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# Clinical Predictors of Metabolic Syndrome

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By

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# ABSTRACT OF THE THESIS

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Metabolic syndrome refers to the co-occurrence of several cardiovascular risk factors, including insulin resistance, dyslipidemia, obesity, and hypertension. It is an escalating public health challenge with an estimated worldwide prevalence of 25%. Metabolic syndrome is also a powerful prognostic indicator for atherosclerotic cardiovascular disease, which remains the leading cause of morbidity and mortality within the United States.

Two simple clinical measures, resting heart rate (RHR) and heart rate reserve (HRR), have been shown to be associated with metabolic syndrome in the general population. Currently, however, there is a paucity of evidence in the scientific literature describing this association within the adult working population. Given the significant economic impact of cardiovascular disease on the occupational work force, the purpose of this study was to evaluate RHR and HRR as cost-effective screening metrics for the detection of metabolic syndrome.

Data from the biomarker project of the Midlife in the United States (MIDUS II) cross-sectional survey were analyzed using a combination of binary logistic regression, independent samples *t*-testing, prevalence ratio analysis, and generation of receiver operating characteristics (ROC) in order to elucidate the strength of the proposed relationships. All statistical analysis was

performed using JMP v13.0.0. The results suggested that both RHR and HRR are reliable predictors of metabolic syndrome; however, RHR generally had a stronger association within the younger study population regardless of gender. HRR was a stronger predictor among the older subset of participants, and demonstrated a marginally better discriminative ability throughout the sample population. The results for both predictor variables were significant at the $p < 0.05$ level. The utility of RHR and HRR as screening tools for metabolic syndrome, however, was lower than expected, as the area under the ROC curve was less than the desired cut-off level of 0.7.

# CHAPTER 1: INTRODUCTION AND PURPOSE

Cardiovascular disease (CVD) has been the leading cause of morbidity and mortality in the United States since 1920 (American Heart Association, 2017). Heart disease accounts for 23% of all deaths, and its mortality rate over the past year has increased by 1% for the first time since 1969 (CDC, 2017). By 2015, 102.7 million Americans had at least one CVD-related condition, including hypertension, coronary heart disease, stroke, congestive heart failure, or atrial fibrillation. To put the severity of this problem into perspective, consider the statistic that more than one person in the United States dies from a heart disease-related event every minute (Heron, 2016). The cost of this epidemic is staggering with an estimated $555 billion spent in 2016 alone on the treatment and sequelae of heart disease. By 2035, the projected cost will increase to $1.1 trillion, and over 45% of Americans will suffer from a CVD-related condition. Clearly, this represents a tremendous burden on the US economy and healthcare infrastructure.

Unfortunately, the ability to control the growing burden of cardiovascular disease is severely hampered by the increasing prevalence of hypertension, Type 2 diabetes, obesity, hyperlipidemia, and poor diet (American Heart Association, 2017). The clustering of these risk factors was first described by Haller in 1977, and termed ‘metabolic syndrome’ (Sarafidis et al., 2006). This was followed by Reaven coining the term ‘syndrome X’ in 1988, after proposing insulin resistance as the primary underlying factor. Today, metabolic syndrome is an established diagnosis and is based on the co-occurrence of four central features: visceral adiposity, insulin resistance, endothelial dysfunction, and atherogenic dyslipidemia (Huang, 2009). Various definitions for the syndrome have been proposed, with general criteria including abdominal obesity, hypertension, insulin resistance, and hyperlipidemia. The most widely recognized

definition in clinical use today is from the National Cholesterol Education Program Adult Treatment Protocol III guidelines (NCEP ATP III). This definition of metabolic syndrome, which was co-developed by the American Heart Association and the National Heart, Lung, and Blood Institute, incorporates the key elements of visceral obesity, dyslipidemia, and insulin resistance, but also adds hypertension (Table 1).

Table 1. NCEP ATP III Metabolic Syndrome criteria (2005 revision).

| **Risk factor** | **Defining level** |
|---|---|
| *Diagnosis is established when ≥ 3 risk factors are present concurrently | |
| Obesity | Waist circumference >40 inches (M), >35 inches (W) |
| Hyperglycemia/Insulin resistance | Fasting glucose ≥100 mg/dL or use of hyperglycemic medication |
| Hypertriglyceridemia | Fasting triglycerides ≥150 mg/dL |
| Dyslipidemia | HDL cholesterol <40 mg/dL (M), <50 mg/dL (W) |
| Hypertension | Systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg or use of anti-hypertensive medication |

Key: M = men, W = women.

The worldwide prevalence of metabolic syndrome is 25% (Ford, 2002). The prevalence within the United States is 34.2% according to the National Health and Nutrition Examination Survey (NHANES), and increases with advancing age and obesity (Moore et al., 2017). The impact of metabolic syndrome is significant, as it confers a 2-fold risk of cardiovascular disease, a 5-fold risk of type 2 diabetes mellitus, a 2 to 4-fold risk of stroke, a 3 to 4-fold risk of myocardial infarction, and a 2-fold risk of mortality from any of these events (Kaur, 2014). The underlying pathophysiology is delineated by a state of chronic, low-grade inflammation, adipose

tissue hyperplasia, impaired pancreatic beta-cell function, a hypercoaguable state, and vasoconstriction.

The effect of metabolic syndrome on the occupational workforce is staggering, and leads to increased healthcare costs, increased short-term disability costs, and increased presenteeism (Schultz et al., 2009). According to data from the National Health and Nutrition Examination Survey, working-age individuals with metabolic syndrome cost $626 per month in healthcare costs compared to $367 per month for their healthy counterparts (NHANES, 2016). Additionally, a study by Boudreau et al. in 2009 of 170,648 employees revealed that the annual total healthcare costs for individuals with metabolic syndrome versus no metabolic syndrome differed by a magnitude of 1.6 ($5,732 vs. $3,581). Given that corporations are the primary payers of healthcare costs in the United States, they have a vested interest in reducing the prevalence of metabolic syndrome within their employees.

In order to combat the deleterious effects of metabolic syndrome and prevent adverse cardiovascular outcomes, a suitable screening metric must be employed. For the purposes of this study, the characteristics of an appropriate predictor variable included the following: easy to measure, non-invasive, predictive of cardiovascular fitness, reproducible, and cost-effective. Metrics which already predict cardiovascular fitness levels are preferable, since cardiovascular fitness levels have been shown to vary inversely with metabolic syndrome (Kaur, 2014). When considering the constraints of a typical clinical patient visit, two such measures met these criteria. Both resting heart rate (RHR) and heart rate reserve (HRR) are easily obtained from a combination of vital signs data and age. Neither measure involves significant cost or discomfort to the patient, and both provide a real-time, numerical assessment of cardiac function. It should be noted that blood pressure and body mass index (BMI) were also considered, however these

metrics were not chosen as predictor variables because each is already closely associated with metabolic syndrome. Blood pressure is a component criteria of metabolic syndrome, while the height and weight components of BMI may be indirectly related to waist circumference.

Resting heart rate is defined as the number of heart beats occurring in a 60 second period while the subject is in a resting, non-exertional state. It is typically measured with an automated vital signs machine, or by placing a finger over a palpable arterial vessel and counting the number of heart beats that occur in 60 seconds. Heart rate reserve is defined as the difference between an individual's maximum predicted heart rate and his or her resting heart rate, calculated as HRR = maximal heart rate – RHR. Both RHR and HRR reflect the frequency of the cardiac cycle and are reported as beats per minute (bpm).

It is important to note that numerous factors, both intrinsic and extrinsic, affect resting heart rate, and consequently heart rate reserve as well. Generally, resting heart rate decreases as the life expectancy of a mammal increases (Zhang et al., 2009). Intrinsic regulation of heart rate is primarily provided by the autonomic nervous system through the parasympathetic action of the vagus nerve, as well as the sympathetic action of endogenous catecholamines. Extrinsic modulation of heart rate can be due to a myriad of factors, a common example of which is beta-blocker medication, which decreases cardiac chronotropy and subsequently heart rate. Another common example is the reduction in resting heart rate observed in endurance athletes due to cardiovascular conditioning and increased vagal tone. A selection of factors which affect heart rate are listed below in Table 2.

Table 2. Factors which affect resting heart rate.

| Factor | Effect on resting heart rate |
|---|---|
| Elevated body temperature | ⇑ |
| Exercise | ⇑ |
| Age | ⇓ maximum heart rate |
| Gender | ⇑ in females |
| Stress | ⇑ |
| Illness | ⇑ |
| Medications | ⇑ or ⇓ |
| Dehydration | ⇑ |
| Vagal stimulation | ⇓ |
| Elevated barometric pressure | ⇓ |
| Hormone secretion | ⇑ or ⇓ |
| Electrolyte imbalance | ⇑ or ⇓ |

Given the simplicity of measuring resting heart rate and heart rate reserve, it stands to reason that utilizing these metrics could potentially provide a cost-efficient screening methodology for the detection of metabolic syndrome. Clearly, a robust strategy of prevention is necessary to combat the growing epidemic of cardiovascular disease, and screening for metabolic syndrome in our aging workforce could potentially represent an enormous return on investment. The benefits of identifying and treating the components of metabolic syndrome before the occurrence of a significant adverse cardiac event are numerous, and include reduced morbidity and mortality, reduced healthcare costs, increased workplace productivity due to decreased lost man-hours, and a healthier workforce.

Given the overall goal of preventing devastating cardiac events such as stroke or myocardial infarction, why not simply focus on screening for individual cardiovascular risk factors? Not surprisingly, the body of scientific literature suggests that the utility of predicting metabolic syndrome versus individual cardiovascular risk factors is complex. As mentioned previously, metabolic syndrome as a whole confers a greater risk of morbidity and mortality from diabetes, stroke, and myocardial infarction compared to individual cardiovascular risk factors (Kaur, 2014). Metabolic syndrome is also associated with lethargy, poor mood, obstructive sleep apnea, immune dysfunction, and decreased cognitive ability (Huang, 2009). Additionally, the state of chronic, systemic inflammation which occurs with metabolic syndrome has been linked to hepatic steatosis, microalbuminuria, and polycystic ovarian syndrome (Ali, 2015, Paschos et al., 2009). Clearly, the adverse effects of metabolic syndrome are greater than the sum of its component risk factors, and deserving of a thorough preventive strategy.

The purpose of this cross-sectional study is to investigate the association between resting heart rate and heart rate reserve with metabolic syndrome in the US adult working population. The primary hypothesis is that resting heart rate is directly associated with metabolic syndrome, while heart rate reserve is inversely associated with metabolic syndrome. Furthermore, this research seeks to lay a foundation for future studies which could strengthen the body of evidence suggesting that these two low-cost, clinical screening metrics could be used to reliably predict metabolic syndrome in the occupational workforce. Although beyond the scope of this research, further longitudinal analysis of the same sample population would serve to elucidate the potential predictive power of these clinical metrics.

