The Associations Of Resting Metabolic Rate With Chronic Conditions And Weight Loss

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Abstract

Body weight is positively associated with RMR. However, there exists a paucity of research on the associations between baseline and changes in resting metabolic rate (ΔRMR) with chronic conditions and weight loss (WL), with findings being inconsistent. Sex stratified analysis was undertaken. Despite having a significant WL of 6.2 ± 8.5 kg ($P<0.05$), there were no significant ΔRMR (16 ±325 kcal/day, $P > 0.05$). Men and women with high blood pressure had higher baseline RMR, and only women with high LDL had lower baseline RMR than those without the respective chronic condition ($P<0.05$). Regardless of sex, WL was not significantly associated with baseline RMR or ΔRMR ($P>0.05$). This study suggests that participants with a low baseline RMR do not appear to be at a disadvantage for WL. Further, WL can occur without reductions in RMR in individuals with high levels of obesity and obesity-related comorbidities.

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Table of Contents

Abstract ii

Acknowledgements iii

Table of Contents v

List of Tables vii

List of Figures viii

List of Abbreviations ix

1.0 Introduction 1

2.0 Literature Review 2

Introduction 2

Obesity 2

Resting Metabolic Rate 4

Factors Associated with RMR. 5

Methods of Assessing of RMR 7

Summary and Rationale 10

3.0 Manuscript 12

Introduction 12

Methods 13

WMC program protocol 14

Statistical Analysis 16

Discussion 20

4.0 Extended Discussion ..……..……..41

5.0 References..... 35

Appendix A: Resting Metabolic Rate Prediction Equations and Study Demographics 51

List of Tables

Table 1: Missing data analysis……28

Table 2: Participant characteristics stratified by sex……29

List of Figures

Figure 1: Measured baseline RMR by sex, and health risk status of chronic conditions…….30

Figure 2: Measured ΔRMR by sex, and health risk status of chronic conditions……...31

Figure 3: Association between baseline RMR and WL for women (A), and men (B)……32

Figure 4: Association between WL and ΔRMR for women (A), and men (B)……..33

List of Abbreviations

BMI	body mass index
DALY	disability-adjusted life years
HB	Harris-Benedict
HDL	high-density lipoprotein
LDL	low-density lipoprotein
MSJ	Mifflin St. Jeor
NEAT	non-exercise associated thermogenesis
RMR	resting metabolic rate
TEA	thermic effect of activity
TEF	thermic effect of food
VIF	variance inflation factor(s)
WL	weight loss
WMC	Wharton Weight Management Clinic
YLD	years lost due to disability
ΔRMR	change(s) in resting metabolic rate

1.0 Introduction

Since the 1980s, the prevalence of obesity in Canada has increased (1,2). This trend is of growing public health concern as obesity is associated with a greater likelihood of developing a plethora of chronic conditions (3–6). Current guidelines recommend weight loss (WL) for individuals with obesity, as a reduction of 5% in initial body weight has been associated with improvements in metabolic risk factors (7).

To achieve WL, individuals must create a caloric deficit by consuming less energy than they expend. Thus, assessment of daily energy expenditure may be important in WL success. Resting metabolic rate (RMR) is the largest component of daily energy expenditure in most adults (8), and yet it is unclear whether RMR is related with WL success (9–20).

In healthy and lean populations, RMR has been shown to decrease as a result of acute caloric restriction (21–23) and WL (13–18). Moreover, these decreases in RMR can be greater than reductions in caloric intake commonly prescribed to induce WL. Therefore, changes in RMR may be more important to assess than initial RMR measurements. However, research suggests that certain chronic conditions are associated with a depressed RMR (24), and improvements in these conditions could theoretically result in increases as opposed to reductions in RMR normally seen in response to WL. Thus, further research into the associations between chronic conditions and RMR may be warranted.

2.0 Literature Review

Introduction

Obesity is a global pandemic, with rates having more than doubled world-wide in the last 30 years (25). Obesity is also associated with a variety of adverse health outcomes (3–6,26,27), and thus of major public health concern. WL has the potential to improve clinical health markers associated with obesity (7), such as chronic conditions (28,29), however due to the limited long-term success of WL interventions (30) further research is warranted. Daily energy expenditure can be used to create tailored caloric prescriptions. As RMR is the largest component of energy expenditure (8) it may be related to WL success. Thus, this review will examine gaps and inconsistencies in the existing literature regarding the associations of RMR with WL and chronic conditions to illustrate the need for further research in this domain.

Obesity

Overweight and obesity are chronic medical conditions characterized by excessive adipose accumulation (25). Individuals are often categorized as having overweight or obesity based on their body mass index (BMI) (25), which is calculated by dividing body weight in kilograms by height in meters squared. Individuals with a BMI of 25-29.9 kg/m^2 are classified as having overweight and those with a BMI of 30 kg/m^2 or greater as having obesity. Higher levels of obesity have been associated with more adverse health outcomes (31,32), and as such, obesity is often further subdivided into class I (30-34.9 kg/m^2), class II (35.0 – 39.9 kg/m^2), and class III (40.0 kg/m^2 or greater).

The prevalence of obesity has more than doubled since the 1980s and it is now considered a global pandemic with 13% of adults having obesity worldwide (25). In Canada, rates of obesity are much higher (28%) than the global average (33) and are increasing at an alarming rate. This increasing prevalence in obesity is considered a public health concern as

having obesity is associated with a variety of adverse health outcomes (3–6,26,27). For example, obesity is positively associated with an increased risk of developing type 2 diabetes (3–5), cardiovascular disease (3,4), and cancer (6). This is of substantial concern given the adverse impacts of chronic conditions on the health and life expectancy of individuals.

In general, chronic conditions have been known to have the greatest burden on health, with chronic diseases being associated with the greatest number of years lost due to disability (YLDs)[1], disability-adjusted life years (DALYs)[2], and death from 1990 to 2013 (34). In 2013, chronic diseases accounted for 88.5% of deaths in North America (35). Further, cardiovascular disease was the leading cause of death, with 32.2% of all deaths attributed (35). Individuals living with cardiovascular disease also appear to be experiencing a disproportional health burden, with the greatest DALYs (5642 DALYs per 100,000 years) being associated with this condition (35). The increased prevalence in obesity may play a role in the continued high proportion of deaths from chronic conditions. Indeed, obesity has been associated with an increased risk of developing the top five leading causes of death for North Americans (35): 1) cardiovascular disease (3,4), 2) neoplasms (6,36), 3) neurological disorders (37,38), 4) diabetes and other endocrine diseases (3–5), and 5) chronic respiratory conditions (39,40).

Obesity is associated with considerable financial costs, especially within a publically funded healthcare system. Indeed, in 2006, six billion health care dollars were spent on obesity and obesity related conditions in Canada (41). The greatest increase in obesity has been observed at the higher classes (II & III) of obesity (1). As class II & III obesity is associated with greater morbidity (26) and mortality (27), the financial cost associated with obesity is likely to increase.

[1] YLDs is a health metric used to compare the debilitating effects of various medical conditions (101). YLD is

[2] DALYs is another health metric used to quantify the morbidity and mortality burden associated with various medical conditions (101). DALYs is calculated by summing the years of life lost (number of deaths multiplied by standard life expectancy at age of death in years) and YLD (101).

