The Association between Therapeutic Drug Classes and Weight Change in Patients Attending a Medically Supervised Weight Loss Clinic

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Abstract

Introduction: Obesity is a leading public health problem in the developed and developing world. As the prevalence of obesity and its associated comorbidities increases, the number of the medications used by individuals living with obesity is also on the rise. Beyond the utility of these drugs for the treatment of obesity-related chronic diseases, many have unwanted side effects, including weight gain. **Objectives:** To characterize the number of medications used by patients of the Wharton Medical Clinic (WMC) both overall and by obesity class, and; to determine whether the amount of weight change differs according to therapeutic drug classes or chronic condition. **Methods:** Data was derived from a subset of bariatric patients (n=1426) who attended WMC for 3+ months. Study exposures included the number and type of medications taken, and type of the chronic diseases experienced. The primary study outcome was relative weight change. **Results:** Of the 153 medications listed by WMC patients, 32 have side effects that include weight gain. Over 3 months of follow-up, average weight loss was 4.7 kg; percentage weight change was greatest amongst patients with a history of stroke (6.1%), heart attack (5.3%) and hypertension (4.8%). Implications: Barriers to weight loss may include pharmacological treatment for pre-existing conditions. These findings have implications for setting realistic weight loss goals for long-term obesity management.

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Obesity and Medication Use

Obesity is a leading public health problem in the developed and developing world (21). At present, approximately one-third of Canadian adults are at high risk of obesity-related disease, disability and premature death (5). As the prevalence of obesity and its associated comorbidities increases, the number of the medications prescribed, and used, by individuals living with obesity is also on the rise (8). Results of the 2007 to 2011 Canadian Health Measures Survey (CHMS) reported that 41% of individuals, 6 to 79 years old, had taken at least one prescription medication within two days of their household interview (36). At the same time, more than one in six middle-aged (45-64 y) Canadians (M: 18.9%; F: 11.5%) used lipid-modifying agents, combinations of different triglyceride and cholesterol reducers (44), and one in twelve (M: 10.3%; F: 6.6%) used ACE inhibitors (37), which are used as a treatment for a variety of conditions, such as scleroderma, high blood pressure and migraines (24).

Beyond the utility of these drugs for the treatment and management of each obesity-related chronic disease, many have unwanted side effects, and some may even result in weight loss or gain through modulation of neurochemical and metabolic pathways. For instance, neuroleptic drugs (31), tricyclic antidepressant drugs (14), β Adrenergic Receptor Blockers (29) and thiazolidinediones (15) are known to induce weight gain, and Metformin (22) and Fenofibrate (23) are known to induce weight loss in regular users. In individuals with obesity-related chronic disease who are trying to lose weight to normalize their risk profile, adjunctive therapy with some medications may therefore present a paradox of dampened effects. At present, it is not clear to what extent this may occur amongst patients in medically supervised weight loss programs, a high-risk subgroup of individuals living with obesity.

1.0 General Introduction

In 2014, 5.3 million Canadian adults, aged 18 and older, were classified as obese (Body Mass Index (BMI) $\geq$ 30 kg.m^{-2}). The rate of obesity in men increased from 20.1% in 2013 to 21.8% in 2014, which is the highest obesity rate for men reported since 2003. The same increasing trend is seen amongst women from 2013 to 2014 (18.7%) and this rate is also significantly higher from 2003 when it was 14.5% (33). Obesity is multifactorial and difficult to treat. Research has shown that only 20% of individuals defined as overweight ($\geq$25 kg.m^{-2}) are able to successfully maintain a 10% weight loss for at least 1 year (45). As the prevalence of obesity and its associated comorbidities increases, the number of the medications prescribed, and used, by individuals living with obesity is also on the rise (8). In addition to treating obesity and its related comorbidities, these medications may have unwanted side effects. Some of these medications may induce weight gain or weight loss while some are neutral. Individuals with obesity-related chronic diseases who are trying to lose weight to normalize their risk profile, adjunctive therapy with some medications may therefore present a paradox of dampened effects. This issue is particularly concerning in patients who are taking multiple medications, with different side effects. Better understanding of the possible association between different types of medications and chronic diseases with weight change is necessary so that more sustainable weight loss goals can be set for long term weight management.

2.0 Literature Review

2.1 Effect of Weight Loss on Cardiovascular Disease

In Canada, cardiovascular disease (CVD) is the 2nd leading cause of death (35), with more than 4 in 10 Canadians at an elevated risk for coronary heart disease (CHD) (32). Overweight and obesity are correlated with a variety of health conditions such as heart failure, CHD and sudden death associated with heart complications, and is an independent risk factor of for CVD (27). There is increasing evidence that even modest weight loss (5-10%) can fundamentally affect cardiovascular risk factors, and can lead to regression in coronary arterial lesions, cardiac events and to a decreased risk of cardiac mortality (41). For example, the Framingham Heart Study, a cohort study on residents of Framingham, Massachusetts, clearly illustrates that the rate of development of CVD is associated with the degree of overweight. After 26 years of follow up in this study, each standard deviation increase in relative weight was associated with a 22% and 15% increases in cardiovascular complication in women and men, respectively (20). Moreover, the look AHEAD (Action For Health in Diabetes) study (*n*= 5,145, 37% from ethnic/racial minorities, 40.5% male) on individuals with diabetes at baseline, living with overweight and obesity, investigated the association between the magnitude of weight loss and changes in CVD risk factors at 1 year. This secondary study illustrated that the magnitude of weight loss at 1 year is strongly ($P < 0.0001$) associated with improvements in glycaemia, triglycerides, blood pressure and HDL cholesterol. Participants who lost 5 to <10% of their body weight ([means ± SD] 7.25 ± 2.1 Kg) had higher odds of achieving a 0.5% point reduction in HbA_{1c} (Odds Ratio (OR): 3.52 [95% CI: 2.81- 4.40]), a 40 mg/dL decrease in triglycerides (2.20 [1.71-2.83]), a 5mg/dL increase in HDL cholesterol (1.69 [1.37- 2.07]), a 5-mmHg decrease in systolic blood pressure (1.56 [1.27-1.91]) and a 5-mmHg decrease in diastolic blood pressure

(1.48 [1.20-1.82]) (45). In summary, modest weight losses of 5 to <10% were associated with significant improvements in CVD risk factors at 1 year, with even greater benefits amongst those who lost more weight (48).

2.2 Effect of Weight Loss on Diabetes

According to Statistics Canada, there were 1,120,432 males and 890, 915 females aged 12 y+ living with diabetes in 2014 (34). Currently, diabetes is the 6th leading cause of death, in both sexes, in Canada (35). Along with physical activity and diet, even modest weight loss has long term benefits in type II diabetes patients (46). Over 2.8 years of follow-up in the Diabetes Prevention Program (DPP), a three-arm randomized controlled trial, diabetes incidence in high-risk adults was reduced by 31% with metformin and by 58% with intensive lifestyle intervention, compared with placebo (12). In addition, over the 10 year follow up since randomization to DPP, modest weight loss was maintained with metformin (12). The incidence rate of diabetes during the DPP was 11.0 cases per 100 person-years (95% CI: 9.8-12.3) in the placebo group, 7.8 (6.8-8.8) in the metformin group, and 4.8 (4.1-5.7) in the intensive lifestyle group. However, in the follow-up, the 10-year incidence of diabetes was reduced by 18% (7–28) in the metformin group and 34% (24–42) in the lifestyle group compared with placebo (12). In a further analysis of 1079 participants (25-84 y) of the DPP (mean 50.6 years, BMI 33.9 kg/m^2), weight loss was found to be the dominant determinant of the reduced risk of diabetes (hazard ratio per 5-kg weight loss 0.42 [95% CI: 0.35-0.51]; p< 0.0001). There was a 16% reduction in diabetes risk for every kilogram of weight loss, adjusted for changes in diet and physical activity. Moreover, there was a 55% reduction in the risk of diabetes when weight loss exceeded 5 kg (17), and more than 90% reduction in the risk of diabetes in individuals who lost more than 5-7% and *also* met the dietary fat and physical activity goals (17).

2.3 Effect of Weight Loss on Hypertension

There are 7.5 million people in Canada living with hypertension (18). According to the 2014 and 2015 CHMS household and physical measures data, around one-quarter of adults aged 20 to 79 had hypertension in Canada. For both sexes, average blood pressure significantly increases with age. The average blood pressure for males, 20 to 29 years old, increased from 107/69 mmHg to 123/70 mmHg amongst males aged 70 to 79 (33). In addition, overweight and obese individuals were twice as likely to develop hypertension in comparison to individuals with normal weight (Normal weight: 12%; Over weight/Obese: 30%). Weight loss reduces blood pressure in individuals with overweight even if they are in the normal or high normal blood pressure range (39). During an 18-month follow-up period, in a randomized controlled clinical trial, a weight reduction program was shown to be an effective intervention for decreasing blood pressure in overweight adults with high-normal blood pressure (38). The average weight loss at 6, 12, and 18 months of follow-up was 3.7, 2.7 and 1.6 kg for women and 6.5, 5.6 and 4.7 kg for men. The mean (±SE) in systolic pressure for the intervention participants compared with controls was -2.0±1.3 mmHg for women and -3.1±0.7 mmHg for men. For diastolic blood pressure, the corresponding change was -1.1±0.9 mmHg for women and -2.8±0.6 mmHg for men (38). Taken together, these studies reinforce the close association between weight and blood pressure, and the clinical utility of weight loss therapy on hypertension risk within the outpatient setting.

2.4 Major Classes of Weight Increase or Decrease Drugs

Given the increasing prevalence of obesity in North America, primary and secondary prevention efforts are a public health priority (40). However, obesity is multifactorial and difficult to treat, making relapse common. Of note, only 20% of individuals defined as

overweight ($\geq$ 25 kg.m^{-2}) are able to successfully maintain a 10% weight loss for at least 1 year (45). Because repeated weight loss followed by weight regain leads to a decrease in metabolic rate, this subsequently increases the efficiency of fat storage over time (6). While the benefits of medication use for chronic disease risk reduction are well known, some medications contribute to unhealthy weight gain, while others lead to weight loss (and further improve health). Others still may have no effect on weight. Amongst those trying to lose weight any unexpected (medication-induced) increase or decrease in weight may exacerbate the potential for weight loss and regain (e.g. weight cycling), and subsequently lead to poorer health over time. At present, there is no definitive understanding of the association of medication use with weight change as a barrier to weight loss within the clinical weight management setting. In the following section, a summary of weight- and "other" medication side-effects of the WMC medication classes, along with some specific medications in each class, are briefly discussed. Understanding the unique side effects of commonly used medications and their relationship to weight has the potential to foster knowledge and abilities, and consequently better goal setting for successful weight loss maintenance (28).

Tricyclic Antidepressant Medications:

One class of medication that has demonstrated a problematic body weight gain is tricyclic antidepressant medications. Depression is usually associated with a reduction in appetite and a subsequent decrease in body weight (14). Tricyclic antidepressant medications restore the mood and appetite (14), and the long-term administration of antipsychotic drugs induces weight gain, which afflicts up to 50% of patients (4). A comprehensive review of 81 articles by Allison et al. (1) showed the following mean increases in weight among newer antipsychotic agents: ziprasidone, 0.04 kg, risperidone, 2.10 kg, sertindole, 2.92 kg; olanzapine, 4.15 kg and clozapine,

4.45 kg. Antipsychotics induce weight gain through diverse mechanisms, including: i) an increase in appetite due to the interaction of antipsychotics with neural receptors to histamine, serotonin and dopamine, and; ii) antipsychotic-induced hyperprolactinaemia on gonadal adrenal steroids and insulin sensitivity (4), among others. Some of the other side effects of antipsychotic medications include anxiety, drowsiness, headache and insomnia (30).