# CHAPTER 2: LITERATURE REVIEW

The association between resting heart rate, cardiovascular health, and mortality has been well studied within the scientific literature. Jensen et al. (2013) examined the relationship between resting heart rate and mortality in a prospective study of 2,798 employed men aged 53 to 75 years old. The participants were free of known cardiovascular disease or diabetes mellitus at baseline, and had resting heart rates determined by electrocardiogram and $VO_{2\ max}$ performed via a bicycle ergometer. Each individual was then stratified into one of six resting heart rate categories and followed for 16 years. Mortality was studied with multivariate Cox models adjusted for leisure-time physical activity, physical fitness level, and several cardiovascular risk factors. Over the course of the follow-up period, 1,082 deaths occurred (38.7%). Increasing resting heart rate was highly associated with mortality in a progressively increasing manner, after adjusting for all covariates (Jensen et al. 2013). Men in the highest resting heart rate category had a hazard ratio of 3.06 (95% CI 1.97 to 4.75) compared to men in the reference (lowest) category. Additionally, the authors observed a 16% increased risk of mortality with each 10 beat per minute increase of resting heart rate. Limitations of this study included the single measurement of resting heart rate, which did not take into account potential intra-subject or diurnal variation. Additionally, the study participants were relatively homogenous, as the sample consisted of only Caucasian, middle-aged and elderly men from Denmark. Despite these limitations, the authors concluded that resting heart rate was not only a marker of poor general fitness, but also a risk factor for mortality independent of physical fitness level, leisure-time physical activity, or other cardiovascular risk factors.

A meta-analysis by Fox et al (2007) sought to evaluate the strength of the evidence suggesting that resting heart rate is a prognostic factor and potential therapeutic target for individuals with cardiovascular disease. The authors began by citing two, large multi-center prospective cohort studies, the first of which included analysis of 5,713 men aged 42 to 53 years old. Both resting and exercise heart rate were measured at baseline, and all-cause and cardiovascular mortality were assessed during a follow-up period of 23 years. Sudden and non-sudden death due to myocardial infarction increased progressively with increasing resting heart rate, even after adjustment for a number of covariates including age, blood pressure, body mass index, diabetes mellitus, and exercise capacity. In the second study, 24,913 men and women with proven coronary artery disease were followed for 14.7 years, and all-cause and cardiovascular mortality over the study period were assessed. The results revealed that cardiovascular mortality was directly related to baseline resting heart rate, and hazard ratios increased with increasing strata of resting heart rate. After evaluating multiple other large, registry-based studies, the authors concluded that resting heart should be recognized as a factor for cardiovascular risk assessment and risk reduction. Currently, resting heart rate is not recognized as a risk factor in American cardiovascular guidelines.

A more recent review paper by Boudoulas et al. (2015) also attempted to delineate the relationship between resting heart rate and its effects on cardiovascular life expectancy and the arterial system. The authors cited multiple, high-quality studies arising from a variety of international sites and study populations. In a study by Jouven et al. (2005) published in the New England Journal of Medicine, 5,713 asymptomatic young men ranging in age from 32 to 42 years old were followed prospectively for 23 years. Incident death from myocardial infarction (MI) was analyzed, and the results revealed that the risk of sudden death due to MI was higher in

participants with a resting heart rate greater than 75 beats per minute than among those with a lower baseline heart rate. The authors also cited the Framingham study (Gillman et al., 1993), which evaluated 4,530 patients with hypertension aged 34 to 74 years of age with systolic blood pressures greater than 140 mmHg and diastolic blood pressures greater than 90 mmHg. All-cause mortality was assessed over a 36-year follow-up period, and the results revealed that the age-adjusted rate of mortality increased directly with increasing resting heart rate at baseline. The authors also cited the Coronary Artery Surgery Study (Diaz et al., 2005), a prospective cohort study of 24,913 patients with proven coronary artery disease at baseline. The goal of the study was to assess the relationship between resting heart rate and cardiovascular mortality and morbidity. After a follow-up period of 14.7 years, the authors observed a statistically significant increase in the hazard ratio of cardiovascular mortality with increasing baseline heart rate, after adjustment for age, hypertension, gender, left ventricular ejection fraction, and treatment with beta-blocker medication. As a result of this collection of findings, Boudoulas et al. concluded that an elevated resting heart rate negatively affects the cardiovascular system, and can lead to decreased survival.

In regards to the specific relationship between metabolic syndrome and resting heart rate, Jiang et al. (2014) conducted a two-part cross-sectional and longitudinal study of 89,860 employed coal workers in China. Resting heart rate was measured at baseline from electrocardiogram tracings, and the participants were then stratified into six categories based on resting heart rate. Utilizing the NCEP ATP III diagnostic criteria, the cross-sectional analysis revealed that 25.7% of the sample population had metabolic syndrome at baseline. The odds ratio of having metabolic syndrome at baseline was 1.49 (95% CI 1.32 to 1.69) for individuals in the highest strata of resting heart rate compared to the reference (lowest) strata.

The longitudinal analysis followed 43,725 participants for 4 years, and revealed a cumulative incidence of metabolic syndrome of 26.5%. The odds ratio of developing metabolic syndrome at the conclusion of the follow-up period was 1.41 (95% CI 1.21 to 1.65) for individuals in the highest strata of resting heart rate compared to the reference strata. Although the authors adjusted for numerous covariates including age, gender, tobacco use, alcohol intake, level of physical activity, and body mass index, this study did have limitations. First, exposure assessment was based on a single measurement of resting heart rate, which did not take into account heart rate variability. Second, the study population was a homogenous vocational cohort comprised of roughly 80% males, which may have affected the external validity of its results. Despite these limitations, the authors concluded that resting heart rate is an independent risk factor for concurrent metabolic syndrome, and also a powerful predictor of future metabolic syndrome (Jiang et al., 2014).

Inoue at al. (2009) also investigated the relationship between resting heart rate and metabolic syndrome in a longitudinal cohort study of 6,281 male and female participants from Okinawa, Japan. Resting heart rate was calculated by determining the mean R-R interval during 5 seconds of electrocardiogram recording. Participants were stratified into six groups of resting heart rate and followed for an average observation period of 47 months. The authors analyzed multiple covariates, including age, tobacco use, alcohol consumption, and exercise habits. Cox regression was utilized to generate hazard ratios for incremental increases in the study variables. The results revealed a cumulative incidence of metabolic syndrome of 9.9%. Males with elevated resting heart rate were more likely to develop metabolic syndrome than their counterparts in the lowest heart rate group, with a corresponding odds ratio of 1.73 (95% CI 1.28 to 2.32). Additionally, each unit increase in heart rate corresponded to a 1.2-fold increase in the risk of

developing metabolic syndrome for men only. The results for female participants were not statistically significant. Numerous factors may have limited the findings of this study. First, the majority of study participants were healthy volunteers, and may not have been representative of the population. Second, the authors were unable to elucidate the point at which elevated heart rate becomes dangerous. And lastly, baseline resting heart rate was only measured a single time, which may not have accounted for intra-subject variability. The authors subsequently concluded that elevated resting heart rate is a risk factor for developing metabolic syndrome in men only (Inoue et al. 2009).

Although a significant amount of data has been published regarding the relationship between resting heart rate and metabolic syndrome, a relative paucity exists in the literature with regards to heart rate reserve. Cheng at al. (2002) evaluated the association between heart rate reserve and cardiovascular (CVD) and all-cause mortality in a large prospective cohort study of 25,459 healthy men, aged 20-59 years old. A maximal treadmill exercise test and a baseline questionnaire were completed, and all participants were followed until the date of death or the study's end. The average follow-up period was 13 +/- 6.2 years, and there were 724 total deaths, of which 28.3% were due to cardiovascular disease. The authors split the cohort into two age groups for their analysis (20-39 years, 40-59 years), and performed Cox regression while adjusting for a number of covariates including systolic blood pressure, cholesterol levels, body mass index, tobacco use, and alcohol consumption. Their results revealed that among younger men, heart rate reserve was the only factor associated with cardiovascular disease mortality, with a relative risk reduction of 0.6 for every 10 beat per minute increase in HRR. Among men in the older age group, this association was reversed for both cardiovascular and all-cause mortality. The authors concluded that heart rate reserve was inversely associated with cardiovascular

disease mortality, and may also represent an important exercise test parameter to predict CVD mortality in younger men. While these findings do not directly support the hypothesis that heart rate reserve is a predictor of metabolic syndrome, they do certainly suggest that it is associated with the development of cardiovascular disease.

In a study with a primary focus on metabolic syndrome, Choi et al. (2017) evaluated the association between resting heart rate, heart rate reserve, and the occurrence of metabolic syndrome in firefighters. Utilizing participants previously enrolled in the FORWARD study, the analysis included data from 288 professional firefighters that was collected during their bi-annual WEFIT (wellness and fitness) examinations in an outpatient clinic. Resting heart rate was measured by experienced nursing staff, and heart rate reserve was calculated by subtracting RHR from each individual's maximum heart rate as predicted by the equation: 205.8 – (0.685 x age). For the purpose of comparison, the estimated maximum exertional oxygen uptake ($VO_2$ max) was also obtained using a standardized exercise treadmill test performed by an experienced exercise physiologist. Metabolic syndrome was defined using the NCEP ATP III criteria, and the diagnosis constructed from clinical data. RHR, HRR, and $VO_2$ max were grouped into quintiles, and Cox proportional hazards models were utilized for the analysis. The results revealed that the prevalence of metabolic syndrome in this relatively healthy subset of the working population was 14.2%. The prevalence ratios for the co-occurrence of metabolic syndrome between the lowest quintile-based groups and the highest were 1.88, 5.90, and 8.03 for resting heart rate, heart rate reserve, and $VO_2$ max, respectively. Both heart rate reserve and $VO_2$ max had a significant linear association with metabolic syndrome in both the unadjusted and age-adjusted models, while resting heart rate did not. The study did have a few important limitations, including the cross-sectional design, relatively small sample sizes within the age-stratified analysis, estimation of the

$VO_2$-max based on a sub-maximal treadmill test, and estimation of the resting heart rate using only a single 10-second measurement. Despite this, the authors concluded that both heart rate reserve and $VO_2$ max were significantly associated with metabolic syndrome among middle-aged firefighters, and heart rate reserve was inversely associated with metabolic syndrome.

# CHAPTER 3: METHODOLOGY

This research study consisted of a cross-sectional analysis of data from the Midlife in the United States (MIDUS) project, a national longitudinal study of health and well-being conducted by the MacArthur Foundation research network. It was primarily designed to investigate the role of psychological, social, and behavioral factors in accounting for age-related variations in health (Ryff et al., 2017). The original study consisted of a national survey of 7,108 participants aged 25-74, who were living within the United States at the initiation of the study in 1994. Since that time, multiple longitudinal follow-up assessments have been completed, generating further cross-sectional and longitudinal data sets on the same participants.