A WL of 5% or more has been shown to result in clinically significant improvements in metabolic health (7) and as such, WL is recommended for individuals with obesity and obesity related chronic conditions (42,43). The cornerstone of WL interventions is decreasing caloric intake and increasing physical activity (42,43). Generally, much more attention has been given to assessing dietary intake rather than the assessment of total daily energy expenditure, as dietary interventions are typically associated with greater WL than physical activity interventions (44). Currently, a caloric deficit of 500 to 1000 kcal/day is recommended for individuals with obesity to achieve a WL of 1 to 2 lb/week (45). Thus, research into daily energy expenditure may be important to aid medical professionals in setting appropriate caloric prescriptions to support patients in achieving WL.

Resting Metabolic Rate

Energy expenditure is made up of three main components: thermic effect of food (TEF), thermic effect of activity (TEA), and RMR. TEF refers to the caloric cost of the consumption and digestion of food (8,46), which accounts for approximately 6% to 12% of the total energy expenditure per day (8,46). The TEA can either be purposeful physical activity (i.e. exercise) referring to activities such as working out at the gym or playing sports (8,46), or non-purposeful physical activity (i.e. non-exercise activity thermogenesis, or NEAT) referring to any body movement that is not explicitly exercise (i.e. gesturing while you talk or cleaning your house). The TEA can account for 15% to 30% of energy expenditure (46). There is a large inter-individual variation in TEA, with differences in NEAT primarily due to occupation (i.e. labourer vs. office work) (8). RMR accounts for the remaining 60% to 75% of total daily energy expenditure, and is the amount of energy a body needs to maintain itself at rest (8,46,47).

Factors Associated with RMR.

A significant amount of research has been conducted on factors which influence RMR. Age has been shown to have an inverse relationship with RMR (48). Sex has also been shown to influence RMR, with women having a lower RMR than men (49). However, this may be explained by differences in body mass and composition (50). Each kilogram of body fat has been shown to expend between 3 to 6 kcal/day, while lean mass can expend between 12 to 14 kcal/day at rest (51). Indeed, research has found no evidence of differences in RMR for men and women when adjusting for differences in lean muscle mass (50). Further, while 80% of the variance in RMR is due to differences in body mass (8), it remains unclear whether RMR is related with WL success.

Weight Loss.

Baseline RMR and WL

Although RMR may theoretically be related with WL, little research exists on the association between baseline RMR and WL, with findings being inconsistent (9–12). This may be due to population or methodological differences between studies. For example, some studies that observe an association between baseline RMR and WL provided individuals with the same absolute caloric prescription (i.e. 1200kcal/day) regardless of their baseline caloric needs (9,10). However, individuals with a higher baseline RMR may have had a greater WL as they should theoretically have a larger caloric deficit. Conversely, another study that also prescribed the same absolute caloric intake regardless of energy expenditure saw no association between RMR and WL. However, this study used pharmacological agents which are known to increase RMR (12). Only one study used set caloric prescriptions based on baseline energy expenditure and they found no association between baseline RMR and WL in mice (11). Therefore, the association

between baseline RMR and WL has yet to be explored with interventions that prescribe similar caloric reductions in humans. Further, due to the paucity of evidence with contradicting results more research is necessary.

ΔRMR and WL.

Differences in body weight account for 80% of the variance in RMR (8), thus RMR should decrease in response to WL. However, two studies conclude that there is no association between ΔRMR and WL (19,20). These studies observe a wide range of ΔRMR for a given WL and may be underpowered due to their small sample sizes (n<40) (19,20). The majority of research has concluded that decreases in body mass are associated with reductions in RMR (13–18,52). However, both obesity (24,53) and certain obesity related comorbidities (24) are also suggested to depress RMR and may be improved by WL. Thus, it is unclear whether this research that was conducted in healthy (13–16,18) and lean populations (16,18) will translate to a population with severe obesity and obesity-related comorbidities.

To date, only one study has examined the association between WL and ΔRMR in a population with severe obesity and chronic conditions (52). This study was conducted on 14 contestants from the television show the Biggest Loser (52). Participants were prescribed a hypo-caloric diet and experienced a rapid reduction in body weight of 40% (52), which is much greater than typical WL interventions. Indeed, current guidelines for the treatment of overweight and obesity recommend a reduction in body weight of 8 to 10% within 6 months (45); however, participants in this study achieved a 10% WL after only 6 weeks (52), thereby limiting the generalizability of these results to typical WL interventions. Further, severe caloric restriction has been shown to result in much greater reductions (17.1% - 21.4% (54)) in RMR than typically reported for acute caloric restriction (10 – 12% (18,21)) due to metabolic adaptation (55).

Therefore the hypo-caloric diet and severe WL of these participants may have contributed to greater reductions in RMR (40% (52)) than previously reported in the literature (12-15% (13–17)). Thus, further research examining the association between WL and ΔRMR in populations with high levels of obesity and obesity related comorbidities is necessary.

Chronic Conditions.

While WL is often prescribed to individuals with chronic disease, little research exists on the effects of chronic disease on RMR. Further, existing research that has examined these associations tends to focus on clusters of conditions which may mask the individual effects of certain chronic conditions. For example, glucose control (56), and blood pressure (24,57) are positively associated with RMR. Conversely, metabolic syndrome, which is a cluster of chronic conditions that may include high glucose and/or blood pressure, is negatively associated with RMR (24). Additionally, the association between other conditions that make up metabolic syndrome, such as hyperlipidemia and hypoalphalipoproteinemia, with RMR have yet to be examined, which may in part explain the differential influence of metabolic syndrome and the individual conditions on RMR. Thus, research on the individual effects of chronic conditions is warranted.

Methods of Assessing of RMR

Measuring RMR

RMR is most commonly measured using indirect calorimetry (58). Participants lay in a supine position in a darkened room for 30 minutes to a few hours while their expired gases are captured using a hood that encapsulates their entire head or with a mouth piece (58). Although one study found that RMR measurements captured with a mouth piece or face mask are 7-9% higher than measurements captured with a canopy or hood (59), the majority of studies have

concluded that the accuracy of these RMR measures are comparable (60–63). Regardless of collection method used, the oxygen and carbon dioxide measurements are converted to RMR using equations such as the Weir equation[3] (64). These equations use the known relationship between oxygen consumption and carbon dioxide production during aerobic energy production through the electron transport chain to estimate RMR (64). In general, preparatory procedures include abstaining from exercise for 24 hours, and stimulants such as cigarettes or caffeine for a minimum of 4 hours prior to the examination (58). Participants are also instructed to get at least 8 hours of sleep, and fast for a minimum of 5 hours prior to testing (58).

In 2003, a panel of experts was convened by the American Dietetic Association to evaluate existing evidence on preparatory procedures for measuring RMR by indirect calorimetry (60). The panel observed differences in the associations among factors that impact RMR based on obesity status (60). Typically, individuals with obesity had to fast and abstain from physical activity longer so as to not capture the effects of these variables on RMR in their measurement (60). For example, when women with normal weight and obesity were fed the same meal, there was a greater increase in RMR from the TEF and the peak effect of TEF occurred 24 minutes later in women with obesity compared to those with normal weight (65). However, current guidelines for measuring RMR by indirect calorimetry (58) provide universal recommendations for individuals regardless of their BMI which may impact the accuracy of measurements in populations with obesity.