Diabetes Medications:

Weight-related side-effects of diabetic medications are much more varied than antipsychotic medications: some diabetes medications cause weight loss, some cause weight gain and some do not cause a change in weight. For instance, Metformin causes weight loss (19, 9), Thiazolidinedione causes weight gain (15) and Glipizide, Biguanide and Acarbose do not cause a change in weight (30).

Metformin promotes weight loss in patients with obesity and T2DM, largely through decreases in satiety (22). Clinically significant decreases in fasting plasma glucose concentration, insulin concentrations and plasma lipid levels are typically observed with regular Metformin consumption (11). Some of the other side effects of Metformin include diarrhea, gastrointestinal disorder, nausea and vomiting (30).

Thiazolidinedione is derived from three compounds: pioglitazone (Actos), troglitazone (Rezulin) and rosiglitazone (Avandia) (19). Thiazolidinedione leads to weight gain through a range of mechanisms, including a decrease in plasma leptin levels and increased appetite. It has also been associated with changes in body fat distribution by contributing to a decrease in visceral fat and increased subcutaneous adipose fat storage (15). Troglitazone's other side effects include anemia, oedema and cardiac problems and congestive heart failure. Finally, Rosiglitazone's main side effects are anemia, nasopharyngitis and upper respiratory tract

infection, and; Pioglitazone's side effects are hypoglycemia, upper respiratory tract infection and headache (30).

Lipid Medications:

Most of the lipid medications either induce a weight loss or have no effect on weight. According to the medication index Sider (http://sideeffects.embl.de/), out of 13 lipid medications listed by WMC patients, 4 induced weight loss, 9 were neutral, 4 had reports of weight gain *and* weight loss, and 2 had unknown effects. For instance, Cholestyramine, Ezetimibe, Simvastatin and Fenofibric induce weight loss and Colestipol, Colesevelam and Lovastatin have no effect on weight (30). Available literature suggests that *Ezetimibe* significantly decreases body weight, waist circumference, BMI, total fat mass and subcutaneous and visceral fat (9). Furthermore, Ezetimibe significantly decreases the concentration of plasma LDL-apaB-100 by increasing its fractional catabolic rate (9). Ezetimibe's other side effects are headache, upper respiratory tract infection and diarrhea (30).

Blood Pressure Medications:

In addition to the improved arterial blood pressure, patients undergoing treatment with *Indapamide* have shown significant weight loss (47). Indapamide's other side effects are infection, headache and hypochloramia (30).

Metoprolol significantly induces weight gain (mean [SD], 1.2 [0.2] kg), and has been shown to increase triglycerides (3). Previous research suggests that Metoprolol may exaggerate the weight gain amongst individuals living with overweight or obesity (25). Some of the other side effects of Metoprolol include cardiac failure, hypotension and bradycardia (30).

Thyroid Medications

Only one study to date (16) has examined the weight-related effects of *Liothyronine*, a thyroid medication. In this study a standard 1,000 calorie diet was administered to patients with obesity in a randomized cross-over design. Results suggest that from weeks 8 to 16 of the study, the use of *Liothyronine* resulted in an additional 0.39 kg/week of weight loss (16). Some of the side effects of liothyronine include tachycardia, cardiac problems, congestive heart failure, and hypertension (30).

3.0 Study Rationale

At present the possible association between chronic diseases and medication use with weight change within the clinical weight management setting is not well understood. Therefore, the purpose of this study is to explore variation in weight change outcomes amongst individuals with a range of comorbidities and medication classes.

Research suggests that successful weight maintenance - intentional weight loss that has subsequently been maintained for at least 6 months - is associated with larger initial weight loss, reaching a self-determined goal weight, control of over-eating, and self-monitoring of behaviors (13). Weight maintenance is further associated with better coping strategies and ability to handle life stresses, social support, internal motivation to lose weight, self-efficacy, assuming responsibility in life, autonomy, and overall more psychological strength and stability (13). Because of the complex interplay between these psychological factors and the physiological changes associated with long-term weight gain, it is critical to understand how factors such as medication use may be impacting on weight change in the clinical setting. At the present time there is little information regarding the number and type of medications used by individuals

living with obesity (stage I, II, and III). Together, this information will provide perspective on medications and conditions that may be either barriers or promoters to weight loss success – whether through direct means - or by enhancing or impairing motivation and adherence to clinical lifestyle programming.

4.0 Objectives

Objective 1: To characterize the number of medications used by participants of the Wharton Medical Clinic (WMC) both overall, and by BMI category (overweight, obesity class I, II and III).

Objective 2: To determine whether percentage weight change differs according to the therapeutic drug classes and by chronic diseases.

Objective 3: To determine if the relationship between number of medications consumed is related to the achievement of a clinically significant weight loss ($\geq 5\%$).

5.0 Methods

5.1 Wharton Medical Clinic

Data is drawn from patients of the Wharton Medical Clinic (WMC), a medically supervised weight management centre with 6 locations in the Greater Toronto Hamilton Area. This referral-based clinic is comprised of a team of dietitians, medical doctors, and includes behavioral therapy and nutritional counseling, among other services. In so doing, the WMC is involved in the management of obesity to decrease diabetes and cardiovascular-related risk factors, such as high cholesterol and high blood pressure. The ultimate goal of the WMC is to improve the health and the quality of life of patients living with overweight and obesity.

The WMC is fully funded by the Ontario Health Insurance Plan (OHIP) and includes a weight management, brain, heart and diabetes clinic. All participants provided written informed consent for their information to be used.

5.2 Participants

Informed Consent Process:

All patients were provided with details of the clinic and ongoing data collection at their first clinic visit. Patients were subsequently presented with a letter of written informed consent for their review. Patients were informed that they could withdraw consent at any time, and that regardless of their participation, there would not be any differences in the care provided by the clinic. This research is approved by the human participants' research community of York University **(Appendix A)** and data for this analysis is accessed as a secondary analysis, with data extraction on December 5th, 2014.

First Visit Measures:

At the initial consultation, anthropometric measurements are taken (e.g. waist circumference, weight and height) and an exploratory electrocardiograph is administered. Patients are also asked to fill out a questionnaire regarding various aspects of their medical history, including their level of physical activity, diet, physical and psychological conditions (42). A registered dietitian also has a brief consultation with patients during their first visit to WMC to provide an overview of the program. A clinic physician then works with the patient to prescribe a personalized treatment plan to fit the patient's needs and set a realistic weight management and lifestyle change goal for the patient. Following this, the patients are encouraged to attend the clinic every week to be weighed by the physician or the bariatric educator. Regular

contact is maintained between the patient and clinic, and weight management talks and continuing education are provided to the patient as needed (42).

Sample Size

Data for this analysis includes n=1913 participants who attended the clinic for ≥3 months. A three-month threshold was selected to ensure an adequate sample size to examine weight loss maintenance. Patients with a BMI ≤ 25kg.m^{-2} (n=2) and a weight change of 50.4 kg (n=1) were initially excluded. After excluding 381, 79 and 24 patients with missing education information, waist measurements, and smoking status, the final sample size was narrowed to 1426 patients **(Figure 1).**

5.3 SIDER: Side Effect Resources

In order to identify the weight-related side effects of all possible medications of existing clinic patients, the SIDER 4.1: side effect resource (http://sideeffects.embl.de/) was scanned. Side effects of each medication, along with any report of weight gain, neutral and weight loss were recorded **(Appendix C)**. SIDER extracts this information from public documents and package inserts (30). Results were then cross-validated by a medical doctor (Dr. Sean Wharton), and a list of 153 medications was subsequently created to classify drugs into type II diabetes, lipid, blood pressure, thyroid, congestive heart failure, blood-thinner, Meridia, and cholesterol medications. In total, there were 21 type 2 diabetes, 19 lipid, 76 blood pressure, 6 thyroid, 33 congestive heart failure, 3 blood-thinner, 2 weight loss (meridia and orlistat) and 6 cholesterol medications identified for the purposes of the current study.

5.4 Study Variables

Exposure Variable: Number and type of medications used by participants of the WMC and type of chronic diseases (self-reported baseline questionnaire and confirmed with physician).

Outcome Variable: Relative (%) and absolute (kg) amount of weight change and percentage achieving ≥ 5% weight loss over 3+ months of follow-up.

Confounding Variables: Age, sex, waist circumference, education (less than high school, high school/GED, college, university), smoking status (current, former, never), average number of clinic visits and number of medications (0, 1, 2, 3, 4+).

5.5 Statistical Analysis

Descriptive analysis (proc univariate, proc freq (n, %)) is used to determine the number of medications used by participants of the WMC, both overall, and by obesity class (I to III).To determine whether the amount of percentage weight change differs according to the therapeutic drug classes and by chronic disease, multivariable logistic regression analysis was used to estimate the odds of achieving ≥ 5% weight loss by number of medications, and then stratified by cardiovascular related diseases. Model 1 is adjusted for age and sex and model 2 is adjusted for age, sex, education, waist circumference, smoking status, and average number of visits. General linear model analysis is also carried out to quantify the relationship between medication number and weight loss amongst males and females overall, and stratified by select chronic conditions. Due to a limited sample size, separate general linear analyses for patients with a history of stroke (0.7%) and heart attack (1%) was not possible. Statistical significance was set at alpha of 0.05 and all analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC., USA).

6.0 Results

The baseline characteristics for study participants are presented in **Table 1**. In total, 409 males and 1017 females attended the clinic for 3+ months and are included in the final analysis.

On average, the sample is middle-aged (mean age: 51.6 (12.7) years old), with a waist circumference of 119.6 (11.2) cm and 13.3 (8.4) clinic visits. The majority of participants were white (87.2%), obesity class III (48.9%), and were never-smokers (54.4%). In addition, 31.6%, 14.7%, 16.9%, 19.6% and 17.1% of the patients were taking 0, 1, 2, 3, 4+ medications respectively **(Table 1)**. Over 3+ months of follow-up, average weight loss was 4.7 kg, and 40.5% of the sample achieved ≥ 5% weight loss. Of the 153 medications listed by WMC patients, 32 medications had side effects associated with weight gain, 8 had complications of weight loss, and 113 were weight neutral.

Figure 2 illustrates that the percentage weight change was greatest amongst patients with a history of stroke (6.1%), heart attack (5.3%) and hypertension (4.8%). In addition to patients who were taking Meridia (4.8%), patients who were on blood pressure or cardiovascular medications also showed the highest percentage weight loss (4.5%) (**Figure 3**). Average number of medication intake increased with obesity classifications. Individuals identified as being over-weight, obesity class I, II and III took an average number of 1.3, 1.6, 1.7 and 1.9 medications, respectively (**Figure 4**). Results also showed that only 9% of patients classified as overweight took 4+ medications versus 19% of the patients identified as class III obese. In addition, almost half of the patients who were overweight (44%) were taking no medications versus 29% of the patients identified as obese class III (data not shown).

Because of the large discrepancy in sample size [Males: (n=409); Females: (n=1017)] and reported sex differences in previous research, separate generalized linear models were developed for men and women. In males, a significant relationship between medication number and weight loss was found with a p value of 0.02 but this relationship was non-significant amongst females. In addition, no significant relationship between medication number and weight

loss was found amongst females and males in subgroups of participants with diabetes, prediabetes, or hypertension **(Table 2)**. Overall, average weight loss was greater in males (-6.4 kg) in comparison to females (-4.1 kg).

Logistic regression analysis revealed an inverse association between the number of medications reported and the % who were able to achieve ≥5% weight loss **(Table 3).** For instance, in model 1, individuals who reported taking 3 medications had 30% lower odds of achieving a ≥5% weight loss in comparison to the referent group (no prescription medication use).

7.0 Discussion

7.1 Findings

Given the increasing prevalence of chronic diseases and consequent usage of medications (8), it is important to address the association between chronic diseases and medications with weight change in a clinical setting. This study demonstrated the greatest weight change percentage amongst patients with a history of stroke, hypertension and heart attack. In addition, patients who were taking blood pressure, cardiovascular medications and Meridia also showed the highest percentage weight change.

