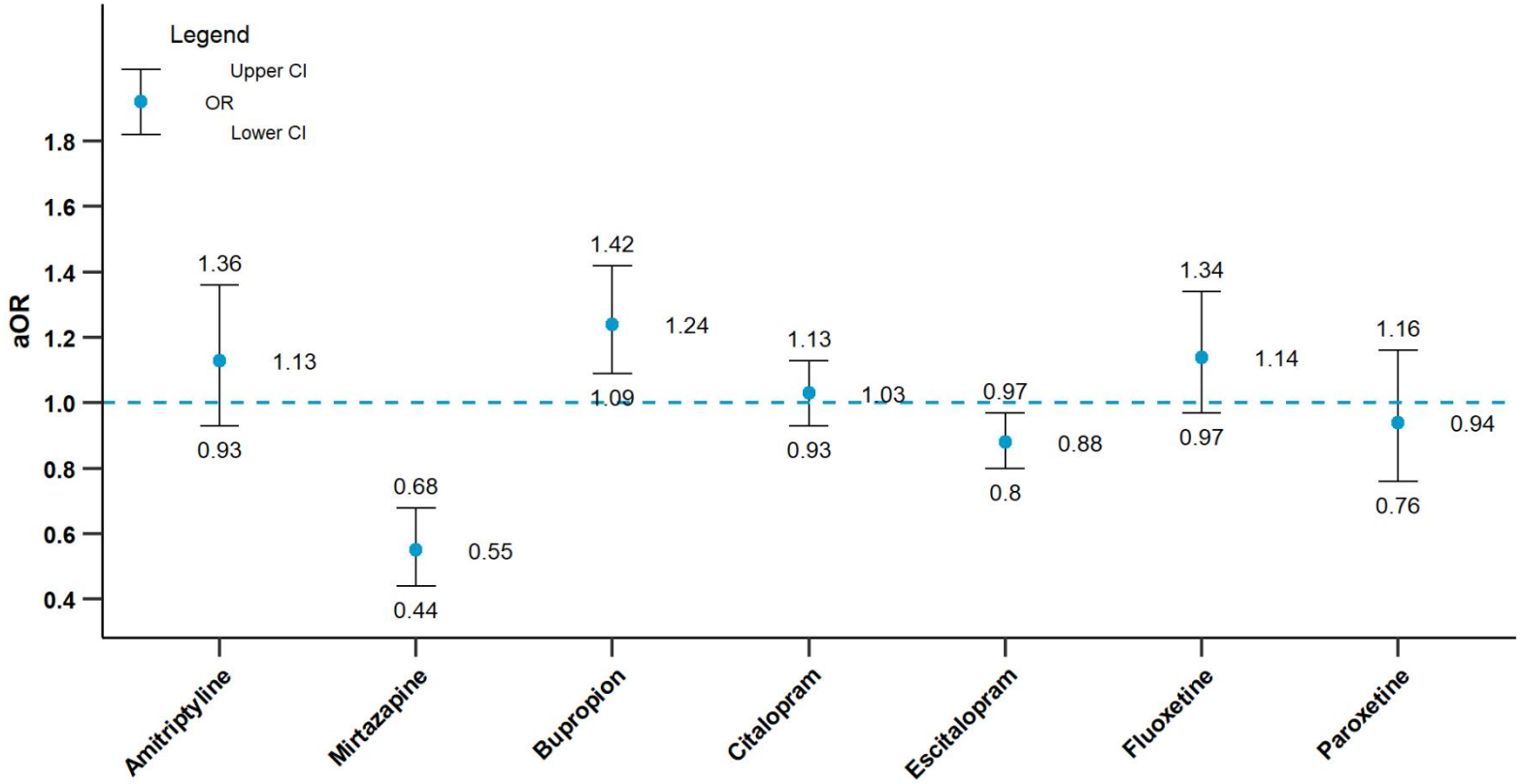


Table 6.2. Characteristics of patients with depression by weight category*

	Weight category				Total N=26,571 n (%)
	Underweight, N=748 (2.8%) n (%)	**Normal weight N=10,978 (41.3%) n (%)**	**Overweight N=8,208 (30.9%) n (%)**	**Obese N=6,637 (25.0%) n (%)**	
Age					
Mean (SD)	33.6 (16.8)	37.2 (14.5)	41.2 (14.0)	39.5 (12.9)	38.9 (14.2)
Median (IQR)	26.9 (20.1)	34.7 (22.1)	40.1 (20.6)	38.0 (18.5)	37.1 (21.0)
Sex					
Men	150 (20.1%)	2,417(22.0%)	2,815 (34.3%)	1,941 (29.3%)	7,323 (27.6%)
Women	598 (80.0%)	8.559 (78.0%)	5,393 (65.7%)	4,695 (70.7%)	19,245 (72.4%)
Missing	-	2(0.0%)	-	1(0.0%)	3(0.0%)
BMI, first measure					
Mean (SD)	17.4 (1.0)	22.2 (1.7)	27.2 (1.4)	35.7 (5.9)	27.0 (6.5)
Median (IQR)	17.7 (1.2)	22.3 (2.9)	27.1 (2.4)	34.0 (6.2)	25.7 (7.5)
Comorbidities					
≥1 comorbidity	91(12.2%**)**	896(8.2%)	783(9.5%)	752(11.3%)	2,522(9.5%)
COPD	60 (8.0%)	395 (3.7%)	269 (3.3%)	229 (3.5%)	953 (3,6%)
Dementia	22 (2.9%)	242 (2.2%)	184 (2.2%)	129 (1.9%)	577 (2.2%)
Diabetes	4 (0.5%)	33 (0.3%)	68 (0.8%)	144 (2.2%)	249 (0.9%)
Epilepsy	12 (1.6%)	144 (1.3%)	114 (1.4%)	110 (1.7%)	380 (1.4%)
Hypertension	9 (1.2%)	116 (1.1%)	200 (2,4%)	259 (3.9%)	584 (2.2%)
Osteoarthritis	3 (0.4%)	135 (1.2%)	142 (1.7%)	149 (2.2%)	429 (1.6%)
Parkinson	0 (0.0%)	3 (0.03%)	5 (0.06%)	2 (0.03%)	10 (0.04%)

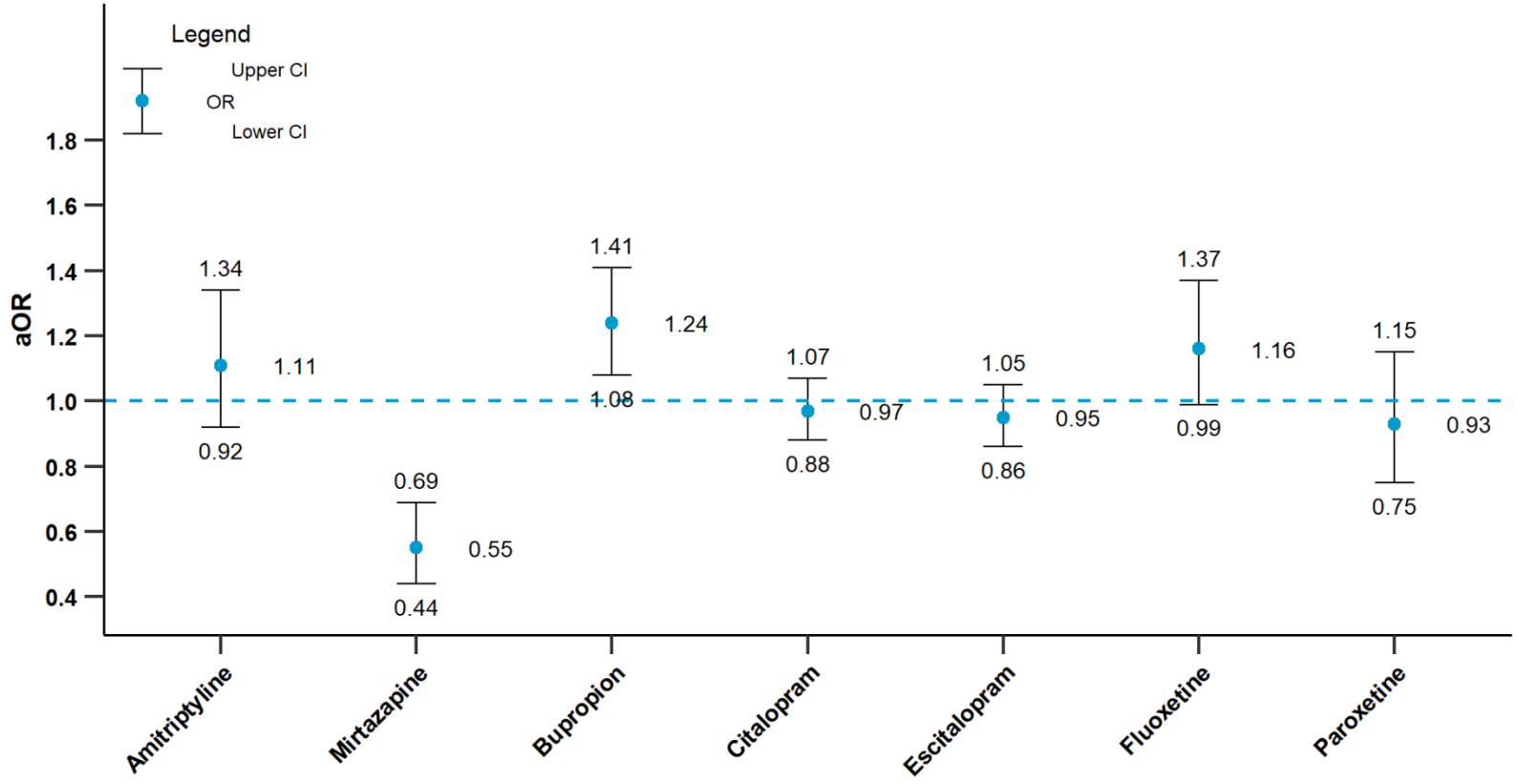
*Patients with BMI measured within 3 years before the first AD prescription. BMI: Body mass index; SD: standard deviation; IQR: interquartile range, COPD: Chronic Obstructive Pulmonary Disease

Figure 6.3A. Association of the type of antidepressant prescribed with obesity status within 1 year after treatment initiation, logistic regression model



Footnote: Adjusted odds ratios (aOR) in the logistic regression model. Upper/lower CI: 95% confidence intervals after adjustment by Bonferroni correction

Figure 6.3B. Association of the type of antidepressant prescribed with obesity status within 1 year after treatment initiation, mixed effects model



Footnote: Adjusted odds ratios (aOR) in the mixed effects model with clustering on networks. Upper/lower CI: 95% confidence intervals after adjustment by Bonferroni correction.

stratified by provinces (Supplemental Figure S4) showed differences in escitalopram prescribing prevalence for patients with obesity compared with normal weight patients in both directions, with a decreased prescribing for patients with obesity in most (seven) provinces and the opposite trend for two provinces.

Association between escitalopram prescribing and obesity status stratified by the type of residence. Logistic and mixed effects models regression analyses showed that there was no difference in escitalopram prescribing in relation to patient's obesity status in rural areas. In urban areas, compared to normal weight patients, patients with obesity were 14% less likely (95%CI: 0.80, 0.93) to receive this AD according to the MVR model (Table 6.3). The above-described analyses were conducted for a subgroup of patients with valid postal codes (n=25,739).

6.5.5. Random forest analysis

MDA of weight category, age, sex, and at least one comorbidity for predicting AD type prescribing is illustrated in Figure 6.4. The most important predictor was "having at least one comorbidity". Age was ranked second, and weight was ranked third most important predictor; however, the importance of age and weight were almost identical (MDA=37.2 and 37.1, respectively). MDA of weight was much higher than that of sex (MDA=16.2). Sex was the least important of all 4 predictors.

6.6. Discussion

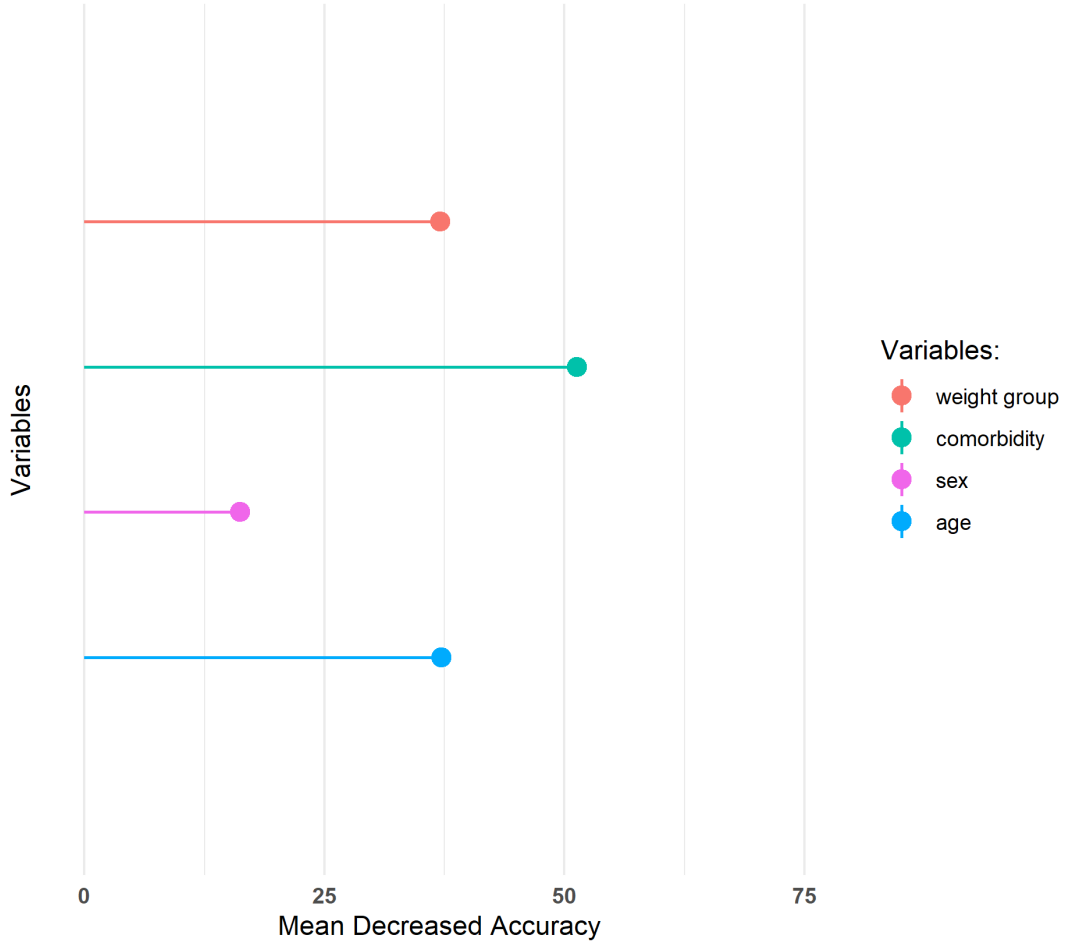
The goal of our study was to examine prescribing of AD known for their obesogenic and cardiovascular adverse effects to patients with obesity and depression compared with normal

Table 6.3. Association between obesity status and prescribing of Escitalopram and Citalopram in relation to urban/rural residence*

AD	Weight group	Logistic regression, unadjusted to network ID				Mixed effects model with adjustment for clustering	
		cOR	95%CI	aOR**	95%CI	aOR***	95%CI
				Citalopram			
All patients	Normal weight (Ref)					1	-
	Obese					0.95	0.88, 1.02
	Normal weight (Ref)	1	-	1	-		
Urban residence	Obese	1.00	0.93, 1.08	0.99	0.92, 1.07		
	Normal weight (Ref)	1	-	1	-		
Rural residence	Obese	1.03	0.88, 1.21	1.02	0.87, 1.20		
				Escitalopram			
All patients	Normal weight (Ref)					1	-
	Obese					0.94	0.88, 1.01
	Normal weight (Ref)	1	-	1	-		
Urban residence	Obese	0.83	0.77, 0.90	0.86	0.80, 0.93		
	Normal weight (Ref)	1	-	1	-		
Rural residence	Obese	0.91	0.77, 1.09	0.95	0.80, 1.13		

* BMI measured within 3 years before the first antidepressant prescription; **adjusted for sex, age, comorbidities; *** adjusted for sex, age, comorbidities and rural/urban residence; AD: antidepressant medications; cOR: crude odds ratio; aOR: adjusted odds ratio

Figure 6.4. Random Forest analysis: Mean Decreased Accuracy of weight category, age, sex, and comorbidities as predictors of prescription AD type



weight patients in Canadian primary care. We found a substantial difference in prescribing selected AD to patients with obesity compared to patients with normal weight. Our conclusions align with the results of Boudreau et al., 2013 (USA) (Boudreau et al., 2013), that primary care providers are less likely to prescribe the obesogenic AD mirtazapine to patients with obesity and more likely to prescribe bupropion, known for its potential to cause weight loss. Of importance, to our knowledge, there were no reports of poor response to bupropion in patients with obesity. It has also been reported that adding bupropion to escitalopram may be beneficial compared with monotherapy with escitalopram, for patients with severe obesity (Jha et al., 2018).

The tendency to prescribe TCA amitriptyline to patients with obesity more frequently than to patients with normal weight is concerning. First, the obesogenic effect may contribute to promoting some of these patients to a higher class of obesity, increasing their risk for obesity-related comorbidities and, possibly, for treatment-resistant depression. Second, patients with obesity as measured by a high BMI were shown to have a poor response to TCA nortriptyline (Puzhko, Aboushawareb, et al., 2020), which is an in vivo metabolic product of amitriptyline. Of note, even though amitriptyline is often prescribed for reasons other than depression, the obesogenic adverse effect should still be accounted for when prescribing to patients with excess weight. Further research, with the involvement of prescribers (e.g., deliberative consultations with health professionals) could help identify reasons for this prescribing pattern and help elucidate whether it is advisable in some cases to replace amitriptyline with other non-obesogenic medications.

Regarding SSRI fluoxetine, considered as either weight neutral or with a weak weight-decreasing effect, it may seem safe for prescribing to patients with obesity; however, attenuated

response to treatment with fluoxetine in this population was reported in two recent quasi-experimental studies (Lin et al., 2014; Papakostas et al., 2005). Longitudinal studies, either RCTs or observational studies with the use of causal inference methods, are needed to further evaluate whether prescribing fluoxetine to patients with obesity may be associated with poorer health outcomes.

SSRIs are the most popular class of AD prescribed to patients of either normal weight status or with obesity. In our sample, the most prescribed AD types were citalopram and escitalopram, both for treatment initiation and the follow up treatment. The marginal national trend showed that patients with obesity were as likely to receive citalopram as normal weight patients, and that patients with obesity from urban areas were less likely to receive escitalopram than participants with normal weight from the same areas. One of the reasons for this may be lower socioeconomic status in patients with obesity in urban areas, driving decisions to prescribe citalopram that is covered by government insurance plans in most provinces. We cannot exclude, however, that one of the reasons may be a widespread weight-based stereotype when patients with obesity are perceived as "lazy" and "weak-willed" (Batsis et al., 2018; Carels et al., 2015), which can affect access to healthcare (Phelan et al., 2015) and, possibly, may contribute to certain prescribing choices; however, this area is understudied and warrants further contextual research. Escitalopram is a therapeutically active S-enantiomer of citalopram and, according to several studies, is of higher efficiency compared with citalopram (Keller, 2013; Ng et al., 2016); even though this was not specifically evaluated in patients with obesity. In the past decade, the efficiency of these two AD and differences in the likelihood of causing cardiovascular adverse effects (Funk et al., 2013; Keller, 2013; Sicras-Mainar et al., 2010) have been debated in the literature. As obesity plays a significant role in the risk of cardiovascular complications (McQuigg

et al., 2008), the fact that in some geographical regions patients with obesity are less likely to receive escitalopram than their normal weight counterparts may be of concern and warrants further investigation.

Our random forest analysis showed that weight category is as important as patient's age as a predictor of prescribing certain type of AD in the Canadian primary care context. This suggests that, for reasons that remain to be clarified, prescribers include patient's weight group in their decision-making on prescribing AD type. The importance of weight category in predicting the type of AD prescribed to a patient, exceeding that of sex and comparable to that of age, is a novel finding and validates the importance of investigation into how obesity may be driving health care delivery.

Our study has certain strengths and limitations. We were able to examine the associations between obesity status and AD prescribing patterns in Canadian primary care, using the all-Canadian primary care EMR database. We established the temporality of the association between obesity status and the first AD prescription. Even though we were restricted by the definition of life-time depression in CPCSSN database, a washout period of no AD prescriptions for 365 days was introduced to exclude patients without acute depression and to study initiation of AD treatment. One of our database limitations was the lack of opportunity to exclude reasons other than depression as an indication for prescribing. Another important limitation emanated from the inclusion of patients whose weight group was established within 3 years before the first AD prescription. For some patients, the weight group could have changed by the time of prescription, suggesting a possibility of exposure misclassification. Yet, this misclassification would have likely to be non-differential (not associated with prescribing certain antidepressant), leading to the underestimation of the differences in prescribing between patients with obesity and normal weight

patients found in our study. Moreover, our sample was restricted to patients with BMI reported before the prescription. This ensured the temporality of association but limited generalizability of our results. For example, PCP who measure BMI before prescribing may be more considerate in prescribing choices. This could have contributed to underestimation or overestimation of associations depending on the type of AD and could have introduced a selection bias. Further, we could not exclude pregnant patients, patients with cancer, and those with eating disorders, all of which could have confounded our results although the size of the cohort would help to mitigate these relative rare confounders. The lack of opportunity to determine the date of depression diagnosis limited causal inference. Finally, the absence of a priori important predictors of prescribing, e.g., the depression type and severity, as well as patient preference and PCP years of experience, education, and beliefs, likely contributed to sub-optimal prescribing models.