Testing conditions and time of year have also been shown to effect RMR measurements. In healthy and lean populations, a decrease of 7 degrees Celsius from ambient room temperature has been shown to result in ΔRMR ranging from a 12% decrease to 30% increase (66). Nevertheless, even under strict laboratory conditions, there is considerable variability in repeat

[3] $RMR = 1.44 \times [3.94 \times VO_2 + 1.11 \times VCO_2]$

RMR measurements ranging from 1.8 to 17.3% (67,68). Further, due to the expertise and expense required to measure RMR, prediction equations are often used.

Predicting RMR

A brief list of existing RMR prediction equations and the population characteristics of samples used to derive these equations can be found in **Appendix A**. Predictive equations use variables that are easy to collect (69), such as weight and age, as this allows for these equations to have a greater utility in a variety of settings (69). An expert panel was convened by the American Dietetic Association to examining the existing body of evidence regarding the accuracy of the Harris-Benedict (HB), Mifflin St. Jeor (MSJ), Owen, and the World Health Organization prediction equations. RMR was defined as being predicted accurately if it was within 10% of the measured value. The panel found that the HB accurately predicted RMR in 45 to 80% of individuals with normal weight, and 38 to 64% of healthy individuals with obesity (70). Conversely, the more recent prediction equations proposed by Owen et al. (1986-1987) had comparable accuracy for healthy individuals with normal weight (73%), but only accurately predicted RMR in 33 to 51% of individuals with obesity (70). While other prediction equations have included a few participants with obesity in their study population (71–74), approximately half of the population studied by MSJ had obesity (69). The greater diversity in the study population may in part explain why the MSJ equation is consistently found to be the most accurate prediction equation (70,75). Indeed, the expert panel found MSJ to be the most accurate equation in predicting for healthy individuals with normal weight (82%) and obesity (70%) (70). The panel concluded by recommending the use of the MSJ equation for predicting RMR in healthy individuals with normal weight and obesity, and that while HB also had some utility for individuals with normal weight, it is likely not applicable for individuals with obesity (70).

In 2013, Frankenfield re-evaluated the use of the aforementioned prediction equations with the addition of those by Muller (74) and Livingston (73) in a large, diverse sample (76). MSJ was once again found to provide the least biased estimate of RMR, and surprisingly, HB was now found to be the least accurate with a tendency to overestimate measured RMR (76).

Two significant limitations for the use of RMR prediction equations during WL interventions exist. Current RMR prediction equations were created and validated for use during weight stable periods (69,71–74,77), thus their utility in accurately predicting RMR throughout WL interventions is unknown. Secondly, while chronic conditions have been shown to influence RMR, current prediction equations were created and validated in populations without the presence of any chronic conditions other than obesity (69,71–74,78,79). This may further inhibit their accuracy in predicting RMR in populations that are prescribed WL.

Summary and Rationale

Obesity is a significant public health concern, with the prevalence of obesity having tripled over the last 30 years in Canada (1). WL is recommended to individuals with obesity (42,43) as even small reductions in body weight (5%) have been shown to improve a variety of metabolic risk factors (7). Daily energy expenditure is used to determine individualized caloric prescriptions. As RMR makes up the largest component of energy expenditure (8,46,47), RMR may influence WL success. Indeed, considerable research has examined the associations of RMR and WL (9–16,18–20,52), however, findings remain inconsistent. The majority of this research has also been conducted in healthy (13–16,18) and lean populations (16,18), thereby limiting the generalizability of these results to typical interventions. Further, as WL has also been shown to improve chronic conditions (56), it is typically prescribed to individuals who have these conditions. Surprisingly, little research exists examining the association between chronic

conditions and RMR. Additionally, despite high blood pressure and glucose being positively associated with RMR, further research into other chronic conditions may help elucidate why metabolic syndrome is associated with a depressed RMR. Thus, the objectives of the study were to examine:

1) differences in baseline, or ΔRMR, by the health risk status of glucose, triglycerides, blood pressure, LDL, and HDL &

2) The independent associations of baseline and ΔRMR with WL and the influence of the health risk status of glucose, triglycerides, blood pressure, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) on these associations in a population with severe obesity and a high prevalence of chronic conditions.

3.0 Manuscript

The Associations Of Resting Metabolic Rate With Chronic Conditions And Weight Loss

Introduction

Since the 1980s, there has been an increasing prevalence of obesity in Canada (2,1). In 2011, over 51% of adults in Canada self-reported as having overweight or obesity (1). In particular, women are more likely to have moderate or severe obesity than men (1). Due to the comorbidities associated with obesity such as type 2 diabetes (3–5), and cardiovascular disease (3,4,80), individuals with obesity are typically prescribed weight loss (WL).

To achieve WL, individuals must create a caloric deficit by consuming less than they expend, thus assessment of daily energy expenditure may be important in WL success. Resting metabolic rate (RMR) is the number of calories the body expends while at rest, and is the largest component of daily energy expenditure in most adults (8), yet it is unclear whether RMR is related with WL success (9–16,18–20,52). Further, RMR has been shown to decrease as a result of acute caloric restriction (21,22), WL (13,18,14–17) and chronic diseases such as metabolic syndrome (24). These changes in RMR (ΔRMR) can be greater than reductions in caloric intake commonly prescribed to induce WL, and therefore ΔRMR may be important to assess. However, the associations between baseline and ΔRMR with WL are also unclear. Additionally, while WL is often prescribed to individuals with chronic disease, the effects of chronic disease on RMR in individuals with severe obesity has yet to be examined. Thus, the objective of this study is two-fold: 1) to explore differences in baseline, or ΔRMR by health risk status for glucose, triglycerides, blood pressure, low-density lipoprotein (LDL), and high-density lipoprotein (HDL); 2) to examine the independent associations of baseline and ΔRMR with WL, and the

influence of the above chronic conditions on these associations in a population with severe obesity and obesity-related comorbidities.

Methods

The Wharton Weight Management Clinics (WMC) are referral-based WL and diabetes management clinics located across Southern Ontario in Canada. WMC aims to educate patients about obesity-related chronic conditions and weight management. WMC uses strategies outlined in the Canadian Clinical Practice Guidelines on the Management and Prevention of Obesity in Adults and Children (81), and the National Institutes of Health Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (3). All services are covered by the Ontario Health Insurance Program, and are provided to patients free of charge. A total of 9529 participants provided their written informed consent from 2008 – 2014 to allow access to their electronic medical records for research purposes. Patients were informed that their participation would not affect their medical treatment and that they could withdraw access at any time. Access to data was facilitated through research collaboration between York University and WMC. Research methods were approved by the York University Institutional Review Board in accordance with the Tri-Council Ethical Conduct for Research Involving Humans.