This study also indicated that as the number of prescription medication intake increased, it became less likely that the patient achieved a clinically significant ≥ 5% weight loss. Additionally, although the findings did not reach statistical significance, as BMI increased, the number of prescription medications tended to increase as well. This makes it challenging to interpret the results in regards to patients living with obesity class III who are taking several medications, with different side effects, at the same time.

In addition, results of this paper illustrated that patients who attended WMC achieved a mean (± SD) weight loss of 4.7±11.2 kg, with almost 40.5% of the patients attaining a ≥ 5% weight loss. This is consistent with the previous research on the patients of the WMC attending the clinic for at least 3 months ([8.1± 6.1 visits and 5.4 ± 4.7 months) which reported a weight loss of (4.2 ± 7.1 kg), with 32% and 9% of these patients achieving weight reductions of 5% or greater and 10% or greater, respectively (43). Moreover, results of a cross-sectional and longitudinal study on community dwelling residents (n=885), aged 72 and older, found that participants consumed on average 2.2 (mean) ± 1.9 (standard deviation) medications (range 0-15) (2). This study reported a linear relationship between number of medication intake and weight loss. After adjustment for age, cognitive impairment, depressive symptoms, vision and hearing impairment, number of chronic diseases, number of medications, and number of hospitalizations in the previous year, the adjusted weight loss was 1.48 (95% CI=0.85-2.59) for those who were consuming two medications, 1.96 (1.08-3.54) for three or four medications, and 2.78 (1.38-5.60) for five or more medications (2). Even though the number of medications in this study is consistent with the number of medications taken by the patients of the WMC [1.3 (overweight), 1.6 (class I), 1.7 (class II), 1.9 (class III)], the relationship between the number of medications and weight loss is contrary to the reported inverse relationship found in our study. For instance, in model 1, individuals who reported taking 3 medications had 30% lower odds of achieving a ≥5% weight loss in comparison to the referent group (no prescription medication use). This may be due to the age difference between these two study samples (≥72 vs 51.6), setting of the studies (Urban Connecticut community vs medically supervised weight management center) or the BMI of the participants (Normal weight vs Obesity class II/III).

7.2 Study Limitations

As with other secondary analyses, there are caveats to the validity and interpretation of study results. One of the main limitations of this study is that people who are on medications may not adhere to them fully (7, 10). Second, baseline questionnaire information may not be missing at random, and the exclusion of participants with incomplete covariate information may introduce bias and decrease overall generalizability to the broader clinic population. For instance, due to high missing frequency, variables such as income, ethnicity, current level of physical activity, drinking status, mental health status and weight perception were excluded which may obscure the overall relationship between weight loss and medication consumption. Additionally, there may not be sufficient data regarding WMC participants who gained weight (≥ 5% above baseline weight), since they are still on a weight loss program and due to the high dropout rate of this population. This information would have been valuable to help us understand the association between weight gain and medication classes better. Furthermore, although all WMC services are OHIP-eligible, participants must be referred by their family doctor and may therefore represent a more health conscious, and more motivated segment of the population living with obesity in Ontario (42, 26). Finally, there may be a referral bias in the first place because almost 86% of the WMC sample is comprised from white patients who may not be fully representative of the broader GTHA population from which patients were drawn.

7.3 Implications and Future Directions

A better understating of the possible association between chronic conditions and medication classes with weight change is necessary so that personalized prescriptions can be made to patients according to their weight and medication use. This will ensure that the patients are

prepared for the possibility that their weight loss “goal” may not be achieved, and that one of the barriers may the medications that they are taking.

7.4 Conclusion

This paper demonstrated that as the number of medication intake increased it became less likely for the individual to achieve a ≥ 5% weight loss and that patients with a history of hypertension or heart attack; and who took blood pressure or cardiovascular medications showed the highest weight change percentage. Future qualitative work is necessary to understand how polypharmacy may be an explicit barrier to long-term weight maintenance within the clinic setting.

Extended Discussion

A. Generalizability of the Results

Gaining knowledge about the association between medications and chronic conditions with weight change is imperative to understanding how barriers to weight loss can be pro-actively discussed as part of the general practitioner or bariatric physician initial consultation. Unfortunately, it is challenging to generalize the findings of this study to all the individuals living with obesity in Ontario. First, WMC patients are comprised from a healthier subset of the population. Of the 1426 patients, only 7.9%, 10.6%, 4.3%, 1.0% and 0.6% had a history of hypertension, diabetes, prediabetes, heart attack and stroke respectively. Second, eventhough the WMC is fully covered by OHIP and is assumed to be accessible to all the patients equally, there is a referral bias. To note, the majority of the patients who are referred to WMC are white (87.2%), women (71.3%). Moreover, this segment of the population overcame the transportation barrier and adhered to the program over ≥3 months of follow up. Hence this segment of the population may represent a more health conscious, motivated segment of the population living with obesity in Ontario (8, 3). Another issue that introduces bias and decreases the overall generalizability to the broader clinic population is that individuals with no reports of income, ethnicity, current level of physical activity, drinking status, mental health status and weight perception were excluded from the sample size. These variables may not be missing at random and may obscure the overall result. In addition, this study demonstrated that as the BMI categories increased from overweight to obesity class III, the number of medications that the patients took also increased. This makes it challenging to generalize the findings of this paper to patients who are classified in obesity class II or III categories. These patients take several medications, with different side effects, at the same time. Originally, this study was interested in

the issue of interaction between several medications. It was planned to investigate the effect of medications that induce weight gain versus medications that induce weight loss, separately, on weight change. Nevertheless, due to the way that coding was done in the data set, looking at this issue was not feasible and will remain as an issue to be looked at in future.

B. Other Findings

Even though the majority of the WMC patients were classified as obese class II (26.9%) or class III (48.9%), most of the patients did not experience comorbidities or functional limitations. This is due to the limitation of the current classification of obesity based on BMI in a clinical setting. The new clinical staging system, Edmonton Obesity Staging System (EOSS), that allows clinicians to demonstrate morbidities and clinical limitations associated with excess weight (5). According to this new staging system most of the WMC patients are categorized in obesity class III and EOSS stages 1 or 2. This healthier population, once again, makes it challenging to generalize the findings of this study to the overall population of the individuals living with obesity who are being categorized in the higher stages of the EOSS.

Although cause and effect relationship cannot be inferred from this study, results demonstrated greatest percentage weight change amongst patients with a history of hypertension, stroke and heart attack and also amongst patients who were taking blood pressure, cardiovascular medication and Meridia. The higher percentage weight change may also be due to the differences in the patient "motivation" to lose weight. More recent and serious health events may provide motivation for weight loss (1). For example, these patients may have been told by their family physician that they need to lose weight for the serious condition that they have been diagnosed with.

Moreover, out of 153 medications rated by the clinical study lead (coauthor: S.W.) and SIDER, 32 and 25 medications induced weight gain, and 8 and 15 medications induced weight loss, respectively. In fact, 24.8% inter-rater agreement between the side effect information of medications (weight gain, loss, neutral) extracted from SIDER versus side effect information evaluated by Dr. Wharton was found. The low value of the Cohen's kappa coefficient is partly due to the clinically meaningful ≥5% weight change (7, 9, 2) versus the public documents and package inserts as sources of information used by SIDER (6). At present, the appropriateness of either definition is unclear; however, given that it will ultimately be the physician who is managing the patient's course of treatment, his or her interpretation of medication side effects will be deciding factor. Future work should attempt to understand (and quantify) physician knowledge of weight as a side-effect of medication use.

In addition, further sensitivity analysis was carried out within disease specific groups of diabetes, prediabetes, stroke, heart attack and hypertension to find the odds of achieving ≥5% weight loss by number of medications. The results of this analysis was not significant for any of the chronic conditions (**Appendix D-Table 3A**).

C. Implications and Future Directions

A number of future directions warrant further investigation. First, there is a need to examine weight change separately in terms of medications that induce weight gain versus medications that induce weight loss. This facilitates a more precise personalized prescription to the patients and consequently leads to better weight change results. Second, to facilitate health behavior changes new theories are needed. A theoretical framework helps to improve the treatment by focusing assessments, directing the best practice interventions and ultimately improving patient outcomes. Integrated Theory of Health Behavior Change, ITHBC, proposes

that health behavior change can be improved by fostering knowledge and beliefs, increasing self-regulation skills and abilities and enhancing social facilitation (4). This theory proposes that individuals are more likely to engage in the recommended health behaviors if they have information about and embrace health beliefs consistent with behavior (4). Knowledge about possible association between chronic diseases or medication use with weight loss would therefore fit within the knowledge portion of the ITBHC. Knowledge about chronic diseases and medication use as barriers to weight loss influences goal setting and consequently leads to a better distal outcome which is weight loss. By improving the knowledge piece in this theory, barriers to weight loss can be pro-actively addressed as part of the initial consultation and consequently more sustainable weight loss prescriptions can be set for the patients according to the chronic diseases that they experience or the medications that they consume.

Table1. Baseline Characteristics of WMC Patients

	Male (N=409)	Female (N=1017)	Overall (N=1426)
Age	52.3 (12.6)	50.8 (12.5)	51.6 (12.7)
Ethnicity			
White	89.0	86.5	87.2
South, East Asian/African	4.9	5.2	5.1
Other	5.9	8.2	7.6
Education			
Less than high school	10.0	6.3	7.4
High school/GED	28.8	29.2	29.1
College	30.6	38.7	36.4
University	30.6	25.7	27.1
BMI (kg/m^2)	41.9 (8.6)	40.7 (7.8)	40.3 (8.8)
Obesity class			
Overweight	1.2	3.9	3.1
Obesity class I	21.2	20.9	21.0
Obesity class II	26.6	27.0	26.9
Obesity class III	50.9	48.1	48.9
Average weight loss	-6.4 (12.7)	-4.1 (10.6)	-4.7 (11.2)
≥ 5% weight loss	41.2	40.5	40.5
Waist circumference (cm)	133.6 (17.6)	118.1 (16.3)	119.6 (18.1)
Hypertension (%)	10.0	6.9	7.9
Diabetes (%)	10.7	10.1	10.6
Pre-diabetes (%)	4.4	4.2	4.3
Stroke (%)	0.7	0.5	0.6
Heart-attack (%)	1.2	0.9	1.0
Smoke			
Never	49.6	56.3	54.4
current	10.7	9.2	9.6
past	49.6	34.4	35.9
Average number of visits	14.9 (9.3)	12.6 (7.9)	13.3 (8.4)
Number of medications			
0	22.5	35.2	31.6
1	12.7	15.5	14.7
2	17.1	16.9	16.9
3	25.2	17.4	19.6
4+	22.5	14.9	17.1

Table 2. Relationship between Medication Number and Weight Loss Across Chronic Conditions

	Average weight loss (Kg)	N	ß	P	r^2
Male	-6.4	409	0.4	**0.02**	0.09
Diabetes	-4.4	44	1.5	0.6	0.2
Prediabetes	-4.0	18	1.7	0.8	0.4
Hypertension	-5.7	41	1.7	0.5	0.2
Female	-4.1	1017	0.2	0.2	0.1
Diabetes	-4.3	103	0.7	0.4	0.1
Prediabetes	-0.5	43	0.9	0.8	0.07
Hypertension	-6.5	70	0.9	0.8	0.4

Adjusted for age, education, waist circumference, smoking status and average number of visits.

Table 3. Odds of ≥ 5% Weight Loss by Number of Medications

	Model 1		Model 2	
	OR	95% CI	OR	95% CI
0 medication (N=451)	1.0	Referent	1.0	Referent
1 medication (N=210)	0.8	(0.6-1.1)	0.8	(0.6-1.2)
2 medications (N=241)	0.9	(0.7-1.2)	0.9	(0.6-1.2)
3 medications (N=279)	**0.7**	**(0.6-0.9)**	**0.6**	**(0.4-0.9)**
4+ medications (N=245)	0.8	(0.6-1.0)	0.7	(0.5-1.0)

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, education, waist circumference, smoking status, and average number of visits.

