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Tingting Liu July 1st, 2015

A Comparison of Biological, Physical, and Psychological Risk Factors for Cardiovascular Disease In Overweight/Obese Individuals With and Without Prediabetes

By

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Doctor of Philosophy

Nursing

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Abstract

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Background: Poor lifestyle choices, coupled with the obesity epidemic, have dramatically increased the number of adults living with prediabetes. Compared with type 2 diabetes, much less is known about the effects of prediabetes on biological, physical, and psychological risk factors that heighten adverse cardiovascular disease (CVD) outcomes among overweight/obese adults. The primary aim of the study was to compare baseline biological, physical, and psychological risk factors for CVD among overweight/obese adults with and without prediabetes.

Methods: A secondary data analysis was performed using a large database of healthy adults employed at an academic health sciences center located in the southeastern United States. Baseline biological, physical and psychological risk factors were included in the analysis. Linear or logistic regression models were used to evaluate the association between prediabetes and biological, physical, and psychological risk factors, controlling for age, gender and education.

Results: Three hundred forty one overweight/obese participants were included in the analysis: 44 had prediabetes (fasting blood glucose≥100 but <126 mg/dl) 297 were without prediabetes. Participant median age with and without prediabetes was 55 and 48 ($p<0.0001$), respectively. The majority of participants were Caucasian (69.5%), high income (median income $100,000-$150,000), and well-educated (median education level 18 years). There were significant differences for several baseline biological risk factors among prediabetics versus nonprediabetics and included higher fasting blood glucose (104.8 vs 86.3 mg/dl, $p<0.0001$), body mass index (31.2 vs 28.8 kg/m^2, $p<0.017$), waist-hip ratio (0.9 vs 0.8, $p=0.014$), triglycerides (111 vs 91 mg/dl, $p=0.0002$). Prediabetics were also more likely to be insulin resistant (47.7% vs 14.1%, $p<0.0001$) than nonprediabetics. Among the baseline physical risk factors examined, participants with prediabetes had much lower cardiorespiratory fitness than those without prediabetes (28.5 vs 32 ml/kg/min, $p=0.029$). Participants with prediabetes were also more likely to have lower self-reported physical functioning (53.8 vs 49.9, $p=0.003$). No differences in baseline psychological risk factors were observed between groups.

Conclusions: Findings from this study suggest that healthy overweight/obese adults with prediabetes were likely at higher biological and physical risk for CVD at baseline compared to those without prediabetes. Early intervention to improve CVD risk progression among persons with prediabetes is essential.

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"I am glad I did it, partly because it was worth it, but mostly because I shall never have to do it again." Mark Twain.

"I would maintain that thanks are the highest form of thought, and that gratitude is happiness doubled by wonder." G.K. Chesterton.

"A teacher affects eternity; he can never tell where his influence stops." Henry Brooks Adams.

"Success in life comes when you simply refuse to give up, with goals so strong that obstacles, failures, and loss only act as motivation." Unknown and anonymous.

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Chapter One

Statement of the Problem

Introduction

This chapter provides a statement of the problem for lowering risk for cardiovascular disease (CVD) among overweight/obese individuals with and without prediabetes. The chapter is organized according to background, purpose of the study, significance of the study, and concludes with a summary.

Background

Prediabetes is emerging as a major health problem in the United States (U.S.), largely due to its strong association with the development of type 2 diabetes mellitus (T2DM), heightened risk for future cardiovascular disease (CVD) and adverse cardiac events (American Diabetes Association, 2015). Prediabetes is defined as blood glucose levels higher than normal but not high enough to be diagnosed as T2DM (American Diabetes Association, 2014), and represents a 'grey area' between normal glucose levels and diabetes. Unsurprisingly, it shares many characteristics with T2DM and is associated with obesity, advancing age and the inability of the body to use the insulin it produces (International Diabetes Federation, 2014). Currently, three indicators (i.e., impaired fasting glucose [IFG], impaired glucose tolerance [IGT], and elevated hemoglobin A1c [HbA1c]) are recommended by the American Diabetes Association to detect prediabetes (American Diabetes Association, 2014), as shown in Table 1. IFG is determined by the fasting plasma glucose test, and IGT is determined by the 75 g oral glucose tolerance test.