Participants were excluded if they were under the age of 18 years (n=2), or had a BMI $\leq$ 25 kg/m^2 (n=7). Participants were also excluded if they had conditions that are known to influence RMR or WL such as hypothyroidism (n=125), were taking medication for depression (n=181), underwent bariatric surgery (n=46) or attended the clinic for less than 3 months (n=4532). The amount of participants who were excluded for attending the clinic less than 3 months is consistent with the high attrition rates for WL interventions (42-70%) reported in the

literature (82,83). Participants were also excluded if they had incomplete data for repeated RMR (n=3958), age (n=70), BMI (n=25), ethnicity (n=819), or smoke status (n=384). Patients were also excluded if they had incomplete data for glucose (n=7513), triglycerides (n=7516), systolic blood pressure (n=21), diastolic blood pressure (n=24), HDL (n=7419), or LDL (n=7527). Visualization of data using scatterplots of RMR with weight and WL identified five RMR measurements as potential points of influence. These five measurements were later excluded from the analysis as RMR measurement reports stated testing issues such as air leaks or improper preparatory procedures. This left a final sample of 339 adults for examination.

Due to the large proportion of individuals excluded for missing data, single imputation was considered. Mean substitution was considered for continuous (i.e. RMR) and mode substitution for categorical (i.e. high glucose, triglycerides, blood pressure, LDL and HDL) variables. However, it is assumed that variables are missing completely at random thus the deletion method has been found to be reliable (84). Further, due to the similar proportions of categorical variables (for example: 43.2% of women and 50.6% of men having high blood pressure), the use of mode substitution could have severely compromised our analysis and biased the results. Lastly, to assess the impact of deletion on the sample demographics, a missing cases analysis was undertaken with presented in **Table 1**. As there was insufficient evidence to say there was a difference in the majority of demographic variables, it was assumed that employing the deletion method did not unfairly bias our study sample.

WMC program protocol

WMC procedures have been previously described in greater depth elsewhere (85). On the initial visit to the clinic, patients complete a questionnaire on demographics, health conditions and WL history. Trained personnel manually measure blood pressure and assess a variety of

anthropometric measurements. Height is measured to the nearest 0.1 cm using a wall mounted tape measure (McArthur Medical Sales, Inc., ON). Weight is measured to the nearest 0.1 kg using Medweigh MS-2510 Digital Health Capacity Platform Scales (Itin Scale Co, Inc., NY).

Patients attend an introductory educational session outlining the basics of the WMC program and an individual meeting with a bariatric educator who provides information on nutrition and meal plans provides weight management support and discusses weight goals. A physician conducts a patient physical examination, reviews patient test results, weight goals and medical history and discusses pharmacotherapy options where necessary.

On the second visit, patients receive a caloric restrictive meal plan of 500-1000 kcal below daily requirements based on their predicted RMR using the Mifflin St Jeor equation (MSJ) (69) as this equation has shown to be more reliable in estimating RMR in populations with obesity (70). Between the initial and third visit patients undergo cardiac testing, exercise stress test, blood work, and indirect calorimetry in no particular order. A baseline electrocardiogram is used to assess heart function at rest for all patients and during an exercise stress test. Results of the exercise stress tests completed by most patients are used to provide tailored physical activity prescriptions and/or identify patients who are at risk of adverse events from physical activity. Blood work is performed at certified medical laboratories under standard fasting conditions. RMR is assessed using indirect calorimetry (CardioCoach, Korr Medical Technologies, Inc., UT). Repeat blood work and RMR measurements are done as deemed necessary by the physician. Adjustments to caloric prescriptions are made throughout the intervention at the discretion of the physician using predicted or repeated RMR measurements and WL results.

On the third visit, patients meet with a bariatric educator and physician to review additional test results, existing chronic conditions, weight management issues, and to determine if there is a need for repeat or additional testing.

At each subsequent visit, blood pressure and body weight are measured, and patients discuss progress with bariatric educators and physicians. Patients are recommended to attend the clinic monthly, but may attend more frequently if desired. Additional lifestyle-intervention and educational workshops presented by WMC multidisciplinary staff (i.e. physicians, exercise specialists, dieticians, and behavioural specialists) are also regularly offered to patients.

Weight, height, age, sex, ethnicity (white/other), predicted and measured RMR (kcal), treatment time (months), fasting glucose (mmol/L), systolic and diastolic blood pressure (mmHg), hypertension (yes, no), HDL (mmol/L), LDL (mmol/L), triglycerides (mmol/L) and smoke status (current, previous, never) were extracted from electronic medical charts. Weight was measured at the time of RMR measurements and was used to assess WL progress. ΔRMR was calculated as final RMR measurement – baseline RMR measurement. Hypertension was defined as having a systolic blood pressure $\geq$ 130 mmHg, or a diastolic pressure $\geq$ 85 mmHg, (86). Low HDL was defined as <1.04 mmol/L for men and $\geq$ 1.3 mmol/L for women (86). High triglycerides was defined as $\geq$ 1.7 mmol/L, high LDL was defined as $\geq$ 3.5 mmol/L and high glucose was defined as a fasting glucose $\geq$ 5.6 mmol/L (86).

Statistical Analysis

Continuous variables are reported as means and standard deviations, and categorical variables are reported as frequencies and prevalence. Independent t-tests were used to examine differences in baseline, and ΔRMR by health risk status for each chronic condition. Paired t-tests were used to examine differences between measured and predicted RMR as well as changes in

weight and RMR. All analyses were conducted for men and women separately due to known differences in RMR (69,77) and WL (87).

Multivariable linear regression analysis was undertaken to examine the association between WL and baseline RMR adjusting for age, BMI, ethnicity, treatment time, and smoke status. The association between ΔRMR and WL was also assessed using multivariable linear regression analysis with adjustment for baseline RMR, age, BMI, ethnicity, treatment time, and smoke status. Further, as obesity related comorbidities are known are known to influence RMR, models were further adjusted for high glucose, high triglycerides, high blood pressure, high LDL, and low HDL.

Multicollinearity was assessed in all models using variance inflation factors (VIF). While a VIF >10 has been proposed as the threshold to warrant further investigation into potential collinearity (88), a more conservative threshold of 2.5 has been proposed for models with smaller R^2 value (89). As the R^2 values for all models were <0.20, the more conservative VIF estimate of 2.5 was used as an indicator of multicollinearity. VIF values for all models were $\leq$ 2.1 (range: 1.1 – 2.1), thus no further investigation into collinearity was undertaken.

Regression lines were plotted using sex-specific ranges in baseline RMR or WL between the 25^{th} and 75^{th} percentile. A p-value of <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4.

Results

Participant characteristics stratified by sex are presented in **Table 1**. For men, baseline RMR was significantly higher when measured by indirect calorimetry (2405 ± 521 kcal/day) than predicted (2147 ± 333 kcal/day) with the MSJ equation (P <0.0001). For women, baseline RMR was also significantly higher when measured by indirect calorimetry (1862 ± 371 kcal/day) than predicted (1663 ± 251 kcal/day) with the MSJ equation (P <0.0001).

Over 13.6 ± 12.8 months of treatment, men lost 8.0 ± 11.0 kg (P <0.0001) and women lost 5.5 ± 7.3 kg of body weight (P <0.0001). As such, a significant decrease in RMR was predicted in both men (P <0.0001) and women (P <0.0001). The decrease in measured RMR was non-significant for men (-48 ± 322 kcal, P=0.18) and women (-5 ± 322 kcal, P=0.79). For men, there was no significant difference between the predicted (-80 ± 110 kcal) and measured ΔRMR (-48 ± 333 kcal, P=0.39). However, for women measured decrease in RMR (-5 ± 322 kcal) was slightly smaller than predicted (-55 ± 73 kcal) using the MSJ equation (P=0.02).