Given the specific objectives of this study regarding metabolic syndrome, the MIDUS 2 biomarker project was selected for data analysis (project 4). This dataset was generated between 2004 and 2009, and consisted of a sample size of 1,255 participants. Of the 1,255 individuals in the biomarker project, 1,052 originated from the MIDUS 2 survey (project 1). This represented a participation rate of 39.4% of individuals from the original MIDUS 2 survey of 4,963. The remaining 203 participants did not originate from the MIDUS 2 survey, and were recruited as an African-American subsample from Milwaukee, WI. Of the 1,255 biomarker participants, individuals who were not employed at the time of the original data collection were excluded, yielding a sample size of 731. After excluding another 22 individuals who were missing values for either resting heart rate or component data necessary to diagnose metabolic syndrome, 709 participants remained. Given that the majority (83%) of the occupational work force in the United States retires by age 70 (Toossi et al., 2017), individuals greater than 70 years of age were

also excluded from the study. This yielded a final sample size of 666 employed participants for the analysis in this research study.

The original data acquisition occurred over a 2-day clinic visit, which was performed at one of three national sites (University of California Los Angeles, University of Wisconsin, and Georgetown University). A detailed physical examination was performed on each participant, including vital signs and an electrocardiogram. Multiple laboratory samples were also obtained, and included fasting blood, a 12-hour urine collection, and saliva. From these samples, numerous biomarkers were measured from the hypothalamic-pituitary axis, autonomic nervous system, immune system, and cardiovascular system. Additionally, two 55-page, self-administered questionnaires were completed, comprising 354 questions. The final version of the dataset contained 1,884 variables, with the most recent version published in 2017.

Assessment of the explanatory variables was performed in the following manner. Resting Heart Rate (RHR) was measured during the first half of the day using the finger palpation technique over the radial artery with the subject in a seated position. A single measurement was collected, and the number of beats per minute was determined by multiplying the number of heartbeats in 15 seconds by 4, to yield the RHR in beats per minute. Heart Rate Reserve (HRR) was calculated using the formula HRR = maximum heart rate – RHR, and also reported as beats per minute.

Estimation of maximal heart rate has traditionally been performed by the age-predicted equation of 220 – age. However, this equation dates to the 1970s and was determined arbitrarily from a total of ten studies (Fox et al., 1971). A more accurate equation to predict maximal heart rate was formulated by Tanaka et al. in 2001, based upon a meta-analysis of 351 studies and 18,712 subjects. This meta-analysis yielded the equation 208 – 0.7 x age, which does not

underestimate maximum heart rate for adults past age 40 as does the traditional equation. Additionally, development of this more recent model included a concurrent laboratory-based study of 514 participants aged 18 to 81, and included verified maximal level of exertion established via conventional exercise testing using measured $VO_2$-max and respiratory exchange ratio. Given the robust methodology and sample size employed in Tanaka's paper, this modified equation was used to determine maximal heart rate for the purposes of this study.

The outcome of interest, metabolic syndrome, was expressed as a categorical variable. The diagnosis of metabolic syndrome was determined using the National Cholesterol Education Program Adult Treatment Protocol III guidelines (NCEP ATP III). Given that the component data were available within the MIDUS 2 dataset, the diagnosis of metabolic syndrome was constructed for each participant. All data were converted into the units delineated in Table 1, seen previously within this paper. Information regarding the participants' use of hyperglycemic medication was not available within the MIDUS dataset, and therefore the criteria for the insulin resistance component of metabolic syndrome was based solely on the fasting blood glucose level.

Descriptive statistics were first generated in order to gain an understanding of the distribution of pertinent variables within the study. The mean, median, standard deviation, and frequency distribution of resting heart rate and heart rate reserve were calculated. Next, the overall prevalence of metabolic syndrome within the study participants was calculated, including the sub-category prevalence within males and females. The mean, median, standard deviation, and frequency distributions of the covariates were also calculated, and examined for potential effect modification or confounding.

In order to assess the difference in mean RHR and HRR among individuals with metabolic syndrome and those without metabolic syndrome, an independent samples *t*-test was performed. Given that RHR and HRR are likely affected by age and gender, a more robust analysis of variance (ANOVA) was then performed in order to assess the same differences in mean RHR and HRR while controlling for age and gender. Next, due to the cross-sectional nature of the data utilized in this study, prevalence ratios were selected as the appropriate measure of effect to analyze the relationship between RHR and HRR with metabolic syndrome. The prevalence ratio represents the proportion of individuals with prevalent disease among the exposed, divided by the proportion with prevalent disease among the unexposed. For the purposes of this study, both RHR and HRR were grouped into quintiles, and the unexposed were defined as the reference quintile of either RHR (the lowest quintile) or HRR (the highest quintile). Prevalence ratios for metabolic syndrome were calculated, and the analysis was repeated after the data was stratified by both age and gender. Age was divided into two groups (35 – 44 years old, and 45 – 70 years old), and gender was split into males and females. The division between the two age strata at 45 years of age was selected due to the significantly increased risk of cardiovascular disease after this age (Wilson et al., 1998). Additionally, a Cochran-Armitage test for linear trend was performed for each predictor variable, and a corresponding $p_{trend}$ value was reported.

Binary logistic regression was also utilized to assess the association and directionality between the two predictor variables and metabolic syndrome. The β-coefficients, prevalence odds ratios, and respective 95% confidence intervals were generated for both RHR and HRR. Two models were evaluated, the first of which was a univariate model without any adjustment. Given the likely effect of age and gender on the predictor and outcome variables, a second

multivariate model was generated which adjusted for age and gender. Finally, receiver operating characteristic (ROC) curves were generated for both RHR and HRR in an attempt to determine which explanatory variable was the best predictor of metabolic syndrome. This analysis was repeated after the data were stratified by age and gender. The area under the ROC curve was calculated, and a value $\geq 0.7$ was considered indicative of a reliable screening metric (Karimollah, 2013). A $p$-value $< 0.05$ was selected as the cutoff for statistical significance throughout the study. All statistical analysis was performed using JMP, version 13.0.0 (JMP, 2016).

# CHAPTER 4: RESULTS

The baseline characteristics of the study participants are shown in Table 3. The mean age was 53.4 years old, and the vast majority of study participants were over the age of 45 (82.7%). The mean resting heart rate was 70.3 beats per minute (bpm), and the mean heart rate reserve was 100.3 bpm. The cut-point between the age subcategories was selected to be 45 years of age, while the cut-points for RHR and HRR were based on their median values. The distribution by gender was 48.2% male (mean age 53.5) and 51.8% female (mean age 53.3). When utilizing the NCEP ATP III criteria for the cut-off values of metabolic syndrome component risk factors, roughly half of the participants had enlarged waist circumferences and elevated systolic blood pressure. Approximately 68% had elevated HDL cholesterol levels. As expected, the majority of study participants had a normal fasting glucose, fasting triglyceride level, and diastolic blood pressure. Additionally, the majority of the sample population was not using an anti-hypertensive medication and had not been diagnosed with diabetes mellitus by a physician. The distribution of the fasting triglyceride level was markedly skewed to the right, resulting in an exceptionally large standard deviation in comparison to the other study variables.

In regards to the primary outcome, roughly 20% of the study participants did not have any component risk factors of metabolic syndrome, while 27% had a single risk factor, and 22% had two risk factors. The overall prevalence of metabolic syndrome within the study population was 30.8%, or 205 out of 666 individuals. The prevalence of metabolic syndrome among males was 37.1%, while the prevalence among females was significantly lower at 24.9%. The prevalence of metabolic syndrome within the younger age group (35 – 44 years old) was 29.1%, which was similar to the prevalence within the older age group (45 – 70 years old) of 31.1%.

Table 3. Descriptive statistics and distributions of study variables (N = 666).

| Continuous Study Variables | Mean | Median | Standard Deviation | Subcategory | Frequency Distribution (%) |
|---|---|---|---|---|---|
| RHR (beats/min)* | 70.3 | 68.0 | 10.9 | 36 - 70.3 | 55.2 |
| | | | | 70.4 - 110 | 44.8 |
| HRR (beats/min)* | 100.3 | 101.0 | 12.4 | 58.4 - 100.3 | 47.2 |
| | | | | 100.4 - 146.1 | 52.8 |
| Age (years)† | 53.4 | 53.0 | 8.4 | 35 - 44 | 17.3 |
| | | | | 45 - 70 | 82.7 |
| Waist circumference (in)‡ | 37.9 | 37.4 | 6.7 | > 40 (M) | 23.3 |
| | | | | ≤ 40 (M) | 25.4 |
| | | | | > 35 (F) | 25.1 |
| | | | | ≤ 35 (F) | 26.2 |
| Fasting glucose (mg/dL)‡ | 99.0 | 95.0 | 22.6 | ≥ 100 | 34.1 |
| | | | | < 100 | 65.9 |
| Fasting triglycerides (mg/dL)‡ | 124.0 | 108.0 | 63.2 | ≥ 150 | 28.4 |
| | | | | < 150 | 71.6 |
| HDL cholesterol (mg/dL)‡ | 54.0 | 51.6 | 17.7 | ≥ 40 (M) | 30.2 |
| | | | | < 40 (M) | 18.5 |
| | | | | ≥ 50 (F) | 37.8 |
| | | | | < 50 (F) | 13.5 |
| Systolic blood pressure (mmHg)‡ | 129.6 | 129.0 | 17.0 | > 130 | 45.6 |
| | | | | ≤ 130 | 54.4 |
| Diastolic blood pressure (mmHg)‡ | 76.2 | 75.0 | 10.3 | > 85 | 19.4 |
| | | | | ≤ 85 | 80.6 |

| Categorical Study Variables | Subcategory | Frequency Distribution (%) | Mean RHR | Mean HRR |
|---|---|---|---|---|
| Gender | M | 48.2 | 68.5 | 102.0 |
| | F | 51.8 | 72.0 | 98.6 |
| Physician-diagnosed diabetes | yes | 8.2 | 76.0 | 93.7 |
| | no | 91.8 | 69.8 | 100.9 |
| Anti-hypertensive medication | yes | 26.8 | 71.8 | 96.2 |
| | no | 73.2 | 69.8 | 101.8 |

*The subcategory cut-points for RHR and HRR were based on their respective mean values.
†The cut-point for age was based on the elevated risk of cardiovascular disease after age 45.
‡The cut-point for metabolic syndrome component variables were based on the NCEP ATP III criteria.

Examination of the crude data revealed both resting heart rate and heart rate reserve to be approximately normally distributed. Quintiles were constructed for both RHR and HRR, and the distribution by gender was calculated for each clinical metric. The gender-specific distribution by quintiles of resting heart rate for male and female study participants appears below in Figure 1, while the equivalent distribution for heart rate reserve appears below that in Figure 2. Female participants generally had higher resting heart rates compared to males, with a mean of 72.0 bpm versus 68.5 bpm. Males tended to have greater heart rate reserve compared to females, with a mean of 102.0 bpm versus 98.6 bpm.

