ASSOCIATIONS BETWEEN HEART RATE VARIABILITY AND METABOLIC SYNDROME RISK FACTORS

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by

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ABSTRACT

Metabolic syndrome (MetS) is a clustering of risk factors for cardiovascular disease (CVD) and type 2 diabetes (T2D) – two major causes of morbidity and mortality worldwide. Heart rate variability (HRV) is a non-invasive measure of cardiac autonomic regulation that predicts mortality and morbidity. Additionally, HRV is reduced in CVD, T2D and MetS. As such, HRV has potential to be a novel cardiometabolic risk factor to be included in clinical risk assessment. Therefore, the purpose of this thesis was to examine the relationships between MetS and HRV. A systematic review of cross-sectional studies examining relationships between HRV and MetS was completed to consolidate existing evidence and to guide future studies. This was followed by a cross-sectional investigation of time and frequency domain and nonlinear HRV in a population with MetS risk factors to determine which MetS risk factors were associated with HRV parameters. A pilot study was then conducted to study the feasibility of conducting a mobile health (mHealth) and exercise intervention in a rural population, which was followed by a 24-week randomized clinical trial to examine the effects of the interactive mHealth exercise intervention compared to standard of care exercise in participants with MetS risk factors. Overall, HRV was reduced in women with MetS compared to those without, though there were no differences in men. Waist circumference and lipid profiles were most commonly related to HRV parameters when studied cross-sectionally. The changes in waist circumference and fasting plasma glucose were associated with the change in HRV parameters when studied longitudinally. Following the intervention period, waist circumference and

blood pressure were improved with no other changes in MetS risk factors. HRV parameters indicative of vagal activity were reduced over the intervention period, but there were no changes in other HRV parameters. There were no differences in changes between the intervention and control groups. In conclusion, MetS and HRV are associated in women but not men. However, there were no clear associations between MetS and HRV to suggest that HRV would be a valuable clinical risk indicator.

Keywords:

Heart rate variability; autonomic nervous system; metabolic syndrome; mobile health; physical activity prescription; cardiovascular risk.

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LIST OF ABBREVIATIONS

α_1	Short-term scaling exponent
AHA	American Heart Association
ApEnt	Approximate entropy
ATPIII	National Cholesterol Education Program–Adult Treatment Panel III
BP	Blood pressure
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eHealth	Electronic health
FPG	Fasting plasma glucose
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein cholesterol
HF	High frequency power
HFnu	High frequency power in normalized units
HOMA-IR	Homeostatis model for insulin resistance
HR	Heart rate
HRV	Heart rate variability
IDF	International Diabetes Federation
LDL	Low density lipoprotein cholesterol
LF	Low frequency power
LFnu	Low frequency power in normalized units
MetS	Metabolic syndrome
MetS-	Without metabolic syndrome
MetS+	With metabolic syndrome
mHealth	Mobile health
RMSSD	Root mean square of successive differences
RRI	R-R intervals
SBP	Systolic blood pressure
SD1	Poincaré plot width
SD2	Poincaré plot length
SDNN	Standard deviation of normal-to-normal intervals
SMS	Short message service (text message)
STEP™	Step Test and Exercise Prescription
T2D	Type 2 diabetes mellitus
TG	Triglycerides
TP	Total power
ULF	Ultra low frequency power
VLF	Very low frequency power
VO_{2max}	Maximal oxygen uptake
WC	Waist circumference
WHO	World Health Organization

CHAPTER 1

Review of the Literature

1.1 Burden of Cardiovascular Disease and Type 2 Diabetes

Cardiovascular diseases (CVD) are the leading cause of death world-wide accounting for 48% of mortality from non-communicable diseases [1]. Additionally, CVDs are responsible for a significant proportion of morbidity accounting for 10% of global disease burden [1]. The Public Health Agency of Canada estimated the cost of CVD in Canada as $22.2 billion in 2000, with $7.6 billion in direct health care costs and $14.6 billion in indirect costs, including lost economic productivity [2].

Type 2 diabetes mellitus (T2D) is an independent risk factor for CVD and cardiovascular complications are common in this patient population. Complications range from microvascular disease including retinopathy to macrovascular disease including coronary heart disease and stroke. In 2004, heart disease was responsible for 68% and stroke was responsible for 16% of all deaths in patients diagnosed with T2D in the United States [3]. In 2009, annual diabetes-related spending was $113 billion in the United States, and this is expected to increase to $336 billion in 2034 [4]. With an increasingly aging and overweight population, the incidence and thus costs associated with CVD and T2D are expected to increase. Strategies for cost effective management of cardiovascular risk factors to prevent or delay disease progression and reduce disease burden are needed.

1.2 Cardiometabolic Risk

The Canadian Cardiometabolic Risk Working Group defines cardiometabolic risk as any factor that increases the risk of cardiovascular morbidity and mortality [5]. Three

primary categories of cardiometabolic risk are: 1) Global cardiometabolic risk, which encompasses all novel and emerging risk factors along with the traditional factors; 2) Metabolic syndrome (MetS), which is a specific set of risk factors that, in combination increase the relative risk of developing CVD and T2D; and 3) Traditional risk scores, such as the Framingham Risk Score, which use validated mathematical algorithms to calculate an absolute cardiovascular risk [5]. The following section will discuss what MetS is and how it can be used in combination with absolute risk scores to classify risk. Importantly, heart rate variability (HRV) will be discussed including methodological details, physiological background, and potential as an emerging, novel cardiometabolic risk factor.

1.2.1 Metabolic Syndrome

Cardiovascular risk factors tend to cluster in a given individual. In 1988, Reaven described what he termed "Syndrome X" – a combination of insulin resistance, hyperglycaemia, hypertension, reduced high density lipoprotein cholesterol (HDL) and increased low density lipoprotein cholesterol (LDL) [6]. The importance of considering the increased risk of developing CVD and T2D in individuals with clustering of these risk factors was recognized. Since that time, Syndrome X has been re-named MetS, and the risk factors have been modified. There are a number of MetS definitions, all with slightly different criteria. The National Cholesterol Education Program – Adult Treatment Panel III (ATPIII) guidelines are most widely used criteria as they are more focused on all-round CVD risk. Diagnosis requires the presence of three of the following five risk factors in an individual: increased waist circumference (WC), blood pressure (BP), fasting plasma glucose (FPG) and triglycerides (TG) and reduced HDL, all of which are

readily measured in clinic settings [7]. MetS increases the five-year risk of developing CVD two-fold, and the lifetime risk of developing T2D five-fold [8].

The Canadian Cardiometabolic Risk Working Group emphasizes that MetS is a relative risk indicator and therefore, its importance will vary based on absolute cardiovascular risk [5]. They suggest that consideration of MetS status along with an absolute risk score may be ideal for clinical risk profiling. As a relative risk indicator, the presence of MetS would approximately double an absolute cardiovascular risk score. For example, an individual with a Framingham Risk Score of 2% with MetS would only have a combined ten year risk of developing CVD of 4%, while an individual with a Framingham Risk Score of 20% with MetS could be considered to have an actual risk of 40% [5]. Longitudinal studies are needed to determine the precise algorithm for the relative risk calculation, but the hypothetical scenario presented by the working group demonstrates that MetS may be particularly dangerous to individuals with high absolute risk scores.

1.2.2 Heart Rate Variability

Control of the heart is complex with input from many systems, including the nervous system. The autonomic nervous system has two main branches: 1) The parasympathetic nervous system, which is responsible for slowing heart rate (HR) and reducing myocardial contractility; and 2) The sympathetic nervous system, which speeds HR and increases myocardial contractility. Proper cardiac control is reliant on the proper function of and balance between these two branches of the autonomic nervous system. Heart rate variability (HRV) is a non-invasive indicator of cardiac autonomic function with important prognostic value. Measurement involves collection of consecutive R-R

intervals (RRI) from an electrocardiogram (ECG) or HR monitor. Commonly, either long-term recordings of 24 hours or short-term recordings of five minutes duration are analysed. Since overall variability is dependent upon the length of the recording, HRV should only be compared within or between individuals if the same length of data was analysed [9]. It is necessary to remove non-sinus rhythm beats, such as premature ventricular contractions, before analysis. A number of different mathematical analyses may be carried out to calculate HRV.

Time domain analysis

Time domain analysis is commonly used due to the relative ease of calculation and because stationary data is not required. Therefore, it can be used to analyse 24 hour data. Primary time domain indices are the standard deviation of normal-to-normal intervals (SDNN), root mean square of successive differences (RMSSD) and the percentage of normal-to-normal intervals greater than 50 ms (pNN50). Administration of low-dose scopolamine to enhance parasympathetic cardiac outflow increased SDNN 23%, RMSSD 49% and pNN50 78%, suggesting significant contribution of vagal activity to each HRV parameter, and substantial contribution to RMSSD and pNN50 [10]. SDNN is an index of total cardiac variability over the recording period, while RMSSD and pNN50 measure short-term variation and are reflective of parasympathetically mediated processes [9]. However, RMSSD is used preferentially over pNN50, as the mathematical algorithm is more robust [9].

Frequency domain analysis

Frequency domain analysis has been used extensively in research. The RRI time series is decomposed into underlying frequencies using Fast Fourier Transform or Autoregressive modeling. Each frequency band is classically considered to represent physiological processes, though there is much debate around this issue. Signal stationarity is essential for valid calculation, so short-term recordings are most applicable, though data can be separated into equal length epochs (i.e. one hour) and averaged for the 24-hour collection period. The power spectrum is composed of four power frequency bands: ultra low (ULF; 0-0.003Hz), very low (VLF; 0.003-0.04Hz), low (LF; 0.04-0.15Hz) and high frequency power (HF; 0.15-0.4Hz). Total power (TP) is often calculated as well, as are both LF and HF in normalized units [LFnu = LF/(LF+HF); HFnu = HF/(LF+HF)] and LF/HF.

The physiological backgrounds of the ULF and VLF bands are not as well studied as other measures. Serrador and colleagues [11] showed that ULF was reduced during an approximately three-hour session of inactivity (i.e. sitting and reading) compared to a day of typical daily activity (i.e. activities of daily living, not exercise). Since ULF was strongly correlated to the quantity of muscle activity, authors suggested that ULF may be related to mechanisms associated with modulation of energy expenditure [11]. Generally, ULF is interpreted to be reflective of thermoregulation or hormonal systems. Bernardi and researchers [12] showed that rhythmic or spontaneous physical activity increased VLF power three- to five-fold compared to rest, suggesting that some aspects of energy expenditure may be represented in VLF as well. There is also evidence to support some contribution of the renin-angiotensin system to VLF power, but enalaprilat administration to block angiotensin converting enzyme only modestly increased VLF

power by 21% [13]. However, atropine administration to abolish vagal outflow reduced VLF power 92% in healthy young adults, suggesting parasympathetic influence is the primary physiological component of the VLF band [13].

Early studies concluded that LF was an index of sympathetic activity [14], but many studies since have proved otherwise. Cardiac noradrenaline spillover, the gold standard measurement of cardiac sympathetic outflow, was not correlated with LF power [15,16] and cardiac β-adrenergic stimulation decreased LF, rather than increased as would be expected [17]. Additionally, in conditions known to increase sympathetic outflow, such as congestive heart failure [18,19] and aging [20,21], LF is decreased. In fact, age is the major determinant of LF oscillations at rest, with reduced LF associated with advancing age [22]. Additionally, in patients with pulmonary hypertension, LF power is negatively associated with muscle sympathetic nerve activity [23]. Exercise is a powerful sympathetic stimulation and LF was decreased during a bout of incremental exercise [24]. On the other hand, LF was reduced in response to atropine, a cholinergic blockade, suggesting parasympathetic influence [13]. There is some evidence to support an association between LF power of HRV and baroreflex function – one of the reflex control mechanisms for autonomic cardiac modulation. LF power and baroreflex sensitivity were positively correlated [16,25] and LF was increased in participants with normal baroreflex function in response to baroreflex stimulation, but not in those with impaired baroreflex sensitivity [26]. These findings provide a basis for future investigations, but are not conclusive. To date, the physiological meaning of the LF power band of HRV remains controversial.

Resting HF is classically considered to be mediated by respiratory sinus arrhythmia when breathing is greater than 0.15Hz, or about nine breaths per minute [9]. HF is often thought to quantify vagal tone since HF power of HRV is nearly completely abolished by parasympathetic blockade with atropine [27,28] or glycopyrolate [29,30]. However, an important distinction is that HF actually reflects the modulation of vagal tone, rather than the tonic level *per se* [31]. HF was reduced following both a parasympathetic blockade with atropine and parasympathetic withdrawal with nitroprusside; despite similar levels of absolute parasympathetic tone in both conditions, HF was lower during the parasympathetic blockade than during parasympathetic withdrawal [31]. Similarly, incremental doses of vagotonic atropine to increase parasympathetic tone were not correlated to HF or other HRV indices [32]. Research supports modulation of vagal tone as the primary underlying physiological process represented by the HF band.

Nonlinear analysis

Nonlinear analyses differ from time and frequency domain analysis as rather than quantifying the amount of variability they examine heart rate qualities such as fractal characteristics and complexity. Detrended fluctuation analysis quantifies the fractal-like properties of the tachogram [33]. RRI fluctuations are calculated in windows and a log-log curve is plotted. The slope of the first arm of the curve defines the short-term scaling exponent (α_1: from 4-11 beats). When α_1 is equal to one, RRI fluctuations are exhibiting fractal-like behaviour [34,35]. Fractal breakdown can occur with either excessive order ($\alpha_1 = 1.5$) or uncorrelated randomness ($\alpha_1 = 0.5$) [34]. Pharmacologic vagal blockade with glycopyrolate increased α_1 from a value indicative of fractal like behaviour towards uniformity [36]. In response to physiological stimuli, α_1 was increased with exercise,

head up tilt greater than 20 degrees [37] and cold hand immersion [35], all of which reciprocally increase sympathetic and reduce parasympathetic activity. Cold face immersion, which co-activates sympathetic and parasympathetic outflow, resulted in breakdown of fractal-like behaviour demonstrated by increased α_1 in all subjects [35]. In contrast to these studies, Tan and associates [38] reported no changes in α_1 following total autonomic blockade or during tilt. However, baseline values of α_1 were lower in this study than others and authors reported that participants did not demonstrate fractal patterns at rest. This group also showed that α_1 was not reproducible within individuals [38]. Thus, the physiological background of α_1 remains unclear. Considering solely autonomic function may be too simplistic as fractal behaviour likely results from the complex interplay of all mechanisms of cardiac control.

Poincaré Plots

Poincaré plots are often considered nonlinear since the visual appearance of the scattergrams may be interpreted, but statistical algorithms can also be applied to quantify plots. To construct the Poincaré plot, each RRI is plotted against the preceding RRI. The width (SD1) and length (SD2) of the scattergram can be calculated. SD1 was reduced with atropine and increased with scopolamine [39] and is considered a measure of short-term variability, primarily of parasympathetic origin, while SD2 is a measure of total variability [40,41]. Since stationarity is not required, SD1 may be used in place of HF to quantify the vagal component during a dynamic stimulus, such as exercise.

Summary of the physiological background of heart rate variability

In summary, modulation of the parasympathetic outflow, rather than parasympathetic tone, appears to be the main contributor to time and frequency domain and Poincaré plot parameters. The physiologic mechanisms related to nonlinear HR dynamics remain debatable, as do specific mechanisms associated with the lower frequency power bands. Since HRV represents complex physiological interactions, it is difficult to isolate specific mechanisms. Physiological manoeuvres, such as tilt, to stimulate autonomic nervous responses also affect hormonal and other body systems. Likewise, pharmacological agents to stimulate or block autonomic processes may have unintended systemic or local effects that may alter HRV.

Although there are a number of limitations associated with HRV data processing and interpretation, it is used extensively in research and it has been suggested as a valuable clinical tool. Since it is non-invasive and RRIs are easily collected, HRV is a useful tool for examining autonomic function in large population studies. These characteristics give HRV the potential to be a useful clinical tool as a novel cardiometabolic risk indicator. The following section explores this potential in greater detail by discussing the prognostic value of HRV.

Predictive value of heart rate variability

A landmark study showed that post-myocardial infarction patients with reduced HRV (24h SDNN < 50 ms) had triple the risk of all-cause mortality compared to those with higher SDNN [42]. Similarly, post-myocardial infarction patients with 24h SDNN < 70 ms had a 2-year mortality of 10% compared to 2% in patients with normal SDNN [43].

Reduced ULF and VLF components of frequency domain analysis have been linked to patient prognosis following myocardial infarction [44-46].

Research has also examined the prognostic value of short-term HRV in general populations. It has been reported that over a mean follow-up of 9.2 years, those who died had impaired autonomic function demonstrated by reduced SDNN, LF and HF, though there were no differences in LF/HF [47]. Importantly, HRV is reduced in T2D [48,49], a population with a high risk of CVD. Furthermore, those presenting with autonomic impairment and T2D had approximately double the risk of mortality compared to those with autonomic impairment, but without T2D [47]. These studies suggest an interactive effect between traditional cardiovascular risk factors and autonomic function.

A number of studies have examined associations between MetS or its component risk factors and HRV [50-64]. Generally, HRV is reduced in MetS compared to healthy populations and some MetS risk factors were associated with HRV parameters. However, these associations vary considerably based on the study population. A critical examination and review of these findings is needed to synthesize results.

More work is needed in this area to determine specific HRV thresholds for CV risk, as to date, they have been arbitrarily determined based on quartiles. Assuming HRV parameters reflect different physiological processes, alteration of specific HRV parameters may indicate risk for specific disease processes. Despite the need for more knowledge of the physiological background of HRV parameters, evidence to date supports the prognostic value of HRV, suggesting it may be a useful global cardiometabolic risk factor to be considered in risk profiles.

1.3 Risk Management

An Archimedes model of the United States population showed that 78% of adults were candidates for CVD prevention activities, including aspirin administration, weight reduction and control of BP, FPG and lipids [65]. If everyone took part in the prevention activities for which they were candidates, incidence of myocardial infarction and stroke would be reduced by 63% and 31%, respectively [65]. Even when more feasible participation levels were considered, myocardial infarction and stroke could be reduced 36% and 20%, respectively [65]. However, with the current modes of intervention delivery, the only cost-effective prevention activity was smoking cessation [65]. Thus, strategies are needed to develop cost-effective prevention programs targeting other important risk factors.

Insufficient physical activity is the fourth leading risk factor for cardiovascular mortality, behind raised BP, tobacco use and raised FPG [1]. According to accelerometer data 85% of Canadians [66] and 90% of Americans [67] are not meeting recommended physical activity guidelines. Greater cardiorespiratory fitness has been shown to provide a strong protective effect, attenuating the effects of MetS on all-cause and cardiovascular mortality in men [68]. Thus strategies for delivery of cost-effective interventions for increased physical activity, especially those aimed at increasing cardiorespiratory fitness, have the potential to substantially reduce CVD burden. The next section discusses the efficacy of exercise training as a cardiometabolic risk modifier by examining effects on MetS and HRV.

1.3.1 Exercise interventions in Metabolic Syndrome

Health behaviour modification, including increased physical activity to meet global guidelines [69], is recommended as a primary treatment strategy for cardiometabolic risk [5,8]. The effects of exercise on individual MetS risk factors have been reviewed extensively [5,70,71]. However, only one meta-analysis has examined the effects of exercise on MetS risk factors in studies on populations with MetS [72]. Of the studies included in the meta-analysis, training interventions were eight to 52 weeks duration, frequency of two to five sessions per week for 40-60 minutes per session at moderate to high intensity, with the exception of one study which examined low intensity exercise. Endurance exercise training reduced WC, SBP and DBP and increased HDL, with no changes in FPG or TG [72]. Authors suggested that the reduction in FPG may have reached statistical significance had baseline values been higher, but since only one study included individuals with T2D, FPG was relatively normal prior to exercise training [72]. High intensity interval training resulted in greater improvements in FPG than moderate intensity continuous exercise of the same volume, while changes in WC and BP were similar between groups [73]. Since few studies included in the systematic review included high intensity exercise, this may also explain lack of change in FPG. However, with low levels of participation in physical activity, moderate intensities may be more acceptable for the general population and therefore more likely to be adopted into daily habits than vigorous activity.

The Diabetes Prevention Study and Diabetes Prevention Program were two landmark studies investigating the effects of lifestyle intervention on disease progression. The Diabetes Prevention Study compared a lifestyle intervention aimed at increasing physical activity and dietary fibre and reducing saturated fats with a 5% weight loss goal to a

control group [74]. Participants were aged 40-65y, overweight and presented with impaired glucose tolerance [74]. After a mean study duration of 3.2y, MetS risk factors WC, SBP, DBP, FPG and TG were reduced to a greater extent in the intervention compared to the control group, with no differences in HDL. Additionally, after two years, the risk of developing type 2 diabetes was 58% lower in the intervention than the control group [74]. At four [75] and nine [76] years following cessation of the intervention, relative risk remained 43% and 38% lower, respectively in the intervention group. Risk reduction was predicted by adherence to the lifestyle changes after the program had stopped [75,76], highlighting the importance of post-program support.