Both men (P = 0.004) and women (P=0.0001) with high blood pressure had a higher baseline RMR than those with normal blood pressure (**Figure 1**, P<0.05). Additionally, while women with high LDL had a slightly lower baseline RMR (1776 ± 305 kcal/day) than those with normal LDL (1889 ± 387 kcal/day, P=0.02), there were no other differences in baseline or ΔRMR (**Figure 2**) regardless of sex, or health risk status of chronic condition (P>0.05).

With and without adjustment for high glucose, high triglycerides, high blood pressure, high LDL, and low HDL, there was no association between baseline RMR (**Figure 3**) or ΔRMR (**Figure** 4) and WL regardless of sex (P>0.05). In the fully adjusted model, high glucose, high triglycerides, high blood pressure, low HDL, and high LDL were not significantly associated

with ΔRMR or WL in men ($P>0.05$). For women, the health risk factors were not related with ΔRMR ($P>0.05$), and only high triglycerides was associated with a 3.2 kg greater WL ($P<0.01$).

Discussion

This study suggests that when patients are prescribed a similar caloric deficit, those with a low baseline RMR do not appear to be at a disadvantage for losing weight. Further, while WL is generally associated with a decrease in RMR in healthy populations, this study suggests that significant WL can occur without a corresponding decrease in RMR in individuals who have high levels of obesity and obesity-related comorbidities. Lastly, while high blood pressure and LDL may influence RMR, the presence or absence of chronic conditions at baseline does not appear to be associated with ΔRMR during a WL intervention.

The cornerstone of WL interventions is prescribing decreased caloric intake and increased physical activity to result in WL (42,43). Thus determining daily energy expenditure may be necessary to set appropriate caloric prescriptions to induce WL. As RMR accounts for 60% to 75% of total daily energy expenditure, RMR may be an important factor in WL. While RMR may theoretically be related with WL, little research exists on the association between baseline RMR and WL, with findings being inconsistent (90,10,11,9). This may be due to population or methodological differences between studies. For example, some studies that observe an association between baseline RMR and WL provided individuals with the same absolute caloric prescription (i.e. 1200 kcal/day) regardless of their baseline caloric needs (10,9). This means that individuals with a higher baseline RMR should theoretically have a larger caloric deficit, which may explain their greater WL. Another study that also prescribed the same absolute caloric intake regardless of their baseline caloric needs found no association between baseline RMR and WL. However, that study provided pharmacological agents known to increase RMR as part of their WL intervention (90). Using the more common approach of prescribing similar calorie deficits, this study and one other (11) observe that baseline RMR was not

associated with WL. Thus, when individuals are provided with similar caloric deficits, those with a low baseline RMR do not appear to be at a disadvantage for WL.

Each kilogram of body mass expends between 3 to 14 kcal/day at rest (51), and thus, RMR should decrease in response to WL. However, two studies conclude that there is no association between ΔRMR and WL (20,19). These studies observe a wide range of ΔRMR that occur for a given WL, but may have been underpowered due to their small sample sizes (n <40) (20,19). In the current study, we had a substantially larger sample, but also conclude that WL is not associated with ΔRMR. While the MSJ equation predicts a decrease in RMR for all participants who lost weight, there was substantial variability in measured ΔRMR. These discrepancies may be due to individuals with severe obesity and high prevalence of obesity-related comorbidities who have may have RMRs that are too low (i.e. floor effect) at baseline to allow their RMR to decrease further.

The majority of research concludes that decreases in body mass are associated with reductions in RMR in healthy populations (14,16) with overweight or mild obesity (13,18,14–17). However, both obesity (24,53) and certain obesity-related comorbidities (24) are known to depress RMR and may be improved by WL. Thus, improvements in these conditions could result in increases in RMR greater than reductions in RMR from WL, and may be why WL was not associated with the expected decrease in RMR for men and women in this study. On the contrary, poor glucose control in type 2 diabetics (24,57) and high blood pressure have been shown to be positively associated with RMR (56). While for women having high triglycerides was associated with greater WL, high glucose and blood pressure were not associated with greater WL for either men or women. However, many medications for these chronic conditions

are known to have influences on metabolic rate (56,91), which may have impacted our ability to observe associations between RMR and WL.

WL has been shown to improve chronic conditions (92,93), however, little research exists regarding the influence of chronic conditions on RMR (24,57,56). Further, research examining the association between chronic conditions and RMR often examines clusters of chronic conditions which may mask their individual effects on RMR. For example, poor glucose control (24,57) and high blood pressure (56) have been individually associated with a higher RMR. Conversely, having metabolic syndrome, which is a cluster of conditions that may include high glucose and blood pressure, is associated with a lower RMR compared to healthy controls (24). In the current study we did not observe a significant difference in RMR based on glucose risk status. This lack of association may be due to the use of a more conservative estimate of poor glucose control ($\geq$5.6 mmol/L) than previously examined in literature ($\geq$ 7.0 mmol/L) (57). This study and others have found that individuals with high blood pressure had a higher baseline RMR than those with normal blood pressure. Conversely, this study is the first to suggest that women with high LDL had a lower baseline RMR than women with normal LDL. However, differences in the health status of chronic conditions were not associated with ΔRMR. Thus, future research is needed to examine the effect of changes in the status of chronic condition(s) on RMR during a WL intervention.

Acute (18,21) and chronically (23) decreased caloric intake is associated with decreases in RMR through differing mechanisms. WL is associated with chronic decreases in RMR due to the reduction in metabolically active body mass (23). However, acute caloric restriction can result in an immediate decrease of 10-12% in RMR independent of changes in body weight (18,21). Thus, baseline RMR measurements taken prior to caloric restriction may capture

decreases in RMR that are due to both the acute effects of caloric restriction and chronic deceases stemming from WL. As the current study took baseline RMR measurements after participants had begun to make dietary alterations, this may explain why the ΔRMR (~1%) observed were less severe than those reported in previous studies (12 – 15%) (13–17). Additionally, as researchers are often unaware of dietary habits prior to the commencement of WL interventions, the severity of dietary changes that may occur could also contribute to the much greater ΔRMR reported previously in the literature.

In a clinical and research settings, RMR is measured by indirect calorimetry (58). However, there is considerable intra-variability in RMR measurement, ranging from 6% to 12% for multi-day repeat measures under strict laboratory conditions (68,94). Further, due to the expertise and expense required to measure RMR, prediction equations are often used in clinical settings. Of the existing RMR prediction equations, the Harris Benedict (77) and MSJ (69) equations are the two most commonly used in clinical settings (95). These are sex-specific equations that use age, height, and weight to predict RMR (69,77). However, these equations were created using a primarily male (77), young (77), white (69,77), healthy (69,77), and normal weight to mildly obese (69,77) population, and do not account for the effects of obesity-related comorbidities, such as blood pressure and LDL, which we found to have an effect on RMR. Further, prediction equations are meant to assess RMR during weight stable periods (69,77), and have not been validated to assess ΔRMR with WL. In the current study, significant discrepancies were observed between predicted and measured RMR regardless of sex. This may underscore the importance of RMR measurements to provide accurate caloric prescriptions in this population.