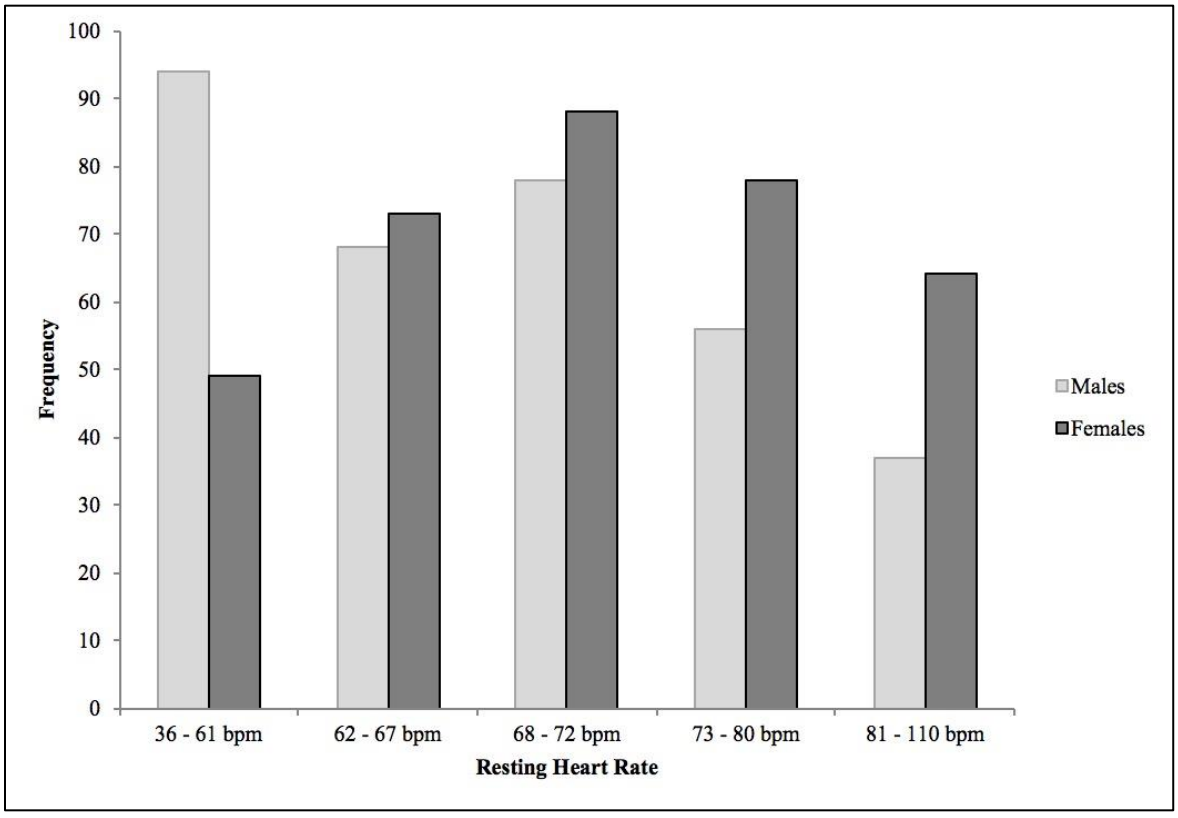


Figure 1. Frequency distribution of males and females by resting heart rate based on quintile subgroups among the total population. N = 321 Males, N = 345 Females.

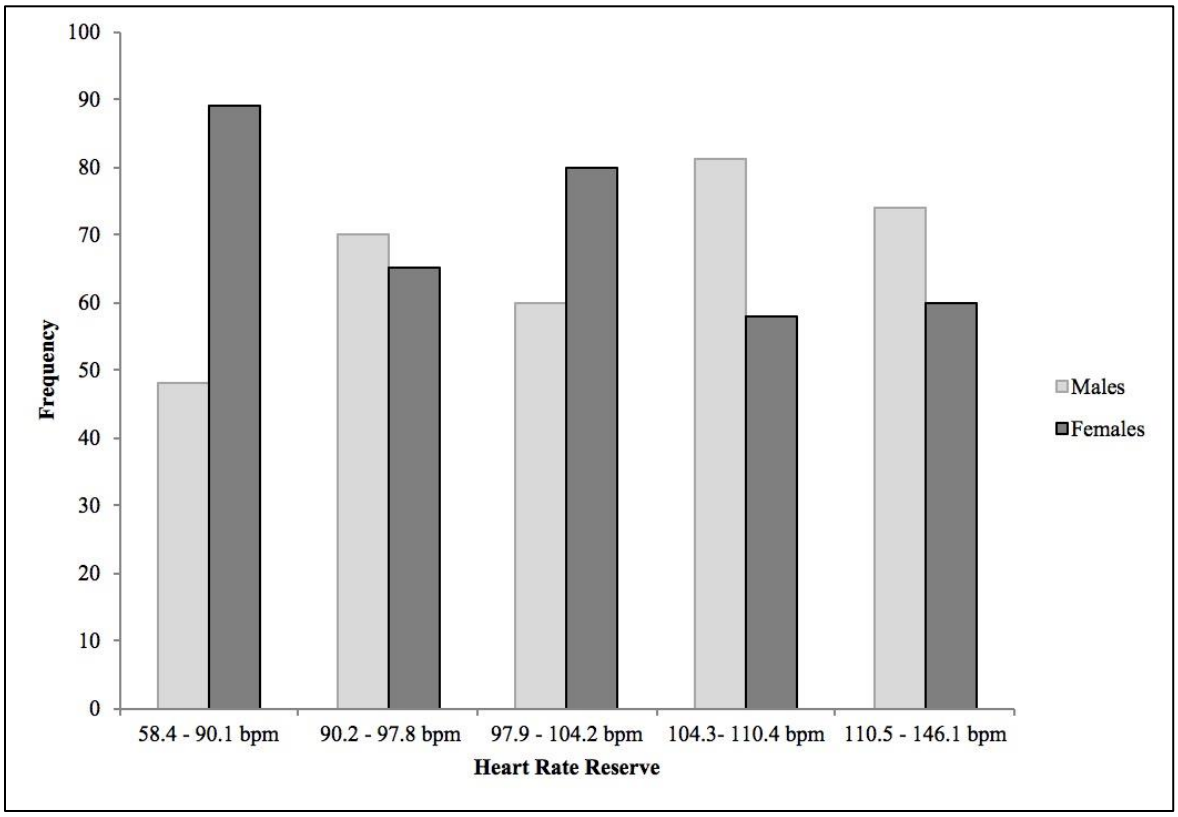


Figure 2. Frequency distribution of males and females by heart rate reserve based on quintile subgroups among the total population. N = 321 Males, N = 345 Females.

Next, the distributions of resting heart rate and heart rate reserve across study participants with and without metabolic syndrome were generated, and are shown in Figure 3. The mean resting heart rate of individuals with metabolic syndrome was 73.5 bpm, compared to 68.8 bpm in healthy individuals. The mean heart rate reserve of individuals with metabolic syndrome was 96.5 bpm, compared to 102.0 in healthy individuals. Given these results, further investigation into the significance of the differences in mean RHR and HRR between these two groups was warranted.

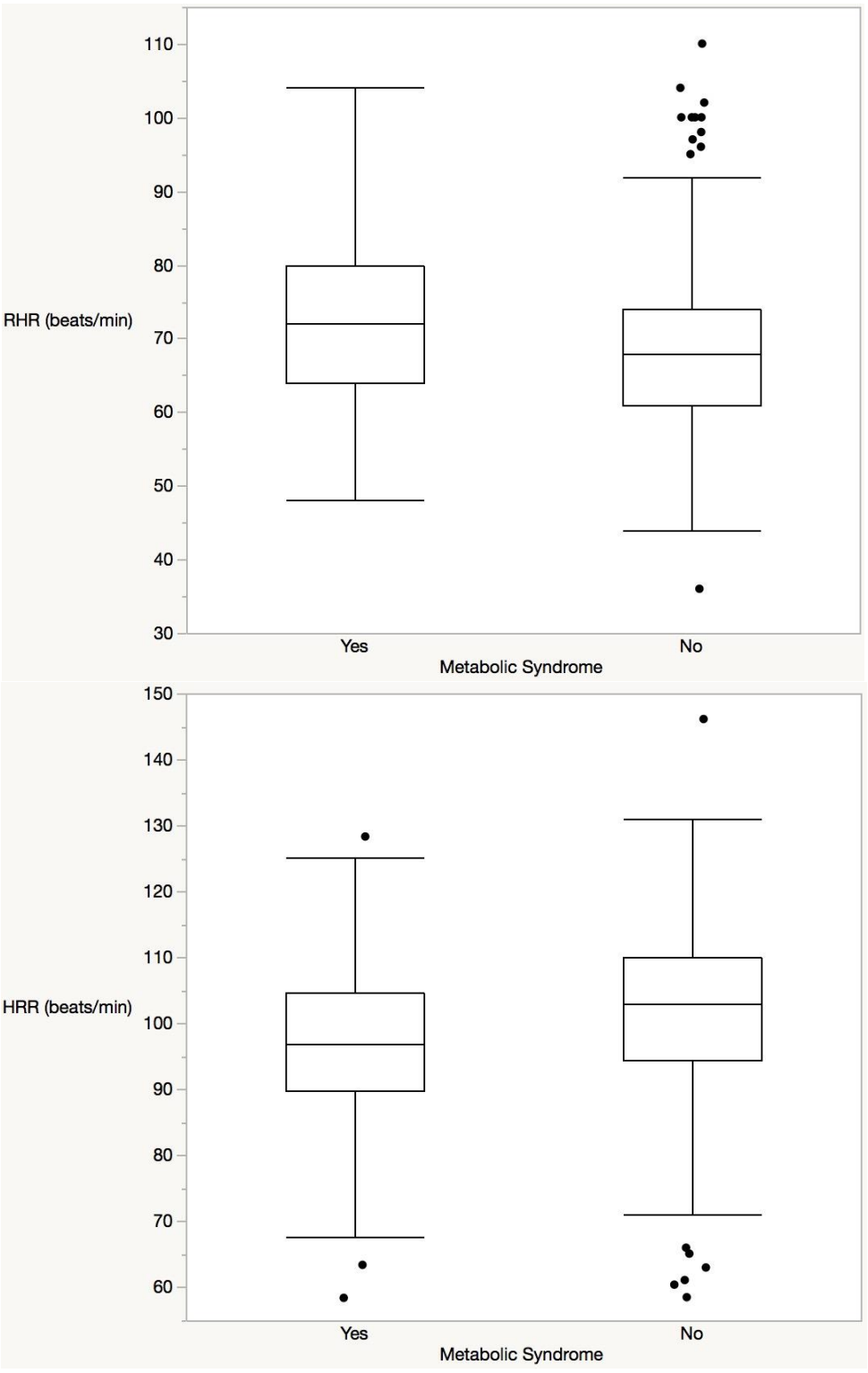


Figure 3. Distribution of resting heart rate (RHR) and heart rate reserve (HRR) across study participants with and without metabolic syndrome (N = 205 'yes', N = 461 'no').

