TRICYCLIC AND SSRI USAGE INFLUENCES THE ASSOCIATION BETWEEN BMI AND HEALTH RISK FACTORS

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ABSTRACT

The prevalence of antidepressant use is increasing. Past studies have reported that the use of antidepressants can influence cardiovascular risk factors including obesity, blood lipids and blood pressure (BP). However, because antidepressants have the potential to influence both body weight and cardiovascular disease (CVD) risk, it is currently unclear if antidepressant use alters CVD risk independent of obesity. Therefore, the aim of this manuscript was to examine if the type of antidepressant (Selective-Serotonin Reuptake Inhibitors (SSRIs) or Tricyclic antidepressants (TCAs)) used influenced the association between obesity and CVD risk. This study demonstrated that for a given body mass index (BMI) certain antidepressant use was associated with exacerbated health risk factors and CVD risk. Clinically, this may indicate that the differences in body weight observed with the use of SSRIs and TCAs may not be associated with the normally expected differences in cardiovascular risk.

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LIST OF ABBREVIATIONS

BMI - Body Mass Index

BP - Blood Pressure

CAD - Coronary Artery Disease

CDC - Centers for Disease Control and Prevention

CHOs - Carbohydrates

CI - Confidence Interval

CIHR - Canadian Institute of Health Research

CVD - Cardiovascular Disease

DBP - Diastolic Blood Pressure

FDA - Food and Drug Administration

FPG - Fasting Plasma Glucose

HbA1c - Glycohemoglobin

HDL - High-Density Lipoprotein

HHS - Department of Health and Human Services

HOMA-IR - Homeostatic Model Assessment of Insulin Resistance

HPA-axis - Hypothalamo-Pituitary-Adrenal axis

IHD - Ischemic Heart Disease

INT - Interaction

LSM - Least Square Means

ME - Main Effect

MET - Metabolic Equivalent

NCHS - National Center for Health Statistics

NE - Norepinephrine/Noradrenaline

NHANES III - Third National Health and Nutrition Examination Survey

NHANES - National Health and Nutrition Examination Survey

OGS - Ontario Graduate Scholarship

OR - Odds Ratio

PA - Physical Activity

SAS - Statistical Analysis Software

SBP - Systolic Blood Pressure

SD - Standard Deviation

SSRIs - Selective-Serotonin Reuptake Inhibitors

TG - Triglyceride

Tricyclic/TCAs - Tricyclic Antidepressants

1.0 GENERAL INTRODUCTION

Depression is one of the leading causes of disease world-wide (1). This is not only concerning due to the negative personal consequences for the individual but also due to the high economic costs. Financial costs associated with depression are not only a result of its treatment but also the healthcare costs required due to comorbidities associated with depression (2). Mood disorders are characterized by both mental and physical adverse effects (3). Psychologically depressive disorders are associated with feelings of sadness, anxiety, fatigue and an inability to feel pleasure in addition to increased frequency of suicidal thoughts (3, 4). Physically, depression increases the risk of developing chronic conditions such as coronary artery disease (CAD), cancer, stroke, epilepsy, alzheimers disease and diabetes between 1.3 to 6 fold (5). Beyond the increased risk of comorbidities, mood disorders are also linked with increased mortality risk and poorer quality of life (5, 6).

In order to lessen the negative consequences associated with depression, medicinal treatment is often advised (1, 3). In the 1950s doctors began regularly prescribing antidepressants after the chemical manipulation of antihistamines and tuberculosis medications revealed desirable psychotropic properties (3, 7). It was soon discovered that these early forms of antidepressants positively influenced the nervous system of patients with psychopathologies (3). However, early antidepressants were poorly understood biologically and therefore were often linked with significant health and safety concerns. More recently, through improved understanding of biological mechanisms antidepressants have been found to be safe and efficacious at treating depression (3). Yet, globally less than half of those diagnosed with depression receive antidepressant medication (8). There are no concrete answers as to why such a large proportion of patients with depression are not receiving treatment however current hypotheses include fear of side effects and suicide risks, insufficient insurance coverage, lack of access to mental health treatment and concerns over drug-drug interactions (3, 8). Regardless,

antidepressant medications use is increasing overall and they are now one of the most prescribed types of medications in the United States (U.S.) (9, 10). In addition, there is also a rising trend in the number of prescriptions patients are receiving once they begin medicinal treatment (11).

Antidepressants can be used to treat a wide variety of illnesses but are used most often for depression (65%) and anxiety (16%) (9). SSRIs and TCAs are two of the most frequently prescribed antidepressants on the market today (11). As with many medications, SSRIs and TCAs have differential side effect profiles, interactions and ease of use (12). Antidepressants have been reported to inadvertently interact with other drugs, particularly alcohol, and some foods (3). Furthermore, certain antidepressants like SSRIs and TCAs influence factors linked with changes in cardiovascular health such as body weight (13–22), blood lipids (23–29) and BP (28, 30–32).

2.0 REVIEW OF RELATED LITERATURE

Prevalence of Depression

The prevalence of depression has decreased in the U.S. over the past couple of years, yet the percentage of people receiving treatment for mental health conditions has increased (11). Thus, it is likely not that there is a higher incidence of depression but merely that more people are seeking treatment (11). This upward trend in treatment is due to the accumulation of many factors such as increased awareness surrounding the need for mental health treatment, promotion of mental health awareness and broadening public acceptance of mental health disorders (11). Within the U.S. depression occurs more often in women (3), people of young age groups (18-44 years of age) and divorcees (33). Furthermore, depressive disorders are more frequent in people of low socioeconomic status, limited education and those who are disabled (33).

Types of Psychotropic Medications and Mechanisms of Action

Psychotropic medications are inclusive of anxiolytics, antipsychotics, stimulants, mood stabilizers and antidepressants (11). Antidepressant medications can then be further subdivided into many types of antidepressants such as monoamine oxidase inhibitors (MAOIs), Tricyclic antidepressants (TCAs), Selective-Serotonin Reuptake Inhibitors (SSRIs), Norepinephrine Reuptake Inhibitors (NRIs), Norepinephrine Dopamine Reuptake Inhibitors (NDRIs) and numerous other agents (34). Antidepressants target receptors and neurotransmitters in the nervous system in order to improve brain chemistry (12, 34). Neurotransmitters are naturally produced chemical messengers stored in neurons throughout the body and released by the nervous system (3). Once activated neurotransmitters leave their neurons, travel through a synapse and attach to specific receptors at other cells or neurons in order to generate their biological effects (3). After neurotransmitters complete their desired task they can either be

degraded or taken back into the neuron(s) they were released from, a process known as reuptake (3). Antidepressants can act to either alter the breakdown of the neurotransmitters themselves or influence their reuptake (4, 7). For example, TCAs inhibit the reuptake of serotonin, norephinephrine (NE), and dopamine while SSRIs inhibit the reuptake of only serotonin (12). Newer antidepressants, like SSRIs, are able to selectively alter the function of particular neurotransmitters while some of the older medications such as MAOIs and TCAs have less selective mechanisms of action within the brain (12). Consequently, older antidepressants tend to be linked with a greater number of side effects than some of the newer antidepressants (12).

