PHYSICAL ACTIVITY, AGING, WAIST CIRCUMFERENCE, AND MEDICATION USE IN RELATION TO METABOLIC HEALTH AND MORTALITY RISK

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Abstract

Research that investigates effective assessment or treatment of conditions associated with physical inactivity and obesity is warranted, as these factors pose a large public health challenge. The first study in this thesis demonstrated that participating in physical activity (PA) even once a week was associated with lower all-cause mortality risk compared to no PA ($P<0.05$). However, only in very old adults was participating in PA more than once per week associated with an even lower mortality risk ($P<0.05$). The second and third studies determined that adults with type 2 diabetes (T2D) or hypertension who were physically active, treated and controlled had a significantly lower mortality risk as those who were physically inactive, regardless of treatment or control ($P<0.05$), a similar mortality risk as adults without T2D ($P>0.05$), and a higher mortality risk compared to physically active adults without hypertension ($P<0.05$). These studies demonstrate the importance of a higher frequency of PA in very old adults, and the benefits of PA on mortality risk in adults with hypertension or T2D.

The fourth study demonstrated that adults with overweight and not attempting weight loss had the greatest error in estimating vigorous energy expenditure, and calories in food. However, among all participants, there was a large individual error in calorie estimation. The overall poor understanding of energy expended through exercise and calories in food may have important implications for weight management. The fifth study determined that adults consider the clinically recommended waist circumference (WC) measurement sites (iliac crest and midpoint) the most difficult sites to self-measure ($P<0.05$). However, there were no differences in the accuracy of self-measurement, or the association between WC and blood pressure between measurement sites, but there were large variations in the prevalence of abdominal obesity between sites (0-18% for normal weight; 21-78% for overweight). Therefore, there may be no

clear advantages of measuring one WC site over another. In summary, even modest amounts of PA are effective for reducing mortality risk, and may be particularly beneficial in very old adults, and among adults with T2D or hypertension. In addition, effective methods for long term weight management are needed.

Key Words: obesity, aging, exercise, calories, energy balance, type 2 diabetes, hypertension

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List of Abbreviations

ANOVA = Analysis of variance

BMI = Body mass index

CI = Confidence intervals

CVD = Cardiovascular disease

HbA1c = Hemoglobin A1c

HDL cholesterol = High density lipoprotein cholesterol

HR = hazard ratio

$HR_{predicted}$ = Predicted maximum heart rate

kcal = Kilocalories

LDL cholesterol = Low density lipoprotein cholesterol

NHANES = National Health and Nutrition Examination Survey

NW = Normal weight

OW = Overweight

PA = Physical activity

SD = Standard deviation

SE = Standard error

T2D = Type 2 diabetes

TZD = Thiazolidinedione

VO_{2peak} = Peak oxygen uptake

WC = Waist circumference

WL = weight loss

Chapter 1. General Introduction

Due to rapid modernization within the past several decades, much of the world now lives in an "obesogenic" environment, characterized by easy access to an abundance of energy dense foods, and activities that require very little energy expenditure [1]. As a result, physical inactivity and obesity are highly prevalent globally and represent major public health challenges. Physical inactivity and obesity have increased in all age groups, and now represent the fourth and fifth leading global risks for mortality [2]. In particular, the prevalence of T2D and cardiovascular disease (CVD) are expected to continue to increase in the future due to obesity, sedentary lifestyles [3] and an increasing aging population [4], which places a great financial burden on the health care system. Therefore, safe and cost-effective management of these conditions is needed.

Obesity is a multifactorial condition, and it is recommended that all obese persons lose weight [5]. Lifestyle interventions, such as caloric restriction and exercise, are typically the first line of treatment prescribed for weight loss [5]. Energy balance is the result of energy intake and energy expenditure. Therefore, it may be important to have an understanding of both components of energy balance in order to successfully manage body weight [6]. However, even when significant weight loss is achieved, few obese persons are able to maintain weight loss over a long term [7]. Therefore, it is important to investigate factors that are associated with successful weight loss and weight management.

Not only has general obesity increased, but so has the prevalence of abdominal obesity [8], which is an independent predictor of health and mortality risk [9,10]. But unlike general obesity, methods for assessing abdominal obesity are not universally standard. Thus, the purpose of this

thesis is to investigate a variety of issues associated with PA, obesity, metabolic health, and mortality risk in various populations that differ in age, body weight and disease status.

Chapter 2. Literature Review

2. 1 Physical Activity and Health

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure and increases heart rate and breathing [11]. Compared to less active individuals, adults who are physically active have a lower risk of CVD, T2D, hypertension and dyslipidaemia [12]. Physical activity is beneficial for mortality risk, as those who are active are reported to have a 30% lower risk of premature mortality as individuals who are physically inactive [13]. Physical activity is also recommended for the prevention and management of obesity [5] and is important for weight maintenance following weight loss [14]. Even without weight loss, PA is associated with decreased abdominal obesity [15] and health risk [16].

The Canadian Physical Activity Guidelines for Adults ages 18-64 years suggests that adults should accumulate at least 150 minutes of moderate or vigorous PA a week for health benefits, as well as include bone and muscle strengthening activities at least 2 days a week [11]. These guidelines are similar for older adults, and also include recommendations for engaging in PA that enhances balance and prevents falls [17]. However, older adults are at a higher risk for health conditions that may be prevented or improved with PA than younger adults, and therefore it is likely that the association between PA and health may differ by age. Furthermore, most studies that have assessed the association between PA and mortality risk have examined total energy expended, or the duration of PA [13], with only a paucity of studies reporting on the association between frequency of PA and mortality risk [18]. However, the few studies that have measured frequency of PA have demonstrated that participating in PA even once a week is associated with lower mortality risk [19–22].

2.2 Older Adults and Physical Activity

In the Western world, older adults (65+ years) are a rapidly increasing segment of the population. In Canada, the proportion of older adults is expected to increase from 15% to 23% by 2030 [4]. Because risk of many chronic conditions increase with age, a larger older adult population infers a greater potential burden to the healthcare system [23]. Therefore, low-cost approaches for improving the health of older adults are needed. In older adults, PA is associated with reduced risk of cardiometabolic disease, greater functional health, better cognitive functioning, and lower mortality risk [13,24–26]. Despite the known health benefits of participating in PA in older adulthood, older adults are less likely to be physically active than younger adults [27]. Recent evidence suggests that in adults 60 years and older, not meeting the current PA guidelines is associated with a 2.8-4.9 years of life lost in normal weight, and 1.3-1.5 years of life lost in overweight [28]. Additionally, it is estimated that if everyone age 60 years and older met the PA guidelines, life expectancy at age 60 would increase by 1.7-3.1 years [28].

Very old adults (80+ years) are a population that is expected to increase from 5.5 million in 2010 to 19 million by 2050 in the United States [29]. Although research investigating PA in very old adults is scarce, there is evidence to suggest that PA is also strongly associated with improved physical functioning in this age group [30], as well as lower mortality risk [31–33]. However, very old adults are even less likely to participate in PA compared to older adults [34]. Given that PA has differential effects on the various aspects of health, the association between PA and mortality risk may differ by age. In particular, older adults may be a population that especially benefit from PA compared to younger age groups. However, it is not known if the association between PA and mortality risk is consistent across the adult age span.

2.3 Obesity and Health

For much of the world, daily tasks now require minimal energy expenditure, and there is an unprecedented availability of energy dense foods [1]. This has resulted in an increased prevalence of obesity in most developed and developing nations [35], including Canada where obesity rates have increased from 6% to 18% between 1985 and 2011 [36]. Obesity is a significant risk factor for major chronic conditions, including CVD, T2D, hypercholesterolemia, osteoarthritis, depression, functional disability, and cognitive decline [37–41]. Indeed, obesity is now the second highest risk factor for disease in North America [42], and is the fifth leading cause of mortality globally [2]. Although obesity is typically associated with deleterious health outcomes, there is some evidence that the association between obesity and health weakens with increasing age [43,44], and that some obese sub-populations are not negatively affected by their weight [45]. Nonetheless, it is projected that obesity rates will continue to increase in the U.S., resulting in 6 million new cases of diabetes, and 5 million new cases of coronary heart disease and stroke by 2030 [46]. Although BMI is the most widely used indicator of obesity ($\geq$30 kg/m^2), it does not take into account body fat distribution, and it is now established that increased abdominal obesity is associated with cardiometabolic health risk [47] and mortality risk [10] independent of overall obesity [47]. Fat that accumulates around the abdominal cavity is significantly associated with increased risk for hypertension [48,49], impaired fasting glucose, T2D, and the metabolic syndrome [50,51]. However, unlike general obesity, there is no universal standard for measuring and classifying abdominal obesity.

2.4 Waist Circumference Measurement

Precise measurement of abdominal fat and specific fat depots requires expensive and time-consuming methods, and the specific measurement site has significant influence on the

association between adipose tissue and metabolic risk factors [52]. Waist circumference is used as a surrogate measure of abdominal adiposity and has been demonstrated to be a good predictor of metabolic health risk and mortality risk [10,53,54]. In the United States and Canada, single sex-specific WC thresholds are used to predict elevated health risk associated with abdominal obesity ($\geq$ 102 cm for males; $\geq$ 88 cm for females) [55]. Several health organizations now recommend measuring both BMI and WC to assess weight-related health risk [5,56,57], including The Canadian Guidelines for Body Weight [56].

For research and clinical purposes, there are five commonly measured WC measurement sites: the superior border of the iliac crest, the last rib, the midpoint between the iliac crest and last rib, the minimal waist, and the umbilicus [58]. Currently, there is no universally accepted WC measurement location, with various health agencies recommending WC measurement at different sites. For example, the World Health Organization and the International Diabetes Federation recommend measurement at the midpoint, the National Institutes of Health and Health Canada recommend WC measurement at the iliac crest [56,57], the American College of Sports Medicine recommends measurement at the minimal waist [59], and the Japanese Metabolic Syndrome Guidelines recommend measurement at the umbilicus [60].

Waist circumference measured at different measurement sites has been reported to influence the absolute magnitude of WC, particularly for females [61,62]. Waist circumference tends to be typically largest at the umbilicus and iliac crest, and smallest at the last rib and minimal waist [63]. These differences will in turn also influence the proportion of individuals classified as having a high WC when the same dichotomous WC threshold values are used to predict health risk. One study reported that up to 10% more females were classified as having a high WC when waist was measured at the iliac crest (recommended site by Health Canada)

compared to the midpoint (recommended site by the World Health Organization) [64]. Furthermore, there is some evidence that WC measurement site may significantly influence the association between WC and cardiometabolic risk factors [62,65,66]. However, whether or not individuals can accurately self-measure their own WC at the various WC measurement sites is not clear, and it is not known if individuals consider any site(s) to be easier or more difficult to measure. This information would be important to know if public health agencies wish to promote self-measurement of WC to assess health risk.

2.5 Physical Activity and Weight Management

Physical activity is a recommended lifestyle treatment for overweight and obesity [5]. In the United States, approximately 50% of adults are attempting to lose weight, with caloric restriction and exercise being the most common methods of weight loss [67]. For weight loss to occur, caloric expenditure must exceed caloric intake in order for there to be a sustained negative energy balance [68]. It has been suggested that exercise without caloric restriction is a modest means for reducing obesity [69]. However, most evidence would suggest that a combination of both exercise and caloric restriction is more beneficial for short term weight loss as well as weight loss maintenance compared to PA alone due to the low levels of PA energy expenditure typically prescribed in research studies [70,71]. Although the weight loss observed with PA is related to the total energy expended through exercise [69], there is a large variability in individuals weight loss in response to exercise due to differences in compensation of energy intake [72]. This would indicate that to manage body weight, an individual may need to understand how to manage both energy expenditure and energy intake [6].

2.6 Calories and Weight Management

A recent meta-analysis of behavioural weight management programs in overweight and obese adults demonstrated that programs that encouraged patients to count calories were associated with the greatest amount of weight loss (3.3 kg) at 12 months [73]. Although energy balance is a product of energy intake and energy expenditure, there are a limited number of studies that have actually investigated whether or not individuals are accurate at estimating calories, and whether accuracy is associated with obesity or weight loss status. For example, Carels et al. (2007) reported that dieters were significantly more accurate at estimating calories in various types of common foods compared to non-dieters, although the mean difference between the groups was only 16 kcals (14%) [74]. Visona and George (2002) observed that regardless of level of dietary restraint, overweight women who were dieting underestimated energy expenditure by 81 kcal, whereas those who were not dieting overestimated energy expenditure by 121 kcal, after one hour of moderate intensity exercise. However, both groups underestimated the amount of calories consumed in an ad libitum post-exercise meal by ~75 kcal [75]. A similar investigation in males reported that overall there was a tendency to overestimate moderate intensity exercise expenditure by 129 kcal, and underestimate a post-exercise meal by 435 kcal. Although dieting status was not reported, males with high dietary restraint were more accurate at estimating exercise energy expenditure compared to males with low dietary restraint, although both groups underestimated caloric content of an *ad libitum* post-exercise meal [76]. However, in both of the aforementioned studies, exercise energy expenditure was estimated using predictive equations, which has been suggested to be less precise than using indirect calorimetry [77].

Whether or not there is a difference in accuracy of calorie estimation by weight status is also unclear. It was reported that obese individuals with a history of weight loss failure under reported energy intake, and over reported physical activity, by approximately 50% [78]. Similarly, obese individuals who were dieting underestimated the caloric content of common types of foods by 53% [79]. Further, there is evidence that calorie estimation may depend on the perceived "healthfulness" of foods, as individuals with obesity who were undergoing a behavioural weight loss intervention underestimated the caloric content of "healthy" food, and overestimated the caloric content of "unhealthy" food. However, in all types of food, absolute error in calorie estimation increased with increasing BMI [80]. Conversely, others have reported that normal weight and overweight individuals have a similar ability to estimate calories [74,76].

Although energy balance is the result of both energy intake and expenditure, only two studies have investigated how accurate individuals are at estimating exercise energy expenditure and caloric content of food with the intent of replacing calories lost during exercise. Willbond (2010) demonstrated that moderate intensity exercise expenditure was overestimated by 300-400%, whereas post-exercise energy intake was underestimated by 200-300% in normal weight males and females [81]. Conversely, Holliday (2014) reported that normal weight adults underestimated moderate intensity exercise expenditure, and accurately estimated vigorous intensity exercise expenditure. Post-exercise energy consumption was similar to actual energy expenditure in both exercise conditions [82]. However, neither of these studies investigated overweight or obese individuals, and weight loss status of the participants was not reported. Thus, it is not clear how body weight class, or weight loss status influences estimation of moderate and vigorous exercise energy expenditure, or calories in food.

2.7 Type 2 Diabetes Management

Overall obesity, and specific fat depots, such as in the abdomen and the liver, are all independently associated with risk for insulin resistance [83]. Insulin is a hormone produced in the pancreas that helps lower blood glucose by allowing muscle, liver, and fat cells to absorb glucose from the blood stream [84]. When insulin attaches to its receptor, it stimulates the translocation of the GLUT4 transporter to the plasma membrane, and glucose is transported into the cell [85]. Insulin resistance is a condition in which cells do not respond properly to insulin and therefore glucose uptake into the cells is impaired [84]. Although the exact mechanism is not yet established, obesity may cause insulin resistance via a number of pathways, including direct drainage of fatty acids from the abdomen into the portal system, the impairment of insulin-mediated glucose uptake by fatty acids in non-adipose tissue, as well as the modulation of insulin action by adipocytokines that are released from adipose tissue [86]. Type 2 diabetes is a chronic metabolic disorder characterized by insulin resistance and the presence of hyperglycemia [87]. Type 2 diabetes is diagnosed by either fasting plasma glucose $\geq$ 7.0 mmol/L, HbA1c $\geq$ 6.5%, 2-hour plasma glucose from an oral glucose tolerance test $\geq$ 11.1 mmol/L, or random plasma glucose $\geq$ 11.1 mmol/L [87]. Type 2 diabetes is a major risk factor for heart disease, stroke and kidney failure, and is the leading cause of lower limb amputation, and new cases of blindness in adults [87]. In Canada, from 1999 to 2009, the prevalence of diabetes increased 70% , with approximately 9% of Canadian adults now living with T2D, and an estimated 20% of cases remaining undiagnosed [90]. A slightly higher proportion of U.S. adults (11.3%) have diagnosed T2D [88].

Management of T2D has improved in the United States, from only 35% of adults with T2D having glycemic control in 1999 to 55% in 2010 [91]. The cornerstone of T2D management is to achieve and maintain blood glucose control (HbA1c of <7.0%), which can be achieved

through a combination of a healthy diet, PA, weight loss, and antihyperglycemic medication [92,93]. According to the Canadian Diabetes Association, adults with T2D should not consume more than 7% of daily energy intake from saturated fat, or more than 10% of daily energy intake from added sucrose or fructose, and should choose carbohydrates with a low glycemic index [94]. It is also recommended that adults with T2D engage in a minimum of 150 minutes of moderate to vigorous aerobic PA a week, with at least 2 days a week of resistance training. Due to the acute insulin sensitizing effect of exercise [95], adults with T2D should not go more than two consecutive days without exercise [94]. Indeed, although insulin-dependent blood glucose uptake at rest is impaired in T2D, muscular contractions during exercise are still able to stimulate blood glucose transport into skeletal muscles via insulin-independent mechanisms [96]. There is evidence that increased blood glucose uptake by the muscle persists for several hours post exercise, and that PA can result in acute improvements in systemic insulin action lasting from 2 to 72 hours post activity [96]. A recent meta-analysis reported that structured exercise training is associated with an overall 0.67% reduction in HbA1c compared to controls [97]. Other benefits of PA for individuals with T2D include weight loss, and reductions in LDL cholesterol and systolic blood pressure [96].

Physical activity has also been associated with lower premature mortality risk in adults with T2D [98–101]. There is evidence that participating in PA at least 3 times/week is associated with lower all-cause and CVD mortality risk compared to participating in less PA [102]. Even participating in some PA but not enough to meet the recommended PA guidelines is associated with significantly lower morality risk compared to participating in no activity [103]. Still, there is evidence that participating in PA even once a week is associated with a significantly lower risk of cardiovascular events, microvascular events, and mortality risk in adults with T2D [104,105].

Moreover, physically active adults with T2D were reported to have a similar mortality risk as physically inactive adults without T2D [106].

When T2D cannot be managed with lifestyle change alone, antihyperglycemic therapy is typically prescribed. Approximately 84% of adults with T2D manage their disease with medication [88]. Antihyperglycemic agents act by either slowing digestion of carbohydrates (alpha-glucosidase inhibitors), increasing insulin secretion (DPP-4 inhibitors, GLP-1 receptor agonists, sulfonylureas and meglitinide), increasing peripheral glucose uptake (insulin, metformin and TZDs), or decreasing hepatic glucose output (insulin, metformin and TZDs) [90]. Metformin is typically the initial drug prescribed due to evidence that it is effective in lowering blood glucose, associated with relatively few side effects, has a low risk of causing hypoglycemia, and is weight neutral [90]. Despite the ability of insulin and sulfonylureas to also be effective for lowering blood glucose, both are associated with weight gain and a higher risk of hypoglycemia compared to the other drug classes. As well, some studies report that rosiglitazaone (TZD) is associated with increased risk of congestive heart failure, fractures, and myocardial infarction [90].

The association between antihyperglycemic therapy and glycemic control on mortality risk is not established. For example, achieving glycemic control has been associated with lower mortality risk in adults with T2D [107,108], yet there is evidence that intensive glucose lowering therapy may lead to increased mortality risk [109,110]. There is also evidence that some antihyperglycemic medications may be associated with increased mortality risk despite improving glucose control [111,112]. Of the TZD drug class, rosiglitazone has been associated with an increased mortality risk compared to pioglitazone [111], as well as other classes of antihyperglycemic agents [112]. It has also been suggested that sulphonylureas may be associated

with an increased mortality risk [113,114]. There is also inconsistent evidence as to whether adults with controlled T2D have a similar mortality risk as adults without T2D [106,115–117].

Thus, in adults with T2D, PA is associated with lower HbA1c and mortality risk [102]. Although most medications for T2D are associated with improved glycemic control, intensive glucose lowering treatment, and some T2D medications, have been associated with higher rates of hypoglycemia and mortality [90,110,111]. However, the joint association between PA, antihyperglycemic medication, and glycemic control on mortality risk in adults with and without T2D is not known.

2.8 Hypertension Management

Obesity is also a significant risk factor for hypertension [37]. Hypertension is a chronic disease that is characterized by a high pressure of blood in the arteries (≥140/90 mmHg), and is a significant risk factor for heart disease and stroke [89]. The prevalence of hypertension is estimated to be 22% in Canadian adults [118] and 30% in U.S. adults [119]. During the past two decades in the United States and Canada, the prevalence of hypertension has remained stable, although the proportion of adults treated with antihypertensive therapy, and those that obtained blood pressure control, has significantly improved [89,118]. Despite a higher proportion of adults with hypertension receiving antihypertensive treatment and obtaining blood pressure control, hypertension is still the leading risk factor for disease burden globally [2], and the fourth leading risk factor for disease burden in North America [42].