6.7. Conclusion

In conclusion, our analysis of a large national primary care database showed that there is a difference in prescribing of AD known for their obesogenic and cardiovascular effects in Canadian primary care to patients with obesity, compared to their normal weight counterparts. Some of our findings are reassuring and some point to areas that need further investigation as they have a strong possibility to lead to less optimal health outcomes. Qualitative studies could shed light on the reasons for the differences in these prescribing patterns. Longitudinal studies using primary care databases with available repeated body weight measures linked to health-administrative and hospital data with information on depression type and severity are needed to examine whether obesity modifies effect of AD prescribing patterns on health outcomes.

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Declaration of competing interest

The authors report no conflict in interest.

Authorship contribution statement

SP was primary investigator and conducted the research under the supervision of TS and GB. All authors contributed on the methods and interpretation of results. The text was written by SP and revised by the other authors.

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6.9. References

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6.10. Supplemental information

Supplementary Table S1. Association between obesity status and antidepressant type chosen to initiate treatment among CPCSSN patients with depression*

AD	Weight group	Logistic regression, unadjusted to network ID				Mixed effects model with adjustment for clustering	
		cOR	Adjusted CI**	aOR***	Adjusted CI**	aOR***	Adjusted CI**
Amitriptyline	Normal weight (Ref)	1	-	1	-	1	-
	Obese	1.10	0.89, 1.36	1.09	0.88, 1.35	1.08	0.87, 1.34
Mirtazapine	Normal weight (Ref)	1	-	1	-	1	-
	Obese	0.55	0.42, 0.72	0.49	0.37, 0.64	0.50	0.38, 0.65
Bupropion	Normal weight (Ref)	1	-	1	-	1	-
	Obese	1.31	1.12, 1.54	1.28	1.09, 1.50	1.28	1.09, 1.50
Citalopram	Normal weight (Ref)	1	-	1	-	1	-
	Obese	1.01	0.92, 1.12	1.01	0.92, 1.12	0.96	0.87, 1.06
Escitalopram	Normal weight (Ref)	1	-	1	-	1	-
	Obese	0.84	0.76, 0.92	0.87	0.79, 0.96	0.94	0.84, 1.04
Fluoxetine	Normal weight (Ref)	1	-	1	-	1	-
	Obese	1.07	0.89, 1.28	1.11	0.93, 1.33	1.13	0.95, 1.36
Paroxetine	Normal weight (Ref)	1	-	1	-	1	-
	Obese	1.10	0.87, 1.38	1.03	0.81, 1.30	1.02	0.81, 1.29

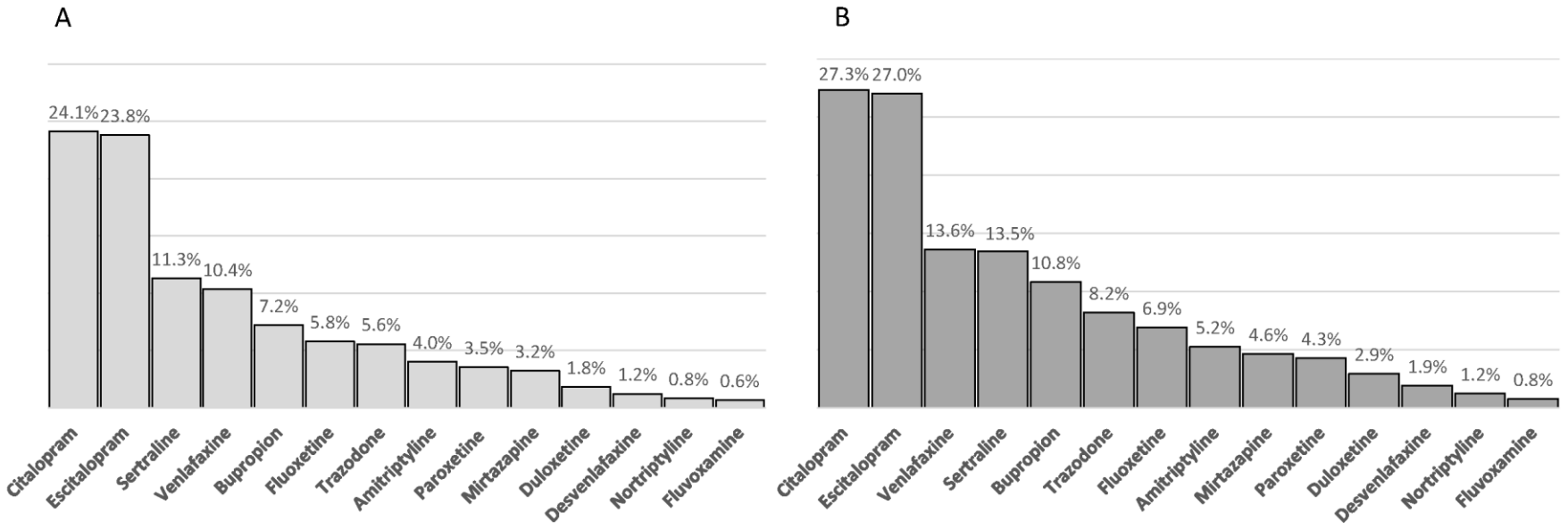
*BMI measured within 3 years before the first antidepressant prescription; **confidence intervals were adjusted by Bonferroni correction; ***adjusted for sex, age, and the following comorbidities: hypertension, diabetes, epilepsy, osteoarthritis, COPD, and dementia; AD: antidepressant medications; cOR: crude odds ratio; aOR: adjusted odds ratio; CI: confidence intervals; COPD: chronic obstructive pulmonary disease

6.10.2. Supplementary Table S2. Highlights

Highlights

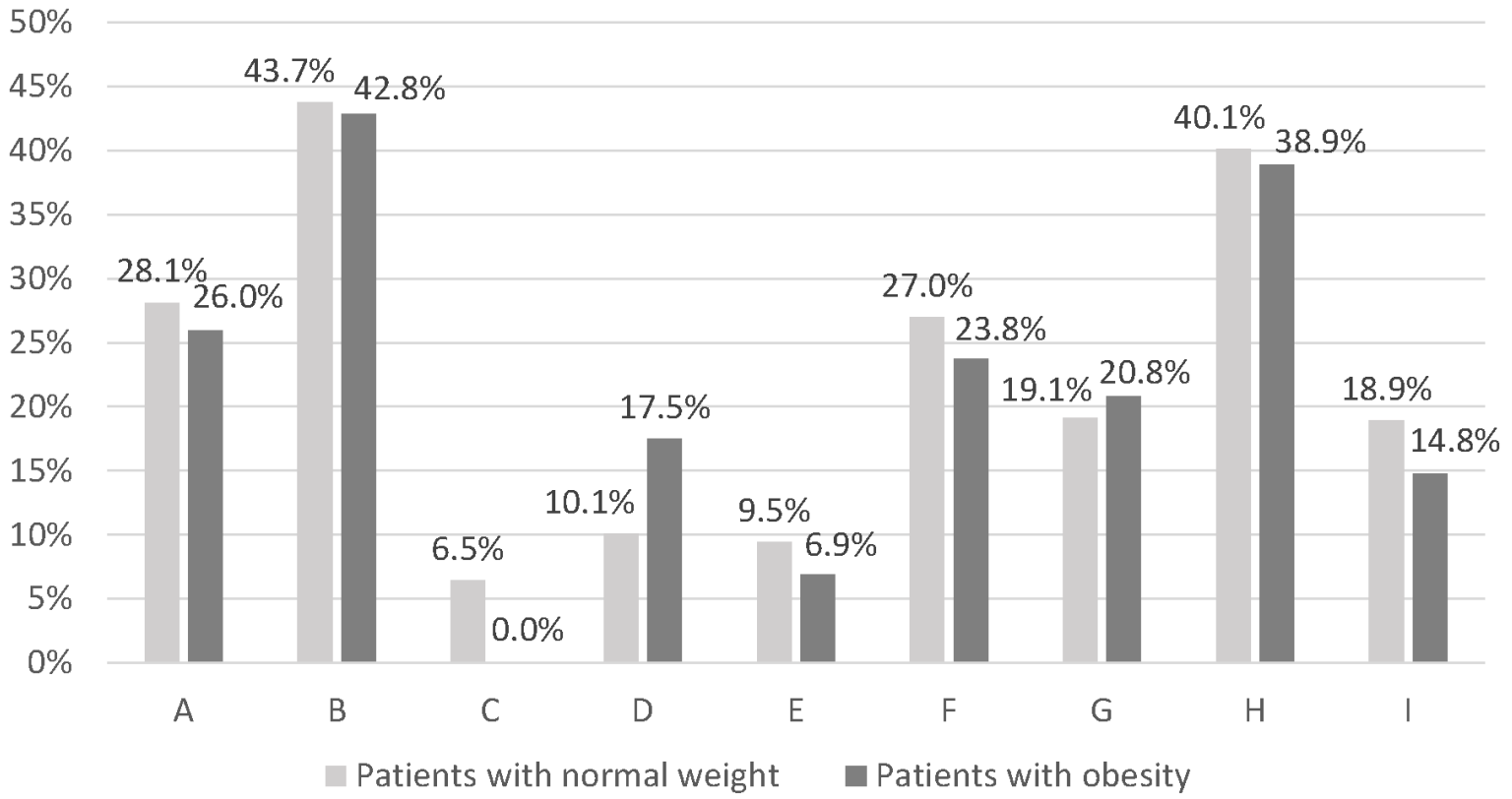
- There is a substantial difference in prescribing selected antidepressants to patients with obesity compared to patients with normal weight; this includes antidepressants known for their weight-modulating and cardiovascular side effects
- Patients with obesity, compared to normal weight patients, were more likely to receive bupropion, fluoxetine, and amitriptyline, and less likely to receive mirtazapine and escitalopram.
- Weight category was among the most important predictors of prescribing patterns, equivalent to age and more important than sex.

6.10.3



Supplementary Figure S3. Prevalence of antidepressants prescribing. A: The first prescription. B: Antidepressants prescribed within the first year after treatment initiation.

6.10.4



Supplementary figure S4. Prevalence of prescribing escitalopram for patients with depression during the first year after treatment initiation, stratified by provinces.

CHAPTER 7: THE ROLE OF THE EXCESS WEIGHT STATUS IN THE RISK OF HOSPITALIZATIONS FOR PATIENTS WITH DEPRESSION PRESCRIBED OBESOGENIC ANTIDEPRESSANTS (MANUSCRIPT 4)

7.1. Preamble

My manuscripts #2 and #3 revealed a substantial difference in AD prescribing to Canadian primary care patients with excess weight in comparison with the normal weight patients. This difference manifested as higher odds for receiving a prescription of the AD that exhibit adverse effects, which may especially be detrimental for people who are overweight or obese. To date, no study examined whether patients with depression and excess weight, when exposed to these AD, are, in fact, at an increased risk for adverse health outcomes. My final manuscript addresses this knowledge gap.

For this manuscript, I used a database of Quebec residents in which the data of Statistics Canada survey had been linked with the longitudinal health-administrative data. Thereby, the information on health service utilization was available. The extracted cohort of interest included patients with depression, who were incident users of AD and whose BMI had been measured before the first prescription. The Cox regression analysis, with exposure to obesogenic AD modeled as time-varying, showed the trend for patients who were jointly exposed to obesogenic AD (as opposed to non-obesogenic AD) and excess weight (as opposed to normal weight) to be at a higher risk for all-cause hospitalizations than patients exposed to only one of these factors. To evaluate robustness of these conclusions, the sensitivity analysis was performed with various duration of exposure latency windows and with or without carry-on period for exposure to treatment, as well as different time lags between BMI measures and AD prescription. One of the limitations of this database was the lack of statistical power to conduct the survival analysis for individual obesogenic AD. I addressed this methodological

problem by utilizing the cosine similarity metric to quantitatively assess the association between the use of individual obesogenic AD and hospitalizations. This method is usually used in unsupervised learning and does not rely as strongly on the sample size as the supervised methods (e.g., regression). This analysis in patients with excess weight showed stronger associations between hospitalizations and the use of certain AD from obesogenic group than it was for other obesogenic AD. Study results emphasize the importance of considering the patient's weight status when selecting an AD for depression treatment.

Title: The role of the excess weight status in the risk of hospitalizations for patients with depression prescribed obesogenic antidepressants.

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7.2. Abstract

BACKGROUND: Patients with excess weight may have poor response to certain antidepressants (AD) and may be more vulnerable to negative consequences of weight-increasing (obesogenic) adverse effects. Clinical guidelines do not provide insight for an individualized approach for AD selection in this population. It is important to evaluate the need

to implement a differential approach to AD selection for patients with excess weight. Our objectives were to estimate the difference in risk for all-cause hospitalizations between people with and without excess weight who were prescribed obesogenic AD, and to quantify the association between the use of individual obesogenic AD and hospitalizations for patients with and without excess weight.

METHODS: The population-based cohort "The Care Trajectories - Enriched Data" ("TorSaDE") was used. In this cohort, the data for the biennial Statistics Canada survey for 2007-2014 were linked with longitudinal health-administrative data. The cohort of incident users of AD, with depression diagnosed and weight status measured before the first AD prescription, was extracted. The role of excess weight before the first AD prescription in the association between exposure to obesogenic AD and all-cause hospitalizations during the 12 months of treatment was examined. Cox regression analysis, with a time-varying exposure to obesogenic AD (versus non-obesogenic AD) and time-fixed weight status, as well as cosine similarity method, were applied. Smooth-hazard function was used to evaluate time-varying hazards.

RESULTS: Of the 1,453 participants, 66.3% were women, mean age was 53.8 years (standard deviation (SD)=18.7), and 738 (50.8%) had excess weight. The hazard ratio for hospitalizations, adjusted for age, sex, income, level of education, comorbidities, and past health service use (aHR) was 1.84 (95%CI: 1.16, 2.90) in patients jointly exposed to excess weight and obesogenic AD compared to the jointly unexposed group; aHR was 1.50 (95%CI: 0.96, 2.34) and 1.79 (95%CI: 0.87, 3.68) compared to patients with only excess weight or only on obesogenic AD, respectively. Differences in cosine similarity between contrasting weight groups were observed for amitriptyline and nortriptyline but not for mirtazapine and paroxetine. The hospitalization hazards varied with time for different exposure groups.

CONCLUSIONS: Patients jointly exposed to excess weight and obesogenic AD had a higher risk for hospitalizations within 12 months after the first AD prescription than patients with neither exposure. The trend for increased risk of hospitalizations was observed for patients jointly exposed to excess weight and obesogenic AD, compared to people with a single exposure, suggesting synergic (super-additive) interactions. We cannot exclude the possibility that patients with excess weight may benefit less from treatment with obesogenic AD than patients without excess weight. The role of excess weight in the association between exposure to obesogenic AD and hospitalizations may depend on specific obesogenic AD.

7.3. Introduction

Antidepressants (AD) are one of the most prescribed groups of medications in primary care [1]. In Canada, the prevalence of AD prescribing was ~13% in 2012 [2]. Moreover, in the Province of Quebec, AD intake increased during the COVID-19 pandemic in all age groups [3]. The efficacy of AD in the treatment of depression has, however, long been debated [4]. Non-response or poor response to AD has been reported in 30-50% of patients [5]. In Canadian primary care, the prevalence of depression resistant to treatment with AD was estimated at 21.7% in 2014 [6].

One of the possible reasons for the low reported efficiency of AD is the lack of a personalized approach to selecting AD [7]. Many factors can contribute to the AD treatment outcome. While some of them, such as certain gene polymorphisms, associated with favourable response to AD [8], may require dedicated sophisticated studies, most of the remaining factors are easily measurable in clinical settings. Among these factors are age [9,10], sex [11,12], type and severity of depression [13], specific symptoms of depression [11,14], and patient's previous response to AD [15].

Another factor associated with AD treatment response is the patient's body weight. The evidence of the different responses to individual AD classes and types in patients with obesity or high BMI, compared to patients with normal weight, has emerged in several studies and was synthesized in a recent scoping review [16]. Yet, these data are not reflected in the guidelines, either in North America or Europe. One of the reasons for this may be data scarcity, limiting the evidence base for weight-based clinical recommendations.

Relatedly, several AD that are commonly prescribed by primary care professionals and specialists are known for their obesogenic (that is, weight increasing) effects. Our recent work [17] showed that, in Canada, prescribers do not always take into consideration weight increasing adverse effects when prescribing AD to people who already have excess weight. This may "promote" patients to a higher weight group, increasing their risk for severe depression and

poor treatment outcomes, in addition to other consequences related to excess adipose tissue. Reliable data are needed to inform a potentially differential approach to selection of an AD conditional on patient weight status. This could optimize therapeutic response while promoting improved overall health.

In recent years, efforts have been made to understand the differential response to AD classes and individual AD in patients with excess weight and to evaluate the putative increased risks for AD adverse effects in patients with obesity. One of the obstacles that limits the progress in this area is the ethical issue regarding conducting RCTs with medications with known adverse effects that can be detrimental for a specific population. In addition, scarcity of data makes it difficult to generate a hypothesis about which of the more than 15 commonly prescribed AD would be the best candidates for such studies. Observational studies, while more appealing, present their own limitations, with few appropriate sources of data, since most medical databases lack either reliable BMI measures, valid depression rating scales scores, or quality data on prescribing. Therefore, this important topic remained understudied.

Based on our previous work, we hypothesized that people who are overweight or with obesity would have a higher risk for hospitalizations when treated with obesogenic AD compared to 1) people without excess weight treated with obesogenic AD, and 2) people with excess weight treated with non-obesogenic AD. We pursued these objectives using the population-based cohort, “The Care Trajectories - Enriched Data” (TorSaDE), which was established in 2019 to study the health trajectories of the Quebec population. This cohort has data on BMI, prescribing, and health services utilization. We could not directly evaluate the effectiveness of depression treatment, as there were no suitable measures available. However, “all-cause hospitalizations” is an indicator of general health and accounts for both AD effects (that is, the therapeutic and adverse effect). Our primary objective was to quantify the difference in the risk for hospitalizations between people with and without excess weight who

were prescribed obesogenic AD during the standard depression treatment period (12 months). Our secondary objective was to quantify the association between the use of individual obesogenic AD and hospitalizations.

7.4. **Methods**

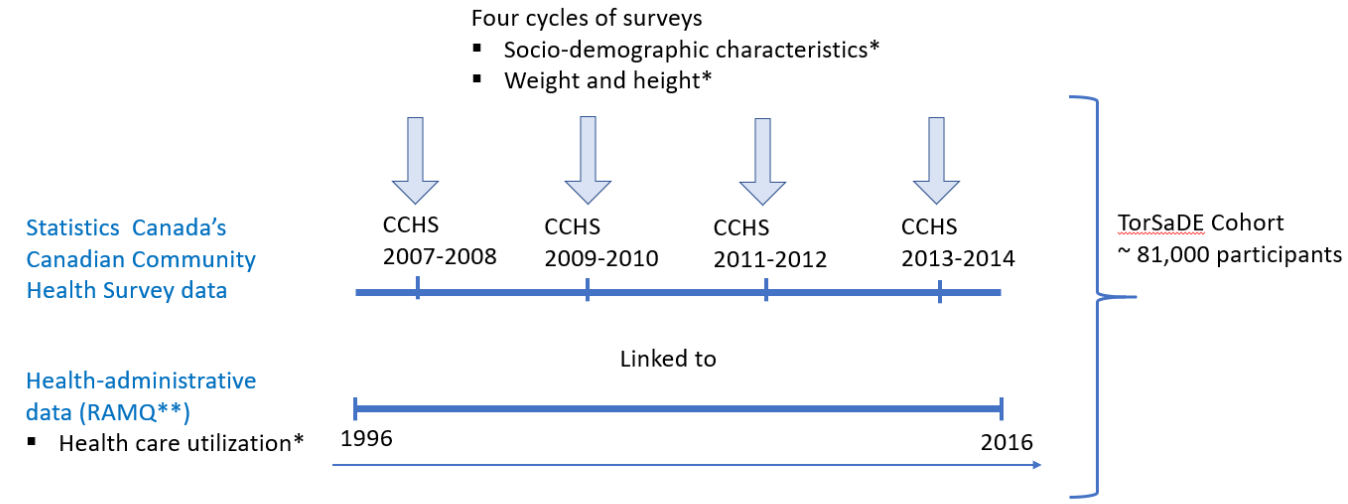
7.4.1. Data source and population

Population. The cohort was extracted from "The Care Trajectories - Enriched Data" (TorSaDE). The TorSaDE cohort is a substructure of the Quebec SUPPORT Unit (Support for People and Patient-Oriented Research and Trials) [18]. The cohort includes data from four cycles of the Statistics Canada's Canadian Community Health Survey (CCHS) (2007-2008, 2009-2010, 2011-2012, 2013-2014) linked with longitudinal health-administrative data for a 21-year period (1996-2016) held by the *Régie de l'assurance maladie du Québec* (RAMQ) (Figure 7.1). TorSaDE represents over 90% of all CCHS participants who live in Quebec and accepted to share their data with the Quebec Institute of Statistics (ISQ) and agreed to data linkage. The CCHS is a cross-sectional survey that collects information related to socioeconomic and health status, health care utilization, and health determinants. The survey is held every two years and targets Canadians 12 years of age and older who are living in private residences [19]. The exceptions are Canadians living on First Nations reserves, full-time members of the Canadian Armed Forces, institutionalized individuals, or people living in certain remote areas (< 3% of the Canadian population) [19]. The RAMQ database comprises population-level data on all universally funded medical health services in the Province of Quebec, including hospitalizations, medical visits, drugs prescription, and the date and cause of death. The TorSaDE cohort for 4 survey cycles includes data on 81,093 CCHS participants [18].