An unpaired *t*-test was then performed in order to assess the significance of the differences in the mean resting heart rate and heart rate reserve for participants with and without metabolic syndrome. Each *t*-test was performed assuming equal variances, because the variances were approximately equal within the metabolic syndrome subgroups. The results revealed a statistically significant difference of the means for both RHR and HRR when comparing individuals with metabolic syndrome to those without metabolic syndrome (Table 4). The resultant *p*-values for both clinical metrics were < 0.0001, well below the chosen significance level of the study ($\alpha = 0.05$).

Table 4. Unpaired *t*-test comparisons of resting heart rate (RHR) and heart rate reserve (HRR) for individuals with and without metabolic syndrome (N = 666).

| Clinical metric | Metabolic Syndrome | N | Mean | *t* | DF | *p*-value* |
|---|---|---|---|---|---|---|
| RHR (beats/min) | Yes | 205 | 73.49 | -5.18 | 664 | < 0.0001 |
| | No | 461 | 68.84 | | | |
| HRR (beats/min) | Yes | 205 | 96.55 | 5.26 | 664 | < 0.0001 |
| | No | 461 | 101.99 | | | |

*The reported *p*-value denotes a two-tailed test.

Given the likely effects of age and gender on resting heart rate and heart rate reserve, an analysis of variance (ANOVA) was generated with the same goal of determining the significance of the differences in mean RHR and HRR among participants with and without metabolic syndrome. The analysis was adjusted for age and gender, and the resultant least squares means appear in Table 5. Again, a statistically significant difference in the mean RHR and HRR among the outcome groups was demonstrated for both clinical metrics ($p < 0.0001$).

Table 5. ANOVA comparisons of resting heart rate (RHR) and heart rate reserve (HRR) for individuals with and without metabolic syndrome (N = 666), adjusted for age and gender.

| Clinical metric | Metabolic Syndrome | N | LSMean | *F* ratio | DF | *p*-value* |
|---|---|---|---|---|---|---|
| RHR (beats/min) | Yes | 205 | 73.32 | 19.60 | 3 | < 0.0001 |
| | No | 461 | 68.06 | | | |
| HRR (beats/min) | Yes | 205 | 100.17 | 55.35 | 3 | < 0.0001 |
| | No | 461 | 106.10 | | | |

*The reported *p*-value denotes a two-tailed test.

Next, prevalence ratios of metabolic syndrome for resting heart rate and heart rate reserve were generated. For these analyses, both RHR and HRR were stratified by quintile. The reference quintile for RHR was defined as the quintile which contained those participants with the lowest resting heart rates (Q1, 36 to 61 bpm). The reference quintile for HRR was defined as the quintile which contained participants with the highest values of heart rate reserve (Q5, 105.5 to 146.1 bpm). The prevalence ratios, corresponding 95% confidence intervals, and quintile-based prevalence of metabolic syndrome for all 666 study participants appear in Table 6.

Table 6. The prevalence ratios of resting heart rate (RHR) and heart rate reserve (HRR) for metabolic syndrome in 666 employed adults.

| Clinical Metric | Five Subgroups | N | Metabolic Syndrome Prevalence Ratio | 95% Confidence Interval | Prevalence of Metabolic Syndrome (%) |
|---|---|---|---|---|---|
| RHR | Q1 (36 - 61) | 139 | 1.00 | n/a | 15.8 |
| (beats/min) | Q2 (62 - 67) | 135 | 1.87 | 1.18 to 2.97 | 29.6 |
| N= 666 | Q3 (68 - 72) | 164 | 1.96 | 1.26 to 3.07 | 31.1 |
| | Q4 (73 - 80) | 131 | 2.17 | 1.38 to 3.41 | 34.4 |
| | Q5 (81 - 110) | 97 | 3.09 | 2.00 to 4.78 | 49.0 |
| HRR | Q5 (110.5 - 146.1) | 131 | 1.00 | n/a | 16.8 |
| (beats/min) | Q4 (104.3 - 110.4) | 133 | 1.43 | 0.88 to 2.33 | 24.1 |
| N = 666 | Q3 (97.9 - 104.2) | 138 | 1.77 | 1.12 to 2.80 | 29.7 |
| | Q2 (90.2 - 97.8) | 132 | 2.44 | 1.58 to 3.76 | 40.9 |
| | Q1 (58.4 - 90.1) | 132 | 2.55 | 1.66 to 3.91 | 42.8 |

Q1 to Q5: quintile-based subgroups. The reference subgroups for analysis were Q1 for RHR, and Q5 for HRR.

As seen in Table 6, the prevalence of metabolic syndrome increased with each increasing quintile of resting heart rate. Similarly, the prevalence ratios of metabolic syndrome progressively increased with each increasing quintile of resting heart rate to a maximum of 3.09 for Q5 ($p_{trend} < 0.0001$). Based upon the confidence intervals, the results for all quintiles of resting heart rate were statistically significant. In contrast, the prevalence of metabolic syndrome increased with each decreasing quintile of heart rate reserve. The prevalence ratio of metabolic syndrome also progressively increased with each decreasing quintile of heart rate reserve to a maximum of 2.55 for Q1 ($p_{trend} < 0.0001$). The results were statistically significant for all quintiles except Q4. A graphical representation of the prevalence ratios for metabolic syndrome stratified across quintiles of resting heart rate and heart rate reserve appears in Figure 4.

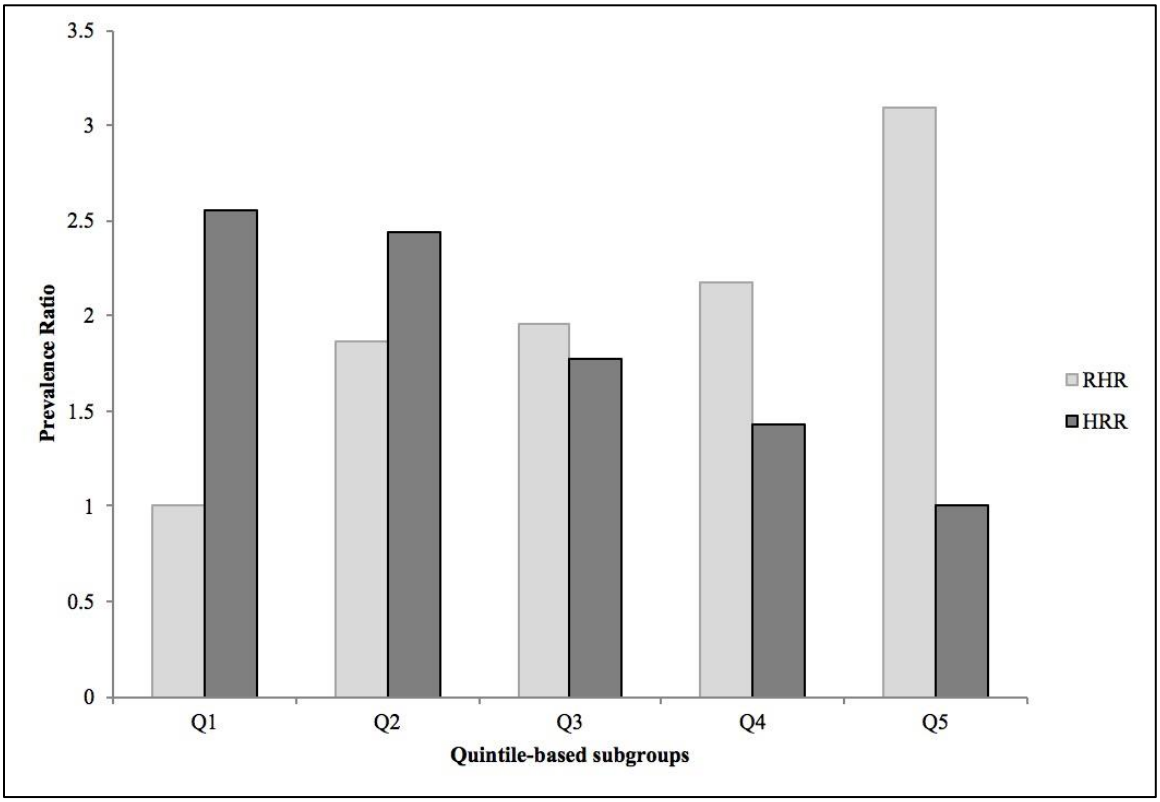


Figure 4. The prevalence ratios of resting heart rate (RHR) and heart rate reserve (HRR) for metabolic syndrome in 666 employed adults. Q1 (lowest) to Q5 (highest): quintile-based subgroups. The reference subgroup was Q1 for RHR and Q5 for HRR.

The prevalence ratio analysis was then repeated after the data was stratified into two age groups, younger (35 to 44 years of age) and older (45 to 70 years of age). The results appear in Tables 7 and 8. Among the 117 younger participants shown in Table 7, the prevalence ratios of metabolic syndrome increased with each increasing quintile of resting heart rate and with each decreasing quintile of heart rate reserve. The maximum prevalence ratio observed for RHR was 4.94 in Q5, however the results among quintiles were not uniformly statistically significant. The maximum prevalence ratio observed for HRR was 3.60 in Q1, and again the results were not consistently statistically significant.

Table 7. The prevalence ratios of resting heart rate (RHR) and heart rate reserve (HRR) for metabolic syndrome in 117 younger (35 - 44 years old) employed adults.

| Clinical Metric | Five Subgroups | N | Metabolic Syndrome Prevalence Ratio | 95% Confidence Interval | Prevalence of Metabolic Syndrome (%) |
|---|---|---|---|---|---|
| RHR | Q1 (36 - 61) | 35 | 1.00 | n/a | 11.4 |
| (beats/min) | Q2 (62 - 67) | 18 | 2.92 | 0.94 to 9.03 | 33.3 |
| N= 117 | Q3 (68 - 72) | 27 | 2.92 | 1.01 to 8.46 | 33.3 |
| | Q4 (73 - 80) | 21 | 2.50 | 0.80 to 7.85 | 28.6 |
| | Q5 (81 - 110) | 16 | 4.94 | 1.78 to 13.63 | 56.3 |
| HRR | Q5 (110.5 - 146.1) | 63 | 1.00 | n/a | 22.2 |
| (beats/min) | Q4 (104.3 - 110.4) | 19 | 1.42 | 0.63 to 3.19 | 31.6 |
| N = 117 | Q3 (97.9 - 104.2) | 21 | 1.07 | 0.44 to 2.62 | 23.8 |
| | Q2 (90.2 - 97.8) | 9 | 2.50 | 1.19 to 5.27 | 55.6 |
| | Q1 (58.4 - 90.1) | 5 | 3.60 | 1.90 to 6.81 | 80.0 |

Q1 to Q5: quintile-based subgroups. The reference subgroups for analysis were Q1 for RHR, and Q5 for HRR.