Blood Pressure

The use of antidepressant medications has been connected to both hypotension and hypertension, depending on the type of antidepressant, through alterations to sympathetic activation (28, 30–32). SSRIs are reported to have inhibitory effects on the sympathetic nervous system, consequently lowering mean arterial pressure (32). Contrastingly, resting hypertension experienced with TCA use has been attributed to their norepinephrine (NE) re-uptake blocking properties which is indicative of increases in sympathetic activation (28, 30, 32), or increases in BMI typically observed with their use (13–17). Differences in the activation of the sympathetic nervous system is of great clinical importance given that sympathetic stimulation has been linked to increased risk of cardiovascular and metabolic disease in patients with psychopathological disorders (32). This study will assist in delineating whether or not the hypertensive effects of TCAs that were previously noted in the literature are independent of BMI, therefore suggesting the differences may be due to alterations in autonomic function.

Glycemic Control

SSRI use is often connected with hypoglycaemia and favourable insulin sensitivity (23, 35–37) while glycaemic dysfunction is often associated with TCA use (16, 23, 35, 37–40). In approximately two-thirds of case reports variations in glycaemic indicators are reported within one month of beginning treatment (37). Short-term treatment, three months, with SSRIs has been observed to enhance insulin sensitivity thus increasing the prevalence of hypoglycaemia (36). In contrast, long-term treatment with TCAs has been linked with an 84% increase in the risk of diabetes (38). The hyperglycaemic effects associated with the use of TCAs has been linked with numerous mechanisms such as weight gain, elevated cortisol levels due to hypothalamo-pituitary-adrenal axis (HPA-axis) dysregulation, as well as their NE re-uptake blocking properties consequently stimulating gluconeogenesis and glycogenolysis (36). Furthermore, the hyperglycemic effects associated with TCA use do not only increase a patient's risk of diabetes but insulin resistance has also been hypothesized to increase triglyceride (TG) levels independent of obesity (41, 42).

Blood Lipids and Inflammation

Past studies have linked depression with obesity (13) and inflammation (28, 43, 44), which are both factors in development of dyslipidemia (23, 27, 29, 45, 46), as well as the pathogenesis of heart failure coronary artery disease (CAD) (47, 48). Some studies observed SSRIs to have beneficial effects on lipid homeostasis (23–25), while another study has reported a negative SSRI influence (26), though these changes tended to be highly correlated with changes to body weight (26). However, SSRI use has been associated the decreased productions of inflammatory markers (28, 43, 49) which could prompt positive changes to lipid homeostasis regardless of BMI. In contrast, TCA use is connected with inflammation (28) and

hypertriglyceridemia both of which are frequently attributed to weight gain and specifically increased intra-abdominal fat (27–29). In literature to date, it is unclear if the use of antidepressants is connected with changes to lipid homeostasis independent of BMI.

Cardiovascular Risk

The increased mortality rate seen in mood disorder patients has largely been attributed to the increased prevalence of cardiovascular disease (CVD), which has been commonly associated with the metabolic syndrome (28, 50). Although depression and CVD are frequently linked (30, 48, 51, 52), research on antidepressant usage in relation to prevalence of CVD is divided (32, 52). This is likely due to the wide range of cardiac factors that antidepressants could influence, including BMI, autonomic regulation, BP and cholesterol levels. Even though obesity and weight gain are clearly associated with increased cardiovascular risk (48, 53), it is uncertain if antidepressant use influences the association between obesity and CVD risk. Thus, the aim of this thesis is to examine if the type of antidepressant used (SSRIs/TCAs) influences the association between obesity and CVD risk.

3.0 MANUSCRIPT

3.1 BACKGROUND

The current prevalence of depression is between 8 to 12% worldwide (54). Beyond the increased risk of coronary artery disease (CAD), cancer, stroke, epilepsy, alzheimers disease, diabetes (5) and all cause mortality, mood disorders have also been linked to poorer quality of life (5, 6) and increased likelihood of obesity (13). Since the mid-1990's the use of antidepressants in the U.S. has increased substantially (11). The prevalence of SSRIs has risen from 55 to 67% of all antidepressant prescriptions, while the use of TCAs has decreased from 35 to 11% (11). Even though the use of TCAs has decreased over recent years they are reported to have a greater efficacy at treating certain types of depression such as melancholic and psychotic (3). Given that psychopathological patient care is becoming increasingly individualized it is still of clinical importance to research TCAs since it is likely they will continue to be prescribed both now and in the future (3).

SSRIs and Tricyclics are also commonly used for a wide range of syndromes including anxiety, attention deficit, nervous system disorders and other non-psychiatric disorders (9). Antidepressant use has been associated with a one to three kg weight gain in 10 to 40% of patients receiving pharmaceutical treatment (14). However, the different classes of antidepressants are reported to influence body weight differently (13–15). Short-term use of SSRIs is associated with weight loss (18–21) while weight restoration, or gain occurs with long-term use (13, 16, 22). On the other hand, long-term treatment with TCAs has been more frequently linked with weight gain (13–17). Furthermore, TCAs have been linked with hypertriglyceridemia (27, 29) and both TCAs and SSRIs have been associated with blood pressure (BP) dysregulation (28, 30–32). However, because antidepressant use influences both body weight and CVD risk it is currently unclear if antidepressant use alters CVD risk

independent of obesity. Thus, the objective of this study is to determine if the type of antidepressant used (SSRIs/TCAs) influences the association between obesity and CVD risk.

3.2 METHODS & PROCEDURES

Participants

The sample included 96 154 participants from the NHANES. NHANES is a cross-sectional study that is a U.S. nationally representative survey which utilizes a multistage probability cluster design. The National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) collects the data through interviews, physical examinations and laboratory tests. Prior to examination, all participants gave their informed written consent and study protocol was approved by NCHS. Further details pertaining to study design and methods have been previously reported (55, 56).