The Diabetes Prevention Program similarly compared an intensive lifestyle intervention, but to pharmacological therapy with metformin or placebo plus standard lifestyle recommendations [77]. Participants were aged 25y and up, overweight and had impaired glucose tolerance [77]. At an average follow-up of 2.8y, incident diabetes was reduced by 31% in the metformin group and 58% in the intensive lifestyle intervention group compared to the placebo group [77]. Following this intervention, all participants were invited back for a long-term follow-up with the intensive lifestyle intervention and after ten years, the incidence of diabetes was equal in all groups, now receiving equal lifestyle advice and support [78]. This is supported by a recent meta-analysis which demonstrated the effectiveness of both pharmacological and lifestyle interventions in reversing MetS [79]. When MetS was treated with anti-diabetic, lipid controlling or appetite suppressant pharmacotherapy, the odds of MetS reversal was increased 60% compared to control with no intervention, and when MetS was treated with lifestyle intervention (dietary or exercise advice or supervised exercise), the odds of MetS reversal was increased almost

four-fold compared to control [79]. Although the heterogeneity of studies included in the analysis prevented conclusive results, there was an 87% probability that lifestyle interventions were more effective than pharmacological interventions [79]. Together, these studies highlight the importance of lifestyle interventions, including physical activity, to treat MetS risk factors and importantly to prevent development of disease.

1.3.2 Exercise interventions to improve HRV

Studies investigating the effect of exercise on HRV have had mixed results. An early study showed that young adults with mild hypertension who completed 22 minutes of calisthenics followed by 20 minutes of jogging a minimum of five times per week increased resting RRI and HFnu and reduced LFnu [80]. A 30-week exercise training intervention, walking or jogging three to four times per week for 30 minutes per day at 68-81% HR reserve increased SDNN in middle-aged to older men [81]. Similarly, in post-menopausal women, lower intensity exercise at 50% of maximal oxygen uptake (VO_{2max}) three to four times per week for 45 minutes increased RMSSD, SDNN and absolute values of frequency domain HRV parameters, with no change in LFnu or HFnu [82]. One study in T2D patients with and without cardiac autonomic neuropathy showed improvement in HRV parameters following six months of aerobic exercise three times per week at 70-85% of HR reserve [83]. Other studies also showed improvements in HRV in sedentary men following eight weeks of exercise training 6 days per week for 30-60 minutes per session [84,85], and these improvements were partially preserved following 10 months of post-program home-based exercise [84]. Conversely, one study showed no change in HRV parameters at rest or during exercise in older men and women

after eight weeks of aerobic exercise training three times per week for 60 minutes each session [86].

Other studies found that while resting HRV was not altered with endurance training, HRV was altered during exposure to stressors [87-89]. One session of high-intensity training and one session of low-to-moderate intensity exercise per week for 14 weeks reduced HR and increased HRV at the same absolute workload following training, but there were no differences in resting HRV, or HRV at the same relative workload [88]. Similarly, in obese women with and without T2D, 16 weeks of moderate intensity endurance training (65%VO_{2max}) four days per week increased post-exercise HR recovery, HF and LF with no changes in resting HRV [87]. Six months of exercise training two days per week for 70 minutes at moderate intensity did not affect resting HRV in T2D patients, but HFnu was increased and LF/HF reduced during an orthostatic challenge [89]. Reasons for discrepancies between trials may be due to exercise program or population characteristics.

Frequency of exercise training may be an important factor, as those with sessions five to six times per week [80,84,85] showed improved HRV, while in those with training sessions four times per week or less, results were mixed. In four studies that did not show changes in resting autonomic function, exercise training frequency was only two or three times per week or only one session per week was supervised and the remaining were completed at home, so compliance to the exercise protocol may not be as high as reported.

Exercise duration, on the other hand, did not affect HRV modifications toward vagal dominance following an eight-week aerobic exercise intervention [85]. Thirty or 60-minute sessions six times per week at approximately 75% VO_{2max} had similar effects on frequency domain HRV parameters and fractal correlation properties of RRI data [85]. Again, moderate-to-vigorous activity on most days of the week appears to be important for HRV modification, though duration longer than 30 minutes does not seem to have added value.

Exercise intensity may play a role in modifying HRV. Cornelissen and associates [90] showed that healthy adults aged 55 years and older completing three one-hour exercise sessions per week for ten weeks reduced RRI when intensity was both 33% and 66% of HR reserve. However, only the lower intensity group increased TP, though there were no changes in other HRV parameters in either group [90]. However, a number of exercise interventions with moderate-to-vigorous intensity exercise reported change [80,81,83-85]. Differences may be due to participant characteristics. Overtraining has been shown to reduce HRV in athletes [91], so in the general population and especially in sedentary and patient populations HRV may be reduced at lower training loads. Kiviniemi and colleagues [92,93] developed a protocol whereby daily training intensity was prescribed according to morning HRV. If HRV was increased, higher intensity exercise was prescribed, or if HRV was reduced lower intensity exercise or a day of rest was ordered [92,93]. This unique protocol may produce the ideal exercise training program optimizing frequency and intensity based on individual physiological state.

Age may be important factor in HRV responses to exercise. Lee and colleagues [94] examined the effects of low doses of atropine (which are parasympathomimetric, as

opposed to higher doses, which are parasympatholytic) on changes in RRI and HRV in young and old fit and unfit individuals. While resting RRI was increased in fit individuals compared to unfit, the responses to parasympathomimetic atropine were affected by age and fitness did not attenuate age-related declines in response [94]. Thus the lack of change in HRV in response to exercise training may be due to reduced function or sensitivity of the sinus node with age, which may not be modified with intervention. One study in older women showed that exercise improved HRV when 50%, 100% or 150% of national exercise guidelines was completed; however, in women aged > 60y, there were no improvements at lower exercise doses – only higher ones [95]. These findings suggest that improved HRV may be less attainable in older age groups and that achievement of National physical activity guidelines may be especially important in older populations to manage cardiometabolic risk.

In the Diabetes Prevention Program, intensive lifestyle modification (physical activity and low fat diet) reduced HR and increased SDNN and RMSSD compared to metformin or placebo [96]. Importantly, reductions in HR and increases in SDNN and RMSSD over time were associated with lower risk of incident diabetes, independent of weight loss and physical activity in the lifestyle modification group, supporting the use of HRV or the change in HRV in response to an intervention, as a risk indicator [96]. HRV was measured from 10s ECG segments, so neither frequency domain nor nonlinear parameters could be examined, which also have important prognostic power, as reviewed earlier. Nevertheless, these results are promising and suggest that lifestyle modifications are important for risk reduction in a diabetes prevention strategy.

1.4 Strategies for exercise programming

There is a plethora of evidence to support exercise as an important component of cardiovascular risk reduction and diabetes prevention programs. While supervised exercise is important in clinical studies to ensure program compliance and to properly control factors such as exercise intensity and duration, implementation of such programs at a population level would be costly and impractical. The following section discusses two strategies for exercise intervention that have potential to cost-effectively reach a large population and effectively reduce cardiometabolic risk.

1.4.1 Exercise Prescription in Primary Care

Exercise prescription in primary care has proved to successfully engage patients in healthy physical activity behaviours [97] and receiving a written prescription is more effective than oral advice [98]. The Step Test and Exercise Prescription (STEP™) is an effective tool for testing fitness and providing a written exercise prescription in primary care [99] and it has been validated in adults aged 18-85 years [100,101]. The STEP™ fitness assessment involves stepping up and down a set of two steps (each with a rise of 20cm) 20 times at a pace the participant would normally climb the stairs [99]. Since there was no difference in outcome when the test was completed at a normal or a fast pace, a normal pace was selected to make the test safer for a broader population [101]. Post-exercise HR is palpated from the radial artery and included in a predictive equation for VO_{2max}. Appendix 1 provides the full STEP™ protocol including the predictive equation. Following the step test, an exercise prescription is written including fitness, fitness rating, a target exercise HR and recommendations for aerobic exercise based on national guidelines.

Implementation of STEP™ requires few resources. In primary care it can be delivered either by a physician or allied health professional, and counseling can be done individually or in groups. Additionally, STEP™ is also valid when a standard staircase or kitchen step stool is used in place of the original STEP™ unit [102]. Since few resources are needed, STEP™ could also be implemented in community settings to reduce the burden on family health teams and to reach individuals who do not have a family physician.

A recent systematic review and meta-analysis showed that STEP™ was the only exercise prescription in primary care intervention protocol that showed significant effects on cardiorespiratory fitness [103], which is important considering that increased cardiorespiratory fitness reduced cardiovascular mortality [68]. Authors hypothesized that this was due to one feature that was unique to STEP™, which was the inclusion of prescription of a target exercise HR [103]. Global guidelines recommend accumulating 150 minutes of moderate-to-vigorous aerobic activity weekly for optimal health benefits [69]; thus, inclusion of target exercise HR could be an important component to the exercise prescription to ensure that the appropriate exercise intensity is reached.

STEP™ has proved to be an effective tool, particularly as a first-line treatment for MetS. A recent review showed that STEP™ effectively improved MetS risk factors by reducing WC, BP and FPG, although there were no changes in TG or HDL despite positive changes in total and LDL cholesterols [99]. STEP™ intervention has also improved more novel cardiometabolic risk factors, including carotid artery β-stiffness index, distensibility and strain [99]. Thus, STEP has the potential to be an important tool, either in the clinic or community, for cardiometabolic risk management. Since STEP

interventions have consistently improved cardiorespiratory fitness and cardiometabolic risk factors, HRV may also be positively influenced, though this has not yet been examined.

1.4.2 Mobile Health Interventions

Electronic health (eHealth) is defined as "an emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies" [104]. mHealth is a branch of eHealth with essentially the same goals, but with the added benefit of mobility and portability, since the technological medium is a mobile phone. In the United States, 85% of the population owns a mobile phone, and in this group smartphone ownership has risen from 33% in May 2011 to 53% in November 2012 [105]. With the rapid growth of smartphone users, mHealth interventions allow for the potential to reach a broad population. Importantly, many lower income and minority groups have opted to own a smartphone instead of a home computer as a more cost-effective means to combine mobile phone and internet service [106]. In fact, world-wide, the use of short message service (SMS – text messaging) is approximately double that of the internet [107].

There are a number of potential benefits to mHealth interventions. Firstly, as already mentioned, they have the potential for broad reach, since a large proportion of the population owns a mobile phone [105]. Secondly, much like other eHealth interventions, they allow for interactivity to engage users. Interactivity is important for communication between users or between users and technology and it is sometimes considered necessary for behaviour change [108]. Thirdly, since many keep their mobile phone nearby at all

times, it has the potential to act as a trigger or call to action to complete a behaviour. The iStepLog smartphone application was developed to supplement the 10,000 Steps internet-based program and researchers showed that participants used the smartphone application 71.2% of the time and the website only 28.8% of the time [109]. With the opportunity to use either medium for intervention support, smartphone was more popular, possibly because of the increased convenience. Fourth, with internet connectivity, smartphones can empower users by allowing the ability to search for health information when it is needed.

While mHealth interventions have the potential to reach a broad population, there are some limitations. First, since technology changes so quickly, it is difficult to run and complete robust clinical trials before new and improved applications and technologies are available and privacy must be ensured according to HIPPA or other governing bodies. Secondly, there are subgroups of the population with less access to mobile phones, and some of these are important groups for health interventions, such as the elderly [106]. Lastly, additional costs to activate some features of mobile phones may prevent or limit the ability of some to use mHealth interventions to their fullest potential [106].

A recent meta-analysis of mHealth interventions to increase physical activity reported increased pedometer steps, but no change in moderate-to-vigorous physical activity duration [110]. This may be due to differences in populations, as the three studies included in the analysis that examined pedometer steps included adults and one of these was for chronic obstructive pulmonary disease rehabilitation, which may have increased motivation to comply to the intervention. In contrast the studies examining changes in moderate-to-vigorous physical activity duration included one group of children, one of

teenagers, and the remaining three were of adults, including one group of post-natal women. Older adults are more compliant with technology interventions [111], which may account for differences. The results of the meta-analysis should be interpreted with caution. Authors noted that due to the few numbers of published studies, those included in the analysis were rather heterogeneous [110]. Study duration ranged from two to 52 weeks, age ranged from children to older adults, and intervention delivery varied greatly, despite the fact that mobile phones were used in all studies. Additionally, most studies using mobile platforms did not use the full range of features and many used only SMS for reporting and follow-up.

Research to date supports the use of mHealth interventions for diabetes management. In a meta-analysis of 22 studies, Liang and associates [112] reported that reductions in glycated hemoglobin (HbA1c) were 0.5% greater in the mHealth groups compared to control groups, and this difference was even greater in T2D (0.8%). Trials included in this meta-analysis were three to 12 months duration and the interventions using the mobile phone were diverse. Most interventions included transmission of self-monitored FPG, though some used the mobile phone for education only. Twelve of the trials used mobile phone in conjunction with internet as the medium for intervention delivery. Two trials compared internet-based to mobile phone-based interventions. One showed that improvements in HbA1c levels, satisfaction levels and adherence to study protocols were similar between groups [113], while the other showed no change in HbA1c in either group, but there were differences in intervention use [114]. The mobile phone-based group responded to more reminders to check glucose, but the internet-based group submitted more measurements without reminders. Submission of measurements was

higher in the mobile phone group at the beginning of the intervention and decreased in both groups such that in the final month of a three-month intervention, only one of eighteen receiving email reminders and three of twenty-two receiving SMS reminders continued to submit measurements [114]. Together these findings suggest that while the overall results of mHealth versus internet-based interventions may be similar, use of these technologies is different. Interventions may have greater impact if device use is investigated and future protocols are developed according to use patterns.

Evidence also supports the use of mHealth technology for BP control in patients with T2D and uncontrolled hypertension. Logan and colleagues [115] tested the effects of a one-year self-care support intervention, in which participants received a smartphone and Bluetooth enabled BP monitor. Once participants submitted BP measurements, they received automated feedback via smartphone application. If BP was outside of pre-determined limits, they were prompted to take additional measurements and to schedule physician follow-up appointments if needed. Compared to a control group, who monitored BP, but did not get feedback, the intervention group reduced daytime ambulatory systolic BP by 9 mmHg, while there was no change in the control group [115]. Importantly, all of the self-care messages were automated and neither researchers, nor health care workers were regularly in contact with participants throughout the trial.

Interventions utilizing mHealth technology have shown potential as important tools for disease management. To date, one pilot study has examined the effects of an eHealth intervention with a mHealth component in an attempt to control MetS risk factors and thus, prevent disease progression [116]. The study enrolled 226 workers with at least one MetS risk factor according to ATPIII guidelines. The workplace eHealth program

consisted of a four-week education module (60 minutes per session) plus access to telephone counseling, SMS messages and/or email messages for six months. Additionally, pedometers were used to record daily step counts and BP monitors and body fat scales were available in "eHealth zones", which were installed in each participating workplace, to measure BP twice daily and body fat once weekly. SMS messages were sent once weekly to counsel regarding mean step counts, BP and body fat or to follow-up when BP exceeded a threshold limit of 160/100 mmHg. Emails were sent monthly with a summary of readings. Following six months, WC, SBP, DBP and TG were reduced, with no changes in HDL [116]. FPG was also reduced, though only in the group that started with MetS, not in the group with less than three MetS risk factors at screening [116]. Additionally, the number of risk factors was reduced at follow-up – nine percent of the population ended the study with zero risk factors, whereas everyone commenced the study with at least one. In summary, this six-month eHealth intervention improved MetS risk; however, it was limited to a population of workers whose employers accepted the Healthy Workplace Program. Additionally, FPG was not monitored, despite the relative ease of obtaining those measures. Future research is needed to examine the efficacy of a mHealth intervention aimed at home monitoring and management of risk factors, which would allow for the inclusion of a broader population.

1.5 Thesis overview

The overall objective of this thesis was to examine relationships between MetS risk factors and HRV parameters. This was accomplished both cross-sectionally, by examining associations between MetS components and HRV, and longitudinally by investigating associations between changes in MetS components and changes in HRV in

response to a novel intervention combining exercise prescription in primary care with a mHealth home monitoring intervention for reducing cardiovascular risk. It was hypothesized that HRV parameters would be associated with MetS risk factors. Additionally, it was hypothesized that both MetS and HRV would be improved with a mHealth-supported exercise intervention and that the changes in HRV will be associated with changes in MetS risk factors.

Chapter 1 has provided basic background information on HRV and MetS. A literature review examining the effects of lifestyle intervention, primarily increased physical activity and exercise, on modification of MetS risk factors and HRV suggests that there may be a link between the two cardiovascular risk factors. While exercise is known to improve cardiovascular risk, a large proportion of the population does not engage in sufficient amounts of physical activity to get full benefits. This chapter also examined the potential of written exercise prescription in primary care settings or mHealth supported interventions for health promotion.

Chapter 2 is a systematic review to synthesize the cross-sectional evidence to date that has examined differences in HRV in populations with or without MetS and/or associations between HRV parameters and MetS risk factors. This study found that HRV was lower in women with MetS compared to those without, but that findings in men were mixed. One study included in the review suggested that autonomic dysfunction may be the factor responsible for insulin resistance, as alterations in HRV (SDNN and α_1) were seen in persons with one or more risk factors, while alterations in insulin resistance were not apparent until at least two risk factors were present [52]. The review concluded that

more rigorous analysis was needed in future examinations to gain greater understanding of potential mechanisms associated with autonomic dysfunction in MetS.

Chapter 3 is a cross-sectional investigation of associations between HRV parameters and MetS risk factors. As hypothesized, autonomic impairment (demonstrated by reduced HRV) was generally seen in women with MetS, but not men. Multiple linear regression models were run with and without insulin resistance included to determine whether it strengthened the predictive model. Insulin resistance was associated only with HR, which may be reflective of sympathetic activity in MetS populations. While these findings suggest that insulin resistance contributes to sympathetic hyperactivity, but not impaired vagal function in MetS, cross-sectional studies do not allow for conclusive findings, and longitudinal studies are needed.

Chapter 4 is a pilot study to test the feasibility of a mHealth intervention to increase physical activity and improve the cardiometabolic risk profile in a rural population. This eight-week study proved that the technology was acceptable and feasible for participants and researchers. Additionally, despite the short intervention period, fitness and some MetS risk factors were improved and HRV was modified. However, due to the single-sample design of the study, it cannot be concluded that the mHealth support provided any additional benefit to the exercise prescription.

Chapter 5 sought to examine longitudinal associations between changes in HRV parameters and MetS risk factors caused by increased physical activity. To promote increased activity, a randomized controlled trial was run comparing a mHealth application to support increased physical activity to standard of care exercise

prescription. Only changes in HR, SDNN and α_1 were associated with changes in MetS risk factors.

Chapter 6 summarizes the overall thesis and provides direction for future research and knowledge translation activities.

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CHAPTER 2

Heart Rate Variability and the Metabolic Syndrome – A Systematic Review

2.1. Introduction

Metabolic syndrome (MetS) is a clustering of risk factors that increases the relative risk of developing cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2D) more in combination than the simple addition of individual risk [1]. CVDs are the leading cause of mortality worldwide [2] and it has been suggested that management of MetS risk factors could substantially reduce risk [3]. Cardiac autonomic function, which can be measured non-invasively with heart rate variability (HRV), has been suggested as a potential mechanism underlying the development of MetS and CVD because of its predictive power [4]. Autonomic dysfunction characterized by reduced HRV is predictive of development of coronary heart disease [4,5] and T2D [6,7] and of all-cause and cardiac mortality [8,9]. From this perspective, HRV could be a valid tool for monitoring the progression of CVD.

To gain insight into the potential relationship between autonomic function and development of CVD, a number of cross-sectional studies have examined relationships between HRV and MetS [10-23]. Studies have examined differences between HRV in individuals with (MetS+) or without MetS (MetS-) and have investigated associations between HRV parameters and individual MetS risk factors. A number of different MetS definitions, data collection protocols and analyses have been used, which makes interpretation of results difficult. Therefore, the purpose of this systematic review was to

describe the evidence in the literature examining relationships between HRV and MetS and to provide recommendations for future studies.

2.2. Methods

2.2.1 Study Inclusion/Exclusion Criteria

The population of interest was adults aged ≥ 18 years. Studies were required to utilize one of the major MetS definitions [24-27] – therefore, the search was limited to the years 1999 (following publication of WHO guidelines) to 2012. Studies were included if they examined differences in standard HRV parameters [time domain (standard deviation of normal to normal RR intervals (SDNN), root square mean of successive differences (RMSSD); frequency domain (ultra low (ULF: 0-0.003Hz), very low (VLF: 0.003-0.04Hz), low (LF: 0.04-0.15Hz) and high (HF: 0.15-0.4Hz) frequency and total power (TP)) or non-linear (Poincaré plot standard deviation of instantaneous (SD1) and continuous variability (SD2); detrended fluctuation analysis short-term scaling exponent alpha (α_1); beta-index (β) and approximate entropy)] between MetS+ and MetS-, or if they examined associations between HRV and the overall number of MetS components present or between HRV and individual MetS risk factors. Studies were limited to those examining humans. Only papers published in English were included in this review.