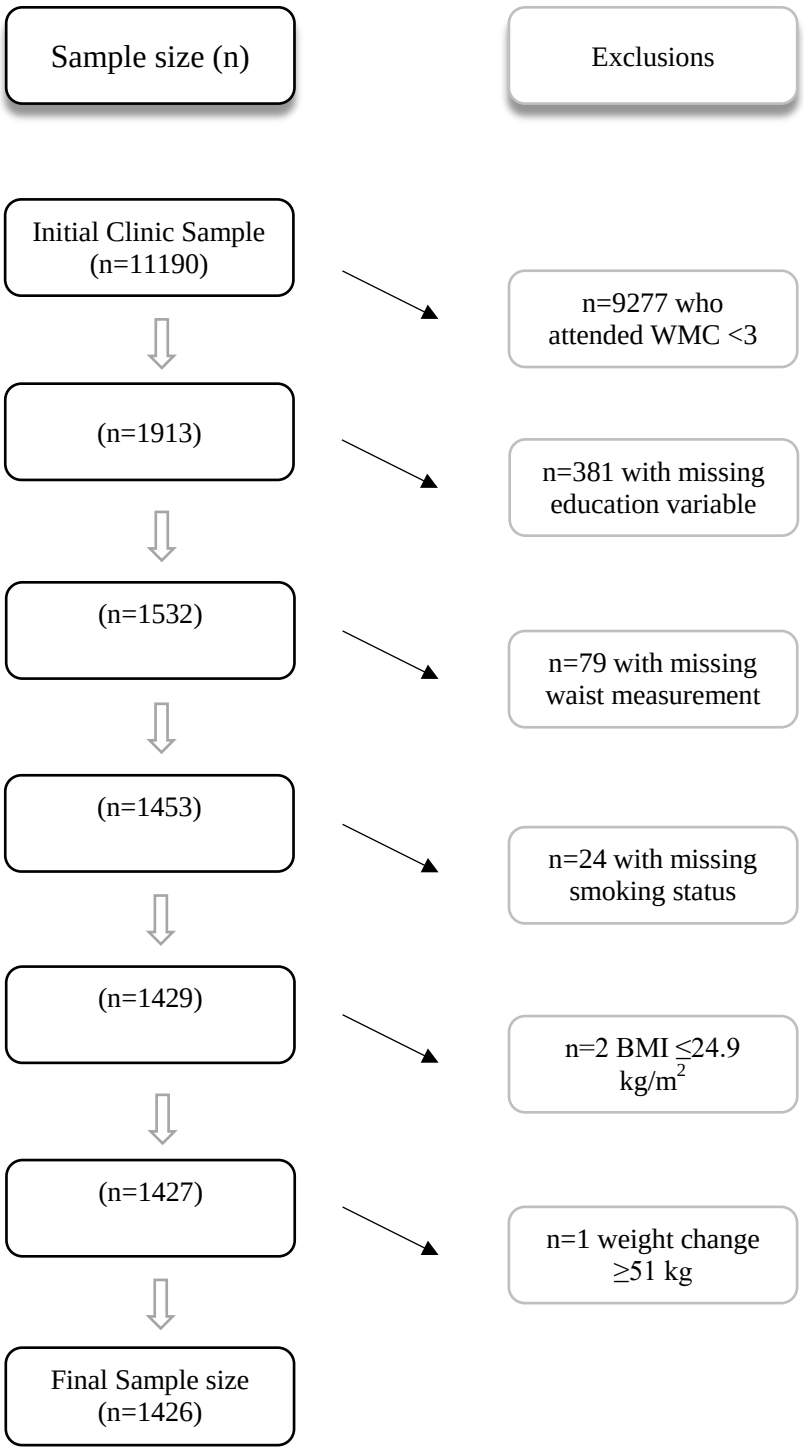

Figure 1: Derivation of Final Analytic Sample

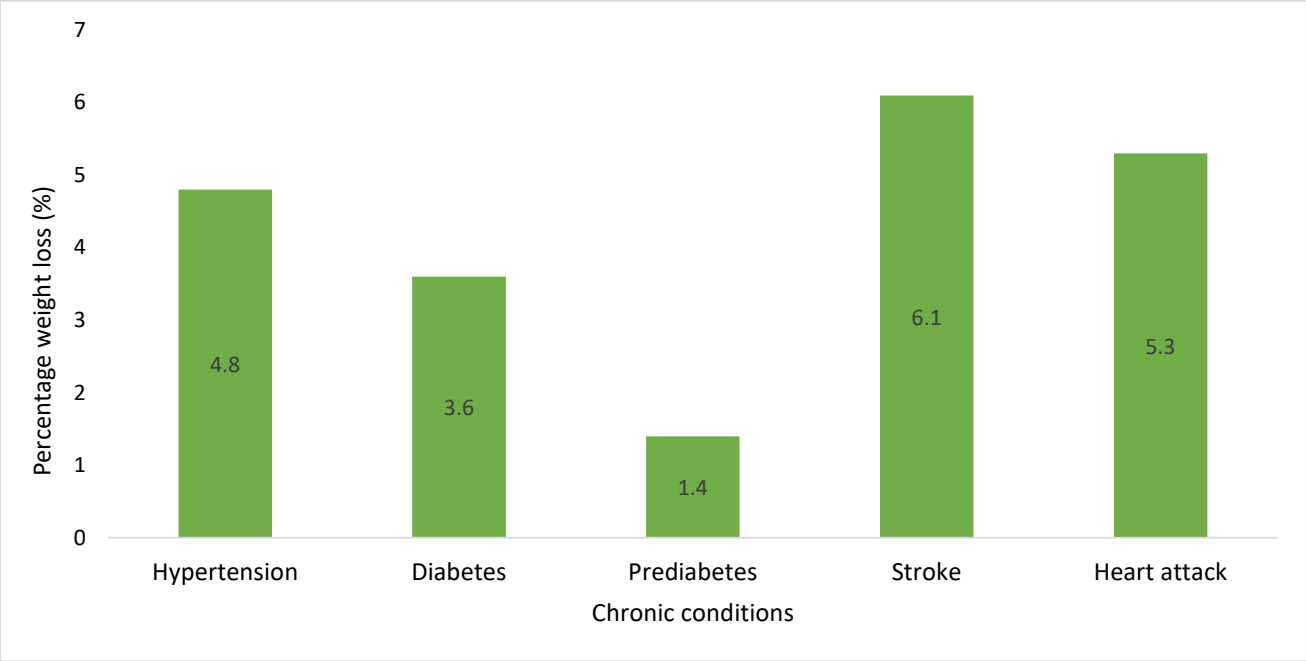

Figure 2: Percentage Weight Loss by Chronic Condition

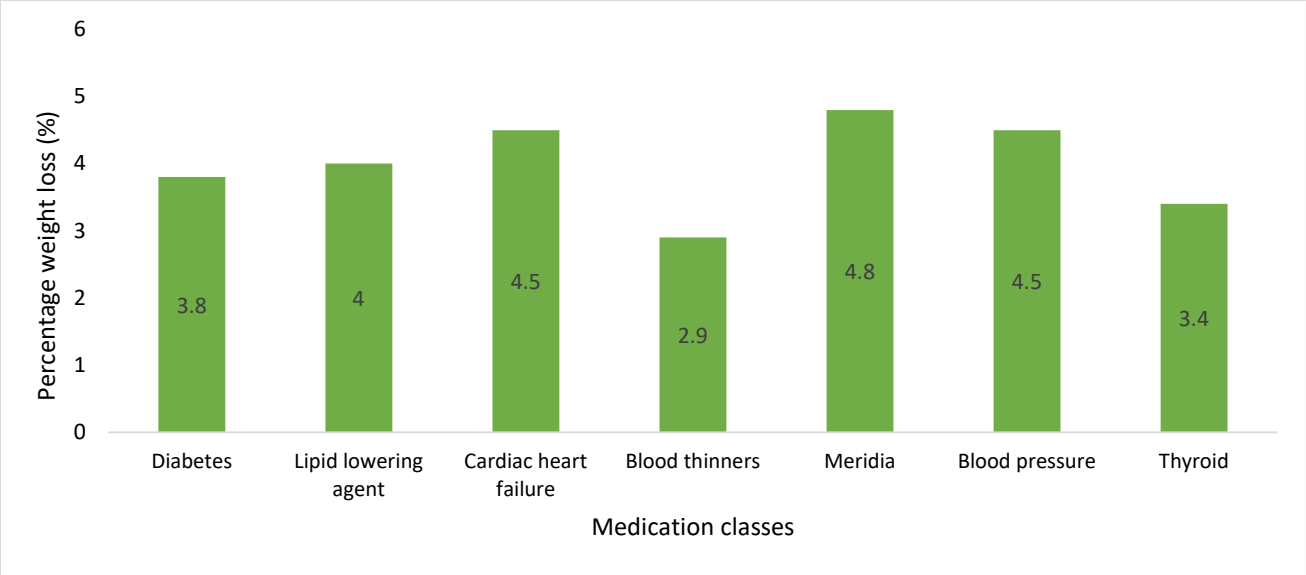

Figure 3: Percentage Weight Loss by Medication Classes

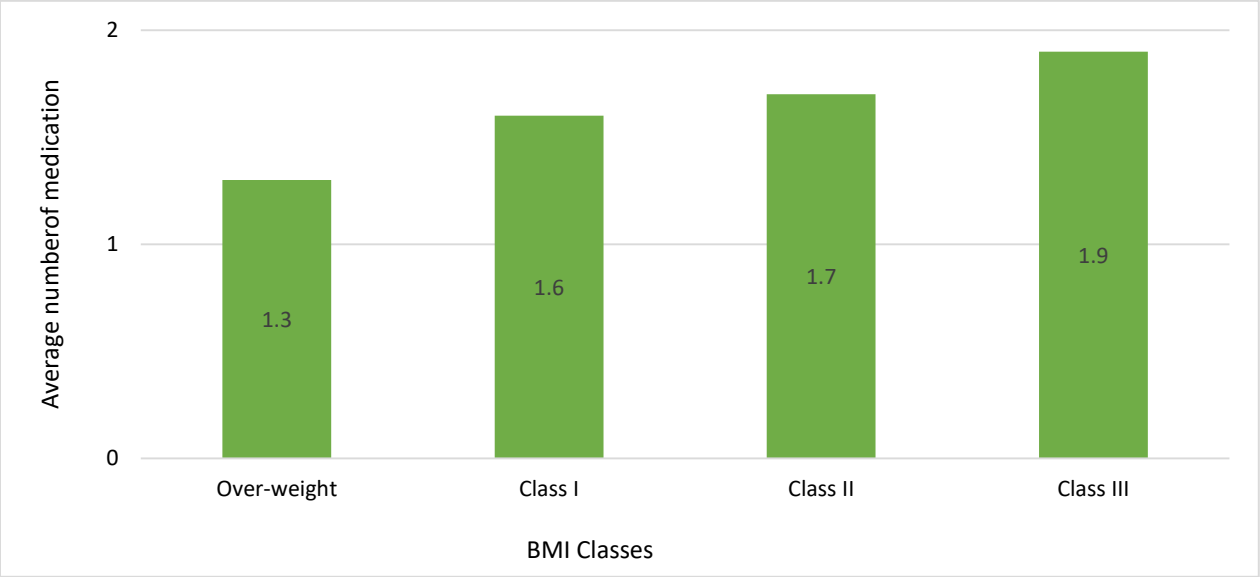

Figure 4: Average Number of Medication Intake by BMI Classes

References

1. Allison, D. B., Mentore, J. L., Heo, M., Chandler, L. P., Cappelleri, J. C., Infante, M. C., & Weiden, P. J. (1999). Antipsychotic-induced weight gain: a comprehensive research synthesis. *American journal of Psychiatry*, 156(11), 1686-1696.