The goal of hypertension management is to attain and maintain blood pressure control (<140/90 mmHg), which can be achieved through lifestyle changes and pharmacotherapy [120]. Non-pharmacological treatments, such as diet and PA, are the first line of treatment for patients with hypertension [120]. According to the Canadian Hypertension Education Program guidelines,

adults with hypertension are advised to consume a diet that is high in fruits, vegetables, whole grains, lean meats, and low-fat dairy, to limit foods high in saturated fat and cholesterol, and to consume no more than 2000 mg of sodium/day [121]. They also recommend engaging in moderate or vigorous PA for 30-60 minutes 4-7 days/week [121]. Physical activity in adults with hypertension is associated with lower blood pressure, reduced adiposity and inflammation, enhanced endothelial function, improved baroreflex sensitivity, regression of left ventricular hypertrophy, blood glucose control, improved lipid profile, and lower risk of cardiovascular events [122,123]. In middle-aged and older males with hypertension, a single 45 minute bout of aerobic exercise reduced systolic blood pressure by up to 13 mmHg 16 hours post-exercise, with an average reduction of 7.3 mmHg 24 hours post-exercise [124]. Furthermore, chronic aerobic exercise lasting at least 4 weeks is associated with an average reduction of 6.9/4.9 mmHg in adults with hypertension, likely due to a decrease in systemic vascular resistance [125]. Participation in regular moderate or vigorous activity is also associated with significantly lower cardiovascular and all-cause mortality risk, even after adjusting for blood pressure [126] or antihypertensive treatment [127]. Even a modest amount of PA of at least twice a week for 30 minutes was associated with a 35% lower risk of all-cause mortality, and new-onset diabetes in adults with hypertension [128].

When high blood pressure cannot be managed with lifestyle change alone, antihypertensive therapy is typically prescribed. Pharmacotherapy for hypertension is often referred to as one of the major successes of modern medicine [129], and approximately 76% of adults with hypertension take antihypertensive medication to help manage their disease [89]. Antihypertensive agents typically lower blood pressure by either decreasing extracellular fluid and blood volume (thiazide diuretics), causing vasodilation of vasculature (calcium channel

blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers), reducing heart rate and cardiac output (beta-blockers), or by reducing total peripheral resistance (alpha-adrenergic blockers) [130–132]. Beta-blockers and alpha-blockers are not recommended for initial treatment because they have been associated with higher risk of cardiovascular events compared to the use of initial therapy with an angiotensin receptor blocker [133], and a diuretic [134], respectively. A meta-analysis of different blood pressure lowering regimens concluded that any common antihypertensive medication was associated with reduction in risk of CV events compared to placebo [135], however, it is uncertain if pharmacological treatment of hypertension is also associated with lower risk of premature mortality [129].

Studies investigating the association between antihypertensive treatment and blood pressure control on mortality risk show equivocal results [136–140]. A recent systematic review that investigated the effects of antihypertensive treatment on adults with mild hypertension (systolic blood pressure 140-160 mmHg or diastolic blood pressure 90-100 mmHg) found that treatment for 5 years did not reduce coronary heart disease, stroke, or total cardiovascular events compared to placebo [141]. Interestingly, in over 10 years of follow-up in the Reykjavik Study, males with untreated hypertension had a *lower* risk for myocardial infarction, CVD, and all-cause mortality compared to males with treated hypertension, with no differences between treated and untreated females [142]. Conversely, data from NHANES indicates that adults with hypertension who are treated and uncontrolled, and untreated and uncontrolled, had a 57% and 34% higher all-cause mortality risk, respectively, compared to adults with hypertension who are both treated and controlled [137]. However, PA, which is also associated with lower mortality risk in hypertension [143], was not assessed.

Thus, PA is associated with lower blood pressure and mortality risk in adults with hypertension. Although antihypertensive therapy is associated with improved blood pressure control, the association between antihypertensive therapy and blood pressure control on mortality risk is not consistent. As well, the joint association between PA, antihypertensive therapy, and blood pressure control is not known.

2.9 Summary, Objectives and Hypotheses

In summary, although PA is associated with improved health outcomes and lower mortality risk in all age groups [144], it is not known if the association between PA and mortality risk is consistent across the adult age span. For both T2D and hypertension, PA and pharmacotherapy are recommended to help achieve blood glucose control [90], and blood pressure control [121], respectively. However, the joint association of PA, pharmacotherapy, and metabolic control on mortality risk is not known for either disease. Physical activity is also recommended for weight loss and weight maintenance [14], and in order to manage weight one should be able to accurately estimate exercise energy expenditure and energy intake [6]. Despite the potential importance of calorie estimation for weight management, whether or not the ability to accurately estimate calories during exercise and in food is influenced by BMI, weight loss status, or exercise intensity, is not known. Finally, although BMI is the most widely used indicator of obesity, WC is now established as a simple and reliable measure of health risk independent of overall obesity [9]. Yet, there is currently no universal WC measurement landmark, it is not clear whether adults are able to accurately self-measure their WC at common WC measurement sites, and it is not known which WC measurement sites adults naturally measure, or find easiest or most difficult to measure. Therefore, the objectives of this dissertation were:

Objective 1: To determine if the association between frequency of weekly PA and mortality risk differs among middle-aged, old, and very old adults.

Hypotheses: A) Physical activity 1-2 times per week will be associated with a lower all-cause mortality risk compared to no PA in all age groups. B) In old and very old adults, a higher frequency of PA will be associated with a lower mortality risk compared to a lower frequency of PA.

Objective 2: To determine the joint association between PA, antihyperglycemic therapy, and blood glucose control on cardiovascular and all-cause mortality risk in adults with and without T2D.

Hypotheses: A) Adults with T2D who are physically active, treated, and controlled will have a lower mortality risk compared to physically inactive adults regardless of treatment or control. B) Adults with T2D who are physically active, treated, and controlled will have a higher mortality risk compared to adults without T2D.

Objective 3: To determine the joint association of PA, antihypertensive treatment, and blood pressure control on all-cause mortality risk in adults with and without hypertension.

Hypotheses: A) Adults with hypertension who are physically active, treated, and controlled will have a lower all-cause mortality risk compared to adults with hypertension who are physically inactive regardless of antihypertensive treatment or blood pressure control. B) Adults with hypertension who are physically active, treated, and controlled will have a higher mortality risk compared to adults without hypertension.

Objective 4: To determine if body weight class, weight loss status, or exercise intensity is associated with accuracy of estimated exercise energy expenditure, and calories in a meal.

Hypotheses: A) Regardless of body weight class or weight loss status, all adults will overestimate vigorous intensity exercise energy expenditure to a greater extent than moderate intensity exercise energy expenditure. B) Regardless of body weight class or weight loss status, all adults will underestimate calories in a meal. C) Adults who are overweight and not attempting weight loss will have a greater error in calorie estimation compared to normal weight adults who are and are not attempting weight loss, and overweight adults who are attempting weight loss.

Objective 5: To determine A) If normal weight and overweight/obese adults are willing to self-measure their WC, B) Which WC measurement site(s) adults naturally measure, C) Which WC site(s) adults find easiest or hardest to self-measure, D) If adults are able to accurately self-measure their WC at five common WC measurement sites, and E) If the association between WC and blood pressure differs according to WC measurement site.

Hypotheses: A) The majority of adults will not be willing to self-measure their WC, B) Adults will naturally measure their WC most often at the umbilicus, C) Adults will find the midpoint the most difficult site to self-measure, D) Overweight and obese adults will be less accurate at self-measuring their WC compared to normal weight adults, and E) The association between blood pressure and WC will not be influenced by WC measurement site.

Chapter 3. Manuscript 1: The Association between Frequency of Physical Activity and Mortality Risk across the Adult Age Span

This manuscript has been published in the ***Journal of Aging and Health***. The co-authors of this manuscript are Michael C. Riddell, Alison K. Macpherson, Karissa L. Canning, and Jennifer L. Kuk. Ruth Brown and Jennifer Kuk designed the study. Ruth Brown performed the statistical analyses and wrote the manuscript. Michael Riddell, Alison Macpherson, Karissa Canning and Jennifer Kuk critically revised the manuscript.

Citation: Brown RE, Riddell MC, MacPherson AK, Canning KL, Kuk JL. The association between frequency of physical activity and mortality risk across the adult age span. *Journal of Aging and Health* 2013, 25(5):803-14.

Abstract

Objectives: To determine if the association between frequency of leisure-time PA and mortality risk differs across adulthood. **Methods:** 9249 adults from the NHANES III (1988-1994) were categorized as middle-aged (40-64y), old (65-79y) or very old (≥80y), and as inactive (0 bouts of physical activity/week), lightly active (1-2 bouts/week), moderately active (3-4 bouts/week) or very active (5+ bouts/week). **Results**: In all age categories, lightly, moderately, and very active adults had a lower mortality risk compared to inactive adults ($p<0.001$). In very old adults only, being very active was associated with a lower mortality risk compared to being lightly active (HR 0.80, 95% CI 0.64-0.98; $p=0.03$) and moderately active (HR 0.80, 95% CI 0.65-0.98; ($p=0.03$). **Discussion**: The association between PA frequency and mortality risk is strongest in very old adults. All adults and particularly very old adults may benefit from participating in PA five or more times a week.

Key Words: Aged, 80 and over; Leisure Activities; Survival; Age Groups

Introduction

Physical activity is associated with many health benefits, including decreased risk of CVD, T2D, hypertension, dyslipidaemia, and lower mortality risk [13]. Active individuals have been reported to have a 30% lower mortality risk during follow-up compared to inactive persons, with inverse associations between PA and mortality risk also being observed in the older adult population (Physical Activity Guidelines Advisory Committee, 2008), and a handful of studies demonstrating this association in very old adults [31–33]. Many studies that have examined the relationship between PA and mortality risk have looked at volume of PA, and there is a paucity of studies that have directly examined the association between frequency of PA and mortality risk [18]. Prior studies that have looked at PA frequency have reported that in older adults, participation of PA once or just a few times a week is associated with lower mortality risk compared to being physically inactive [19,20]. Although few studies have examined the association between PA and mortality risk at different stages of adulthood, those that have generally show that PA is associated with lower mortality risk in both younger and older adults [24,25]. However, prior research only compared low to high PA, and did not include a very old age group, which is a population that is expected to steadily increase [29]. Individuals of various ages are at risk for different health problems, and because PA has differential effects on the various aspects of health, the association between PA and mortality risk may differ by age. In particular, PA is strongly associated with improved physical functioning in very old adults [30], a factor that is important for this age group. Thus, older adults may be a population that particularly benefit from participating in PA compared to younger age groups. Therefore, the objective of this study was to determine if the association between the frequency of PA and mortality risk differs among middle-aged, old and very old adults.

Methods

Participants

Data for the NHANES III was collected on a national sample of 33, 994 individuals' aged two months and older in the United States between 1988 and 1994. A detailed explanation of the data collection methods has been previously reported [145,146]. Mortality information for NHANES III survey participants was provided by the National Centre for Health Statistics using probabilistic record matching with death certificate data found in the National Death Index (NCHS Linked Mortality File) through December 31, 2006. All survey participants gave written informed consent prior to participation, and the methods were approved by the National Centre for Health Statistics. Subjects were excluded from this analysis if they were younger than 40 years old, died within the first year after they were sampled, or had missing information for PA, CVD, T2D, or lipid medications, doctor's diagnosis of CVD or T2D, BMI, self-rated health status, or self-reported mobility impairment. The final sample size was 9,249.

Questionnaires and Physical Examination

Monthly PA was assessed with questionnaires. Participants were asked if they performed the following activities in the last month: walking one mile without stopping, biking, jogging, swimming, dancing, aerobics, calisthenics, gardening, and weight lifting. They could also list up to four additional activities. Information on the monthly frequency of the activity as well as the intensity of the activity was recorded, and each activity was assigned a metabolic equivalent value. Only activities that were at least a moderate intensity (metabolic equivalent ≥ 3), for example walking or gardening, were included in the analysis. Activity was divided into inactive (0 bouts/week), lightly active (1-2 bouts/week), moderately active (3-4 bouts/week) and very active (5 or more bouts/week). Questionnaires were also used to assess age, sex, education (less

than high school, high school, more than high school), ethnicity (white or non-white), smoking status (past smoker, current smoker, never smoker), BMI based on self-reported height and weight, medications (CVD, T2D, lipid), self-reported doctor's diagnosis of hypertension, heart attack, stroke, congestive heart failure and T2D, as well as self-reported health status and mobility impairment.

Age was classified into: middle-aged (40-64 years), old (65-79 years), and very old (80+ years). Participants were classified as having CVD if they reported a diagnosis of hypertension, heart attack, stroke, or congestive heart failure, if they were taking any CVD medications or blood pressure medications, or if they had a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg. Participants were classified as having T2D if they reported a doctor's diagnosis of T2D, if they reported taking diabetes medications, or if they had a fasting blood glucose level of ≥7.0 mmol/L. Participants were considered dyslipidaemic if they reported taking any lipid medications, if fasting total cholesterol was ≥6.2 mmol/L, or if fasting triglycerides were ≥2.3 mmol/L. Self-rated health status was reported as excellent, very good, good, fair, or poor. Participants were classified as having a mobility impairment if they reported any difficulty with walking from room to room on one level, rising from an armless chair, or if they reported using any device to help them move, such as a cane, walker, or wheelchair.

Statistical Analyses

One-way analysis of variance was used to assess baseline differences between activity groups with inactive as the referent with Bonferroni-adjusted post-hoc analyses. Chi-square tests were used to assess baseline group differences in the categorical variables. Linear and logistic regressions were used to assess trends for differences in subject characteristics across PA levels within each age category and across age categories within each PA level. Hazard ratios for

group differences in mortality risk were estimated by Cox proportional hazard analyses for all ages combined in order to explore interactions between PA, age and sex, and for all age categories separately to determine relative mortality risk within an age group. Bonferroni adjustments were used for all post hoc comparisons. The first multivariable model was adjusted for age, sex, education, ethnicity, and smoking status, and the final fully adjusted model included these variables in addition to CVD, T2D, dyslipidaemia, BMI, self-reported health status, and mobility impairment. All analyses were sample weighted to be representative of the US population and were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). Statistical significance was considered at $P < 0.05$.

Results

Subject characteristics are presented in **Table 3.1** stratified by PA level and age category. More women were inactive than men within all age groups. There were no differences in the prevalence of dyslipidaemia across physical activity groups within each age category. There was a trend for higher prevalences of CVD, T2D, and mobility problems with decreasing PA level at all ages ($P_{trend} <= 0.001$). Body mass index decreased with increasing PA level within all age groups ($P_{trend} <= 0.001$). For all ages, self-rated health tended to be good or excellent with increasing levels of PA, and fair or poor with decreasing levels of PA ($P_{trend} <= 0.001$). There was a trend for higher prevalence of CVD, T2D, mobility impairment, and white ethnicity with increasing age within each PA level ($P_{trend} <= 0.001$). Education level, BMI, and self-rated health declined with age within each PA level ($P_{trend} <= 0.001$).

During the follow-up of 12.1 ± 4.5 years, there were 3,738 deaths (40%). Results for the first multivariable model and the fully adjusted second model were similar, thus results are only presented for the fully adjusted model. In the analysis with all ages combined, age and PA level

were both independently associated with mortality risk ($P < 0.001$). There was no significant interaction between sex and activity level ($P = 0.86$), however there was a significant age by PA level interaction for mortality risk ($P = 0.04$). Thus, when stratified by age category, lightly active (middle-aged: HR 0.71, 95% CI 0.54-0.94; old: 0.77, 0.63-0.93; very old: 0.73, 0.59-0.90; $P < 0.05$), moderately active (middle-aged: 0.59, 0.81-0.86; old: 0.81, 0.67-0.97; very old: 0.73, 0.58-0.92; $P < 0.05$), and very active individuals (middle-aged: 0.72, 0.55-0.96; old: 0.73, 0.60-0.89; very old: 0.59, 0.47-0.73; $P < 0.05$) had a lower mortality risk compared to inactive within each age category (**Figure 3.1**). In the very old adults only, very active also had a lower mortality risk compared to lightly active (0.80, 0.64-0.99; $P = 0.03$) and moderately active (0.80, 0.65-0.98; $p = 0.03$) **(Figure 3.1).**

Discussion

We observed that in a nationally representative U.S. sample of middle-aged, old, and very old adults, participating in moderate-vigorous PA one time a week or more is associated with a lower mortality risk compared to being completely inactive. However, this is the first study to show that very old adults who participate in moderate-vigorous PA five or more times per week have a significantly lower mortality risk compared to very old adults who are physically active but participate in a lower frequency of PA. Thus, in agreement with the previous PA guidelines, these results suggest that all adults and in particular very old adults should be encouraged to participate in PA five or more times/week.

Despite the known health benefits of regularly participating in PA, in 2008, ~25% of the overall US adult population and ~32% of U.S. older adult population participated in no leisure time PA [147]. Physical inactivity is a known contributor to many chronic diseases in older Americans including vascular disease, T2D and some forms of cancer [34], and medical costs are

higher for inactive adults than active adults [148]. Accordingly, adults who meet the 2008 Physical Activity Guidelines have a lower mortality risk compared to adults who did not meet the guidelines [149]. However, one study reported that older adults who were physically active even once per week were at a lower mortality risk compared to inactive older adults [19]. Our study confirms these observations by demonstrating that even very low levels of PA are associated with lower mortality risk in all adults, but extends these findings in that engagement in higher frequencies of PA is associated with even lower mortality risk in adults 80 years or older. Beneficial effects of PA on mortality risk in very old adults have been observed in several other studies [30,150,151]. Among individuals without heart disease, the volume of PA is associated with a greater benefit on mortality risk for adult's ≥ 75 years, compared to those < 75 years [152]. Due to the natural deterioration of health that is associated with aging, older adults are much more likely to be at risk for health problems which may be preventable by PA (i.e. vascular disease, diabetes, respiratory disease and cancer). Together, this suggests that being physically active in late adulthood may be associated with greater declines in mortality risk than being physically active in early or middle adulthood.

Although the present analysis was able to assess PA levels using intensity and frequency of PA, information on duration of activity was not available. The volume of PA is most commonly used to prescribe PA [147], and the most current guidelines no longer give a recommended frequency for PA. In the present study, a frequency of PA of five times a week or greater was associated with a 27% lower mortality risk for very old adults. Although we cannot discount that the beneficial effect of a higher PA frequency is due to a higher volume of PA, there is evidence that elderly men who expend the recommended ≥ 1000 kcal/week in just one or two days ("weekend warriors") still have a higher mortality risk compared to those who

accumulate ≥ 1000 kcal/week but are regularly active throughout the week [153]. Additionally, it has been reported that even one acute bout of exercise can significantly reduce blood pressure up to 16 hours, blood glucose for several days, and triglycerides up to 72 hours post exercise, with the effects usually being greatest in high risk or diseased populations [95]. Thus, a higher frequency of PA may make it more likely that the individual chronically benefits from the acute effects of PA. Therefore, at least in older adults, frequency of PA perhaps should be considered when prescribing PA.

Despite findings that adults ≥ 80 years can benefit from PA, there is evidence that very old adults participate in less PA than middle-aged and old adults [154]. Older adults may have additional barriers that prevent them from exercising, such as a greater number of co-morbidities [155], fear of injury [156], and they may not agree with some of the PA recommendations [157]. Thus, the issue of addressing the higher rates of physical inactivity in this age group may be more complex than other populations.

Several limitations of this analysis warrant mention. This study used prospective observational data and therefore no causal relationships can be determined. It may be that adults who did not participate in any activity were in poorer health to begin with, which was evident by the higher prevalence of co-morbidities, lower self-reported health, and higher mobility impairment in the inactive groups at any age. However, it is important to note that even after accounting for the effect of poor health by adjusting for common metabolic health disorders (CVD, T2D and dyslipidaemia) as well as self-rated health status and mobility impairment, the significant association between PA and a decreased mortality risk was still present. We also limited analyses to only those individuals who were still alive at least one year after their information was collected to minimize potential bias of poor health leading to decreased PA.

Nevertheless, our data does not account for differences in the severity of these conditions and may have contributed to the differences observed here. Further, given the large age range of our cohort, we cannot exclude the possibility that differences in education, norms regarding behaviors or other unknown factors may have influenced the results here. We have attempted to adjust for some of these factors by adjusting for education and ethnicity, but cannot ignore that there may be secular or cohort differences in how these factors influenced the associations observed in the present study. Another limitation was that PA was only evaluated for the month prior to the survey interview, and lifetime PA patterns were not known. However, there is evidence to suggest that there is no modifying effect of past PA on the association between current activity and mortality risk in adults [152]. Still, we cannot preclude that individuals may have altered their PA patterns after our assessment. However, these changes in PA patterns would likely result in an underestimation in the importance of PA observed in this study.

In conclusion, across adulthood engaging in any number of moderate to vigorous PA bouts per week is associated with significantly lower mortality risk compared to being completely inactive. However, in adults 80 years and older, engaging in PA five or more times/week was associated with an even lower mortality risk. Therefore, although PA may be beneficial for all ages, the association between PA frequency and mortality risk is strongest in very old adults. Thus, in accordance with the previous PA guidelines, all adults, and in particular very old adults may benefit from participating in PA five or more times a week.

Table 3.1. Baseline characteristics of 9249 adults from the NHANES III (1988-1994) Survey stratified by physical activity level and age category.