Table 1

Normal Range, Prediabetes, and Type 2 Diabetes Mellitus

Conditions / Criteria	Normal Range	Prediabetes	T2DM
IFG	70≤IFG<100 mg/dl	100≤IFG<126 mg/dl	≥126 mg/dl
IGT	<140 mg/dl	140≤ IGT<200 mg/dl	≥200 mg/dl
HbA1c	<5.7%	5.7%≤HbA1c≤6.4%	≥6.5%

Ninety percent (90%) of adults with prediabetes are overweight or obese and this group of people is up to 12 times more likely to develop T2DM than those with a normal glucose level (Garber, 2012). Adults with T2DM are two to four times more likely to have CVD than adults without T2DM (American Heart Association, 2012). The national prevalence rates of T2DM have increased in parallel with rates of obesity (Barnes, 2011). As a result, far greater emphasis and resources are now directed at prevention of T2DM, especially since one-third of the U.S. population is obese and this number is expected to rise to 50% by 2020 (Garber, 2012; Neeland et al., 2012). Early identification of prediabetes is of paramount importance and essential for reducing T2DM, future risk of CVD and subsequent adverse cardiac outcomes (Grundy, 2012).

Estimates are that 86 million adults living in the U.S. have prediabetes and this number is anticipated to dramatically rise over the next 2 to 3 decades if poor health choices such as dietary excess and physical inactivity continue as prevalent lifestyle behaviors (Centers for Disease Control and Prevention, 2014). Screening guidelines for prediabetes have been recommended by many professional health organizations, such as the U.S. Preventive Service Task Force (U.S. Preventive Service Task Force, 2008), the American Association of Clinical Endocrinologists (Handelsman et al., 2011), the

American College of Physicians (Vijan, 2010), the Endocrine Society (Rosenzweig et al., 2008), the American Diabetes Association (American Diabetes Association, 2015) and the International Diabetes Federation (Alberti, Zimmet, & Shaw, 2007). Although there is currently a lack of scientific consensus on these recommendations (Hollander & Spellman, 2012), most of these recommendations are based on a range of important and proven risk factors for T2DM.

The American Diabetes Association for example, recommends that overweight or obese (body mass index [BMI]$\geqslant$25 kg/m^2) adults of any age with risk factors for T2DM, and all adults aged 45 years or older, be screened in the clinical setting at 1 to 3 year intervals depending on the initial results of a fasting plasma glucose test, HbA1c, or an oral glucose tolerance test and risk status (American Diabetes Association, 2015); those with higher glucose levels would require more frequent follow-up. The International Diabetes Federation proposes a different screening strategy, beginning with a self-administered questionnaire to predict an individual's risk, followed by measurement of plasma glucose to detect cases of IFG or IGT if increased risk for prediabetes and T2DM is identified (Alberti et al., 2007). Variables included in the questionnaire to determine the risk are generally include age, weight, height, waist circumference, history of hypertension, high blood glucose levels (including gestational diabetes), and physical activity level (Colagiuri, 2011). In contrast, the U.S. Preventive Service Task Force (USPTF) criteria for prediabetes screening differ substantially from the screening recommendation. The USPTF currently recommends that only asymptomatic adults with sustained blood pressure higher than 135/80 mmHg be screening for prediabetes/T2DM (U.S. Preventive Service Task Force, 2008).

Although prediabetes screening guidelines are recommended by a number professional organizations, implementation of screening procedures in most practice setting remains infrequent (American Diabetes Association, 2015). Prediabetes therefore, often goes undetected and untreated until it progresses to overt T2DM and symptoms become more recognizable. In a recent U.S. national survey conducted by the Centers for Disease Control and Prevention, for instance, only 14% of persons aged 20 years or older with prediabetes had knowledge of their condition, indicating that screening for prediabetes is likely to be critically underutilized (Centers for Disease Control and Prevention, 2013a).