NHANES III (1988-1994) and NHANES continuous data (1999-2010) were combined to provide sufficient sample size for the analysis of different subclasses of antidepressant use. Participants were excluded from the data set if they were under 18 years of age (n = 41 198), if they were pregnant (n = 1 196) or they had a BMI <15 kg/m^2 or >70 kg/m^2 (n = 768). Additionally, participants with missing data for BMI (n = 18 133), antidepressant use (n = 14), SBP (n = 38 512), DBP(n = 39 576), HDL(n = 30 809), TGs (n = 56 127), fasting plasma glucose (FPG: n = 63 849), glycohemoglobin (HbA1c: n = 36 994), insulin (n = 64 244), HOMA-IR (n = 64 336), chronic disease (cancer: n = 43 723, diabetes: n = 16 942, CVD: n = 43 866, obstructive respiratory disease: n = 43 798), smoking status (n = 43 704) and dietary information were not included (carbohydrates (CHO): n = 12 724, fat: n = 12 478). This left 18 274 eligible participants.

Survey Methods

Age, gender, ethnicity (white, black, other), poverty-income-ratio (income, scored one to five), medication use (user/non-user), smoking status (current smoker/non-smoker) and physical activity (PA) status were assessed by individual questionnaire. Income score is calculated as the family earnings divided by the poverty guidelines provided by the Department of Health and Human Services (HHS). If income was missing, mean substitution was performed. PA was coded as: moderate intensity greater than or equal to one time of moderate intensity PA / week; or vigorous intensity greater than or equal to one time of vigorous intensity PA /week; or inactive (zero min of moderate or vigorous PA /week). Moderate PA was defined as a metabolic equivalent (MET) score between three and six while vigorous PA was a MET score greater than six. When individuals performed both moderate and vigorous PA they were classified as vigorous PA. If the participant reported doing no physical activity they were recorded as inactive. In NHANES III blood lipids and glycemic indicators were measured using standard procedures after a 10-16 hour fast prior to morning testing or after a six hour fast for afternoon/evening tests. In NHANES 1999-2004 participants were asked to fast for 8 to 24 hours and greater than or equal to nine hours for NHANES 2005-2010. Any additional details on blood lipid or glycemic measurement techniques can be found elsewhere (55, 56). Chronic disease history was obtained through self-reported doctor diagnoses of cancer, diabetes and CVD (yes/no). CVD was a history of heart failure, angina, or stroke in NHANES III and a history of heart failure, angina, stroke, myocardial infarction or coronary heart disease in NHANES 1999 to 2010. A 24-hour dietary recall interview was also performed to obtain dietary information on CHOs and fat (grams, gm).

A minimum of three BP (mmHg) readings were taken by trained BP technicians. Anthropometric measures such as weight, height and BMI were also assessed by trained health

technicians at the mobile examination center. Self-reported height and weight were used to substitute missing BMI data in NHANES III.

Prescription Medication Categorization

Data on prescription medication use was obtained through household interviews. Type of prescription medication usage within the last 30 days was recorded. Whenever possible the prescription container was examined by the interviewer. In NHANES III the medications were assigned a four-digit code based on the National Drug Directory of the Food and Drug Administration (FDA). In NHANES continuous the Lexicon Plus ® system was used to sort medications by therapeutic classification and drug ingredients. The two most common antidepressant drug categories were analyzed in this study: 1) Selective-Serotonin Reuptake Inhibitors (SSRIs; n=219) and 2) Tricyclic antidepressants (TCAs; n=116).

Statistical Analysis

Demographic characteristics were stratified by user and non-user for each antidepressant type. Continuous variables are shown as a mean ± standard deviation (SD). Categorical variables are presented as sample size (n) and prevalence (%). Group differences in continuous variables were analyzed using t-tests and chi-square tests (x^2) were used for categorical variables. Linear regression analyses were used to examine the influence of antidepressant usage on the association between BMI and health risks using first order drug and BMI interaction and main effect (ME) terms. The odds ratio (OR, 95% confidence interval (CI)) of prevalent chronic disease was assessed using logistic regression. All regression analyses were adjusted for age, sex, ethnicity, income, smoking status, PA, as well as dietary CHOs and fat intake. Further adjustment for prevalent CVD was performed when assessing blood pressure and blood lipids

while diabetes status was adjusted for when analyzing glycemic markers. Due to the amalgamation of continuous and NHANES III data sets, weighted adjustments could not be used. All analyses were completed with SAS (ver. 9.2). Statistical significance was defined as $P<0.05$.

3.3 RESULTS

Participant Characteristics

Participant characteristics are shown in Table 1. Age did not differ by SSRI use (P>0.05), while individuals using TCAs were older than their non-user counterparts (P<0.05). Individuals taking SSRIs and TCAs were more likely to be female than non-users (P<0.05). Those taking SSRIs had a 1.0±6.3 kg/m^2 higher BMI than non-users (P<0.05) with no difference by TCA use (P>0.05). SSRI users had a 0.4±1.6 higher income while TCA users had a 0.4±1.4 lower income than their respective non-users (P<0.05). PA levels did not differ by SSRI use (P>0.05), while TCA users had significantly lower PA levels than those not using TCAs (P<0.05).

Individuals taking SSRIs had a higher prevalence of CVD, 4±20 mmHg lower SBP, 2±12 mmHg lower DBP and 0.09±0.44 mM higher HDL than those not using SSRIs (P<0.05). Those using TCAs had a higher prevalence of diabetes and CVD, 7±21 mmHg higher SBP, 4±10 mmHg higher DBP, 0.28±1.07 higher TG and 1.6±8.0 higher HOMA-IR than those not using TCAs (P<0.05). There were no significant differences (P≥0.05) in smoking status, CHO or fat intake, FPG and HbA1c by SSRI or TCA use.

Cardiovascular Disease Risk Factors

For a given BMI, individuals taking SSRIs tended to have significantly better health risk profiles with lower SBP (P=0.002), marginally lower DBP (P=0.056) and higher HDL (P=0.003) compared to non-users (Table 2) with adjustment for age, sex, ethnicity, income, smoking status, PA, total CHOs and fat intake and CVD. Conversely, those who used TCAs had significantly (P<0.05) worse health risk profiles with higher DBP and TGs as compared to non-users for a given BMI (Table 2). Insulin resistance (HOMA-IR) was higher in TCA users and those with larger BMIs, whereby the differences in insulin resistance between TCA users and non-users was greater with higher BMIs (Interaction Effect: P=0.013; Figure 1).