PA level	**Inactive**	**Light**	**Moderate**	**Very Active**
Middle-aged				
Total (N=5311)	1119 (21)	1416 (27)	803 (15)	1973 (37)
Age (y)	52.3 ± 7.6	51.2 ± 7.7	51.3 ± 7.7	51.7 ± 7.8*
Males	420 (37)	671 (47)	404 (50)	1067 (54)*
BMI (kg/m^2)	28.9 ± 6.4	28.3 ± 5.8	27.9 ± 5.5	27.5 ± 5.3*
Education				
< High school	625 (56)	585 (41)	244 (30)	580 (29)*
High school	316 (28)	476 (34)	284 (35)	616 (31)
> High school	177 (16)	355 (25)	275 (34)	777 (40)*
White Ethnicity	305 (27)	576 (41)	405 (50)	952 (48)*
Smoking Status				
Never	461 (41)	577 (41)	329 (41)	809 (41)
Past	267 (24)	390 (28)	257 (32)	644 (33)*
Current	390 (35)	449 (32)	271 (27)	520 (26)*
CVD	529 (47)	582 (42)	302 (37)	740 (38)*
T2D	172 (15)	201 (14)	96 (12)	189 (10)*
Dyslipidaemia	286 (26)	384 (27)	236 (29)	518 (26)
Deaths	283 (25)	234 (17)	114 (14)	307 (16)*
Self-rated health				
Very Good/Exc	227 (20)	477 (34)	336 (42)	932 (47)*
Good	391 (35)	554 (39)	298 (37)	697 (35)
Fair/Poor	500 (45)	385 (27)	169 (21)	344 (17)*
Mobility Impairment	169 (15)	87 (6)	45 (6)	82 (4)*
Old				
Total (N=2719)	703 (26)	508 (19)	379 (14)	1129 (42)
Age (y)	72.4 ± 4.3	71.4 ± 4.0	71.4 ± 4.0	71.4 ± 4.0*
Males	256 (36)	265 (52)	182 (48)	629 (56)*
BMI (kg/m^2)	28.4 ± 6.8	27.8 ± 5.3	27.4 ± 4.5	26.7 ± 4.5*
Education				
< High school	482 (69)	316 (62)	192 (51)	478 (42)*
High school	140 (20)	115 (23)	107 (28)	307 (27)
> High school	81 (12)	77 (15)	80 (21)	344 (30)*
White Ethnicity	311 (44)	270 (53)	247 (65)	765 (68)*
Smoking Status				
Never	309 (44)	233 (46)	174 (46)	486 (43)
Past	269 (38)	171 (34)	155 (41)	504 (45)
Current	125 (18)	104 (20)	50 (13)	139 (12)
CVD	507 (72)	325 (64)	258 (68)	684 (61)*

T2D	200 (28)	105 (21)	59 (16)	178 (16)*
Dyslipidaemia	196 (28)	165 (32)	112 (30)	335 (30)
Deaths	511 (73)	305 (60)	208 (55)	6245 (55)*
Self-rated health				
Very Good/Exc	103 (15)	141 (28)	134 (35)	482 (43)*
Good	210 (30)	183 (36)	136 (36)	338 (34)
Fair/Poor	390 (55)	184 (36)	109 (29)	259 (23)*
Mobility Impairment	330 (47)	91 (18)	61 (16)	171 (15)*
Very old				
Total (N=1219)	495 (41)	176 (14)	129 (11)	419 (34)
Age (y)	84.7 ± 3.1†	83.7 ± 3.1†	83.6 ± 2.6†	83.9 ± 3.1*†
Males	169 (34)	97 (55)	74 (57)	237 (56)*
BMI (kg/m^2)	25.1 ± 4.9†	25.5 ± 4.3†	25.3 ± 4.5†	24.8 ± 3.5*†
Education				
< High school	316 (64)	102 (58)	64 (50)	231 (55)*
High school	95 (19)	38 (22)	31 (24)	83 (20)
> High school	83 (17) †	36 (20) †	34 (26) †	105 (25)* †
White Ethnicity	391 (79) †	152 (86) †	110 (85)	364 (87) †
Smoking Status				
Never	291 (59) †	93 (53) †	73 (57) †	248 (60) †
Past	173 (35) †	73 (41) †	51 (39) †	148 (35) †
Current	30 (6) †	10 (6) †	5 (4) †	23 (5) †
CVD	366 (74) †	133 (76) †	95 (74) †	287 (69) †
T2D	82 (17) †	23 (13)	20 (16) †	57 (14) †
Dyslipidaemia	106 (21)	35 (20)	26 (20)	83 (20)†
Deaths	480 (97) †	164 (93) †	123 (95) †	384 (92)*†
Self-rated health				
Very Good/Exc	100 (20)	67 (38)	38 (29) †	165 (39)* †
Good	161 (33)	60 (34) †	49 (38)	133 (32) †
Fair/Poor	233 (47)	49 (28)	42 (33) †	121 (29)* †
Mobility Impairment	340 (69) †	63 (36) †	38 (29) †	142 (34)* †

* = significant trend across PA level within age group ($P < 0.05$). † = significant trend across age within a PA group ($P < 0.05$). BMI = body mass index; CVD = cardiovascular disease; Exc = excellent; PA = physical activity, T2D = type II diabetes. Values are means ± SD or n (%).

Figure 3.1

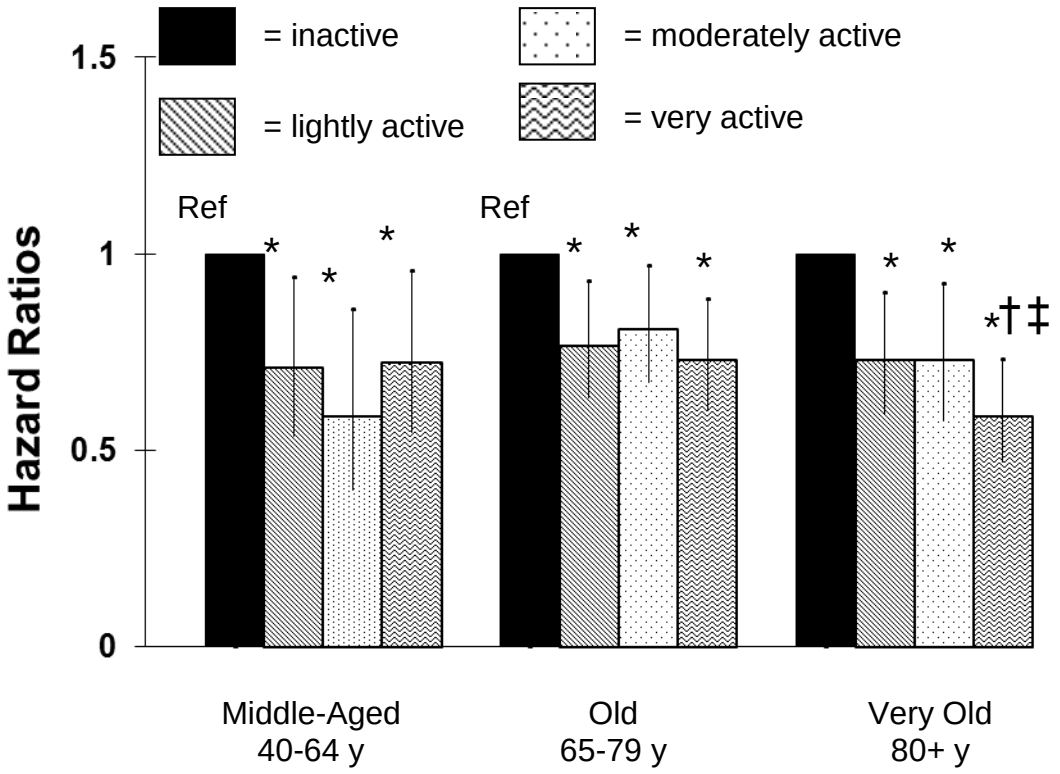

Figure 3.1. Hazard ratios for mortality risk in 9,249 adults from the NHANES III (1988-1994) survey stratified by age and physical activity level. Group comparisons were made between all physical activity levels within each age group. * = different from inactive within that age group ($P < 0.05$), † = different from lightly active within that age group ($P < 0.05$), ‡ = different from moderately active within that age group ($P < 0.05$). PA = physical activity.

Chapter 4. Manuscript 2: All-Cause and Cardiovascular Mortality Risk in U.S. Adults with and Without Type 2 Diabetes: Influence of Physical Activity, Pharmacological Treatment and Glycemic Control

This manuscript is published in **the *Journal of Diabetes and its Complications***. The co-authors of this manuscript are Michael C. Riddell, Alison K. Macpherson, Karissa L. Canning, and Jennifer L. Kuk. Ruth Brown and Jennifer Kuk designed the study. Ruth Brown performed the statistical analyses and wrote the manuscript. Michael Riddell, Alison Macpherson, Karissa Canning, and Jennifer Kuk critically revised the manuscript.

Citation: Brown RE, Riddell MC, MacPherson AK, Canning KL, Kuk JL**:** All-cause and cardiovascular mortality risk in U.S. adults with and without type 2 diabetes: influence of physical activity, pharmacological treatment and glycemic control. *Journal of Diabetes and Its Complications* 2014, 28(3): 311-315.

Abstract

Aims: This study determined the joint association between PA, pharmacotherapy, and HbA1c control on all-cause and cardiovascular mortality risk in adults with and without T2D. **Methods**: 12,060 adults from NHANES III and NHANES continuous (1999-2002) surveys were used. Cox proportional hazards analyses were included to estimate mortality risk according to physical activity, pharmacotherapy, and glycemic control (HbA1c <7.0%) status, with physically active, treated and controlled (goal situation) as the referent. **Results**: Compared to the referent, adults with T2D who were uncontrolled, or controlled but physically inactive had a higher all-cause mortality risk ($p < 0.05$). Compared to the referent, only adults with T2D who were physically inactive had a higher CVD mortality risk, regardless of treatment or control status ($p < 0.05$). Normoglycemic adults had a similar all-cause and CVD mortality risk as the referent ($p > 0.05$). **Conclusions:** Physical activity and glycemic control are both associated with lower all-cause and cardiovascular mortality risk in adults with T2D. Adults with T2D who are physically active, pharmacologically treated, and obtain glycemic control may attain similar mortality risk as normoglycemic adults.

Key Words: Leisure Activities; HbA1c; NHANES; Type 2 Diabetes Mellitus

Introduction

Type 2 diabetes is an established risk factor for myocardial infarction, stroke, lower extremity amputation, blindness, kidney failure, and premature mortality [88]. Cardiovascular disease is a major complication of T2D and is the leading cause of death in this population [88]. Type 2 diabetes affects 11.3% of the U.S. adult population, of which 84% are receiving antihyperglycemic therapy [88], with approximately half of adults and two thirds of older adults achieving glycemic control as defined as HbA1c <7.0% (53 mmol/mol) [158]. For the management of hyperglycemia, pharmacotherapy is recommended, as well as lifestyle modification, which includes participating in regular PA [159]. Physical activity has been reported to be associated with decreased baseline glycosylated hemoglobin (HbA1c) levels [97] and decreased mortality risk in individuals with T2D [160]. There is also substantial evidence that pharmacotherapy for T2D can significantly reduce HbA1c [161]. However, evidence regarding mortality outcomes of achieving a controlled HbA1c (<7.0% (53 mmol/mol), is equivocal, as some have reported lower mortality risk [107,108], no effect on mortality risk [162], as well as increased mortality risk [110,163]. There is also mixed evidence regarding if antihyperglycemic treatment lowers mortality risk to that of normoglycemic populations [115–117].

Although PA and pharmacological therapy are both recommended for T2D management, to our knowledge the joint association between PA, pharmacological treatment of T2D, and control of HbA1c with mortality risk has not been investigated. Therefore, the objectives of this study were to determine the joint associations between PA, antihyperglycemic treatment, and glycemic control on all-cause, and CVD mortality risk.

Methods

Participants

Data was obtained from persons in the United States who participated in the NHANES III survey (1988-1994; n = 33 994), and NHANES Continuous surveys 1999-2000 (n = 9 965) and 2001-2002 (n = 11 039). A detailed explanation of the data collection methods has been previously reported [145,146,164]. Mortality information for NHANES III and NHANES Continuous survey participants was provided by the National Centre for Health Statistics using probabilistic record matching with death certificate data found in the National Death Index (NCHS Linked Mortality File) through December 31, 2006. All participants gave written informed consent prior to participation, and the methods were approved by the National Centre for Health Statistics. The total number of participants from all three surveys was 54 998. Individuals were excluded if they were considered to have type 1 diabetes as defined as self-report diagnosis of diabetes before the age of 30 and taking insulin since diagnosis [108] (n=148), if they were younger than 40 years (n = 36 910), or if they had missing information for HbA1c (n=22 287), or years since diagnosis for adults with T2D (n=1 562), leaving a final sample size of 12 060 men and women for this sample.

Questionnaires and Physical Examination

During the physical examination, height and weight were measured by a trained technician and BMI was calculated. HbA1c was measured using blood samples via venipuncture and plasma glucose was measured after a 6-12 hour fast during the physical examination. In NHANES III only, an oral glucose tolerance test was conducted in mobile center examinees over the age of 40 years. Use of any prescription medications was reported during the household

interview and T2D drugs were identified. Individuals reported if they had a doctor's diagnosis of T2D, and the length of time since diagnosis.

Physical activity in NHANES III was assessed as the monthly frequency of the following activities: walking, jogging, biking, swimming, calisthenics, gardening, weight lifting, aerobics, and dancing. Participants could also list up to four additional activities. In the NHANES continuous surveys, respondents reported PA frequency in terms of the number of times per day, week, or month, as they preferred. Participants were asked about transportation, home or yard physical activity, or any other moderate or vigorous leisure time activity. For the purpose of this analysis, monthly PA from all questionnaires was converted to weekly PA. Since it has been shown that engaging in PA just once a week is beneficial for mortality risk [19,20], physically active was defined as participating in ≥1 time/week of physical activity, and physical inactivity was defined as participating in no weekly physical activity.

Questionnaires were used to assess age, sex, education (less than high school, high school, more than high school), ethnicity (white or non-white), and smoking status (current, past, or never). Individuals were considered hypertensive if they had self-reported doctor's diagnosis of hypertension, if they were taking antihypertensive medications, if their systolic blood pressure was ≥ 140 mmHg (> 130 mmHg if had T2D), or if their diastolic blood pressure was ≥90 mmHg (> 80 mmHg if had T2D). Type 2 diabetes was defined as self-reported doctor's diagnosis of T2D, or taking antihyperglycemic drugs, or having an HbA1c of ≥ 6.5% (48 mmol/mol), or a fasting plasma glucose of > 7.0 mmol/L, or a 2-hour plasma glucose of > 11.0 mmol/L after an oral glucose tolerance test. Individuals were considered dyslipidaemic if they were taking lipid medications, if their fasted cholesterol was ≥ 6.2 mmol/L, or if their fasted triglycerides were ≥ 2.3 mmol/L. History of CVD was defined as having a doctor's diagnosis of coronary heart

disease, or prior diagnosis of a heart attack or stroke. For the purpose of this analysis, acceptable glucose control was defined as an HbA1c <7.0 % (53 mmol/mol), while ≥ 7.0 % (53 mmol/mol) was the criterion for uncontrolled glucose. Individuals were classified as either being treated or not being treated with antihyperglycemic drugs. Death was categorized as all-cause, or CVD (ICD-10 codes 53-75).

Statistical Analyses

Group differences in subject characteristics were determined with one-way analysis of variance (ANOVA) and chi-square tests. Cox proportional hazards were used to estimate differences in all-cause and CVD mortality risk, according to physical activity level, antihyperglycemic treatment and HbA1c control. The proportional hazards assumption was verified for all models. Adults with T2D who were physically active, treated and controlled (goal situation) was the referent group. In a separate model hazard ratios stratified by glycemic control were adjusted for HbA1c to determine if baseline HbA1c differed between treatment and physical activity groups. Multivariate analyses were adjusted for age, sex, education, ethnicity, and smoking status in the first model, and then additionally adjusted for dyslipidaemia, CVD, hypertension, BMI, and years since diagnosis in the final, fully adjusted models. All statistical analyses were performed with SAS vs. 9.3 and results were considered statistically significant at $p < 0.05$.

Results

The average follow-up time was 9.2 ± 4.9 years, during which there were 3306 (27.4%) all-cause deaths, of which 45.6% were CVD related (n = 1509). Subject characteristics according to PA status, glycemic control, and antihyperglycemic treatment are presented in **Table 4.1**. There were 1511 (12.5%) adults with T2D, wherein 46% participated in PA at least

once a week, 43% had glycemic control (HbA1c < 7.0%), and 71% were pharmacologically treated. The average number of years since T2D diagnosis was 10.9 ± 8.8 years. Adults with T2D, who were physically active, treated and controlled, had a higher HbA1c and BMI, and a higher prevalence of hypertension and CVD than normoglycemic adults ($p < 0.05$). All results were similar between the first multivariable model and the fully adjusted model for all-cause and CVD mortality, and thus only results for the fully adjusted models are reported. There were no interaction effects between physical activity, antihyperglycemic treatment, or HbA1c control for all-cause or CVD mortality ($p > 0.05$ for all).

There was a significant main effect of being physically active (all-cause HR, 95%CI= 0.71, 0.66-0.76, $p < 0.001$; CVD 0.64, 0.58-0.72, $p < 0.001$), and having glycemic control (all-cause 0.73, 0.63-0.86, $p < 0.001$; CVD 0.73, 0.58-0.93, $p < 0.01$) but not antihyperglycemic medication usage (all-cause 1.12, 0.96-1.31, $p = 0.14$; CVD 1.18, 0.94-1.47, $p = 0.16$). Adjustment for HbA1c within HbA1c control strata did not alter the significant effects of physical activity and antihyperglycemic treatment on all-cause or CVD mortality risk.

The hazard ratios for all-cause (**Figure 4.1**) mortality risk are presented by PA, antihyperglycemic treatment, and HbA1c control. Compared to adults with T2D who were physically active, treated and controlled (goal referent), adults with T2D who were uncontrolled, regardless of physical activity or treatment status, or controlled but physically inactive, had a higher all-cause mortality risk ($p < 0.05$). Physically active, untreated and controlled adults with T2D, and normoglycemic adults, had a similar all-cause mortality risk as compared to the referent ($p > 0.05$) (**Figure 4.1**).

The hazard ratios for CVD (**Figure 4.2**) mortality risk are presented by PA, antihyperglycemic treatment, and HbA1c control. Compared to the referent, physically inactive

adults with T2D had a higher CVD mortality risk. Conversely, physically active adults had a similar CVD mortality risk, regardless of treatment or control status (P>0.05). Normoglycemic adults had a similar CVD mortality risk as the referent regardless of PA status (p > 0.05) (**Figure 4.2).**

Discussion

To our knowledge this is the first study to determine the joint association between PA, pharmacotherapy, and glycemic control for all-cause and CVD mortality risk in adults with and without T2D. The importance of PA was particularly evident for CVD mortality risk as adults with T2D who were physically inactive, regardless of treatment or control status, had a higher mortality risk compared to adults with T2D who were active, treated and controlled. Interestingly, the goal situation for T2D of being physically active, being pharmacologically treated, and having glycemic control had a similar mortality risk as normoglycemic adults. Altogether these results demonstrate the potential importance of PA and glycemic control in populations with T2D.

Several studies have shown an inverse association between PA and mortality risk in populations with T2D [99,160]. To our knowledge we are the first to assess this association in conjunction with treatment and glycemic control, and demonstrate that PA is independently associated with lower all-cause and CVD mortality risk. This occurred despite defining physically active as participating in *any* moderate or vigorous physical activity a week. However, several studies have shown that any amount of PA is associated with lower mortality risk compared to being physically inactive [19,20], including in adults with T2D [100,101]. The beneficial health effects of PA may be attributed to, but are not limited to, improved antioxidant and anti-inflammatory status [165], reduced hyperglycemica [166], increased exercise capacity and

muscle strength, as well as improved baroreflex sensitivity [167]. Physical activity is well known to improve CVD risk factors [123] as well as reduce risk of CVD and CVD related death in populations with T2D [101]. Our results further support the evidence of the benefits of PA for persons with T2D independent of pharmacological treatment, or glycemic control. Although there are clear benefits of physical activity for managing T2D, in the present study fewer adults with T2D were physically active compared to adults without T2D (46 vs 59%). Given the strong inverse association between PA and mortality risk, our results reinforce the positive benefits of participating in PA, particularly for adults with T2D.

Achieving glycemic control (HbA1c < 7.0% (53 mmol/mol)) is often the goal for T2D management as there is evidence that controlled T2D is associated with lower mortality risk and macrovascular and microvascular complications [107,168]. A recent investigation reported that independent of PA, uncontrolled HbA1c was associated with increased mortality risk compared to controlled HbA1c [169]. We further these observations in demonstrating that in adults with T2D, poor glycemic control, irrespective of PA or treatment status, was associated with higher all-cause mortality risk compared to those who were active, treated, and controlled. However, even when glycemic control was achieved, those who were physically inactive still had a higher all-cause mortality risk compared to active adults who were treated and controlled. Additionally, active adults with controlled T2D did not differ in mortality risk with treatment status. The individuals with controlled glycemic status, who reported a doctor's diagnosis of diabetes but no pharmacological treatment, were likely managing their diabetes through lifestyle management only [170]. Persons with T2D who were managing their disease with lifestyle only were reported to have had lower HbA1c compared to persons who were receiving pharmacological treatment [158], which is consistent with the results for glycemic control in the present study. Thus, in adults

with T2D, it appears that both being physically active and obtaining glycemic control is beneficial for mortality risk.

For adults living with T2D, being physically active is important, and many may require pharmacological treatment to attain glycemic control as most cannot achieve this with lifestyle alone. Indeed, individuals with T2D who were physically active, treated and controlled had a similar all-cause and CVD mortality risk compared to adults without T2D. Although other studies have reported an increased risk in all-cause [115,116] and CVD mortality [171] in adults with T2D, these studies did not specifically compare subgroups of individuals who differed in PA, pharmacological treatment, and glycemic control status. It was recently reported that adults with T2D who participate in as little as 1-2 hours a week of light PA achieve similar mortality risk as normoglyecmic adults [106].We extend these observations by showing that the subgroup of adults with T2D who were physically active, pharmacologically treated, and controlled had a similar mortality risk as normoglycemic adults. These results are encouraging given that they indicate that lifestyle modification and pharmacological treatment of diabetes may successfully lower mortality risk to that of normoglycemic populations. However, due to the observational design of this study, we cannot imply causation, and further research would be needed to confirm these findings.