Cohort extraction (Figure 7.2). A sample of adult incident AD users who had been diagnosed with depression before the first AD prescription was extracted.

Figure 7.1. The Care Trajectories - Enriched Data (TorSaDE) cohort,

Quebec SUPPORT Unit



*Data used in the present study
**RAMQ: *Régie de l'assurance maladie du Québec*

The date of the first prescription was considered as cohort entry. We excluded patients with a prescription for any AD in the 12 months before cohort entry. We then followed up participants for 12 months, which corresponded to 3-months of acute depression treatment and 9 months of maintenance treatment according to the CANMAT 2016 guidelines [13]. To ensure that weight status preceded prescribing decision, we only included participants who had had their interview, and therefore weight status assessed, before the first prescription of an AD.

To extract the sample of patients with depression, the administrative databases of the Quebec Public Health Insurance Board (RAMQ) and the Quebec Registry of Hospitalizations (Maintien et exploitation des données pour l'étude sur la population hospitalière [Med-Écho]) were used. The RAMQ databases are comprised of claims data from physicians and pharmacists. In the Province of Quebec, the RAMQ oversees medical services for all permanent residents, and the public drug insurance plan. The file on medical services provides information

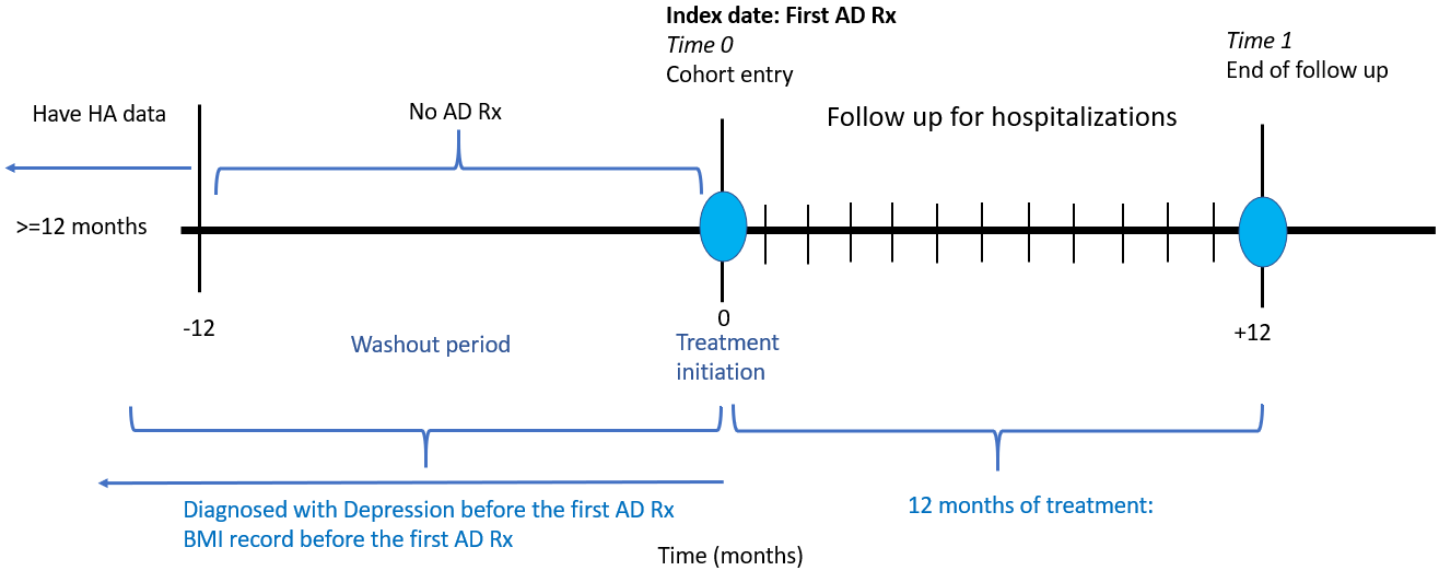
on the date of medical service, a diagnosis (as defined by the International Classification of Diseases, Ninth Revision [ICD-9]), and the physician's specialty. The Med-Écho file provides information on the date of hospital admission and discharge, as well as on primary and secondary diagnoses (as defined by ICD-9, or the ICD-10 [starting from 2006]). The data file on pharmaceutical services provides information on medications and includes the date of dispensing, medication identity, including Drug Identification Numbers (DIN) and American Hospital Formulary Service (AHFS) classification numbers, days of supply, and prescriber's specialty. The eligibility periods for public drug insurance plan were established using a corresponding RAMQ file (Période d'admissibilité – Assurance médicaments) that provides information on the start and end dates of eligibility for the plan. The algorithm for depression diagnosis was adapted from Lunghi et al., 2016 [20] and Fiest et al, 2014 [21]. Since all people diagnosed with depression were targeted, we acted conservatively and included all patients who had a record of a depression diagnosis in at least one data source, either hospitalization or medical services data files. We used case definitions proposed by Fiest et al., 2014, to maximize sensitivity without loss of specificity: case definition #6 for ICD-10 codes and case definition#6 for ICD-10 codes [21] (Supplementary Table S1). The date of depression diagnosis was established as either the date of hospitalization for depression, or the first physician visit during which the diagnosis was made, whichever occurred sooner [20].

Exclusion criteria were the following. People who were younger than 18 years of age at the time of the prescription were excluded. Participants who had had the first prescription of AD in the database before the record of depression diagnosis were excluded as well. People who had not continuously been admissible for the public drug insurance plan during the 12-month follow-up period and the 12-month washout period were excluded. To ensure that BMI definition preceded the first AD prescription, people whose weight and height had been reported after the first AD prescription were excluded (Figure 7.2).

7.4.2. Measures

Exposure 1: Prescribing of obesogenic AD. The RAMQ data file on pharmaceutical services was used to determine exposure to AD. All AD prescribed by health providers working in the Province of Quebec (AHFS code 28:16.04) were included. AD were classified into individual types using DIN codes in the file. Patients were classified as exposed or non-exposed to obesogenic AD at cohort entry. The antidepressants constituting the obesogenic group included tricyclic antidepressants (TCA) nortriptyline, amitriptyline, and trimipramine, mirtazapine (noradrenergic and specific serotonergic [NaSSA] group), and paroxetine (selective serotonin reuptake inhibitors [SSRI] group). These AD have consistently been associated with an increased risk of excess weight [22]. Since many participants switched to alternative groups of AD (obesogenic or non-obesogenic) at some point during the 12 month follow-up, exposure to obesogenic AD was modeled as a time-varying exposure for the Cox model. Every day of follow-up was considered as exposed or non-exposed. The start of exposure to obesogenic ADs was the first day of prescription for obesogenic AD. For the main analysis, patients with ≥30 days of cumulative use of obesogenic AD during the follow-up period were classified as exposed. We selected this 30 days latency period since 1) it takes at least two weeks to see the therapeutic effect of AD and 2) clinically relevant weight gain is not expected to occur earlier than after at least 30 days of receiving AD. Since the true length of the latency period is uncertain, we conducted a sensitivity analysis by varying this period as 0 days, 60 days, and 90 days. The end of the exposure period was the last day of prescription of obesogenic AD plus a two-day grace period. In a sensitivity analysis, we added a carry-on period of seven days to allow for continuous exposure since the effect of AD may not stop immediately after discontinuing the medication.

Figure 7.2. Cohort of antidepressants new users with depression extracted from TorSaDE data.



Exposure 2: Excess weight. Weight and height had been measured during the interview prior to cohort entry. Weight and height were used to calculate BMI. BMI was further categorized into weight categories using WHO and Health Canada standards: 25–29.99 kg/m2 = overweight, ≥30 kg/m2 = obese, 18.5–24.99 kg/m2 = normal, <18.5kg/m2 = underweight. Participants with overweight and obesity were classified as having excess weight. Participants with normal weight and those underweight (a small portion of the sample) were categorized as having no excess weight. Since weight and height were only measured once, BMI was modeled as a time-fixed exposure in the Cox model. The time elapsed between the measures of height and weight and cohort entry was used to stratify patients in a sensitivity analysis to verify that different time gaps did not change study results.

Outcome: Hospitalization was defined as hospital admission for any cause in the MedEco database during the study period. For the Cox regression analysis, all participants were followed up until the first hospitalization within the 12 months follow-up. The outcome was defined as time to the first hospitalization. To quantify associations between AD use and

hospitalization by cosine similarity, all hospitalizations within the 12-month follow-up were cumulatively used in the analysis.

Covariates. The following covariates were retained in the final model as the *a priori* determined confounders: age, sex, level of education, household income, rurality level, comorbidity index, and previous health service use. Age was considered as the number of years of life at the time of AD prescription. Comorbidity index and previous service use (number of hospitalizations per year) were recorded within the year preceding the interview. Other covariates were reported at the time of the interview. Level of education was categorized into 1) secondary school education or lower; 2) postsecondary level; 3) university education. The household income included 2 categories: 1) ≤$40,000/year; 2)>$40,000/year. Rurality is represented in the TorSaDE data by seven categories according to Statistics Canada Classification of Statistical Sectors. For the purpose of analysis, these categories were collapsed into three categories: 1) metropolitan areas and strong metropolitan influence zone; 2) moderate and weak metropolitan influence zone and 3) no metropolitan influence zone and territories. The comorbidities variable was presented by the Charlson comorbidity index (numerical) [23]. The number of hospitalizations was defined as: 1) 0 hospitalizations, 2) 1-3 hospitalizations, and 3) >3 hospitalizations. All covariates were modeled as time-fixed in the Cox regression model.

7.4.3. Statistical analysis:

Cox regression. The Andersen-Gill extension of the proportional hazards Cox regression model, that allows for incorporation of time-varying and time-fixed covariates [24], was used. We generated conditional estimates for treatment with obesogenic AD and excess weight with respect to the hazard of first hospitalization when adjusting for time-varying exposure and time-fixed covariates. To study the effect of the joint exposure to excess weight and obesogenic AD,

the variable was modeled as follows: 1) patients without excess weight and without exposure to obesogenic AD (reference group for the main analysis); 2) patients with excess weight without exposure to obesogenic AD; 3) patients without excess weight who were exposed to obesogenic AD and 4) the joint exposure group (that is, people with excess weight who were exposed to obesogenic AD). To obtain more meaningful group contrasts, the reference group was further shifted to group 2 and then to group 3. Patients were followed up until the date of the first hospitalization, the end of the follow-up period, or death, whichever came first. Model performance was evaluated by the likelihood ratio test (LRT), and AIC and BIC criteria.

Relative excess risk for joint exposure to excess weight and obesogenic AD due to interaction was calculated as follows: $RER1_{HR} = HR_{11} \_ HR_{10} \_ HR_{01} + 1$, where HR_{11} is observed joint effect of both exposures while HR_{10} and HR_{01} are observed effects of each of the two exposures [25,26]. Since interactions on the additive scale is considered the more relevant public health measure [27], with $RERI_{HR}$ being the best choice of measures of additivity when Cox proportional hazards model is applied [28], we have focused on evaluating the interactions on the additive scale. To access the robustness of the RER1 estimate, we calculated the uncertainty indices using the values consistent with the 95% confidence intervals limits for each exposure category.

Survival curves. The marginal survival curves for the four above-described groups were created from the adjusted Cox model where time-fixed exposure to weight and time-varying exposure to treatment were used. The Cox model was refitted using inverse probability weighting. For each subpopulation, a logistic regression model was built to calculate the odds of being in this subpopulation against the reference population (no exposure to either excess weight or obesogenic AD) accounting for the other variables in the model. The inverse probabilities of being in a specified subpopulation were then used in the Cox model as weights. The model was

refitted taking into account these weights. Finally, survival curves for the four subpopulations were created based on a refitted weighted Cox model. This analysis was done using the function *ggadjustedcurves* in the R package *survminer* [29] and a *marginal* method.

Estimating risks at various points in the follow-up time

The average HRs obtained in the Cox regression and the survival curves do not account for the possible time-dependent variations of effects of exposure on the outcome during the follow-up period. To examine how the hazards may be changing with time for the four exposure groups, we used the R package *casebas*e with the *fitSmoothHazard* function [30]. This function samples person-moments, corresponding or not to an event, and then uses logistic regression to fit the hazard [31]. We used the cubic spline of follow-up time and adjusted for all the covariates used in the Cox model. To test the hypothesis that the effect of obesity and/or excess weight on the hazard interacts with time, we further introduced the interaction term in the model. The results for all four exposure groups were illustrated by the graphs. For this analysis, we used the definition of exposure with a zero-day latency period.

The proportional hazard assumption for Cox regression was verified by plotting hazards on the logarithmic scale (Supplementary figure S5) using the *fitSmoothHazard* function with the cubic spline of the time.

Sensitivity analysis. The following sensitivity analyses were performed to test the robustness of our results: 1) patients with cumulative use of obesogenic AD <30 days were classified as exposed to obesogenic AD; 2) patients with cumulative use of obesogenic AD <60 days, and subsequently with <90 days, were classified as non-exposed; 3) carry on period of seven days after the end of the two days grace period was introduced; 2) different cut-offs for the time lag

between BMI measure and cohort entry (≤3 years, ≤2 years) were used; 3) patients with concurrent prescriptions for two or more AD at cohort entry were excluded.

Quantification of association between the use of individual AD and hospitalizations

The cosine similarity index, commonly used in an unsupervised learning approach, was used for quantitative assessment of the associations between the studied parameters in different participant groups. Specifically, we wished to compare the associations between the use of individual AD, especially those belonging to obesogenic AD, and the number of hospitalizations in the two groups of participants: with and without excess weight. Our dataset presented in form of a sparse matrix [32], i.e., with predominant zero values and relatively rare non-zero values (the latter being, most commonly, integers). The cosine similarity metric was deemed as the most appropriate for this objective. The cosine similarity metric is defined as the cosine of the angle between two vectors projected in a multi-dimensional space [33,34]:

$$Cosine(x, y) = \frac{\sum_{i=1}^{n} x_i y_i}{\|x\|_2 \|y\|_2},$$

In our case, the studied parameters were the use of individual AD and the number of hospitalizations within each month of the follow-up period. A higher association between two studied vectors is reflected by a correspondingly higher cosine similarity metrics [34,35]. This approach was previously applied to similar sparse matrices, including healthcare data [34,36]. The resulting cosine similarity metrics (*lsa* package in R) were compared between the patients with and without excess weight. The differences in cosine similarity metrics between patients with and without excess weight were calculated and illustrated in the form of a graph.

Data manipulations were performed with SAS software (version SAS 9.4, SAS Institute, Cary, NC). The analysis was performed using R studio software, version 4.0.2 [37].

Because of the restrictions related to the Covid-19 pandemic, the analysis was conducted using the remote data for TorSaDE cohort.

7.5. Results

7.5.1. Sample description.

The extraction of the sample is shown in Figure 7.3.

Figure 7.3. Cohort extraction

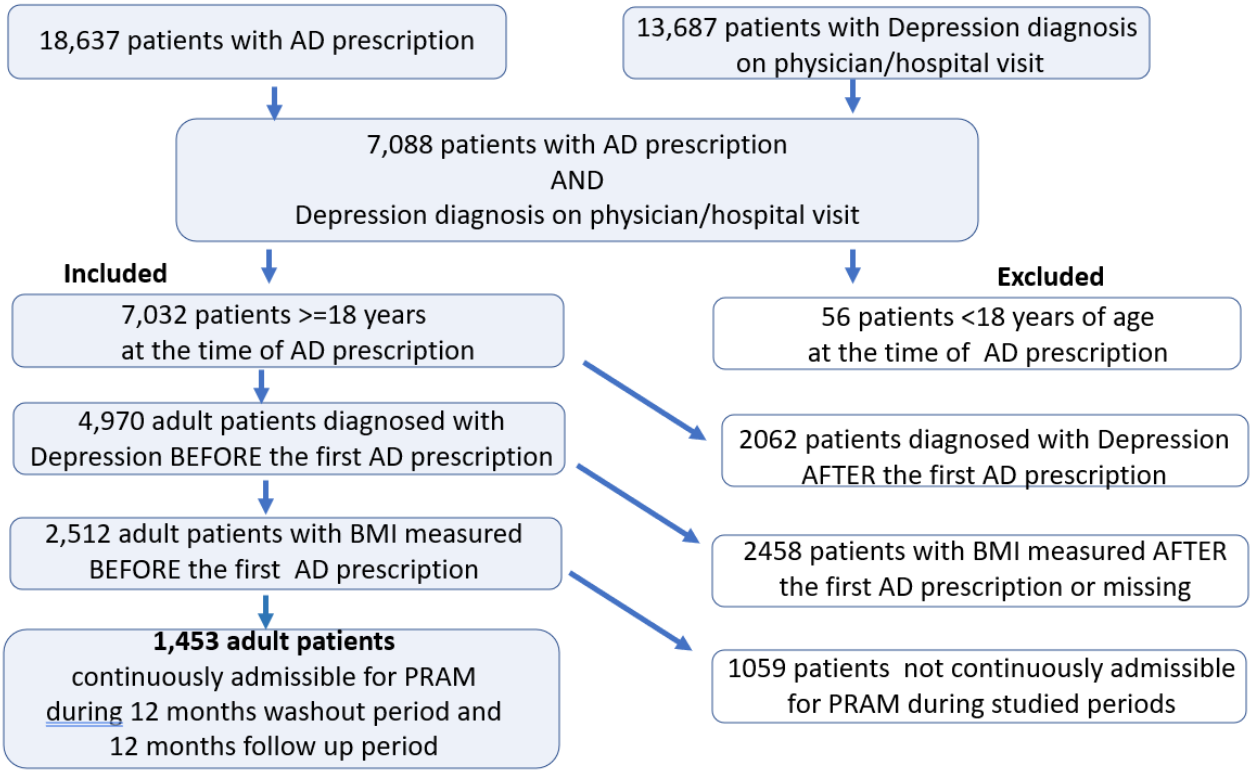


Table 7.1. Patient characteristics, N=1453

Characteristics	Excess weight (n=738)	No excess weight (n=715)
Age		
Mean, SD	55.0 (17.6)	52.1(19.5)
Sex		
F	468 (63.4%)	496(69.4%)
Number of hospitalizations 1 year before the interview		
0	583 (79%)	580 (81.1%)
1-2	140 (19.0%)	116 (16.2%)
>3	15 (2.0%)	19 (2.7%)
Education		
Secondary school or lower	376(51.0%)	349 (48.8%)
Postsecondary, including CEGEP	268 (36.3%)	274(38.3%)
University education	94 (12.7%)	92 (12.9%)
Household income		
≤$40,000	522 (70.7%)	492 (68.8%)
>$40,000	216 (29.3%)	223(31.2%)
Rurality level		
Metropolitan areas	480(65.0%)	502 (70.2%)
Moderate/weak metropolitan influence areas	160 (21.7%)	128 (17.9%)
No metropolitan influence areas	98(13.3%)	85(11.9%)
Comorbidity index		
Mean, SD	0.53 (1.40)	0.46 (1.43%

SD: standard deviation; CEGEP: a post-secondary pre-university education in Quebec.

The sample of 1,453 eligible patients was extracted for the study. Of these, 489 (33.7%) were men and 964 (66.3%) were women. The average age was 53.8 (standard deviation [SD]=18.7) years; 715 (49.2%) did not have excess weight, and 738 (50.8%) had excess weight. There were few differences in patient characteristics between the weight groups (Table 7.1).

At cohort entry, 1,095 (75.4%) and 358 (24.6%) patients had prescriptions for non-obesogenic and obesogenic AD, respectively. There were also switches from non-obesogenic

to obesogenic AD during the follow-up period. Forty people were prescribed two AD, including at least one obesogenic AD, on the same day. Because of a substantial number of switches, exposure to obesogenic AD was modeled as a time-varying variable. The most prescribed group was SSRI, and the least prescribed was MAOI. During the follow-up period, several obesogenic AD were prescribed, including amitriptyline to 208 (14.3%) patients, mirtazapine – to 141 (9.7%) patients, paroxetine-to 63 (4.3%) patients, and nortriptyline – to 19 (1.3%) patients.

7.5.2. Examining the role of excess weight in the association between exposure to obesogenic AD and all-cause hospitalization with Cox regression analysis.

The results of the Cox regression analysis are shown in Table 7.2 and in Figure 7.4. There were 302 hospitalizations during 66,751 person-weeks of follow-up.