There are several strengths and limitations in the current study that warrant mentioning. Strengths of this study include a large sample of individuals with high levels of obesity and

obesity-related comorbidities, which are more typical of individuals who require WL intervention. Additionally, participants were prescribed similar caloric deficits of 500 to 1000 calories per day. Limitations of this study include a primarily white and female population, which may impact the generalizability of these results. Also, we were unable to examine the effect of each chronic condition in isolation on RMR as most participants had more than one chronic condition, and very few individuals with obesity have no other chronic conditions. Fat free mass has been shown to account for over 60% of inter-individual variance of RMR (96). Due to a lack of measurements of fat free mass, we are unable to determine if preservation or increases in fat free mass may have contributed to ΔRMR observed. However, findings from a recent follow-up study conducted on individuals who had lost significant weight suggests that fat free mass may not be closely related to RMR in individuals with obesity and obesity related comorbidities (97). Indeed, six years after concluding the WL intervention, participants had significant reductions in RMR despite increases in fat and fat free mass (97). Additionally, due to a lack of follow-up on glucose, triglycerides, blood pressure, HDL, and LDL measurements, we were unable to determine if ΔRMR were as a result of changes in these factors. Lastly, although we had clinical measures of RMR, the day-to-day variability in RMR may have impaired our ability to assess ΔRMR. Nonetheless, ΔRMR in this population appear to be quite small and may not be related with WL.

In summary, when caloric prescriptions are based on individual energy requirements, there was no evidence of an association between baseline RMR and WL for both sexes. These findings are particularly noteworthy as they imply having a low baseline RMR during WL interventions does not put individuals at a disadvantage for WL. Further, in populations with high levels of obesity and obesity-related comorbidities, reductions in weight may occur without

corresponding reductions in RMR. Only a few medical conditions were associated with RMR and they did not predict ΔRMR. In addition, measuring RMR may not lead to understanding variations in RMR within a population; however, it may be beneficial on an individual basis for initiating meal plans and following patients during weight management.

Table 1: Missing case analysis

Variable	Missing data	Complete cases	P-value
Age (years)	49.1 ± 13.3	52.5 ± 13.0	<0.0001
Baseline Weight (kg)	112.2 ± 25.3	112.4 ± 25.6	0.8612
Baseline BMI (kg/m^2)	40.3 ± 7.7	40.3 ± 7.9	0.9801
Baseline RMR (kcal/day)	2018 ± 495	1993 ± 480	0.3247
Predicted baseline RMR (kcal/day)	1802 ± 341	1790 ± 343	0.4837
Treatment time (month)	10.6 ± 12.7	10.7 ± 9.9	0.8779
Weight change (kg)	-4.6 ± 7.1	-5.5 ± 7.7	0.0304
Measured ΔRMR (kcal)	-5 ± 314	0 ± 323	0.7712
Predicted ΔRMR (kcal)	-46 ± 71	-55 ± 77	0.0262

Table 2: Participant characteristics stratified by sex

Variable	Women	Men
Sample size (n, %)	250	89
Age (years)	52.6 ± 12.3	54.8 ± 12.5
Baseline Weight (kg)	106.4 ± 21.5	131.0 ± 29.7
Baseline BMI (kg/m^2)	40.0 ± 7.8	41.9 ± 9.0
Baseline RMR (kcal/day)	1862 ± 371	2405 ± 521
Predicted baseline RMR (kcal/day)	1663 ± 251*	2147 ± 333*
Ethnicity (White, %)	222 (88.8)	79 (88.8)
Smoke status		
Never	132 (52.8)	39 (43.8)
Current	24 (9.6)	9 (10.1)
Previous	94 (37.6)	41 (46.1)
Glucose (High, %)	108 (43.2)	45 (50.6)
Triglyceride (High, %)	74 (29.6)	36 (40.5)
Blood Pressure (High, %)	128 (51.2)	60 (67.4)
HDL (Low, %)	126 (50.4)	39 (43.8)
LDL (High, %)	61 (24.4)	17 (19.1)
Treatment time (month)	12.3 ± 9.5	14.6 ± 10.2
Weight change (kg)	-5.5 ± 7.3†	-8.0 ± 11.0†
Measured ΔRMR (kcal)	-5 ± 322	-48 ± 333
Predicted ΔRMR (kcal)	-55 ± 73†*	-80 ± 110†

*Different from measured RMR ($P<0.05$)

†Significant change from baseline to end of treatment ($P<0.05$)

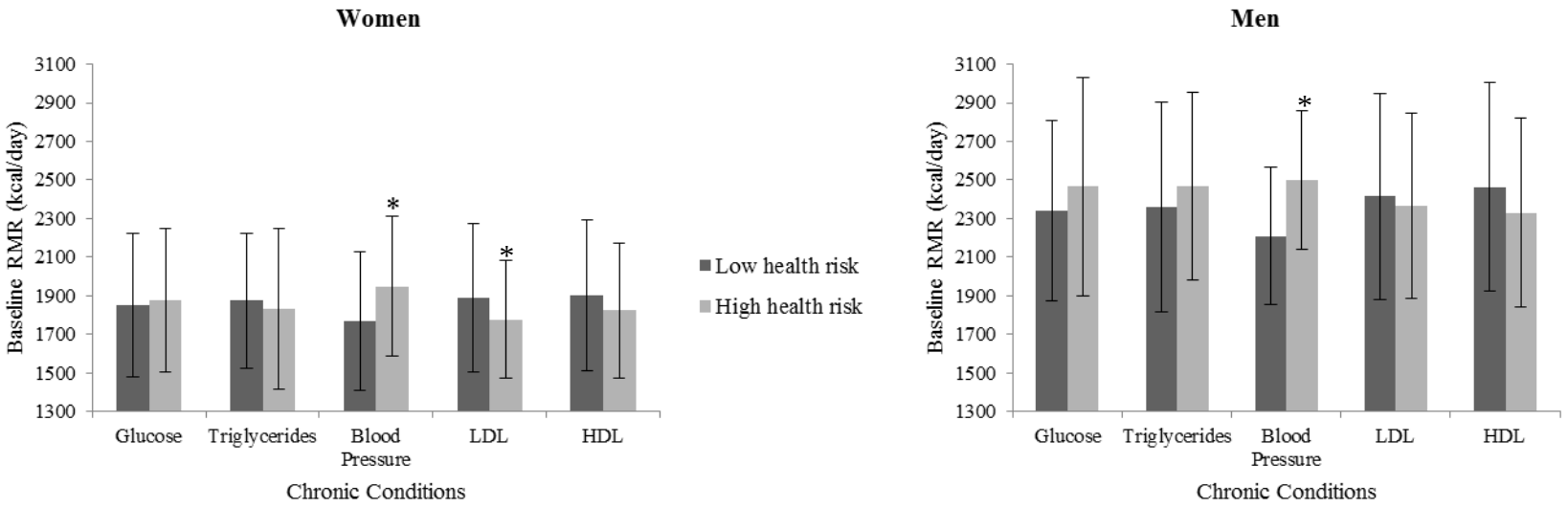

Figure 1: Measured baseline RMR by sex, and health risk status of chronic conditions. *Significantly different from low health risk within chronic condition ($P<0.05$).