The major strength of this study was the use of large samples of U.S. adults from the population-based NHANES surveys. As NHANES collects data on many health and lifestyle parameters, we were also able to show the independent associations of physical activity, as well as treatment and control of T2D, after adjusting for numerous health-related risk factors. Limitations of this study also warrant mention. The current study used prospective observational data and therefore no causation can be implied. Development of T2D, or any change, start or

discontinuation of medications after baseline is not known. All PA was self-reported, and lifetime PA patterns were not known. However, Bembom et al., (2009) reported that the association between PA level assessed at the time of the study and mortality risk is not modified by previous or lifetime physical activity levels [152]. We were also unable to apply sample weights to the analysis due to the combined use of NHANES III and continuous surveys. Thus, our results are not necessarily reflective of the U.S. population, but make our analysis no less internally valid. As well, we did not have a large enough sample size to examine if there were any differences in mortality risk between individuals on different classes of T2D medications.

In conclusion, both PA and glycemic control appear to be associated with lower all-cause and CVD mortality risk in adults with T2D. Since individuals with T2D tend to be less physically active than the general population, targeted efforts may be needed to increase PA among adults with T2D. In adults with T2D, PA, pharmacological treatment, and glycemic control was associated with a similar mortality risk as adults without T2D.

Table 4.1. Baseline characteristics of 12 060 adults from the NHANES III, and NHANES Continuous (1999-2000, 2001-2002) surveys.

	Controlled T2D				Uncontrolled T2D				Normoglycemic	
	Treated		Untreated		Treated		Untreated			
	Physically Active	**Physically Inactive**	**Physically Active**	**Physically Inactive**	**Physically Active**	**Physically Inactive**	**Physically Active**	**Physically Inactive**	**Physically Active**	**Physically Inactive**
Total	190 (1.6)	191 (1.6)	116 (1.0)	153 (1.3)	326 (2.7)	373 (3.1)	65 (0.5)	97 (0.8)	6230 (51.7)	4319 (35.8)
Age (years)	66.5 ± 11.3	69.1 ± 11.2	65.5 ± 12.5	67.5 ± 12.1	63.5 ± 11.1*	64.9 ± 11.6	63.0 ± 11.6	64.1 ± 11.5	59.5 ± 13.7*	62.0 ± 14.6*
Men	43.7	43.5	51.7*	37.9*	55.2*	41.0	60.0*	38.1*	52.2*	41.4
White	39.5	35.6	40.5	35.3	38.7	31.1	44.6	23.7*	41.0	36.9
Education										
< high school	79.0	82.7	70.7*	78.4	72.4	86.1*	73.8	84.5	63.9*	75.6
High school	13.7	10.5	13.8	13.1	16.3	8.6*	10.8	7.2*	16.8	14.8
> high school	7.4	6.8	15.5*	8.5	11.4	5.4	15.4*	8.3	19.3*	9.6
Smoking										
Never	44.8	46.6	44.8	47.7	48.5	50.1	38.5	54.6*	45.7	47.9
Past	45.3	41.9	37.1	33.3*	42.0	33.5*	41.5	29.9*	36.3	28.2*
Current	10.0	11.5	18.1*	19.0*	9.5	16.4	20.0*	15.5	18.0*	23.9*
HbA1c	6.2 ± 0.5	6.1 ± 0.5	5.9 ± 0.6*	5.9 ± 0.6*	8.9 ± 1.8*	9.1 ± 1.7*	9.0 ± 1.8*	8.9 ± 2.0*	5.4 ± 0.4*	5.4 ± 0.4*
HBP	82.6	89.0	75.9	82.4	79.5	79.1	75.4	80.4	47.4*	54.2*
CVD	23.7	36.1*	24.1	28.1*	19.6	25.5	15.4	29.9*	9.7*	12.9*
DYSLIPID	39.5	41.9	42.2	33.3	45.7	39.7	47.7	37.1	34.5	32.8
BMI (kg/m^2)	29.4 ± 4.9	29.8 ± 5.4	28.4 ± 4.6	28.7 ± 5.1	30.3 ± 6.0*	29.6 ± 5.0	28.3 ± 3.8	29.6 ± 5.2	27.5 ± 4.5*	28.0 ± 5.2*
Years since diagnosis	9.5 ± 8.9	10.4 ± 8.9*	9.0 ± 8.3	12.1 ± 9.5*	11.3 ± 8.1*	11.8 ± 8.9*	11.3 ± 9.7*	9.9 ± 8.4	NA	NA
Drug classes										
SU	136 (71.6)	127 (66.5)	NA	NA	204 (62.6)*	221 (59.3)*	NA	NA	NA	NA
TZD	11 (5.8)	10 (5.2)	NA	NA	29 (8.9)	20 (5.4)	NA	NA	NA	NA
Insulin	31 (16.3)	47 (24.6)*	NA	NA	108 (33.1)*	146 (39.1)*	NA	NA	NA	NA
Biguanide	47 (24.7)	37 (19.4)	NA	NA	69 (21.2)	61 (16.4)*	NA	NA	NA	NA
Deaths										

All-cause	68 (35.8)	85 (44.5)	52 (44.8)	81 (52.9)	132 (40.5)	166 (44.5)	30 (46.2)	45 (46.4)	1301 (20.9)	1346 (31.2)
CVD	30 (15.8)	40 (20.9)	22 (19.0)	42 (27.4)	57 (17.5)	80 (21.5)	12 (18.5)	20 (20.6)	567 (9.1)	639 (14.8)

* = significantly different from physically active, treated and controlled (Goal type 2 diabetes condition) ($p < 0.05$). BMI = body mass index; CVD = cardiovascular disease; HBP = high blood pressure; DYSLIPID = dyslipidemia; SU = sulphonylurea; TZD = thiazolidinedione. Values are means ± SD, N (%), or %. Note: row 1 is row %, all else are column %.

Figure 4.1

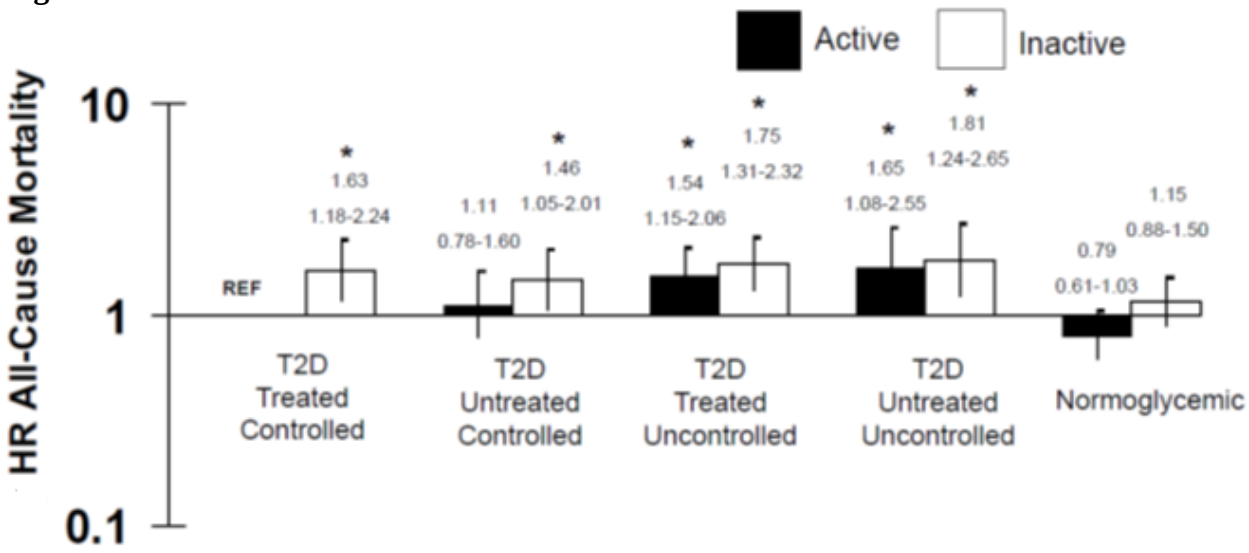

Figure 4.1. Hazard ratios and 95% confidence intervals for all-cause mortality risk according to physical activity level, antihyperglycemic treatment status and HbA1c control status. The model was adjusted for age, sex, education, ethnicity, smoking status, cardiovascular disease, hypertension, dyslipidemia, body mass index, and years since T2D diagnosis. HR = hazard ratio.

Figure 4.2

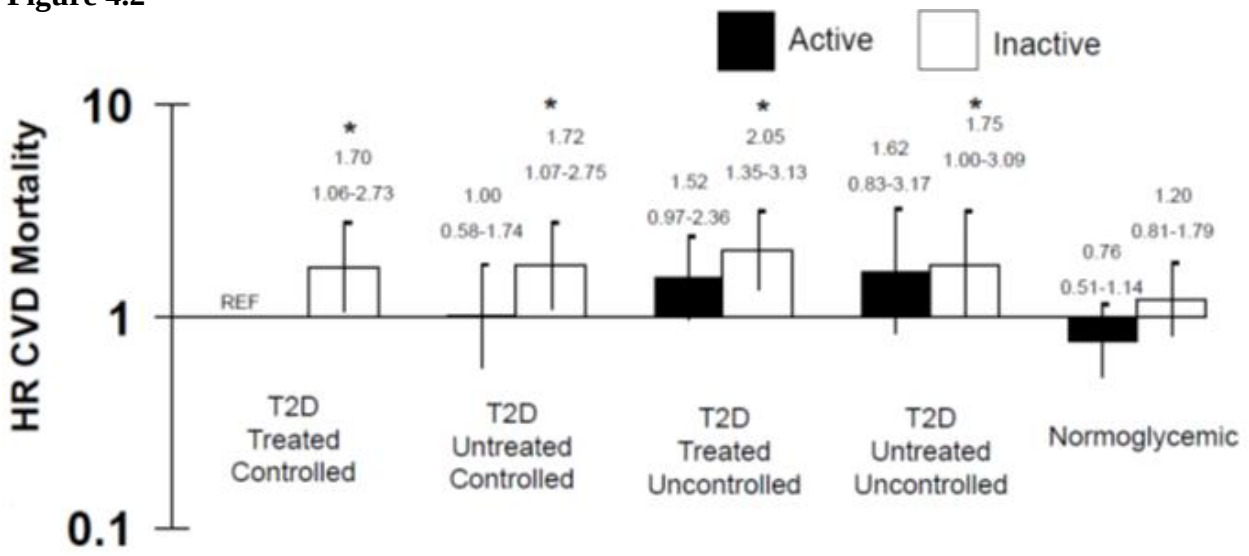

Figure 4.2. Hazard ratios and 95% confidence intervals for cardiovascular disease mortality risk according to physical activity level, antihyperglycemic treatment status, and HbA1c control status. The model was adjusted for age, sex, education, ethnicity, smoking status, cardiovascular disease, hypertension, dyslipidemia, body mass index, and years since T2D diagnosis. HR = hazard ratio.

Chapter 5. Manuscript 3: The Joint Association of Physical Activity, Blood Pressure Control, and Pharmacological Treatment of Hypertension for All-Cause Mortality Risk

This manuscript is published in the ***American Journal of Hypertension***. The co-authors of this manuscript are Michael C. Riddell, Alison K. Macpherson, Karissa L. Canning, and Jennifer L. Kuk. Ruth Brown and Jennifer designed the study. Ruth Brown performed the statistical analyses and wrote the manuscript. Michael Riddell, Alison Macpherson, Karissa Canning, and Jennifer Kuk revised the manuscript.

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Abstract

Background: The purpose of this study was to determine the joint association between PA, pharmacological treatment, and control of blood pressure on all-cause mortality risk. **Methods**: 10 665 adults from NHANES III and NHANES continuous (1999-2000 and 2000-2001) surveys were used. Cox proportional hazards analyses were used to estimate differences in mortality risk by PA, pharmacological treatment, and blood pressure control, with physically active, treated and controlled as the referent. **Results**: The average follow-up time was 8.6 ± 4.8 years. The main effect of PA was significant independent of pharmacological treatment and blood pressure control ($p<0.001$). Compared to physically active adults with treated and controlled hypertension, physically inactive adults with hypertension had a higher mortality risk (inactive, treated and controlled hypertension: HR 1.42, 95% CI 1.17-1.72, $p<0.01$; inactive, treated and uncontrolled hypertension: 1.55, 1.30-1.84, $p<0.01$; inactive, untreated, and uncontrolled hypertension: 1.27, 1.07-1.52, $p<0.01$), whereas physically active adults with hypertension did not significantly differ in mortality risk (active, treated and uncontrolled hypertension: 1.17, 0.98-1.40, $p=0.08$; active, untreated and uncontrolled hypertension: 0.90, 0.76-1.08, $p=0.25$). Physically active, normotensive individuals had a lower mortality risk compared to the referent (0.72, 0.60-0.86, $p<0.01$), whereas physically inactive, normotensive individuals had a similar mortality risk as the referent (1.08, 0.90-1.30, $p=0.42$). **Conclusions**: Physical activity may be as or even more important than pharmacotherapy for mortality risk in adults with hypertension. However, mortality risk remained higher than physically active normotensive populations. Thus, prevention of hypertension is imperative for reduction of premature mortality risk.

Key Words: Leisure Activities; Blood Pressure; Hypertension; NHANES; Mortality; Anithypertensive Agent

Introduction

Hypertension is an established risk factor for myocardial infarction, stroke, and premature mortality [89]. Hypertension affects approximately 30% of U.S. adults, of which 81% are aware of their condition, 76% are treated with antihypertensive medications, and only 53% of individuals with hypertension obtain blood pressure control targets of <140/90 mmHg [119]. For the management of hypertension, pharmacotherapy is recommended, as well as lifestyle modification, which includes participation in regular physical activity [120,159]. Physical activity has been shown to reduce blood pressure [122] and mortality risk [143] in hypertensive populations. There is also substantial evidence that pharmacotherapy for hypertension can significantly reduce resting blood pressure [172]. Achieving blood pressure control (<140/90 mmHg) has been associated with improved survival among hypertensive patients [136–138], yet some studies report that blood pressure control has no effect on mortality risk [139,140]. It is also unclear whether antihypertensive treatment lowers mortality risk to that of normotensive populations, with studies showing mixed results [136,173].

Although PA and pharmacological therapy are both recommended for hypertension management, to our knowledge the joint association between PA, pharmacological treatment of hypertension, and control of blood pressure with mortality risk has not been investigated. Therefore, the objectives of the study were to determine the joint associations between PA, antihypertensive treatment, and blood pressure control on mortality risk.

Methods

Participants

Data were obtained from persons in the United States who participated in the NHANES III survey (1988-1994; n = 33 994), and NHANES Continuous surveys 1999-2000 (n = 9965)

and 2001-2002 (n = 11039). A detailed explanation of the data collection methods has been previously reported [145,146,164]. Mortality information for NHANES III and NHANES Continuous survey participants was provided by the National Centre for Health Statistics using probabilistic record matching with death certificate data found in the National Death Index (NCHS Linked Mortality File) through December 31, 2006. All participants gave written informed consent prior to participation, and the methods were approved by the National Centre for Health Statistics. The total number of participants from all three surveys was 54 998. Individuals were excluded if they were younger than 40 years, or if they had missing information for PA, systolic or diastolic blood pressure, or hypertension medications, leaving a final sample size of 10 665 men and women.

Questionnaires and Physical Examination

Blood pressure was measured with a mercury sphygmomanometer according to the standardized blood pressure measurement protocols by the American Heart Association.[(17)] Blood pressure was determined as the average of six readings; three sets of measurements were taken by interviewers during the household questionnaire visit, and again by a physician during the physical examination. Use of any prescription medications was reported during the household interview and the names of the drugs were recorded. A pharmacist reviewed all reported medications and coded them into therapeutic classes (i.e. hypertension) for all three NHANES surveys.

Physical activity in NHANES III was assessed with a questionnaire that inquired about monthly frequency of the following activities: walking, jogging, biking, swimming, calisthenics, gardening, weight lifting, aerobics, dancing, and up to four additional activities. Each activity was assigned a metabolic equivalent score (MET) using a standardized coding scheme [174] and

only activities that were at least a moderate intensity (MET ≥ 3) were included in the analysis. In the NHANES continuous surveys, respondents answered questions about PA in terms of number of times per day, week, or month, as they preferred. The data were standardized to monthly frequency. Participants were asked about walking or biking as transportation to work, school or to run errands, if they had performed home or yard work that lasted at least 10 minutes and was at a moderate or vigorous effort, and if they had engaged in any moderate or vigorous leisure time activity. For the purpose of this analysis, monthly PA from all questionnaires was converted to weekly PA and only activities that were at least a moderate intensity [174] were included in the analysis. Since it has been shown that engaging in PA just once a week is beneficial for mortality risk [19,20], physically active was defined as participating in ≥1 time/week of PA, and physical inactivity was defined as participating in no weekly PA.

Questionnaires were used to assess age, sex, education (less than high school, high school, more than high school), ethnicity (white or non-white), and smoking status (current, past, or never). Self-reported height and weight were used to calculate BMI. Individuals were considered hypertensive if they had self-reported doctor's diagnosis of hypertension, if they were taking antihypertensive medications, or if their systolic blood pressure was ≥ 140 mmHg or if their diastolic blood pressure was ≥90 mmHg. T2D was defined as self-reported doctor's diagnosis of T2D, or taking antihyperglycemic drugs. Individuals were considered dyslipidaemic if they were taking lipid medications, if their fasted cholesterol was ≥ 6.2 mmol/L, or if their fasted triglycerides were ≥ 2.3 mmol/L. Presence of cardiovascular disease (CVD) was defined as having a doctor's diagnosis of coronary heart disease, or prior diagnosis of a heart attack or stroke. For the purpose of this analysis, uncontrolled blood pressure was defined as a systolic blood pressure ≥ 140 mmHg (> 130 mmHg for individuals with T2D), or a diastolic

blood pressure of $\geq$ 90 mmHg (> 80 mmHg for individuals with T2D). Controlled blood pressure was defined as having a blood pressure of <140/90 mmHg, (<130/80 mmHg for individuals with T2D). Individuals were classified as either being treated or not being treated with antihypertensive drugs.

Statistical Analyses

Group differences in subject characteristics were determined with one-way analysis of variance (ANOVA) and chi-square tests. Kaplan Meier survival curves stratified by treatment, control and physical activity were used to assess unadjusted survival times. Cox proportional hazards analyses were used to assess differences in all-cause mortality risk by PA level, antihypertensive treatment, and blood pressure control. Adults with hypertension who were physically active, treated with antihypertensive medication, and had controlled blood pressure were the referent group (goal for hypertension). To minimize potential bias of poor health leading to decreased PA, an identical model was conducted excluding individuals who died within the first year after they were examined. In a separate model, hazard ratios stratified by blood pressure control were adjusted for systolic and diastolic blood pressure to account for differences in blood pressure between treatment and PA groups. Multivariate analyses were performed to adjust hazard ratios for age, sex, education, ethnicity, smoking status, T2D, dyslipidaemia, CVD, and BMI. All statistical analyses were performed with SAS vs. 9.3 and results were considered statistically significant at $p < 0.05$.

Results

The average follow-up time was 8.6 ± 4.8 years, with 2832 deaths (25.8%). Subject characteristics by PA, blood pressure control, and antihypertensive treatment are presented in **Table 5.1**. Physically active individuals with treated and controlled hypertension (goal situation)

had a lower prevalence of T2D compared to all other hypertensive groups. However, they had a higher systolic blood pressure and prevalence of T2D compared to normotensive adults ($p < 0.001$).

Unadjusted survival curves stratified by PA, treatment, and control are presented in **Figure 5.1.** Log-rank tests were significantly different between active and inactive within each treatment and blood pressure control group, between treated and untreated within each blood pressure control and physical activity group, and between controlled and uncontrolled within each PA and treated group ($p < 0.05$, **Figure 5.1**).

Hazard ratios for all-cause mortality risk by PA, antihypertensive treatment, and blood pressure control are shown in **Figure 5.2**. There were no interactions between PA, antihypertensive treatment, or blood pressure control ($p > 0.05$). Being physically active (HR, 95%CI=0.71, 0.66-0.78, $p < 0.001$) and having controlled blood pressure (HR = 0.84, 0.78-0.92, $p = 0.004$) were both independently associated with lower mortality risk, whereas being treated with antihypertensive medication was independently associated with higher mortality risk (HR = 1.29, 1.18-1.40, $p < 0.001$) **(Figure 5.2).** Adjustment for systolic and diastolic blood pressure within blood pressure control groups did not alter the significant association of PA or antihypertensive treatment on mortality risk. Compared to adults with hypertension who were physically active, treated and controlled, adults who had hypertension and were physically inactive, regardless of treatment or control status, had a higher mortality risk ($p < 0.05$ for all). Adults with hypertension who were physically active had a similar mortality risk regardless if blood pressure was controlled, or if treated with antihypertensive drugs ($p > 0.05$ for all). Compared to hypertensive adults who were active, treated and controlled, normotensive adults who were physically active had a lower mortality risk (HR = 0.72, 0.60-0.86, $p < 0.001$),

whereas normotensive inactive adults had a similar mortality risk (HR = 1.08, 0.90-1.30) (p = 0.42) **(Figure 5.2).** Exclusion of individuals who died within the first year of being examined did not change the significance of any of the results.