Patients with excess weight had a significantly shorter time-to-hospitalization than patients without excess weight. The average HR for excess weight on time to first hospitalization was 1.28 (95% CI: 1.02,1.61) (Figure 7.4). Patients exposed to treatment with obesogenic AD tended to be hospitalized sooner than those exposed to treatment with non-obesogenic AD. The average HR for obesogenic AD treatment was 1.31 (95% CI: 0.91, 1.88) (Figure 7.4).

The average HRs by excess weight status and exposure to treatment with obesogenic AD were estimated (Table 7.2). Column 1 of Table 7.2 shows that, compared to the jointly unexposed group (patients without excess weight who were treated with non-obesogenic AD), the average adjusted HR (aHR) for 1) people with excess weight treated with obesogenic AD (i.e., jointly exposed) was 1.84; 95%CI: 1.16, 2.90; 2) people exposed to excess weight but not to treatment with obesogenic AD was 1.23; 95%CI: 0.96, 1.56; 3) people exposed to treatment

Table 7.2. Hazard ratios for hospitalization in patients with depression treated with obesogenic antidepressants, by the weight status

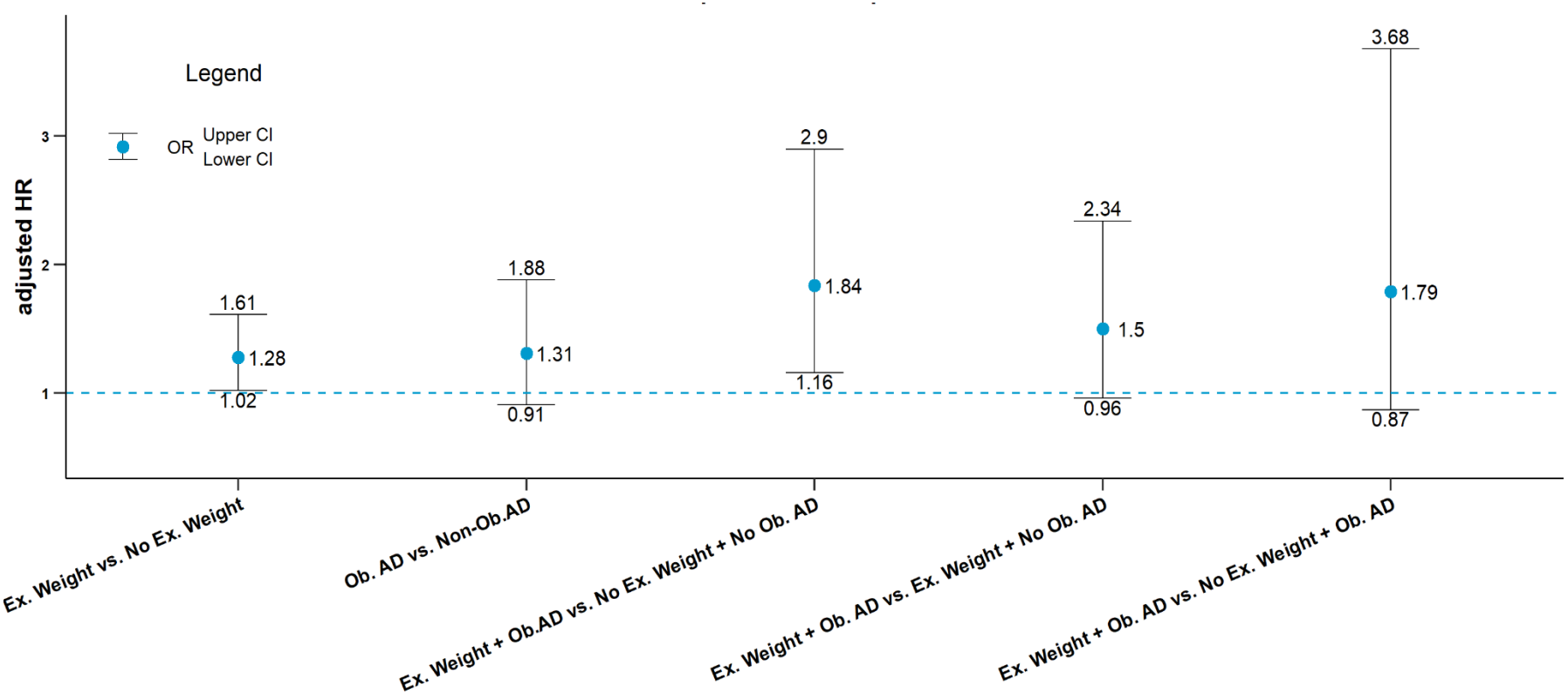
Treatment*	**Excess weight status**	**aHR (95% CI)** for hospitalizations**			
Treatment with obesogenic AD	Yes	1.84 (1.16, 2.90)	1.50(0.96, 2.34)	1.79(0.87, 3.68)	1.00
	No	1.03(0.55, 1.92)	0.84(0.45, 1.55)	1.00	0.56(0.27,1.16)
No treatment with obesogenic AD	Yes	1.23(0.96, 1.56)	1.00	1.19(0.64, 2.21)	0.67(0.43, 1.04)
	No	1.00	0.82(0.64, 1.04)	0.97(0.52, 1.81)	0.54(0.35,0.86)

Likelihood ratio test p<0.0001

*people who had <30days of cumulative use of obesogenic AD were classified as nonexposed to obesogenic AD; grace period of two days included; no carry-on period introduced.

**Adjusted to age, sex, household income, level of education, comorbidities, and past health service use.

Figure 7.4. Hazard ratios for obesity and treatment with obesogenic antidepressants for patients with depression



with obesogenic AD but not to excess weight was 1.03; 95%CI: 0.55, 1.91. As shown in the second column of Table 7.2 and in Figure 7.4, compared to the participants with excess weight not treated with obesogenic AD, the participants with joint exposure to excess weight and obesogenic AD had an aHR of 1.50, 95%CI: 0.96, 2.34. Column 3 of Table 7.2 and Figure 7.4 shows that, compared to people without excess weight who were treated with obesogenic AD, people with the joint exposure to excess weight and obesogenic AD had an aHR of 1.79; 95%CI: 0.87, 3.68. The last column of Table 7.2 shows that, when compared with people jointly exposed to obesogenic AD and excess weight, the average aHR estimates for participants were below 1 for all three groups, with a significant difference for jointly non-exposed group.

The relative excess risk due to interactions ($RER1_{HR}$) on the additive scale for the joint exposure to excess weight and obesogenic AD was 0.58, with the limits of uncertainty: -1.32, 2.39. The proportion of the risk due to the interaction (proportion attributable to interactions [AP]) = 32%; and the synergy index (SY) = 3.23, suggesting super-additive interactions.

The marginal survival curves (Figure 7.5) show the probability of remaining hospitalization-free had all patients, contrary to fact, belonged to one of the four exposure groups. The curve for the joint exposure shows the lowest survival rates, while the curve for the exposure to excess weight but not to treatment with obesogenic AD shows higher survival rates. The highest survival rates were observed for the curve for the jointly unexposed.

The smooth-in-time hazard function plots on Figures 7.6 A and 7.7 B show that the hospitalization hazard is increased within the first days of follow-up in all exposure groups, then monotonously decreases until about 100 days of follow-up, and then increases again, with the steepest increase in the jointly exposed. After introducing the interaction term between the

Figure 7.5. Marginal probability of remaining hospitalization-free

for treatment with obesogenic antidepressants by the excess weight status

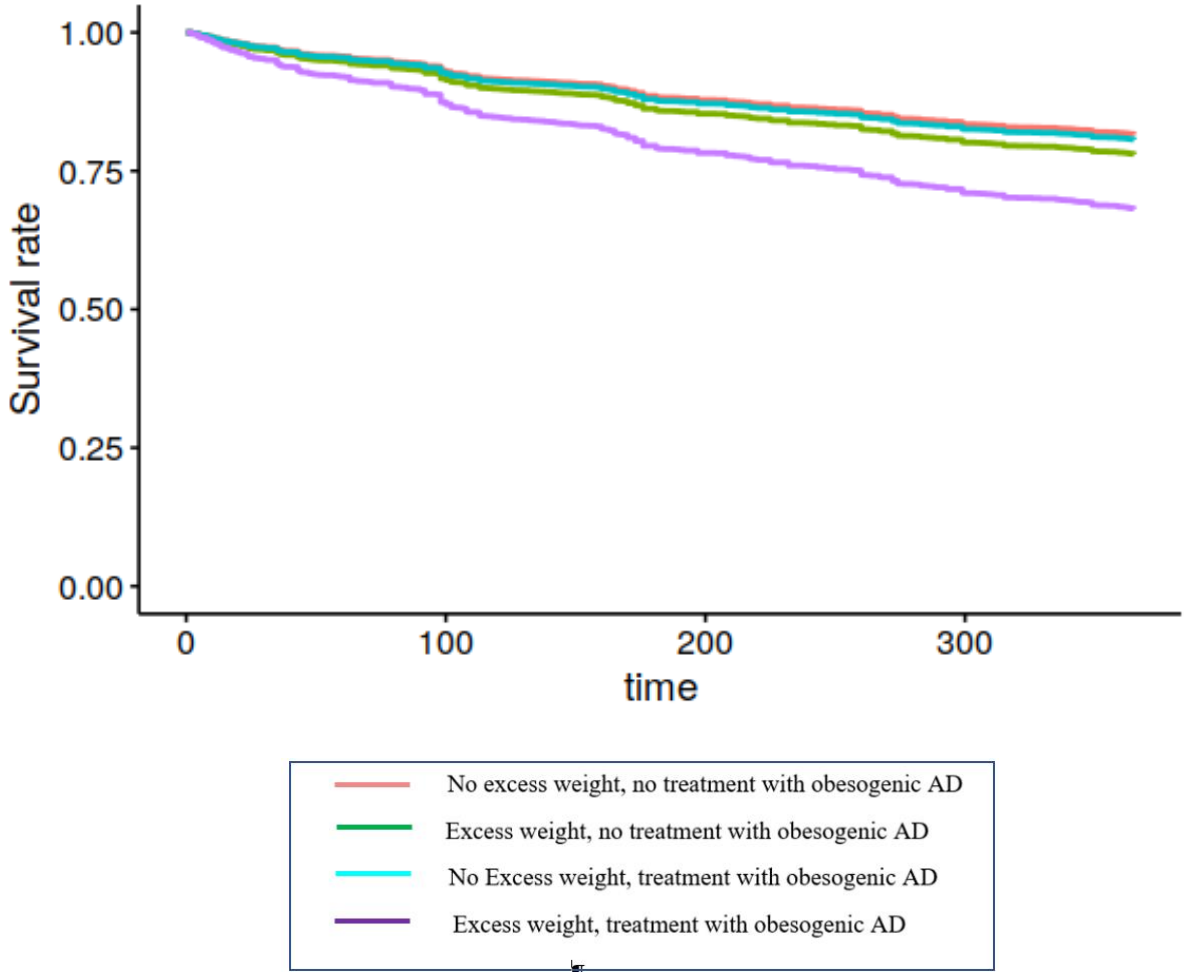


Figure 7. 6A. Smooth-in-time hazard function for the four exposure groups,

with (right figure) and without (left figure) 95% confidence intervals

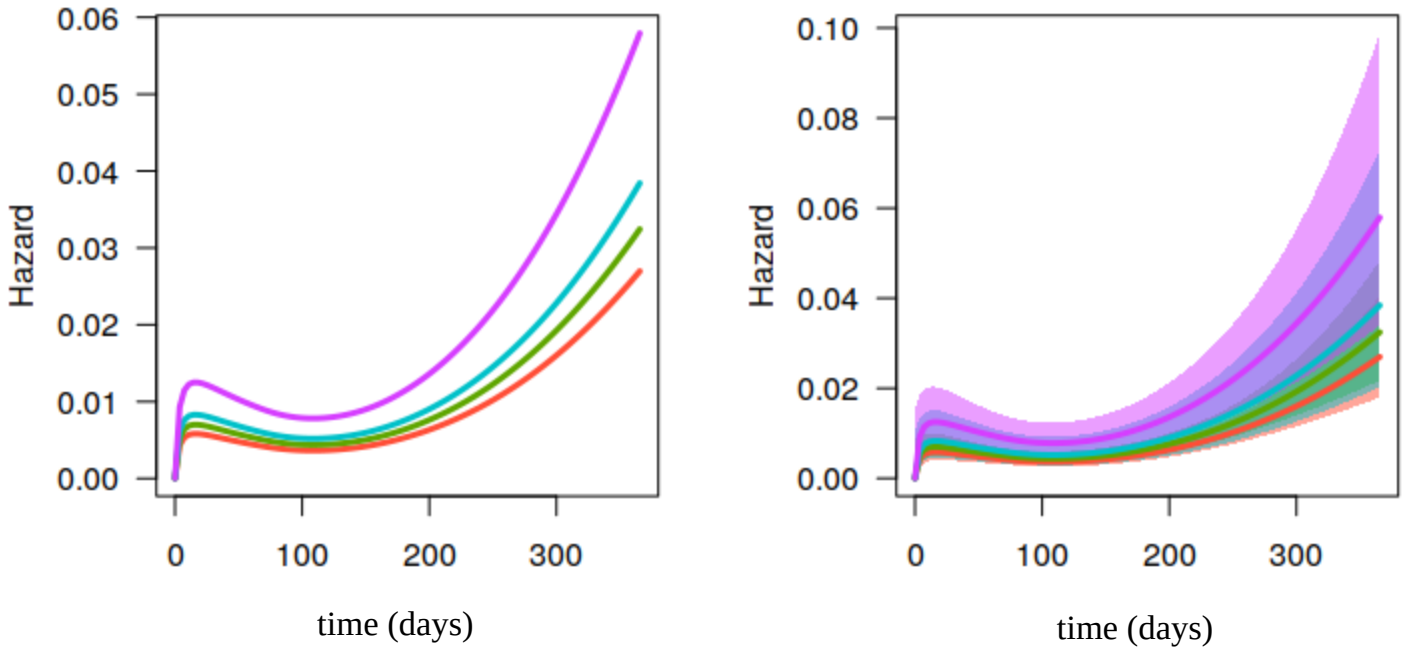


Figure 7. 6B. Smooth-in-time hazard function for each exposure group

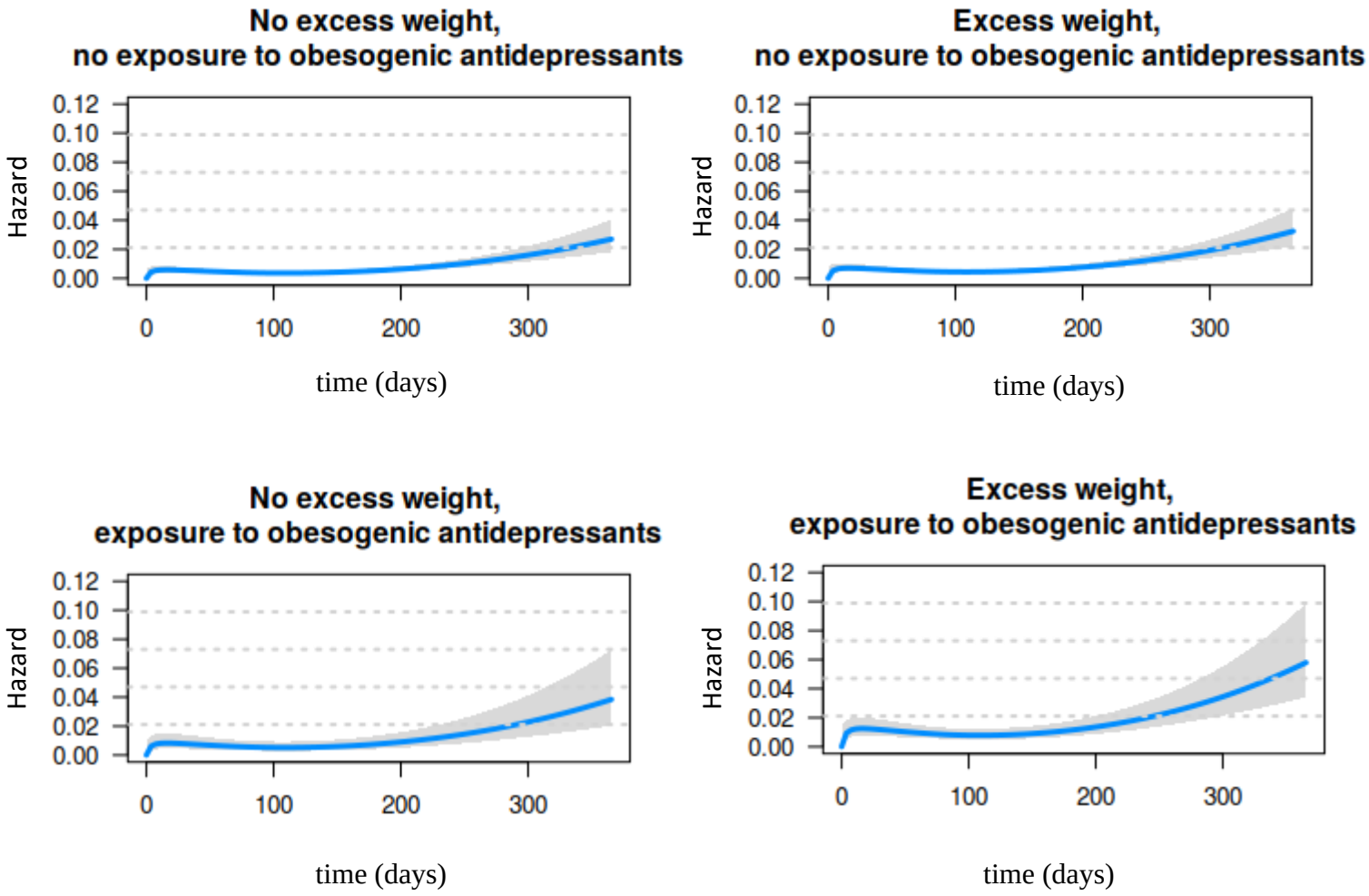


Figure 7. 7A. Smooth-in-time hazard function for the four exposure groups, interaction with time, with (right figure) and without (left figure) 95% confidence intervals