2.2.2 Search Strategy

EMBASE and PubMed (1999-December 2012) databases were searched for articles with the key words “heart rate variability” and “metabolic syndrome”. In press articles that could be accessed electronically ahead of print were searched and included in the review.

Reference lists of included papers were examined to select papers that were not identified through database searches.

2.2.3 Quality Appraisal

Articles were reviewed and scored with a Downs and Black scale [28] modified to be appropriate for the cross-sectional studies included in this review. A maximum score of 17 was attainable. Data were extracted (with a form created specifically for this review) on sample size, population demographics, HRV analysis details, MetS classification, HRV in MetS+ versus MetS-, HRV associations with the number of MetS components and with each MetS risk factor – that is, waist circumference (WC), systolic and diastolic blood pressure (SBP; DBP), fasting plasma glucose (FPG), triglycerides (TG) and high density lipoprotein cholesterol (HDL). Authors were contacted in an attempt to clarify data, when needed.

2.3. Results

2.3.1 Identification of Studies

The initial search returned 72 articles. Twenty-five were excluded because they were not original journal articles (i.e. review papers, editorials, letters, notes or abstracts) and twelve were duplicates across databases. Therefore, 35 abstracts were reviewed. Seventeen papers were excluded from the review because analysis did not examine associations between MetS and HRV directly (n=6), experimental design was longitudinal and cross-sectional analyses were not included (n=5), the population did not meet inclusion criteria (due to disease, age or MetS definition that was not standard) (n=4), or heart rate parameters other than standard measures of variability were examined

(n=2). Eighteen full-text articles were reviewed. Four papers were excluded because standard MetS definitions were not used (n=2), HRV analyses were not standard (n=1), or associations between MetS and HRV were not directly examined (n=1) (Figure 1).

2.3.2 Summary of Included Studies

The 14 studies included in the review are summarized in Table 2.1. Quality scores ranged from 7-14 out of a maximum of 17. Despite known sex differences and age effects, not all studies adjusted for these variables. Only three studies separated analysis by sex [10,13,17] and three study populations included only males [11,14,15]. Additionally, heart rate (HR) is known to affect HRV and only one study included an adjustment for this variable [17].

Most studies analysed short-term HRV over a period of three [17] or five [10-13,15,18-20,22] minutes. The ECG recording was collected in the supine [10-13,17,22] or seated position [18-20], or unspecified [15]. One study did not describe short-term HRV analysis – therefore, only 24h HRV from this study was included in this review [21]. Five studies analysed HRV over a 24hr period, four in free living conditions [10,16,21,23] and one under more stable conditions in a laboratory [14]. Since short- and long-term HRV are not directly comparable, these analyses will be considered separately in this review.

2.3.3 Heart rate variability according to metabolic syndrome status

Table 2.2 summarizes the eight studies that examined differences in short-term HRV between MetS+ and MetS- [10-13,17-21]. Scores ranged from 7-14.

Figure 2.1: Study flow diagram

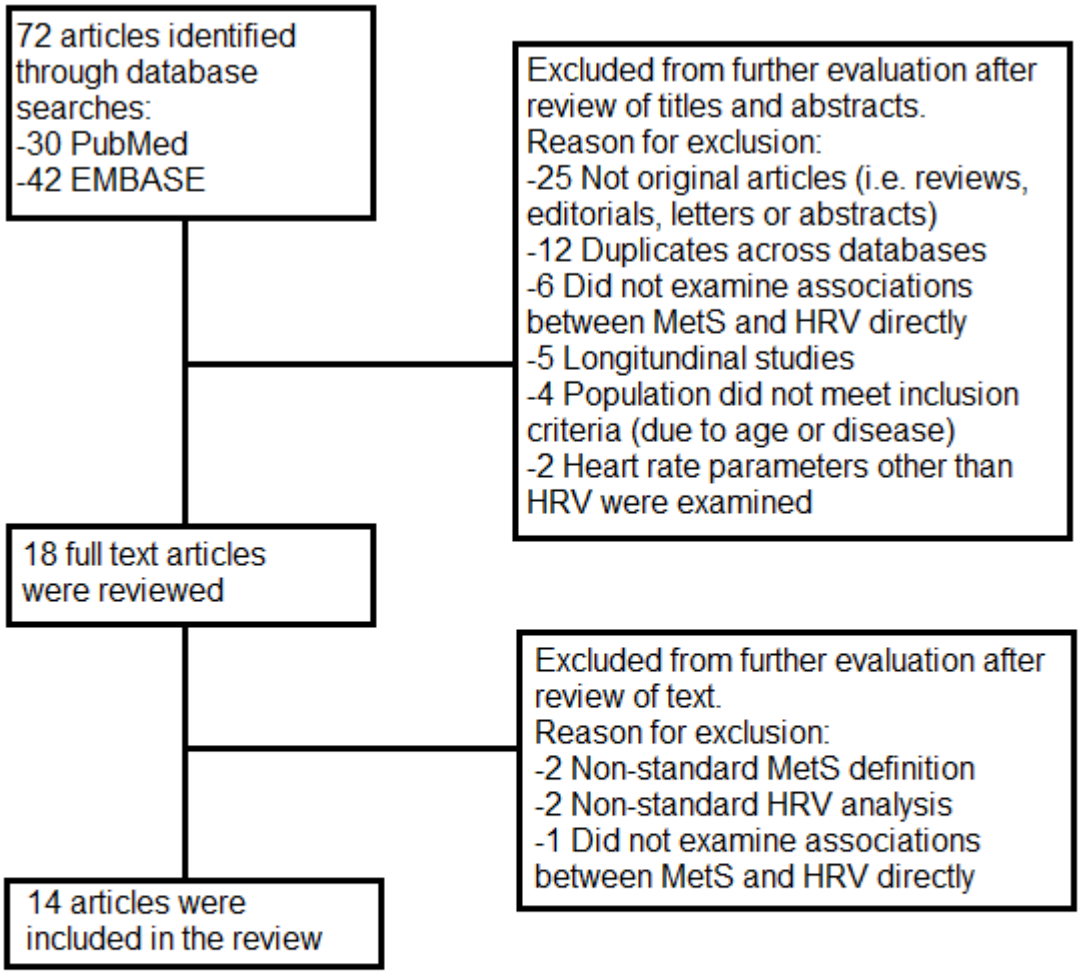

Table 2.1: Summary of literature included in the review

Reference	Score	N	Age Range (y)	Country	Population	MetS defini-tion	HRV analysis
Assoumou et al, 2010 [10]	13	1101	~65	France	Older adults	ATPIII	24 h & 5 min
Brunner et al, 2002 [11]	10	183	45-63	United Kingdom	Working men	ATPIII	5 min
Chang et al, 2010 [12]	14	1298	≥20	Taiwan	General population	ATPIII	5 min
Chang et al, 2012 [13]	7	129	19-62	Taiwan	Intellectual disabilities	ATPIII	5 min
Gehi et al, 2009 [14]	13	288	45-60	United States	Veteran men	AHA	24 h
Hemmingway et al, 2005 [15]	10	2197	45-68	United Kingdom	Working Men	ATPIII	5 min
Jarczok et al, (in press) [16]	13	2441	17-65	Germany	Industrial workers	Harm-onized	24 h
Koskinen et al, 2009 [17]	11	2283	24-39	Finland	Young adults	ATPIII, IDF	3 min
Lee et al, 2011 [18]	7	1027	NR	South Korea	Adults with Schizophrenia	ATPIII	5 min
Min et al, 2009 [19]	12	986	20-87	South Korea	General population	ATPIII	5 min
Min et al, 2008 [20]	12	1041	20-87	South Korea	General population	ATPIII, IDF	5 min
Rasic-Milutinovic et al, 2010 [21]	10	47	NR	Serbia	Aged <65y	ATPIII	24 h & 5 min
Soares-Miranda et al, 2012 [22]	11	163	18-21	Portugal	Young adults	ATPIII, IDF	5 min
Stein et al, 2007 [23]	12	1267	>65	United States	Older adults	ATPIII	24 h

Table 2.2: Summary of investigations examining heart rate variability alteration in metabolic syndrome.

	MetS+ compared to MetS-		
Reference	**Total Population**	**Men**	**Women**
Short-term HRV			
Assoumou et al, 2010 [10]	↓TP, VLF, LF, LF/HF, LFnu, HFnu	NS	↓LFnu, LF/HF
Brunner et al, 2002 [11]	NR	↓SDNN, TP, LF, HF	NR
Chang et al, 2010 [12]	↓SDNN, HF, LF	NR	NR
Chang et al, 2012 [13]	NS	NS	↓TP, VLF, LF
Koskinen et al, 2009 [17]	NR	↓HF ↑LF/HF	↓HF, HFnu ↑LFnu, LF/HF
Lee et al, 2011 [18]	Schizophrenia – NS Healthy - ↓SDNN, RMSSD, LF, HF	NR	NR
Min et al, 2009 [19]	↓SDNN, HF, LF	NR	NR
Min et al, 2008 [20]	↓SDNN, HF, LF	NR	NR
24h HRV			
Assoumou et al, 2010 [10]	↓TP, ULF, VLF, LF	NS	↓TP, VLF
Gehi et al, 2009 [14]	NR	↓TP, VLF, LF	NR
Rasic-Multinovic et al, 2010 [21]	↓HF, ↑LF/HF	NR	NR

HF – high frequency; HFnu – high frequency, normalized units; HRV – heart rate variability; LF – low frequency; LFnu – low frequency, normalized units; MetS+ - with metabolic syndrome; MetS- - without metabolic syndrome; NR – not reported; NS – not significant; RMSSD – root mean square of successive differences; SDNN – standard deviation of normal-to-normal intervals; TP – total power; ULF – ultra low frequency; VLF – very low frequency.

The six studies that scored highest (10-14) showed HRV differences in MetS+ and MetS- women. Three studies showed that in a general population, SDNN, HF and LF were reduced in MetS+ compared to MetS- [12,19,20]. Two large studies, one of older adults (aged 65.6y) [10] and one of young adults (aged 29-34) [17] showed that some HRV parameters were altered in MetS+ compared to MetS- women, but both showed no differences in men. Young MetS+ women had reduced HFnu and increased LFnu and LF/HF [17], while older MetS+ women had reduced LFnu and LF/HF [10]. Contrary to these results, in a smaller cohort of middle-aged men (aged 45-63y) SDNN, TP, LF and HF were reduced and HR increased in MetS+ compared to MetS-, with no differences in LF/HF [11].

Two lower scoring studies (7) examining more specific populations showed similar results. There were no differences in HRV in MetS+ compared to MetS- in male adults with intellectual disabilities, although MetS+ women with intellectual disabilities had reduced TP, VLF and LF [13]. There were no differences in MetS+ versus MetS- in schizophrenics, but in healthy adults, MetS+ showed reduced SDNN, RMSSD, LF and HF [18].

Three studies examined 24h HRV differences between MetS+ and MetS- [10,14,21] (Table 2.2), all of which received moderate-to-high scores (10-13). Two studies examined middle-aged (aged 46-60y) [14] or older adults (aged 65.6y) [10] and showed reduced TP, VLF and LF in MetS+ with no differences between HF or LF/HF. ULF was reduced in older adults with MetS [10], but not in the population of all males [14]. In a small sample of the general population aged less than 65y, lnHF was reduced and lnLF/HF was increased in MetS+ compared to MetS- [21]. Night-time HRV was

reported in one study, which showed that TP, VLF, LF, LF/HF and LFnu were reduced and HFnu increased in MetS+ compared to MetS- [10].

2.3.4 Heart rate variability and the number of metabolic syndrome components present

Four studies described changes in short-term HRV parameters with increasing number of MetS components [10,12,17,20]. All scored moderate-to-high on the modified Downs and Black scale (11-14). Chang et al. [12] showed that SDNN was reduced when one or more risk factors were present compared to zero risk factors. Two studies showed that there were no differences in frequency domain measures of HRV until at least three MetS risk factors were present [10,12]. Min and researchers [20] reported reductions in HRV with increasing number of MetS components, but did not report p-values, so significance is unknown. Koskinen and colleagues [17] showed that the number of MetS components present was indirectly related to HF, LF and TP and directly related to LF/HF; however, after adjustment for age and resting HR, the inverse relationship to HF and relationship to LF/HF persisted in women only.

The relationship between number of MetS components and HRV was also described by three high scoring (12-13) studies that examined 24h HRV [10,14,23]. One study examined the association between HRV and the number of MetS risk factors present, in which all HRV parameters except for HF were associated with the number of components [10]. Another study reported on differences between the presence of 0, 1, or ≥2 components [23]. SDNN, TP and ULF were lower in individuals with 2 or more components compared to those with 0 or one component [23]. α_1 was reduced in individuals with 1 or ≥2 components compared to those with 0 components, but there

were no differences between those with 2 and those with 1 components [23]. In older men, it was reported that individuals with all 5 components had an 18-50% reduction in HRV values compared to those with zero risk factors and that each one unit increment in the number of risk factors present reduced VLF by 8% and LF by 15% [14].

2.3.5 Associations between heart rate variability and individual metabolic syndrome risk factors

Table 2.3 summarizes the six short-term and four 24h HRV studies that used regression or correlation to investigates associations between HRV parameters and MetS risk factors.

2.3.5.1 Heart rate variability and waist circumference

Three moderate-to-high scoring studies (11-13) examining large populations showed associations with WC [10,17,20]. WC was negatively associated with SDNN, VLF, LF, HF [20], LF/HF and LFnu [10]. Sex differences were present and conflicting. One study of older adults showed that WC was negatively associated with LF/HF and LFnu in women, but no associations in men [10], while a study of young adults showed WC to be associated with reduced HF, LF and TP in men with no associations in women [17]. These relationships persisted after adjustment for age and HR. Three low-to-moderate scoring studies (7-11) also showed equivocal results [13,15,22]. There were no associations between WC and HRV in young adults aged 18-21 [22], but in women with intellectual disabilities, increasing WC was associated with reduced VLF and LF/HF [13]. In a large cohort of men aged 45-68y, WC had strong inverse relationships with

Table 2.3: Summary of investigations examining associations between HRV and individual MetS risk factors.

Reference	↑ WC	↑ BP	↑ FPG	↑ TG	↓ HDL
Short-term HRV					
Assoumou et al, 2010 [10]	Men: *NS* Women: ↓LFnu, LF/HF All: ↓LFnu, LF/HF	NS	NS	NS	Men: ↓TP, VLF Women: ↓LFnu, LF/HF All: ↓LFnu, LF/HF
Chang et al, 2012 [13]	Men: *NS* Women: ↓VLF, LF/HF	NS	Men: *NS* Women: ↓TP, HF	Men: ↓TP, VLF, HF Women: *NS*	Men: ↓LF/HF Women: *NS*
Hemmingway et al, 2005 [15]	↓SDNN, HF, LF, ↑HR	↓SDNN, HF, LF, ↑HR	↓SDNN, HF, LF, ↑HR	↓SDNN, HF, LF, ↑HR	↓SDNN, HF, LF
Koskinen et al, 2009 [17]	Men: ↓TP, LF, HF Women: *NS*	Men & Women: ↓TP, LF, HF, ↑LF/HF	Men: *NS* Women: ↓HF	NS	NS
Min et al, 2008 [20]	↓SDNN, HF, LF	↓SDNN, HF, LF	↓SDNN, HF, LF	↓SDNN, HF, LF	NS
Soares-Miranda et al, 2012 [22]	NS	SBP: ↓SDNN, RMSSD, HF, SD1, ↑HR	↓HFnu, ↑LF/HF	↓HF, HFnu, ↑LF/HF, HR	NS
24h HRV					
Assoumou et al, 2010 [10]	NS	Men: ↓TP, LF, HF Women: *NS* All: ↓TP	Men: *NS* Women: ↓HF, ↑LF/HF All: ↓HF	Men: ↓TP, ULF, VLF, LF, HF Women: *NS* All: *NS*	Men: *NS* Women: ↓TP, ULF, VLF, LF All: ↓TP, ULF, VLF, LF
Gehi et al, 2009 [14]	↓LF	↓VLF, LF	↓LF	↓ULF, VLF, LF, TP	NS

Table 2.3 continued

Jarczok et al (in press) [16]	↓SDNN, RMSSD, LF, HF	↓SDNN, RMSSD, LF, HF	↓SDNN, RMSSD, LF, HF	↓SDNN, RMSSD, LF, HF	↓RMSSD, HF, ↑LF
Stein et al, 2007 [23]	NR	NR	↓SDNN, VLF, ↑HR	NR	NR

BP – blood pressure; FPG – fasting plasma glucose; HDL – high density lipoprotein cholesterol; HF – high frequency; HFnu – high frequency, normalized units; HR – heart rate; HRV – heart rate variability; LF – low frequency; LFnu – low frequency, normalized units; MetS+ - with metabolic syndrome; MetS- - without metabolic syndrome; NR – not reported; NS – not significant; RMSSD – root mean square of successive differences; SDNN – standard deviation of normal-to-normal intervals; TG – triglycerides; TP – total power; ULF – ultra low frequency; VLF – very low frequency; WC – waist circumference.

SDNN, LF and HF [15]. In this study, the relationships between HRV and WC were stronger than relationship between HRV and all other MetS risk factors [15].

Four studies examining 24h HRV scored 13 (high scores). One study showed that WC was associated with all HRV parameters and that WC was the risk factor with strongest associations [16], while another study showed no associations [10]. A study of males showed that LF was reduced with increased WC [14]. When night-time HRV was examined, WC showed no association with HRV [10].

2.3.5.2 Heart rate variability and blood pressure

Relationships between BP and short-term HRV are inconsistent in the literature. One moderate-scoring study showed that HF, LF and TP were indirectly, and LF/HF directly associated with SBP in men and women when adjustments were made for age, but when HR was also adjusted for, only increased LF/HF was associated with increased SBP in women [17]. A high-scoring study found that SDNN, VLF, LF and HF were negatively related to both SBP and DBP [20], but a study of older adults showed no associations between HRV and BP [10]. A moderate-scoring study of young adults showed SBP to be associated with reduced SDNN, RMSSD, SD1 and HF and increased HR [22]. All HRV parameters had strong linear associations with BP in men [15], but no associations were seen in adults with intellectual disabilities [13].

24h HRV was generally associated with BP. One study demonstrated that all HRV parameters were related with both SBP and DBP, although low HRV was more strongly associated with DBP [16]. Another study showed that hypertension was negatively associated with TP in older adults, but when sex differences were investigated,

hypertension was negatively associated with TP, LF and HF in men, but there were no associations in women [10]. One study reported that hypertension was associated with VLF and LF in men [14]. Night-time HRV was not associated with BP [10].

2.3.5.3 Heart rate variability and fasting plasma glucose

Associations between FPG and short-term HRV vary. Three moderate-to-high-scoring studies showed differing results. One showed that all HRV parameters were negatively related to FPG [20], while another showed that FPG was associated with reduced HF in women, but not in men [17]. However, when HR and age were accounted for, no associations persisted [17], nor were there any relationships in older adults [10]. Moderate-to-low-scoring studies showed that increased FPG was associated with reduced HFnu and increased LF/HF in young adults [22] and with reduced HF and TP in women with intellectual disabilities [13]. In males, FPG had strong linear associations with all HRV parameters [15].

In long-term HRV studies, multivariate analysis showed that increased FPG was associated with reduced 24h RMSSD, SDNN, HF and LF and increased HR [16]. A positive linear relationship was demonstrated between FPG and HR in the range of 4.4-6.4mmol/L and a negative linear relationship was shown between FPG and both SDNN and VLF [23]. A study of older men showed that increased FPG was associated with reduced LF [14], while another study showed no associations between FPG and HRV in men, but negative and positive associations with HF and LF/HF, respectively, in women [10]. One study showed no associations between night-time HRV and FPG [10], while

another reported that increased FPG was associated with reduced RMSSD, SDNN, HF and LF and increased HR [16].

2.3.5.4 Heart rate variability and triglycerides

Differing associations have also been shown between short-term HRV and TG. Two moderate-to-strong studies reported no associations between TG and HRV [10,17], though an inverse relationship in women was demonstrated following adjustment for age and HR [17]. Another strong study with a broader population showed that all HRV parameters studied (SDNN, VLF, LF, HF) were negatively related to TG [20]. Moderate-to-low scoring studies also showed varying relationships. In young adults, HF and HFnu were indirectly and LF/HF and HR directly associated with TG [22]. Men showed strong linear associations between TG and all HRV parameters [15], but men with intellectual disabilities showed indirect associations only with HF, VLF and TP [13].

Long-term HRV studies also have had mixed findings. One study showed that TG was associated with all HRV parameters studied [16], while another showed no associations in the whole population or in women [10]. In men, TG was negatively associated with all HRV indices except for LF/HF [10], or negatively associated with only ULF, VLF, LF and TP [14]. There were no associations between day-time HRV and TG, but TG was negatively associated with night-time TP, LF and HF in men [10]. There were no relationships between night-time HRV and TG in women [10].