Discussion

To our knowledge this is the first study to determine the joint association between PA, pharmacotherapy, and control of hypertension. Based on this large-scale analysis of the NHANES data, we demonstrate that PA is independently associated with a dramatically lower mortality risk for adults with hypertension, regardless of pharmacological treatment and control status. Moreover, our finding that adults with hypertension who were able to attain the goal situation (i.e. active, treated, and controlled blood pressure) had a similar mortality risk as normotensive adults who were inactive, demonstrates the value of PA, and attainment of goal blood pressure in this patient population. However, it is still worth noting that those with hypertension who were able to attain the goal situation still had higher mortality risk compared to those without hypertension who were physically active. Altogether these results demonstrate that PA and controlled blood pressure are important independent factors for the prevention of premature mortality risk.

Several studies have shown an inverse association between PA and mortality risk in populations with hypertension [143,175]. To our knowledge the present study is the first to assess this association in conjunction with treatment and control of hypertension, and to show that PA is associated with decreased mortality risk independent of these two factors. One study reported that hypertensive adults who were physically active had a reduced CVD mortality risk, compared to those who were hypertensive and physically inactive [175]. Additionally, in a cohort of hypertensive men, increased exercise capacity was associated with lower mortality risk

independent of BMI [176]. The present study extends these findings by showing that among hypertensive adults, PA is associated with reduced mortality risk even if hypertensive individuals are not treated with pharmacotherapy and/or do not obtain controlled blood pressure, compared to those who are physically inactive. Therefore, in adults with hypertension, PA may be critical for lowering premature mortality, especially for those who are treated but do not achieve blood pressure control. This is striking considering that our definition of active was participating in one or more bouts of moderate or vigorous PA a week. However, numerous epidemiological studies have shown that the greatest gains from engaging in PA arise from transitioning from inactive to at least once per week [19,20]. There are several possible reasons why PA is beneficial for adults with hypertension. These include, but are not limited to, increased exercise capacity and muscle strength, reduced adiposity and inflammation, reduced blood pressure, enhanced endothelial function, improved baroreflex sensitivity, improved mental health and the regression of left ventricular hypertrophy [123]. Although there are clear benefits of PA for managing hypertension, in this study, only 53% of hypertensive adults participated in PA compared to 62% of normotensive adults. Given the strong inverse association between PA and mortality risk, our results reinforce the benefits of PA, particularly for adults with hypertension.

For adults living with hypertension, being physically active, treated, and controlled would be the most ideal condition. However, these individuals still had a higher mortality risk compared to physically active adults without hypertension. Our results are in line with several other studies that have reported that treated and controlled hypertensive adults have a higher mortality risk compared to adults without hypertension [140,173]. In contrast, Gu et al., (2008) reported that hypertensive adults who were treated and controlled did not have a greater mortality risk compared to normotensive adults. These discrepant results may be in part due to

the failure to consider for differences in PA. Active, hypertensive adults who are treated and controlled may still have a higher mortality risk than normotensive physically active adults due to irreversable target organ damage prior to attaining treatment or achieving control [177] even with intensive therapy [178]. Indeed, 20% of U.S. adults with hypertension are undiagnosed [89]. Another explanation is that individuals with disease may have had other co-morbidities or lifestyle factors that increased mortality risk. Although, we did adjust for comorbidity and lifestyle risk factors (education, ethnicity, CVD, T2D, dyslipidaemia, BMI, and smoking) this may not have fully captured the severity of health differences between our groups. Nevertheless, observations from this analysis suggest that medications and lifestyle modification do not sufficiently normalize mortality risk to physically active non-diseased conditions, highlighting the importance of disease prevention. It is important to note that although antihypertensive treatment was independently associated with a higher mortality risk, this may be because individuals who were being treated were more likely to be sicker than participants who were not treated. From the current data we cannot conclude that hypertension should not be pharmacologically treated.

The major strength of this study was the use of large samples of U.S. adults from the population-based NHANES surveys. As NHANES collects data on many health and lifestyle parameters, we were also able to show the independent associations of PA, pharmacological treatment, and blood pressure control of hypertension after adjusting for numerous health-related risk factors. Limitations of this study also warrant mention. The current study used prospective observational data and therefore no causation can be implied. Development of hypertension or any other co-morbidity, or change in medication usage after baseline is not known. Further, due to limited sample sizes, we cannot preclude that certain hypertensive medications have differential effects on mortality risk. Physical activity was self-reported, and lifetime PA

patterns were not known. We were also unable to apply sample weights to the analysis due to the combined use of NHANES III and continuous surveys. Thus, our results are not necessarily reflective of the U.S. population, but make our analysis no less internally valid.

In conclusion, this study demonstrates that PA is associated with lower mortality risk in adults with hypertension, regardless of treatment or control status. Thus, PA may be a very important aspect of managing hypertension. Since mortality risk of adults with hypertension in even the most ideal condition (treated, controlled, and physically active), remained higher than that of physically active normotensive populations, it is imperative that efforts are made to prevent development of hypertension.

Table 5.1. Baseline characteristics of 10,665 adults from the NHANES III and NHANES Continuous (1999-2000, 2001-2002) surveys.

	Treated and Controlled		**Treated and Uncontrolled**		**Untreated and Uncontrolled**		**Normotensive**	
	Active	**Inactive**	**Active**	**Inactive**	**Active**	**Inactive**	**Active**	**Inactive**
N	820 (7.7)	664 (6.2)	898 (8.4)	915 (8.6)	1304 (12.2)	1106 (10.4)	3022 (28.4)	1926 (18.1)
Age (years)	64.7 ± 12.0	67.4 ± 12.2*	69.1 ± 11.6*	70.2 ± 11.5*	64.6 ± 13.0	65.8 ±13.7*	54.8 ± 11.9*	55.7 ± 12.5*
Men (%)	52.8	42.6*	46.0*	32.2*	56.7*	46.8*	53.3	43.3*
Education (%)								
< High school	76.0	82.5*	76.7	83.0*	72.6*	84.3*	66.9*	78.2
High school	12.0	10.5	11.9	9.7	14.3	9.9	14.1	12.6
> High school	12.0	7.0*	11.4	7.3*	13.1	5.7*	19.0*	9.2
Ethnicity (%white)	31.6	30.6	35.0	32.1	38.0*	33.4	37.4*	34.4
Smoking (%)								
Never	40.4	45.2*	51.0*	51.2*	47.0*	47.4*	46.0*	44.5*
Past	47.8	39.2*	40.1*	34.3*	38.3*	29.4*	33.0*	27.7*
Current	11.8	15.6*	8.9	14.5*	14.7*	23.2*	21.0*	27.8*
PA bouts/week	6.1 ± 4.1	0*	6.5 ± 4.3	0*	6.4 ± 4.2	0*	6.3 ± 4.3	0*
SBP (mmHg)	123.7 ± 11.0	124.0 ± 10.9	156.8 ± 16.0*	158.7 ± 17.5*	154.2 ± 16.0*	157.5 ± 17.6*	119.9 ± 11.0*	120.5 ± 11.0*
DBP (mmHg)	71.0 ± 9.8	69.0 ± 10.2	78.1 ± 12.8*	77.4 ± 13.8*	81.8 ± 12.6*	80.9 ± 12.6*	73.0 ± 8.0*	72.5 ± 8.4*
T2D (%)	9.3	16.0*	28.8*	32.6*	16.0*	22.6*	3.8*	6.2*
CVD (%)	26.8	30.2*	25.1	30.5*	7.6*	10.9*	4.5*	5.5*
Dyslipidemia (%)	34.5	31.0	32.9	27.8*	20.3*	17.2*	16.4*	14.6*
BMI (kg/m^2)	28.5 ± 5.5	28.9 ± 6.2*	27.7 ± 5.3*	28.7 ± 6.5	27.1 ± 5.1*	27.3 ± 5.8*	26.6 ± 4.7*	27.4 ± 5.5*

* = significantly different from physically active, treated and controlled hypertension ($p < 0.05$). BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; T2D = type 2 diabetes; SBP = systolic blood pressure.

Figure 5.1

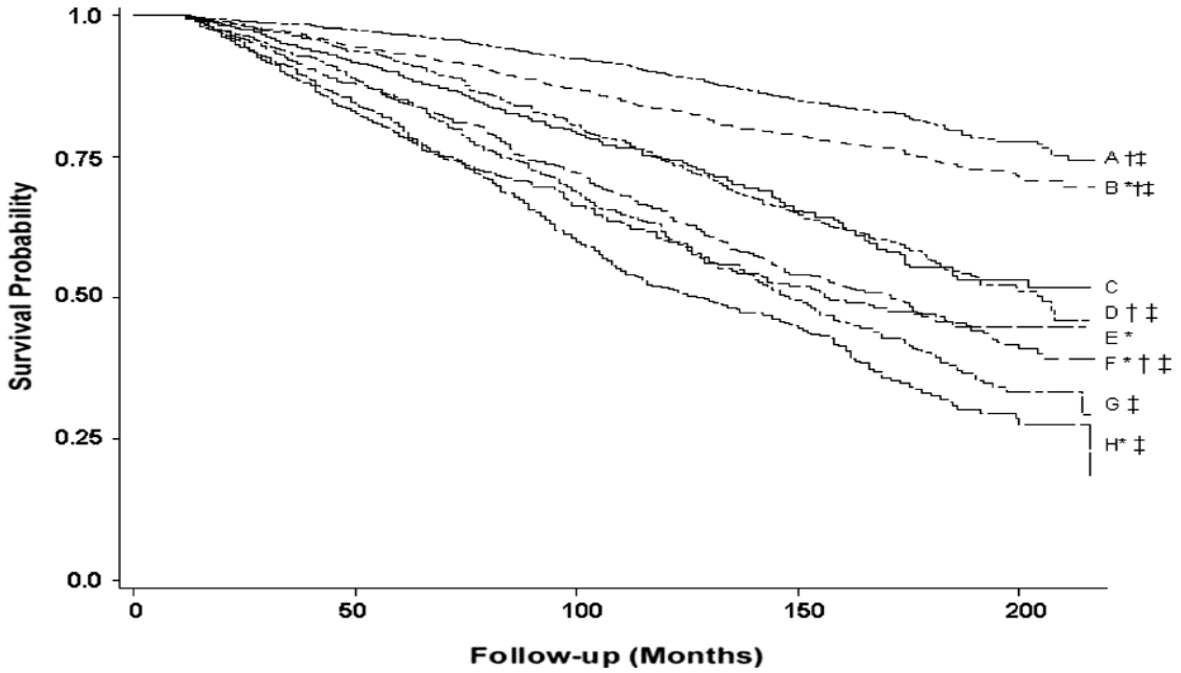

Figure 5.1. Unadjusted survival curves by antihypertensive treatment, blood pressure control, and physical activity. A = normotensive, active; B = normotensive, inactive; C = active, treated, controlled hypertensive; D = active, untreated, uncontrolled hypertensive; E = inactive, treated, controlled hypertensive; F = inactive, untreated, uncontrolled hypertensive; G = active, treated, uncontrolled hypertensive; H = inactive, treated, uncontrolled hypertensive. * = significantly different from physically active within treatment - control groups ($p < 0.05$). † = significantly different from treated within control - physical activity groups ($p < 0.05$). ‡ = significantly different from controlled within treated - physical activity groups ($p < 0.05$).

Figure 5.2

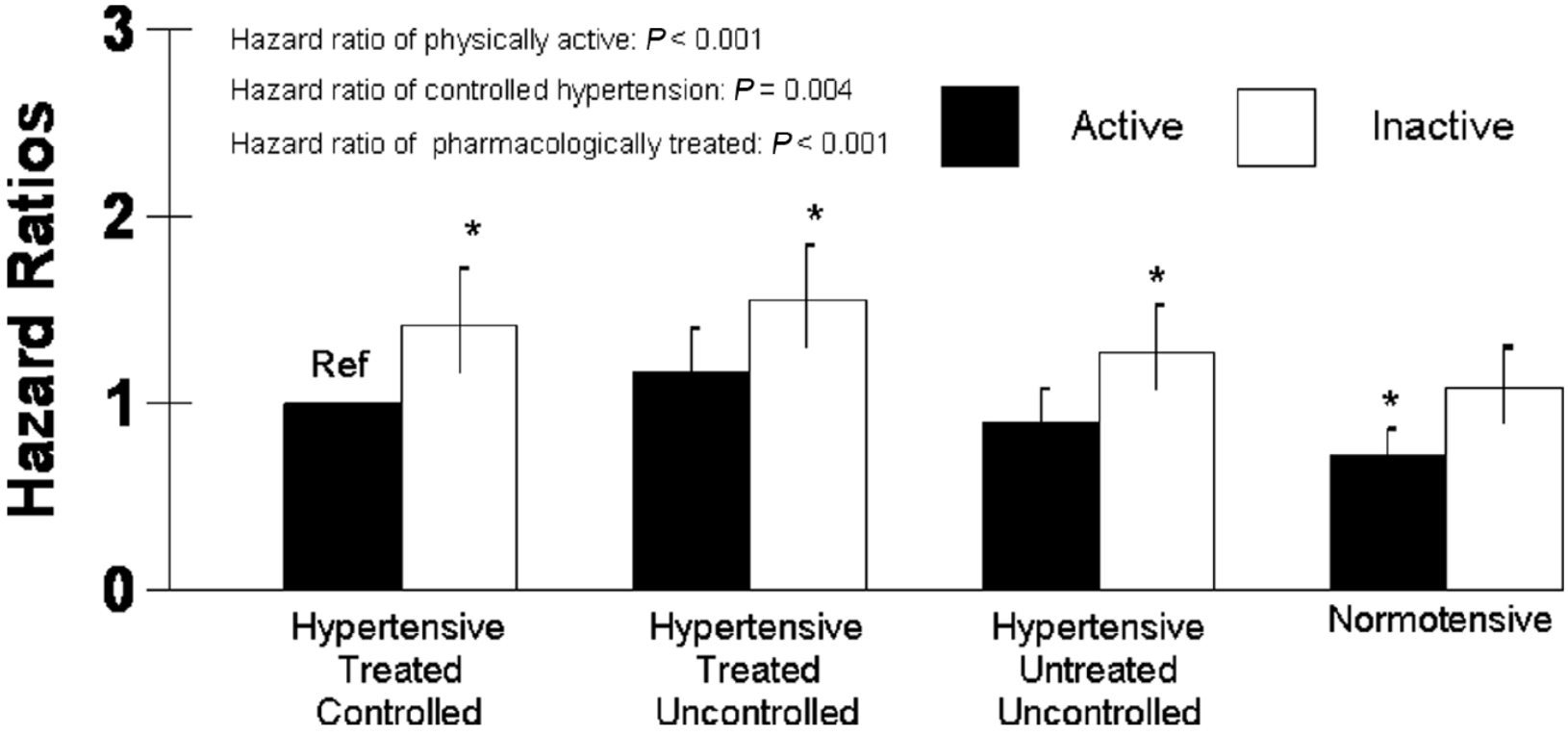

Figure 5.2. Mortality risk by physical activity level, antihypertensive treatment status and blood pressure control status. The model was adjusted for age, sex, education, ethnicity,smoking status, cardiovascular disease, type II diabetes mellitus, dyslipidemia and body mass index. * = significantly different mortality risk compared to active, treated, and controlled hypertensive adults $p < 0.05$).

Chapter 6. Manuscript 4: Calorie Estimation in Adults Differing in Body Weight Class and Weight Loss Status

The co-authors of this manuscript are Karissa L. Canning, Michael Fung, Dishay Jiandani, Michael C. Riddell, Alison K. Macpherson, and Jennifer L. Kuk.

Ruth Brown and Jennifer Kuk designed the study. Ruth Brown, Karissa Canning, Michael Fung and Dishay Jiandani collected the data. Ruth Brown performed the statistical analyses and wrote the manuscript. Michael Riddell, Alison Macpherson and Jennifer Kuk critically revised the manuscript.

Abstract

Introduction: Knowledge of calories is important for weight management, yet few studies have investigated whether individuals can accurately estimate calories during exercise and in food. The objective of this study was to determine if accuracy of estimation of moderate or vigorous exercise energy expenditure and calories in food is associated with body weight class or weight loss status. **Methods**: Fifty-eight adults who were either normal weight (NW) or overweight (OW), and either attempting (WL) or not attempting weight loss (noWL), exercised on a treadmill for 25 minutes. Subsequently, participants estimated the number of calories they expended through exercise, and created a meal that they believed to be calorically equivalent to the exercise energy expenditure. **Results**: The mean difference between estimated and measured calories in exercise and food did not differ within or between groups following moderate exercise. Following vigorous exercise, OW-noWL overestimated energy expenditure by 72%, and overestimated the calories in their food by 37% ($P<0.05$). OW-noWL also significantly overestimated exercise energy expenditure compared to all other groups ($P<0.05$), and significantly overestimated calories in food compared to both WL groups ($P<0.05$). However, among all groups there was a considerable range of over and underestimation (-280 kcal to +702 kcal), as reflected by the large and statistically significant absolute error in calorie estimation of exercise and food. **Conclusion**: The overall poor ability to estimate calories during exercise and in food, especially for overweight adults not attempting weight loss, may be a potential contributor to the generally poor weight loss success observed when attempted through diet and exercise.

Key Words: body mass index; weight loss; energy expenditure; energy intake; exercise intensity

Introduction

Approximately 50% of adults in the United States are attempting to control their weight, with the most common methods including exercise and caloric restriction [67]. Weight loss occurs when energy intake is less than energy expenditure [68]. Therefore, to successfully manage body weight, it would be beneficial for an individual to be able to accurately estimate the number of calories expended through exercise and consumed in a meal [6]. Previous research has demonstrated that adults generally underestimate calories in meals [179,180], and the few studies that have investigated how accurately adults estimate exercise energy expenditure have reported mixed findings [76,81,82]. Further, whether or not calorie estimation differs by weight class and weight loss status is not clear. For example, while both dieters and non-dieters underestimated calories in a post-exercise meal [75], dieters have been reported to be more accurate at calorie estimation compared to non-dieters [74]. Additionally, some studies have demonstrated that obesity is associated with poorer calorie estimation [79,80]. However, no study has simultaneously examined the effect of body weight class and weight loss status on calorie estimation accuracy. Furthermore, although knowledge of calories is reported to be important for weight management [73], whether or not calorie estimation ability is associated with better weight management has not been tested.

To date, only two studies have attempted to simultaneously determine how accurately adults estimate exercise energy expenditure and calories in food [81,82]. However, neither study examined participants with overweight or obesity, or the effects of weight loss status on caloric estimates. Further, only one study has examined the impact of exercise intensity on the accuracy of calorie estimation [82]. Given the importance of calorie estimation for weight management, the present study aimed to determine if accuracy of estimation of moderate or vigorous exercise

energy expenditure and calories in food is influenced by body weight class and intention to lose weight.

Methods

Participants

Adults between the ages of 18-65 years were recruited via poster advertisement from a large urban university setting. Participants were screened for eligibility as assessed by a Physical Activity Readiness Questionnaire (PAR-Q) form. Participants were assessed over three visits that were at the same time of day approximately one week apart. Participants were instructed to refrain from exercising at least 24 hours prior, and to avoid eating, smoking, or drinking caffeinated beverages for a minimum of two hours prior to each experimental session. Informed written consent was obtained prior to participation. The procedures for this study have been approved by the local university ethics board and conform to the Declaration of Helsinki.

Procedures and Protocol

Participants were categorized into 1 of 4 groups based on weight and weight loss status: normal weight (NW) (BMI $\geq$18 and <25 kg/m^2), or overweight/obese (OW) (BMI $\geq$ 25 kg/m^2), and either attempting (WL) or not attempting weight loss (noWL). During the first session, participants completed a variety of demographic, health, and lifestyle related questionnaires, including a question that inquired whether or not participants were currently attempting weight loss. To determine BMI, height was measured by a stadiometer (Seca Telescopic Height Rod, Model 220, Hamburg, Germany), and weight was measured with a mechanical scale (SECA 700, Hamburg, Germany). Cardiorespiratory fitness was assessed using a modified Balke protocol [181], which is an incremental exercise test to volitional exhaustion on a treadmill, using indirect calorimetry (Cardio Coach CO2, Model 9002-CO2; KORR Medical Technologies, Salt Lake City, UT, USA).

For the second and third visits, participants were instructed to indicate their level of hunger immediately prior to exercise using a 150 mm visual analog scale that ranged between "I am not hungry at all" to "I have never been more hungry" [81]. Participants wore an electronic heart rate monitor (Polar FT1; Polar Electro Oy, FI-90440 Kempele, Finland) and exercised at either a moderate intensity (50-70% age-predicted maximum heart rate - HR_{max}) or vigorous intensity (70-85% HR_{max}) (CDC, 2011) for 20 minutes on a treadmill, with an additional 2.5 minute warm-up and 2.5 minute cool down. The trials were conducted in a random order. VO_2 measures were averaged over 15 second intervals for the entire 25 minute exercise protocol using indirect calorimetry (CardioCoach CO2, Model 9002-CO2, KORR Medical Technologies, Salt Lake City, Utah) to calculate energy expenditure [182]. Approximately 10-20 minutes post-exercise, participants again indicated their level of hunger using the same 150 mm visual analog scale, and were asked to estimate how many calories they expended during the entire 25 minute protocol. Subsequently, participants were presented with a variety of pre-weighed foods, including whole wheat sliced bread, sliced turkey, cheese, mayonnaise and mustard, pasta with pasta sauce, chicken breast, salad, Italian salad dressing, Ranch salad dressing, and chocolate candy. They were verbally instructed to create a meal, using any combination of the foods provided, that was equivalent to the number of calories that they estimated to have expended during the exercise bout. The participants were informed that they did not have to consume the meal they created, but that they had the option of eating any of the food once the task was complete. The foods chosen were then weighed with an electronic scale (Ohaus, Model V11P15, Ohaus Corporation, Pine Brook, New Jersey) to the nearest gram, and the caloric content of the food was calculated using the nutrition information provided on the food packaging. Any food that the participants did consume was covertly recorded, and their *ad libitum* energy intake was calculated.