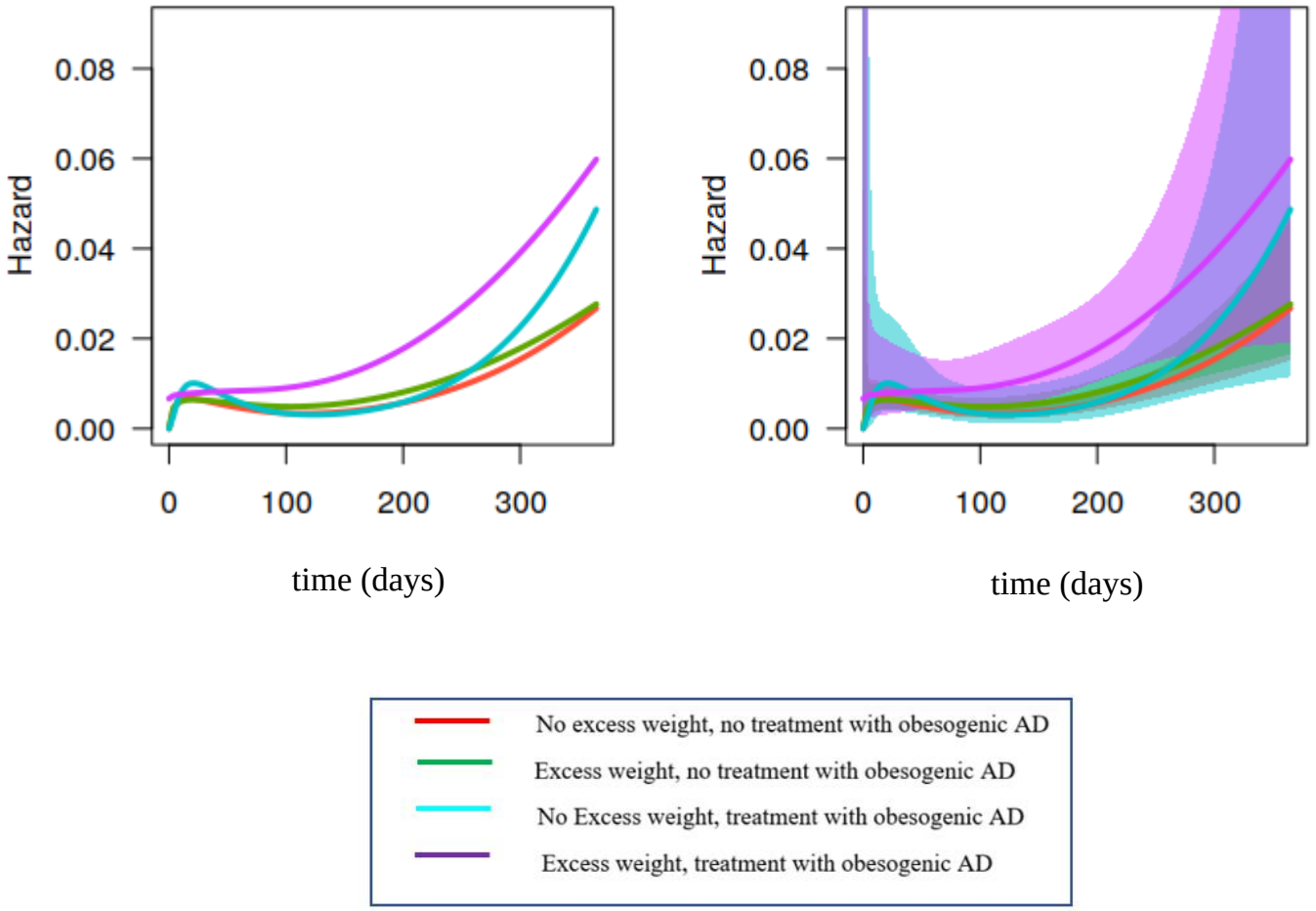
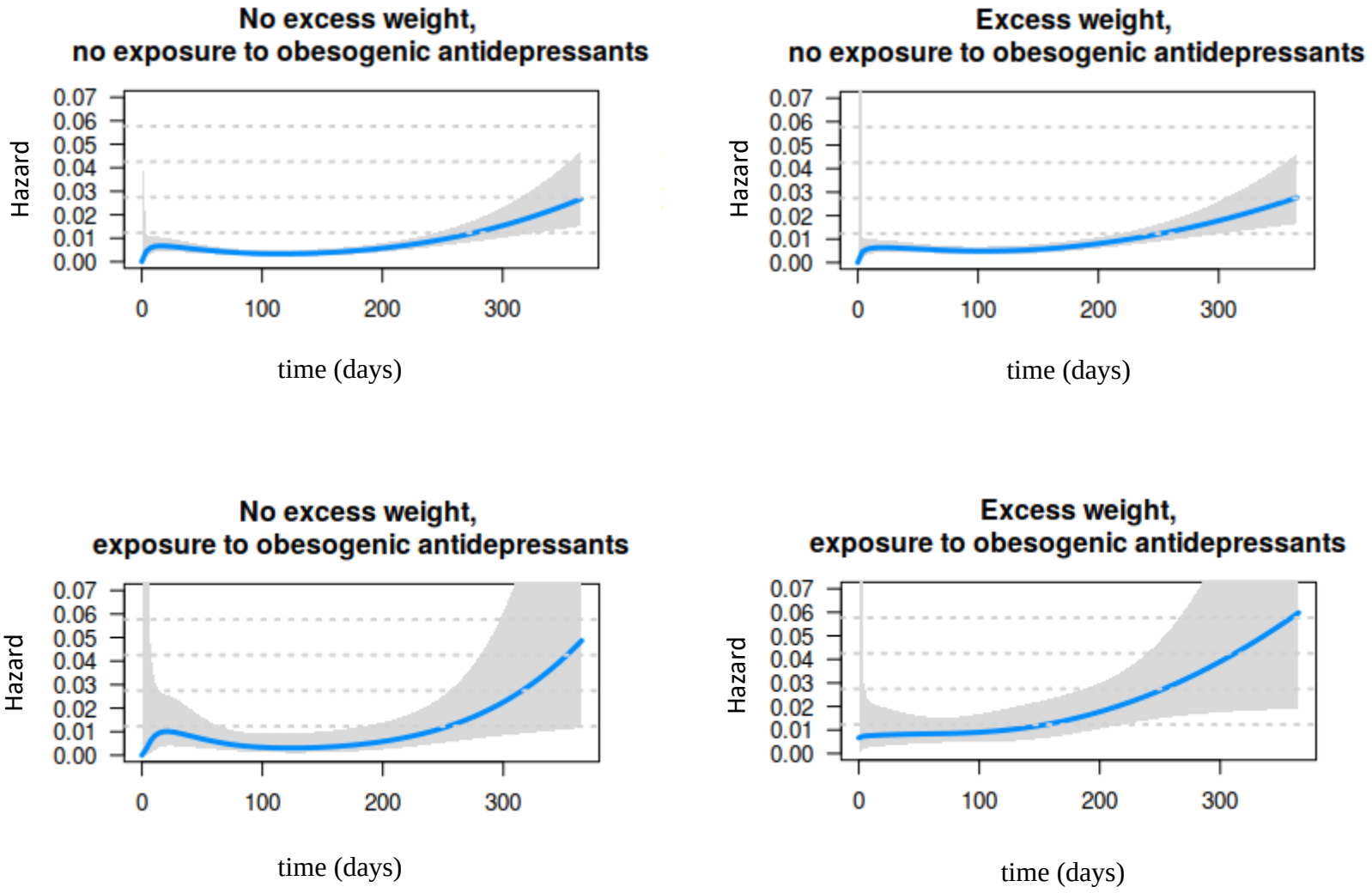


Figure 7. 7B. Smooth-in-time hazard function for each exposure groups,

interaction with time



exposure and the cubic spline of time (Figure 7.7 A and B), we observed non-proportionality of hazards, more prominent at the beginning and the end of the follow-up period.

Sensitivity analyses.

Carry-on period of seven days added. Table 7.3 shows the results of Cox regression for the analysis with different reference groups. We did not observe substantial changes in the differences of risks for hospitalizations between the groups from those observed with the main analysis. Even though the aHR estimates were lower, the 95%CI were not markedly different between the two analyses.

Different duration of latency period. HR for 0-, 60-, or 90-day latency exposure periods are shown in Supplementary Table S2. While there was a difference in the aHR estimates and the level of precision with all three lengths of the latency period, the sensitivity analyses demonstrated the same trend as the main analysis, with 95%CI showing marked and significant differences between the jointly exposed and jointly unexposed groups.

Different cut-offs for the time lag between BMI measure and cohort entry. After excluding data from people whose BMI was measured $\leq$ 2 years and $\leq$3 years before cohort entry, we observed trends similar to that yielded by our main analysis, with lower precision for differences between groups (Supplementary table S3).

Exclusion of patients with double prescriptions. (Supplementary Table S4). We observed the same trend for differences in aHR between the groups as in the main analysis.

The data in the supplementary tables are shown for the analyses with the jointly unexposed group as the reference. Shifting the reference group to any of the 3 other groups showed the same trends as in the main analysis (data not shown).

Table 7.3. Hazard ratios for hospitalization in patients with depression treated antidepressants, carry-on period of seven days added

Treatment*	**Excess weight status**	**aHR (95% CI)* for hospitalizations**			
Excess weight, whole sample			1.28 (1.02, 1.61)		
Treatment with obesogenic AD, whole sample			1.18 (0.82,1.68)		
Treatment with obesogenic AD	Yes	1.68(1.07, 2.62)	1.38(0.89, 2.13)	1.90(0.92, 3.89)	1.00
	No	0.88(0.48, 1.65)	0.73(0.39, 1.35)	1.00	0.53(0.26,1.08)
No treatment with obesogenic AD	Yes	1.22(0.96, 1.55)	1.00	1.38(0.74, 2.56)	0.73(0.47, 1.13)
	No	1.00	0.82(0.64, 1.05)	1.13(0.61, 2.11)	0.60(0.38,0.93)

Likelihood ratio test p<0.0001

*people who had <30days of cumulative use of obesogenic AD were classified as nonexposed to obesogenic AD; grace period of two days included carry-on period of 7 days added.

**Adjusted to age, sex, household income, level of education, comorbidities, and past health service use.

7.5.3. Examining associations between individual obesogenic AD and hospitalizations by Cosine similarity metric

The cosine similarity metric was used to quantitatively assess the association between the use of AD and hospitalization (Table 7.4). Specifically, we observed that in absolute values of the four tested AD, this metric was the highest with mirtazapine (Table 7.4). We could not include trimipramine in this similarity analysis due to low patient numbers.

It was also notable that the use of nortriptyline in patients with normal weight showed the smallest association with hospitalization (Table 7.4). Therefore, we conducted an additional analysis in which the cosine similarity metrics obtained in patients with normal weight were subtracted from the corresponding values from patients with excess weight (Figure 7.8). This analysis demonstrated the differences more prominently. In particular, both the use of amitriptyline and nortriptyline demonstrated higher relative associations with hospitalization in patients with excess weight (respectively, 0.21 and 0.43, Figure 7.8).

7.6. Discussion

In our study, we evaluated the difference between the health service use (the all-cause hospitalization), which served as an indicator of general health, between patients with or without excess weight, who suffer from depression and were prescribed AD known for their obesogenic adverse effects. We paid specific attention to the risk of hospitalization in patients with the joint exposure to excess weight and obesogenic AD, in comparison with the separate effects of either exposure. In addition, we quantified the strength of association between the use of an obesogenic

.

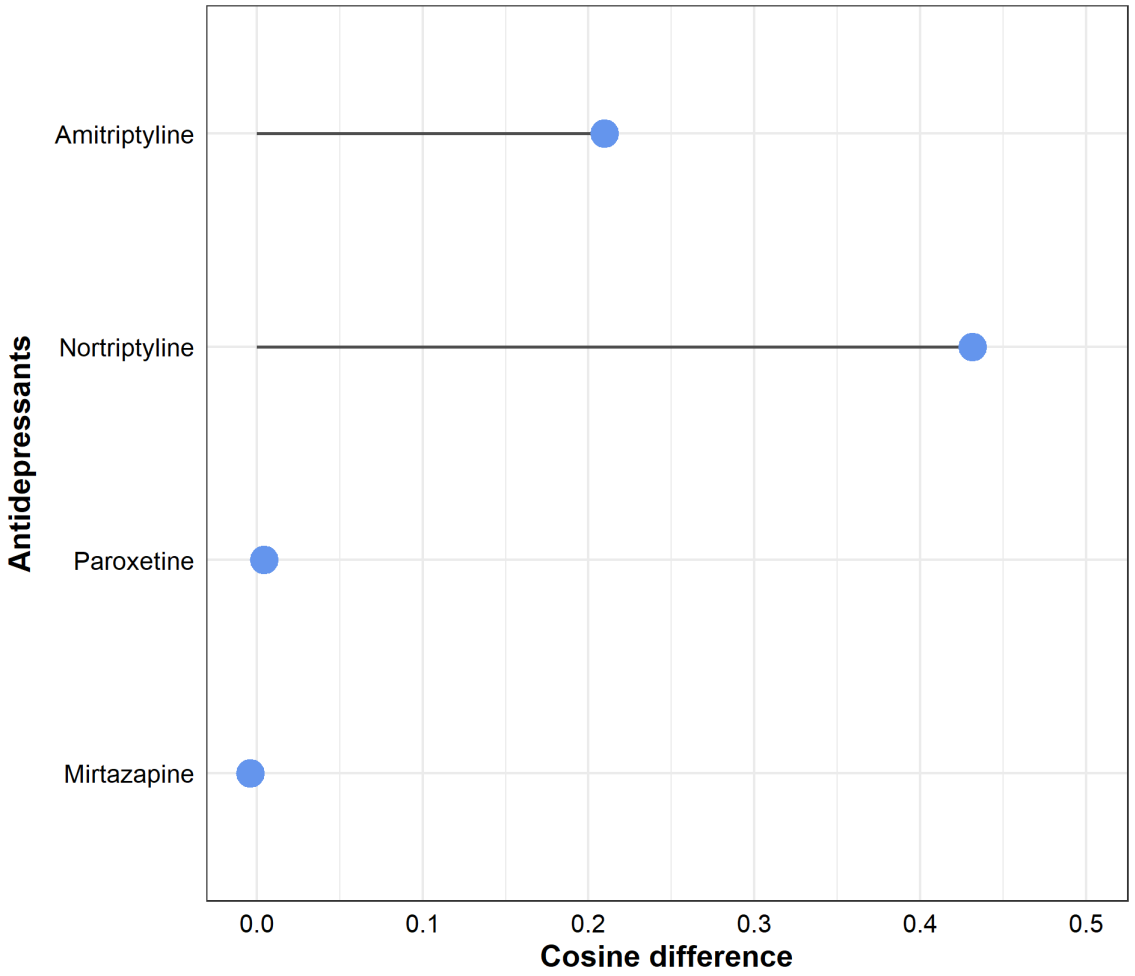
Table 7.4. Cosine similarity matrix:

similarity between prescriptions for individual obesogenic antidepressants and hospitalizations in each month of follow-up,

for patients with and without excess weight

	Ami_use_highBMI	Nort_use_highBMI	Paro_use_highBMI	Mirt_use_highBMI	Ami_use_normBMI	Nort_use_normBMI	Paro_use_normBMI	Mirt_use_normBMI
Ami_hosp_highBMI	0.738837401	0.848791541	0.834469922	0.791241279	0.581269751	0.65634213	0.72126797	0.807341606
Nort_hosp_highBMI	0.641720594	0.69621228	0.682468512	0.65125631	0.530657394	0.440831015	0.630222587	0.662904041
Paro_hosp_highBMI	0.653135884	0.719418168	0.685247927	0.664960378	0.526343079	0.562731434	0.649241052	0.689363462
Mirt_hosp_highBMI	0.838990711	0.84901241	0.849688802	0.842381026	0.734180264	0.704026667	0.822269162	0.877855479
Ami_hosp_normBMI	0.693504038	0.718516991	0.768731449	0.700146725	0.529069907	0.61177529	0.666889073	0.747970082
Nort_hosp_normBMI	0.443059756	0.459619408	0.49817351	0.428689671	0.276926801	0.264906471	0.386606572	0.498810681
Paro_hosp_normBMI	0.709093856	0.758333333	0.747222142	0.739162317	0.594867761	0.718049122	0.68064081	0.756045593
Mirt_hosp_normBMI	0.804982684	0.878125	0.869980066	0.837702121	0.703716693	0.608780778	0.810353096	0.846264856

Figure 7.8. Difference in cosine similarity for individual obesogenic antidepressants between excess weight and no excess weight groups



AD and hospitalization. The latter was done by calculating the differences in the cosine similarity metrics between patients with excess weight *vs.* those without.

The Cox regression analysis revealed that patients with excess weight, who were treated with obesogenic AD, were at a 1.84 times greater risk for hospitalization than patients with no excess weight, who were treated with non-obesogenic AD. Furthermore, among the patients with excess weight, those who were treated with obesogenic AD exhibited a trend to have a 1.5 times higher risk for hospitalizations, in comparison with the patients who were treated with non-obesogenic AD. Finally, among the patients treated with obesogenic AD, we observed a trend for patients with excess weight for a 1.79 times higher risk for hospitalizations, compared to the patients without excess weight.

The calculated measures of interactions on the additive scale suggest that 32% of the risk for jointly exposed to the excess weight and treatment with obesogenic AD could be attributed to the interactions between the two exposures. Specifically, the Synergy Index of 3.23 indicated super-additive interactions. A valid assessment of interactions, however, is based on the assumption that confounders for both exposures have been accounted for [27]. The Direct Acyclic Graph (Supplementary Figure S6) demonstrates the presence of unmeasured confounders in the association between excess weight and hospitalizations. Therefore, our results imply the effect modification of the association between prescription of obesogenic AD and all-cause hospitalizations by the excess weight status, rather than the interaction between the exposures [27].

More specifically, our results suggest that treatment with obesogenic AD may be associated with the higher health risks for patients with depression and excess weight than for patients with normal weight. The weight gain associated with obesogenic AD may reach 3.3 kg during the acute treatment (4-12 weeks) and more than 5 kg when the treatment exceeds 4 months [22]. Such a

substantial weight increase may be more detrimental for the general health of patients who already are overweight. For example, this weight gain may "promote" them to the "obese" weight class. Similarly, the patients with the obesity class I may move up to a higher obesity class. Obesity is consistently associated with multiple health risks, including Type 2 diabetes, hypertension, heart disease, and musculoskeletal problems [38]. Several studies found that obese patients with depression are a highly stigmatized population with poor quality of life and frequent use of health services [39-41]. Moreover, patients in high obesity classes are more likely to have multiple comorbidities [42]. Therefore, there is a possibility that the health problems related to weight increase may partly explain the trend for patients with excess weight who receive obesogenic AD to be at a higher risk for hospitalizations than for participants without excess weight.

It is also possible that other adverse effects of obesogenic AD were in part responsible for this observed trend. In this regard, it is important that TCAs are consistently associated with cardiovascular complications. One of such complications is the life-threatening ventricular arrythmia known as "Torsade de Pointes" [43,44]. Another adverse effect associated with obesogenic AD, such as the TCAs [45,46] and mirtazapine [45], is the increased risk for diabetes. Admittedly, our follow-up period might have not been long enough to document the manifestations of this effect. Of note, our comparison (that is, patients receiving non-obesogenic AD) included citalopram which is also associated with the Torsade de Pointes arrhythmia [47,48]. Furthermore, the non-obesogenic SSRI sertraline, another medication in the control group, is associated with Type 2 diabetes [45]. Thereby, the inclusion in our control group the patients receiving these medications aimed to balance out the cardiovascular and diabetes-promoting adverse effects.

Another factor, namely, the poor response to certain obesogenic AD could have contributed to the trend observed in patients with excess weight. This response could be different for individual

AD types [16]. Insufficient statistical power precluded us from examining these associations in a regression analysis. For this reason, an alternative analysis utilizing the cosine similarity metric was carried out. This analysis demonstrated that the TCA amitriptyline and nortriptyline exhibited higher associations with hospitalization in patients with excess weight, as opposed to patients without excess weight. This analysis also revealed no such differences with regard to the NaSSA mirtazapine and the SSRI paroxetine. These findings indicate a differential association with hospitalizations between patients with and without excess weight for different AD classes. The findings also suggest that adverse effects and attenuated response to treatment, characteristic for individual AD types or AD classes, could have contributed to an elevated risk for hospitalizations in patients with excess weight. Supporting this hypothesis, the cardiovascular and other adverse effects of TCAs were previously shown to be prominent in patients with obesity [49]. In addition, two other studies [50,51] found that, in comparison with patients without obesity and/or those with normal BMI, patients with either obesity or high BMI are characterized by a weaker response to the TCA nortriptyline. Importantly, TCAs constituted a substantial proportion of obesogenic AD in our study. Therefore, it cannot be excluded that the suboptimal response to TCAs in patients with excess weight could have been a contributor to the observed trend for a higher risk of hospitalization. Our outcome was hospitalization for any cause. Therefore, it is possible that the increased risk for hospitalization might have been due to a suboptimal response to the treatment combined with the adverse effects of obesogenic AD.

The smooth-in-time hazard function plots indicate that, upon treatment with obesogenic AD, the hospitalization hazard may differ between patients with and without excess weight, depending on the follow-up time. These differences may reflect subpar treatment effects or an earlier start of adverse effects in patients with excess weight. Specifically, the increase in the

hospitalization hazard in this group was observed right after the first days of the follow-up and became more prominent towards the end of the follow-up period. In patients without excess weight, the decrease in hospitalization hazard was observed after the initial increase and lasted for more than 100 days, which roughly corresponded to the period of acute treatment (three months). In contrast, we observed a less prominent decrease in hazards during the early months of follow-up in patients without excess weight treated with non-obesogenic AD, compared to those treated with obesogenic AD. One possible explanation of this phenomenon is that obesogenic AD may be especially beneficial for those patients in the no excess weight group who are underweight. This hypothesis, however, needs further testing. The hazards in patients treated with non-obesogenic AD increased more monotonously, with a slightly more prominent decrease during the early months of treatment in patients without excess weight. This difference could reflect a lower efficacy of pharmacological treatment in patients with excess weight in our sample, reported in the literature [16]. Alternatively, this difference could be attributed to increased health risks related to excess weight status. Yet, the observed difference in hazards is less obvious for the groups treated with non-obesogenic AD than for those treated with obesogenic AD. One could speculate that these findings indicate a less prominent modifying role of excess weight on adverse effects and/or treatment efficiency of non-obesogenic AD.

In summary, our findings suggest that the excess weight population is more likely to experience the negative consequences of treatment with obesogenic AD than the normal weight population. This may be explained by the weight-increasing or other adverse effects of obesogenic AD, alone or in a combination with a diminished treatment response. It is also possible that TCAs are more responsible for this phenomenon than mirtazapine and paroxetine. The risk to benefit ratio of prescribing these specific AD to patients with excess weight should be addressed in further

research, using a longitudinal cohort of patients with depression, repeated BMI measures to exclude misclassification of exposure to excess weight, available measures on exposure to individual obesogenic AD, and important covariates, which we could not account for in our study, such as the type and severity of depression.

7.7. Strength and limitations

This was the first study to evaluate the role of excess weight in the association between treatment with obesogenic AD (as opposed to non-obesogenic AD) and hospitalizations, during acute and maintenance depression treatments. In addition, we applied the cosine similarity method, commonly used in unsupervised learning, to health data, in order to overcome the limitations of the utilized database. In specific, the latter yielded insufficient statistical power to examine the associations for each individual AD by traditional statistical methods. In addition, the data were presented in a form of a "sparse matrix". Furthermore, we were able to use a cohort of incident users, and to ensure the temporality between BMI measures and the first prescription of an AD in patients who had been diagnosed with depression before the first AD prescription. In addition to the calculation of average aHRs for the studied groups, we presented marginal survival curves and time-dependent hazards. We also calculated the measures of interaction between the two exposures on the additive scale.