Likelihood of Chronic Disease

Neither SSRIs nor TCAs significantly altered the relationship between BMI and cancer (P= 0.30 and P= 0.49 respectively, results not shown). However, individuals taking SSRIs were less likely to have prevalent CVD than non-users (OR, 95% CI= 0.50, 0.33-0.75) for a given BMI, with no differences by TCA use (OR= 0.74, 0.44-1.24) (Figure 2).

3.4 DISCUSSION

The findings from this study demonstrate that for a given BMI, antidepressant use is associated with differences in health risk factors and CVD risk. Individuals who used SSRIs tended to have a better cardiometabolic profile, while TCA users generally had a worse cardiometabolic profile than was expected given their BMI. Clinically, this may suggest that the differences in body weight observed with antidepressant use may not be associated with the normally expected differences in cardiovascular risk.

Antidepressant use has been linked to both hypotension and hypertension, depending on the type of antidepressant, through alterations to sympathetic activation (28, 30–32). SSRIs are reported to have inhibitory effects on the sympathetic nervous system, consequently lowering mean arterial pressure (32). Contrastingly, TCA use was associated with significantly higher resting DBP for a given BMI. Increases in BP with TCA use could be attributed to the blocking of noradrenaline (NE) re-uptake which is indicative of increases in sympathetic activation (28, 30, 32), or increases in BMI typically observed with their use (13–17). However, the hypertensive effects of TCAs were observed independent of BMI, suggesting these differences may be due to alterations in autonomic function. Therefore, both SSRIs and TCAs differentially influence blood pressure independent of body weight.

Past studies have linked depression with obesity (13) and inflammation (28, 43, 44, 57), which are both factors in development of dyslipidemia and decreased HDL (23, 27, 29, 45, 46), as well as the pathogenesis of heart failure and coronary artery disease (CAD) (47, 48). However, SSRI use has been linked with decreased production of inflammatory markers (43, 49), and may potentially explain why SSRI use was associated with higher HDL levels, with and without adjustment for BMI. In contrast, TCA use is often connected with hypertriglyceridemia that is commonly attributed to weight gain (27, 29). We extend previous research (27, 29) by

demonstrating the association between TCA use and hypertriglyceridemia is truly independent of BMI. The association between TCAs and hypertriglyceridemia may be due to the higher insulin resistance observed in TCA users. Insulin resistance has been hypothesized to increase TG levels independent of obesity (41, 42). Thus, our findings suggest that antidepressant use influences blood lipids and insulin sensitivity independent of body weight.

Although depression and CVD are frequently linked (30, 48, 51, 52), research on antidepressant usage in relation to prevalence of CVD is divided (32, 52). This is likely due to the wide range of cardiac factors that antidepressants can influence, including autonomic regulation, BP and cholesterol levels. We observed that SSRI use was associated with lower SBP for a given BMI. Though four mmHg lower SBP may appear to be a small magnitude, this magnitude of decrease has been related to an 19% lower incidence of stroke and 14% lower incidence of ischemic heart disease (IHD)(58). Conversely, a four mmHg higher DBP observed with TCA use has been linked with a 16 to 21% increase in the incidence of CAD (59). Therefore, SSRI and TCA use may be associated with differential and clinically relevant changes in CVD risk independent of BMI.

This study had limitations and strengths. The data is from cross-sectional surveys and these results do not allow one to infer causation. Moreover, due to combining of NHANES III and continuous data, the results are not representative of the current U.S. population. It is also worth noting that we investigated two agents that are commonly prescribed as antidepressants but did not strictly examine depressive disorders. SSRIs and TCAs are used for an array of both psychiatric and non-psychiatric disorders and we were unable to ascertain what condition(s) the medications were specifically prescribed for. A strength was the use of chronic disease history data collected through personal interviews which has been shown to generate a low cognitive burden on survey respondents and produce a low recall bias when compared to self-administered questionnaires (60). Another key strength was the rigorous adjustment for

numerous confounding variables that have been shown to be associated with CVD risk in addition to adjustments for prevalent chronic conditions in order to reduce potential bias from previously established indications and contraindications for each antidepressant.

In summary, for a given BMI when compared against non-users, SSRI users tended to have a better cardiometabolic profile, while TCA users generally had a worse cardiometabolic profile. Future longitudinal studies are needed to explore and test for causal relations. When health professionals are prescribing antidepressant medications, further consideration should be given to the cardiovascular risk profile of individual patients.

3.5 GENERAL CONCLUSION

Regular treatment of mental disorders began in the early 1900's (7). Initially the treatment of mental health issues was very intrinsic and primitive including techniques such as lobotomy and electroshock therapy (3). However, within just a couple of decades psychopharmaceuticals were derived and quickly became a primary treatment choice replacing these more drastic measures (3). MAOIs were one of the first antidepressants to hit the market with TCAs following shortly after, by the 1970's-1990's SSRIs gained popularity and became the medication of choice (3, 7). At the beginning of the 90's newer generation antidepressants such as SNRIs started to be developed and distributed (7). Since then, development of more effective antidepressants that differentiate themselves from previous medications has been lacking (61). It is probable that the short-comings of pharmaceutical companies to develop newer fasting acting products with fewer side effects is partially a result of decreasing profitability due to patents expiring and consequently increased generic availability (61). Furthermore, the treatment of depression is complicated given that the biological mechanisms behind depression are still not fully understood (61).

Currently, depression is considered a severe global health concern with World Health Organization (WHO) figures indicating a prevalence of 350 million people afflicted worldwide (61). The preliminary stages of treatment with antidepressants can be frustrating given that approximately two-thirds of patients do not respond to initial treatment (4, 61). The process of treatment response is also time consuming with most antidepressants taking weeks to month before therapeutic responses become noticeable (4). However, once the appropriate medication is determined antidepressants are effective in treating 80 to 90% of patients with moderate to severe depression (3, 61). Yet, fewer than 50% of those with depressive disorders receive medicinal treatment with some populations below 10% (8). The low use of antidepressants has been attributed to a lack of access to sufficient treatment, the social stigma attached to mental

health disorders, increased risk of suicide and side effects obtained from antidepressant use (3, 8, 61). Although antidepressant use has been reported to come with undesirable consequences such as weight changes (13–22) and worsened cardiovascular risk factors (23–32), the risk of suicide is far greater in patients with untreated depression than when medicinally treated (51). Further, this thesis demonstrates that users of certain antidepressants have a better cardiometabolic profile for a given BMI. Clinically, this may suggest that the differences in body weight observed with antidepressant use may not be associated with the normally expected differences in cardiovascular risk. Thus, when prescribing antidepressant medications further consideration should be given to the cardiovascular risk profile of individual patients. These recommendations coincide with previous suggestions that psychopathological patient care needs to be further individualized in order to best support patients.