T2DM is well established to contribute to systemic micro and macrovascular changes that lead to CVD (Konig, Lamos, Stein, & Davis, 2013). Prediabetes however, is also increasingly recognized to place individuals at risk for CVD as a consequence of similar underlying biological changes in lipid, inflammatory, and metabolic responses process that occur in T2DM (Grundy, 2012). These biological changes in addition to the occurrence of prediabetes are higher among overweight (BMI: 25-29.9 kg/m^2) and obese adults (BMI$\geq$30 kg/m^2) (Nathan et al., 2007; Rubin et al., 2008; Tapp et al., 2006). For example, cross-sectional data from the 2005-2006 National Health and Nutrition Examination Survey showed that 34.4% of patients with prediabetes had elevated triglycerides (TG) (150 mg/dl), and 28.3% had reduced high-density lipoprotein cholesterol (HDL-C) level (<40 mg/dl in men and <50 mg/dl in women) (Yang, Lee, & Chasens, 2011), which are known risk factors for CVD. The additional burden that overweight/obesity contributes to biological risk in adults with prediabetes has not been well studied, but is thought to be in part mediated by adipose tissue deposition in the

abdominal viscera, heightened inflammatory response, proinflammatory cytokine release, adipokine dysregulation, and insulin resistance (Bastard et al., 2006; Berg & Scherer, 2005; Kim et al., 2006; Shoelson, Lee, & Goldfine, 2006).

Few studies have examined the relationship between overweight/obesity, prediabetes, and biological risk factors associated with CVD. Among those that have, excess intra-abdominal adiposity, in particular, has been shown to be accompanied by an increased secretion of free fatty acids, which can induce insulin resistance in muscle, β-cell dysfunction in the pancreas, increased levels of inflammatory markers, such as tumor necrosis factor-alpha [TNF-α], interleukin-6 [IL-6], resistin, and decreased secretion of adiponectin, a cardioprotective adipokine (Galic, Oakhill, & Steinberg, 2010). Increased secretion of IL-6 from intra-abdominal adipocytes stimulates hepatic secretion of C-reactive protein (CRP). Elevated levels of these inflammatory markers are significantly associated with the development of carotid stiffness, an early predictor of atherosclerosis (Diamant et al., 2005).

Abdominal obesity, also known as central obesity, is significantly related to prediabetes. Abdominal obesity is the accumulation of abdominal fat resulting in an increase in waist circumference. The waist circumference (>102 centimeters or 40 inches in men and >88 centimeters or 35 inches in women) and the waist-hip ratio (>0.9 for men and >0.85 for women) are both suggested as useful measurement indices of abdominal obesity (National Cholesterol Education Program, 2002). Cross-sectional data from the 2005-2006 the NHANES showed that 67.7% of prediabetic patients had abdominal obesity (Yang et al., 2011). It is less clear, however, whether overweight/obese adults without prediabetes have similar biological risks for CVD as those with prediabetes. The

current study is designed to answer this question by examining the effects of prediabetes on biological risk for CVD among overweight/obese adults with and without prediabetes.

Lifestyle interventions are recommended as the most effective strategy for treating prediabetes in adults (Grundy, 2012). The Diabetes Prevention Program (DPP) was a landmark multicenter clinical trial aimed at determining whether modest weight loss through dietary changes and increased physical activity (intervention) or treatment with an oral antiglycemic agent metformin (Glucophage) (control) could prevent or delay the onset of T2DM among 3,234 overweight/obese participants with prediabetes over a mean follow-up period of 2.8 years. The DPP clinical trial showed that approximately 11% of people with prediabetes in the control group developed T2DM, compared to approximately half that number (4.8%) in the lifestyle-intervention group which included 1079 participants (Knowler et al., 2002). Investigators have shown however, that without intervention, approximately one third of adults with prediabetes will progress to T2DM, another third will remain prediabetic, and another third will revert back to normal glucose levels (Garber, 2012). In addition, two thirds of those with both IFG and IGT, who are at the highest risk, will go on to develop T2DM (Garber, 2012). Previous lifestyle intervention research targeting prediabetes has primarily focused on weight loss, increasingly physical activity, changes in anthropometric measures, blood glucose, and lipid abnormalities. Far less is known whether lifestyle interventions lower inflammatory responses similarly in overweight/obese adults with or without prediabetes, since low-grade, chronic, systemic inflammation has been implicated in the development of obesity-related pathologies, in particular the transition to T2DM and progression to CVD (Dagogo-Jack, Egbuonu, & Edeoga, 2010; Emanuela et al., 2012).