2.3.5.5 Heart rate variability and high density lipoprotein cholesterol

In most studies, HDL was not associated with any short-term HRV parameter [15,17,20,22]. However, one strong study showed that LF/HF and LFnu were associated

with HDL in the entire population and in older women and TP and VLF were associated with HDL in older men [10]. Additionally, LF/HF was associated with HDL in men with intellectual disabilities [13].

HDL was not associated with 24h HRV in men [10,14], but it was associated with all HRV except SDNN in a general population [16], and with 24h TP, ULF, VLF and LF in women [10]. HDL was negatively associated with night-time TP and VLF in the whole population and with night-time VLF and LF in women, though there were no associations in men [10].

2.4. Discussion

The key findings of this systematic review are that: 1) HRV generally is reduced in MetS+ compared to MetS- in women, but results in men are inconsistent; 2) SDNN and α_1 are reduced with increasing number of MetS components present in an individual, though differences for other HRV parameters may not be apparent until three MetS risk factors are present; and 3) time and frequency domain HRV parameters are associated with MetS risk factors and sex differences are apparent.

Most papers reported on standard frequency domain parameters of HRV. These findings are important because frequency bands are thought to reflect different components of the autonomic nervous system. A number of investigators have shown that the HF band is reflective of parasympathetic activity, while the LF band reflects a combination of sympathetic and parasympathetic activity and the LF/HF ratio is a measure of sympathovagal balance [29]. Papers generally reported that HF and LF were reduced, suggesting reduced vagal activity [11,17-20] and that in women, LF/HF was increased

[10,17] suggesting altered sympathovagal balance. Both of these HRV states are associated with poor health outcomes, though both lifestyle [30] and pharmacological interventions [31] have shown promise in normalizing HRV in MetS patients.

Non-linear HRV analysis has been used in recent years to describe the qualitative, rather than quantitative characteristics of heart rate. Only one short-term [22] and one long-term study [23] examined non-linear HRV. Soares-Miranda and colleagues [22] reported that SD1 was reduced in young MetS+ adults compared to MetS-. SD1 is considered to be primarily a measure of parasympathetic activity [32], and supports the results from frequency domain HRV analysis. Stein and researchers [23] examined α_1, which describes the short-term scaling qualities of the heart rate signal. α_1 was reduced when one or more MetS components were present, suggesting that breakdown of fractal-like R-R interval dynamics may be an early contributor to development of MetS and subsequent CVD. The breakdown of fractal complexity occurs when there is a lack of variability and when there is uncorrelated randomness [33]. Fractal breakdown has also been associated with co-activation of the sympathetic and parasympathetic nervous systems [34,35], which suggests that this pattern of autonomic regulation, which is unlike the usual reciprocal interplay between the two autonomic nervous system branches, may be an important mechanism in the progression to CVD. Reduced α_1 has been shown to predict arrhythmic and non-arrhythmic cardiac mortality in patients with depressed left ventricular function following a myocardial infarction [36].

Despite these general conclusions, there were inconsistencies between studies. There are a number of potential explanations for these mixed findings. Data collection methods were not consistent between studies. Specifically, for the short-term data, some ECGs

were collected while participants were seated and some were supine. Posture affects HRV and results from the seated position are more reproducible [37]. Data were generally collected for 5 min, though one study collected data for only 3 min. Perhaps the most important contributor to differences in results was breathing rate during the data collection period. Some studies required their participants to breathe at a constant rate in time with a metronome, while others allowed free breathing. Respiratory sinus arrhythmia is the primary contributor to the HF band of frequency domain HRV. In persons with low breathing rates (less than 0.15Hz), this increase of power will show in the LF band instead. Despite these methodological variances, differences in HRV according to MetS status in women were consistently shown, while differences in men were generally lacking.

The findings of this systematic review are important as they give insight into mechanisms underlying the development of MetS and subsequently CVD and T2D. A review of autonomic nervous system function in MetS showed that the individual risk factors – obesity, hypertension, hyperglycemia and dyslipidemia – all were associated with increased sympathetic and reduced parasympathetic activity [38]. It has been suggested that autonomic alterations may precede risk factor development [4], and this is supported by longitudinal studies which have found that individuals who developed CVD or T2D over an observational study period generally had lower baseline HRV than those who did not develop disease [5-7,39]. While this systematic review supports the hypothesis that autonomic dysfunction is associated with MetS in women, the cross-sectional design of the studies included does not allow causality to be inferred. Studies examining differences in HRV according to presence of MetS risk factors could offer some insight

into causality on the premise that, if autonomic dysfunction precedes development of MetS, it would be expected that HRV would already be reduced when only one or two components were present compared to those with no risk factors. With the exception of SDNN and α_1, altered HRV was not apparent until three or more risk factors were present. However, while this may suggest that HRV is not reduced until MetS is present, it may be that those with lower HRV are more likely to accumulate three or more risk factors, and therefore develop MetS compared to those with higher HRV, who may only develop one or two risk factors. Robust longitudinal studies are needed for clarification.

Insulin resistance has been hypothesized as an underlying mechanism responsible for the clustering of MetS risk factors in individuals [40]. Chang and colleagues [12] examined the association of HRV and insulin resistance with the number of MetS components present in an individual. They showed that HRV was already altered in persons with one MetS risk factor, but insulin resistance was not apparent until two MetS factors were present. Thus, it was suggested that autonomic modifications may precede changes in insulin resistance. Interestingly, sympathetic hyperactivity is associated with insulin resistance [41-43]. This suggests that one of the reasons for discrepancies in the literature regarding associations between MetS risk factors and HRV may be the presence of insulin resistance. Since all five components are associated with insulin resistance, it may actually be insulin resistance and not the MetS risk factors *per se* that is responsible for reductions in HRV. This may also explain the underlying mechanism for reduced HRV in those with three or more compared to those with two or fewer components.

There is no previously published systematic review of the associations between HRV and MetS. Robust methods were used for this review, which included strategies to further

seek out articles beyond simple database searches. However, articles were limited to those published in English. Additionally, there is potential for publication bias. Studies reporting non-significant differences between MetS+ and MetS- may not have been accepted for publication, and therefore, lack of difference between MetS+ and MetS- may be under-reported in the literature.

There were considerable differences between the studies included in this review, which prevented meta-analysis. Differences in data collection, including patient position (i.e. supine versus seated), breathing protocol (spontaneous versus paced), length of ECG recording and type of HRV analysis all affect HRV, and therefore prevent data synthesis.

Since studies included in this review were cross-sectional in design, causality cannot be inferred. Well designed longitudinal studies with robust measures and appropriate control or adjustments for confounding variables are needed to examine associations between HRV and the progression of cardiometabolic risk factors to CVD.

Few studies reported associations between MetS risk factors and non-linear HRV parameters. Examination of these relationships could offer unique insight into mechanisms underlying the development of risk factors and disease.

In conclusion, this systematic review of the literature showed that HRV is reduced in women with MetS, though findings in men are inconclusive. Although HRV has been shown to be reduced with increasing presence of MetS components, SDNN and α_1 are the only parameters that were reduced with fewer than three risk factors in combination. Additionally, HRV is associated with all individual MetS risk factors, though associations vary by population. Future studies should use consistent methods to allow

for better comparability between studies. Additionally, more comprehensive analyses should be performed to ensure that confounders are appropriately accounted for and to investigate potential mechanisms.

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CHAPTER 3

Associations between heart rate variability, insulin resistance and metabolic syndrome risk factors – a cross-sectional study

3.1 Introduction

Heart rate variability (HRV) has been utilized in the non-invasive assessment of cardiac autonomic regulation. Alterations in HRV parameters including reduced standard deviation of normal-to-normal RR intervals (SDNN) and reductions in the HRV spectral frequency bands have been shown to predict cardiac and all-cause mortality in patients with cardiovascular disease (CVD) [1,2] and in the general population [3,4]. Additionally, low HRV may predict the onset of coronary heart disease in individuals with type 2 diabetes mellitus (T2D) [5]. The metabolic syndrome (MetS) is an important clinical clustering of cardiovascular risk factors, which increases the risk of developing CVD and T2D [6]. It is unclear whether a relationship between HRV and MetS could provide an early marker of CVD and T2D risk.

The Cardiovascular Risk in Young Finns Study investigated the association between three-minute supine HRV and MetS components (n=2283) [7]. This study showed that in frequency domain analysis, the number of MetS components present was inversely related to high- and low-frequency (HF, LF) and total power (TP) and directly related to the LF/HF ratio in women [7]. This study was, however, limited to persons between the ages of 24 and 39 years of age, so findings cannot be generalized to a broad population. Min and colleagues [8] examined the relationship between five-minute seated HRV and MetS in a sample of Korean men and women aged 20-87 years (n=1041). They found

that the logarithmically transformed values of the SDNN, LF, HF and very low frequency (VLF) were lower in those with MetS compared to those without MetS [8].

Each MetS component exhibits different associations with HRV parameters, though there are many discrepancies between studies. Although there is no single risk factor that appears to be consistently related to HRV, generally, waist circumference (WC), systolic (SBP) and diastolic blood pressure (DBP), fasting plasma glucose (FPG) and triglycerides (TG) have strong support from the majority of studies examining short-term HRV [7-12], while high density lipoprotein cholesterol (HDL) has only shown association with HRV in two studies [9,11]. Relationships between MetS, the individual components of MetS and non-linear short-term HRV have only been examined in one published study to date and this study only examined Poincaré plot parameters in a young population aged 18-21 years [12]. To date, the relationship between other non-linear parameters, including detrended fluctuation analysis short term scaling exponent (α_1) and approximate entropy (ApEnt), have not been examined in MetS, nor have Poincaré plot parameters been examined in a more representative population of adults.

Insulin resistance has been implicated as an important mechanism linking the clustering of MetS risk factors and autonomic dysfunction, ultimately leading to CVD and T2D [13,14]. Chang and colleagues [15] noted that HRV was reduced in individuals with one risk factor, but insulin resistance was not apparent until two risk factors were present. However, the relationships between HRV, insulin resistance and MetS have not been studied.

Therefore, the purpose of this study was three-fold: first, to determine whether individuals with MetS would have abnormal linear and non-linear HRV compared to those without MetS; second, to determine which MetS risk factors were most strongly associated with HRV parameters (both linear and non-linear); and third, to examine whether insulin resistance was associated with HRV. It was hypothesized that all HRV parameters would be reduced in MetS; that MetS risk factors except for HDL would be associated with HRV parameters; and that insulin resistance would be associated with HRV parameters.

3.2 Methods

This study was part of a multicentre trial conducted between August 2009 and December 2011 at the Gateway Rural Health Research Institute (Seaforth, Ontario) and the Laboratory for Brain and Heart Health at Western University (London, Ontario). Participants were eligible if they were aged 18-70 years and presented with at least one MetS risk factor according to published guidelines [16]. Exclusion criteria were SBP > 180 mmHg and/or DBP > 110mmHg; type 1 diabetes; history of myocardial infarction, angioplasty, coronary artery bypass or cerebrovascular ischemia/stroke; symptomatic congestive heart failure; atrial flutter; unstable angina; unstable pulmonary disease; use of medications known to affect heart rate (HR); second or third degree heart block; history of alcoholism, drug abuse or other emotional cognitive or psychiatric problems; pacemaker; unstable metabolic disease; and orthopedic or rheumatologic problems that could impair the ability to exercise. In total, 224 participants (aged (mean±SD) 57.2±9.0 y, range 23-70y; 72% female) provided informed consent and volunteered for this study,

which was approved by the University of Western Ontario Research Ethics Board (#15828).

Participants reported to the laboratory following an overnight fast, where they were assessed for MetS risk factors. WC was measured at the midpoint between the iliac crest and last rib [17], and participants were considered at risk if WC was greater than 88cm (women) or 102cm (men) [16]. Supine BP was calculated as the average of the last two of three measurements taken at one minute intervals (BpTRU™, VSM MedTech Ltd., Coquitlam, BC or manual). A resting SBP $\geq$ 135 mmHg and/or DBP $\geq$ 85 mmHg qualified as a MetS risk factor [16]. Blood was drawn and sent to a central laboratory for FPG, TG, HDL and insulin analysis. MetS risk factors were FPG $\geq$ 6.1 mmol/L, TG $\geq$ 1.7 mmol/L and HDL $\leq$ 1.03 mmol/L (men) or 1.29 mmol/L (women) [16]. Those presenting with three or more risk factors were categorized as with MetS (MetS+), and those with two or fewer risk factors were considered without MetS (MetS-) [16]. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated with standard methods [18].

Following a light, standardized snack, participants were instrumented for collection of a lead II ECG recording. A respiratory belt (Pneumotrace II, ADInstruments, Colorado Springs, Colorado) was secured around the thorax for collection of respiratory rate. RR intervals (RRI) were collected during ten minutes of supine rest. External stimuli, such as light and noise were controlled to ensure signal stability. Participants were instructed to remain still and awake. All measures were sampled at 1000Hz, input into a data acquisition board (PowerLab ML795, ADInstruments) for analog-to-digital signal conversion with LabChart7Pro software (ADInstruments) and stored for offline analysis.

Lab Chart files were converted to text files for analysis with HRV software (Hearts v7, Heart Signal Co., Oulu, Finland).

A predictive stepping test was used to estimate maximal oxygen uptake (VO_{2max}). The protocol has been published elsewhere [19]. Briefly, participants stepped up and down a set of two 20cm stairs, 20 times, at a pace considered normal. Age, sex, body weight, radial pulse measured immediately upon completing the step test and time to complete test were entered into the predictive equation.

HRV Analysis

Editing of the HR time series was performed by a single investigator. All ECG signals were manually scanned for ectopic or non-sinus beats, which were deleted from the time series. 90% of data were needed for inclusion. Time domain HRV analyses included HR, SDNN and the root square mean of successive differences (RMSSD). The HRV spectrum was computed with the non-parametric fast Fourier transform method. LF (0.04-0.15Hz), HF (0.15-0.4Hz), LF/HF and TP were examined. A Poincaré plot was formed by plotting each RRI against the following one to create a scatter plot. The standard deviation of the width (SD1) and length (SD2) were calculated. The detrended fluctuation analysis method was used to examine fractal characteristics of heart rate fluctuations. The root-mean square fluctuations of integrated and detrended data were measured in observation windows and then plotted against the size of the window on a log-log scale. α_1 was calculated from the slope of the line (from 4-11 beats). ApEnt quantifies the regularity of time series data by calculating the likelihood that runs of patterns that are close will remain close on the next incremental comparison. A greater

ApEnt value represents greater unpredictability in a system. ApEnt was calculated from 500 beats and was computed with length, m=2 and tolerance, r=20%

Statistical Analysis

In total, 23 participants were removed from analysis due to poor data quality, excessive non-sinus rhythm beats or missing data. An additional four were removed from ApEnt analysis as 500 heart beats were not available for analysis. Insulin was not analyzed in 28 participants, who were then excluded from analysis including HOMA-IR. Unpaired t-tests were used to examine differences between normally distributed HRV parameters in MetS+ versus MetS-. Welch's correction was used for variables with unequal variance. A two-sample Wilcoxon test was used when variables were not normally distributed. Since sex differences have been demonstrated [7,9] analyses were run on the entire group and separately for men and women. Multiple linear regression was used to determine which components of MetS were associated with HRV parameters, while adjusting for other variables. An *a priori* decision was made to force age, sex, study site and VO_{2max} into the model to account for potential confounding variables. All MetS components were initially included in the model and the model was run using a backward elimination model-building algorithm, with alpha set at 0.1, serially removing the least important variable. Regression diagnostics were run to test for influential observations and outliers, which were removed when necessary. To test associations with insulin resistance, multiple linear regression models including HOMA-IR were completed as above. Data are presented as mean ± standard deviation (SD) for normally distributed variables, as median and interquartile range (IQR) for non-normally distributed variables, and as regression coefficients (beta estimates) and 95% confidence interval (CI) for multiple

linear regression results, unless otherwise stated. Statistical analysis was performed with R Statistical Software (version 2.15.1) [20].

3.3 Results

Participant Characteristics

Participant characteristics are shown in Table 3.1. Age was similar in MetS+ and MetS-. As expected, MetS+ had greater HOMA-IR, WC, SBP, DBP, FPG and TG, and lower HDL compared to MetS-. Additionally, there were no differences in fitness. In women, MetS+ had greater HOMA-IR, SBP, DBP, FPG and TG, and lower HDL compared to MetS-, but there were no differences in WC. In men, TG was greater and HDL less in MetS+ compared to MetS-, but there were no differences in HOMA-IR, WC, SBP, DBP or FPG. VO_{2max} was higher and HDL lower in men compared to women.

Heart rate variability in participants with or without metabolic syndrome

Overall, there were no differences in time domain HRV parameters between groups in the whole population or in men. Time domain HRV analysis in women revealed that SDNN was lower (38.0(27.0) ms, 44.5(29.3) ms; p=0.020) and HR higher (68(13) bpm, 64(12) bpm; p=0. 018) in MetS+ compared to MetS-, but there were no differences in RMSSD.

After logarithmic transformation for normality, lnLF (5.81±1.09 ln ms^2, 6.11±1.00 ln ms^2; p=0.044) was lower in MetS+ than MetS-, with no differences in lnHF, lnTP or LF/HF. In men, there were no differences in frequency domain measures of HRV between MetS- and MetS+. In women, lnLF (5.73±1.06 ln ms^2, 6.13±1.05 ln ms^2; p=0.022) and lnTP (6.48±1.07 ln ms^2, 6.87±1.04 ln ms^2; p=0.030) were lower in

Table 3.1: Participant Characteristics

	MetS-	MetS+	*p* (MetS- vs MetS+)	*p* (Men vs Women)
n	95	129		
Men	21	41		
Women	74	88		
Age (y)	58(12)	59(10)	*0.778*	*0.75*
Men	57(12)	59(9)	*0.451*	
Women	58(11)	59(11)	*0.887*	
WC (cm)	103.3±14.6	107.3±11.1	*0.036**	*0.09*
Men	105.6±13.0	109.0±10.6	*0.307*	
Women	102.6±15.0	106.5±11.3	*0.089*	
SBP (mmHg)	131(25)	135(17)	*0.020**	*0.84*
Men	135(22)	134(15)	*0.914*	
Women	130(23)	138(20)	*0.014**	
DBP (mmHg)	80±11	85±11	*0.008**	*0.06*
Men	84±11	86±10	*0.596*	
Women	79(11)	84(13)	*0.009**	
FPG (mmol/L)	5.1(0.8)	5.3(1.2)	*0.018**	*0.15*
Men	5.4(0.5)	5.4(1.2)	*0.726*	
Women	5.0(0.6)	5.3(1.2)	*0.019**	
TG (mmol/L)	1.01(0.56)	1.75(0.98)	*<0.001**	*0.16*
Men	1.13(0.63)	1.77(1.08)	*0.002**	
Women	1.00(0.31)	1.75(0.93)	*<0.001**	
HDL (mmol/L)	1.57(0.50)	1.12(0.36)	*<0.001**	*<0.001*
Men	1.21(0.30)	0.96(0.21)	*0.002**	
Women	1.65(0.42)	1.19(0.31)	*<0.001**	
VO_{2max} (ml/kg/min)	30.9±6.3	30.4±5.9	*0.510*	*<0.001*
Men	35.8±4.2	34.9±5.2	*0.527*	
Women	29.6±6.2	28.3±4.9	*0.146*	
HOMA-IR	1.56(1.19)	2.80(2.47)	*<0.001**	
Men	1.77(0.58)	2.95(2.59)	*0.051*	
Women	1.33(1.23)	2.62(2.41)	*<0.001**	

DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein cholesterol; HOMA-IR, insulin resistance; MetS-, without metabolic syndrome; MetS+, with metabolic syndrome; SBP, systolic blood pressure; TG, triglycerides;VO_{2max}, maximum oxygen uptake; WC, waist circumference.

MetS+ compared to MetS-, but there were no differences in lnHF, LF/HF (Figure 3.1).

Overall and in men, there were no differences in non-linear HRV parameters between MetS+ and MetS-. In women, SD2 (46.8(31.6) ms, 58.4(29.9) ms; p=0.014) was reduced in MetS+ compared to MetS-, but there were no differences in other non-linear HRV measures (Figure 3.2).

Heart rate variability and metabolic syndrome components

Table 3.2 presents the results for each best-fit multiple linear regression model, including predictors with alpha <0.1. All models were adjusted for age, sex, study site and fitness and MetS components were tested for inclusion in the final models. For time domain parameters, testing at a conventional alpha level of 0.05, only DBP was associated with HR (p=0.010), although SBP remained in the model to improve the fit. TG was associated lnSDNN (p=0.029), and both WC (p=0.037) and FPG (p=0.012) were associated with lnRMSSD.

In the frequency domain, TG (p=0.047) and HDL (p=0.039) were associated with lnLF and WC was associated with lnHF (p=0.024) and lnLF/HF (p<0.001). No MetS components were associated with lnTP (p>0.05).