Table 8. The prevalence ratios of resting heart rate (RHR) and heart rate reserve (HRR) for metabolic syndrome in 549 older (44 - 70 years old) employed adults.

| Clinical Metric | Five Subgroups | N | Metabolic Syndrome Prevalence Ratio | 95% Confidence Interval | Prevalence of Metabolic Syndrome (%) |
|---|---|---|---|---|---|
| RHR | Q1 (36 - 61) | 104 | 1.00 | n/a | 17.3 |
| (beats/min) | Q2 (62 - 67) | 117 | 1.68 | 1.01 to 2.79 | 29.1 |
| N= 549 | Q3 (68 - 72) | 137 | 1.77 | 1.09 to 2.89 | 30.7 |
| | Q4 (73 - 80) | 110 | 2.05 | 1.26 to 3.34 | 35.5 |
| | Q5 (81 - 110) | 81 | 2.74 | 1.70 to 4.43 | 47.5 |
| HRR | Q5 (110.5 - 146.1) | 69 | 1.00 | n/a | 11.8 |
| (beats/min) | Q4 (104.3 - 110.4) | 114 | 1.94 | 1.14 to 4.04 | 22.8 |
| N = 549 | Q3 (97.9 - 104.2) | 117 | 2.62 | 1.29 to 5.30 | 30.8 |
| | Q2 (90.2 - 97.8) | 123 | 3.39 | 1.70 to 6.73 | 39.8 |
| | Q1 (58.4 - 90.1) | 126 | 3.51 | 1.77 to 6.95 | 41.3 |

Q1 to Q5: quintile-based subgroups. The reference subgroups for analysis were Q1 for RHR, and Q5 for HRR.

Among the 549 older participants shown in Table 8, the prevalence ratios of metabolic syndrome also increased with each increasing quintile of resting heart rate and with each decreasing quintile of heart rate reserve. The maximum prevalence ratio observed for RHR was 2.74 in Q5, and the results among all quintiles were statistically significant. The maximum prevalence ratio observed for HRR was 3.51 in Q1, and again all of the results were statistically significant.

The final iteration of the prevalence ratio analysis involved stratification by gender (321 males, 345 females). The results appear in Tables 9 and 10. Among the male participants shown in Table 9, the prevalence ratios of metabolic syndrome increased with each increasing quintile of resting heart rate and with each decreasing quintile of heart rate reserve. The maximum prevalence ratio observed for RHR was 3.57 in Q5, and the results for all quintiles were statistically significant. The maximum prevalence ratio observed for HRR was 2.56 in Q1, however the results were not statistically significant across all quintiles.

Among the female participants shown in Table 10, the prevalence ratios of metabolic syndrome also increased with each increasing quintile of resting heart rate and with each decreasing quintile of heart rate reserve. The maximum prevalence ratio observed for RHR was 3.81 in Q5, and the results among all quintiles were not uniformly statistically significant. The maximum prevalence ratio observed for HRR was 3.50 in Q1, and again the results were not consistently statistically significant.

Table 9. The prevalence ratios of resting heart rate (RHR) and heart rate reserve (HRR) for metabolic syndrome in 321 employed males.

| Clinical Metric | Five Subgroups | N | Metabolic Syndrome Prevalence Ratio | 95% Confidence Interval | Prevalence of Metabolic Syndrome (%) |
|---|---|---|---|---|---|
| RHR | Q1 (36 - 61) | 91 | 1.00 | n/a | 18.7 |
| (beats/min) | Q2 (62 - 67) | 64 | 2.09 | 1.23 to 3.54 | 39.1 |
| N= 321 | Q3 (68 - 72) | 77 | 2.22 | 1.34 to 3.68 | 41.6 |
| | Q4 (73 - 80) | 55 | 2.24 | 1.32 to 3.80 | 41.8 |
| | Q5 (81 - 110) | 34 | 3.57 | 2.18 to 5.84 | 66.7 |
| HRR | Q5 (110.5 - 146.1) | 72 | 1.00 | n/a | 22.2 |
| (beats/min) | Q4 (104.3 - 110.4) | 76 | 1.13 | 0.63 to 2.01 | 25.0 |
| N = 321 | Q3 (97.9 - 104.2) | 60 | 1.73 | 1.01 to 2.95 | 38.3 |
| | Q2 (90.2 - 97.8) | 68 | 2.38 | 1.46 to 3.88 | 52.9 |
| | Q1 (58.4 - 90.1) | 45 | 2.56 | 1.55 to 4.23 | 56.8 |

Q1 to Q5: quintile-based subgroups. The reference subgroups for analysis were Q1 for RHR, and Q5 for HRR.

Table 10. The prevalence ratios of resting heart rate (RHR) and heart rate reserve (HRR) for metabolic syndrome in 345 employed females.

| Clinical Metric | Five Subgroups | N | Metabolic Syndrome Prevalence Ratio | 95% Confidence Interval | Prevalence of Metabolic Syndrome (%) |
|---|---|---|---|---|---|
| RHR | Q1 (36 - 61) | 48 | 1.00 | n/a | 10.4 |
| (beats/min) | Q2 (62 - 67) | 71 | 2.03 | 0.79 to 5.21 | 21.1 |
| N= 345 | Q3 (68 - 72) | 87 | 2.10 | 0.84 to 5.26 | 21.8 |
| | Q4 (73 - 80) | 76 | 2.78 | 1.13 to 6.84 | 29.0 |
| | Q5 (81 - 110) | 63 | 3.81 | 1.57 to 9.22 | 39.7 |
| HRR | Q5 (110.5 - 146.1) | 59 | 1.00 | n/a | 10.2 |
| (beats/min) | Q4 (104.3 - 110.4) | 57 | 2.24 | 0.92 to 5.50 | 22.8 |
| N = 345 | Q3 (97.9 - 104.2) | 78 | 2.27 | 0.96 to 5.36 | 23.1 |
| | Q2 (90.2 - 97.8) | 64 | 2.77 | 1.18 to 6.49 | 28.1 |
| | Q1 (58.4 - 90.1) | 87 | 3.50 | 1.56 to 7.87 | 35.6 |

Q1 to Q5: quintile-based subgroups. The reference subgroups for analysis were Q1 for RHR, and Q5 for HRR.

Binary logistic regression was then performed in order to examine the relationship between the continuous clinical metrics of resting heart rate and heart rate reserve with that of the categorical outcome, metabolic syndrome. Both RHR and HRR were modeled independently, and the regression coefficients and corresponding *p*-values generated from the likelihood ratio test were reported. Two models were evaluated, the first of which was unadjusted for any covariates and appears in Table 11. In Model 1, a direct relationship was observed for RHR as an independent predictor of metabolic syndrome, such that the probability of having metabolic syndrome increased with each unit increase of RHR. An inverse relationship was observed for HRR, such that the probability of having metabolic syndrome increased with each unit decrease of HRR. The resultant *p*-values for both clinical metrics were $< 0.0001$, well below the chosen significance level of the study ($\alpha = 0.05$). Graphical representations of the logistic fit of both RHR and HRR with metabolic syndrome appear in Figures 5 and 6, respectively.

Table 11. Model 1 - Univariate logistic regression coefficients for resting heart rate (RHR) and heart rate reserve (HRR) as independent predictors of metabolic syndrome (N = 666).

| Clinical Metric | β | $\chi^2$ | DF | *p*-value* | Prevalence Odds Ratio | 95% Confidence Interval |
|---|---|---|---|---|---|---|
| RHR | 0.04 | 24.65 | 1 | < 0.0001 | 1.04 | 1.02 to 1.06 |
| HRR | -0.04 | 25.45 | 1 | < 0.0001 | 0.97 | 0.95 to 0.98 |

*The reported *p*-value was generated from the likelihood ratio test.

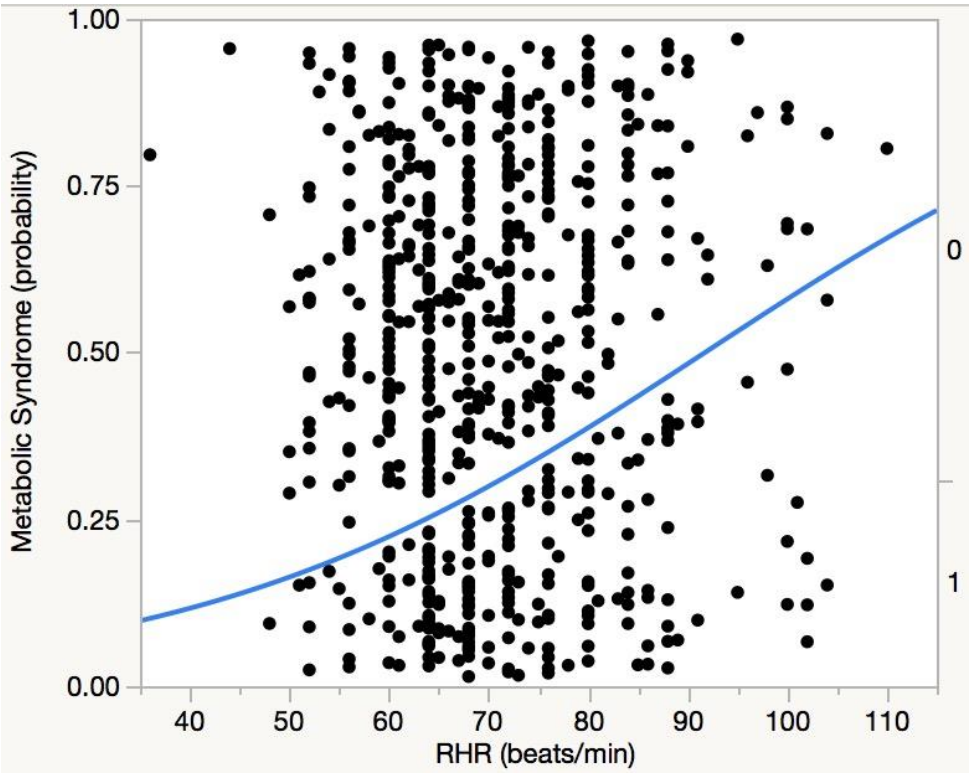


Figure 5. Logistic fit of metabolic syndrome by resting heart rate (N = 666).