Our study also had limitations. Firstly, the low statistical power precluded the estimation of individual AD-specific risks for hospitalizations in the Cox regression. This limitation was addressed by applying the aforementioned cosine similarity metric. This enabled gaining the insights into putative implied associations between individual obesogenic AD and hospitalizations. Secondly, the weight status was only measured at the baseline. This could have allowed for

misclassification of exposure. In particular, people who had initially been without excess weight, but gained weight while receiving AD, could have been misclassified as people without excess weight. This misclassification would cause an underestimation of the observed difference in associations. Thirdly, a follow-up period of one year might not have been long enough for observation of the changes in health utilization. In particular, if one wished to observe whether said changes had been related to the presumed adverse effects of weight gain in patients who had initially been overweight or had had obesity. Our aim, however, was to examine whether prescribing obesogenic AD within the standard periods of acute and maintenance depression treatment could affect health outcomes. Therefore, we deemed a longer period of follow-up as not mandatory in this setting. The fourth limitation was the absence of information on depression severity in our database. The severity of depression may be associated with the risk for hospitalization. If we had included patients with and without AD prescriptions, this might have caused the "confounding by indication" phenomenon. For this reason, we included only the patients with depression who had been prescribed pharmacological treatment, which is a clear indication for patients with moderate or severe depression [13]. Nonetheless, our work is still not completely immune to confounding by indication because of the absence of another important variable, namely, the data on chronic pain. This latter is important because TCAs are often prescribed off-label for chronic pain. The excess weight patients are more likely to experience chronic pain and could thus have required hospitalizations. Even though we adjusted for the comorbidity index in our analyses, we could not distinguish between people with and without chronic pain. Therefore, some confounding leading to an overestimation of the observed associations could have been possible. Yet our consideration addressing the above limitation is the following. The obesogenic group in our study was also prescribed AD of other (non-TCA) classes.

In addition, certain non-obesogenic AD can also be prescribed for chronic pain. This, in our opinion, suggests that this putative confounding effect could not be fully responsible for the trends observed in our study.

7.8. Conclusion

In comparison with patients without excess weight who received non-obesogenic AD, patients with excess weight, who receive obesogenic AD, were observed to be at a higher risk for hospitalizations within 12 months after treatment initiation. More importantly, we observed a trend for patients with excess weight treated with obesogenic AD for the higher risk of hospitalizations compared to patients with excess weight treated with non-obesogenic AD. These findings suggest that obesogenic AD may be not the best treatment option for patients who are overweight or have obesity. Study results should be interpreted with caution since no causal inference can be implied. The results of the cosine similarity analyses led us to hypothesize that the TCA amitriptyline and nortriptyline may have contributed more strongly, than mirtazapine and paroxetine, to differing associations between the use of obesogenic AD and hospitalizations in patients with excess weight *vs.* those without. It is recommended to reproduce these observations in a larger cohort of patients with depression where there will be enough statistical power to evaluate the individual obesogenic AD by traditional statistical analyses. Such cohort should plan for repeated measurements of BMI, as well as other important covariates not presented in my database (e.g., severity and type of depression) during AD treatment, permitting the utilization of causal inference methods.

7.9. Acknowledgements

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Authorship contribution statement

SP was primary investigator and conducted the research under the supervision of TS, CR, GB, and TAB. All authors contributed to the methods and interpretation of results. The text was written by SP and revised by the other authors.

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7.10. References

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7.11. Supplemental information.

7.11.1. Supplementary Table S1. ICD-9 and ICD-10 codes for detection of depression diagnosis in health-administrative data, adapted from Fiest et al., 2014 (Fiest et al., 2014)

Group	Code	Diagnosis
		ICD-9 Case definition #3 by Fiest et al., 2014
Depressive disorder and dysthymia	300.4	Dysthymic disorder
	311	Depressive disorder, not elsewhere classified
Bipolar, atypical and unspecified mood disorder	296.5	Bipolar I disorder, most recent episode (or current) mild depression
	296.6	Bipolar I disorder, most recent episode (or current) mixed
	296.82	Atypical depressive disorder
	296.9	Unspecified episodic mood disorder
Adjustment disorder and prolonged depressive reaction	309	Adjustment disorder with depressed mood
	309.1	Prolonged depressive reaction
	309.28	Adjustment disorder with mixed anxiety and depressed mood
		ICD-10 Case definition #6 by Fiest et al., 2014
Depressive disorder and dysthymia, mixed anxiety and depressive disorder	F32.0	Mild depressive episode
	F32.1	Moderate depressive episode

	F32.2	Severe depressive episode without psychotic symptoms
	F32.3	Severe depressive episode with psychotic symptoms
	F32.8	Other depressive episodes
	F32.9	Depressive episode, unspecified
	F33.0	Recurrent depressive disorder, current episode, mild
	F33.1	Recurrent depressive disorder, current episode, moderate
	F33.2	Recurrent depressive disorder, current episode, severe without psychotic symptoms
	F33.3	Recurrent depressive disorder, current episode, severe with psychotic symptoms
	F33.8	Recurrent depressive disorder, other
	F33.9	Recurrent depressive disorder, unspecified
	F34.1	Dysthymia
	F41.2	Mixed anxiety and depressive disorder
Bipolar disorder	F31.3-31.6	
	F31.3	Bipolar affective disorder, current episode mild or moderate depression
	F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms
	F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms
	F31.6	Bipolar affective disorder, current episode mixed
Other mood disorders	F34.8	Other persistent mood disorders
	F34.9	Persistent mood disorder, unspecified
	F38	Other single mood disorders
	F38.1	Other recurrent mood disorders
	F38.8	Other specified mood disorders
	F39	Unspecified mood disorders
	F99	Mental disorder, not elsewhere specified

Fiest,·K.·M.,·Jette,·N.,·Quan,·H.,·St·Germaine-Smith,·C.,·Metcalfe,·A.,·Patten,·S.·B.,·et·al.·(2014).·Systematic·review·and·assessment·of·validated·case·definitions·for·depression·in·administrative·data.·*BMC·Psychiatry,·14*,·289.·doi:10.1186/s12888-014-0289-5¶

7.11.2. Supplementary Table S2. Hazard ratios for hospitalization in patients with depression treated antidepressants, different duration of latency periods

Treatment*	**Excess weight status**	**aHR (95% CI)* for hospitalizations**		
		Patients with cumulative use ≤30 days included	Patients with cumulative use ≤60 days excluded	Patients with cumulative use ≤90 days excluded
Treatment with obesogenic AD, whole sample		1.18 (0.85, 1.64)	1.27(0.84, 1.93)	1.38 (0.87, 2.17)
Excess weight, whole sample		1.28 (1.02, 1.61)	1.28 (1.02, 1.61)	1.28 (1.02, 1.61)
Treatment with obesogenic AD	Yes	1.63(1.07, 2.48)	1.96(1.20, 3.22)	2.02(1.17, 3.50)
	No	0.98(0.57, 1.68)	0.74(0.32, 1.69)	0.97(0.43, 2.22)
No treatment with obesogenic AD	Yes	1.23(0.96 1.57)	1.21(0.95, 1.53)	1.24(0.98, 1.57)
	No	1.00	1.00	1.00

Likelihood ratio test p<0.0001

* grace period of two days included no carry-on period introduced.

**Adjusted to age, sex, household income, level of education, comorbidities, and past health service use.

7.11.3. Supplementary Table S3. Hazard ratios for hospitalization in patients with depression treated obesogenic antidepressants, different time lags between BMI measures and cohort entry

Treatment	**Excess weight status**	**aHR (95% CI)* for hospitalizations**	
		BMI measured <=3 years before cohort entry	BMI measured <=2 years before cohort entry
Excess weight, whole sample		1.25(0.91, 1.71)	1.30(0.89, 1.89)
Treatment with obesogenic AD, whole sample		1.25(0.76, 2.06)	1.11 (0.63, 1.97)
Treatment with obesogenic AD	Yes No	1.74(0.90 3.36) 1.07(0.49, 2.37)	1.60(0.74, 3.46) 0.98(0.41, 2.34)
No treatment with obesogenic AD	Yes No	1.22(0.88, 1.69) 1.00	1.27(0.85, 1.88) 1.00

Likelihood ratio test p<0.0001

*people who had <30days of cumulative use of obesogenic AD were classified as nonexposed to obesogenic AD; grace period of two days included.

**Adjusted to age, sex, household income, level of education, comorbidities, and past health service use.

7.11.4. Supplementary Table S4. Hazard ratios for hospitalization in patients with depression treated antidepressants, exclusion of patients with concurrent prescriptions for ≥ 2 AD

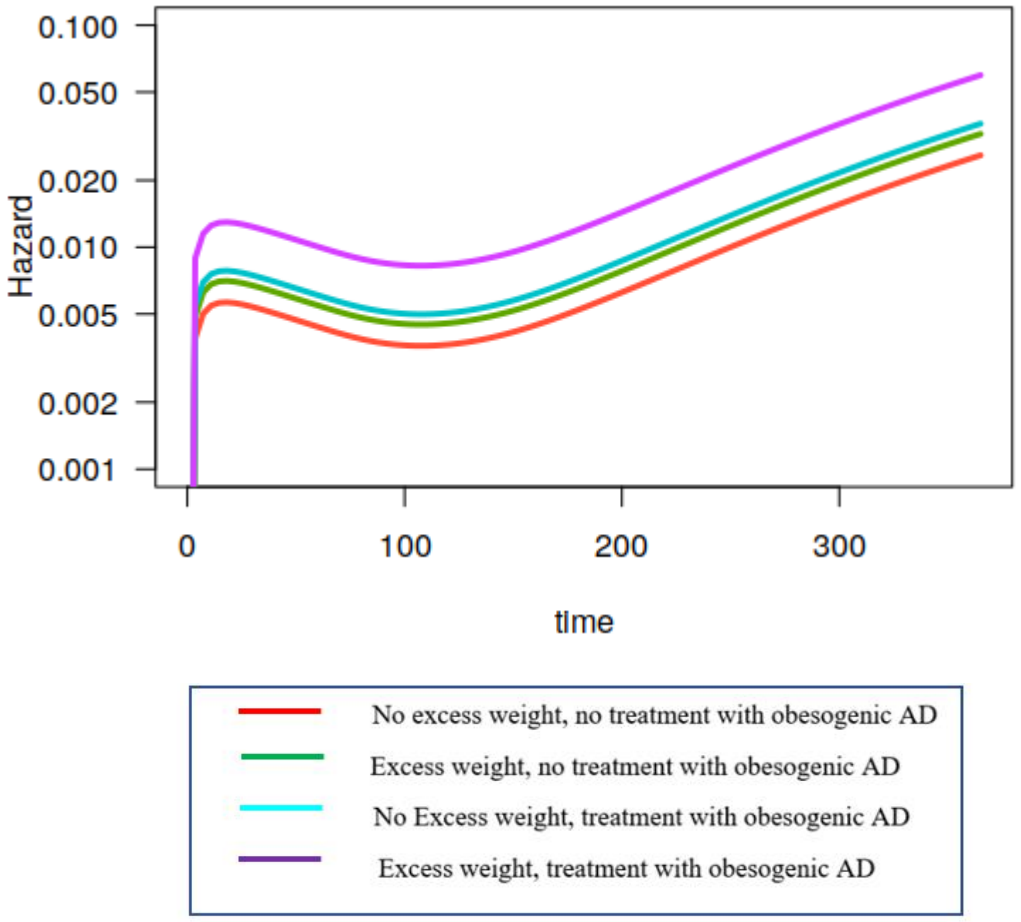
Treatment	Excess weight status	aHR (95% CI)* for hospitalization
Treatment with obesogenic AD, whole sample		1.30 (0.90, 1.89)
Excess weight, whole sample		1.29 (1.02, 1.63)
Treatment with obesogenic AD	Yes	1.83(1.15, 2.91)
	No	1.05(0.57, 1.97)
No treatment with obesogenic AD	Yes	1.25(0.97,1.59)
	No	1.00

Likelihood ratio test p<0.0001

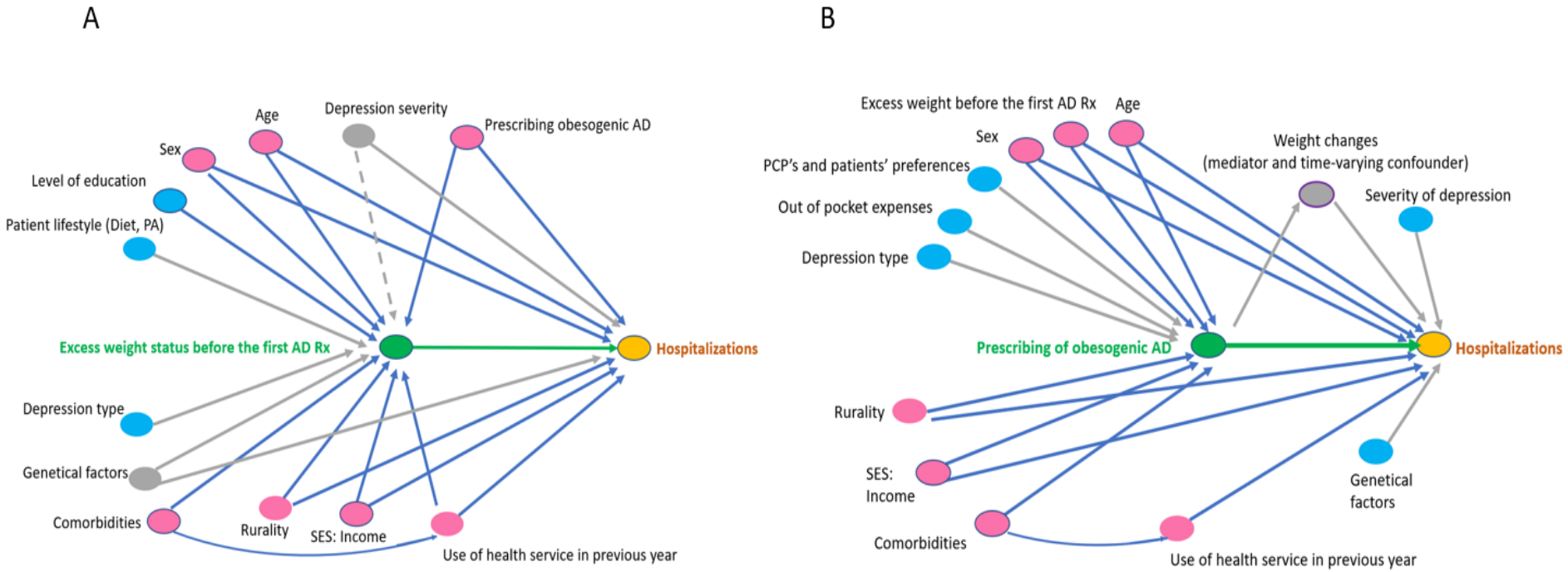
*people who had <30days of cumulative use of obesogenic AD were classified as nonexposed to obesogenic AD; grace period of two days included.

**Adjusted to age, sex, household income, level of education, comorbidities, and past health service use.

7.11.5. Supplementary Figure S5. Hospitalization hazards for the treatment groups by excess weight status on the logarithmic scale



7.11.6. Supplementary Figure S6. Direct Acyclic Graphs (DAGs) for the associations between excess weight and hospitalizations (A) and between prescribing obesogenic AD and hospitalizations (B)



CHAPTER 8: DISCUSSION

This dissertation was conducted to address the emerging need for individualized approaches to pharmacological treatment of depression in patients with excess weight. The study objectives were to synthesize the evidence on the role of excess body weight in response to AD treatment in people with depression by AD classes and individual AD, to evaluate AD prescribing patterns in Canadian primary care, with the focus on AD with known obesogenic and cardiovascular adverse effects, and to examine the role of the excess weight status in the association between prescribing of AD with obesogenic adverse effects and health care utilization, as the indicator of general health.

In my first manuscript (Chapter 4), I synthesized the current evidence on the differential response to treatment with individual AD in patients with excess weight and identified the knowledge gaps in this area. In my second manuscript (Chapter 5), I evaluated the AD prescribing prevalence for people with obesity, including for obesity classes I-III. I also described the differences in AD prescribing and evaluated the number of individual AD prescribed for patients of different weight groups. In the third manuscript (Chapter 6), I evaluated the differences in prescribing individual AD for patients with obesity *vs* normal weight patients, with the focus on AD that are known for their obesogenic and cardiovascular adverse effects. Finally, in my last manuscript (Chapter 7), I examined the role of excess weight in the association between prescription of obesogenic AD during the standard course of depression treatment, and all-cause hospitalization. Towards this, I analyzed the database which provided information on weight, AD prescribing, and health service utilization (all-cause hospitalization) as the indicator of general health.

8.1 Summary

Over the past decades, consumption of AD has increased [226]; however, only half of the patients taking them will respond adequately [227]. In addition, approximately 55% will experience one or more worrisome adverse effects [228]. Such suboptimal outcomes imply an emerging need for better prediction of treatment response. The importance of individualized approaches to AD selection, based on clinical and genetic factors, to optimize treatment outcomes was highlighted by researchers in the field of Precision Medicine [226,229,230]. This dissertation addresses the importance of the depression-obesity phenotype as one of the factors requiring a personalized approach to AD selection.

The evidence synthesized in my first manuscript suggests that, even though patients with obesity and overweight patients have a poor response to certain AD, the individualized approach to AD selection may help optimize treatment response. Of concern, the findings of my second manuscripts and third manuscripts suggested that presently in Canada, patients with excess weight have higher odds to be prescribed certain AD with obesogenic and cardiovascular side effects that may be detrimental for this population. Moreover, my final manuscript demonstrated that patients with excess weight, prescribed obesogenic AD, had a trend for the higher risk of all-cause hospitalizations, than those treated with non-obesogenic AD, with the possibility that this association may depend on the individual AD types.

As demonstrated by the scoping review (the first manuscript), poor response in patients with excess weight was associated with the obesogenic TCA nortriptyline in two studies that analyzed RCT data. Nortriptyline, therefore, may not be the optimal treatment option for patients with excess weight, especially considering its obesogenic adverse effect. Of interest, in my fourth manuscript, the use of nortriptyline exhibited the strongest (among all obesogenic AD) association with hospitalizations in patients with excess weight. A similar, albeit somewhat weaker, trend was also observed for amitriptyline. In light of these observations, the tendency to more frequently prescribe the TCA amitriptyline to patients with obesity than to

patients with normal weight (the finding of my third manuscript) is concerning. The obesogenic effect of this AD may contribute to promoting these patients to a higher obesity class, as well as to increasing their risk for developing comorbidities and more severe depression. Furthermore, nortriptyline is a metabolic product of amitriptyline. Therefore, the possibility of an attenuated response to amitriptyline in patients with excess weight cannot be ruled out. The exact mechanism linking the excess weight and response to AD treatment is still unclear and most likely includes a complex interplay between several biological processes, and socio-behavioural and genetic factors. Several putative mechanisms contributing to the weakened response to treatment with TCAs in patients with excess weight can be considered. These mechanisms include a contribution of TCAs to leptin resistance [231] in patients with obesity, possibly due to an antihistaminergic activity of these medications. This results in the histamine H1-receptor-mediated dysregulation of hypothalamic nuclei involved in maintaining energy balance [231]. Another potential mechanism could be related to the high lipophilicity of TCAs, which leads to the low blood concentration of these medications. An association between low blood concentration and poor clinical response in patients with obesity was demonstrated for nortriptyline [40]. Surprisingly, in a recent study [232], no association was found between BMI and serum concentration of amitriptyline, making the contribution of this factor in the low therapeutic response to TCAs controversial.

Furthermore, in my third manuscript, patients with obesity were found to be more likely to be prescribed fluoxetine. Fluoxetine is either weight neutral or may cause some weight loss during the acute phase of treatment. Therefore, it is seemingly safe to be prescribed to patients with excess weight. However, given an attenuated response to fluoxetine treatment in patients with high BMI (as highlighted in my scoping review), fluoxetine may not be the most optimal AD choice for depression treatment in this population.

An important and encouraging finding of my scoping review was that venlafaxine XR and the combination of bupropion with escitalopram may be more beneficial for patients with morbid obesity than for patients with normal weight. Considering the similar pharmacological profiles of these two treatment options, and the abundance of available AD recommended by the guidelines, this information may be worth taking into consideration by the prescribers.

Another worrisome finding related to AD prescribing in Canadian primary care was the high prevalence of AD prescribing in patients with excess weight in comparison with patients with normal weight, with the highest prevalence being in patients with obesity classes II and III. The access to the national sample of primary care patients allowed for demonstration of the consistency of these findings across Canadian provinces. The high prevalence of AD prescribing may reflect a more severe course of depression in patients with obesity [4,82,85] that require pharmacological treatment. Considering the cross-sectional nature of the analysis and a sample of prevalent users, these findings may also reflect a longer duration of treatment to reach the therapeutic effects in patients with obesity [38,39,101]. Of importance, these results may also suggest that obesogenic adverse effects of AD might "promote" patients with normal weight or overweight to the obese group during the course of treatment, contributing to the obesity epidemic in Canada.

Another important finding was the high number of different AD types prescribed to patients with obesity, the phenomenon especially prominent in young patients. Of interest, with an increase in BMI, the number of different AD types increased in young patients, followed a U-shaped trend in the middle-aged patients, and decreased in older patients. On one hand, this finding may arise from the difficulties with making the optimal AD choice in young people with excess weight, thereby necessitating a high number of AD switches. On the other hand, it may suggest that PCPs try to avoid concurrent prescribing of several AD to older patients, but not to younger ones, in order to decrease the adverse effects due to drug-drug interactions.