For non-linear HRV parameters, WC (p=0.030) and FPG (p=0.018) were associated with SD1, and FPG (p=0.009), TG (=0.048) and HDL (p=0.002) were associated with SD2. WC was associated with α_1 (p=0.023) and FPG was associated with ApEnt (p=0.033).

Figure 3.1: Differences in frequency domain heart rate variability. Black bars, women without metabolic syndrome; white bars, women with metabolic syndrome; striped bars, men with metabolic syndrome; dotted bars, men with metabolic syndrome. * p<0.05 compared to women without metabolic syndrome.

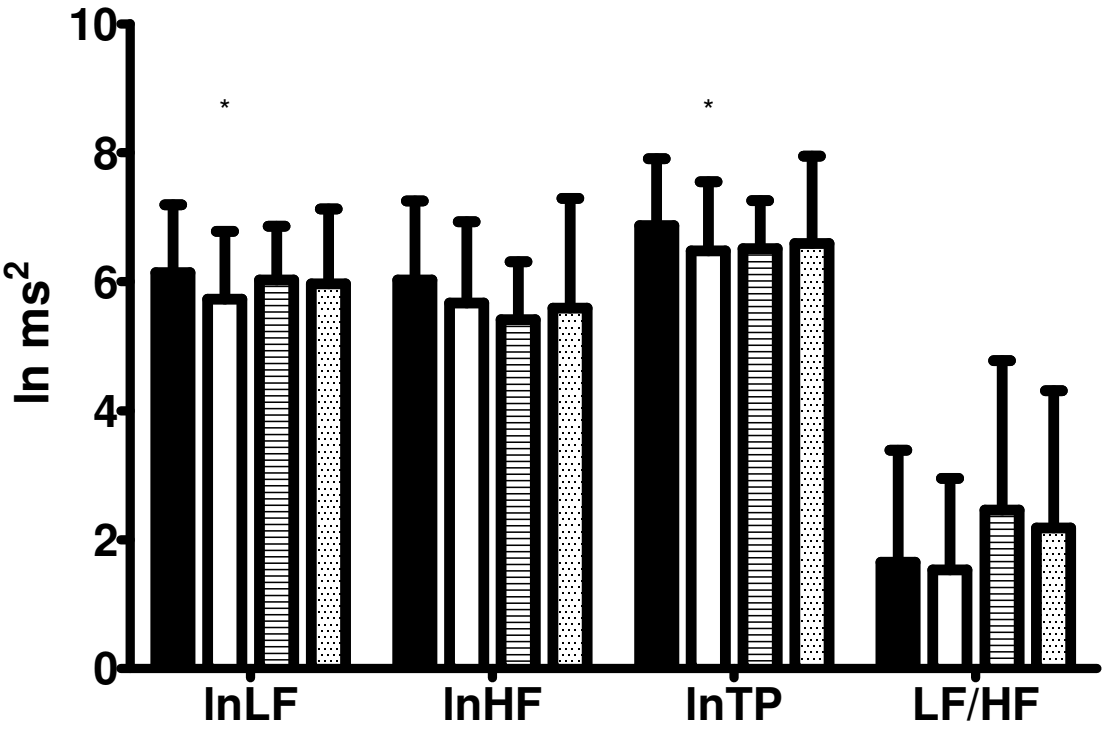

Figure 3.2: Differences in Poincaré plot variables. Black bars, women without metabolic syndrome; white bars, women with metabolic syndrome; striped bars, men without metabolic syndrome; dotted bars, men with metabolic syndrome. * p<0.05 compared to women without metabolic syndrome.

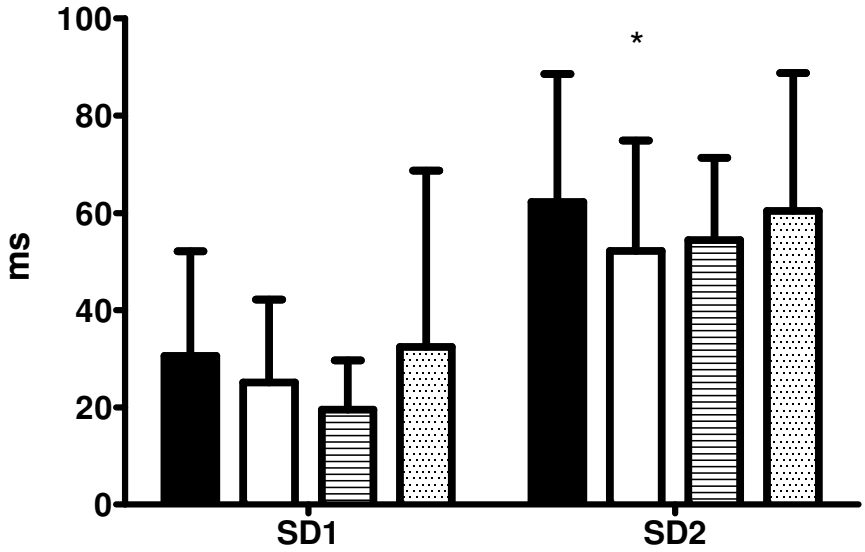

Table 3.2: Multiple linear regression results with metabolic syndrome risk factors

	β	95% Confidence Interval	p-value	F-statistic	Adjusted R^2
HR				*6.289*	*0.209*
SBP	-0.053	(-0.006, 0.000)	*0.062*		
DBP	0.009	(0.002, 0.016)	*0.012**		
lnSDNN				*3.380*	*0.097*
TG	-0.074	(-0.141, -0.008)	*0.029**		
HDL	0.358	(-0.011, 0.727)	*0.057*		
lnRMSSD				*3.556*	*0.125*
WC	-4.38×10^{-5}	$(-8.51\times10^{-5}, -2.52\times10^{-6})$	*0.037**		
FPG	-0.260	(-0.462, -0.585)	*0.012**		
lnLF				*3.106*	*0.087*
TG	-0.152	(-0.303, -0.002)	*0.047**		
HDL	0.880	(0.043, 1.717)	*0.039**		
lnHF				*3.404*	*0.078*
WC	-4.55×10^{-5}	$(-8.50\times10^{-5}, -5.97\times10^{-6})$	*0.024**		
lnTP				*4.553*	*0.082*
TG	-0.125	(-0.271, 0.020)	*0.091*		
LF/HF				*2.877*	*0.079*
WC	4.64×10^{-5}	$(1.95\times10^{-5}, 7.32\times10^{-5})$	*<0.001**		
SBP	-2.34×10^{-4}	$(-5.08\times10^{-4}, 4.11\times10^{-5})$	*0.095*		
lnSD1				*3.436*	*0.110*
WC	-3.41×10^{-5}	$(-4.49\times10^{-5}, -2.31\times10^{-6})$	*0.030**		
FPG	-0.125	(-0.229, -0.213)	*0.018**		
SD2				*4.054*	*0.145*
FPG	-4.798	(-8.387, -1.209)	*0.009**		
TG	-3.457	(-6.878, -0.035)	*0.047**		
HDL	30.847	(11.540, 50.152)	*0.002**		
α_1				*2.346*	*0.045*
WC	-1.07×10^{-5}	$(1.51\times10^{-6}, 2.00\times10^{-5})$	*0.023**		
ApEnt				*2.351*	*0.039*
FPG	-6.31×10^{-3}	$(-1.21\times10^{-2}, -5.07\times10^{-4})$	*0.033**		

ApEnt, approximate entropy; α_1, short-term scaling exponent; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein cholesterol; HF, high frequency power; HR, heart rate; LF, low frequency power; RMSSD, root mean square of successive differences; SBP, systolic blood pressure; SD1, Poincaré plot width; SD2, Poincaré plot length; SDNN, standard deviation of normal to normal intervals; TG, triglycerides; TP, total power; WC, waist circumference.

Heart rate variability and insulin resistance

Table 3.3 shows multiple linear regression results with HOMA-IR included as a variable. HOMA-IR was associated with HR (p=0.003) and improved the fit of the model (Adjusted R^2 0.220). The models for lnSDNN, lnLF and ApEnt were essentially unchanged with the addition of HOMA-IR, while the inclusion of HOMA-IR in the models for lnRMSSD, lnHF, lnTP, LF/HF, lnSD1, SD2 and α_1 reduced the adjusted R^2 value.

3.4 Discussion

The main finding of this study was that HRV profiles were less favourable in MetS+ compared to MetS-, and that differences existed in both linear and non-linear HRV parameters in women, but not in men. Additionally, this study showed that HDL and TG were associated with overall variability, but abdominal obesity and FPG were associated with beat-to-beat HRV controlled primarily by the parasympathetic nervous system. This study was the first to report that Poincaré plot analysis showed reduced parameters in MetS+ compared to MetS- in women, but not men. SD2, which was reduced in women, is considered a marker of long-term variation [21,22]. Physiological modelling showed that the length of the Poincaré plot was correlated equally to both LF and HF spectral powers, which suggests that it is affected by both sympathetic and parasympathetic input [22,23]. Multiple linear regression showed that 14.5% of the variance of SD2 was explained by FPG, TG and HDL in this population. There were no differences in SD1, α_1 or ApEnt in MetS+ compared to MetS-. Interestingly, all of the non-linear parameters that were not significantly different between MetS+ and MetS- were shown by multiple

Table 3.3: Multiple linear regression results with metabolic syndrome risk factors and HOMA-IR

	β	95% Confidence Interval	p-value	F-statistic	Adjusted R^2
HR				*6.550*	*0.220*
IR	1.298	(0.460, 2.135)	*0.003**		
SBP	-0.144	(-0.247, -0.040)	*0.007**		
DBP	0.039	(0.039, 0.409)	*0.017**		
lnSDNN				*2.822*	*0.092*
TG	-0.090	(-0.160, -0.022)	*0.011**		
HDL	0.500	(0.057, 0.870)	*0.017**		
lnRMSSD				*2.260*	*0.053*
TG	-0.208	(-0.421, 0.005)	*0.055*		
HDL	1.086	(-0.172, 2.344)	*0.090*		
lnLF				*3.138*	*0.097*
SBP	0.011	(-0.001, 0.022)	*0.069*		
DBP	-0.021	(-0.041, -0.001)	*0.039**		
TG	-0.173	(-0.331, -0.016)	*0.031**		
HDL	1.152	(0.233, 2.071)	*0.014**		
lnHF				*3.200*	*0.047*
lnTP				*3.262*	*0.064*
TG	-0.143	(-0.293, 0.006)	*0.060*		
LF/HF				*1.876*	*0.056*
WC	$3.27x10^{-5}$	($5.13x10^{-8}$, $6.53x10^{-5}$)	*0.049*		
TG	$-1.57x10^{-2}$	($-3.17x10^{-2}$, $4.84x10^{-4}$)	*0.057*		
lnSD1				*2.310*	*0.055*
TG	-0.104	(-0.210, 0.002)	*0.055*		
HDL	0.535	(-0.095, 1.164)	*0.096*		
SD2				*3.478*	*0.111*
TG	-4.607	(-8.336, -0.879)	*0.016**		
HDL	36.813	(14.917, 58.710)	*0.001**		
α_1				*1.524*	*0.012*
ApEnt				*1.873*	*0.028*
HDL	-0.111	(-0.221, 0.002)	*0.046*		

ApEnt, approximate entropy; α_1, short-term scaling exponent; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein cholesterol; HF, high frequency power; HR, heart rate; HOMA-IR, insulin resistance; LF, low frequency power; RMSSD, root mean square of successive differences; SBP, systolic blood pressure; SD1, Poincaré plot width; SD2, Poincaré plot length; SDNN, standard deviation of normal to normal intervals; TG, triglycerides; TP, total power; WC, waist circumference.

linear regression to be associated with WC or FPG. For both MetS+ and MetS- groups, mean WC was greater than sex-specific cut-offs for MetS risk, and mean FPG lower than MetS thresholds. Hence, any alterations in these HRV parameters that would have been attributed to increased WC as a MetS risk factor may have been equal in both groups.

The results of this study agree with most others that HRV is reduced in women with MetS, but not in men [7,9]. However, some studies have shown alterations in HRV in men with MetS [10]. In the present study, the only MetS risk factors that were different between men with and without MetS were TG and HDL, with no differences between WC, BP or FPG. Additionally, fitness (VO_{2max}) was higher in men than women. Therefore, the MetS+ men may have been healthier than the MetS+ women, which may explain why HRV was not reduced in MetS+ men.

Generally, studies have shown that HRV analysed in both the time and frequency domains are reduced in MetS, but differences exist regarding which parameters are affected. One study showed that all time and frequency domain HRV was reduced in MetS+ compared to MetS- with the exception of LF/HF [10], while others showed no differences at all [11,24]. Another study showed that participants with MetS had reductions in only SDNN, HF, LF and VLF [8]. This is similar to the present study, which showed reduced lnSDNN and lnLF in MetS+ compared to MetS-, but there were no differences in HF. These finding are important as two longitudinal studies of initially healthy populations showed that reduced SDNN, lnLF and lnHF were associated with an increased risk of developing coronary heart disease [25,26]. Frequency domain measures and SDNN were primarily predicted by TG and HDL in this study, which suggests that

management of dyslipidemia may be an important MetS treatment strategy to normalize the HRV parameters that predict mortality.

In this study, lnHF, RMSSD and SD1 were not different between MetS+ and MetS-. These HRV parameters are reduced or abolished with atropine administration, suggesting a strong contribution from the parasympathetic nervous system [22,27]. Reduced HF is predictive of mortality in healthy populations [25,26] and following myocardial infarction [2]. Although there were no differences between groups in this study, both groups had lower HRV than a healthy population [28]. Our population did not include healthy people with no MetS risk factors. Therefore, parameters reflective of vagal activity might actually be more sensitive to disease and the presence of one risk factor may be sufficient to alter cardiac autonomic health. An alternate explanation may be that our population was older (average aged 57.1years). Reductions in HRV parameters reflective of vagal activity may have been due to age or other factors rather than presence of MetS risk factors as the model to predict HF only explained 7.8% of the variance.

It is generally accepted that there is no HRV parameter that is reliably indicative of sympathetic activity. A recent review of autonomic activity in MetS reported a strong association between sympathetic activity and HR in a MetS population; hence authors suggested that HR may be a valid surrogate measure of sympathetic activity [29]. In the current study, MetS+ had a higher HR than MetS- in women. Though more research is needed to confirm validity of the measure, this may suggest that sympathetic activity is increased in MetS. Reviews of the literature have shown that sympathetic activity measured by norepinephrine spillover and muscle sympathetic nerve activity is increased in MetS [14,29,30]. It has been hypothesized that increased sympathetic activity in MetS

may be associated with increased insulin resistance. In this population, both HR and HOMA-IR were increased in MetS+ women but not in men. Interestingly, despite a broad range of HOMA-IR, average HOMA-IR indicated normal insulin resistance in both MetS+ and MetS-. This study does not support previous hypotheses that insulin resistance was a mechanism involved in alterations in HRV in MetS [15]. Addition of HOMA-IR to the multiple linear regression models generally reduced the adjusted R^2 term, suggesting that it actually worsened the fit of the model. However, for HR and lnLF– HRV parameters that arguably may be associated with sympathetic activity – addition of HOMA-IR modestly improved the model. These findings suggest that alterations in insulin resistance may be associated with increased sympathetic activity, but findings do not support associations between insulin resistance and other HRV parameters in MetS.

Potentially a significant contribution to the discrepancy in results may be that MetS components may affect HRV to a different extent. Liao and researchers [31] showed that in patients with multiple metabolic syndrome (defined as any combination of hypertension, diabetes and dyslipidemia), there was a general reduction in HRV parameters with an increasing number of metabolic disorders in a single individual (with the exception of LF/HF, which showed no difference). However, there were differences based on which metabolic risk factors were present. A combination of hypertension with either dyslipidemia or diabetes had additive effects, while a combination of diabetes and dyslipidemia had the lowest HRV, with more than simply additive effects [31]. Thus, simply the presence (or not) of MetS may not be sufficient to cause alterations in HRV, rather, specific combinations of risk factors may be a more important determinant.

Since this was a cross-sectional study causality cannot be inferred. This study was limited to a sample of relatively healthy adults – therefore findings may not be generalizable to populations with overt disease. Participants were not restricted from taking medications prior to ECG recording. Since certain anti-hypertensive medications are known to improve HRV, these may have affected our results.

In conclusion, women with MetS have a less favourable HRV profile than women without MetS, but these relationships were not apparent in men. There is no single MetS risk factor that independently predicts all HRV parameters. Insulin resistance improves model fit for HRV parameters that may be associated with sympathetic function, but not for HRV parameters classically associated with parasympathetic function.

3.5 References

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CHAPTER 4

Diabetes and Technology for Increased Activity (DaTA Study): The effects of exercise and technology on heart rate variability and metabolic syndrome risk factors[1].

4.1 Introduction

An increasingly aging, overweight and sedentary population has a greater risk of developing cardiovascular disease (CVD) and type 2 diabetes (T2D). Metabolic syndrome (MetS) is a clustering of risk factors including hypertension, dysglycemia, dyslipidemia and abdominal obesity. Clustering of these factors doubles the five-year risk of developing CVD and increases the risk of developing T2D five-fold [1]. Expert panels have called attention to the importance of targeting the cardiovascular risk factors of MetS in order to prevent CVD and T2D [1,2].

Heart rate variability (HRV) is a simple, non-invasive measure that can be used to quantify autonomic nervous system function [3]. Diminished HRV predicts all cause and cardiovascular mortality [4-7], and is associated with MetS risk factors [8-11]. In patients with an increased risk of CVD, impaired autonomic function may be especially dangerous. Patients with T2D with low HRV have double the risk of mortality compared

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[1] The results from this paper have been published: (1) Stuckey M, Fulkerson R, Read E, Russell-Minda E, Munoz C, Kleinstiver P, et al. Remote monitoring technologies for the prevention of metabolic syndrome: the Diabetes and Technology for Increased Activity (DaTA) study. J Diabetes Sci Technol 2011;5(4):936-944. (2) Stuckey M, Russell-Minda E, Read E, Munoz C, Shoemaker K, Kleinstiver P, et al. Diabetes and Technology for Increased Activity (DaTA) study: results of a remote monitoring intervention for prevention of metabolic syndrome. J Diabetes Sci Technol 2011;5(4):928-935. They are reprinted here with permission from the journal.

to those with normal HRV [4]. There is evidence that lifestyle changes may have positive autonomic effects [12-14], but these modifications may not be maintained long-term [15].

In Southwestern Ontario, cardiovascular risk is greater and access to healthcare is less in rural communities compared to urban centres. The incidence of obesity, diabetes and hypertension is higher in rural areas, specifically Huron County, compared to nearby urban centres (London, Ontario) [16]. Additionally, Huron County has a 27.5% vacancy rate for general and family practitioners compared to 0% in London and 20.2% vacancy provincially in Ontario [17].

Remote monitoring technology has the potential to bridge the gap between healthcare providers and patients in underserviced areas. Remote monitoring programs using mobile telephones have effectively reduced individual risk factors in a number of studies. Submitting home blood pressure (BP) measurements via short message service (SMS; text messaging) and/or internet effectively reduced BP in uncontrolled hypertensive patients [18] and obese hypertensive patients[19]. Patients with uncontrolled hypertension who took BP measurements with a Bluetooth enabled BP monitor which transmitted readings through a cellular telephone to a secure database monitored by research personnel improved BP control in diabetics with uncontrolled hypertension [20]. Studies examining remote monitoring of blood glucose via cellular telephone to manage diabetes have had promising, but mixed results. Some research found that glycated haemoglobin (HbA1C) decreased [21-24], while one study showed no change [25].

Recent systematic reviews have examined the utility of remote monitoring technologies for behaviour change in diabetic populations [26,27]. These papers agreed that one of the

major shortcomings in the published literature was that the clinical outcome variable was measured, but the intended behaviour change was not. Remote monitoring of behaviour change concurrently with physiological measures would allow immediate data assessment by practitioners and the ability to provide more appropriate, targeted feedback to patients.

Therefore, the aims of this study were to investigate the feasibility and utility of using remote monitoring technology to monitor home BP, blood glucose, HRV and physical activity and to examine changes in home and clinic measures following an eight-week lifestyle intervention. It was hypothesized that an intervention to increase physical activity supported by home health monitoring technologies, would result in improvement in risk factors for CVD and T2D, including MetS risk factors and HRV.

4.2 Methods

Twenty-five participants volunteered to participate in this study and provided informed consent. Participants were included if they had at least two MetS risk factors according to ATPIII guidelines: waist circumference (WC) $\geq$ 88cm (women) or 102cm (men); resting systolic BP (SBP) $\geq$ 135 mmHg and/or diastolic BP (DBP) $\geq$ 85 mmHg; fasting plasma glucose (FPG) $\geq$ 6.1 mmol/L; triglycerides (TG) $\geq$ 1.7 mmol/L; and high density lipoprotein cholesterol (HDL) $\leq$ 1.03 mmol/L (men) or 1.29 mmol/L (women) [2]. Exclusion criteria were SBP > 180 mmHg and/or DBP > 110mmHg; type 1 diabetes; history of myocardial infarction, angioplasty, coronary artery bypass or cerebrovascular ischemia/stroke; symptomatic congestive heart failure; atrial flutter; unstable angina; unstable pulmonary disease; use of medications known to affect heart rate (HR) (such as

beta blockers), or use of other medication that may interfere with study objectives; second or third degree heart block; history of alcoholism, drug abuse or other emotional cognitive or psychiatric problems; pacemaker; unstable metabolic disease; and orthopedic or rheumatologic problems that could impair the ability to exercise. One participant withdrew from the study shortly following baseline testing due to hospitalization for a respiratory illness unrelated to the study. Twenty-four participants (aged 56.6 ± 9.0y; 6 male) reported to Gateway Rural Health Research Centre at baseline (V0) and after four (V1) and eight (V2) weeks of intervention. This study was approved by Institutional Review Board Services (Aurora, Ontario, Canada; #RP-2008).