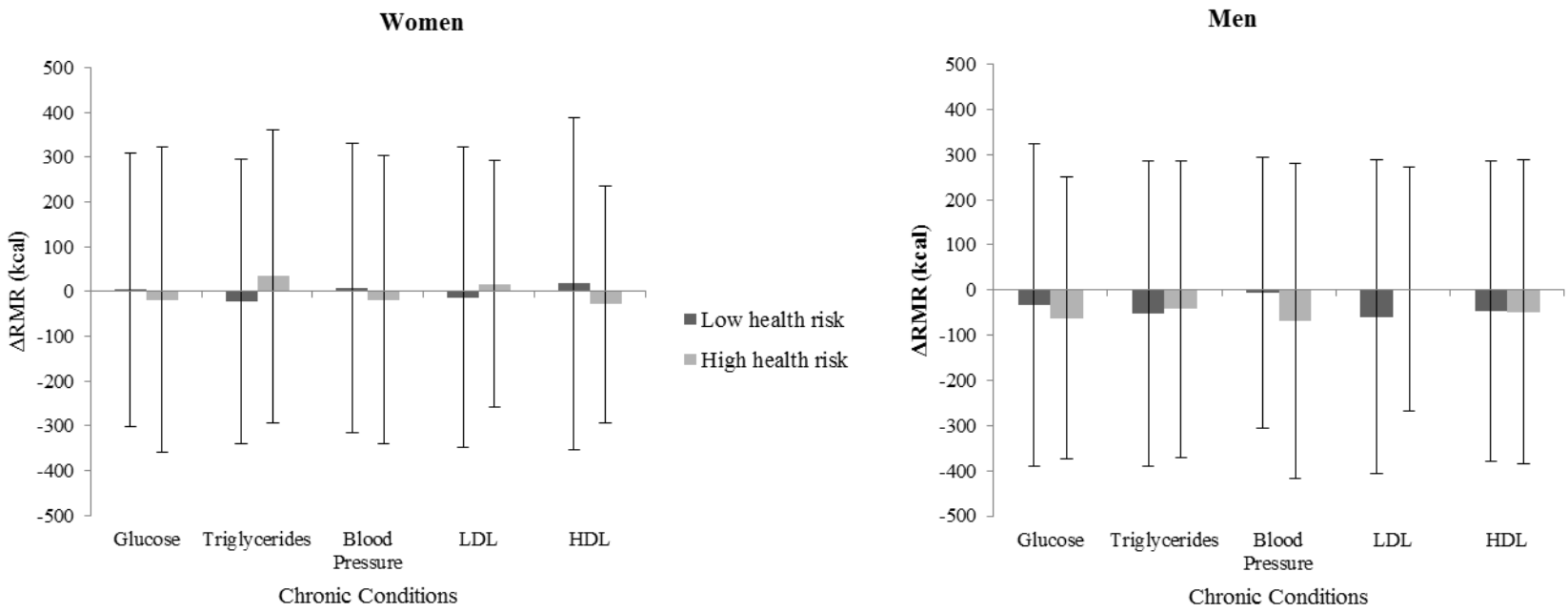

Figure 2: Measured ΔRMR by sex, and health risk status of chronic conditions. No significant differences in RMR based on health risk for all chronic condition ($P>0.05$).

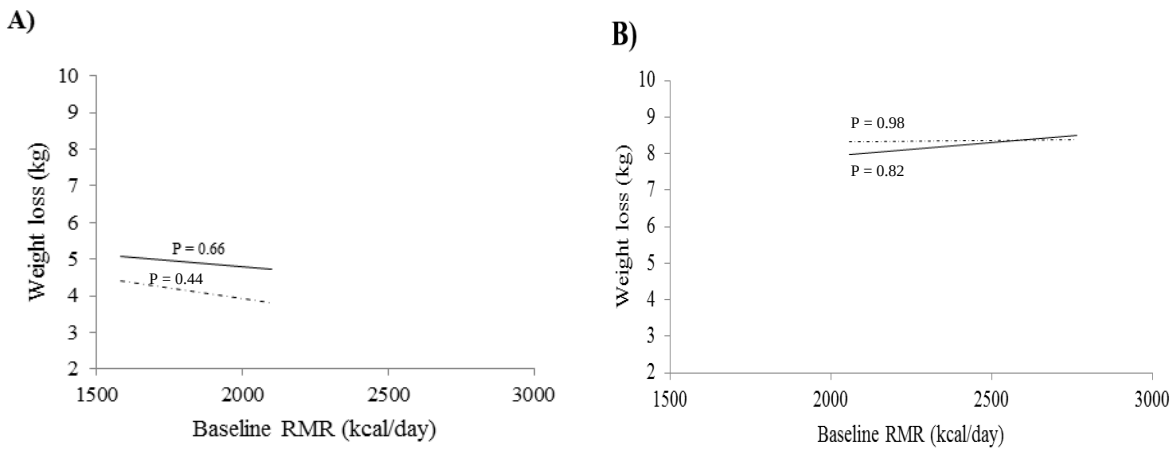

Figure 3: Association between WL and baseline RMR for women (A), and men (B). Regression lines are constructed using mean age, BMI, and treatment time. The solid line was adjusted for age, BMI, treatment time, ethnicity and smoke status. The broken line was further adjusted for high glucose, triglycerides, blood pressure, LDL and low HDL.

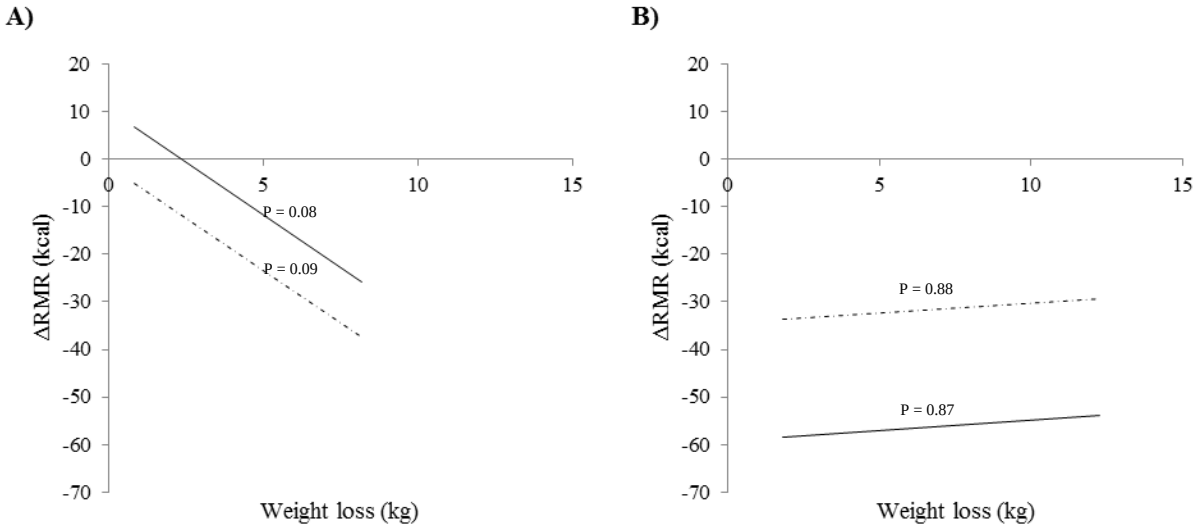

Figure 4: Association between ΔRMR and WL for women (A), and men (B). Regression lines are constructed using mean age, BMI, treatment time and baseline RMR. The solid line was adjusted for age, BMI, treatment time, ethnicity smoke status and baseline RMR. The broken line was further adjusted for high glucose, triglycerides, blood pressure, LDL and low HDL.