Statistical Analyses

Differences in baseline characteristics between the 4 groups were assessed using ANOVA for continuous variables and chi-square tests for categorical variables. The main outcome variables were measured energy expenditure, estimated energy expenditure, measured food energy, and food energy consumed in the *ad libitum* meal. The error in calorie estimation was determined as both the mean difference as well as the absolute difference between the main outcome variables. Differences in the main outcome variables, as well as for the error in calorie estimation were assessed with a 4 x 2 (group x intensity) mixed models repeated measures ANOVA with post hoc tests. Due to either time constraints or dietary preferences, only 41 out of the 58 participants chose to eat a post exercise meal. Therefore, differences between calories consumed and energy expended were analyzed only in this subsample. Alpha was considered statistically significant at $P<0.05$. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Characteristics of the 58 participants are shown in **Table 6.1**. The NW-noWL group had a significantly lower BMI, and higher cardiorespiratory fitness compared to the OW groups ($P < 0.05$). All groups exercised at a similar percentage of HR_{max} during the moderate condition ($62.6 \pm 4.5\%$ HR_{max}) and vigorous condition ($75.3 \pm 5.4\%$ HR_{max}). As expected, all groups expended significantly more calories during the vigorous condition (mean 207.2 ± 79.5 kcal) than the moderate condition (mean 152.6 ± 57.0 kcal), over the 25 minutes of exercise ($P<0.001$). There were also no differences in hunger pre to post exercise within or between any of the groups (data not shown).

There were no within group differences in the moderate exercise intensity condition between estimated and measured energy expenditure, or calories in food (**Figure 6.1A,** P>0.05). In the vigorous exercise intensity condition, OW-noWL overestimated energy expenditure by 72%, and overestimated the calories in their food by 37% relative to the measured energy expenditure (**Figure 6.1B**) (P<0.05). In both exercise conditions, all groups, except for OW-WL, consumed nearly double the calories in the *ad libitum* meal compared to the calories they expended during exercise (**Figure 6.1 A+B**) (P<0.05).

Differences in the mean error and absolute error of calorie estimation are presented in **Table 6.2** and **Table 6.3**, respectively. Following moderate intensity exercise, there were no differences between groups in the mean error of calorie estimation of exercise or food (P>0.05). Although the mean error in selecting food calories to match moderate intensity energy expenditure did not differ between groups (P>0.05), the number of calories in the food ranged from 88% under to 273% over what was actually expended (**Table 6.2**). As well, the absolute error in calorie estimation was significantly greater than zero for all groups for all comparisons, with no differences between the groups (**Table 6.3**).

Following vigorous intensity exercise, OW-noWL overestimated energy expenditure to a greater degree compared to all other groups (P<0.05) (**Table 6.2**), and also significantly overestimated calories in food compared to both WL groups (P<0.05) (**Table 6.2**). Although the mean error in selecting food calories to match vigorous intensity energy expenditure did not differ between groups (P>0.05), the number of calories in food ranged from 106% under to 339% over what was expended (**Table 6.2**). As well, the absolute error in calorie estimation was significant for all groups for all comparisons (P<0.05), with OW-noWL having a higher absolute error in estimating energy expenditure compared to the NW groups (P<0.05) (**Table 6.3**).

Discussion

The present study is the first to show that current weight status, intention to lose weight, and exercise intensity, are all associated with exercise and food calorie estimation. In particular, those with elevated body weight who are not attempting to lose weight appear to be more prone to errors in estimating energy expenditure and energy in food following vigorous exercise. Although on average participants were able to match energy in food to energy expended during exercise, there was a considerable range of over and underestimation within all groups, as reflected by the large absolute error in calorie estimation of exercise and food. Overall, these findings demonstrate an overall poor ability to estimate energy expended through exercise, and calories in food, which may have important implications for weight management.

Given the popular theory that excess energy intake is the primary driver of the obesity epidemic [183], it is important to investigate if individuals have an understanding of the caloric content of food. In the present study, only OW-noWL overestimated food calories by 68%, while all other groups underestimated food calories by ~25%, after vigorous exercise. This extends the work of Carels et al. (2006) who reported that a higher baseline BMI was associated with greater error in calorie estimation [80], as we demonstrate that weight loss status may significantly alter calorie estimation. In contrast to previous research that has demonstrated that adults generally underestimate calories in food [76,81,179], we demonstrate that the mean error between estimated and actual calories in food was similar, there was a large inter-individual range in the errors observed. However, this may be in part due to the actual caloric content of the meals being relatively small, as a previous study reported that adults consistently underestimate calories in large meals, yet are reasonably accurate at estimating calories in small meals [184]. Nevertheless, the interpretation that adults are accurate at estimating calories in food

may be misleading as there was a considerable amount of individual variability among all groups that ranged from a 760 kcal underestimation to a 468 kcal overestimation of calories in food. Given that an understanding of calories consumed and expended are both important factors for successfully maintaining long term weight loss [185], a lack of understanding in either of these components of energy balance may lead to problems with weight management.

Studies that have investigated whether BMI or dieting status influences accuracy of exercise energy expenditure estimation have shown mixed results. For example, among NW adults, there have been reports of both overestimation [81] as well as underestimation [82] of moderate energy expenditure. As well, Visona and George (2002) reported that OW adults who were dieting underestimated moderate energy expenditure, while non-dieters overestimated moderate energy expenditure [75]. Conversely, our results demonstrate that on average both NW and OW adults accurately estimated moderate intensity expenditure, regardless of whether or not they were attempting weight loss. However, due to the wide range of under and overestimation, all groups had a significantly large absolute error in estimation of moderate energy expenditure that ranged between 57 and 104 kcal. On the other hand, the only other study to investigate how exercise intensity influences calorie estimation reported that NW adults underestimate moderate intensity expenditure, but accurately estimate high intensity expenditure [82]. This is in contrast to the present study, in which the mean difference between estimated and measured energy expenditure was not different for NW adults for either moderate or vigorous exercise. However, OW-noWL overestimated vigorous energy expenditure, and to a significantly greater degree compared to all other groups. Yet, OW-noWL also overestimated the energy content of their meals, and despite their larger errors, were able to match energy in food with energy expended

through exercise. Thus, the complex association between calorie estimation and weight management may require further investigation.

It is recommended that in order to maintain a healthy body weight, individuals must be able to correctly match energy intake with energy expenditure [186]. In one study by Willbond et al. (2010), it was reported that NW adults chose post exercise meals that contained 2-3 times the number of calories than what was expended during moderate intensity exercise [81]. Conversely, Holliday and Blannin (2014) demonstrated that NW participants were able to accurately match calories in a post exercise meal to the energy expended during moderate and high intensity exercise [82]. The present study extends these previous findings by including both NW and OW adults who were and were not attempting weight loss. Regardless of BMI or weight loss status, these findings are in accordance with those of Holliday and Blannin (2014), in that on average participants were able to match calories in a post exercise meal to the energy expended during moderate and vigorous intensity exercise. However, again there was a large variability in the individual accuracy, as some individuals constructed meals that contained 220kcal less, to 543 kcal more than the number of calories they expended during exercise. Given that the higher rates of overweight and obesity today compared to 30 years ago is estimated to be due to an energy surplus of 370 kcal/day [187], the observed error in calorie estimation in the present study may help explain why many adults struggle with weight management.

Although participants accurately matched calories in food to calories expended during exercise, most individuals consumed significantly more calories in a post exercise *ad libitum* meal compared to the energy they expended. This finding is consistent with other studies [76,82] even though there were fewer food options in the present study compared to the large buffet type meals that others have provided. Interestingly, OW-WL was the only group that did not

consume more calories than they expended. This may have been due to the fact that this group was trying to lose weight and therefore may have a better understanding of calories and were consciously restricting their caloric intake. In contrast, NW-WL consumed nearly double what they expended, with some of these individuals consuming up to 5 times the number of calories that they burned during exercise. However, because diet was not tracked over time, we cannot infer that the amount of food that was eaten represents a typical meal or daily intake for these individuals.

Although it has been reported that knowledge of calories is important for weight management, it is possible that even if individuals do have an understanding of calories, this may not influence their food choices. For example, recent legislation in the United States requiring restaurants to post calorie information for regular food and drink items [188] has not resulted in consumers purchasing lower calorie meals, [189,190], even when they notice the available calorie information [191]. Further research is needed to investigate the association between calorie estimation and weight management.

Strengths and limitations of this study warrant mention. Unlike other studies that used predictive equations to determine exercise energy expenditure [75,76], the current study used indirect calorimetry, which accounts for individual variability in economy [77]. This is also the first study to examine the joint effects of BMI class, weight loss status, and exercise intensity on calorie estimation. Although the groups were not balanced, the repeated measures ANOVA were conducted with the PROC MIXED procedure, which has the capacity to handle unbalanced data. Further, the current sample is significantly larger than past studies [81,82]. Though there were several non-significant differences between groups, these differences are likely not clinically relevant (i.e. measured food energy – measured energy expenditure: 7 to 25 kcal) given the

proposed caloric surplus hypothesized to be responsible for the rise in obesity prevalence [187]. A retrospective sample size analysis determined that this study would have needed a minimum of 252 participants per group to see statistically significant group differences. Although information for $\%HR_{peak}$ was available, we chose to calculate exercise intensity based on predicted $\%HR_{max}$, as the majority of individuals would not have access to incremental exercise testing and would have to rely on age-predicted formulas to calculate exercise intensity. However, the $\%HR_{max}$ was 4.9% higher than the $\%HR_{peak}$, and thus the magnitude of difference has minimal clinical relevance. The present study was also unable to distinguish between participants with overweight versus obesity. As well, although there was a range of common foods, it is possible that the food provided was not representative of what all of the participants typically eat. Although there were group differences in age and ethnicity, there is currently no literature to suggest that either of these variables would influence ability to estimate calories. Finally, because participants engaged in aerobic exercise only, these results may not be generalizable to other forms of exercise.

In conclusion, BMI, weight loss status, and exercise intensity, may all be important factors to consider when investigating calorie estimation. There was a large degree of variability in error of calorie estimation for both exercise and food, indicating that many individuals have a poor understanding of calories. Nevertheless, the large observed errors in calorie estimation even in individuals who are attempting to lose weight is concerning, and may be a potential contributor to the generally poor weight loss success observed when attempted through diet and exercise.

Table 6.1. Subject characteristics according to BMI class and weight loss status.

	NW-noWL	**NW-WL**	**OW-noWL**	**OW-WL**
N	18	12	13	15
Age (years)	21.6 ± 2.5	27.6 ± 11.8	27.3 ± 13.9	35.3 ± 15.7 [a]
Sex (% male)	38.9	33.3	38.5	26.7
Ethnicity (% white)	50.0	66.7	38.5	73.3
BMI (kg/m²)	21.4 ± 2.3	23.1 ± 1.6	27.8 ± 2.8 [ab]	28.4 ± 2.6 [ab]
VO2 peak (ml/kg/min)	49.8 ± 10.2	42.0 ± 11.5	33.7 ± 10.7 [ab]	35.3 ± 11.8 [a]

[a] = significantly different compared to the NW-noWL group (P<0.017). [b] = significantly different from the NW-WL group (P<0.017). NW = normal weight, WL = attempted weight loss, BMI = body mass index, WC = waist circumference, VO2 = volume of oxygen.

Table 6.2. Mean error in estimating exercise energy expenditure and calories in food by BMI and weight loss status.

	NW-noWL	NW-WL	OW-noWL	OW-WL
Kilocalories	**Moderate Intensity Condition**			
Estimated energy expenditure - Measured energy expenditure	2 ±125 (-97 to 444)	-43 ± 48 (-123 to 50)	37 ± 149 (-109 to 321)	-24 ± 104 (-177 to 198)
Estimated food energy – measured food energy	-28 ± 91 (-195 to 188)	-54 ± 89 (-280 to 32)	40 ± 145 (-135 to 404)	-40 ± 111 (-218 to 123)
Measured food energy – measured energy expenditure	29 ± 123 (-135 to 319)	11 ± 90 (-105 to 213)	-3 ± 66 (-83 to 142)	17 ± 146 (-133 to 417)
Measured energy intake –measured energy expenditure	157 ± 179 (-85 to 478)	187 ± 242 (-52 to 678)	171 ± 215 (-69 to 554)	109 ± 230 (-133 to 467)
	Vigorous Intensity Condition			
Estimated energy expenditure - Measured energy expenditure	-2 ± 117 * (-167 to 361)	-53 ± 72 ***** (-187 to 102)	150 ± 271 (-87 to 754)	4 ± 145 ***** (-279 to 274)
Estimated food energy – Measured food energy	-21 ± 139 * (-306 to 243)	-66 ± 97 ***** (-302 to 50)	96 ± 194 (-215 to 468)	-51 ± 224 ***** (-760 to 176)
Measured food energy – Measured energy expenditure	20 ± 147 (-220 to 416)	13 ± 116 (-104 to 284)	54 ± 174 (-112 to 543)	55 ± 206 (-172 to 702)
Measured energy intake – Measured energy expenditure	180 ± 169 (-45 to 431)	203 ± 290 (-87 to 787)	147 ± 210 (-70 to 531)	59 ± 147 (-69 to 410)

Differences are presented as mean ± standard deviation (range). BMI = body mass index; NW = normal weight; OW = overweight/obese; WL = weight loss; EE = energy expenditure; kcal = kilocalories; EI = energy intake. * = significantly different compared to the OW-noWL group ($P<0.05$).

Table 6.3. Absolute error in estimating exercise energy expenditure and calories in food by BMI and weight loss status.

	NW-noWL	NW-WL	OW-noWL	OW-WL
Kilocalories	**Moderate Intensity Condition**			
Estimated energy expenditure - Measured energy expenditure	77 ± 97 * (9 to 444)	57 ± 27 * (27 to 123)	104 ± 110 * (6 to 321)	88 ± 56 * (2 to 198)
Estimated food energy – measured food energy	78 ± 56 * (12 to 194)	66 ± 79 * (1 to 280)	100 ± 110 * (35 to 404)	98 ± 62 * (16 to 218)
Measured food energy – measured energy expenditure	88 ± 89 * (5 to 319)	66 ± 58 * (4 to 213)	53 ± 37 * (110 to 142)	103 ± 101 * (7 to 417)
Measured energy intake –measured energy expenditure	157 ± 179 * (5 to 478)	200 ± 230 * (28 to 787)	207 ± 177 * (23 to 554)	171 ± 182 * (7 to 467)
	Vigorous Intensity Condition			
Estimated energy expenditure - Measured energy expenditure	78 ± 85 *† (10 to 361)	72 ± 52 *† (8 to 187)	198 ± 235 * (24 to 754)	120 ± 75 * (1 to 279)
Estimated food energy – Measured food energy	96 ± 100 * (5 to 305)	84 ± 80 * (19 to 302)	157 ± 146 * (3 to 468)	139 ± 180 * (15 to 760)
Measured food energy – Measured energy expenditure	102 ± 105 * (4 to 416)	89 ± 70 * (6 to 284)	110 ± 143 * (9 to 543)	123 ± 172 * (10 to 702)
Measured energy intake – Measured energy expenditure	180 ± 169 * (45 to 431)	235 ± 259 * (28 to 787)	169 ± 190 * (9 to 531)	90 ± 128 * (10 to 410)

Differences are presented as mean ± standard deviation (range). BMI = body mass index; NW = normal weight; OW = overweight/obese; WL = weight loss; EE = energy expenditure; kcal = kilocalories; EI = energy intake. * = significant absolute error within a group ($P<0.05$); † = significantly different compared to the OW-noWL group ($P<0.05$).

Figure 6.1

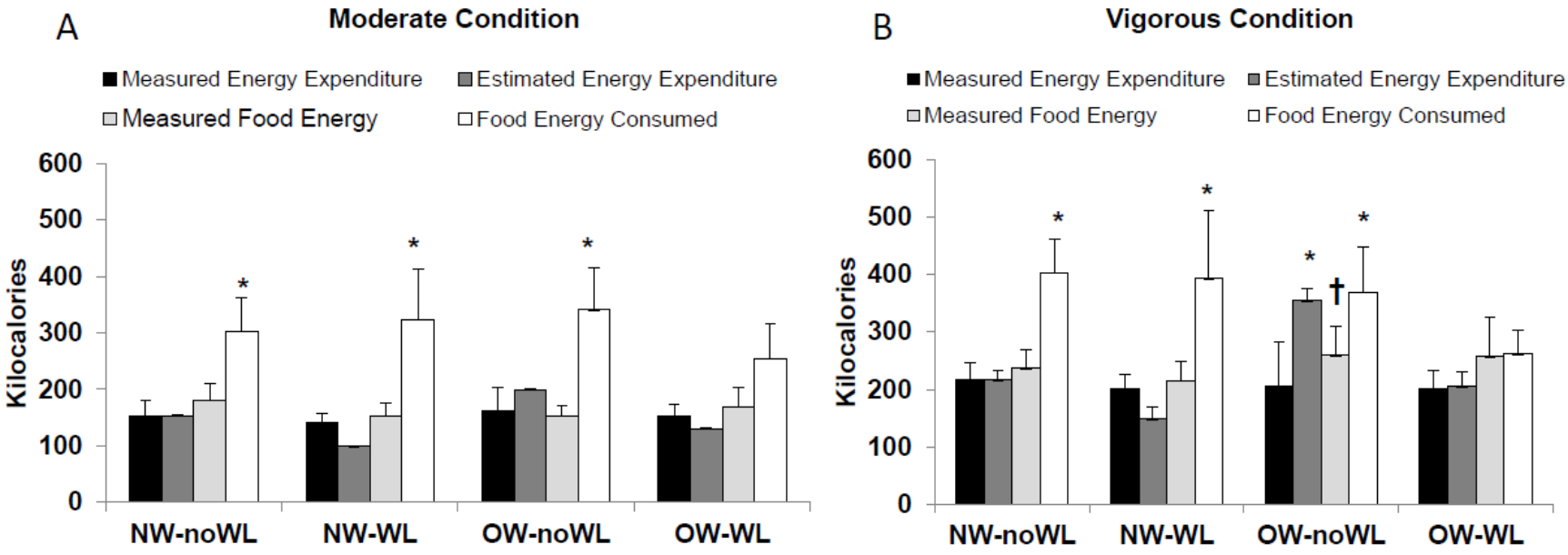

Figure 6.1. Measured exercise energy expenditure (black bars), estimated exercise energy expenditure (dark grey bars), measured food energy (light grey bars), and ad libitum energy intake (white bars) following moderate intensity exercise (Panel A) and vigorous intensity exercise (Panel B), according to BMI and weight loss status. Data is presented as mean ± standard error. NW = normal weight; OW = overweight/obese; WL = weight loss; * = significantly different from measured energy expenditure within a group ($P<0.05$). † = significantly different from estimated energy expenditure within a group ($P<0.05$).

Chapter 7. Manuscript 5: Waist Circumference at Five Common Measurement Sites in Normal Weight and Overweight Adults: Which Site is Most Optimal?

The co-authors of this manuscript are Karissa L. Canning, Michael D.T. Fung, Dishay Jiandani, and Jennifer L. Kuk. Ruth Brown and Jennifer Kuk designed the study. Ruth Brown, Karissa Canning, Michael Fung, and Dishay Jiandani collected the data. Ruth Brown performed the statistical analyses and wrote the manuscript. Jennifer Kuk critically revised the manuscript.

Abstract

Objectives: To determine 1) if adults would measure their own WC, 2) which WC site(s) are most intuitive and easy to measure, and 3) if measurement accuracy, as well as the association between WC and blood pressure, differs across five measurement sites. **Methods**: Participants (n=198; 26.3±12.4 years) measured their WC first with no instruction, and then using visual instructions for the iliac crest, last rib, midpoint, minimal waist, and umbilicus. Technicians repeated the measurements at the same locations. **Results**: Only 58-68% of females reported that they would measure their own WC compared to 78-92% of males. Without instruction, participants most commonly measured their WC at the umbilicus or iliac crest. The minimal waist and umbilicus were reported to be moderately easier to self-measure compared to the iliac crest and midpoint ($P<0.05$). Prevalence of abdominal obesity varied significantly by sex and measurement site, especially for females (normal weight: 0-18%; overweight: 51-79%). Measurement site did not influence accuracy of WC self-measurement, or the association between WC and blood pressure ($P>0.05$). **Conclusion**: All five WC measurement sites are reasonable to recommend as we did not observe a clear clinical or practical advantage of measuring one WC site over another. However, to fairly compare WC measurements between studies, a universal WC landmark is needed.

Key Words: Blood Pressure, Abdominal Obesity; Body Composition; Body Mass Index

Introduction

Abdominal obesity is associated with adverse health outcomes, such as hypertension, diabetes, dyslipidemia, and the metabolic syndrome, independent of total adiposity.[9,51] Waist circumference (WC) is now widely acknowledged as a simple and reliable measure of abdominal obesity and predictor of metabolic health risk.[53,54,192,193] Although many health authorities recommend measuring WC in addition to body weight to monitor weight-related health risk,[5,57] there is not yet a universal standard protocol for measuring WC. For example, the World Health Organization and the International Diabetes Federation recommend measuring WC at the midpoint between the superior border of the iliac crest and the last rib,[194,195] whereas the National Institutes of Health recommends measuring WC at the superior border of the iliac crest.[57] Other commonly used measurement sites include the minimal waist, umbilicus, and last rib.[58]

Several studies have reported that the WC,[61,63,64] as well as the prevalence of abdominal obesity,[61] is significantly influenced by the WC measurement site. However, the measurement site that is most strongly associated with health risk is not clear. Moreover, if health agencies wish to promote WC measurement as a way to monitor health risk, it is important to know if and where adults can accurately measure their WC. Investigations of whether adults can accurately measure their own WC, or if measurement accuracy is influenced by body weight status has resulted in mixed findings.[196–198] Furthermore, it is currently not known if certain measurement sites are more difficult to measure than others from the patient's perspective. Therefore, the objectives of this study were to determine 1) if individuals are willing to measure their own WC, 2) which WC measurement site(s) adults naturally measure, 3) which WC measurement site(s) adults find the easiest or hardest to self-measure, 4) if individuals can accurately measure their

WC at five commonly measured WC measurement sites, and 5) which WC measurement site(s) is most strongly associated with blood pressure.