Table 1. Characteristics of participants, stratified by drug and use category

Drug Category	SSRIs			TCAs		
Use Category	Non-User	User	P-value	Non-User	User	P-value
n (%)	18 055 (98.8)	219 (1.2)		18 158 (99.4)	116 (0.6)	
Age (years)	49.3±18.5	51.2±15.4	0.06	49.2+18.5	58.5+17.6	<0.0001
Sex (Female)	9 083 (50.3)	157 (71.7)	<0.0001	9 160 (50.5)	80 (69.0)	<0.0001
BMI (kg/m^2)	28.1±6.1	29.1±6.3	0.01	28.1±6.1	28.4±7.0	0.62
Ethnicity						
White	8 474 (46.9)	159 (72.6)	<0.0001	8 569 (47.2)	64 (55.2)	0.17
Black	3 898 (21.6)	15 (6.9)		3 889 (21.4)	24 (20.7)	
Other	5 683 (31.5)	45 (20.6)		5 700 (31.4)	28 (24.1)	
Income (0-5)	2.5±1.5	2.9±1.6	0.001	2.5±1.5	2.1±1.4	0.003
Smoking Status						
Smoker	4 222 (23.4)	55 (25.1)	0.55	4 246 (23.4)	31 (26.7)	0.40
Dietary Factors						
CHO Intake (gm)	250±117	236±107	0.07	250±117	229±112	0.05
Fat Intake (gm)	77±43	74±36	0.20	77±43	72±49	0.33
Physical Activity (≥1/wk)						
Inactive	6 619 (36.7)	85 (38.8)	0.73	6 642 (36.6)	62 (53.5)	<0.0001
Moderately active	9 126 (50.6)	109 (49.8)		9 184 (50.6)	51 (44.0)	
Vigorously active	2 310 (12.8)	25 (11.4)		2 332 (12.8)	3 (2.6)	
Diabetes (%)	1 652 (9.2)	23 (10.5)	0.49	1 651 (9.1)	24 (20.7)	<0.0001
CVD	1 730 (9.6)	34 (15.5)	0.003	1 743 (9.6)	21 (18,1)	0.002
Health Risk Factors						
SBP (mmHg)	125±20	121±20	0.004	125±20	132±21	0.0002
DBP (mmHg)	72±11	70±12	0.002	72±11	76±10	0.0006
HDL (mM)	1.35±0.40	1.44±0.44	0.002	1.35±0.40	1.34±0.37	0.66
TG (mM)	1.57±1.05	1.56±0.88	0.82	1.57±1.05	1.85±1.07	0.004
FPG (mM)	5.8±1.8	5.7±1.5	0.52	5.8±1.8	6.0±2.6	0.30
HOMA-IR	3.4±3.9	3.9±5.2	0.16	3.4±3.9	5.0±8.0	0.04
HbA1c (%)	5.6±1.0	5.6±0.7	0.32	5.6±1.0	5.8±1.4	0.08

Continuous data as mean±SD and categorical data presented as n (%) within' Use category'.

SSRIs, Selective-Serotonin Reuptake Inhibitors; TCAs, Tricyclic antidepressants; N, sample size; BMI, body mass index; Income, poverty-income ratio; CHO, carbohydrates; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; TGs, fasting serum triglycerides; FPG, fasting plasma glucose; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycohemoglobin.

P<0.05, significantly different from non-users within that drug category.

Table 2. The association of antidepressant usage on health risk factors by drug category

Drug Category	SSRIs		
	Predicted LSM Value		
	Non-User	User	P-value
SBP (mmHg)	125±1	121±1	0.002
DBP (mmHg)	71±1	69±1	0.056
HDL Cholesterol (mM)	1.34±0.005	1.41±0.02	0.003
TG (mM)	1.57±0.01	1.50±0.07	0.32
FPG (mM)	7.1±0.02	6.9±0.1	0.45
HOMA-IR	5.0±0.05	5.3±0.2	0.14
HbA1c (%)	6.4±0.01	6.4±0.06	0.49
Drug Category	TCAs		
	Predicted LSM Value		
	Non-User	User	P-value
SBP (mmHg)	125±1	127±2	0.19
DBP (mmHg)	71±1	75±1	<0.0001
HDL Cholesterol (mM)	1.34±0.005	1.29±0.03	0.13
TG (mM)	1.57±0.01	1.78±0.09	0.023
FPG (mM)	7.1±0.02	6.9±0.1	0.21
HOMA-IR	*	*	*
HbA1c (%)	6.4±0.01	6.3±0.08	0.35

Predicted Least Square Adjusted Means (LSM±SEE) values are adjusted for: BMI, age, sex, ethnicity, income, smoking status, PA, total CHOs and fat intake. Further adjustment for CVD was performed when assessing blood pressure and blood lipids while diabetes status was adjusted for when analyzing glycemic markers.

SSRIs, Selective-Serotonin Reuptake Inhibitors; TCAs, Tricyclic antidepressants; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; TGs, fasting serum triglycerides; FPG, fasting plasma glucose; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycohemoglobin; Income, poverty-income ratio; PA, physical activity; CHOs, carbohydrates.

* Significant interaction effect (see Figure I).