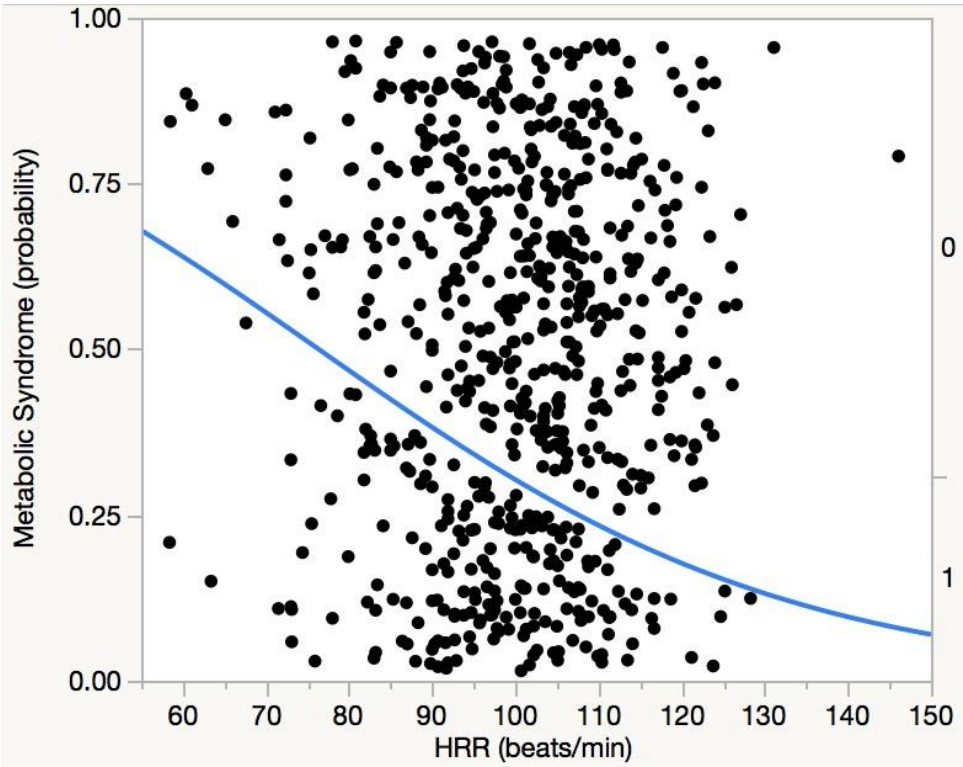


Figure 6. Logistic fit of metabolic syndrome by heart rate reserve (N = 666).

The second logistic regression model was multivariate and adjusted for age and gender, given their effects on the predictor variables and metabolic syndrome. In Model 2 (shown in Table 12), a direct relationship was again observed for RHR as an independent predictor of metabolic syndrome, such that the probability of having metabolic syndrome increased with each unit increase of RHR while controlling for age and gender. An inverse relationship was observed for HRR, such that the probability of having metabolic syndrome increased with each unit decrease of HRR while controlling for the same covariates. The analysis revealed that RHR, HRR, and gender were statistically significant predictors of metabolic syndrome, while age was not. The resultant *p*-values for the full models of both clinical metrics were < 0.0001, again below the chosen significance level of the study ($\alpha = 0.05$).

Table 12. Model 2 - Multivariate logistic regression coefficients for resting heart rate (RHR) and heart rate reserve (HRR) as independent predictors of metabolic syndrome, adjusted for age and gender (N = 666).

| Clinical Metric | β | $\chi^2$ | DF | *p*-value* | Prevalence Odds Ratio | 95% Confidence Interval |
|---|---|---|---|---|---|---|
| Full Model | - | 47.56 | 3 | < 0.0001 | - | - |
| RHR | 0.05 | 33.36 | 1 | < 0.0001 | 1.05 | 1.03 to 1.06 |
| Age | 0.02 | 2.22 | 1 | 0.14 | 1.02 | 1.00 to 1.04 |
| Gender | 0.39 | 19.67 | 1 | < 0.0001 | 2.19 | 1.54 to 3.12 |
| | | | | | | |
| Full Model | - | 47.56 | 3 | < 0.0001 | - | - |
| HRR | -0.05 | 33.36 | 1 | < 0.0001 | 0.95 | 0.94 to 0.97 |
| Age | -0.02 | 2.12 | 1 | 0.15 | 0.98 | 0.96 to 1.01 |
| Gender | 0.39 | 19.67 | 1 | < 0.0001 | 2.19 | 1.54 to 3.12 |

*The reported *p*-value was generated from the likelihood ratio test.

Finally, receiver operating characteristic (ROC) curves were generated for both resting heart rate and heart rate reserve as clinical predictors of metabolic syndrome. These were generated in order to test the accuracy of each clinical metric as a potential screening tool for metabolic syndrome. The ROC curve for resting heart rate appears in Figure 7, and the curve for heart rate reserve appears below in Figure 8. The area under the ROC curve for resting heart rate was 0.62, below the study's desired cut-off value of 0.7 for a fair screening test. The area under the ROC curve for heart rate reserve was only marginally better, at 0.63. Neither ROC curve demonstrated significant discriminative ability.

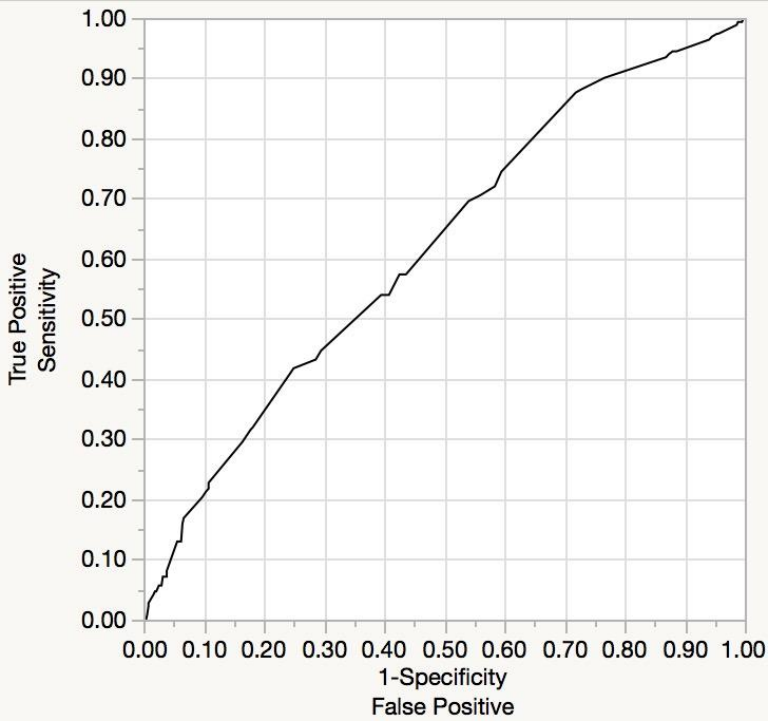


Figure 7. Receiver operating characteristic curve for resting heart rate as a predictor of metabolic syndrome (N = 666). The area under the curve = 0.62.

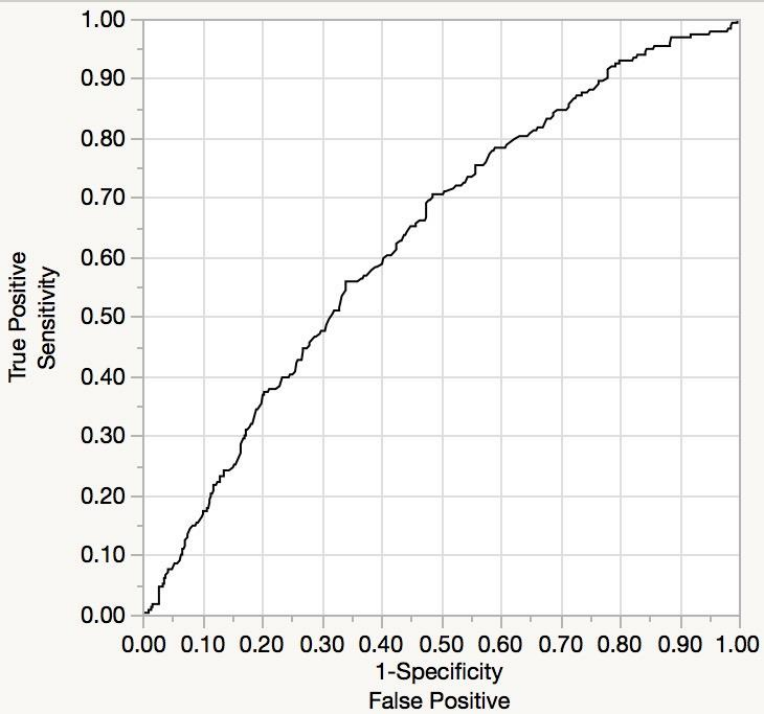


Figure 8. Receiver operator characteristic curve for heart rate reserve as a predictor of metabolic syndrome (N = 666). The area under the curve = 0.63.

The ROC curve analysis was then repeated after the data were stratified by age and gender. Age was stratified in the same manner as it was within the study's previous analyses, and consisted of younger (35 to 44 years of age) and older (45 to 70 years of age) subgroups. The area under the curve for the younger participants was 0.65 for both RHR and HRR, while that for the older participants was 0.61 for RHR and 0.63 for HRR. Stratification by gender revealed similar results. The area under the curve for males was 0.65 for RHR and 0.66 for HRR, while that for females was 0.63 for both RHR and HRR. Each of these values fell below the study's desired cut-off value of 0.7, and thus stratification by age and gender failed to reveal significant discriminative ability among the subgroups.

# CHAPTER 5: DISCUSSION

To the author's knowledge, this is the first study of its type to examine both resting heart rate and heart rate reserve as predictors of metabolic syndrome within a wide range of occupational groups of the United States. The overall prevalence of metabolic syndrome observed among the participants in this study was approximately 31%, which is higher than the reported worldwide prevalence of metabolic syndrome of 25% (Ford et al., 2002). This result is concerning because the sample analyzed within this study consisted of only employed individuals, who are presumably healthier than the general population. As alluded to previously within this paper, it is clear that metabolic syndrome represents a rapidly expanding disease process within the American work force.

In regards to the distribution of resting heart rate and heart rate reserve among males and females, the results suggested that males generally have lower resting heart rates and elevated heart rate reserve compared to females. Zhang et al. (2009) reported an identical trend in resting heart rate, while Dalleck et al. (2006) observed an identical trend in heart rate reserve among equal numbers of males and females enrolled in their study. This result is not surprising and is in accordance with the preponderance of the scientific literature which report similar findings.

After the diagnostic criteria of metabolic syndrome were applied to all participants, the results of this study revealed that the mean resting heart rate of individuals with metabolic syndrome was higher than those without the syndrome. Additionally, the mean heart rate reserve of participants with metabolic syndrome was lower than that of individuals without metabolic syndrome. The same associations were observed after adjusting for age and gender, contributing to the validity of the underlying relationship between RHR, HRR, and metabolic syndrome

revealed by this research. These statistically significant associations also provide evidence to support the study's secondary hypothesis, namely that RHR is directly associated with metabolic syndrome while HRR is inversely associated. The results of a similar study by Choi et al. (2017) among an occupational cohort of firefighters revealed the same relationships between RHR, HRR, and metabolic syndrome.