At each visit, BP was measured in the seated position with an automated BP cuff (BPTru™, VSM MedTech Ltd., Coquitlam, BC). Clinic BP was calculated as the average of the last two of three measures. Anthropometric measures included WC measured as the midpoint between the lower rib and iliac crest (cm) [28]; body mass index (BMI), calculated as weight in kilograms divided by the square of the height in metres (kg/m^2); and body weight (kg). Blood was drawn from the anticubital vein and samples were sent to a central processing lab for analysis of FPG, lipid profile and HbA1C.

An exercise specialist administered the Step Test Exercise Prescription (STEP™) to estimate fitness (VO_{2max}; ml/kg/min) and counsel participants regarding physical activity [29]. Participants were instructed to step up and down a set of two steps twenty times at a comfortable pace. HR was measured immediately following the test by palpation of the radial artery and input into the prediction equation for calculation of VO_{2max} (Appendix 1).

A personalized exercise program was prescribed based on the fitness level determined by the stepping test and a certified personal trainer helped participants set SMART (specific, measurable, attainable, realistic, timed) goals. Exercise prescription followed American College of Sports Medicine [30] guidelines, with a target exercise HR of 70-85% of age predicted maximum HR. Goals included increasing pedometer-monitored steps per day with the overall goal of achieving 10,000 steps per day [31]. The exercise prescription and goals were updated at V1.

Home Monitoring

Participants received a smartphone (Blackberry® Curve 8300, Research in Motion, Waterloo, Ontario) equipped with health monitoring software (Healthanywhere™, IgeaCare Inc., Markham, Ontario), a Bluetooth™ enabled BP monitor (A & D Medical, UA-767PBT, San Jose, California), a glucometer (Lifescan One Touch Ultra2™, Milpitas, California, with wireless Bluetooth™ adapter Polymap, PWR-08-03, Tucson, Arizona) and a pedometer (Omron, HJ-150, Koyoto, Japan). One-on-one technology training was included at V0 and lasted approximately 30 minutes. Participants were instructed regarding proper use of devices and techniques to get accurate measurements. Blood glucose measures were to be submitted twice daily – fasted upon waking and non-fasted before bed, BP measures were to be submitted three times per week upon waking, pedometer steps were to be input nightly, and body weight input weekly. Real-time measurements were sent to a secure central database that was monitored regularly by researchers. Limits were set for blood glucose at 3mmol/L and 15mmol/L, systolic BP (SBP) at 60 mmHg and 210 mmHg and diastolic BP (DBP) at 40 mmHg and 120 mmHg.

Readings that were outside of these limits triggered alarms that automatically sent a message to the study physician's smartphone to follow up with the participant.

During the week following V0 and V2 visits, participants received a HR and activity monitor (Suunto Memory Belt, Vantaa, Finland), which was worn twice for five minutes of seated rest and once for 24 hours. Data were downloaded from the monitor to a personal computer and converted to text files for analysis (Heart Signal Co, Oulu, Finland). Standard deviation of normal to normal R-R intervals (SDNN) was calculated from the entire file for both five-minute and 24-hour recordings. Frequency domain analysis was performed on the entire file for five-minute readings, and 24 hour HRV was calculated as the average of one hour epochs. An autoregressive model (order 20) was used to estimate power spectrum density for very low frequency (VLF: 0.003-0.04 Hz), low frequency (LF: 0.04-0.15 Hz), high frequency (HF: 0.15-0.4 Hz) and total power (TP: 0.003-0.4 Hz) [3]. Values were logarithmically transformed to attain normal distribution. Fractal HR dynamics were calculated from the HR time series. This value represents the qualitative characteristics and correlation features of HR behaviour. The root-mean square fluctuations of integrated and detrended data were measured in observation windows then plotted against the size of the window on a log-log scale. The slope of the line was calculated (α_1) to reflect short term HR behaviour. Recordings with less than 80% qualifying beats were excluded from analysis.

Database and Data Security

Real-time data were transmitted from the smartphone to the server and database via secure internet protocol. Personal identifiers were not stored in the Smartphone. All communication of data between participant devices and the server were encrypted using

secure sockets layer (SSL) certificates before storage. Data transfers between the smartphones and the server were encrypted and only accessible using the Verisign certified HTTPS session that employs SSL with a 128-bit encryption across all channels for the Smartphone to server (key pair) and server to database. All data were encrypted end-to-end according to the latest encryption standards and were authenticated and checked for integrity to ensure that data was sent from an authorized source and had not been tampered with. All clinical variables were transmitted as numbers only, were not accompanied by identifiable information and were linked to participant data once on the protected server.

Access to data was limited to authorized researchers with valid user identification and passwords. If a smartphone was lost or needed to be replaced, safeguards (secure link) were reprogrammed by changing the participant log in and password to ensure personal health information was accessed by authorized personnel only. Healthanywhere accounts were also controlled and protected remotely so that if a device was lost accounts were deactivated to prevent unauthorized access to participant health information.

Statistical Analysis

SPSS software (Version 17) was used for analysis. Paired t-tests were used to observe differences between V0 and V2 measures of BP, FPG, lipid profile, fitness, anthropometrics and HRV. Paired t-tests were also used to examine changes in home monitoring data from week 1 to week 8 (average of measures sent in week 1 and week 8, respectively). Mean substitution was used for missing data. Pearson correlation was used to determine whether any relationships existed between MetS risk factors and HRV. All results are shown as mean ± standard deviation unless otherwise specified.

4.3 Results

Participant characteristics are shown in table 4.1. At baseline, participants had 3.46 ± 1.22 of five metabolic risk factors (range 2 to 5). Based on ATPIII guidelines for MetS [2], 95.8% of participants had abdominal obesity, 91.7% had high BP, 33.3% had impaired fasting plasma glucose, 62.5% had high triglycerides and 62.5% had low HDL. Six participants had T2D at study enrolment, and one was diagnosed with T2D shortly after enrolment by remote monitoring blood glucose measurements and confirmed by blood draw results.

Clinic DBP was reduced from 84±8 mmHg to 80±13mmHg ($p=0.046$) despite no change in clinic SBP (V0: 141±10, V2: 139±19; $p>0.05$) (Table 4.2). However, the percentage of participants with sufficient BP control, defined according to ATPIII criteria (clinic BP less than 130/85 mmHg and not medicated for hypertension) increased from 8.3 to 33.3% from V0 to V2. Similar to clinic BP results, there was no change in remotely monitored SBP (Week 1: 136±17 mmHg; Week 8: 132±19 mmHg; $p>0.05$). DBP on the other hand decreased from 88±12 mmHg in week 1 to 84±10 mmHg in week 8 ($p<0.001$) (Table 4.3).

There was no change in clinic (table 4.2) or home monitored blood glucose (table 4.3). Likewise, there were no changes in triglycerides, LDL or HDL (table 4.2). Total cholesterol decreased from 5.48±1.27 mmol/L at V0 to 5.19±1.11 mmol/L at V2

Table 4.1: Participant Characteristics

Characteristics	
n	24
Age	56.6±8.9 years
Number of males	6 (25%)
Metabolic Syndrome Risk Factors (of 5)	3.46±1.22
Above Metabolic Syndrome Thresholds:	
Waist Circumference	95.8%
Blood Pressure	91.7%
Fasting Plasma Glucose	33.3%
Triglycerides	62.5%
High Density Lipoprotein Cholesterol	62.5%

Table 4.2: Clinic values before and after the eight-week intervention

Clinic measure	V0	V2	p-value
Waist Circumference (cm)	111.5 ± 9.0	107.7 ± 11.6	0.002*
Systolic Blood Pressure (mmHg)	141 ± 10	139 ± 19	0.475
Diastolic Blood Pressure (mmHg)	84 ± 8	80 ± 13	0.046*
Fasting Plasma Glucose (mmol/L)	6.0 ± 2.4	5.5 ± 1.1	0.221
Triglycerides (mmol/L)	1.80 ± 1.32	1.53 ± 0.74	0.153
High Density Lipoprotein Cholesterol (mmol/L)	1.34 ± 0.33	1.35 ± 0.40	0.655
Low Density Lipoprotein Cholesterol (mmol/L)	3.14 ± 1.54	3.13 ± 1.07	0.983
Total Cholesterol (mmol/L)	5.48 ± 1.27	5.19 ± 1.11	0.009*
HbA1C (%)	6.0 ± 0.8	5.9 ±0.6	0.182
VO_{2max} (ml/kg/min)	29.3 ± 5.6	34.7 ± 7.0	<0.001*

Table 4.3: Home monitoring values during week 1 and week 8 of the eight-week intervention

Home Monitoring Measurement	WEEK 1	WEEK 8	p-value
Systolic Blood Pressure (mmHg)	136 ± 15	133 ± 18	0.165
Diastolic Blood Pressure (mmHg)	88 ± 10	84 ± 9	<0.001*
Fasted Morning Blood Glucose (mmol/L)	6.7 ± 2.4	6.3 ± 1.2	0.264
Non-Fasted Evening Blood Glucose (mmol/L)	7.5 ± 2.8	6.9 ± 1.5	0.213
Pedometer Steps (steps/day)	5671 ± 1989	6757 ± 2455	0.003*
Body Weight (Kg)	92.7 ± 14.0	92.1 ± 13.8	0.312

(p=0.009). Waist circumference decreased from 111.5±9.0 cm at V0 to 107.7±11.6 cm at V2 (p=0.002), but there was no change in body weight (Table 4.3).

There was an 18% increase predicted VO_{2max} from 29.34±5.60 ml/kg/min at V0 to 34.68±7.02 ml/kg/min at V2 (p<0.001). Pedometer steps increased from 5671±2670 steps/day in week 1 to 6757±3698 steps per day in week 8 (p=0.003).

Twelve participants had acceptable 24h HRV recordings both V0 and V2 (table 4.4). HFnu increased from 24.5±12.0 at V0 to 28.0±12.1 at V2 (p=0.03) and LFnu decreased from 75.5±12.0% at V0 to 72.0±12.1 at V2 (p=0.03) (Figure 4.1). There were no changes in other 24h HRV variables. Thirteen participants had acceptable 5min HRV recordings at both V0 and V2 (Table 4.5). There were no changes in 5min seated HRV over the intervention period. DBP was correlated with 24h LF:HF (R=0.64). No other relationships were seen between BP and HRV variables.

Compliance to the self-monitoring protocol was high with overall compliance of 96.8±4.0%. Compliance for BP readings was 95.0±14.1%; AM blood glucose 97.3±4.8%; PM blood glucose 97.8±4.7 %; pedometer steps 96.8±3.7%; and body weight 91.8±11.4%. A technology survey was administered at V2 to determine comfort with technology and attitudes toward remote monitoring. Despite the fact that only four participants had used smartphones prior to the study, only one participant was not comfortable using the smartphone for study purposes. Using a likert scale from 1-4 (strongly disagree – strongly agree), it was noted that participants were comfortable with the devices and that the remote monitoring protocol resulted in an increased sense of security (3.58±0.50), assisted participants in adopting new practices to improve wellbeing

Table 4.4: 24h heart rate variability (n=12)

	V0	V2	p-value
RRI	822 ± 127	849 ± 131	0.288
HR	75 ± 11	72 ± 11	0.075
SDNN	150.3 ± 68.9	150.8 ± 57.9	0.962
lnLF	6.39 ± 0.78	6.41 ± 0.85	0.731
lnHF	5.18 ± 1.00	5.39 ± 1.09	0.107
LF/HF	3.9 ± 2.0	3.4 ± 2.6	0.223
α_1	1.367 ± 0.175	1.367 ± 0.171	0.982

α_1, short-term scaling exponent; HF, high frequency; HR, heart rate; LF, low frequency; RRI, R-R interval; SDNN, standard deviation of normal to normal intervals; TP, total power.

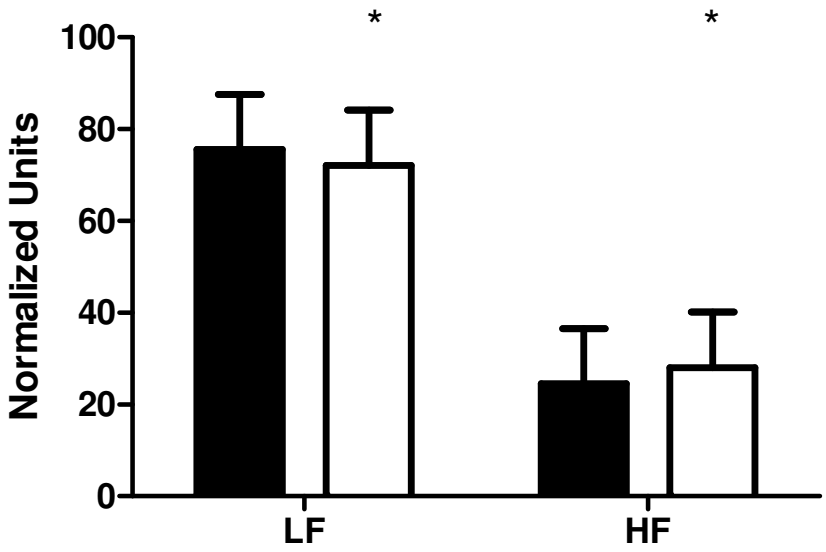

Figure 4.1: Changes in 24 hour LFnu and HFnu heart rate variability from V0 (black bar) to V2 (white bar). n=12; * p=0.03

Table 4.5: 5min seated heart rate variability (n=13)

	V0	V2	p-value
RRI	796 ± 147	867 ± 172	0.06
HR	78 ± 13	72 ± 13	0.10
SDNN	58.6 ± 29.7	62.4 ± 32.6	0.70
LF	848.2 ± 1048.1	888.0 ± 1254.3	0.91
HF	307.6 ± 638.7	231.5 ± 359.7	0.67
LF/HF	5.8 ± 4.3	6.9 ± 7.8	0.60
α_1	1.388 ± 0.182	1.448 ± 0.205	0.10

α_1, short-term scaling exponent; HF, high frequency; HR, heart rate; LF, low frequency; RRI, R-R interval; SDNN, standard deviation of normal to normal intervals; TP, total power.

(3.83±0.38), did not take too much time (1.25±0.44) and did not interfere with activities of daily living (1.33±0.48).

4.4 Discussion

The main finding of this study was that a technology driven, remote health monitoring protocol was feasible in a rural population. Not only was the technology well accepted by the participants, but it also resulted in improved fitness, WC, DBP and total cholesterol. Furthermore, physical activity was increased and HRV was modified despite the small sample size.

Previous studies using remote patient monitoring to control BP have primarily shown better results than the current study with BP reductions of 9.1-11.0 mmHg SBP and 7.2-11.2 mmHg DBP [19,20]. This may be in part due to intervention methodology, as one trial included weekly feedback with diet and activity recommendations via text message [19]. Our participants received an updated physical activity prescription at V1, but the weekly tailoring of lifestyle recommendations likely resulted in greater BP reductions. The results of the current study were based on a small sample, in which two participants had large increases in BP. Despite the fact that SBP was unchanged, the percentage of participants with adequate BP control (defined by ATPIII MetS criteria < 130/85 mmHg and not medicated for BP) increased from 8.3 to 33.3%. Additionally, it has been estimated that even a small reduction in DBP of 2 mmHg would result in a 17% decrease in the prevalence of hypertension, a 6% reduction in the risk of coronary heart disease and a 15% reduction in the risk of stroke or transient ischemic attack [32]. Therefore, the 4 mmHg decrease in DBP in the current study may have clinical significance.

Studies have reported either decreases [21-24] or no change [25] in HbA1C following remote blood glucose monitoring interventions with cellular phones, but changes in home-monitored blood glucose were not reported in these studies. The current study showed no change in FPG, but baseline values were lower than in comparable studies and the intervention period was shorter than other trials. Additionally, the American College of Sports Medicine and American Diabetes Association joint position statement recommends 150 minutes of moderate to vigorous activity per week to reduce blood glucose [33]. Considering that the pedometer steps only increased 1086 steps/day, participants may not have completed a sufficient amount of moderate to vigorous physical activity to affect FPG levels.

Moderate intensity exercise is recommended as a first-line therapy for MetS [28]. A recent study examined the effects of a four-week therapeutic lifestyle modification in rural women with MetS and showed that the intervention group had significant reductions in body weight, WC, TG, FPG, SBP and LDL and increased HDL [34]. These results differ from ours and likely result from differences in intervention delivery. Oh and colleagues [34] provided information booklets to participants at the onset of the trial and the intervention group attended education and exercise sessions three times per week for two hours each time. Education sessions included both nutrition and exercise advice. In the present study tailored exercise prescription was provided, but the exercise was unsupervised and dietary advice was not given. Tjønna and colleagues [35] noted greater improvements in MetS in a group of patients completing high intensity interval training compared to a continuous moderate exercise group, thus reinforcing that higher intensities are better for reducing cardiovascular risk. Our participants were prescribed

moderate intensity activity with a target HR of 70-85% of age-predicted maximum. Greater improvements may have been elicited from higher intensity activities, but as our participants were in an unsupervised setting, moderate intensity was chosen for safety.

Although only three participants achieved their step goal and averaged 10,000 steps/day by week 8, the increase in PA (mean increase of 1086 steps/day) was sufficient to improve markers of MetS. This was despite the fact that the population sample remained classified as low active based on daily step count [31]. Individual exercise prescriptions were tailored to include other activities as well as walking. Several participants participated in physical activities that are not conducive to pedometer monitoring including cycling, swimming, and resistance training. Therefore, activity may have increased more than was measured by the pedometer. The fact that VO_{2max} increased 18% (5.34 ml/kg/min) over an 8-week intervention period, suggests that activity levels increased during the study. It is also possible that although the increase in steps per day was small, the intensity at which the steps were taken may have been greater. Participants were taught how to take their radial pulse and instructed to attain their target HR (70-85% of age-predicted maximum) during exercise sessions. Unfortunately, activity intensity was not measured by HR monitor or accelerometry, nor was it recorded in an exercise journal.

HRV is an index of autonomic function that has been shown to be reduced in MetS [8-11]. Aerobic exercise training in hypertensives has been shown to improve HRV [12-14], though changes in HRV tend to be more apparent during a stressor that induces sympathetic stimulation and parasympathetic withdrawal, than during supine rest. Since HRV in the current study was recorded during seated rest, subtle changes in autonomic

function may have occurred that our experimental protocol was not sensitive enough to detect. Since this feasibility study analysed home HRV measurements, the five-minute HR recordings for seated HRV analysis were not performed under tightly controlled laboratory conditions as recommended [3]. As variations in temperature, light, movement and breathing frequency can all affect HRV [3], lack of control of these factors may be responsible for the lack of change in short-term HRV.

Compliance to technology use was higher in this trial (96.79 ± 4.01%) than others [21,24]. Compliance to a three-month intervention was only 72% [24], and only two of fifteen patients submitted all blood glucose and pedometer readings in a three-month pilot study [21]. In the present study, four of 24 participants completed all measures and 12 others missed less than five of an average 207 total readings. Discrepancies may be due to longer intervention period [21,24] and broader age range [24] compared to the present study. The high compliance in this trial may be explained by the age of our sample, as older adults have been shown to have greater compliance than younger adults [24]. This may be in part because of fewer commitments to care-giving and employment and greater interest in disease prevention. The high compliance to this study may also be a result of the short time period. A four-month study examining home BP monitoring found that weekly compliance was high throughout, but tended to decrease in the last four weeks [20]. The participants in the present study with lowest compliance were either shift workers (n=2) or had family/care-giver commitments (n=1).

Other research has shown that one of the greatest barriers to the use of technology is the time commitment by physicians to monitor the database [20]. Our study required less physician intervention as triage of clinically important measurements was automated thus

limiting physician burden. Participants also had access to their personal data throughout the study that provided self-reflection, goal setting and self-motivation that served as positive and negative support.

This pilot study was conducted in a sample of highly motivated volunteers and may therefore lack external validation. Since there was no control group, it cannot be concluded that improvements in health and activity were a result of self-monitoring technologies. However, the purpose of this pilot study was to test the feasibility and utility of a remote monitoring and activity protocol in a rural population. Future randomized trials are needed to compare the impact of an exercise prescription alone with that of an exercise prescription combined with self-monitoring. A baseline pedometer measurement was not attained prior to exercise prescription. Therefore, it is likely that habitual activity prior to the onset of pedometer monitoring was in fact lower than the week 1 measurements obtained in this study. Despite the fact that only twelve participants had acceptable HR data for 24h HRV analysis and thirteen for 5min HRV, modifications were seen in LFnu and HFnu. However, a greater sample size would have been ideal and may have shown greater change. The technology survey was not a validated questionnaire. However, the responses will still be able to direct protocol modifications to improve a larger trail.