2. Agostini, J. V., Han, L., & Tinetti, M. E. (2004). The relationship between number of medications and weight loss or impaired balance in older adults. *Journal of the American Geriatrics Society*, *52*(10), 1719-1723.

3. Bakris, G. L., Fonseca, V., Katholi, R. E., McGill, J. B., Messerli, F. H., Phillips, R. A., ... & Anderson, K. M. (2004). Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *Jama*, *292*(18), 2227-2236.

4. Baptista, T. (1999). Body weight gain induced by antipsychotic drugs: mechanisms and management. *Acta Psychiatrica Scandinavica*, *100*(1), 3-16.

5. Birmingham, C. L., Muller, J. L., Palepu, A., Spinelli, J. J., & Anis, A. H. (1999). The cost of obesity in Canada. *Canadian Medical Association Journal*, *160*(4), 483-488.

6. Blackburn, G. L., Wilson, G. T., Kanders, B. S., Stein, L. J., Lavin, P. T., Adler, J., & Brownell, K. D. (1989). Weight cycling: the experience of human dieters. *The American journal of clinical nutrition*, *49*(5), 1105-1109.

7. Brown, M. T., & Bussell, J. K. (2011). Medication adherence: WHO cares?. *Mayo Clinic Proceedings*, *86(4)*, 304-314.

8. Canadian Institute for Health Information. (2012). Prescribed Drug Spending in Canada, 2012: A Focus on Public Drug Programs. Retrieved from https://secure.cihi.ca/free_products/Prescribed_Drug_Spending_in_Canada_EN.pdf

9. Chan, D. C., Watts, G. F., Gan, S. K., Ooi, E. M., & Barrett, P. H. R. (2010). Effect of ezetimibe on hepatic fat, inflammatory markers, and apolipoprotein B-100 kinetics in insulin-resistant obese subjects on a weight loss diet. *Diabetes Care*, *33*(5), 1134-1139.

10. Cramer, J. A. (2004). A systematic review of adherence with medications for diabetes. *Diabetes care*, *27*(5), 1218-1224.

11. Defronzo, R. A., Barzilai, N., & Simonson, D. C. (1991). Mechanism of Metformin Action in Obese and Lean Noninsulin-Dependent Diabetic Subjects. *The Journal of Clinical Endocrinology & Metabolism*, *73*(6), 1294-1301.

12. Diabetes Prevention Program Research Group. (2009). 10-year follow-up of diabetes incidence and weight loss in the Diabets Prevention Outcomes Study. *The Lancet, 374(9702),* 1677-1686.

13. Elfhag, K., & Rössner, S. (2005). Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. *Obesity reviews*, *6*(1), 67-85.

14. Fernstrom, M. H. (1995). Drugs that cause weight gain. *Obesity research*, *3*(S4), 435S-439S.

15. Fonseca, V. (2003). Effect of thiazolidinediones on body weight in patients with diabetes mellitus. *The American journal of medicine*, *115*(8), 42-48.

16. Gelvin, E. P., Kenigsberg, S., & Boyd, L. J. (1959). Results of addition of liothyronine to a weight-reducing regimen. *Journal of the American Medical Association*, *170*(13), 1507-1512.

17. Hamman, R. F., Wing, R. R., Edelstein, S. L., Lachin, J. M., Bray, G. A., Delahanty, L., ... & Wylie-Rosett, J. (2006). Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes care*, *29*(9), 2102-2107.

18. Hypertension Canada. (2016). Welcome to hypertension Canada. Retrieved from https://www.hypertension.ca/en/

19. Kahn, C. R., Chen, L., & Cohen, S. E. (2000). Unraveling the mechanism of action of thiazolidinediones. *The Journal of clinical investigation*, *106*(11), 1305-1307.

20. Kannel, W. B., d'Agostino, R. B., & Cobb, J. L. (1996). Effect of weight on cardiovascular disease. *The American journal of clinical nutrition*, *63*(3), 419S-422S.

21. Katzmarzyk, P. T., & Janssen, L. (2004). The economic costs associated with physical inactivity and obesity in Canada: an update. *Canadian journal of applied physiology, 29(1),* 90-115.

22. Lee, A., & Morley, J. E. (1998). Metformin Decreases Food Consumption and Induces Weight Loss in Subjects with Obesity with Type II Non-Insulin-Dependent Diabetes. *Obesity research*, *6*(1), 47-53.

23. Lee, H. J., Choi, S. S., Park, M. K., An, Y. J., Seo, S. Y., Kim, M. C., ... & Kim, D. K. (2002). Fenofibrate lowers abdominal and skeletal adiposity and improves insulin sensitivity in OLETF rats. *Biochemical and biophysical research communications*, *296*(2), 293-299.

24. Mayo Clinic. (2016). High blood pressure (hypertension). Retrieved from http://www.mayoclinic.org/diseases-conditions/high-blood-pressure/in-depth/ace-inhibitors/art-20047480

25. Messerli, F. H., Bell, D. S., Fonseca, V., Katholi, R. E., McGill, J. B., Phillips, R. A., ... & Lukas, M. A. (2007). Body weight changes with β-blocker use: results from GEMINI. *The American journal of medicine*, *120*(7), 610-615.

26. Pampel, F. C., Krueger, P. M., & Denney, J. T. (2010). Socioeconomic disparities in health behaviors. *Annual review of sociology*, *36*, 349.

27. Poirier, P., Giles, T. D., Bray, G. A., Hong, Y., Stern, J. S., Pi-Sunyer, F. X., & Eckel, R. H. (2006). Obesity and cardiovascular disease pathophysiology, evaluation, and effect of weight loss. *Arteriosclerosis, thrombosis, and vascular biology*, *26*(5), 898-918.

28. Ryan, P. (2009). Integrated theory of health behavior change: background and intervention development. *Clinical nurse specialist CNS*, *23*(3), 161.

29. Sharma, A. M., Pischon, T., Hardt, S., Kunz, I., & Luft, F. C. (2001). Hypothesis: β-adrenergic receptor blockers and weight gain a systematic analysis. *Hypertension*, *37*(2), 250-254.

30. Sider. (2015). Sider 4.1: Side Effect Resources. Retrieved from http://sideeffects.embl.de/

31. Stanton, J.M. (1995). Weight gain associated with neuroleptic medication: a review. *Schizophernia Bulletin*, 21(3), 463.

32. Statistics Canada. (2015). Canadian Health Measures Survey: Omega-3 fatty acid levels of adults, 2012 and 2013. Retrieved from http://www.statcan.gc.ca/daily-quotidien/151118/dq151118d-eng.htm

33. Statistics Canada. (2016). Canadian Health Measures Survey: Household and physical measures data, 2014 and 2015. Retrieved from http://www.statcan.gc.ca/daily-quotidien/161013/dq161013c-eng.htm

34. Statistics Canada. (2016). Diabetes by age group and sex (Number of persons). Retrieved from http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health53a-eng.htm

35. Statistics Canada. (2015). Leading causes of death, by sex (Both sexes). Retrieved from http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/hlth36a-eng.htm

36. Statistics Canada. (2015). Prescription medication use by Canadians aged 6 to 79. Retrieved from http://www.statcan.gc.ca/pub/82-003-x/2014006/article/14032-eng.htm

37. Statistics Canada. (2015). Top five prescription medications used, by sex, age group and medication class, household population aged 25 to 79, Canada, 2007 to 2011. Retrieved from http://www.statcan.gc.ca/pub/82-003-x/2014006/article/14032/tbl/tbl4-eng.htm

38. Stevens, V. J., Corrigan, S. A., Obarzanek, E., Bernauer, E., Cook, N. R., Hebert, P., ... & Whelton, P. K. (1993). Weight loss intervention in phase 1 of the Trials of Hypertension Prevention. *Archives of internal medicine*, *153*(7), 849-858.

39. Stevens, V. J., Obarzanek, E., Cook, N. R., Lee, I. M., Appel, L. J., West, D. S., ... & Millstone, M. (2001). Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. *Annals of Internal medicine*, *134*(1), 1-11.

40. Tremblay, M. S., Katzmarzyk, P. T., & Willms, J. D. (2002). Temporal trends in overweight and obesity in Canada, 1981-1996. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity*, *26*(4), 538-543.

41. Van Gaal, L. F., Wauters, M. A., & De Leeuw, I. H. (1997). The beneficial effects of modest weight loss on cardiovascular risk factors. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity*, *21*, S5-9.

42. Wharton, S., VanderLelie, S., Sharma, A. M., Sharma, S., & Kuk, J. L. (2012). Feasibility of an interdisciplinary program for obesity management in Canada. *Canadian Family Physician*, *58*(1), e32-e38.

43. Wharton, S., VanderLelie, S., Sharma, A. M., Sharma, S., & Kuk, J. L. (2012). Feasibility of an interdisciplinary program for obesity management in Canada. *Canadian Family Physician*, *58*(1), e32-e38.

44. Who Collaborating Centre for Drug Statistics Methodology. (2016). ATC/DDD Index. Retrieved from https://www.whocc.no/atc_ddd_index/?code=C10&showdescription=yes

45. Wing, R. R., & Phelan, S. (2005). Long-term weight loss maintenance. *The American journal of clinical nutrition*, *82*(1), 222S-225S.

46. Wing, R. R., Koeske, R., Epstein, L. H., Nowalk, M. P., Gooding, W., & Becker, D. (1987). Long-term effects of modest weight loss in type II diabetic patients. *Archives of internal medicine*, *147*(10), 1749-1753.

47. Witchitz, S., Kamoun, A., & Chiche, P. (1975). A double-blind study in hypertensive patients of an original new compound, indapamide. *Current medical research and opinion*, *3*(1), 1-8.

48. Wing, R. R., Lang, W., Wadden, T. A., Safford, M., Knowler, W. C., Bertoni, A. G., ... & Look AHEAD Research Group. (2011). Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes care*, *34*(7), 1481-1486.

References

1. Clarke, L. H. (2002). Older women's perceptions of ideal body weights: the tensions between health and appearance motivations for weight loss. *Ageing and Society*, *22*(06), 751-773.

2. Hamman, R. F., Wing, R. R., Edelstein, S. L., Lachin, J. M., Bray, G. A., Delahanty, L., ... & Wylie-Rosett, J. (2006). Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes care*, *29*(9), 2102-2107.

3. Pampel, F. C., Krueger, P. M., & Denney, J. T. (2010). Socioeconomic disparities in health behaviors. *Annual review of sociology*, *36*, 349.

4. Ryan, P. (2009). Integrated theory of health behavior change: background and intervention development. *Clinical nurse specialist CNS*, *23*(3), 161.

5. Sharma, A. M., and R. F. Kushner. (2009). A proposed clinical staging system for obesity. *International journal of obesity*, 33, 289-295.

6. Sider. (2015). Sider 4.1: Side Effect Resources. Retrieved from http://sideeffects.embl.de/

7. Van Gaal, L. F., Wauters, M. A., & De Leeuw, I. H. (1997). The beneficial effects of modest weight loss on cardiovascular risk factors. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity*, *21*, S5-9.

8. Wharton, S., VanderLelie, S., Sharma, A. M., Sharma, S., & Kuk, J. L. (2012). Feasibility of an interdisciplinary program for obesity management in Canada. *Canadian Family Physician*, *58*(1), e32-e38.

9. Wing, R. R., Lang, W., Wadden, T. A., Safford, M., Knowler, W. C., Bertoni, A. G. & Look AHEAD Research Group. (2011). Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes care*, *34*(7), 1481-1486.