Interestingly, the prevalence of metabolic syndrome among males was higher than the prevalence among females within this study (37.1% vs. 24.9%). These results are in accordance with those of Beigh et al. (2012), who reported a 29% prevalence among males versus 23% among females. Novak et al. (2013) also observed a higher prevalence of metabolic syndrome among males (16%) versus females (10%) within their large sample of 1,262 Swedish adults. Both authors also reported a higher prevalence of component hypertension for men versus women, consistent with the vast majority of the scientific literature. This finding was substantiated by the present study as well, with hypertension occurring in 65% of males and 53% of females.

When the dataset was analyzed as a whole, the prevalence ratios of metabolic syndrome for resting heart rate increased with each increasing quintile of RHR, while the prevalence ratios for heart rate reserve increased with each decreasing quintile of HRR. Both clinical metrics were observed to be predictors of metabolic syndrome; however, resting heart rate was observed to be a stronger predictor across the general study population when treated as a categorical variable. These results support the primary research hypothesis of this study, and are in accordance with those reported by Inoue et al. (2009) and Jiang et al. (2015) for resting heart rate. However, they contrast with the findings of Choi et al. (2017), who reported that heart rate reserve was a stronger predictor of metabolic syndrome.

After the dataset was stratified into younger and older subsets, the resulting prevalence ratios revealed slightly different results. Within the younger group (35 to 44 years of age), the prevalence ratios again increased with each increasing quintile of resting heart rate, and increased with each decreasing quintile of heart rate reserve. Resting heart rate also appeared to be a stronger predictor than heart rate reserve; however, the results were not statistically significant in roughly half of the quintiles analyzed. Within the older group (45 to 70 years of age), the same trend and directionality was observed for the prevalence ratios of metabolic syndrome for both resting heart rate and heart rate reserve; however, heart rate reserve was revealed to be the stronger predictor. Additionally, the results within the older subset were statistically significant for all quintiles of RHR and HRR. These results contrast with those of Choi et al (2017), who found that within their younger group of firefighters heart rate reserve was a stronger predictor of metabolic syndrome compared to resting heart rate. Among the group of older firefighters, these authors also observed that heart rate reserve was a more robust predictor of metabolic syndrome based upon the magnitude of the observed prevalence ratios, which is in agreement with the results of this study. Given that firefighters as a whole demonstrate a higher level of cardiovascular fitness compared to the general working population, it is certainly plausible that heart rate reserve is a more robust indicator of cardiovascular health in this subpopulation. Heart rate reserve takes into account resting heart rate and maximal predicted heart rate, unlike resting heart rate alone. In firefighters with a high level of physical fitness, vagal tone is increased, resting heart rate is decreased, and heart rate reserve is accentuated. The lower statistical significance among the younger adults in the MIDUS data set may have been due to the relatively small subgroup sample size, which was comprised of 117 participants representing 17.3% of the total study population.

When the prevalence ratio analysis was repeated after the dataset was stratified by gender, the results suggested that resting heart rate was a stronger predictor of metabolic syndrome for both males and females. This result was statistically significant within the male subset, but not within the female subset. When heart rate reserve was employed as the predictor, the results were not statistically significant within either subset. The stratified analysis was based on small subgroup sample sizes, which reduced statistical power. Interestiungly, the prevalence of metabolic syndrome was higher in all quintiles of RHR and HRR for males compared to females, which is in accordance with the findings of Beigh et al. (2012) and Novak et al. (2013) cited above.

The results of the univariate logistic regression analysis also confirmed the hypotheses of this study, and revealed that resting heart rate was directly associated with metabolic syndrome while heart rate reserve was inversely associated. The same associations were observed in the multivariate model, which was adjusted for both age and gender. While the prevalence odds ratios generated in either model were not large in magnitude for either RHR or HRR, the beta coefficients and corresponding 95% confidence intervals were all statistically significant. Additionally, gender was found to be a statistically significant predictor, while age was not. As a sensitivity analysis, the multivariate analysis was repeated three times, with age coded as a dichotomous categorical variable first, broken into categorical quartiles during the second attempt, and coded as a continuous variable within the final model. The relatively small sample size of the age subgroups, coupled with the fact that the vast majority (82.7%) of the participants were in the higher risk age category for cardiovascular disease (greater than age 45), may have contributed to the lack of a significant relationship for age within this study. Thus, the logistic regression analysis led to the conclusion that the odds of having metabolic syndrome increase

with increasing resting heart rate, and also increase with decreasing heart rate reserve. Again, these results are in accordance with the results reported in the above cited studies.

Unfortunately, neither clinical metric displayed a receiver operating characteristic with significant discriminative ability, even after stratification by age and gender. The area under each curve fell short of the 0.7 cutoff delineated earlier in this study. The area under the curve for heart rate reserve was essentially the same as that for resting heart rate. The results suggest that neither resting heart rate nor heart rate reserve can be reliably utilized as independent screening variables for metabolic syndrome based on specific cut points. However, given the significant association between the two clinical metrics and the prevalence of metabolic syndrome, they could still be employed as useful screening tests. Data regarding utilizing RHR or HRR as screening tools for cardiovascular disease is scarce within the literature, and to this author's knowledge non-existent for metabolic syndrome. Further research is warranted in this area, given that metabolic syndrome is comprised of a clustering of modifiable component risk factors and is therefore treatable.

Several important factors limit the scope of this study's findings. First, the independent variable assessment was constrained because resting heart rate was only measured a single time. This does not take into account the diurnal variation nor the intra-person variation in heart rate. The measurement was also performed by multiple technicians at different sites utilizing the finger palpation technique over a peripheral artery, leading to a degree of subjectivity in detecting heart beats and poor inter-rater reliability. A more precise methodology utilized by Inoue et al. in 2009 involved calculating resting heart rate from the mean R-R intervals recorded via an electrocardiogram tracing over a period of 5 seconds. While this technique still does not take into account day-to-day variability in heart rate, it does eliminate the potential for inter-rater

discordance. However, the standard recommendation for assessing heart rate is to perform two consecutive measurements of resting heart rate for 30 seconds each (Palatini et al., 2006)

Next, certain factors which affect resting heart rate were not addressed in this study. While the study questionnaire inquired regarding the use of anti-hypertensive or other medications, it did not report the specific classes of blood pressure medications used. An important and commonly prescribed class of anti-hypertensive medication is beta blockers, which reduce cardiac chronotropy and subsequently heart rate. This may have led to differential misclassification and a bias of the results towards the null hypothesis, as participants with truly elevated resting heart rates had measured values which were artificially low. In contrast, hydration status and recent cigarette smoking were not assessed at the time of heart rate measurement, leading to potentially inaccurate exposure assessment. This may have represented non-differential misclassification, adding to the degree of information bias within the study and also biasing the findings towards the null hypothesis.

Additionally, some MIDUS study participants were missing reported data for resting heart rate or component data necessary to formulate the diagnosis of metabolic syndrome. This resulted in a decrease of the final sample size analyzed within this study, and a consequent decrease in statistical power. Of particular importance was the lack of data regarding participants' use of hyperglycemic medication, which is a sub-category criteria of the insulin-resistance component of metabolic syndrome. This particular information was not available within the MIDUS data set, and may have resulted in a decreased observed prevalence of metabolic syndrome and therefore the raised likelihood of a type I error. If the true number of individuals who met the diagnostic criteria for metabolic syndrome was underestimated due to a lack of information regarding hyperglycemic medication, then the results of the study may have

been biased towards the null hypothesis assuming that this was a non-differential misclassification error.

The external validity of this study may be limited as well, owing in part to the underrepresentation of certain socio-demographic groups within the original MIDUS 2 survey. In particular, the subsample of participants who were recruited via random-digit-dialing (RDD) underrepresented African Americans, the young, and individuals with less formal education (Ryff et al., 2017).

And finally, this study was cross-sectional in nature and therefore no conclusions could be drawn regarding the temporality of any observed associations. Despite these limitations, this study provides evidence to strengthen the association between resting heart rate, heart rate reserve, and metabolic syndrome. Unfortunately, neither elevated resting heart rate nor decreased heart rate reserve were revealed to be reliable dichotomous screening measures. The cross-sectional analysis revealed a monotonically increasing association across the quintiles of both predictor variables, suggesting that there may not be a threshold cut point due to the nature of this association. The current body of research has focused on determining a cutoff point that demarcates a dangerous resting heart rate in relation to cardiovascular disease. The BEAUTIFUL study, which was the first prospective randomized controlled trial to address this issue, suggested that 70 beats per minute is the threshold above which patients are at increased risk of future cardiovascular events (Fox et al., 2008). If such a cutoff value exists for resting heart rate and heart rate reserve in relation to metabolic syndrome, then determination of these thresholds could be an important next step within preventive medicine for the occupational workforce.

# CHAPTER 6: CONCLUSION

The impact of metabolic syndrome on the occupational workforce within the United States is staggering and multifaceted. This study revealed that two simple, cost-effective clinical metrics can be utilized to enhance the screening methodology and risk factor assessment of metabolic syndrome within employed adults. Elevated resting heart rate and decreased heart rate reserve were both associated with a statistically significant increase in the prevalence of metabolic syndrome. Resting heart rate was a stronger predictor of metabolic syndrome among both males and females across the general study population, while heart rate reserve was observed to be a stronger predictor among the older subset of participants regardless of gender. Additionally, resting heart rate was shown to demonstrate a direct relationship with metabolic syndrome, while heart rate reserve demonstrated an inverse relationship. Finally, the discriminative ability of heart rate reserve was only marginally better than that of resting heart rate. The primary research hypothesis of this study was substantiated, although neither clinical metric displayed a combination of high sensitivity and specificity based on a cut-point criterion to be used as a standalone screening tool.

As alluded to previously, a robust strategy of prevention for metabolic syndrome is clearly necessary in order to prevent the numerous deleterious effects of cardiovascular disease. The rapidly spiraling healthcare costs of this disease burden, coupled with the high prevalence of metabolic syndrome within the workforce revealed by this study, demands significant and timely intervention. In order to provide clinicians and subsequently corporations with reliable screening methodology, further research is necessary in order to delineate the threshold resting heart rate above which the risk of metabolic syndrome is significant. Current preventive measures should

focus on reducing resting heart rate and increasing heart rate reserve through regular physical exercise. Given that metabolic syndrome as a whole and its components are modifiable risk factors, a reduction in this disease process would significantly enhance the overall health of our occupational workforce. Until that time, patient education regarding healthy lifestyle modification in both the clinical setting and the industrial environment are paramount.

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