More attention should be paid to avoid polypharmacy in younger patients, especially since young patients with depression may be at increased risk for suicides when exposed to certain AD [233,234]. Prescribing a higher number of AD may inadvertently increase this risk. More precise guidelines on individualized selection of AD for patients with obesity would help optimize treatment and decrease the number of adverse effects in all age groups.

The results of the random forest analysis (manuscript #3) showed that weight was an important predictor of prescribing individual AD across Canadian provinces, with the relative importance of this variable being equal to that of the age and exceeding that of the sex. These data were in line with the findings of manuscript #2 where age, but not sex was the significant predictor of AD prescribing (vs. non-prescribing). The importance of age as a predictor of AD prescribing for the UK was previously reported by Mars and colleagues (2017) who showed a progressive increase in the AD prescribing prevalence with an age increase [235].

Further, the logistic and mixed effects regression models demonstrated the difference in prescribing of AD, which are known for their obesogenic and cardiovascular adverse effects, between patients with obesity and their normal weight counterparts (manuscript #3). In particular, patients with obesity had higher odds for being prescribed the weight-reducing AD bupropion and lower odds for being prescribed obesogenic mirtazapine, which was reassuring. On the other hand, however, patients with obesity also exhibited a trend to more likely receive the obesogenic AD amitriptyline, which is known for its cardiovascular adverse effects. In addition, obese patients from urban areas were less likely to receive the SSRI escitalopram, which is considered as more effective and exerting fewer cardiovascular adverse effects (e.g., "Torsade de Pointes" arrhythmia) than citalopram [184,188,189,193]. Escitalopram is not covered by government insurance plans in some Canadian provinces (e.g., Quebec); therefore, one of the explanations for this difference in prescribing may be lower socioeconomic status in patients with obesity in urban areas. Since patients with obesity are already at an increased risk of

cardiovascular complications [236], lower odds for patients with obesity to receive escitalopram warrant further investigation.

In light of the differences in prescribing demonstrated by the first and second manuscripts, the trend that patients with excess weight have a higher risk for hospitalizations when prescribed obesogenic AD, as compared to their normal weight counterparts, found in the fourth manuscript, is especially concerning. This trend may be explained by obesogenic and/or other (e.g., cardiovascular) adverse effects, which could be more prominent in people who already have excess weight. In addition, other factors, unaddressed in the database, could have contributed to this trend. The weight increase may be as high as 3.3 kg during acute treatment and more than 5 kg when treated longer than 4 months [157]. For patients who already are overweight or obese, this weight gain may mean advancing to a higher weight group or obesity class, with subsequently higher risks for the excess weight-related complications and more severe depression [237].

The analysis based on cosine similarity metric suggested that difference in the associations between AD use and hospitalizations in patients with and without excess weight may be different for individual obesogenic AD. A lower level of weight gain during the treatment was reported for paroxetine in comparison with TCAs [157]. This may, in part, explain a negligible difference in the association of paroxetine use with hospitalizations between the contrasting weight groups, as demonstrated by the cosine similarity analysis. This explanation, however, is not applicable for NaSSA (mirtazapine), since the weight gain for NaSSA and TCA classes was comparable [157]. It is possible that it is not the actual weight gain, but other related effects that may have contributed to the health risks. For example, both TCAs and mirtazapine were associated with dyslipidemia through activation of the sterol regulatory binding protein (SREBP) [238]. TCAs were reported as the most potent SREBP activator, whereas mirtazapine activated SREBP to a much lesser extent [238]. Another mechanism that could have contributed

to a higher risk for hospitalization in TCAs users may be related to a suboptimal response to treatment in patients with excess weight, reported for TCAs. Furthermore, TCAs and certain SSRIs are known to be associated with the life-threatening cardiac ventricular arrythmia, "Torsade de Pointes" (TdP) [171,239]. Upon TCAs use, the risk for this arrythmia appears to be at the highest level. This is due to a two-sided mechanism. In particular, ventricular repolarization may become disrupted both through blockade of sodium and calcium channels, and through blockade of the rapidly activating component of the delayed rectifier current [177]. The risk of TdP for patients taking mirtazapine is debatable [191,192], while paroxetine has been reported as causing a low risk for TdP [193]. It can be stipulated that a poor response to depression treatment, with a simultaneously elevated risk for cardiovascular and other (e.g., metabolic) adverse effects, may explain (in part or in full) the more prominent difference in the association between hospitalization and TCA use for patients with excess weight, compared to patients without excess weight, with this difference being less obvious for other obesogenic AD.

8.2 Implications for practice and policy.

This dissertation highlighted the emerging need for individualized approaches to pharmacological treatment of depression in patients with excess weight.

The scoping review demonstrated that, while evidence is scarce, the existing data on the response to treatment with several individual AD in relation to the weight status can be considered by prescribers to avoid suboptimal choices. Moreover, a stronger response to certain AD and AD combinations in patients with the high obesity classes indicates a window of opportunity to optimize depression treatment in these patients, suggesting that a poor response to certain AD in patients with excess weight may be overcome by individualized approaches to AD selection. While more evidence is needed to evaluate the response to individual AD in obese patients, stakeholders and experts may already take into consideration the existing

evidence, especially whether the quality and strength of the present evidence allow the addition of obesity-specific recommendations to the guidelines.

Further, even though the reasons contributing to the increased risk of hospitalization for patients with the joint exposure to excess weight and obesogenic AD still need to be evaluated by subsequent studies, my findings suggest that obesogenic AD may not be the best option to be prescribed for patients with depression who have excess weight. Moreover, it is advisable to re-consider prescribing obesogenic AD to patients with borderline BMI who are at risk of changing their normal weight status to the overweight, or to patients who have other, unrelated to AD intake, risk factors for weight gain. Of note, even though it is known that amitriptyline may be prescribed for reasons other than depression (e.g., chronic pain), its obesogenic side effect should be kept in mind when prescribing to patients with excess weight. Further research, directly involving the prescribers, could help elucidate whether in some cases it is advisable to replace amitriptyline with other medications.

Another important problem to be addressed by stakeholders is weight monitoring during treatment. To date, the metabolic monitoring guidelines for antipsychotics use have been established. In contrast, no such guidelines exist for AD treatment [52]. Considering the alleged risks for general health that may, at least in part, be attributed to the weight gain during treatment, implementation of similar monitoring guidelines for AD will help diminish negative consequences of the associated weight-related adverse effects [52], both to patients and the society.

Of importance, the high prevalence of prescribing pharmacological treatment to patients with depression and obesity, and the differences in prescribing individual AD (found by my second manuscript) may suggest that the primary care patients with obesity in Canada may not be receiving a standard of care due to the "obesity bias". In line with this, Boudreau et al., 2013, suggested weight bias as one of the reasons for patients with obesity to be less

likely to receive psychotherapy treatment in the USA [202]. PCPs may be bypassing the first-line treatment (psychotherapy) because of the assumption that patients with excess weight are less motivated and non-adherent to recommendations for behavioral changes [207]. Negative attitudes towards patients with obesity that could have an impact on decision-making by health professionals were also described in other studies [208,209,240,241]. More attention should be paid by stakeholders to ensure that patients with obesity in Canada are guaranteed equal access to all available treatments of depression.

8.3 Implication for research

My study findings highlight the need to promote individualized approaches to AD selection for depression treatment in patients with excess weight. Presently, however, studies on the response to individual AD in patients with overweight or obesity are scarce. There could be several reasons for the lack of research on this subject.

First, among stakeholders, physicians, and researchers there is low awareness of the differential response to AD in patients with excess weight. My dissertation and the included manuscripts contributed and will contribute to raising awareness on this important topic. Other reasons may include the ethical considerations about conducting RCTs for medications with known adverse effects, and the difficulty with selecting the most suitable candidate among more than 15 commonly prescribed AD for targeted studies. As for observational studies, the available data sources often present heterogeneous data, yielding insufficient statistical power for individual medications to be analyzed by conventional statistical methods.

The above-mentioned problem prompted me to apply the cosine similarity metric, which is the distance metric typically used in unsupervised learning. This approach permitted quantifying the associations between the use of individual AD and hospitalizations. The similarity algorithms were previously used for testing the associations between patients'

clinical and socio-demographic characteristics on one side, and treatment options and clinical outcomes variables on the other side, advancing the computational toolset for Precision Medicine. This approach is especially interesting since it diminishes the need for costly RCTs [242]. The utility of similarity algorithms may, however, be limited by the characteristics of the dataset at hand. In this regard, it is important that the cosine similarity metric, utilized in my project, is an optimal metric to analyze the associations within a "sparse matrix", that is, the matrix that features many zero values and relatively rare non-zero values. As often the case with observational databases using health-administrative data, my cohort did present as a "sparse matrix". In comparison, other unsupervised learning methods (e.g., hierarchical agglomerative clustering or k-means clustering), which were shown suitable for the datasets rich in continuous variables, such as depression rating scale scores [243], would not be applicable towards "sparse matrices". Furthermore, the cosine similarity metric is commonly used to assess document similarity, which is another example of the "sparse matrix" data. In contrast to document comparisons, there are very few studies published to date [244-246] on the application of cosine similarity for biomedical data. In these studies, either transcriptome data [244] or EMR data [245,246] were analyzed. In this regard, it is another important finding of my study that the cosine similarity metric can be utilized to assess associations in health-administrative medical datasets whose data yield insufficient statistical power for conventional statistical methods. In particular, the results of the analyses conducted with the help of the cosine similarity metric led me to the hypothesis about which of the four obesogenic AD may play a more prominent role in the observed associations. This, in my view, is another confirmation of the hypothesis-generating potential of unsupervised computational methods.

In my dissertation, I applied another machine learning algorithm, random forest, to estimate the importance of weight as a variable predicting the prescribing of individual AD, in comparison with other patient-related variables, such as age and sex. In one of my published

abstracts, related to this thesis [247] (Appendix B), random forest was applied to examine the importance of weight in AD prescribing (vs. non-prescribing) in the national sample of patients with depression. Random forest can be recommended as a useful tool to evaluate the importance of patient-related characteristics which can subsequently be analyzed by conventional statistical models. The importance of the weight status in prescribing individual AD types, equal to that of age and exceeding that of sex, is a novel finding. This finding should encourage researchers to consider the inclusion of weight in the list of factors associated with prescribing.

Of note, the combination of machine learning approach and statistical modeling is a useful tool to predict response to treatment with a clinically meaningful accuracy [248], even when only demographic and clinical variables (that is, without the inclusion of genetic factors) are assessed. This approach, in the form of the elastic net regularized regression analysis, was applied in one of the primary studies [248] included in my scoping review (manuscript #1) to evaluate predictors of AD treatment response. In that study, BMI was among the most important predictors of treatment response to specific AD, with clinically relevant and significant effect estimates. Unfortunately, most researchers do not include BMI, or other indices of a patient's weight status, in their predictive models. This can be attributed either to the lack of awareness of the importance of body weight or to missing body weight data in most datasets. Furthermore, machine learning is a powerful computational tool that allows for an evaluation of the contribution of multiple predictors even when the number of observations is limited (the "wide data"). A potential limitation is that a researcher still needs to decide which of prospective predictors are to be included in the dataset subjected to machine learning. Even if many data entries on a potentially clinically relevant variable are missing in the dataset, it is still advisable to consider the inclusion of this factor in the machine learning analysis. The missing data can be dealt with by any of the established approaches. This can be illustrated by

an example from my manuscript #2. In particular, I applied the Multiple Imputation by Chained Equations (MICE) technique to impute a high proportion of BMI measures missing in my dataset, with no substantial impacts on the estimates, as has been shown by sensitivity analysis. Of note, the accuracy and precision of estimated exposure effects for the complete cases and the imputed datasets, as well as the relative bias, were further evaluated [249,250] using the plasmode simulation method [251,252]. The validity of this approach for the real-world health data has been addressed in my abstract related to this dissertation [249,250] (Appendix B). This method allows for keeping the original dataset covariates, while the exposure and outcome variables are generated based on the associations estimated using the original data. The thus obtained partly simulated dataset contains no unmeasured confounders and can help estimate a potential confounding impact of the covariates to be analyzed (e.g., weight status or BMI), and facilitate the decision as to whether a complete cases analysis is justified, or data imputation is advisable [249]. Disregarding a potential contribution of weight status because of missing data in the dataset is not a valid approach, in my view, as it may contribute to decreased predictive accuracy of the model.

8.4 Limitations

My study had certain limitations, and many of these limitations were defined by the nature of the data sources used in the analysis.

The association between AD prescribing (vs. non-prescribing) and prescribing of certain AD with obesogenic and cardio-vascular adverse effects, were examined using the national population-based primary care EMR data (CPCSSN). While this source allowed for evaluation of prescribing across Canada in a sample representative of primary care patients, its use was associated with several limitations.

First, it was not feasible to distinguish between the incident and prevalent cases, since the CPCSSN detection algorithm had been designed to identify life-time depression. This permitted only a cross-sectional analysis in manuscript #2 and precluded from the utilization of causal inference methods in manuscript #3. In addition, since CPCSSN algorithm for definition of depression was, in part, based on prescribing of AD, this could have led to the overestimation of AD prescribing prevalence for patients of all weight groups in CPCSSN data.

Second, it was not feasible to exclude the reasons, other than depression, which could have caused AD prescribing. A potential confounder in the association between obesity and AD prescribing (vs. no prescribing), unaddressed in CPCSSN database, is the diagnosis of an eating disorder in patients with depression. Certain eating disorders (e.g., bulimia nervosa, binge eating, or night eating) are indications for AD prescribing [253]. At the same time, these disorders can affect patients' weight. If the sample included a substantial proportion of patients who were obese or overweight and had these eating disorders, this could have led to an overestimation of the association between the excess weight and AD prescribing for depression (vs. non-prescribing). I deemed this as unlikely since more often than not, people with eating disorders are either underweight or have normal weight [254]. Therefore, underestimation of the association between excess weight and AD prescribing for depression is a more likely outcome. Furthermore, the prevalence of eating disorders among adult primary care patients in Canada is low [255]. For the aforementioned reasons, I considered the confounding effect of potential eating disorders as not likely to have a substantial impact on the study results. Yet, this confounder cannot be ruled out and should count as a potential limitation.

The third limitation is the fact that I could not consider other important covariates that could have acted as confounders in the association between the weight status and AD prescribing (vs non-prescribing). These covariates are depression severity and type. Severe depression can affect patients' appetite, most commonly causing weight loss [256]. This fact is

recognized and paid attention to by prescribers. In particular, only moderate and severe depression are considered as indications for pharmacological treatment [198]. It is, however, difficult to predict the direction of confounding effect since patients with atypical depression, in contrast to those with typical depression, have an increased appetite which could cause weight gain [256]. These covariates are, therefore, important and need to be included in subsequent models for better predictive accuracy.

The fourth limitation is that I could not identify and exclude pregnant patients, or patients with cancer, which could have confounded the results. To this end, I expected that the size of the cohort would help reduce the input of these confounders.

Finally, other a priori important predictors of AD prescribing, such as patient preference, education, and beliefs, and PCP experience level [257,258] were unmeasured in this database. This could, therefore, affect the accuracy of the prescribing models established in this study.

The advantage of the TorSaDE database used in the analysis for manuscript #4 over CPCCSN data was the presence of the information on health outcomes. A limiting factor was that the number of participants in this source was substantially lower than that in the CPCSSN. Therefore, I could not conduct conventional statistical analyses for each individual obesogenic AD and had to apply the analyses to several obesogenic AD combined as a group. This could potentially cause the effects of individual obesogenic AD being "diluted" (i.e., masked) in the group analysis. While I could address this problem by applying the cosine similarity method, conventional statistical analyses of associations between individual obesogenic AD and hospitalization are needed to be addressed by further research.

Similar to CPCSSN data, TorSaDE database was characterized by the absence of information on the type and severity of depression. To ensure a relatively homogenous sample in terms of depression severity, I included only patients who were prescribed pharmacological treatment [198], which, as mentioned above, is a characteristic of moderate and severe depression.

Yet this study could still be affected by confounding depression severity. This is important since depression severity may be associated with the risk for hospitalizations [76,259,260]. I deemed as unlikely that an association would exist between depression severity and prescribing obesogenic AD (vs. prescribing non-obesogenic AD). In contrast, another exposure, the excess weight, can be associated with depression severity in patients in whom depression had been diagnosed before the weight has been documented, thereby confounding the weight data of these patients before the cohort entry. While I do not expect this phenomenon to be frequent, I, however, cannot rule out a certain confounding effect associated with it.

Another limitation of TorSaDE data was the fact that weight status had been documented only at baseline, which in some patients had been more than 3 years before the cohort entry (i.e., the first AD prescription). This could have introduced an information bias, leading to misclassification of exposure to excess weight. More specifically, people whose weight status changed at the time of the first AD prescription could have been placed in the wrong weight group. Importantly, the common natural trend for both men and women is to gain weight with age until they reach their seventh decade of life [261]. Therefore, it is more likely that patients with excess weight could have been misclassified as those without excess weight. I deem the opposite misclassification as unlikely. The misclassification of patients with excess weight as normal weight patients would have underestimated the observed difference in the aHR between the exposure groups. An important related problem is that weight changes could also be caused by adverse effects of AD. The AD-induced weight change, therefore, can be on the causal path between AD prescription and hospitalization and may be considered both a mediator and time-varying confounder in this association, as shown in Supplementary Figure S6, Chapter 7 (Direct Acyclic Graph [DAG]). Therefore, this confounder cannot be accounted for in the conditional regression model and requires the use of causal inference methods, e.g., marginal structural models (MSM). MSMs are causal models for the estimation, from

observational data, of the causal effect of a time-dependent exposure in the presence of time-dependent covariates that may be simultaneously confounders and intermediate variables [262]. The lacking information on weight changes during the treatment precluded me from conducting this analysis, which is another limitation of this study.

The misclassification of exposure to treatment could also be caused by the information bias associated with the use of health-administrative data. With these data sources, it is not possible to confirm that the medication was actually consumed. Considering that prescriptions had been filled, I deemed it likely that the medications were, in fact, taken by the patients. Yet there still is a possibility of a non-differential misclassification that could have biased the estimates towards the null.

Another limitation of working with health-administrative data is that the ascertainment of treatment exposure status is based on the accuracy of the number of days of supply. Therefore, should these data be inaccurate, the days when participants were actually unexposed could have been misclassified as exposed days (and vice versa). This misclassification of exposure is likely to be non-differential, with a possibility to bias the estimates towards the null. To partly alleviate the effect of such possible inaccuracy in the data, a grace period of 2 days, during which the participants were still considered exposed, has been introduced by me after the end prescription date.

A further limitation was introduced by the 12 months follow-up period, such as defined by the clinical guidelines [198]. From the clinical perspective, a period of one year might not have been sufficiently long to notice the changes in healthcare utilization which would be related to possible adverse effects of weight gain in patients who had initially been overweight or had had obesity. Since my aim was to examine whether the prescription of obesogenic AD during the standard periods of the acute and maintenance depression treatments (i.e., 12 months) could affect health outcomes, I felt that a longer follow-up period would not be justified. Another

consideration was that a longer duration of the follow-up period could increase the likelihood of the survival bias and could, therefore, add more uncertainty to study results.

The unmeasured confounders could have affected the interpretation of the study results. It is important to highlight that, even though the study for manuscript #4 was designed to evaluate the interactions between prescribing of obesogenic AD and excess weight in relationship with all-cause hospitalizations, and the calculated RER1 implies synergic interactions on the additive scale, a valid assessment of these interactions is based on an assumption that confounders for both exposures have been accounted for [263]. According to the DAG on Supplementary Figure S6 (Chapter 7), there are unmeasured confounders in the association between excess weight and hospitalizations. For this reason, the effect modification of the excess weight status on the association between prescription of obesogenic AD and all-cause hospitalizations, rather than the interaction between the two exposures [263], was suggested in the discussion of the study results.

In addition, it is known that HRs estimated by the Cox model are prone to a survivor bias, meaning conditioning on past survival due to the "depletion of susceptibles" phenomenon (exposed participants are removed from the sample at a faster rate than unexposed during the follow-up) [264]. This could have led to an underestimation of the true differences between the exposure groups in the manuscript #4.

Importantly, as with any observational study, this work could be susceptible to the "confounding by indication" bias [265]. TCA is one class within the obesogenic AD group, and these drugs are often prescribed for chronic pain [266]. Excess weight patients are more likely to have chronic pain [267] and this could have been the cause why they required hospitalizations. Even though I adjusted for the comorbidity index in the analyses, some residual confounding, which would lead to overestimation of the observed associations, is still possible. The obesogenic AD group in my study also included AD that are not commonly prescribed for

chronic pain. This, in my view, would support the notion that the "confounding by indication" bias would not have fully been responsible for the trends observed in my study.

Despite the aforementioned limitations, I was able to conduct a series of studies that helped shed light on the problems associated with AD prescribing in Canada. These problems are associated with the lack of an individualized approach to patients with excess weight. The presented study aimed to demonstrate that the "one size fit to all weight groups" attitude may be associated with increased health risks. The limitations of my study need to be overcome by further studies in this important area.