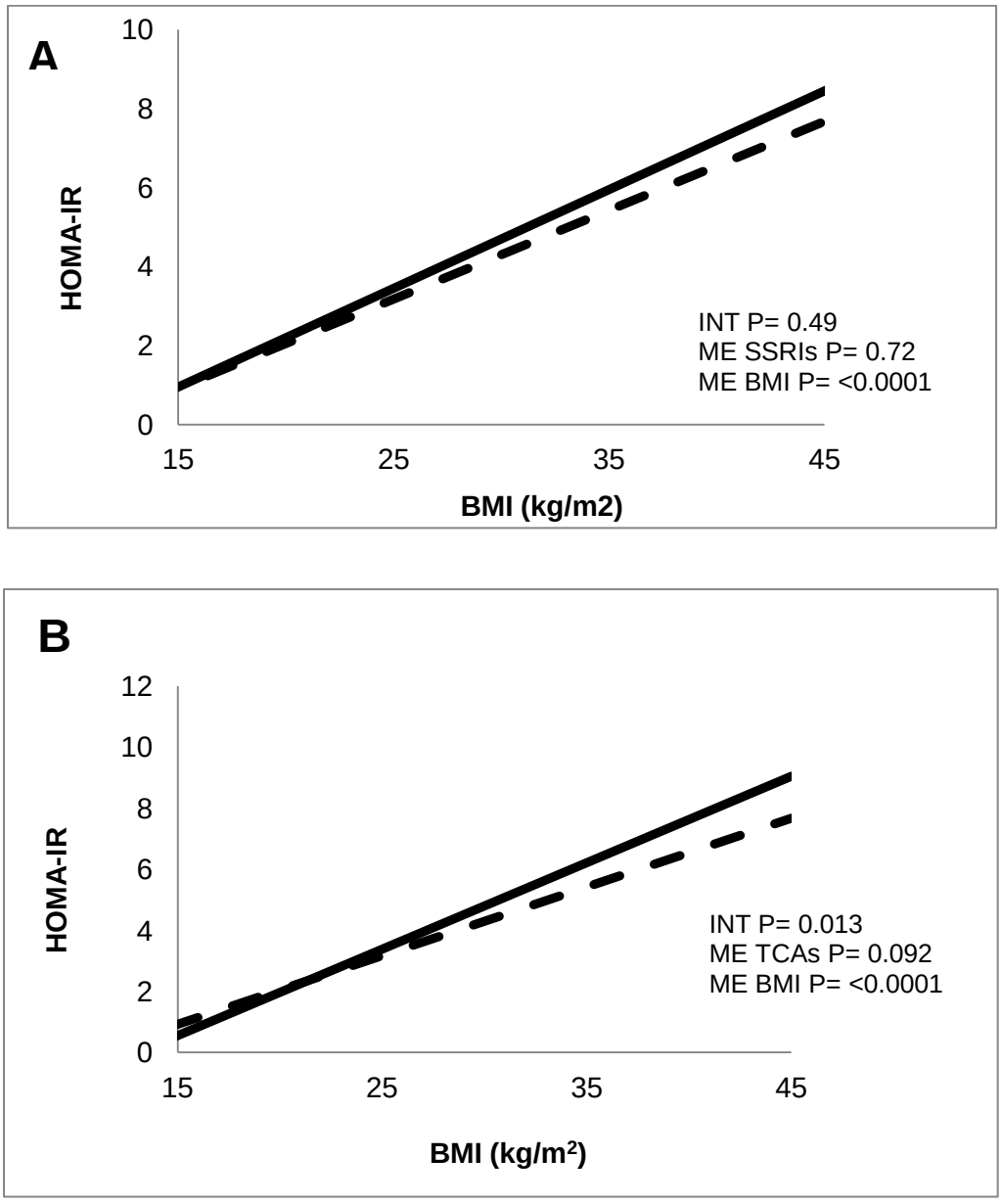
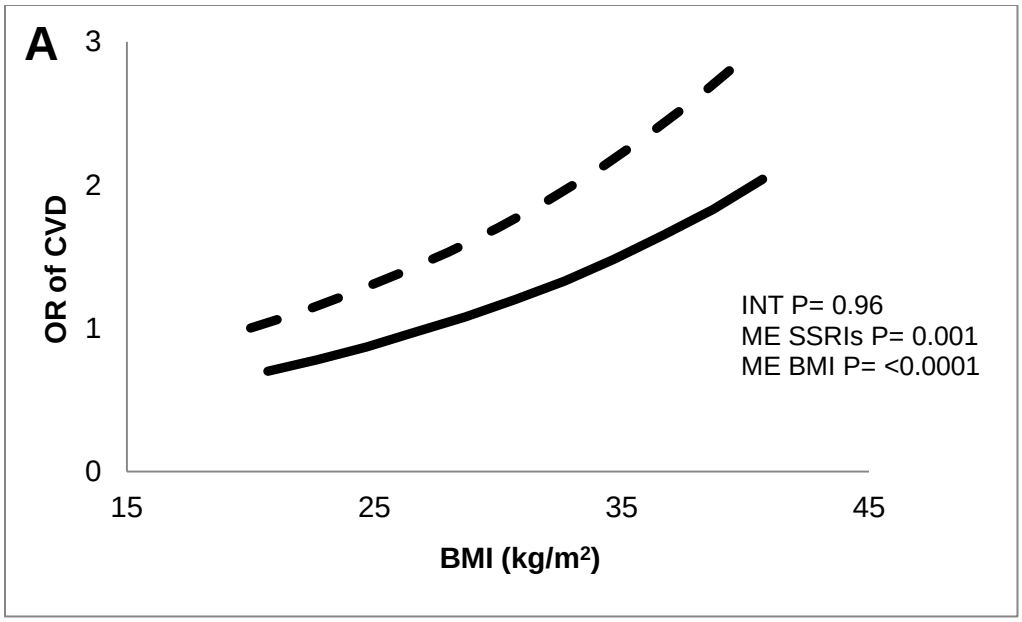


Figure 1. The relationship between BMI and HOMA-IR in SSRI (A) and TCA (B) users.

HOMA-IR. homeostatic model assessment of insulin resistance; BMI, body mass index; SSRIs, Selective-Serotonin Reuptake Inhibitors; TCAs, Tricyclic antidepressants; INT, interaction; ME, main effect.

Legend: solid line= SSRI or TCA user, dashed-line= SSRI or TCA non-user.