Very little is known about the cardiorespiratory levels of overweight/obese persons with prediabetes. Evidence supports that change in cardiorespiratory fitness parameters may occur prior to developing T2DM. High-risk individuals for T2DM, defined as individuals aged 20 to 65 who have a family history of diabetes or history of gestational diabetes, and/or presence of one to three risk metabolic factors for T2DM, including obesity, hypertension, and dyslipidemia, have been shown to experience lower cardiorespiratory fitness (hereafter referred to as "fitness") than those with low risk for T2DM (Leite, Monk, Upham, & Bergenstal, 2009). Large prospective cohort studies of diverse populations have consistently shown that low fitness is an independent predictor of long-term CVD and all-cause mortality (Barlow et al., 2012; Lyerly et al., 2009; Rankinen, Church, Rice, Bouchard, & Blair, 2007). Thus, overweight/obese persons with prediabetes and lower fitness may be at greater risk for developing CVD than those without prediabetes. Favorable effects of lifestyle interventions on fitness have been observed in two randomized trials among overweight/obese persons with T2DM and overweight/obese adolescents (Jakicic et al., 2009; Rynders et al., 2012). Both trials have shown that fitness increased significantly in response to lifestyle interventions. The potential role that lifestyle interventions may have on fitness outcomes in overweight/obese prediabetic adults has not been well studied and warrants further investigation.

Still lacking is the evidence concerning the psychological characteristics of overweight/obese persons with prediabetes. For instance, depressive symptoms have been shown to be more prevalent among persons with a higher BMI than normal weight individuals (Atlantis & Baker, 2008; de Wit et al., 2010), and depression is also more

common in T2DM than in the general population (Gonzalez, Fisher, & Polonsky, 2011). Less is known about depressive symptoms among those with prediabetes compared to euglycemic individuals. Lifestyle interventions have also been shown to improve depressive symptoms among prediabetics in some studies (Ruusunen et al., 2012), but not in others (Maciejewski, Patrick, & Williamson, 2005; Rubin et al., 2005). In the proposed secondary analysis study, physical and psychological health outcomes will be compared at baseline and evaluated at 1 year as an exploratory aim among overweight/obese individuals with and without prediabetes enrolled in an individualized health partner program.

The health partner program was offered by the Center for Health Discovery and Well Being at Emory University, the Parent Study for the secondary analysis. At the time of the study enrollment and completion, participants had to be employees of Emory University for a minimum of 2 years and attended the program free of charge. Members of the general public who paid for the membership fee could also attend. The health partner and the participant collaborated to establish a tailored health action plan with defined goals and strategies that were achievable and practical based upon the location of the participants' home and workplace. Plans were individualized but could include changes in diet or exercise, modification of risk-related behaviors (e.g., tobacco use, alcohol use), and stress reduction techniques such as yoga, interactions with religious leaders, meditation, or other alternative approaches.

Purpose of the Study

The increasing recognition of the role that prediabetes plays in the risk for CVD underscores the need for further research in this area. The link between prediabetes and

development of CVD is not well understood. Because the numbers of adults who are overweight and have prediabetes are anticipated to dramatically increase over the next several decades, a greater understanding of the underlying biological risk factors as well as interventions that may mitigate development of CVD merits further investigation. Therefore, the purpose of the secondary analysis study was to compare baseline biological, physical, and psychological risk factors of overweight/obese adults with and without prediabetes. As an exploratory aim, the longitudinal effects of a health partner program on measures of biological, physical, and psychological risks in the target population was evaluated at 1 year.