Appendix A
Ethics:

YORK
UNIVERSITÉ
UNIVERSITY

Certificate #:	**2013 - 123**
Initial Approval:	**05/01/13-05/01/14**
Amendments:	**Amendment Approved: 11/13/14** **2nd Amendment Approved: 06/08/16** **3rd Amendment Approved: 07/21/16**
Renewals:	**05/05/14-05/05/15** **05/29/15-05/29/16** **05/25/16-05/25/17**
Current Approval Period:	**05/25/16-05/25/17**

ETHICS AMENDMENT APPROVAL

OFFICE OF RESEARCH ETHICS (ORE)
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To: **Professor Jennifer Kuk**
Department of Kinesiology
Faculty of Health
jennkuk@yorku.ca

From: Alison M. Collins-Mrakas, Sr. Manager and Policy Advisor, Research Ethics
(on behalf of Erin Ross, Vice-Chair, Human Participants Review Committee)

Date: Thursday, July 21, 2016

Title: **Wharton Weight Management Clinic Longitudinal Study**

Risk Level: Minimal Risk

Level of Review: Delegated Review

With respect to your research project entitled, **"Wharton Weight Management Clinic Longitudinal Study",** the committee notes that, as there are no substantive changes to either the methodology employed or the risks to participants in and/or any other aspect of the research project, a renewal of approval re the proposed amendment(s) to the above project is granted.
Any further changes to the approved protocol must be reviewed and approved through the amendment process by submission of an amendment application to the HPRC prior to its implementation.
Ongoing research – research that extends beyond one year – must be renewed prior to the expiry date.
Any adverse or unanticipated events in the research should be reported to the Office of Research ethics (ore@yorku.ca) as soon as possible.
For further information on researcher responsibilities as it pertains to this approved research ethics protocol, please refer to the attached document, **"RESEARCH ETHICS: PROCEDURES to ENSURE ONGOING COMPLIANCE".**
Should you have any questions, please feel free to contact me at: 416-736-5914 or via email at: acollins@yorku.ca.

Yours sincerely,
Alison M. Collins-Mrakas M.Sc., LLM
Sr. Manager and Policy Advisor,
Office of Research Ethics

RESEARCH ETHICS: PROCEDURES to ENSURE ONGOING COMPLIANCE

Upon receipt of an ethics approval certificate, researchers are reminded that they are required to ensure that the following measures are undertaken so as to ensure on-going compliance with Senate and TCPS ethics guidelines:

1. **RENEWALS:** Research Ethics Approval certificates are subject to annual renewal. **It is the responsibility of researchers to ensure the timely submission of renewals.**
    a. As a courtesy, researchers will be reminded by ORE, in advance of certificate expiry, that the certificate must be renewed. Please note, however, it is the expectation that researchers will submit a renewal application prior to the expiration of ethics certificate(s).
    b. **Failure to renew an ethics approval certificate** (or to notify ORE that no further research involving human participants will be undertaken) **may result in suspension of research cost fund and access to research funds may be suspended/ withheld**.
2. **AMENDMENTS:** Amendments must be reviewed and approved **PRIOR** to undertaking/making the proposed amendments to an approved ethics protocol;
3. **END OF PROJECT**: ORE must be notified when a project is complete;
4. **ADVERSE EVENTS**: Adverse events must be reported to ORE as soon as possible;
5. **POST APPROVAL MONITORING:**
    a. More than minimal risk research may be subject to post approval monitoring as per TCPS guidelines;
    b. A spot sample of minimal risk research may similarly be subject to Post Approval Monitoring as per TCPS guidelines.

FORMS: As per the above, the following forms relating to on-going research ethics compliance are available on the Research website:

a. Renewal
b. Amendment
c. End of Project
d. Adverse Event

Appendix B
WMC Questionnaire:

Name: _____ Date: _____

Ethnicity: _____ Sex: M / F (Please circle)

How long have you attended the Wharton Medical Clinic? _____

Why do you think you have a weight problem? (Rank the top 3, with 1 being the most important)
__ Over Eating __ High Fat Diet __ Junk Food
__ Not Physically Active __ Genetics __ Environment
__ Lack of Will Power __ Medical Condition (ie. Thyroid, depression drugs, etc.)
__ Other (specify):_____

How much would you ideally like to weigh (ie. goal weight)? _____
How long do you think it would take for you to attain that weight loss? _____

How much weight loss do you think is realistic? _____
How long do you think it would take for you to attain that weight loss? _____

What is the minimal weight loss that you would be satisfied with? _____
How long do you think it would take for you to attain that weight loss? _____

Do you think you need to lose weight to become healthy? Y N
If so, how much weight do you need to lose? _____

What do you think you need to do to achieve your goal weight loss? (Rank the top 3, with 1 being the most important)

__ Eat Less __ Eat Better Food __ Meal Replacement
__ More Physical Activity __ Genetic Modification __ More Will Power
__ Surgery __ Weight Loss Drugs __ Weight Loss Supplements
__ Other (specify): _____

Would you be satisfied with a small weight loss (ie. 5%) if your health and function was improved?
Strongly Agree *Agree* *Neutral* *Disagree* *Strongly Disagree*

Would you be satisfied with a small weight loss (ie. 5%) if your health and function was normalized?
Strongly Agree *Agree* *Neutral* *Disagree* *Strongly Disagree*

If there was a pill that could permanently cure you of your weight problem tomorrow without dieting, exercise or surgery, how much would you be willing to pay for it?
$_____

Would you be willing to experience any of the following conditions or events if it meant you could be normal weight?

Y	N	Blind	Y	N	Severe Heart Disease
Y	N	Paraplegic (Can't walk)	Y	N	Never eat your favourite foods
Y	N	Exercise for 1-2 hours per day	Y	N	Life Sentence in Jail
Y	N	Have only 5 more years to live	Y	N	Live 20 years less than expected

Would you be willing to stay at your current weight if it meant you could:

Y	N	Be completely healthy (disease free) and fully functional
Y	N	Be a millionaire/win the lottery
Y	N	Be famous
Y	N	Live forever

Have you ever experienced weight discrimination, or had a negative experience because of your weight? Y N

If yes, please answer the following questions. (<u>Circle All</u> that apply, and <u>Star the answer</u> in regards to your worst experience).

When did it happen to you? *Childhood* *Adolescence* *Adulthood*

Type of experience: *Verbal* *Physical* *Discrimination*
Physical Barrier (i.e. inappropriate seats, etc.) *Other:*_____

Age of the perpetrator: *Child* *Adolescent* *Adult* *N/A*

Gender of the perpetrator: *Male* *Female* *N/A*

Their relation to you: *Peer/Friend* *Boyfriend/Girlfriend* *Parent*
Child *Spouse* *Sibling* *Other Family*
Stranger *Physician* *Nurse* *Other Health Professional*
Boss/Supervisor *Teacher/Professor* *Other*:_____

Location: *Home* *Work* *Medical Facility* *Public Place Mode*
Transportation *School* *Other:*_____

Physical activity and sedentary time:

What would you consider your ***current*** physical activity level to be:

Very Active *Moderately Active* *Average* *Below Average* *Very Poor*

Are you satisfied with the level of your physical activity? Y N

How important was a change in physical activity in development of your obesity?
Not at all Important *Somewhat Important* *Neutral* *Important* *Very Important*

Can you currently walk 4 miles briskly without fatigue? Y N

Do you intend to change your physical activity in the next few months? Y N

Do you have injuries or pain that may interfere with regular physical activity? Y N

During the week, how many hours per day do you usually spend watching TV shows or videos?
I don't watch TV or videos *Less than 1 hour a day* *1-2 hours a day*
3-4 hours a day *More than 4 hours a day*

During the weekend, how many hours per day do you usually spend watching TV shows or videos?
I don't watch TV or videos *Less than 1 hour a day* *1-2 hours a day*
3-4 hours a day *More than 4 hours a day*

During the week, how many hours per day do you usually use the computer to surf the Internet or
Play video games?
I don't play video games or use the computer *Less than 1 hour a day*
1-2 hours a day *3-4 hours a day* *More than 4 hours a day*

During the weekend, how many hours per day do you usually use the computer to surf the Internet or play video games?
I don't play video games or use the computer *Less than 1 hour a day*
1-2 hours a day *3-4 hours a day* *More than 4 hours a day*

Diet History:

Rate your current diet
Very Poor *Poor* *Average* *Good* *Very Good*

How often do you eat breakfast?
7 days per week *5-6 days per week* *3-4 days per week*
1-2 days per week *I do not eat breakfast*

How often do you eat after 8 o'clock in the evening?
Regularly *Occasionally* *Never*

Check if you eat (check all that apply):

While cooking *In the middle of the night* *While watching TV*

While reading *When angry or depressed* *When bored*

In the car

Appendix C

SIDER Excel Sheet (coauthor: S.W.)

Generic Name	Brand Name	Weight Side effects	Other Side Effects
METFORMIN	(GLUCOPHAGE)	neutral, insignificant weight loss	Diarrhea
INSULIN		weight gain	Infection
PIOGLITAZONE	(DUETACT, ACTOS)	weight gain	Infection
GLIMEPIRIDE	(AMARYL)	weight gain	Headache, influenza
SULFONYLUREA		weight gain	Skin reaction
ROSIGLITAZONE	(AVANDIA)	weight gain	Anemia
METFORMIN & ROSIGLITAZONE	(AVANDAMET)	weight gain	Troubled breathing
EXANTIDE	(BYETTA)	weight loss	Agitation
VILDAGLIPTIN	(GALVUS)	weight neutral	Asthenia, Dizziness
GLIPIZIDE		weight gain	Asthenia, Headache
BIGUANIDE		weight neutral	Anaphylactic shock
GLYBURIDE		weight gain	Swallowing problem
GLYBURIDE & METFORMIN	(GLUCOVANCE)	weight gain	Anxious feeling
GLIPIZIDE	(GLUCOTROL)	weight gain	Asthenia, Headache
MIGLITOL	(GLYSET)	weight neutral	Bloated full feeling
SITAGLIPTIN	(JANUVIA)	weight neutral	Anxiety
SITAGLIPTIN & METFORMIN	(JANUMET)	weight neutral	Bloated feeling
REPAGLINIDE	(PRANDI)	weight neutral	Headache, Rhinitis
ACARBOSE	(PRECOSE)	weight neutral	Constipation
TROGLITAZONE	(Rezulin)	weigh gain	Anemia
NATEGLINIDE	(STARLIX)	weight neutral	Infection
CHOLESTYRAMINE		weight neutral	Constipation
COLESTIPOL	(COLESTID)	weight neutral	Abdominal pain
COLESEVELAM	(WELCHOL)	weight neutral	Flatulence
EZETIMIBE	(ZEITA)	weight neutral	Headache
SIMVASTATIN	(ZOCOR)	weight neutral	Infection
SIMVASTATIN & EZETIMIBE	(VYTORIN)	weight neutral	Abdominal fullness
FENOFIBRATE	(ANTARA, FENOGLIDE)	weight neutral	Abnormal liver
FENOFIBRIC	(LOFIBRA, TRILIPIX)	weight neutral	Abnormal liver
GEMFIBROZIL	(LOPID)	weight neutral	Dyspepsia
ATORVASTATIN	(LIPITOR)	weight neutral	Infection, Diarrhea
AMLODIPINE	(CADUET)	weight neutral	Headache, Fatigue
FLUVASTATIN	(LESCOL)	weight neutral	Angiopathy