In conclusion, an exercise prescription combined with eight weeks of self-monitoring of health and activity measures resulted in increased fitness and activity, which improved cardiovascular risk profile as demonstrated by reductions in WC, DBP and total cholesterol and improved 24h HRV profile with increased HFnu and reduced LFnu.

4.5 References

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CHAPTER 5

Effects of a mHealth exercise intervention on heart rate variability and metabolic syndrome risk factors in primary care.

5.1 Introduction

Cardiovascular diseases (CVD) are the leading cause of death world-wide [1] and type 2 diabetes mellitus (T2D) is an independent risk factor for CVD. In 2004, heart disease was responsible for 68% and stroke was responsible for 16% of all deaths in patients diagnosed with T2D in the United States [2]. Central obesity, high blood pressure (BP), dysglycemia and dyslipidemia are some of the major cardiometabolic risk factors implicated in the development of CVD and T2D [3,4]. Clustering of these risk factors, termed metabolic syndrome (MetS) increases the risk of disease progression more in combination than additive risk [3,4].

Mechanisms associated with the progression from MetS to T2D and CVD are poorly understood. Autonomic dysfunction has been hypothesized to be an important component of CVD progression [5,6]. Abnormal cardiac autonomic function, as indicated by low heart rate variability (HRV), is associated with increased all-cause and cardiovascular mortality in post-myocardial infarction patients [7,8] and with the development of T2D in a general population [9,10]. Furthermore, individuals with T2D and low HRV were more likely to develop CVD than those with normal HRV values [11,12]. Low HRV is also characteristic of MetS populations [13]. Autonomic dysfunction is consistently reported in females with MetS, while findings are more controversial in males [14-16]. A systematic review showed that MetS risk factors are

associated with different HRV parameters and suggested that impaired autonomic function, or low HRV, may be an important mechanism in the continuum of CV risk [17]. However, to date studies are cross-sectional and associations between longitudinal changes in MetS and HRV have not been examined.

Physical activity is recommended as a first line treatment for MetS [3,4]. Lifestyle changes have proved to reduce disease progression [18,19] and long-term follow-up has determined that lifestyle changes are more effective than metformin in reducing the incidence of T2D [20]. Exercise also improves HRV in the general population [21,22] and in T2D [23,24]. These concomitant improvements in MetS risk factors and HRV in response to exercise suggest that they may be linked mechanistically. However, longitudinal associations have not been examined.

Despite the well-known health benefits of physical activity, accelerometer data has shown that 85% of Canadians [25] and 90% of Americans [26] do not meet national physical activity guidelines. Electronic health (eHealth) is a relatively new field in which electronic medium is used to support health. While studies are still in their infancy some successes have been noted [27]. Mobile health (mHealth) is a branch of eHealth that has the potential to be better than general eHealth interventions because of the portability. Eighty-five percent of the American population owns a mobile phone, and in this group Smartphone ownership has risen from 33% in May 2011 to 53% in November 2012 [28]. With the quickly growing number of smartphone users, mHealth interventions allow for the potential to act as a trigger for behaviour or to provide information at the time that it is needed. We recently showed that a mHealth supported exercise intervention increased activity and improved MetS risk factors in a rural population [29]. Additionally,

participants found the technology acceptable and motivational [30]. Despite a small sample size and short follow-up period, improvements in 24h HRV were apparent (unpublished data; Chapter 4). However, due to the single group design of the pilot study, it is unknown whether the mHealth component had added benefit compared to the exercise intervention alone.

The purpose of this randomized controlled trial was two-fold: 1) to examine associations between longitudinal changes in HRV parameters and MetS components; and 2) to isolate the mHealth component by comparing the effects of an exercise intervention supported by mHealth technology to exercise prescription alone. We hypothesized that changes in MetS components would be associated with changes in HRV parameters and that the mHealth supported group would have greater improvements in MetS risk factors and HRV than the control group.

5.2 Methods

This study was part of a 12-month randomized controlled trial, in which 149 participants from rural Southwestern Ontario were block randomized to either the exercise prescription plus mHealth technology intervention group (EX+T; n=75) or the exercise prescription only active control group (EX-C; n=74). This paper reports interim results at 24 weeks. At screening, participants were required to have a minimum of two of five MetS risk factors according to National Cholesterol Education Program – Adult Treatment Panel III (ATPIII) criteria – waist circumference ≥ 88cm (women) or 102cm (men); systolic blood pressure (SBP) ≥ 135mmHg and/or diastolic BP (DBP) ≥ 85 mmHg; fasting plasma glucose (FPG) ≥ 6.1 mmol/L; fasting triglycerides (TG) ≥ 1.7

mmol/L; fasting high density lipoprotein cholesterol (HD) ≤ 1.29 mmol/L (women) or 1.02 mmol/L (men) [31]. Exclusion criteria were systolic blood pressure (SBP) > 180 mmHg and/or diastolic blood pressure > 110mmHg; type 1 diabetes; history of myocardial infarction, angioplasty, coronary artery bypass or cerebrovascular ischemia/stroke; symptomatic congestive heart failure; atrial flutter; unstable angina; unstable pulmonary disease; use of medications known to affect heart rate (HR); second or third degree heart block; history of alcoholism, drug abuse or other emotional cognitive or psychiatric problems; pacemaker; unstable metabolic disease and orthopedic or rheumatologic problems that could impair the ability to exercise. The study was approved by the University of Western Ontario research ethics board (#15828) and participants provided informed consent to participate.

Participants reported to the Gateway Rural Health Research Institute (Seaforth, Ontario) at baseline (V0), 12 weeks (V1) and 24 weeks (V2). Automated BP was measured in the supine position (BPTru™, VSM MedTech Ltd., Coquitlam, BC) and the average of the last two of three measures was used to determine clinic BP. WC was measured as the midpoint between the lower rib and iliac crest (cm) [32]. Blood was drawn and sent to a central laboratory for measurement of FPG, TG and HDL.

Autonomic testing

Following a light, standardized snack, participants were instrumented for collection of a lead II ECG (Colin Pilot 9200, Colin Medical Instruments, San Antonio, Texas) and respiratory rate by belt transducer (Pneumotrace II, ADInstruments, Colorado Springs, Colorado) secured around the thorax. Data were collected during ten minutes of supine

rest. External stimuli, such as light and noise were controlled to ensure signal stability. Participants were instructed to remain still and awake. All measures were sampled at 1000Hz, input into a data acquisition board (PowerLab ML795, ADInstruments) for analog-to-digital signal conversion with LabChart7Pro software (ADInstruments) and stored for offline analysis.

Exercise testing and prescription

Fitness (VO_{2max}; ml/kg/min) was estimated with the Step Test Exercise Prescription (STEP™) tool, which has been validated in adults aged 18-85y [33,34]. The full protocol has been published elsewhere [35]. Briefly, participants were instructed to step up and down a set of two steps twenty times at a comfortable pace. Heart rate (HR) was measured immediately following the test by palpation of the radial artery and age, weight, sex, time to complete test and post-test HR were used to calculate predicted VO_{2max} (Appendix 1). Fitness was classified by age, sex and VO_{2max} as poor, fair, good or excellent. A tailored exercise program including target HR based on fitness level [poor =70% maximum age-predicted HR (HR_{max}); fair = 75% HR_{max}; good = 80% HR_{max}; excellent = 85% HR_{max}] was prescribed based on the results of STEP™ and an exercise specialist helped participants set SMART (specific, measurable, attainable, realistic, timed) goals. For EX+T, goals included increasing steps per day with pedometer monitoring, with the overall goal of achieving 10,000 steps per day. The exercise program and goals were updated at each visit.

Mobile Health Intervention

Participants received a smartphone (Blackberry Curve 8300 or 8530, Research in Motion, Waterloo, ON) equipped with health monitoring application (Healthanywhere, BioSign, Markham, ON), a Bluetooth enabled BP monitor (A & D Medical, UA-767PBT, San Jose, CA), a glucometer (Lifescan One Touch Ultra2™, Milpitas, CA) with Bluetooth adapter (Polymap Wireless, PWR-08-03, Tucson, AZ) and a pedometer (Omron, HJ-150, Kyoto, Japan). A group training session (approximately two-hour duration) was delivered at V0, during which participants were instructed on proper use of devices and techniques to get proper measurements. FPG and BP measures were to be submitted thrice weekly upon waking and pedometer steps were to be input nightly. Details of data transfer, biometric thresholds for alerts and database security are reported elsewhere [30].

Heart rate variability analysis

R-R intervals (RRI) were extracted from continuous ECG recordings for analysis with HRV software (Hearts v7, Heart Signal Co., Oulu, Finland). The HR time series was edited by a single investigator. All ECG signals were manually scanned for ectopic or non-sinus beats, which were deleted from the time series. Datasets were excluded from analysis when more than 10% of beats were edited. Time domain HRV analyses included HR, SDNN and the root square mean of successive differences (RMSSD). The HRV spectrum was computed with the non-parametric fast Fourier transform method. Low frequency (LF: 0.04-0.15Hz), high frequency (HF: 0.15-0.4Hz), LF/HF and total power (TP: 0.003-0.4Hz) were examined [36]. These measures are repeatable over short- and long-term [37]. Each RRI was plotted against the following one to create a Poincaré plot. The standard deviation of the width (SD1) and length (SD2) were calculated [38,39]. The detrended fluctuation analysis method was used to examine fractal

characteristics of heart rate fluctuations [40]. The root-mean square fluctuations of integrated and detrended data were measured in observation windows and then plotted against the size of the window on a log-log scale. The short-term scaling exponent (α_1) was calculated from the slope of the line (from 4-11 beats) [41].

Statistical Analysis

Baseline characteristics were compared between groups with unpaired t-tests for outcome measures with normal distribution or a two sample Wilcoxon test for outcome measures that were not normally distributed. Analysis of covariance (ANCOVA) was used to examine differences in mean change between EX+T and EX-C for MetS risk factors, fitness, HOMA-IR and HRV parameters with sex and baseline values as covariates. Age was also included as a covariate for HRV parameters. Paired t-tests were used to examine changes from V0 to V2 for the whole population when there were no differences between groups for mean change, or for EX+T and EX-C separately when differences were shown by ANCOVA. Multiple linear regression models were used to investigate how changes in MetS components predicted changes in HRV, while adjusting for other variables and baseline values. An *a priori* decision was made to force age, sex, group and VO_{2max} into the equation to adjust for potential confounders. Backwards elimination was used to create the most appropriate model. All MetS components were originally included in the model and the least important was serially excluded using the criteria $p<0.1$. This strategy sought to identify a parsimonious set of predictors for the outcome of interest. Upon completion of the initial model, diagnostics were run to test for influential observations and outliers were removed when necessary. All results are shown as mean ± standard deviation for normally distributed data, median (interquartile

range; IQR) for non-parametric data, and multiple linear regression results are presented as estimate (95% confidence interval; CI), unless otherwise specified. R statistical software was used for analysis [42].

5.3 Results

Participant Characteristics

After removal of incomplete data, 116 participants (62 EX+T; 54 EX-C) were included in the final analysis (Table 5.1). FPG (p=0.008) and HOMA-IR (p=0.010) were higher in EX+T compared to EX-C, but groups were otherwise similar.

Longitudinal changes in metabolic syndrome risk factors and heart rate variability parameters

There was no difference between groups in mean change for any MetS risk factor, VO_{2max} or HOMA-IR (p>0.05). Figure 5.1 shows changes in MetS risk factors over time. WC (V0: 103.5±13.2 cm; V2: 99.7±12.4 cm; p<0.001), SBP (V0: 141±19 mmHg; V2: 131±15 mmHg; p<0.001) and DBP (V0: 86±11 mmHg; V2: 81±9 mmHg; p<0.001) were reduced over time across the whole population with no differences between groups (p>0.05). There were no changes in FPG (V0: 5.0(0.8) mmol/L; V2: 5.0(0.6) mmol/L), TG (V0: 1.36 (0.96) mmol/L; V2: 1.32(0.91) mmol/L), HDL (V0: 1.40 (0.53) mmol/L; V2: 1.38(0.51) mmol/L) or HOMA-IR (V0: 1.63(1.75); V2: 1.54(2.09)) over time (p>0.05). VO_{2max} increased in the whole population with no differences between treatment groups (V0: 30.77±6.22 ml/kg/min; V2: 32.81±6.24 ml/kg/min; p<0.001). RMSSD, lnHF and SD1 were reduced at V2 compared to V0 (p=0.048, 0.032 and 0.049,

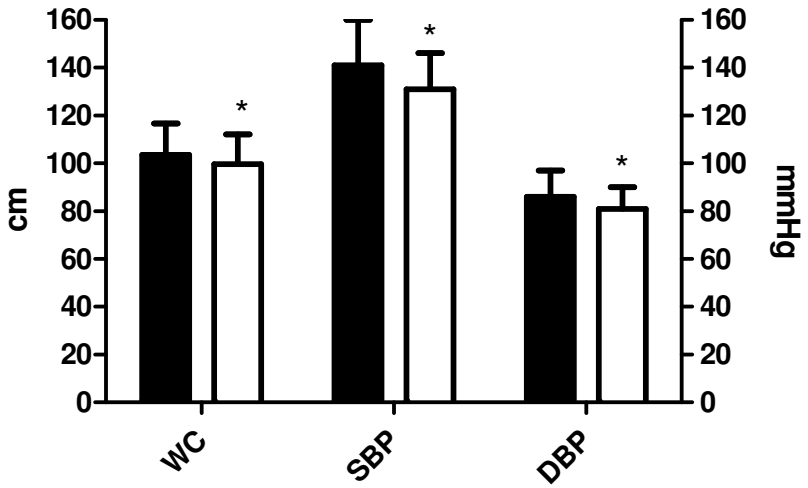
Table 5.1: Participant characteristics

	Exercise + Technology	**Exercise Only**	***p***
N	62	54	
Age (y)	58.0 (14.0)	59.5 (11.8)	*0.482*
WC (cm)	105.2±12.6	101.7±13.8	*0.151*
SBP (mmHg)	141±20	142±19	*0.926*
DBP (mmHg)	86±13	87±10	*0.690*
FPG (mmol/L)	5.1 (0.9)	4.9 (0.5)	*0.013**
TG (mmol/L)	1.42(0.76)	1.31 (1.05)	*0.791*
HDL (mmol/L)	1.34 (0.57)	1.45 (0.47)	*0.312*
HOMA-IR	1.90 (1.66)	1.37 (1.01)	*0.010**
VO_{2max} (ml/kg/min)	30.0±6.3	31.4±6.3	*0.236*

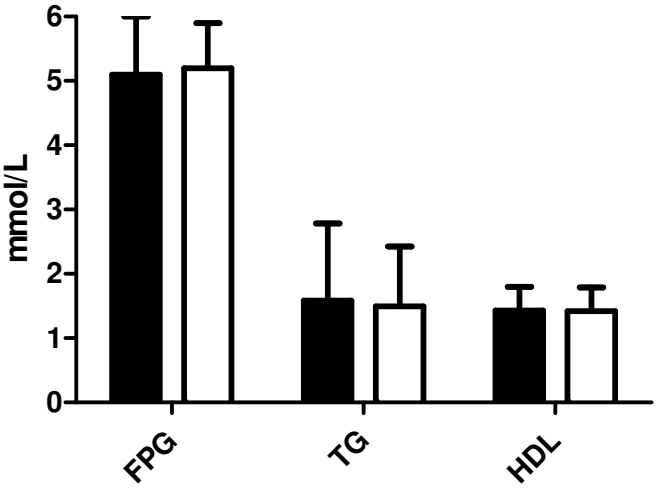
DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein cholesterol; HOMA-IR, insulin resistance; SBP, systolic blood pressure; TG, triglycerides; VO_{2max}, maximal oxygen uptake; WC, waist circumference.

Figure 5.1: Changes in metabolic syndrome risk factors over time. A) waist circumference, systolic and diastolic blood pressure; B) fasting plasma glucose, triglycerides and high density lipoprotein cholesterol; at V0 (black bar) and V2 (white bar). * p<0.05

A)



B)



respectively), but there were no other significant changes in HRV parameters over time (Table 5.2).

Associations between changes in metabolic syndrome risk factors and heart rate variability

Multiple linear regression (Table 5.3) showed that the change in HR and SDNN were associated with the change in WC (p=0.033) and FPG (p=0.048), respectively. The change in α_1 was associated with the change in SBP (p=0.045) and TG was included in the model to improve the fit (p=0.066). The change in MetS risk factors over the intervention period were not associated with the change in HRV parameters RMSSD, lnLF, lnHF, lnTP, LF/HF or SD1.

5.4 Discussion

The main findings of this study were that: 1) WC, SBP and FPG were the only MetS components that independently predicted changes in HRV, and only changes in HR, SDNN and α_1 were associated with MetS component changes; 2) RMSSD, lnHF and SD1 were reduced following the intervention period with no other changes in HRV; and 3) WC, SBP and DBP were reduced following the 24-week intervention with no change in other MetS risk factors and no differences between treatment groups.

Previous studies have examined associations between HRV parameters and MetS risk factors in cross-sectional studies [13-16]. To our knowledge, this was the first study to examine these associations over a longitudinal intervention period. Interestingly,

Table 5.2: Changes in heart rate variability from baseline to 24 weeks

	V0	V2	*p*
HR (bpm)	63±9	62±8	*0.099*
SDNN (ms)	45(30)	42(23)	*0.371*
RMSSD (ms)	1114(1966)	753(1449)	*0.048**
lnLF (ms^2)	6.03±1.07	5.93±0.84	*0.270*
lnHF (ms^2)	5.87±1.39	5.60±1.00	*0.032**
lnTP (ms^2)	7.48±0.90	7.37±7.39	*0.183*
LF/HF	1.15(1.77)	1.51(1.86)	*0.169*
SD1 (ms)	23.7(20.3)	19.4(17.7)	*0.049**
α_1	1.01±0.33	1.06±0.26	*0.112*

α_1, short-term scaling exponent; HF, high frequency power; HR, heart rate; LF low frequency power; RMSSD, root mean square of successive differences; SD1, width of the Poincaré plot; SDNN, standard deviation of normal-to-normal intervals; TP, total power.

Table 5.3: Multiple linear regression examining contribution of change in metabolic syndrome risk factors to change in heart rate variability parameters.

	Estimate	95% CI	p	F-statistic	Adjusted R^2
HR				*5.786*	*0.224*
WC	0.129	(0.011, 0.247)	*0.033**		
SDNN				*6.075*	*0.2314*
FPG	-3.332	(-6.629, -0.035)	*0.048**		
α_1				*16.58*	*0.541*
SBP	-0.003	(-0.006, -7.0×10^{-5})	*0.045**		
TG	-0.038	(-0.078, 2.5×10^{-3})	*0.066*		

α_1, short-term scaling exponent; FPG, fasting plasma glucose; HR, heart rate; SBP, systolic blood pressure; SDNN, standard deviation of normal to normal intervals; TG, triglycerides; WC, waist circumference.

associations with changes in HRV and MetS risk factors overtime were different than cross-sectional associations. Changes in the HRV parameters that are traditionally considered to be reflective of vagal activity during supine rest (RMSSD, HF, SD1) were not independently predicted by change in MetS risk factors, though in cross-sectional analyses, these HRV parameters were independently predicted by WC and FPG (chapter 3). On the other hand, parameters with sympathetic influence, reflecting overall variability, or fractal complexity were associated with changes in MetS risk factors. The change in HR was independently predicted by changes in WC. In the Diabetes Prevention Program, a higher baseline HR was related to incident diabetes [10]. Preliminary results have suggested that HR may be reflective of sympathetic activity in MetS population [43]. Abdominal obesity is often considered a cornerstone of MetS, and in fact is a mandatory risk factor in some MetS definitions [32]. Visceral fat is hypothesized to be one of the major contributors to insulin resistance [44], which is associated with sympathetic hyperactivity [45-47]. Together, these findings suggest that improvements in abdominal obesity may be responsible for normalization of sympathetic activity seen as a reduction in HR.

Importantly the change in SDNN was independently predicted by the change in FPG. A longitudinal study showed that in T2D, those within the lowest quartile of two-minute SDNN had approximately double the risk of incident coronary heart disease and incident myocardial infarction compared to those in the higher three quartiles [11]. These findings suggest that improvements in FPG would increase SDNN and therefore, potentially reduce the risk of cardiovascular complications of T2D. However, the

increased risk with reduced SDNN was not apparent in participants without T2D [11] and reduced SDNN did not predict the development of T2D in a general population [9].