4.0 Extended Discussion

Obesity has been associated with a variety of adverse health outcomes (3–6,26,27), such as an increased likelihood of developing chronic diseases. A modest WL of 5% of initial body weight has been shown to improve metabolic risk factors (7). Thus, given the increasing rates of obesity over the last 30 years (25), research into factors associated with WL success is a necessary pursuit. Current guidelines recommend a caloric restriction of 500-1000 kcal/day to illicit a WL of 1-2 lb/week for individuals with overweight and obesity (45). As RMR is the largest component of energy expenditure (8) it may be related to WL success. Indeed, prior to this thesis considerable research had examined the association between RMR and WL (9–16,18–20,52), however little research (52) has been conducted in populations with obesity. Further, while WL is recommended for individuals with chronic conditions (42,43), little research exists on the effects of chronic conditions on RMR with contradicting findings. Thus, findings from this study have attempted to address the gap in the literature regarding the associations of RMR with WL and chronic conditions in individuals with high levels of obesity and prevalence of chronic conditions.

In contrast to the majority of existing research suggesting that there is a positive association between baseline RMR and WL (9,10), the current study found no evidence of an association between baseline RMR and WL. Discrepancies may be attributable to their use of the same absolute caloric (i.e. 1200 kcal/day) (9,10) as opposed to similar caloric deficits (i.e. 500 – 1000 kcal) that is more commonly prescribed and was used in the current study. Nonetheless, these findings are noteworthy because they counter the common rhetoric that individuals with a low baseline RMR are at a disadvantage for WL. Further, while additional research is necessary,

these results may suggest that individuals with conditions that depress RMR may also lose weight when provided with personalized caloric prescriptions.

While WL is recommended for individuals with severe obesity and obesity related comorbidities (42,43), the majority of research in this area has been conducted in healthy (13–16,18) and lean populations (16,18). The current study examined a population that is more representative of those who are prescribed WL, and we found no evidence of an association between WL and ΔRMR. This is surprising as research suggests that decreases in RMR as a result of WL are in large part to blame for the less than expected WL observed during interventions (15). Further, there was a large range in the ΔRMR (-1108 to 1368 kcal/day) observed in this study and we were unable to identify any factors that predicted this change. This may underscore the necessity to measure RMR throughout WL interventions in order to aid medical professionals in determining accurate caloric prescriptions for individual patients.

To date there has been little research conducted on the associations of chronic conditions with RMR. Results from this study suggest that high blood pressure and LDL can result in differences in RMR. However, current RMR prediction equations were created using populations without the presence of chronic conditions except for obesity (69,71–74,78,79). Thus, differences in RMR due to the presence of chronic conditions may have contributed to the discrepancies between measured and predicted RMR that was observed in this study. While this once again underscores the potential importance of measuring RMR, measuring RMR may not be feasible for the majority due to the expense and expertise required. Thus, further research is necessary to determine factors that influence RMR so that a more appropriate prediction equation may be created.

Limitations of this study include a primarily white and female population, which may impact the generalizability of these results. However, as recent trends in obesity suggest that women are more likely to have class II or III obesity (1), women likely make up a greater proportion of individuals who require WL. We were unable to examine the effects of each chronic condition in isolation on RMR as only 8% of women and 2% of men did not have any chronic conditions. However, as research suggests that a small proportion of individuals (1.4 to 11.3%) with overweight and obesity have no other chronic conditions (98), the clinical population may in fact be representative of individuals with obesity. Due to a lack of data, we were also unable to examine the effects of fat free mass and changes in the health risk status of chronic conditions on ΔRMR. Strengths of this study include providing participants with caloric prescriptions (500-1000 kcal/day deficit) currently recommended for the treatment of overweight and obesity (45). Additionally, the use of a study population which is typical of individuals who are recommended to lose weight (i.e. high levels of obesity and prevalence of chronic conditions) was also a strength of this study.

In summary, this study builds on our existing knowledge of factors associations with RMR. Based on findings from this study, it appears that WL and chronic conditions were not associated with ΔRMR, yet it remains unclear what factors are related to ΔRMR during WL interventions. Further, differences in predicted and measured RMR may be attributed to differences in RMR based on health risk status. Thus, measuring RMR may be necessary to aid medical professionals in determining accurate caloric prescription for individual patients.

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Appendix A: Resting Metabolic Rate Prediction Equations and Study Demographics

Author	Prediction Equation	Study Demographics
Harris & Benedict (1918) (77)	Men: 66 + (13.7 x weight) + (5 x height) – (6.8 x age) Women: 665 + (9.6 x weight) + (1.8 x height)– (4.7 x age)	Men: 136 Women: 103 Weight: 25 – 124.9 Age 21-70 Height 151-200
Cunningham (1980) (78)	RMR = 500 + (22 x lean body mass)	Same population as Harris & Benedict
WHO (1985) (99)	Men: Age 18-30: 692.2 + (15.057 x weight) Age 30-60: 873.1+ (11.472 x weight) Age ≥60: 587.7 + (11.711 x weight) Women: Age 18-30: 486.6 + (14.818 x weight) Age 30-60: 845.6 + (8.126 x weight) Age ≥60: 658.5 + (9.082 x weight)	Men: 3514 Women: 1376 Age: 19-82 Height: not provided Weight: not provided
Owen (1986-1987) (71,72)	Men: 879 + (10.2 x weight) Women: 795 + (7.18 x weight)	Men: 60 Age: 38 ± 15.6 (18-82) Height 175 ± 6.9 (163-188) Weight: 86.6 ± 23.8 (59.8-171.4) BMI: 28.2 ± 7.5 (20.4-58.7) Women: 44 (8 athletes) Age: 35 ± 12.2 (18-65) Height: 164 ± 6.8 (150-180) Weight: 74.9 ± 24.9 (43.1-143.3) BMI: 27.8 ± 8.6 (18.2-49.6)

Author	Prediction Equation	Study Demographics
Mifflin St. Jeor (1990) (69)	Men: 5 + (10 x weight) + (6.25 x height) – (5 x age) Women: 161 + (10 x weight) + (6.25x height) – (5 x age)	Men: 251 Women: 247 Age: 45 ± 14 (19-78) Weight: 78.9 ± 16.7 (46-143) Height: 171.3 ± 9.6 (146-201) BMI: 26.9 ± 4.6 (17-42)
Muller (2004) (100)	764 + (11 x weight) – (3.5 x age) + (Male(y/n) x 240)	Men = 388 Women = 658 Age: 44.2 ± 17.3 Weight: 78.0 ± 23.0 Height: 169.9 ± 10.0 BMI: 27.1 ± 7.7
Livingston (2005) (73)	Men: 293 x weight$^{0.4330}$ – (5.92 x Age) Women: 248 x weight$^{0.4356}$ – (5.09 x Age)	Included participants from: - Harris & Benedict - Owen - Additional population of: Men = 633 Age: 18-96 Weight: 33-278 Women = 789 Age: 18-96 Weight: 36 – 261

Age is in years
Height is in centimeters
Weight is in kilograms
Lean body mass is in kg