LOVASTATIN	(MEVACOR)	weight neutral	Flatulence
PRAVASTATIN	(PRAVACHOL)	weight neutral	Nausea
ROSUVASTATIN	(CRESTOR)	weight neutral	Headache
NIACIN	(ADVICOR)	weight neutral	Diarrhea, Nausea
LOVAZA		weight neutral	Infection, Influenza
AMILORIDE	(MIDAMOR)	weight neutral	Hyperkaliemia
BUMETANIDE	(BUMEX)	weight neutral	Hypochloremia
CHLOROTHIAZIDE	(DIURIL)	weight neutral	Abdominal pain
CHLORTHALIDONE	(HYGROTON)	weight neutral	Hypokalemia
FUROSEMIDE	(LASIX)	weight neutral	Creatinine increase
HYDROCHLOROTHIAZIDE	(HYDRODIURIL, ESIDRIX)	weight neutral	Infection
INDAPAMIDE	(LOZOL)	weight neutral	Infection
SPIRONOLACTONE	(ALDACTONE)	weight neutral	Agranulocytosis
BENAZEPRIL	(LOTENSIN)	weight neutral	Dizziness, Fatigue
CAPTOPRIL	(CAPOTEN)	weight neutral	Dizziness, Cough
ENALAPRIL	(VASOTEC)	weight neutral	Headache, Dizziness
FOSINOPRIL	(MONOPRIL)	weight neutral	Sexual dysfunction
LISINOPRIL	(ZESTRIL, PRINIVIL)	weight neutral	Dizziness
MOEXIPRIL	(UNIVASC)	weight neutral	Cough increased
PERINDOPRIL		weight neutral	Headache, Cough
ACEON		weight neutral	Headache, Cough
QUINAPRIL	(ACCUPRIL)	weight neutral	Chest pain, Diarrhea
RAMIPRIL	(ALTACE)	weight neutral	Headache
TRANDOLAPRIL	(MAVIK)	weight neutral	Blood urea increased
CANDESARTAN	(ATACAND)	weight neutral	Kidney abnormality
EPROSARTAN	(TEVETEN)	weight neutral	Infection
IRBESARTAN	(AVAPRO)	weight neutral	Diabetics, Headache
LOSARTAN	(COZAAR)	weight neutral	Infection
TELMISARTAN	(MICARDIS)	weight neutral	Infection
VALSARTAN	(DIOVAN)	weight neutral	Diarrhea
ACEBUTOLOL	(SECTRAL)	weight gain	Headache
ATENOLOL	(TENORMIN)	weight gain	Depression
BETAXOLOL	(KERLONE)	weight gain	Fatigue, Dyspepsia
BISOPROLOL		weight gain	Headache, Fatigue
HYDROCHLOROTHIAZIDE	(ZIAC)	weight neutral	Dizziness, Cough
BISOPROLOL	(ZEBETA)	weight gain	Headache, Fatigue
CARTEOLOL	(CARTROL)	weight gain	Arrhythmia
METOPROLOL	(LOPRESSOR, TOPROL)	weight gain	Abdominal pain
NADOLOL	(CORGARD)	weight gain	Dizziness, Fatigue
PROPRANOLOL	(INDERAL)	weight gain	Sleep disorder
SOTALOL	(BETAPACE)	weight gain	Fatigue, Dizziness

TIMOLOL	(BLOCADREN)	weight gain	Stinging
ATENOLOL & CHLORTHALIDONE	(TENORETIC)	weight gain	Cold arms and legs
NADOLOL & BENDROFLUMETHIAZIDE	(CORZIDE)	weight gain	Blurred vision
PROPRANOLOL & HYDROCHLOROTHIAZIDE	(INDERIDE)	weight gain	Abdominal pain
TIMOLOL & HYDROCHLOROTHIAZIDE	(TIMOLIDE)	weight gain	Chest pain
BENAZEPRIL & HYDROCHLOROTHIAZIDE	(LOTENSIN)	weight neutral	Blurred vision
Enalapril & HYDROCHLOROTHIAZIDE	(VASERETIC)	weight neutral	Blurred vision
LISINOPRIL& HYDROCHLOROTHIAZIDE	(PRINZIDE, ZESTORETIC)	weight neutral	Body aches or pain
MOEXIPRIL & HYDROCHLOROTHIAZIDE	(UNIRETIC)	weight neutral	Blurred vision
AMLODIPINE	(NORVASC)	weight neutral	Headache
BEPRIDIL		weight neutral	Nausea, Dizziness
NISOLDIPINE	(SULAR)	weight neutral	Headache
VERAPAMIL	(CALAN, ISOPTIN)	weight neutral	Constipation
VERELAN		weight neutral	Constipation
IRBESARTAN & HYDROCHLOROTHIAZIDE	(AVALIDE)	weight neutral	Headache, Sunburn
LOSARTAN &HYDROCHLOROTHIAZIDE	(HYZAAR)	weight neutral	Dry mouth
VALSARTAN & Hydrochlorothiazide	(DIOVAN)	weight neutral	Flu-like symptoms
AMLODIPINE & BENAZEPRIL	(LOTREL)	weight neutral	Confusion
CAS 76095-16-4	(LEXXEL)		Headache
TRANDOLAPRIL & VERAPAMIL	(TARKA)	weight neutral	Chest pain, Chills
DOXAZOSIN MESYLATE	(CARDURA)	weight neutral	Dizziness, Malaise
PRAZOSIN HYDROCHLORIDE		weight neutral	
PRAZOSIN	(MINIPRESS)	weight neutral	Dizziness
PRAZOSIN		weight neutral	Drowsiness
POLYTHIAZIDE		weight neutral	Agranulocytosis
TERAZOSIN HYDROCHLORIDE	(HYTRIN)	weight neutral	Dizziness, Asthenia
CLONIDINE HYDROCHLORIDE	(CATAPRES)	weight neutral	Infection
CHLORTHALIDONE		weight neutral	Hypokalemia
CLONIDINE & CHLORTHALIDONE	(CLORPRES)	weight neutral	Blood in urine
GUANFACINE HYDROCHLORIDE	(TENEX)	weight gain	Dry mouth
METHYLDOPA	(ALDOMET)	weight gain	
CHLOROTHIAZIDE		weight neutral	Agranulocytosis
METHYLDOPA	(ALDOCHLOR, ALDORIL)		Agranulocytosis

CARVEDILOL	(COREG)	weight gain	Infection
LABETALOL HYDROCHLORIDE	(NORMODYNE)	weight gain	Malaise, Fatigue
IRBESARTAN	(AVAPRO)	weight neutral	Diabetics
DILTIAZEM	(TIAZAC)	weight neutral	Edema
METHIMAZOLE	(TAPAZOLE)	weight neutral	Agranulocytosis
LEVOTHYROXINE	(LEVOXYL, SYNTHROID)	weight loss	Decreased urine
LIOTHYRONINE	(TRIIODOTHYRONINE, CYTOMEL)	weight loss	Angina pectoris
LIOTRIX	(THYROLAR)	weight loss	Chest pain
THYROXINE		weight loss	Abdominal cramps
L-THYROXINE	(THYROXINE)	weight loss	Abdominal cramps
FUROSEMIDE	(Furocot)	weight neutral	Creatinine increased
HYDRAZIDE		weight neutral	
CAPTOPRIL	(CAPOTEN)	weight neutral	Dizziness, Cough
ENALAPRIL	(VASOTEC)	weight neutral	Headache, Dizziness
LISINOPRIL	(ZESTRIL, PRINIVIL)	weight neutral	Blood urea increased
BENAZEPRIL	(LOTENSIN)	weight neutral	Dizziness, Fatigue
RAMIPRIL	(ALTACE)	weight neutral	Headache
DIGOXIN	(LANOXIN)	weight neutral	Dizziness, Diarrhea
LOSARTAN	(COZAAR)	weight neutral	Cough, Diarrhea
CANDESARTAN	(ATACAND)	weight neutral	Kidney abnormality
TELMISARTAN	(MICARDIS)	weight neutral	Arthritis
VALSARTAN	(DIOVAN)	weight neutral	Headache, Diarrhea
IRBESARTAN	(AVAPRO)	weight neutral	Diabetic, Headache
BISOPROLOL	(ZEBETA)	weight gain	Headache, Fatigue
CARVEDILOL	(COREG)	weigh gain	Infection
CRYSTODIGIN			
BUMETANIDE	(BUMEX)	weight neutral	Hypochloremia
TORSEMIDE	(DEMADEX)	weight neutral	Headache, Dizziness
HYDROCHLOROTHIAZIDE	(HYDRODIURIL)	weight neutral	Infection
METOLAZONE	(ZAROXOLYN)	weight neutral	Dizziness
ISOSORBIDE DINITRATE	(DILATRATE)	weight neutral	Hemolytic anemia
ISORBIDE MONONITRATE	(IMDUR)	weight neutral	Sleep disturbance
HYDRALAZINE	(APRESOLINE)	weight neutral	Angina pectoris
SPIRNOLACTONE	(ALDACTONE)	weight neutral	Agranulocytosis
AMLODIPINE	(NORVASC)	weight neutral	Headache
FELODIPINE	(PLENDIL)	weight neutral	Abdominal pain
DOBUTAMINE	(DOBUTREX)	weight neutral	Angina pectoris
MILRINONE	(PRIMACOR)	weight neutral	Ventricular arrhythmia
PLAVIX	(CLOPIDOGREL)	weight neutral	Abdominal pain
ASPIRIN		weight neutral	Respiratory alkalosis
SIBUTRAMINE	(MERIDIA)	weight loss	Anaphylactic shock

ORLISTAT	(XENICAL)	weight loss	Abdominal pain
SIMVASTATIN		weight neutral	Infection
ATORVASTATIN	(LIPITOR)	weight neutral	Infection, Diarrhea
FLUVASTATIN	(LESCOL)	weight neutral	GI disorder
LOVASTATIN	(MEVACOR, ALTOPREV)	weight neutral	Flatulence
PRAVASTATIN	(PRAVACHOL)	weight neutral	Musculoskeletal pain
ROSUVASTATIN	(CRESTOR)	weight neutral	Headache, Dizziness

SIDER Excel Sheet

Generic Name	Brand Name	Weight Side effects (S.W.)	Weight Side effects (E.K.S.)
METFORMIN	(GLUCOPHAGE)	neutral, insignificant weight loss	weight loss
INSULIN		weight gain	mixed
PIOGLITAZONE	(DUETACT, ACTOS)	weight gain	mixed
GLIMEPIRIDE	(AMARYL)	weight gain	mixed
SULFONYLUREA		weight gain	weight neutral
ROSIGLITAZONE	(AVANDIA)	weight gain	mixed
METFORMIN & ROSIGLITAZONE	(AVANDAMET)	weight gain	weight gain
EXANTIDE	(BYETTA)	weight loss	weight gain
VILDAGLIPTIN	(GALVUS)	weight neutral	weight gain
GLIPIZIDE		weight gain	weight neutral
BIGUANIDE		weight neutral	weight neutral
GLYBURIDE		weight gain	weight gain
GLYBURIDE & METFORMIN	(GLUCOVANCE)	weight gain	weight neutral
GLIPIZIDE	(GLUCOTROL)	weight gain	weight loss
MIGLITOL	(GLYSET)	weight neutral	weight neutral
SITAGLIPTIN	(JANUVIA)	weight neutral	weight neutral
SITAGLIPTIN & METFORMIN	(JANUMET)	weight neutral	weight neutral
REPAGLINIDE	(PRANDI)	weight neutral	weight loss
ACARBOSE	(PRECOSE)	weight neutral	weight neutral
TROGLITAZONE	(Rezulin)	weigh gain	weight gain
NATEGLINIDE	(STARLIX)	weight neutral	weight loss
CHOLESTYRAMINE		weight neutral	weight loss
COLESTIPOL	(COLESTID)	weight neutral	weight neutral