In this study, changes in α_1 were independently predicted by changes in SBP, with each mmHg decrease in SBP predicting a small, but significant increase in α_1. The breakdown of fractal complexity (seen as alterations of α_1) are associated with either lack of variability or with complete randomness [41,49], both of which are seen in patients with advanced disease such as congestive heart failure, complex arrhythmias or post-myocardial infarction patients [50]. Reductions in SBP are known to lower cardiovascular risk and these findings suggest, that mechanistically, it may be related to fractal behaviour of heart rate dynamics.

Previous studies have shown that exercise improves HRV [21-24]. This is contrary to our results which showed that RMSSD, lnHF and SD1 – parameters considered primarily reflective of vagal activity under resting conditions – were reduced over the 24-week intervention period rather than increased as expected. However, in some studies, resting HRV was not a sensitive enough measure to detect subtle changes in autonomic function. Improvements in autonomic function were detected when HRV was measured during recovery from moderate intensity exercise [51] or when reflex autonomic control was assessed by baroreflex sensitivity [52]. Additionally, one study examined the dose response of exercise for changes in HRV. Completing approximately 50% of national recommendations for exercise resulted in improvements in lnLF, lnVLF and lnTP, while meeting national recommendations or exceeding them by 50% improved all time and frequency domain HRV parameters examined except for HR and LF/HF [53]. Although the participants in the current study were prescribed exercise according to national

physical activity guidelines, it cannot be concluded that targets were met since exercise was unsupervised. Therefore, changes may not have been seen in this study if recommendations were not followed appropriately.

Exercise also has benefits for MetS population and is the recommended first-line treatment for cardiometabolic risk factors [4]. A recent meta-analysis of exercise effects on cardiovascular risk factors in T2D showed that aerobic exercise resulted in reduced glycated hemoglobin (a measure of glycemic control over the past 12 weeks), SBP and TG, with no changes in HDL or WC [54]. This paper did not examine changes in either FPG or DBP. Our intervention may have failed to change FPG as the mean was within healthy limits and only seven individuals (6%) had a FPG > 6.1mmol/L to qualify as a risk factor. Similarly, the mean TG was also within a healthy range. On the other hand, SBP and DBP were elevated outside normal ranges (>135/85) at V0 and therefore had greatest potential for improvement.

This intervention used the STEP™ tool for exercise counseling, which has proved to effectively increase fitness and improve MetS risk factors [35]. Indeed, the 7% and 6% reductions in SBP and DBP, respectively, are similar to changes that have been seen with other interventions using STEP™ [35] and are in line with changes in BP with exercise in hypertensive populations [55]. The 7% increase in VO_{2max} was lower than other studies employing the STEP™ intervention [35], which suggests that exercise goals may not have been met and may explain in part lack of change of some MetS risk factors.

Contrary to our hypothesis, there were no differences between EX+T and EX-C. A six-month lifestyle intervention including health monitoring, counseling, education, exercise

and diet improved WC to a greater extent in the intervention compared to the control group, with no differences in other MetS risk factors [56]. The addition of diet to the intervention is likely responsible for the improvements in WC. Another study examined an eHealth-based intervention which included monitoring of BP, steps and body fat; a four-week education module; telephone counseling; and text and email messages for six months [57]. After six months, all MetS risk factors had improved except for HDL; however, this was a pilot study, so a control group was not included [57].

Two systematic reviews have had conflicting results regarding the effectiveness of eHealth on physical activity and weight loss [27,58]. A review of eHealth interventions showed that only three of thirteen studies showed improvements in physical activity [27], while a review of SMS studies showed that three of three studies successfully increased physical activity and eleven of fourteen studies resulted in weight loss [58]. mHealth may be more effective than other types of eHealth interventions due to their portability and convenience and their ability to trigger behaviours or provide support at the appropriate time. Since the participants in our intervention primarily used their smartphone as a data portal for submitting measures, the full potential of the smartphone-based intervention may not have been realized. Telemonitoring of blood pressure [59] and self-management of blood glucose via mobile phone [60] is more effective than usual care. This mHealth intervention may not have had as much success as it was essentially a self-management protocol with little interaction between the research team and participants. Other mHealth interventions have used text messaging for feedback and encouragement throughout the study. While participants attended an intensive training

session, more regular contact (either automated or personalized) may have increased the success of the intervention.

This study was limited to a small, rural population presenting with MetS risk factors; therefore, results may not be generalizable to urban or other populations. Since the exercise was unsupervised and pedometer steps were self-reported, the actual amount of exercise completed cannot be confirmed. Additionally, since dietary changes were not tracked, some participants may have chosen to change their diet, which may have contributed to positive changes in MetS risk factors and HRV, and these would not be accounted for in the analysis. Although there is some evidence that HR may be indicative of sympathetic activity in MetS [43], direct measures such as measurement of muscle sympathetic nerve activity would have been ideal. However, these measures are expensive, time consuming and impractical for large populations.

In conclusion, this six-month intervention showed that changes in HR, SDNN and α_1 were associated with changes in MetS risk factors, but HRV parameters more specifically indicating vagal activity were not. These associations were seen despite the fact that HRV was not improved by the intervention and the only MetS risk factors that were improved were WC, SBP and DBP.

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CHAPTER 6

Thesis Summary, Discussion and Conclusions

6.1 Summary of the Thesis

6.1.1 Associations between heart rate variability and metabolic syndrome risk factors

The purpose of this thesis was to examine relationships between heart rate variability (HRV) and metabolic syndrome (MetS) risk factors. Chapter 1 was a review of the literature, which discussed cardiometabolic risk and proposed that based on prognostic value and relationships with MetS risk factors, HRV may have potential as a novel cardiometabolic risk factor. Studies examining associations between HRV and MetS were identified and synthesis of results was recommended.

Chapter 2 was a systematic review with the purpose of describing studies to date examining the associations between MetS and HRV. This paper showed that HRV was reduced in women with MetS, though findings were inconsistent in men. This paper also noted that most HRV indices were not reduced until three or more MetS components were present – only 24-hour short-term scaling exponent (α_{1}) and five-minute standard deviation of normal-to-normal intervals (SDNN) were altered with less than three components. Associations between individual MetS risk factors and HRV parameters were also reviewed in this paper. It was concluded that associations between MetS risk factors and HRV parameters varied depending on the population and that greater consistency in methodology was needed. Additionally, it was suggested that associations with insulin resistance should be further investigated.

Chapter 3 was a cross-sectional examination of the associations between HRV, MetS risk factors and insulin resistance. HRV was not lower in MetS compared to those without MetS in men. In women, however, HRV was generally lower in MetS, but there were no differences in HRV parameters reflective of vagal activity. HRV parameters reflective of parasympathetic activity were independently predicted by waist circumference (WC) and fasting plasma glucose (FPG), while those reflecting overall variation were predicted by triglycerides (TG) and high density lipoprotein cholesterol (HDL). Insulin resistance was only associated with heart rate (HR)

Chapter 5 was a 24-week intervention study, which showed that the changes in MetS risk factors were generally not associated with changes in HRV parameters. The change in WC was associated with the change in HR; the change in SDNN was associated with the change in FPG; and the change in α_1 was associated with the change in systolic blood pressure (SBP).

6.1.2 Exercise intervention as a cardiometabolic risk modifier

Chapter 1 also reviewed the role of exercise as a cardiometabolic risk modifier. Generally, exercise and physical activity have proved to reduce WC and blood pressure (BP) and increase HDL in MetS [1]. Studies examining the effects of exercise on HRV are equivocal with some interventions improving HRV [2-5], while others had no effects [6]. Exercise prescription may be an important factor. Evidence suggests that frequency of training may be important to effectively modify HRV, while intensity and duration may be less important.

Novel interventions for improving exercise uptake were also examined. The Step Test and Exercise Prescription (STEP) test has effectively modified both traditional and novel cardiometabolic risk factors [7] and was the only exercise counseling intervention in primary care that improved fitness [8]. Mobile health (mHealth) interventions were also reviewed, which showed promise as a tool for self-management for weight loss, physical activity and diabetes management. It was suggested that a unique intervention combining exercise prescription and self-management with mHealth technology had potential as an intervention to reduce cardiometabolic risk.

Chapter 4 was a pilot study to determine the feasibility and utility of an intervention utilizing the STEP intervention supported by self-management with a mHealth application. Twenty-four participants with at least two MetS risk factors volunteered for this study, which proved that the intervention was feasible and acceptable in a rural population. Despite the short intervention length (eight weeks), WC, DBP and total cholesterol were reduced and fitness and physical activity were increased [9,10]. The high (HF) and low frequency (LF) powers of HRV in normalized units were altered following the intervention and DBP was correlated with LF/HF, but there were no other changes in HRV or correlations between HRV and MetS risk factors. Despite these promising changes, it remained unclear whether the mHealth intervention was of any added benefit compared to the exercise prescription alone.

Chapter 5 was a randomized controlled trial comparing the effects of a 24 week mHealth supported exercise intervention to standard of care exercise advice with STEP. Participants with two or more MetS risk factors were randomly allocated to either an intervention (n=75) or active control (n=74) group. The intervention group received the

mHealth supported exercise intervention described in chapter 4, while the control group received only the exercise testing and prescription. Over the 24-week intervention period, there were no differences in changes between the intervention and control groups. WC, SBP and DBP were reduced with no changes in other MetS risk factors. Root mean square of successive differences (RMSSD), lnHF and Poincaré plot width (SD1) were reduced over the intervention period with no changes in other HRV parameters.

6.2 Discussion and Future Directions

Recent reviews discussed cardiac autonomic function in the progression of type 2 diabetes mellitus (T2D) [11,12]. The reviews hypothesized that vagal modulation is reduced initially at the onset of disease and is in fact the first sign of autonomic dysfunction. The results of this thesis showed that in a population with or without MetS, there were no differences in vagal indices RMSSD, lnHF or SD1. This suggests that either vagal indices are reduced before even development of one risk factor and therefore, no differences are apparent between groups, or that vagal changes occur later in the progression of disease. Unfortunately, since this thesis did not include a population of healthy individuals with zero MetS risk factors, this cannot be determined. Over a 24-week intervention that improved BP, vagal HRV indices RMSSD, lnHF and SD1 were reduced. There were no mean changes in MetS status, so the reduction in vagal HRV indices over time may have been indicative of disease progression despite improvements in some MetS components (Chapter 5). Additionally, WC and FPG were primarily associated with all three vagal indices (Chapter 3), suggesting that these two MetS components may be important in the treatment of cardiometabolic risk. The Diabetes Prevention Program Outcomes Study showed that the risk of developing T2D was 56%

lower for participants in whom FPG was reduced to normoglycemia compared to those with persistently elevated FPG [13]. Reduced SDNN has been shown to be a predictor of mortality and changes in SDNN were related to changes in FPG (Chapter 5), though in a cross-sectional examination SDNN was predicted by lipid profiles (Chapter 3). Future studies should examine the importance of cross-sectional versus longitudinal change associations between HRV parameters and MetS risk factors.

Although parasympathetic dysfunction has been implicated as the first sign of disease, the results of this thesis suggest that alterations in HRV associated with overall variation, complexity and perhaps sympathetic activity may be a better indicator of MetS. Vagal indices may already be reduced with the presence of one risk factor, making it a poor indicator of disease progression. However, in cross-sectional studies, only SDNN and α_1 were reduced when less than three MetS risk factors were present (Chapter 2). Evidence suggests that increased sympathetic activity may be present in MetS and that it may, in fact be mechanistically linked directly to insulin resistance and the progression of disease [14-16]. The studies included in this thesis were not designed to measure sympathetic activity directly. Other studies have shown that norepinephrine spillover and muscle sympathetic nerve activity are increased in MetS [15,16]. The current study showed that heart rate was increased in MetS compared to those without and preliminary findings have suggested that heart rate may be a surrogate measure of sympathetic activity in MetS [14].

Exercise interventions have shown promise in improving MetS and HRV. The DaTA study (chapter 4) showed some improvements in MetS risk factors and 24h HRV parameters over eight weeks, but over a 24-week intervention period (chapter 5) some

MetS risk factors were improved, but 5min resting HRV parameters reflective of vagal activity were actually lower instead of higher as expected. VO_{2max} was increased 18% in chapter 4, but only 7% in chapter 5. These differences in fitness improvements may be responsible for inconsistent findings. Aerobic fitness is protective against mortality [17] and improvements in autonomic function accompanying increased fitness may play a role.

Exercise is known to have positive health benefits beyond those directly associated with HRV. Intensive lifestyle intervention programs reduced the risk of developing T2D in prediabetes and changes were maintained over a long-term follow-up, though there was a strong relationship between reduced disease progression and continuance of lifestyle intervention behaviours [18]. These finding highlight the importance of post-program support for long-term maintenance. Knowledge translation activities are important to translate research protocols into useable programs.

mHealth applications have the potential to reach a broad population and provide a convenient and effective medium for delivery of interventions. Although there is a growing body of literature in this field, studies to date are heterogeneous with respect to study population, intervention delivery and reported outcomes. With rapid technological developments it is difficult to plan and implement robust clinical mobile health trials within the current research environment before technology is outdated. Many published mHealth interventions do not use the technology to its full potential and better results may be realized by utilizing as many smartphone features as possible in an intervention. Future research should examine published literature to determine the most beneficial use of mobile technology for optimal health results. Smartphone applications are being

developed at a fast rate, with many aimed at health and behaviour management. However, a review cautioned that few applications are based in theory [19] and that the success of mobile health interventions could be maximized by developing evidence-based applications specific to population needs. This will be important if mHealth becomes integrated into clinical practice in the future.

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APPENDIX 1:

The STEP™ Protocol

The STEP™ Protocol includes two basic components: the stepping fitness test and an exercise prescription.

Part A: The stepping fitness test

Begin the stepping fitness test by demonstrating the stepping pattern to patients: stepping one foot at a time up both steps and back down again ("up, up, together, down, down, together"). Emphasize that only one foot is on the middle step at any one time. Also remind the patient that one step is counted after stepping up to the top step and returning back down to the starting position. Instruct the patient to complete 20 consecutive stepping cycles at a self-selected normal pace (similar to the pace they would use to climb stairs). When the patient is ready to begin, start the timer as their first foot leaves the ground. During the test, count each step aloud as they complete it. Offer encouragement and watch for signs of fatigue or balance problems (or any signs of concern for their safety). Although the individual self-selects the pace to complete the stepping test, encourage them to maintain a consistent speed. For example, if they are "racing" through it, be sure to encourage the patient to slow down to ensure valid results. As the patient performs the last step, be prepared to take their heart rate when they complete the test. Take the post-exercise heart rate, palpating radially in a 6 second count. The patient can rest while you complete the equation for predicted aerobic capacity.

Part B: Exercise prescription

Calculate the patient's target training heart rate, using 70-85% of their age-predicted maximal heart rate as a target. Generally, individuals with lower aerobic fitness levels should be advised to stay at the lower end of their target HR zone (70%). Those with high fitness levels should be encouraged to aim for the higher range (80-85%) depending on their current physical activity/exercise regimes and their limitations.

Complete the exercise prescription note for the patient, including: date of test, predicted VO_2max, target training heart rate (including beats per minute and beats in 10 seconds), and frequency of activity. (Appendix Figure 1) It is helpful to provide patients with a copy of Canadian physical activity guidelines during this process, which highlight that Canadian adults should aim for at least 150 minutes of moderate- to vigorous-intensity physical activity each week and that this can be accumulated in a minimum of 10-minute bouts (CSEP, 2011). During the exercise prescription process, it can be helpful to describe the term VO_2max as well as training heart rate to patients. The definitions below have been applied for this purpose.

- **VO_2max** is a measure of your cardiorespiratory (or aerobic) fitness. It is a score of how well your heart, lungs, and muscles work together. The higher this number is, the more fit you are. You can become more fit by increasing your aerobic physical activity. Some examples of aerobic physical activity include walking, swimming, or shovelling the driveway.

- **Training Heart Rate** – In order to improve your fitness, it is important to check your heart rate during physical activity. This training heart rate has been

prescribed specifically for you based on your exercise results. The easiest way to check your pulse is to count how many times you feel your heart beat in 10 seconds.

Appendix Figure 1: STEP Worksheet

STEP™ Test

Calculation Worksheet

Participant Data:

Sex (male=1, female=2)	
Age (years)	
Weight (kg)	
Time required for STEP test (sec)	
Heart Rate after STEP test (bpm)	

Calculations:

Step	Calculation	Answer
1	(1511/time)*weight/heart rate	=
2	([Ans Step1] *0.124) – (age*0.032) – (sex*0.633) + 3.9	=
3	([Ans Step 2] *1000)/weight	=

→ VO_2max

Appendix Figure 2: STEP Exercise Prescription

EXERCISE PRESCRIPTION

Date: _____

VO_2max: _____ ml/kg/min

Classification:
Needs Improvement Fair Good Excellent

Training Heart Rate: _____ beats/min

_____ beats in 10 sec

Type of activity: _____

You should try to be active on most days of the week, and include activities that strengthen muscles and bones on 2 days of the the week.

Time: Complete a minimum of **10 minutes per session**, to reach a total of at least **150 minutes per week** to achieve health benefits.

Interrupt time sitting still every 20 minutes

APPENDIX 2

Certificate of Ethics Approval

Office of Research Ethics

The University of Western Ontario
Room 4180 Support Services Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
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Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. R.J. Petrella
Review Number: 15828 **Review Level:** Full Board
Review Date: January 13, 2009
Protocol Title: A multi-centre, prospective, Randomized study To determine the effects of Exercise Managed Intervention (ARTEMIStudy).
Department and Institution: Geriatric Medicine, Parkwood Hospital
Sponsor: CIHR-CANADIAN INSTITUTE OF HEALTH RESEARCH
Ethics Approval Date: March 10, 2009 **Expiry Date:** December 31, 2012
Documents Reviewed and Approved: UWO Protocol, Letter of information & consent form dated December 7/08, Poster Ad and Newspaper Ad both dated December/08
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

[redacted]

Chair of HSREB: Dr. Joseph Gilbert

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Cook S, **Stuckey MI**, Petrella RJ. Implementing the Healthesteps program for healthy living in family health teams. Association of Family Health Teams of Ontario Annual Meeting, Oct 16, 2012. (Workshop Presentation).

Stuckey MI, Shapiro S, Sabourin KJ, Petrella RJ. Acceptability and feasibility of remote monitoring for diabetes prevention. American Diabetes Association 72nd Scientific Sessions, Philadelphia, PA, USA, June 8-12, 2012. (Poster Presentation)

Foisey L, Cook S, Intzandt B, **Stuckey M**, Petrella R. Engaging and enabling rural communities in chronic disease prevention: the Healthesteps Program. American College of Sports Medicine Annual Meeting, San Francisco, CA, USA, May 30-June 2, 2012 (Poster Presentation)

Stuckey MI, Shaprio S, Sabourin KJ, Intzandt B, Miskie D, Munoz C, Petrella RJ. Remote health monitoring to increase activity and reduce metabolic risk factors in a rural population. eHealth 2012, Vancouver, BC, Canada, May 27-30, 2012. (ePoster Presentation)

Stuckey MI, Shapiro S, Sabourin KJ, Munoz C, Petrella RJ. Remote monitoring technology to improve blood pressure in a rural population. World Congress of Exercise is Medicine, Denver, CO, USA, May 31-June 4, 2011. (Poster Presentation)

Stuckey MI, Shapiro S, Sabourin KJ, Munoz C, Petrella RJ. Effects of a 12-week remote health monitoring intervention on metabolic syndrome risk factors. Canadian Obesity Summit, Montreal, QC, Canada, April 28-May1, 2011. (Oral Presentation)

Stuckey MI, Russell-Minda E, Kiviniemi A, Fulkerson R, Read E, Munoz C, Petrella RJ. Exercise and remote monitoring to improve blood pressure and heart rate variability in a rural population. The 23rd Scientific Meeting of the International Society of Hypertension, Vancouver, BC, Canada, September 26-30, 2010. (Poster Presentation)

Stuckey MI, Russell-Minda E, Fulkerson R, Read E, Munoz C, Petrella RJ. Physical activity and remote blood pressure monitoring to reduce the risk of cardiovascular disease in a rural population. World Congress on Heart Disease, Vancouver, BC, Canada, July 24-27, 2010. *Journal of Heart Disease* 2010; 7(1): 40. (Poster Presentation)

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Invited Lectures:

Fogg Behaviour Model 101- Introduction to an Industry-Based Persuasive Design Model and its Application for Health Research. Physical Therapy Seminar Series, Western University. London, Ontario, November 5, 2012.

Fogg Behaviour 201. Lawson Health Research Institute, Aging, Rehabilitation and Geriatric Care Research Centre LAYRS student luncheon. London, Ontario, August 30, 2012.

Fogg Behaviour 101. Lawson Health Research Institute, Aging, Rehabilitation and Geriatric Care Research Centre LAYRS student luncheon. London, Ontario, August 16, 2012.

Baby steps to a healthier future: Designing for behaviour in health research. Mobile Health 2012: Baby Steps to a healthier future. Stanford University, Palo Alto, California May 17, 2012.

Heart rate variability in metabolic syndrome. Western University School of Kinesiology Bioscience Graduate Seminar. London, Ontario March 26, 2012.

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