The primary aim of this study was to:

1. Compare baseline biological, physical, and psychological risk factors in overweight/obese adults with and without prediabetes, controlling for age, gender, and educational level.

The research questions are:

RQ1a: Do participants who are overweight/obese with prediabetes have greater biological risk factors for CVD as measured by lipid profile (TG, low-density lipoprotein cholesterol [LDL-C], and HDL-C), inflammatory profile (IL-6, IL-8, TNF-α, and CRP), and metabolic profile (insulin resistance and microalbuminuria) than overweight/obese adults without prediabetes?

RQ1b: Do participants who are overweight/obese with prediabetes have greater physical (fitness and physical activity level) and psychological risk

factors (depressive symptoms) than overweight/obese adults without prediabetes?

The exploratory aim of this study was to:

2. Determine if a health partner program reduces biological, physical, and psychological risk factors in overweight/obese adults with and without prediabetes at 1 year, controlling for age, gender, and educational level.

The research questions to be tested are:

RQ2a: What are the differences in biological risk factors as measured by lipid profile (TG, LDL-C, and HDL-C), inflammatory profile (IL-6, IL-8, TNF-α, and CRP), metabolic profile (insulin resistance and microalbuminuria) among overweight/obese participants with prediabetes enrolled in a health partner program at 1 year compared to overweight/obese participants without prediabetes?

RQ2b: What are the differences in physical (fitness and physical activity level), psychological risk factors (depressive symptoms), and health status among overweight/obese participants with prediabetes enrolled in a health partner program at 1 year compared to overweight/obese participants without prediabetes?

Significance of the Study

Understanding baseline biological, physical, and psychological status in overweight/obese adults with and without prediabetes has important scientific and clinical implications, particularly in the light of the high morbidity and mortality associated with subsequent T2DM and CVD development. This study will have particular

relevance for clinical practice and the broader field of public health. First, clarifying whether overweight/obese adults without prediabetes has similar biological, physical, and psychological risks for CVD as those with prediabetes may lead to the development and testing of screening tools aimed at identifying such risks in this population. Second, this study may contribute to the growing body of literature of the added influence of prediabetes has on physical and psychological function in overweight/obese adults and whether a health partner program influences these risks related to CVD. Third, the findings may inform future research on whether the biological risk factors are influenced by prediabetes and to what extent. Fourth, the findings may contribute further to the development of evidence-based guidelines among high-risk prediabetic individuals on lifestyle modifications to improve their physical and psychological functioning.

Summary

The primary aim of this study was to compare baseline biological, physical, and psychological risk factors in overweight/obese adults with and without prediabetes. As an exploratory aim, the health partner program of the parent study was evaluated to determine if biological, physical, and psychological risk factors in overweight/obese adults with and without prediabetes were influenced at the one year follow-up.

Chapter Two

Review of the Literature

Introduction

This chapter provides the scientific underpinning for lowering risk for cardiovascular disease (CVD) among overweight/obese individuals with and without prediabetes. First, the influence of type 2 diabetes mellitus (T2DM) and prediabetes on the risk for developing subsequent CVD is presented. Second, major studies are presented that provide robust evidence of the strong relationship between prediabetes and CVD, and the effect of lifestyle interventions on lowering or reversing the incidence of prediabetes, prevention of T2DM and CVD. Third, an overview of the conceptual framework guiding the study, including operational definitions and comprehensive literature review of major concepts is provided.

Epidemiology of Type 2 Diabetes Mellitus and Prediabetes

Diabetes is a major public health problem worldwide and it is increasing by epidemic proportions. Globally, the total number of people with diabetes is projected to rise from 387 million cases in 2014 to 592 million cases by 2035 (International Diabetes Federation, 2014). In the United States (U.S.), the prevalence of diabetes has been increasing for the past two decades. For example, the estimated number of Americans with diabetes grew considerably and steadily from 7.8 million cases in 1993 (Kenny, Aubert, & Geiss, 1995), to 29.1 million cases in 2012 (Centers for Disease Control and Prevention, 2014). If the current trends continue, 1 in 3 U.S. adults will be diabetic by 2050 (National Center for Chronic Disease Prevention and Health Promotion, 2012).