COLESEVELAM	(WELCHOL)	weight neutral	weight neutral
EZETIMIBE	(ZEITA)	weight neutral	weight loss
SIMVASTATIN	(ZOCOR)	weight neutral	weight neutral
SIMVASTATIN & EZETIMIBE	(VYTORIN)	weight neutral	weight neutral
FENOFIBRATE	(ANTARA, FENOGLIDE)	weight neutral	mixed
FENOFIBRIC	(LOFIBRA, TRILIPIX)	weight neutral	weight loss
GEMFIBROZIL	(LOPID)	weight neutral	weight loss
ATORVASTATIN	(LIPITOR)	weight neutral	mixed
AMLODIPINE	(CADUET)	weight neutral	mixed
FLUVASTATIN	(LESCOL)	weight neutral	weight neutral
LOVASTATIN	(MEVACOR)	weight neutral	weight neutral
PRAVASTATIN	(PRAVACHOL)	weight neutral	mixed
ROSUVASTATIN	(CRESTOR)	weight neutral	weight neutral
NIACIN	(ADVICOR)	weight neutral	weight neutral
LOVAZA		weight neutral	weight neutral
AMILORIDE	(MIDAMOR)	weight neutral	weight loss
BUMETANIDE	(BUMEX)	weight neutral	weight neutral
CHLOROTHIAZIDE	(DIURIL)	weight neutral	mixed
CHLORTHALIDONE	(HYGROTON)	weight neutral	weight neutral
FUROSEMIDE	(LASIX)	weight neutral	weight neutral
HYDROCHLOROTHIAZIDE	(HYDRODIURIL, ESIDRIX)	weight neutral	weight neutral
INDAPAMIDE	(LOZOL)	weight neutral	weight loss
SPIRONOLACTONE	(ALDACTONE)	weight neutral	weight neutral
BENAZEPRIL	(LOTENSIN)	weight neutral	weight neutral
CAPTOPRIL	(CAPOTEN)	weight neutral	weight loss
ENALAPRIL	(VASOTEC)	weight neutral	weight neutral
FOSINOPRIL	(MONOPRIL)	weight neutral	mixed
LISINOPRIL	(ZESTRIL, PRINIVIL)	weight neutral	mixed
MOEXIPRIL	(UNIVASC)	weight neutral	weight neutral
PERINDOPRIL		weight neutral	weight neutral
ACEON		weight neutral	weight neutral
QUINAPRIL	(ACCUPRIL)	weight neutral	weight neutral
RAMIPRIL	(ALTACE)	weight neutral	weight gain
TRANDOLAPRIL	(MAVIK)	weight neutral	weight neutral
CANDESARTAN	(ATACAND)	weight neutral	weight neutral
EPROSARTAN	(TEVETEN)	weight neutral	weight neutral
IRBESARTAN	(AVAPRO)	weight neutral	weight gain
LOSARTAN	(COZAAR)	weight neutral	weight gain
TELMISARTAN	(MICARDIS)	weight neutral	weight neutral
VALSARTAN	(DIOVAN)	weight neutral	weight neutral

ACEBUTOLOL	(SECTRAL)	weight gain	weight gain
ATENOLOL	(TENORMIN)	weight gain	weight neutral
BETAXOLOL	(KERLONE)	weight gain	mixed
BISOPROLOL		weight gain	weight gain
HYDROCHLOROTHIAZIDE	(ZIAC)	weight neutral	weight neutral
BISOPROLOL	(ZEBETA)	weight gain	weight gain
CARTEOLOL	(CARTROL)	weight gain	weight neutral
METOPROLOL	(LOPRESSOR, TOPROL)	weight gain	weight gain
NADOLOL	(CORGARD)	weight gain	weight gain
PROPRANOLOL	(INDERAL)	weight gain	weight neutral
SOTALOL	(BETAPACE)	weight gain	weight neutral
TIMOLOL	(BLOCADREN)	weight gain	weight loss
ATENOLOL & CHLORTHALIDONE	(TENORETIC)	weight gain	weight neutral
NADOLOL & BENDROFLUMETHIAZIDE	(CORZIDE)	weight gain	mixed
PROPRANOLOL & HYDROCHLOROTHIAZIDE	(INDERIDE)	weight gain	mixed
TIMOLOL & HYDROCHLOROTHIAZIDE	(TIMOLIDE)	weight gain	weight gain
BENAZEPRIL & HYDROCHLOROTHIAZIDE	(LOTENSIN)	weight neutral	weight neutral
Enalapril & HYDROCHLOROTHIAZIDE	(VASERETIC)	weight neutral	weight neutral
LISINOPRIL& HYDROCHLOROTHIAZIDE	(PRINZIDE, ZESTORETIC)	weight neutral	weight neutral
MOEXIPRIL & HYDROCHLOROTHIAZIDE	(UNIRETIC)	weight neutral	weight neutral
AMLODIPINE	(NORVASC)	weight neutral	mixed
BEPRIDIL		weight neutral	weight neutral
NISOLDIPINE	(SULAR)	weight neutral	mixed
VERAPAMIL	(CALAN, ISOPTIN)	weight neutral	weight neutral
VERELAN		weight neutral	weight neutral
IRBESARTAN & HYDROCHLOROTHIAZIDE	(AVALIDE)	weight neutral	weight neutral
LOSARTAN &HYDROCHLOROTHIAZIDE	(HYZAAR)	weight neutral	weight neutral
VALSARTAN & Hydrochlorothiazide	(DIOVAN)	weight neutral	weight neutral
AMLODIPINE & BENAZEPRIL	(LOTREL)	weight neutral	weight neutral
CAS 76095-16-4	(LEXXEL)		weight neutral
TRANDOLAPRIL & VERAPAMIL	(TARKA)	weight neutral	weight neutral

DOXAZOSIN MESYLATE	(CARDURA)	weight neutral	mixed
PRAZOSIN HYDROCHLORIDE		weight neutral	
PRAZOSIN	(MINIPRESS)	weight neutral	weight neutral
PRAZOSIN		weight neutral	weight neutral
POLYTHIAZIDE		weight neutral	weight neutral
TERAZOSIN HYDROCHLORIDE	(HYTRIN)	weight neutral	weight gain
CLONIDINE HYDROCHLORIDE	(CATAPRES)	weight neutral	weight gain
CHLORTHALIDONE		weight neutral	weight neutral
CLONIDINE & CHLORTHALIDONE	(CLORPRES)	weight neutral	weight neutral
GUANFACINE HYDROCHLORIDE	(TENEX)	weight gain	weight gain
METHYLDOPA	(ALDOMET)	weight gain	weight gain
CHLOROTHIAZIDE		weight neutral	weight neutral
METHYLDOPA	(ALDOCHLOR, ALDORIL)		weight gain
CARVEDILOL	(COREG)	weight gain	mixed
LABETALOL HYDROCHLORIDE	(NORMODYNE)	weight gain	weight neutral
IRBESARTAN	(AVAPRO)	weight neutral	weight gain
DILTIAZEM	(TIAZAC)	weight neutral	weight gain
METHIMAZOLE	(TAPAZOLE)	weight neutral	weight neutral
LEVOTHYROXINE	(LEVOXYL, SYNTHROID)	weight loss	mixed
LIOTHYRONINE	(TRIIODOTHYRONINE, CYTOMEL)	weight loss	weight neutral
LIOTRIX	(THYROLAR)	weight loss	weight gain
THYROXINE		weight loss	weight loss
L-THYROXINE	(THYROXINE)	weight loss	weight loss
FUROSEMIDE	(Furocot)	weight neutral	weight neutral
HYDRAZIDE		weight neutral	
CAPTOPRIL	(CAPOTEN)	weight neutral	weight loss
ENALAPRIL	(VASOTEC)	weight neutral	weight neutral
LISINOPRIL	(ZESTRIL, PRINIVIL)	weight neutral	mixed
BENAZEPRIL	(LOTENSIN)	weight neutral	weight neutral
RAMIPRIL	(ALTACE)	weight neutral	weight gain
DIGOXIN	(LANOXIN)	weight neutral	weight neutral
LOSARTAN	(COZAAR)	weight neutral	weight gain
CANDESARTAN	(ATACAND)	weight neutral	weight neutral
TELMISARTAN	(MICARDIS)	weight neutral	weight neutral
VALSARTAN	(DIOVAN)	weight neutral	weight neutral
IRBESARTAN	(AVAPRO)	weight neutral	weight gain
BISOPROLOL	(ZEBETA)	weight gain	weight gain
CARVEDILOL	(COREG)	weigh gain	mixed
CRYSTODIGIN			

BUMETANIDE	(BUMEX)	weight neutral	weight neutral
TORSEMIDE	(DEMADEX)	weight neutral	weight neutral
HYDROCHLOROTHIAZIDE	(HYDRODIURIL)	weight neutral	weight neutral
METOLAZONE	(ZAROXOLYN)	weight neutral	weight neutral
ISOSORBIDE DINITRATE	(DILATRATE)	weight neutral	weight neutral
ISORBIDE MONONITRATE	(IMDUR)	weight neutral	mixed
HYDRALAZINE	(APRESOLINE)	weight neutral	weight loss
SPIRNOLACTONE	(ALDACTONE)	weight neutral	weight neutral
AMLODIPINE	(NORVASC)	weight neutral	mixed
FELODIPINE	(PLENDIL)	weight neutral	weight neutral
DOBUTAMINE	(DOBUTREX)	weight neutral	weight neutral
MILRINONE	(PRIMACOR)	weight neutral	weight neutral
PLAVIX	(CLOPIDOGREL)	weight neutral	weight neutral
ASPIRIN		weight neutral	weight neutral
SIBUTRAMINE	(MERIDIA)	weight loss	mixed
ORLISTAT	(XENICAL)	weight loss	weight loss
SIMVASTATIN		weight neutral	weight neutral
ATORVASTATIN	(LIPITOR)	weight neutral	mixed
FLUVASTATIN	(LESCOL)	weight neutral	weight neutral
LOVASTATIN	(MEVACOR, ALTOPREV)	weight neutral	weight neutral
PRAVASTATIN	(PRAVACHOL)	weight neutral	mixed
ROSUVASTATIN	(CRESTOR)	weight neutral	weight neutral

Appendix D

Table 3A: Odds of ≥ 5% Weight loss by Number of Medications

	Model 1		Model 2	
	OR	95% CI	OR	95%CI
0 medication	1.0	Referent	1.0	Referent
1 medication	0.8	(0.6-1.1)	0.8	(0.6-1.2)
2 medications	0.9	(0.7-1.2)	0.9	(0.6-1.2)
3 medications	**0.7**	**(0.6-0.9)**	**0.6**	**(0.4-0.9)**
4+ medications	0.8	(0.6-1.0)	0.7	(0.5-1.0)
Diabetes				
0	1.0	Referent	1.0	Referent
1	1.3	(0.9-1.9)	1.7	(0.7-4.2)
2	0.8	(0.6-1.3)	0.8	(0.3-2.0)
3	1.0	(0.7-1.5)	0.9	(0.3-2.8)
4	0.8	(0.5-1.3)	1.0	(0.3-3.7)
Prediabetes				
0	1.0	Referent	1.0	Referent
1	1.3	(0.9-1.9)	1.7	(0.7-4.1)
2	0.9	(0.6-1.3)	0.7	(0.3-2.04)
3	1.0	(0.7-1.5)	0.9	(0.3-2.6)
4	0.8	(0.6-1.3)	1.0	(0.3-3.4)
Stroke				
0	1.0	Referent	1.0	Referent
1	1.4	(0.9-1.9)	1.6	(0.6-4.0)
2	0.9	(0.6-1.3)	0.8	(0.3-2.0)
3	1.0	(0.7-1.5)	0.9	(0.3-2.6)
4	0.8	(0.6-1.3)	0.9	(0.3-3.3)
Heart attack				
0	1.0	Referent	1.0	Referent
1	1.3	(0.9-1.9)	1.7	(0.7-4.1)
2	0.9	(0.6-1.3)	0.7	(0.3-2.0)
3	1.0	(0.7-1.5)	0.9	(0.3-2.6)
4	0.8	(0.6-1.3)	0.9	(0.3-3.4)
Hypertension				
0	1.0	Referent	1.0	Referent
1	1.4	(0.9-1.9)	1.7	(0.7-4.1)
2	0.9	(0.6-1.3)	0.7	(0.3-2.0)
3	1.0	(0.7-1.5)	0.9	(0.3-2.6)
4	0.8	(0.6-1.3)	1.0	(0.3-3.4)

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, education, waist, smoking status, number of medications and average number of visits.