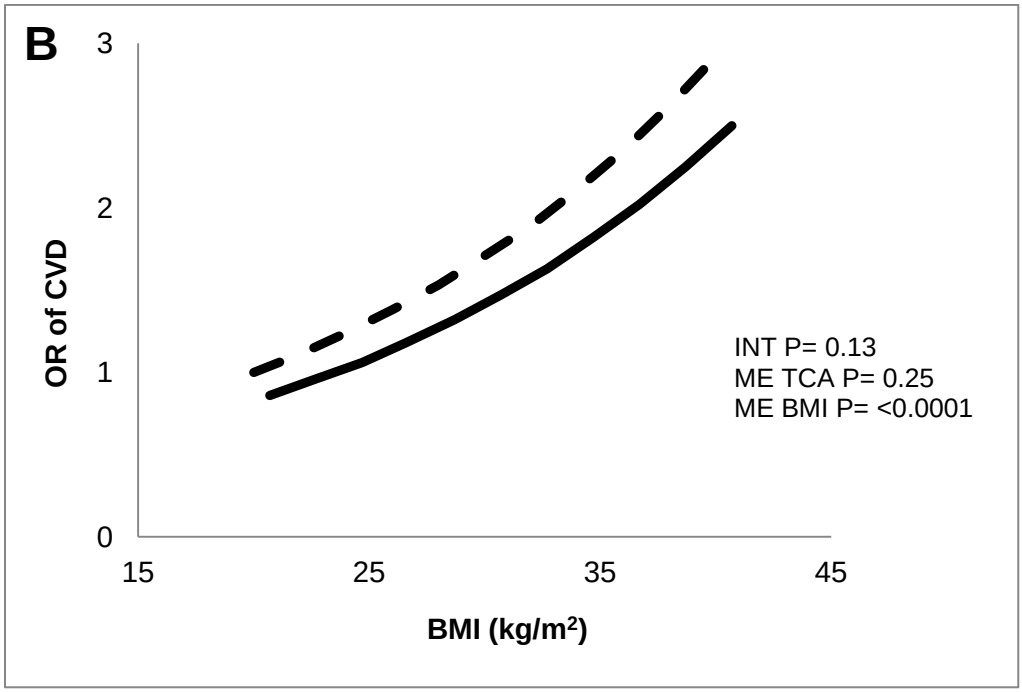


Figure 2. The relationship between BMI and CVD in SSRI (A) and TCA (B) users.

OR, odds ratio; CVD, cardiovascular disease; BMI, body mass index; SSRIs, Selective-Serotonin Reuptake Inhibitors; TCAs, Tricyclic antidepressants; INT, interaction; ME, main effect.

Legend: solid line= SSRI or TCA user, dashed-line= SSRI or TCA non-user.

4.0 REFERENCES

1. Richards D. Prevalence and clinical course of depression: a review. *Clin Psychol Rev* 2011;31:1117–25.

2. Katon WJ. State of the art. 2011:7–23.

3. Wrobel S. Science, serotonin, and sadness: the biology of antidepressants: a series for the public. *FASEB J* 2007;21:3404–17.

4. Duric V, Duman RS. Depression and treatment response: dynamic interplay of signaling pathways and altered neural processes. *Cell Mol Life Sci* 2013;70:39–53.

5. Ramasubbu R, Beaulieu S, Taylor VH, Schaffer A, McIntyre RS. The CANMAT task force recommendations for the management of patients with mood disorders and comorbid medical conditions: diagnostic, assessment, and treatment principles. *Ann Clin Psychiatry* 2012;24:82–90.

6. Yohannes a M, Willgoss TG, Baldwin RC, Connolly MJ. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *Int J Geriatr Psychiatry* 2010;25:1209–21.

7. Lieberman J. History of the Use of Antidepressants in Primary Care. *J Clin Psychiatry* 2003;5:6–10.

8. Wittayanukorn S, Qian J, Hansen R a. Prevalence of depressive symptoms and predictors of treatment among U.S. adults from 2005 to 2010. *Gen Hosp Psychiatry* 2014;36:330–6.

9. Mark TL. For what diagnoses are psychotropic medications being prescribed?: a nationally representative survey of physicians. *CNS Drugs* 2010;24:319–26.

10. Mojtabai R, Olfson M. National trends in long-term use of antidepressant medications: results from the U.S. National Health and Nutrition Examination Survey. *J Clin Psychiatry* 2014;75:169–77.

11. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry* 2009;66:848–56.

12. Ferguson JM. SSRI Antidepressant Medications: Adverse Effects and Tolerability. *J Clin Psychiatry* 2001;3:22–27.

13. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry* 2010;71:1259–72.

14. Schwartz TL, Nihalani N, Jindal S, Virk S, Jones N. Psychiatric medication-induced obesity: a review. *Obes Rev* 2004;5:115–21.

15. Vanina Y, Podolskaya A, Sedky K, *et al.* Body weight changes associated with psychopharmacology. *Psychiatr Serv* 2002;53:842–7.

16. Kivimaki M, Hamer M, Batty D, *et al.* Antidepressant Medication Use , Weight Gain , and Risk of Type 2 Diabetes. 2010;33.

17. Berken H, Stern C. Weight Gain of Tricyclic Antidepressants. *J Affect Disord* 1984;7:133–138.

18. Croft H, Settle E, Houser T, Batey S, Donahue R, Ascher J. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release Bupropion and Sertraline.pdf. *Clin Ther* 1999;21:643–648.

19. Goldstein DJ, Rampey a H, Roback PJ, *et al.* Efficacy and safety of long-term fluoxetine treatment of obesity--maximizing success. *Obes Res* 1995;3 Suppl 4:481S–490S.

20. Lawton CL, Wales JK, Hill a J, Blundell JE. Serotoninergic manipulation, meal-induced satiety and eating pattern: effect of fluoxetine in obese female subjects. *Obes Res* 1995;3:345–56.

21. Michelson D, Amsterdam JD, Quitkin FM, *et al.* Changes in weight during a 1-year trial of fluoxetine. *Am J Psychiatry* 1999;156:1170–6.

22. Fava M, Judge R, Hoog SL, Nilsson ME, Koke SC. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. *J Clin Psychiatry* 2000;61:863–7.

23. McIntyre RS, Soczynska JK, Konarski JZ, Kennedy SH. The effect of antidepressants on lipid homeostasis: a cardiac safety concern? *Expert Opin Drug Saf* 2006;5:523–37.

24. Beyazyüz M, Albayrak Y, Eğilmez OB, Albayrak N, Beyazyüz E. Relationship between SSRIs and Metabolic Syndrome Abnormalities in Patients with Generalized Anxiety Disorder: A Prospective Study. *Psychiatry Investig* 2013;10:148–54.

25. Ye Z, Chen L, Yang Z, *et al.* Metabolic effects of fluoxetine in adults with type 2 diabetes mellitus: a meta-analysis of randomized placebo-controlled trials. *PLoS One* 2011;6:e21551.