Methods

Participants

Participants were 198 adults between 18-65 years who were recruited via poster advertisement from a large urban university setting (n=184), and from a medical weight management clinic (n=14). Participants were excluded from the blood pressure analyses if they reported taking medications for hypertension (n=5) or if they were missing information for blood pressure (n=15), leaving a sample size of 178 adults. Prior to the assessment, participants were instructed to refrain from exercising for at least 24 hours, and to refrain from eating or drinking anything with caffeine for at least 2 hours. Written informed consent was obtained from all participants, and all procedures in this study were approved by the local university ethics board and conformed to the Declaration of Helsinki.

Blood Pressure and Anthropometric Measurements

Blood pressure was measured with an automatic blood pressure machine (BpTRU Medical Devices, Model BPM-200, Coquitlam, BC, Canada) six times, with one minute between each measurement. The first measurement was discarded and the final blood pressure was an average of the final five measurements. Height was measured with a stadiometer (Seca Telescopic Height Rod, Model 220, Hamburg, Germany), and weight was measured with a mechanical scale (SECA 700, Hamburg, Germany). Participants were categorized as either normal weight (NW; BMI $\geq$18 and <25 kg/m^2), or overweight (OW; BMI $\geq$ 25 kg/m^2). Body fat percentage was assessed as the average of two bioelectrical impedance analyzers (Tanita Body

Composition Analyzer, Model BC-418, Tanita Corporation, Tokyo, Japan, and Omron Fat Loss Monitor, Model HBF-306C, Omron Healthcare, Inc., Bannockburn, Illinois).

First, participants were asked to measure their WC with no instruction using a tension-sensitive non-elastic tape measure, and location of measurement was recorded by the investigator. Subsequently, participants measured their WC at five commonly measured anatomical sites using simple visual and written instructions in a random order: the superior border of the iliac crest, the last rib, the midpoint between the superior border of the iliac crest and the last rib, the minimal waist, and the umbilicus. After each measurement, participants were asked, "On a scale of 1 to 5, 1 being easy, and 5 being difficult, how easy or difficult was it to measure your waist at that site?" Participants were also asked the following questions: "Would you measure your own WC in addition to your body weight, and why?", and "Would you measure your own WC if it were a better predictor of your health than your body weight, and why?" Waist circumference was then measured twice by a different investigator at the same five anatomical sites.

Statistical Analyses

All analyses were performed separately for males and females. Differences in baseline characteristics by BMI status were assessed with ANOVA for continuous variables and chi-square tests for categorical variables. Differences between self- and technician-measured WC, differences in WC between sites, and differences in measurement difficulty scores between sites, were compared with repeated measures ANOVA. The degree of reproducibility between self- and technician measured WC at each measurement site was determined using intra-class correlation coefficients (ICC). For illustrative purposes, Bland-Altman plots were used to illustrate WC measurement agreement between the participant and the technician, and to

investigate measurement bias.[199] Pearson correlations were used to determine the associations between SBP and DBP with WC, as well as the associations between self- and technician-measured WC, at each measurement site. The associations between blood pressure and WC were adjusted for age and ethnicity. Differences in the strength of the correlations between blood pressure and WC at each measurement site were determined with Steiger's Z test,[200] with Bonferroni adjustments for multiple comparisons. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Characteristics of the participants by sex and BMI class are shown in **Table 7.1**. Females who were OW had a higher SBP, and were less likely to report that they would measure their own WC even if WC was a better predictor of health, compared to NW ($P<0.05$). Of the individuals who indicated they would measure their own WC, the most common rationales were that WC gave a better indication of body fat distribution (45%), and that both WC and body weight were important measures for health (27%). Of the individuals who reported that they would not measure their own WC, the most common rationales were that they did not consider WC to be an important measurement (49%) and that they did not care about their WC measurement (41%).

Regardless of BMI, the majority of males naturally measured their WC without instruction at the iliac crest or the umbilicus, whereas half of the females naturally measured their WC at the umbilicus (**Table 7.2**). None of the WC measurement sites were rated as particularly difficult to measure as all sites had a measurement difficulty score that ranged between 1.8 to 2.9 out of 5 (**Table 7.2**). However, both the minimal waist and the umbilicus

were rated to be modestly easier to measure compared to the commonly clinically recommended sites (i.e. iliac crest and midpoint ($P<0.05$).

In males with OW, WC values were similar between measurement sites ($P>0.05$). Among NW males and all females, WC varied significantly between measurement sites, with the largest values typically at the iliac crest or umbilicus (**Table 7.2**). In NW, 10% (technician-measured) and 18% (self-measured) of females had a high WC when measured at the iliac crest while the prevalence of high WC was 0-6% at all other sites (**Table 7.2**). In OW, the prevalence of high WC was 21-78%, with 12-15% more adults were classified as having a high WC at the iliac crest or umbilicus compared to the minimal waist.

Intra-class correlations coefficients were high at all sites for individuals with OW (males 0.954-0.971 and females 0.921-0.943), and more variable among individuals with NW (males: 0.748-0.932 and females: 0.460-0.680) (**Table 7.2**). Self- and technician-measured WC were strongly correlated at all measurement sites, with R^2 ranging between 0.91-0.95 for males (**Figure 7.1**) and between 0.87-0.91 for females (**Figure 7.2**). Self- and technician-measured WC did not differ in either males or females at any measurement site ($P>0.05$) (**Figure 7.1 and 7.2).** However, the 95% limits of agreement were wide, particularly in females (Males: -6.7 to 8.8 cm; Females: -11.9 to 12.3 cm). For most sites, there was no evidence of a systematic measurement bias ($P>0.05$). However, for males, there was a small but statistically significant over self-measurement at the last rib with increasing WC ($R^2 = 0.04$, $P = 0.04$ (**Figure 7.1F**), and for females, a small but statistically significant under self-measurement at the umbilicus with increasing WC ($R^2 = 0.04$, $P = 0.03$), (**Figure 7.2J**).

In both sexes, the association between systolic blood pressure and WC (males: $r = 0.13 – 0.18$, $P>0.05$; females: $r = 0.21$ to 0.26, $P<0.05$) and diastolic blood pressure and WC (males: $r =$

0.02 to 0.04, P>0.05; females: r = 0.20 to 0.26, P<0.05) did not differ between any measurement site (P>0.05). Correlations between blood pressure and self-measured WC were similar to correlations with technician-measured WC.

Discussion

The present study provides evidence that the iliac crest and umbilicus may be the most intuitive WC sites to measure, and that there are minimal differences in the difficulty and accuracy of self-measured WC at the different sites. Although the absolute WC size and the prevalence of abdominal obesity are influenced by WC measurement site, the association between WC and blood pressure did not differ between WC measurement sites. Therefore, there does not appear to be one most optimal WC measurement site that provides a significant clinical or practical advantage.

In the current study that consisted of primarily university educated adults, 73-91% indicated that they would be willing to measure their own WC if it was a better predictor of health risk than body weight. However, in a study of the general population, only 50% said they would be willing and only 1% reported routinely measuring their own WC.[201] It is not surprising that many individuals do not consider WC to be an important measurement for their health, as few primary care physicians measure WC in clinical practice, or inform even high-risk patients of the health consequences associated with abdominal obesity.[201] Thus, although WC is a simple measurement that can be used to monitor weight-related health risk independently of body weight, it is clear that some individuals still do not consider their WC to be a meaningful measure of their health, and would not measure WC even if they believed it was. Given the strong evidence linking abdominal obesity to deleterious cardiometabolic health,[202] greater effort may be needed to promote the routine measurement of WC in health care and the general public.

The present study is the first to show that while none of the WC sites were rated as particularly difficult to measure, the clinically recommended iliac crest and midpoint were rated as moderately more difficult to measure compared to the minimal waist and umbilicus. The umbilicus was also the most intuitive measurement site for approximately half of the participants. However, the umbilicus may be inappropriate to use for certain individuals with greater abdominal obesity due to an enlarged pannicular fold that results in the downward translation of the umbilicus.[61] Indeed, it is not unusual to observe WC measures at the umbilicus to be more akin to the level of the hip or even upper thigh. Thus, there does not appear to be a sufficient practical advantage to suggest a change in WC measurement. However, given that the WC site that participants intuitively measured was highly variable, a universal WC landmark and education of the general public about WC self-measurement is needed.

Whether or not adults can accurately measure their WC is important to determine prior to promoting the self-measurement of WC among the general public. Most studies that have reported that there is no difference between self- and technician-measured WC derived this conclusion using correlation coefficients,[197,198,203] which may be misleading given that correlations only assess the strength of the relationship between two variables, and not the agreement between them.[199] In the present study, we observed strong correlations as well as similar values between self- and technician-measured WC at all measurement sites. To our knowledge, we are also the first to observe that the degree of measurement reproducibility was high among adults with OW, but lower and more variable among those with NW. However, the high intra-class correlations among those with OW is encouraging given that individuals with OW or obesity are most likely to benefit from self-monitoring of WC measures. We also observed wide limits of agreement between the self- and technician measured WC, especially for

females, indicating a considerable degree of under and over measurement of WC at all sites. Furthermore, while it has been reported that waist size does not influence the ability of females to measure their WC at the minimal waist,[197] others have demonstrated that under self-measurement of WC is greater with increasing waist size for both sexes at the umbilicus,[196] as well as the midpoint.[203,204] In the present study, we observed that with increasing waist size, there was an over self-measurement of WC at the last rib in males, such that the maximum bias observed between those with the highest and lowest WC was ~ 3 cm, and an under self-measurement of WC at the umbilicus in females (maximum bias ~4 cm). However, although these biases were statistically significant, they are likely not clinically relevant as most individuals would be within the reported measurement error for WC.[204] Therefore, accuracy of WC self-measurement is variable, but does not appear to differ by WC measurement site.

The now widely used WC cut-offs of 102 cm in males and 88 cm in females were originally determined using WC measured at the midpoint,[205] which is the recommended WC measurement site of the World Health Organization.[194] The iliac crest is the recommended WC measurement site in Canada and the United States,[5,57] and is typically a higher absolute WC value compared to the midpoint in females, but not males.[62,63,66] Therefore, larger WC cut-offs may be needed in women if using the iliac crest. The universal use of cut-points made using WC measures at the midpoint has potentially large impacts on estimates of abdominal obesity between studies using different measurement sites. Indeed, we observed the prevalence of abdominal obesity in OW ranged from ~21% to 78% depending on sex and measurement site, and indicates that even small variations in WC can influence the prevalence of abdominal obesity when dichotomous cutoffs are used.[61,62,65] Therefore, measurement site should be taken into

consideration when attempting to compare studies that report the prevalence of abdominal obesity.

In the present study, the association between blood pressure and WC was not dependent on WC measurement site. This finding is consistent with that of Mason et al.[206] who demonstrated that several metabolic risk factors, including blood pressure, were similarly associated with WC measured at the iliac crest, midpoint, last rib, and minimal waist in a sample of primarily white adults. In contrast, WC measurement at the midpoint was reported to be superior compared to measurement at the iliac crest in its association with diastolic blood pressure in overweight females ($r = 0.38$ versus 0.31),[62] and with systolic blood pressure in Asian adults (males: $r = 0.27$ versus 0.23; females: $r = 0.37$ versus 0.34),[66] which translates into an additional 2-5% variance explained with the midpoint than the iliac crest. With few exceptions, even in the statistically significant observations, the advantages of one WC site over another in predicting blood pressure and other metabolic risk factors is minimal,[62,65,66,206] and is unlikely to be of a magnitude that is clinically relevant.

The major strength of this study is that we examined both practical and clinical aspects of WC measurement at five commonly used sites. However, our investigation of associations between WC and metabolic risk was limited to blood pressure. We also did not have enough individuals with a BMI ≥ 30 kg/m² to be able to discriminate between those with overweight versus obesity.

In conclusion, there were minimal differences in the ease or accuracy of WC self-measurement among five commonly used WC measurement sites. Waist circumference measurement site significantly influenced both WC size and the prevalence of abdominal obesity, but not the association between WC and blood pressure. Thus, all five WC

measurement sites are reasonable to recommend as we did not observe any clear clinical or practical advantages for one WC measurement site over another. However, in order for WC measurement to be comparable between studies, a universal WC landmark is needed.

Table 7.1. Subject characteristics by sex and weight class

	Males		Females	
	NW	**OW**	**NW**	**OW**
N	49	33	69	47
Age (years)	22.2 (5.2)	25.6 (12.4)*	22.0 (6.5)	35.8 (16.5)*
Ethnicity (%)				
White	67	52	46	60
Black	3	12	10	19
Asian	16	30	33	15
Other	14	6	10	16
BMI (kg/m^2)	22.2 (1.8)	28.4 (3.6)*	21.5 (1.9)	30.0 (4.5)*
Body Fat (%)	10.7 (4.1)	23.8 (6.4)*	21.5 (4.3)	36.8 (7.4)*
SBP (mmHg)	119 (8)	119 (9)	111 (10)	118 (13)*
DBP (mmHg)	74 (8)	74 (8)	71 (7)	75 (9)
Would measure their own WC (%)	77.6	90.9	68.1	57.5
Would measure their own WC if better predictor of health than body weight (%)	89.8	90.9	91.2	73.3*

Data is presented as means (SD) unless otherwise indicated. NW = normal weight; OW =overweight; WC = waist circumference. * = significantly different compared to normal weight group within each sex ($P<0.05$).

Table 7.2. Waist circumference, prevalence of high waist, and measurement difficulty score according to waist circumference measurement site.

	Iliac Crest	Midpoint	Last Rib	Minimal Waist	Umbilicus
Male NW					
Self-measured WC (cm)	79.5 (5.6)	77.5 (5.3)	76.5 (6.0)[a]	76.2 (6.0)[a]	77.4 (5.7)
Tech-measured WC (cm)	77.9 (6.0)	76.6 (6.0)	76.2 (5.6)	75.5 (5.7)[ab]	78.0 (5.8)
ICC between Self and Tech WC	0.748	0.822	0.930	0.854	0.932
High Waist Tech (%)	4.1	4.1	2.0	2.0	4.1
High Waist Self (%)	4.1	4.1	2.0	4.1	4.1
Measurement difficulty score	2.4 (1.0)	2.6 (0.8)	2.6 (1.0)	2.1 (0.8)[abc]	1.9 (0.8)[abc]
Naturally measured WC (%)	40.0	4.4	4.4	6.7	44.4
Male OW					
Self-measured WC (cm)	94.1 (13.6)	93.0 (14.4)	91.8 (13.9)	90.8 (12.9)	93.1 (13.2)
Tech-measured WC (cm)	93.8 (13.7)	92.1 (14.0)	90.8 (13.1)	89.5 (12.5)	94.1 (14.2)
ICC between Self and Tech WC	0.965	0.971	0.963	0.954	0.956
High Waist Tech (%)	36.4	30.3	27.3	21.2	33.3
High Waist Self (%)	33.3	33.3	24.2	30.3	39.4
Measurement difficulty score	2.6 (1.1)	2.8 (1.2)	2.5 (1.1)	2.0 (0.9)[ab]	1.9 (1.0)[abc]
Naturally measured WC (%)	51.5	3.0	0	0	45.5
Female NW					
Self-measured WC (cm)	78.4 (6.0)	72.3 (6.3)[a]	69.1 (5.1)[abe]	69.2 (4.6)[abe]	73.5 (5.6)[a]
Tech-measured WC (cm)	76.5 (6.4)	72.4 (5.5)[a]	70.0 (5.3)[abe]	69.0 (4.9)[abe]	74.6 (5.9)[b]
ICC between Self and Tech WC	0.593	0.460	0.622	0.680	0.661
High Waist Tech (%)	10.1	2.9	0	0	5.8
High Waist Self (%)	18.8	5.8	1.5	1.5	4.4
Measurement difficulty score	2.4 (0.9)	2.8 (1.0)[a]	2.6 (1.0)	1.8 (0.8)[abc]	2.0 (0.9)[abc]
Naturally measured WC (%)	16.2	2.9	5.9	20.6	54.4

Female OW					
Self-measured WC (cm)	98.7 (15.9)	95.3 (15.4)	91.5 (15.3)[abe]	90.9 (14.9)[abe]	96.5 (14.4)
Tech-measured WC (cm)	98.4 (16.1)	94.5 (15.0)	91.7 (13.8)[abe]	90.2 (13.4)[abe]	99.3 (15.4)
ICC between Self and Tech WC	0.940	0.936	0.931	0.943	0.921
High Waist Tech (%)	78.2	61.7	55.3	53.2	78.7
High Waist Self (%)	78.7	63.8	51.0	55.3	76.6
Measurement difficulty score	2.5 (1.1)	2.9 (1.2)	2.9 (1.3)	2.2 (1.2)[bc]	2.0 (1.1)[abc]
Naturally measured WC (%)	15.9	11.4	0	20.5	52.3

Data is presented as means (SD) unless otherwise indicated. High waist circumference was classified according to International Diabetes Federation criteria (white/black/other males: ≥ 102 cm; Asian males ≥ 90 cm; white black/other females: ≥ 88 cm; Asian females: ≥ 80 cm). [a] = significantly different compared to the iliac crest (P<0.05), [b] = significantly different compared to the midpoint (P<0.05), [c] = significantly different compared to the umbilicus (P<0.05), [d] = significantly different compared to the last rib (P<0.05); [e] = significantly different compared to the umbilicus (P<0.05). NW = normal weight; OW = overweight. ICC = intra-class correlation coefficient.

Note: Measurement difficulty score was based on a 5 point scale, with 1 representing an easy measurement and 5 representing a hard measurement.

Figure 7.1

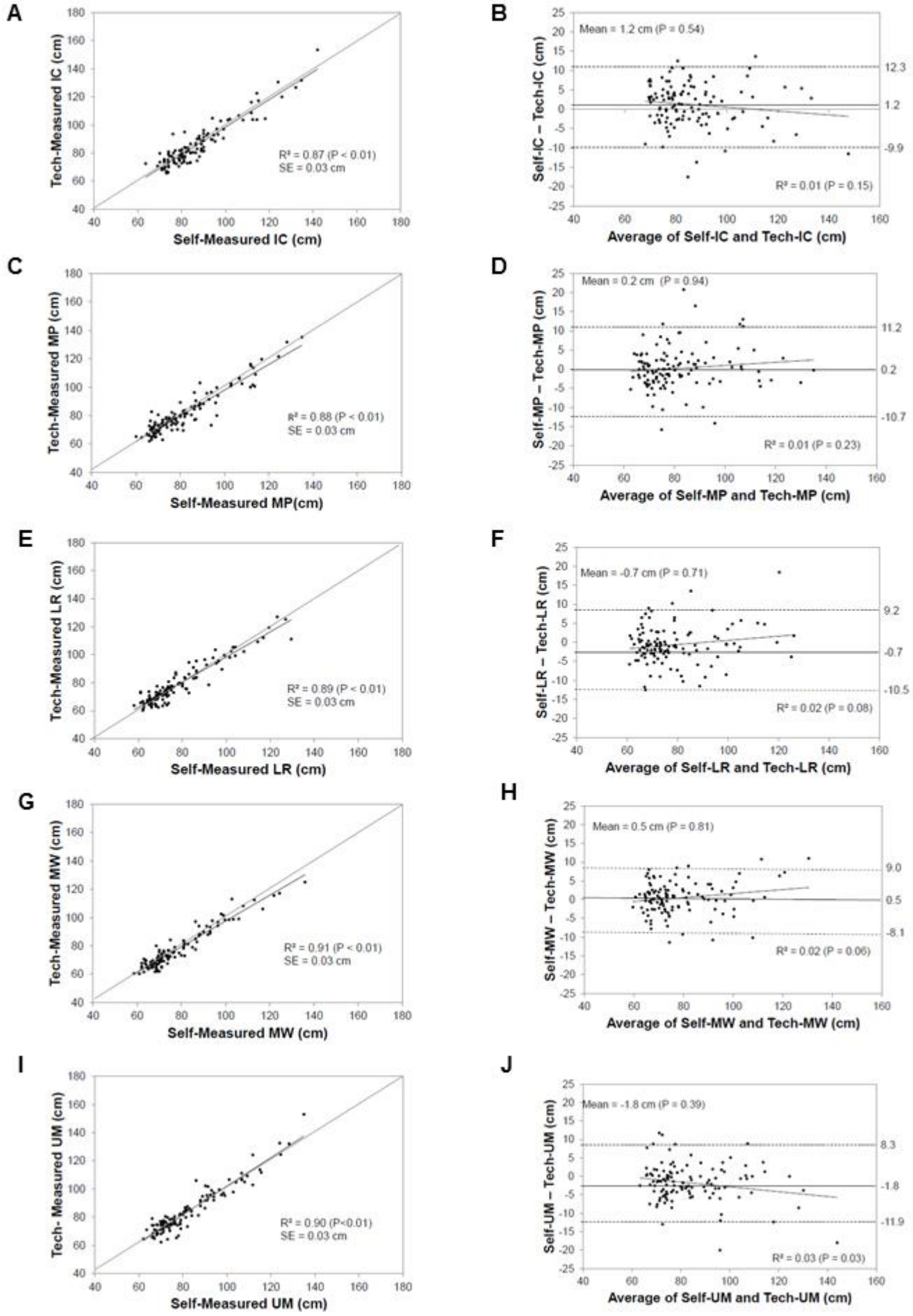
A
Tech-Measured IC (cm)
Self-Measured IC (cm)
R² = 0.87 (P < 0.01)
SE = 0.03 cm
B
Self-IC – Tech-IC (cm)
Average of Self-IC and Tech-IC (cm)
Mean = 1.2 cm (P = 0.54)
12.3
1.2
-9.9
R² = 0.01 (P = 0.15)
C
Tech-Measured MP (cm)
Self-Measured MP(cm)
R² = 0.88 (P < 0.01)
SE = 0.03 cm
D
Self-MP – Tech-MP (cm)
Average of Self-MP and Tech-MP (cm)
Mean = 0.2 cm (P = 0.94)
11.2
0.2
-10.7
R² = 0.01 (P = 0.23)
E
Tech-Measured LR (cm)
Self-Measured LR (cm)
R² = 0.89 (P < 0.01)
SE = 0.03 cm
F
Self-LR – Tech-LR (cm)
Average of Self-LR and Tech-LR (cm)
Mean = -0.7 cm (P = 0.71)
9.2
-0.7
-10.5
R² = 0.02 (P = 0.08)
G
Tech-Measured MW (cm)
Self-Measured MW (cm)
R² = 0.91 (P < 0.01)
SE = 0.03 cm
H
Self-MW – Tech-MW (cm)
Average of Self-MW and Tech-MW (cm)
Mean = 0.5 cm (P = 0.81)
9.0
0.5
-8.1
R² = 0.02 (P = 0.06)
I
Tech- Measured UM (cm)
Self-Measured UM (cm)
R² = 0.90 (P<0.01)
SE = 0.03 cm
J
Self-UM – Tech-UM (cm)
Average of Self-UM and Tech-UM (cm)
Mean = -1.8 cm (P = 0.39)
8.3
-1.8
-11.9
R² = 0.03 (P = 0.03)