8.5 Future directions

My thesis identified the following directions for future research. First, my findings on the differences in AD prescribing between patients with or without excess weight described in the previous chapters should be addressed by qualitative studies. Deliberative consultations with prescribers are recommended as one of the methods to clarify the reasons behind these prescribing differences. The possibility that the "obesity bias" may influence the prescribing decisions should be thoroughly evaluated.

Second, in this dissertation, I observed a trend that patients with excess weight who receive obesogenic AD are at a higher risk for hospitalization in comparison with patients without excess weight. It is recommended to address these observations in a larger cohort of patients with depression to yield sufficient statistical power to evaluate individual obesogenic AD by conventional statistical methods, with repeated BMI measurements during AD treatment, as well as with addressing important covariates (e.g., severity and type of depression), which were not available in the database studied in this dissertation. It is also recommended, given sufficient statistical power, to split the healthcare indicators into those related and not related to depression (e.g., by identifying the reasons for hospitalization), and

to detach the inefficiency of individual AD in people with excess weight (e.g., by using depression scale scores) from potential detrimental effects due to the aforementioned adverse effects.

In addition, the response to treatment with non-obesogenic AD, in particular, those with the reported differential response in patients with excess weight and obesity, should also be addressed by future studies. In a recent (2021) systematic review with meta-analysis [268], the pooled depression remission rate in patients receiving monotherapy with AD of different classes was lower in the obesity group, compared to the normal weight to overweight group, while for the combined therapies (AD with atypical antipsychotics or other psychotropic medications) the remission rate was higher in the obesity group [268]. To evaluate the response to treatment with individual AD and AD combinations and to examine whether there is a causal effect of excess weight on AD treatment response, RCTs specifically aiming to examine causality of association, or observational studies applying causal inference methods, such as marginal structural models, need to be carried out.

Presently, machine learning starts to be more frequently used in Precision Medicine. A combination of machine learning and statistical modeling is a promising approach to build a universal model predicting response to AD treatment that can be used by clinicians [248]. It is, however, important to know which patients' characteristics should be included in predictive models. My study findings suggest that a patient's weight status is one such important variable. The role of other patients' characteristics, both clinical and genetic, should also be thoroughly evaluated.

8.6 Conclusion

This work was the first study to address the prescription of AD to patients with depression and excess weight in Canada, and the association of prescribing patterns with the all-cause

hospitalization as the indicator of general health. The evidence on the differential response to treatment with individual AD in patients with excess weight synthesized in this study can be useful for PCPs as one of the sources facilitating their decision making. Considering the lack of the obesity-tailored guidelines, the findings of the observed positive association between obesity and high prevalence of AD prescribing, prescription of the high number of different AD to obese patients, and documentation of higher odds to be prescribed the AD known for their obesogenic and cardiovascular adverse effects are concerning discoveries for patients with obesity in Canadian primary care. It is especially disconcerting given the trend for increased risk for hospitalization in patients with the joint exposure to excess weight and obesogenic AD, observed in this dissertation. The role of excess weight in the association between prescribing individual obesogenic AD and health outcomes needs to be further evaluated in longitudinal studies.

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APPENDIX A:

ETHICS APPROVAL

McGill

Faculty of Medicine
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September 8, 2014

Dr. Gillian Bartlett-Esquilant
Department of Family Medicine
5858 Cote des Neiges, Suite 300
Montreal, Quebec H3S 1Z1

RE: IRB Study Number A09-B45-14A
Evaluating the impact of obesity on prescribing practices and subsequent health

Dear Dr. Bartlett-Esquilant,

Thank you for submitting the above-referenced study for an ethics review.

As this study involves no more than minimal risk, and in accordance with Articles 2.9 and 6.12 of the 2nd Edition of the Canadian Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans (TCPS 2) and U.S. Title 45 CFR 46, Section 110 (b), paragraph (1), we are pleased to inform you that approval for the study (August 2014) was provided via an expedited review by the Chair on September 8, 2014, valid until **September 7, 2015**. The study proposal will be presented for corroborative approval at the next meeting of the Committee and a certification document will be issued to you at that time.

A review of all research involving human subjects is required on an annual basis in accord with the date of initial approval. The annual review should be submitted at least one month before **September 2015**. Should any modification to the study occur over the next twelve months, please advise IRB appropriately.

Yours sincerely,

Roberta Palmour

Roberta Palmour, PhD
Chair
Institutional Review Board

cc: A09-B45-14A

McGill

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January 12, 2016

Dr. Gillian Bartlett-Esquilant
Department of Family Medicine
5858 Cote des Neiges, Suite 300
Montreal, quebec H3S 1Z1

RE: IRB Study Number A09-B45-14A
Evaluating the impact of obesity on prescribing practices and subsequent health

Dear Dr. Bartlett-Esquilant,

We are writing in response to your request for continuing review for the above mentioned study.

The progress report was reviewed and we are pleased to inform you that full Board re-approval for the study was provided on January 11, 2016. The enclosed certification of annual review is valid **September 12, 2016.**

The Investigator is reminded of the requirement to report all IRB approved protocol and consent form modifications to the Research Ethics Offices (REOs) for the participating hospital sites. Please contact the individual hospital REOs for instructions on how to proceed. Research funds may be withheld, and/or the study's data may be revoked for failing to comply with this requirement.

Should any modification or unanticipated development occur prior to the next review, please notify the IRB promptly.

Regards,

Carolyn Ells, PhD
Co-Chair
Institutional Review Board

cc: A09-B45-14A

McGill

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September 13, 2016

Dr. Gillian Bartlett-Esquilant
Department of Family Medicine
5858 Cote des Neiges, Suite 300
Montreal, quebec H3S 1Z1

RE: IRB Study Number A09-B45-14A
Evaluating the impact of obesity on prescribing practices and subsequent health

Dear Dr. Bartlett-Esquilant,

We are writing in response to your request for continuing review for the above mentioned study.

The progress report was reviewed and we are pleased to inform you that full Board re-approval for the study was provided on September 12, 2016. The enclosed certification of annual review is valid **September 11, 2017.**

The Investigator is reminded of the requirement to report all IRB approved protocol and consent form modifications to the Research Ethics Offices (REOs) for the participating hospital sites. Please contact the individual hospital REOs for instructions on how to proceed. Research funds may be withheld, and/or the study's data may be revoked for failing to comply with this requirement.

Should any modification or unanticipated development occur prior to the next review, please notify the IRB promptly.

Regards,

Roberta Palmour

Roberta Palmour, PhD
Chair
Institutional Review Board

cc: A09-B45-14A

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September 21, 2017

Dr. Gillian Bartlett-Esquilant
Department of Family Medicine
5858 Cote des Neiges, Suite 300
Montreal, QC H3S 1Z1

RE: IRB Study Number A09-B45-14A
Evaluating the impact of obesity on prescribing practices and subsequent health

Dear Dr. Bartlett-Esquilant,

Thank you for submitting an application for Continuing Review for the above-referenced study.

The study progress report was reviewed and an expedited re-approval was provided by the Chair, IRB on September 21, 2017. The renewed ethics certificate is valid from **September 11, 2017 to September 10, 2018**. The re-approval of the ethics oversight for this study will be reported at the next meeting of the Institutional Review Board on October 16, 2017.

The Investigator is reminded of the requirement to report all IRB approved protocol and consent form modifications to the Research Ethics Offices (REOs) for the participating hospital sites. Please contact the individual hospital REOs for instructions on how to proceed. Research funds may be withheld, and/or the study's data may be revoked for failing to comply with this requirement.

Should any modification or unanticipated development occur prior to the next review, please notify the IRB promptly.

Regards,

Roberta Palmour, PhD
Chair
Institutional Review Board

cc: A09-B45-14A

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September 11, 2018

Dr. Gillian Bartlett-Esquilant
Department of Family Medicine
5858 Cote des Neiges, Suite 300
Montreal, QC H3S 1Z1

RE: IRB Study Number A09-B45-14A
Evaluating the impact of obesity on prescribing practices and subsequent health

Dear Dr. Bartlett-Esquilant,

Thank you for submitting an application for Continuing Ethics Review for the above-referenced study.

The study progress report was reviewed and full Board re-approval was provided on September 10, 2018. The renewed ethics certificate is valid until **September 9, 2019**.

The Investigator is reminded of the requirement to report all IRB approved protocol and consent form modifications to the Research Ethics Offices (REOs) for the participating hospital sites. Please contact the individual hospital REOs for instructions on how to proceed. Research funds may be withheld, and/or the study's data may be revoked for failing to comply with this requirement.

Should any modification or unanticipated development occur prior to the next review, please notify the IRB promptly. Regulation does not permit the implementation of study modifications prior to IRB review and approval.

Regards,

Roberta M. Palmour

Roberta Palmour, PhD
Chair
Institutional Review Board

cc: A09-B45-14A

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September 17, 2019

Dr. Gillian Bartlett-Esquilant
Department of Family Medicine
5858 Cote des Neiges, Suite 300
Montreal, QC H3S 1Z1

RE: IRB Study Number A09-B45-14A
Evaluating the impact of obesity on prescribing practices and subsequent health

Dear Dr. Bartlett-Esquilant,

Thank you for submitting an application for Continuing Ethics Review for the above-referenced study.

The study progress report was reviewed and Full Board re-approval was provided on September 16, 2019. The renewed ethics certificate is valid from **September 9, 2019 to September 7, 2020**.

The Investigator is reminded of the requirement to report all IRB approved protocol and consent form modifications to the Research Ethics Offices (REOs) for the participating hospital sites. Please contact the individual hospital REOs for instructions on how to proceed. Research funds may be withheld, and/or the study's data may be revoked for failing to comply with this requirement.

Should any modification or unanticipated development occur prior to the next review, please notify the IRB promptly. Regulation does not permit the implementation of study modifications prior to IRB review and approval.

Regards,

Roberta M. Palmour

Roberta Palmour, PhD
Chair
Institutional Review Board

cc: A09-B45-14A

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September 15, 2020

Dr. Gillian Bartlett-Esquilant
Department of Family Medicine
5858 Cote des Neiges, Suite 300
Montreal, QC H3S 1Z1

RE: IRB Study Number A09-B45-14A
Evaluating the impact of obesity on prescribing practices and subsequent health

Dear Dr. Bartlett-Esquilant,

Thank you for submitting an application for Continuing Ethics Review for the above-referenced study.

The study progress report underwent review and Full Board re-approval was provided on September 14, 2020. The ethics certification renewal is valid to **September 13, 2021.**

The Investigator is reminded of the requirement to report all IRB approved protocol and consent form modifications to the Research Ethics Offices (REOs) for the participating hospital sites. Please contact the individual hospital REOs for instructions on how to proceed. Research funds may be withheld, and/or the study's data may be revoked for failing to comply with this requirement.

Should any modification or unanticipated development occur prior to the next review, please notify the IRB promptly. Regulation does not permit the implementation of study modifications prior to IRB review and approval.

Kind regards,

Roberta Palmour, PhD
Chair
Institutional Review Board

cc: A09-B45-14A

APPENDIX B:

ABSTRACTS

characterization, and further our understanding of disease population variation in general.

Methods: Four analytic tools licensed from different vendors (SÆfetyWorks, Aetion, IHD, and E360) were used to understand the demographic characteristics of patients with AD and the incidence rates (IRs) of 2 endpoints of interest: herpes zoster (HZ) and melanoma. A total of 684,928,490 patients with at least 2 AD diagnostic codes aged ≥12 from 13 distinct healthcare databases across 8 unique countries (United States (US), Canada, United Kingdom (UK), Italy, France, Germany, Belgium, Australia) comprised the study's base population. IRs and incidence proportions (IPs) of HZ and melanoma during 2012–2017 were calculated. A ≥ 6 month washout period prior to the 1st diagnosis of each endpoint was applied.

Results: 525,489 and 74,742 AD patients across 5 US and 8 non-US databases were identified. IRs of HZ and melanoma per 1000 person years (PYs) are 0–10.17 and 0–1.89 for all databases and tools: 7.51–10.17 and 1.21–1.89 for US claim data; 7.40–7.67 and 1.15–1.16 for US EHR data (same data source); 0 for US hospital based data; and 6.11 and 0.31 for UK EMR data. IPs of HZ and melanoma (%) are 0- < 2.57 and 0–0.46 for all databases and tools: 0–2.46 and 0–0.46 in US; 1.74 and 0 in Canada; 1.32 and 0 in Australia, and 0.45- < 2.57 and 0–0.92 in EU respectively. It took ~5 hours to execute all analyses. Variability per tool was observed, but was primarily driven by differences in data in each tool.

Conclusions: Analytic tools enabled rapid analyses for risk characterization for AD using a vast amount data. Variation in results underscores the importance of access and use of a wide range of RWD to further our understanding of disease outcomes in real world settings. Rapidity facilitates iterative learning and the opportunity to develop data-driven and more complex follow up analyses as needed. These tools provide great potential for leveraging real world data for proactive and rapid drug safety surveillance.

135 | Application of machine learning algorithms to a large primary care database analysis: Random Forest in evaluation of body weight and other characteristics as predictors of antidepressants prescribing

Svetlana Puzhko[1]; Gillian Bartlett[1]; David Barber[2]; Tibor Schuster[1]

[1] *McGill UniversityMontreal, QC, Canada;* [2] *Queen's University, Kingston, ON, Canada*

Background: Antidepressants medications (AD) can cause weight gain, and patients with excess weight may have poor response or non-response to AD treatment. Therefore, patient's body weight needs to be considered when prescribing AD. As a first step to optimize pharmacological treatment of depression in obese and overweight patients, it is important to evaluate whether weight is a prominent predictor of AD prescribing. Electronic medical records (EMR) contain data on multiple factors, including patient's body weight and prescribed medications. Advanced machine learning algorithms have promising potential to be more efficient than conventional statistical models when analyzing complex data.

Objectives: Using a large primary care database, to apply a Random Forest (RF) machine learning algorithm to evaluate patient's body weight and other socio-demographic and health characteristics in prediction of AD prescribing, and to compare performance of RF model to an existing approach (multivariable binary logistic regression model).

Methods: Source: EMR from the national Canadian Primary Care Sentinel Surveillance Network (CPCSSN) for 2011–2016; adult patients (18 years of age and older) with depression. **Measure:** Prescribing of at least one AD (outcome), body mass index to categorize patients into weight groups (primary exposure); age, sex, network identification number (ID), and comorbidities (secondary exposure variables). **Analysis:** RF classification model with the number of trees set to 300 and multivariable binary logistic regression (MLR) were used to evaluate weight and other patient characteristics as predictors of AD prescribing.

Results: Among 61699 patients with depression, 41389 were prescribed AD. Five most important predictors of AD prescribing with RF were ranked as follows: network ID (Mean Decrease Accuracy [MDA] = 77.8%), age (MDA = 32.3%), epilepsy (MDA = 31.5%), hypertension (MDA = 21%), and weight (MDA = 13.8%). In the RF model, out-of-bag prediction error = 34%; sensitivity = 93.4%, specificity = 11.6%. Areas Under the Curve were 57.2% and 58.5% for the RF and the MLR, respectively.

Conclusions: RF model showed high sensitivity but low specificity, and its performance was not superior as compared to the MLR model; however, applying RF to analyze large primary care database allowed to determine the importance of socio-demographic and health characteristics in prediction of AD prescribing. Weight was ranked among the most important predictors of AD prescribing.

136 | Reproducibility of a population-based cohort study characterizing newly diagnosed multiple myeloma patients in the UK using an EHR database

Anouchka Seesaghur[1]; Victoria Banks[1]; Joe Maskell[1]; Natalia Petruski-Ivleva[2]; Jocelyn Ruoyi Wang[2]; Pattra W. Mattox[2]; David Neasham[1]; Shannon L. Reynolds[2]; George Kafatos[1]

[1] *Amgen Ltd, Uxbridge, UK;* [2] *Aetion, Boston, MA*

Background: The recent abundance of real-world evidence from studies using large databases, including electronic health records (EHR), has resulted in increasing efforts to improve the reproducibility of research by promoting transparency of the analytical decisions and replicating studies using the same data.

Objectives: To evaluate the reproducibility of a study characterizing newly-diagnosed multiple myeloma (NDMM) patients within a UK-based EHR database.

Methods: A large population-based EHR, from general practices (GP) within the primary care settings in the UK, the Clinical Practice

numbers of matching covariates may be hindered by limited degrees of freedom or an insufficient number of observations per matching covariate (e.g. few treated patients per covariate). Cardinality matching (CM) uses recent advancements in optimization to find the mathematically-guaranteed largest matched sample size meeting prespecified balance criteria, by directly targeting the distributional balance of matching covariates; therefore, CM is not subject to the inherent limitations of regression-based propensity score estimation techniques.

Objectives: We compare the performance of propensity score matching (PSM) and CM while matching on progressively larger numbers of covariates in a rare population (patients undergoing total pancreatectomy); specifically, we match patients undergoing open surgery (OS) to those undergoing minimally-invasive surgery (MIS).

Methods: Retrospective, cross-sectional analysis of U.S. data from the Premier Healthcare Database. Included patients were aged ≥18 years undergoing total pancreatectomy between 10/1/2015-3/31/2019. PSM was performed through nearest-neighbor matching (1:1, caliper=0.15). CM was performed through 1:1 matching permitting a maximum SMD of 0.10 for matching covariates. We performed 3 separate matches: match1 included patient demographic and clinical characteristics (11 covariates, 24 levels); match2 added hospital and provider characteristics (18 covariates, 40 levels); match3 added select comorbidities from the Elixhauser comorbidity index (41 covariates, 63 levels). We compared PSM and CM on post-match sample size and number of imbalanced (e.g., SMD ≥0.10) matching covariates.

Results: A total of 281 patients (OS: 114, MIS: 167) met the study criteria; 28 covariates were imbalanced before matching. Total post-match sample sizes were: PSM=198 (13% loss vs. maximum 1:1 matched sample N=228) and CM=226 (1% loss; match1); PSM=192 (16% loss) and CM=220 (3% loss; match2); and PSM=162 (29% loss) and CM=218 (4% loss; match3). In the 1st, 2nd and 3rd match, there were 4, 5 and 11 imbalanced matching covariates, respectively, for PSM; CM resulted in 0 imbalanced covariates.

Conclusions: In this applied comparison of CM vs. PSM in a small sample of patients undergoing total pancreatectomy, CM outperformed PSM in terms of post-match sample size and covariate balance. Optimization techniques may be superior to regression-based propensity score techniques when matching in rare populations.

4975 | plasmode simulation to address confounding bias due to missing data in a large electronic health records dataset

Svetlana Puzhko, Gillian Bartlett and Tibor Schuster
McGill University, Montreal, QC, Canada

Background: Missing data on salient variables in large databases is an important issue as naïve complete case (CC) analysis may invalidate effect estimates due to confounding induced by non-random case selection. There are different statistical approaches to deal with this issue but no general rule on how to evaluate their applicability and validity. 'Plasmode' simulation studies are a promising tool to systematically assess the potential effect of missing data on a specific real-world dataset.

Objectives: Using plasmode simulation, to compare accuracy and precision of estimated exposure effects using CC and multiple imputation by chained equations (MICE) in the presence of missing data in a large dataset.

Methods: Source. The Canadian Primary Care Practice-based Electronic Medical Record Database (CPCSSN), for 2011-2016. **Measures.** Exposure: obesity; outcome: antidepressants prescribing; covariates: age, sex, comorbidities. **Analysis.** We generated 200 plasmode datasets. Exposure and outcome data, and a missingness pattern were simulated using structure of the original dataset; original data covariates were included. Proportion of missing data was similar to the original dataset and was stochastically dependent on measured covariates. MICE with predictive mean matching was used. CC and MICE were analyzed by binary logistic regression and compared for accuracy and precision.

Results: In the original dataset, 47% data on weight was missing. Each generated plasmode dataset contained 62145 observations; CC datasets lacked data on exposure for 29445 observations. The mean true exposure coefficient (log odds ratio ß) was 0.154, standard error (SE)=0.019; the mean estimates for ß were 0.155 for CC and 0.153 for MICE, respectively; SE=0.026 for both CC and MICE. Relative bias for both CC and MICE was <0.001. The empirical mean root mean square error was 0.6218 for MICE and 0.6041 for CC. Simulation settings inducing stronger associations between the covariates and missing data prevalence did not substantially change the results.

Conclusions: Our results show robustness of the CC analysis regarding confounding bias due to missing data in our specific data setting. Our observations are likely explained by the structure of our data: there was low variation of propensity score levels across individuals, suggesting limited potential confounding impact of the covariates considered. This may suggest that CC analysis of the original data is appropriate, imputing data with MICE would not be of benefit. Plasmode simulation studies are helpful to choose how best to handle missing data in large real-world datasets.

5013 | Discriminative ability of new injury severity score to predict outcomes after fracture repair surgery

Zhenna Huang[1], Deepak Krishnan[2], Chantal Holy[1], Mollie Vanderkarr[1] and Sparks Charisse[1]
[1]*Johnson and Johnson, New Brunswick, NJ;* [2]*Mu-sigma, Bangalore, India*

Background: New injury severity score (NISS) is the simple sum squares of the three most severe injuries (highest abbreviated injury scales) regardless of body region. It is shown to be predictive of survival after injury. The Elixhauser comorbidity index (ECI) has been used as a risk-adjustment tool in quality and safety data.

Objectives: This study aims to investigate whether NISS should be included in addition to ECI for postoperative outcomes prediction following fracture repair surgery.