26. Raeder MB, Bjelland I, Emil Vollset S, Steen VM. Obesity, dyslipidemia, and diabetes with selective serotonin reuptake inhibitors: the Hordaland Health Study. *J Clin Psychiatry* 2006;67:1974–82.

27. Kopf D, Westphal S, Luley CW, *et al.* Lipid Metabolism and Insulin Resistance in Depressed Patients. *J Clin Psychopharmacol* 2004;24:527–531.

28. Penninx BWJH, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Med* 2013;11:129.

29. Van Reedt Dortland a KB, Giltay EJ, van Veen T, Zitman FG, Penninx BWJH. Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. *Acta Psychiatr Scand* 2010;122:30–9.

30. Coupland N, Wilson S, Nutt D. Antidepressant drugs and the cardiovascular system: a comparison of tricylics and selective serotonin reuptake inhibitors and their relevance for the treatment of psychiatric patients with cardiovascular problems. *J Psychopharmacol* 1997;11:83–92.

31. Licht CMM, de Geus EJC, Seldenrijk A, *et al.* Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. *Hypertension* 2009;53:631–8.

32. Licht CMM, Penninx BWJH, de Geus EJC. Effects of antidepressants, but not psychopathology, on cardiac sympathetic control: a longitudinal study. *Neuropsychopharmacology* 2012;37:2487–95.

33. Kessler RC, Berglund P, Demler O, *et al.* The Epidemiology of Major. 2014;289:3095–3105.

34. Se H, Je M, Gr C, Mb S, Sn M. Newer generation antidepressants for depressive disorders in children and adolescents (Review). 2012.

35. Goodnick PJ. Use of antidepressants in treatment of comorbid diabetes mellitus and depression as well as in diabetic neuropathy. *Ann Clin Psychiatry* 2001;13:31–41.

36. Derijks HJ, Meyboom RHB, Heerdink ER, *et al.* The association between antidepressant use and disturbances in glucose homeostasis: evidence from spontaneous reports. *Eur J Clin Pharmacol* 2008;64:531–8.

37. Khoza S, Barner JC. Glucose dysregulation associated with antidepressant agents: an analysis of 17 published case reports. *Int J Clin Pharm* 2011;33:484–492.

38. Andersohn F, Schade R, Suissa S, Garbe E. Long-term use of antidepressants for depressive disorders and the risk of diabetes mellitus. *Am J Psychiatry* 2009;166:591–8.

39. Rubin R, Ma Y, Marrero D, *et al.* Elevated Depression Symptoms, Antidepressant Medicine Use, and Risk of Developing Diabetes During the Diabetes Prevention Program. *Diabetes Care* 2007;31:420–426.

40. Lustman PJ, Griffith LS, Clouse RAYE, Kenneth E. Effects of Nortriptyline on Depression and Glycemic Control in Diabetes□: Results of a Double-Blind , Placebo-Controlled Trial Approximately 5 % of the general population will experience an episode of major depression at some icantly more prevalent in dia. *Psychosom Med* 1997;59:241–250.

41. Olefsky JM, Farquhar JW, Reaven GM. Reappraisal of the role of insulin in hypertriglyceridemia. *Am J Med* 1974;57:551–60.

42. Subramanian S, Chait A. Hypertriglyceridemia secondary to obesity and diabetes. *Biochim Biophys Acta* 2012;1821:819–25.

43. Kenis G, Maes M. Effects of antidepressants on the production of cytokines. *Int J Neuropsychopharmacol* 2002;5:401–12.

44. Wozniak G, Toska A, Saridi M, Mouzas O. Serotonin reuptake inhibitor antidepressants (SSRIs) against atherosclerosis. *Med Sci Monit* 2011;17:RA205–14.

45. Barter P. Effects of Inflammation on High-Density Lipoproteins. *Arterioscler Thromb Vasc Biol* 2002;22:1062–1063.

46. Esteve E, Ricart W, Fernández-Real JM. Dyslipidemia and inflammation: an evolutionary conserved mechanism. *Clin Nutr* 2005;24:16–31.

47. Janssen DGA, Caniato RN, Verster JC, Baune BT. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. *Hum Psychopharmacol* 2010;25:201–215.

48. Stapelberg NJC, Neumann DL, Shum DHK, McConnell H, Hamilton-Craig I. A topographical map of the causal network of mechanisms underlying the relationship between major depressive disorder and coronary heart disease. *Aust N Z J Psychiatry* 2011;45:351–69.

49. Xia Z, DePierre JW, Nässberger L. Tricyclic antidepressants inhibit IL-6, IL-1 beta and TNF-alpha release in human blood monocytes and IL-2 and interferon-gamma in T cells. *Immunopharmacology* 1996;34:27–37.

50. McIntyre RS, Alsuwaidan M, Goldstein BI, *et al.* The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid metabolic disorders. *Ann Clin Psychiatry* 2012;24:69–81.

51. Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL. Depression and cardiac disease: epidemiology, mechanisms, and diagnosis. *Cardiovasc Psychiatry Neurol* 2013;2013:695925.

52. Wulsin LR. Do Depressive Symptoms Increase the Risk for the Onset of Coronary Disease? A Systematic Quantitative Review. *Psychosom Med* 2003;65:201–210.

53. Hu G, Tuomilehto J, Silventoinen K, Barengo N, Jousilahti P. Joint effects of physical activity, body mass index, waist circumference and waist-to-hip ratio with the risk of cardiovascular disease among middle-aged Finnish men and women. *Eur Heart J* 2004;25:2212–2219.

54. Kemp AH, Quintana DS, Gray M a, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biol Psychiatry* 2010;67:1067–74.

55. (CDC) C for D and P. Analytic and Reporting Guidelines for the Third National Health and Nutrition Examination Survey. 1996.

56. (CDC). C for D and P. Analytic and Reporting Guidelines for the National Health and Nutrition Examination Survey, NHANES. 2013.

57. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed Moods: A Review of the Interactions between Inflammation and Mood Disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2014.

58. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–13.

59. Mancia G. Blood pressure reduction and cardiovascular outcomes: past, present, and future. *Am J Cardiol* 2007;100:3J–9J.

60. Bowling A. Mode of questionnaire administration can have serious effects on data quality. *J Public Health (Oxf)* 2005;27:281–91.

61. D'Souza P, Jago C. Spotlight on depression: a Pharma Matters report. *Drugs Today (Barc)* 2014;50:251–67.

5.0 APPENDICES

APPENDIX A