Figure 7.1. Associations between self-measured and technician-measured WC at five measurement sites in males (Panels A,C,E,G,I), and the agreement between the measures using Bland-Altman plots (Panels B,D,F,H,J). Correlation plots have the line of best fit in black and the line of identity in grey. Bland-Altman plots show the mean difference (solid line) and the 95% limits of agreement (dotted line) between self- and technician-measured WC. Significant p-values indicate significant under or over measurement of participant measured WC. Line of identity and significant r-squared values indicate a systematic difference between the measures. WC = waist circumference; IC = iliac crest; MP = midpoint; LR = last rib; MW = minimal waist; UM = umbilicus

Figure 7.2

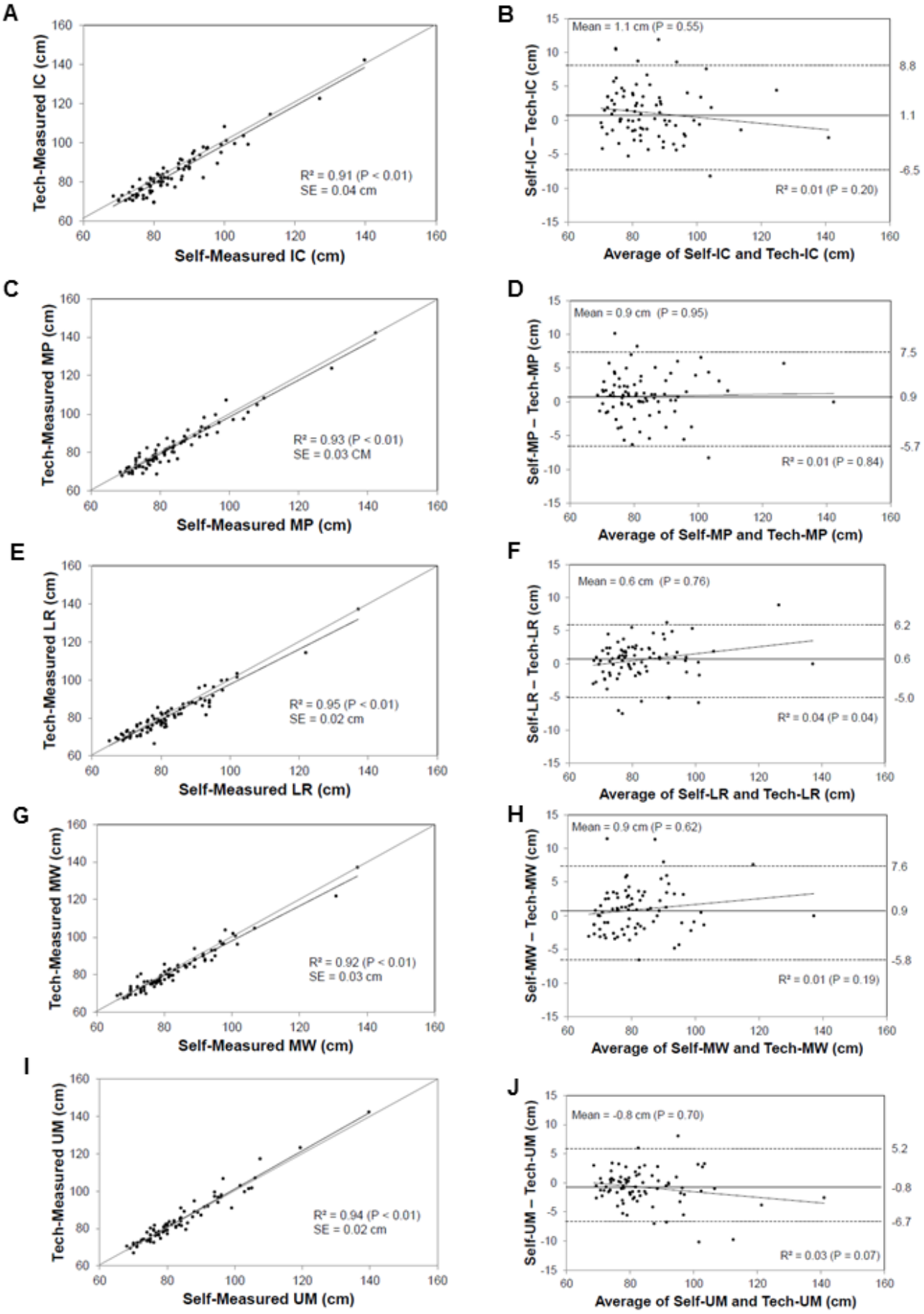
A
Tech-Measured IC (cm)
Self-Measured IC (cm)
R² = 0.91 (P < 0.01)
SE = 0.04 cm
B
Self-IC – Tech-IC (cm)
Average of Self-IC and Tech-IC (cm)
Mean = 1.1 cm (P = 0.55)
8.8
1.1
-6.5
R² = 0.01 (P = 0.20)
C
Tech-Measured MP (cm)
Self-Measured MP (cm)
R² = 0.93 (P < 0.01)
SE = 0.03 CM
D
Self-MP – Tech-MP (cm)
Average of Self-MP and Tech-MP (cm)
Mean = 0.9 cm (P = 0.95)
7.5
0.9
-5.7
R² = 0.01 (P = 0.84)
E
Tech-Measured LR (cm)
Self-Measured LR (cm)
R² = 0.95 (P < 0.01)
SE = 0.02 cm
F
Self-LR – Tech-LR (cm)
Average of Self-LR and Tech-LR (cm)
Mean = 0.6 cm (P = 0.76)
6.2
0.6
-5.0
R² = 0.04 (P = 0.04)
G
Tech-Measured MW (cm)
Self-Measured MW (cm)
R² = 0.92 (P < 0.01)
SE = 0.03 cm
H
Self-MW – Tech-MW (cm)
Average of Self-MW and Tech-MW (cm)
Mean = 0.9 cm (P = 0.62)
7.6
0.9
-5.8
R² = 0.01 (P = 0.19)
I
Tech-Measured UM (cm)
Self-Measured UM (cm)
R² = 0.94 (P < 0.01)
SE = 0.02 cm
J
Self-UM – Tech-UM (cm)
Average of Self-UM and Tech-UM (cm)
Mean = -0.8 cm (P = 0.70)
5.2
-0.8
-6.7
R² = 0.03 (P = 0.07)

Figure 7.2. Associations between self-measured and technician-measured WC at five measurement sites in females (Panels A,C,E,G,I), and the agreement between the measures using Bland-Altman plots (Panels B,D,F,H,J). Correlation plots have the line of best fit in black and the line of identity in grey. Bland-Altman plots show the mean difference (solid line) and the 95% limits of agreement (dotted line) between self- and technician-measured WC. Significant p-values indicate significant under or over measurement of participant measured WC. Line of identity and significant r-squared values indicate a systematic difference between the measures. WC = waist circumference; IC = iliac crest; MP = midpoint; LR = last rib; MW = minimal waist; UM = umbilicus.

Chapter 8: General Discussion

Despite the well-known health benefits of PA in various ages and populations, physical inactivity is highly prevalent, and is now the fourth leading risk factor for mortality globally [2]. Canada's Physical Activity Guidelines recommend that adults accumulate 150 minutes of moderate or vigorous PA/week for health benefits, and that more activity is associated with additional health benefits [11]. A large systematic review that examined the association between PA and specific health outcomes demonstrated a strong dose-response relationship between PA and seven common chronic conditions, thus supporting the PA guideline recommendations [207]. Additionally, there was a clear inverse association between PA and risk of premature mortality [207]. However, the greatest differences in mortality risk is observed between those participating in modest amounts of PA compared to those participating in no activity [207]. This is in line with several epidemiological studies who report that participating in PA even once a week is associated with lower mortality risk compared to participating in no PA [19–22].

Indeed, findings from this dissertation indicated that among all ages, participating in 1-2 bouts of PA/week was associated with lower all-cause mortality risk compared to participating in no PA. However, among very old adults (aged 80+ years), participating in PA at least 5 times/week was associated with a significantly lower risk of premature mortality compared to participating in less activity. Therefore, a higher frequency of PA may be most beneficial for very old adults, who are coincidentally the age group that participates in the least amount of PA [208]. These findings support the previous PA guidelines that recommend participating in moderate or vigorous PA at least 5 days/week. Indeed, participating in more frequent bouts of PA has been associated with lower mortality risk compared to acquiring the recommended amount of weekly PA over 1 or 2 days [153], likely due to the acute positive metabolic responses associated

with PA [95]. These findings indicate that a greater effort may be needed to get very old adults to participate in regular PA.

It has been suggested that PA guidelines should make a greater effort to target physically inactive individuals as they stand to benefit the most from participating in PA, but that most PA guidelines may be discouraging for physically inactive persons [209]. Adults who are physically inactive report greater barriers to PA participation, including a lack of knowledge, skills and resources regarding PA, and a greater prevalence of comorbid conditions that make PA difficult, such as cancer or obesity [209]. The Japanese government has recently been praised for their innovate messaging about PA and health [210]. Although the government recommends 60 minutes/day of moderate to vigorous PA, they also recommend starting with at least 10 minutes/day of PA as a minimal starting dose of PA for individuals who engage in no physical activity [211]. Given that only 15% of Canadian adults and 10% of U.S. adults meet the PA guidelines based on objective measures of PA [212,213], including a minimum PA dose that may be more attainable for physically inactive individuals may be a more promising way to increase PA at a population level. However, there is not yet a clear consensus on an optimal minimal dose of PA, and the effectiveness of such PA messaging needs to be validated.

Physical activity is one of the key recommendations for lifestyle intervention for the management of both T2D and hypertension [120,159]. This dissertation demonstrated the importance of PA for mortality risk in adults with T2D or hypertension, even when either disease is pharmacologically treated or controlled. However, adults with hypertension who were active, treated and controlled still had a higher mortality risk compared to adults without hypertension who participated in PA. Thus, prevention of hypertension, which can be partially accomplished through regular participation in PA, may be imperative for reducing the risk of premature all-

cause mortality in adults. Future research should focus on effective methods for increasing PA participation in adults with T2D and hypertension.

Although individuals with chronic disease, such as hypertension or T2D, benefit from PA [207], they are less likely be physically active than adults without chronic conditions [214,215]. One public health approach to increasing PA among individuals at risk for chronic disease is for physicians to prescribe PA in primary care [216]. While there is some evidence to suggest that this may be associated with a modest increase in PA at least in the short term [217,218], overall there is limited evidence to suggest that a formal PA prescription translates to increased PA in populations at risk for chronic disease [216]. While prescription of PA in primary care is promising in theory, further long-term research is needed to understand if PA prescriptions are indeed effective at increasing PA, and how this may influence risk of chronic disease.

During the past several decades there has been a substantial increase in the prevalence of overweight and obesity in individuals of all ages [219,220]. This is concerning given the myriad of health conditions associated with overweight and obesity [37]. It is suggested that the greater prevalence of obesity is largely due to individuals consuming significantly more energy than they are expending [221]. For example, in order for females to have gone from a mean BMI of 23 kg/m² in the 1970's to 29 kg/m² in 2002 (Brown et al., unpublished data, Appendix B), it is estimated this would have required an energy surplus of 370 kcal/day [187]. Furthermore, Hill (2003) has suggested that a lower energy intake of just 100 kcal/day could prevent weight gain in most of the population [221]. However, in order for individuals to successfully lower energy intake, it is important to have an understanding of the number of calories that are consumed. While the few studies that investigated this concept generally report that individuals tend to overestimate energy expenditure and underestimate energy intake [76,81], results from this

dissertation demonstrate that there was a large individual variability in the accuracy of calorie estimation of both exercise and food. This research is also the first to demonstrate that there may be a greater error in calorie estimation among adults who are overweight and not attempting weight loss compared to individuals with overweight who are attempting weight loss, and individuals with normal weight regardless of weight loss status. These findings may help explain why it is so difficult to lose weight or manage body weight through diet and exercise. Future research should investigate effective methods for improving knowledge of energy intake and expenditure.

Despite public health efforts to combat against the rising prevalence of obesity, no country has been able to successfully lower obesity rates at a population level [194]. Food consumed from restaurants make up one third of the American diet, and is associated with a higher fat and caloric intake [222]. The United States government recently implemented legislation that requires restaurants with greater than 20 locations to post calorie information on their menus [188]. Although many adults report noticing the calorie menu labels, this does not necessarily translate to using the labels to guide meal selection, or purchasing meals with fewer calories [223]. There is some evidence that calorie menu labels may be more likely to be used by females and individuals with higher education [180,223]. However, there is conflicting evidence as to whether this policy has led to customers actually purchasing lower calorie meals [189,223,224]. It was suggested that calorie labeling alone may not be meaningful if individuals do not understand what calories mean, or how the calorie content of an individual meal fits into their total daily caloric intake [222]. As a result, recent studies have explored how PA equivalent labeling (ie. the amount of PA needed to burn off the calories associated with a given meal) may influence meal selection [222]. However, evidence on the effectiveness of such menu labeling is scarce and more

research is in this area is needed. Thus, while calorie menu labeling may allow for greater informed choice when purchasing meals, there is insufficient evidence to suggest that this will impact food selection.

While general obesity has substantially increased during the past several decades, so too has the prevalence of abdominal obesity as assessed by WC [8]. Although BMI and WC are highly correlated [55], WC may be particularly useful in a clinical setting when patients have abdominal obesity but not an obese BMI, and thus may still be at a higher risk for weight-related health conditions [225]. Measurement of WC among the general public is also beneficial, particularly since exercise without caloric restriction can lower WC even when there is not a meaningful change in overall body weight or BMI [226]. Despite the fact that WC is a simple and reproducible measurement [61], only 17% of a sample of North American adults reported having their WC measured in primary care [201], and only 1% reported that they measure their own WC [201]. Clearly greater effort may be needed to educate the general public about the potential value of WC self-measurement.

Despite international health organizations recommending WC measurement [5,57], there is no standard protocol for measuring WC. It has been suggested that the commonly recommended WC measurement sites, the iliac crest (recommended by Health Canada) and the midpoint (recommended by the World Health Organization) may be the easiest sites to measure due to the use of bony landmarks [227]. Interestingly, research from this dissertation represents the first to determine that these sites are moderately more difficult to self-measure compared to the umbilicus and minimal waist. However, overall none of the WC measurement sites were reported to be particularly difficult to self-measure, and the majority of participants indicated that they would be willing to self-measure their own WC. As well, the association between WC and

blood pressure between the various measurement sites did not differ either statistically, or clinically. However, similar to other studies, the magnitude of WC and the prevalence of abdominal obesity differed significantly according to WC measurement site [62,65]. Thus, although there was no clear clinical or practical advantage of measuring one site over another, in order for the magnitude of WC and prevalence of abdominal obesity to be comparable between research studies, a standard measurement protocol is needed.

In conclusion, both physical inactivity and obesity are highly prevalent and associated with increased risk of morbidity and mortality. Even modest amounts of PA are effective for reducing mortality risk, and may be particularly beneficial in the elderly and among adults with T2D or hypertension. Targeted efforts are needed to increase PA among these populations. In addition, many individuals are attempting to lose weight, but most are unable to lose weight and maintain that weight loss over a long term. Therefore, effective methods for long term weight management are also needed.

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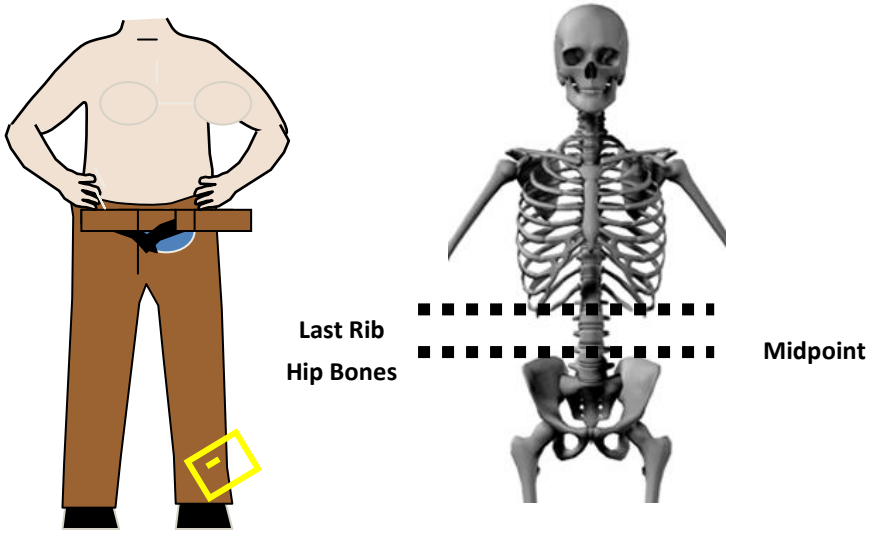
Appendices

Appendix A: Example of Instructions Given to Participants for Waist Circumference Measurement

Stand relaxed with your feet should width apart (25-30 cm or 10-12 inches) in front of a mirror and remove any clothing that would interfere with measuring your waist circumference. Put the tape measure around your waist directly on your skin.

Use the mirror to ensure that you have placed the tape measure correctly (ie. Horizontally, and not twisted or caught on clothing). Relax, press the button, and take the waist measurement at the end of a normal expiration to the closet 0.5 cm.

Use your hands to find **the middle between your rib bones and hip bones** on both sides of your body.



Appendix B: Additional Related Publications

1. Canning KL, **Brown RE**, Wharton S, Sharma AM, Kuk JL. Edmonton Obesity Staging System prevalence and association with weight loss in a community obesity clinic. *International Journal of Obesity* 2015.

2. D Jiandani, A Rhandhawa, **RE Brown**, R Hamilton, AG Matthew, JL Kuk, SMH Alibhai, E Tufts, D Santa Mina. The effect of cycling on prostate-specific antigen (PSA) levels: a systematic review and meta-analysis. *Prostate Cancer and Prostatic Diseases* 2015:1-5. Impact Factor: 2.83.

3. **Brown RE**, Kuk JL, Lee SJ: Associations between visceral fat and liver fat with insulin sensitivity in obese adolescents. *Biochemistry and Cell Biology* 2014, online ahead of print, DOI: 10.1139/bcb-2014-0064. Impact Factor: 2.92.

4. **Brown RE,** Kuk JL**:** Consequences of obesity and weight loss: a devil's advocate position. *Obesity Reviews* 2014, online ahead of print, DOI: 10.1111/obr.12232. Impact Factor: 6.87.

5. **Brown RE**, Kuk JL, Lee SJ: Measurement site influences abdominal subcutaneous and visceral adipose tissue in obese adolescents before and after exercise. *Pediatric Obesity* 2014, online ahead of print, DOI: 10.1111/j.2047-6310.2014.224.x. Impact Factor: 2.28.

6. **Brown RE**, Kuk JL. Age-related differences in the consequences of obesity on cardiovascular disease, type 2 diabetes, osteoarthritis, cancer, physical function, osteoporosis, cognitive function, and mortality risk in the elderly. *Health Aging and Clinical Care in the Elderly* 2014, 6:25-32.

7. Canning KL, **Brown RE**, Jamnik RE, Art Salmon, Chris I Ardern, Kuk JL: Individuals underestimate moderate and vigorous intensity physical activity. *PLoS One* 2014, 16;9(5):e97927. Impact Factor: 3.53.

8. Canning KL, **Brown RE**, Jamnik RE, Kuk JL: The relationship between obesity and obesity-related morbidities weakens with ageing. *Journal of Gerontology* 2014, 69(1):87-92. Impact Factor: 4.31.