T2DM accounts for approximately 90% to 95% of all diagnosed cases of diabetes (Centers for Disease Control and Prevention, 2013a). Often T2DM is diagnosed relatively late in the course of the disease, when complications such as microvascular changes may have already occurred. According to the American Diabetes Association, approximately 25% of people with diabetes in the U.S. go undetected and undiagnosed since they remain asymptomatic for many years, which heightens risk for CVD and poor clinical outcomes (American Diabetes Association, 2015). The economic burden associated with diabetes is also substantial, with the annual national cost totaling 245 billion people affected by diabetes in 2012 (Centers for Disease Control and Prevention, 2014). The impact of diabetes on an individual's health and its economic burden to society has made diabetes prevention an important public health initiative and research priority.

The leading risk factor for T2DM is prediabetes (Grundy, 2012). According to recent data from the National Health and Nutrition Examination Survey (NHANES), the prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) among adults aged 20 years or older was 25.7% and 13.8%, respectively (Cowie et al., 2009). Both IFG and IGT increase progressively and steadily with advancing age, peaking at 75 years of age or older, with a crude prevalence rate of approximately 47% (Cowie et al., 2009). There is also a gender difference in the prevalence of IFG and IGT. For example, IFG was 70% higher in men than in women (Cowie et al., 2009), whereas IGT was more frequently found in women in some (Colagiuri, 2011; Cowie et al., 2006), but not all studies (Cowie et al., 2009). However, the reason for the gender differences is

poorly understood. The prevalence of IFG or IGT does not differ significantly by ethnicity (Cowie et al., 2009).

Hemoglobin A1c (HbA1c) of 5.7% to 6.4% was recommended as a legitimate alternative diagnostic criterion for pre-diabetes by American Diabetes Association in 2010, based largely on the opinion of the International Expert Committee (American Diabetes Association, 2010; International Expert Committee, 2009). Because this is a recent recommendation, there are very few data on the prevalence of HbA1c-defined prediabetes. However, the limited data available showed a substantially lower prevalence of prediabetes using the HbA1c criterion compared to the fasting glucose criterion of $\geqslant$ 126 mg/dl. In one cross-sectional study using the 1999-2006 NHANES data, the prevalence of prediabetes was 12.6% (23 million) using the HbA1c (5.7% to 6.4%) criterion, compared to 28.2% (51.7 million) using the IFG criterion ($\geqslant$126 mg/dl), with only a small overlap (7.7%) according to both criteria (Mann et al., 2010). Consistent with these findings, based on the 2003-2006 NHANES data, about 3.5% of U.S. adults (7.4 million) were at a high risk for T2DM defined by HbA1c of 6.0% to 6.4% compared to the higher prevalence with the newer recommendation. Prevalence of those at high risk for T2DM using the HbA1c criterion was about one-tenth that using fasting plasma glucose/2-hour glucose criteria (29.0% combined, 25.2% IFG, and 13.6% IGT), indicating that many may remain undiagnosed (Cowie et al., 2010).

The different criteria used to identify prediabetes results in different individuals recognized as having prediabetes based on which criteria were used. For example, HbA1c alone would reclassify 37.6 million Americans with IFG as not having prediabetes and 8.9 million without IFG as having prediabetes (Mann et al., 2010). A large number of

individuals (8 million) with fasting glucose in the range of 110-125 mg/dl would be reclassified as not having prediabetes by the HbA1c criterion. Fasting glucose in this range is associated with up to 7-time risk for incident T2DM than that in the range of 100-109 mg/dl (Levitzky et al., 2008). Using HbA1c alone in order to detect high-risk individuals for prediabetes would result in a significant number of them not being identified and not receiving preventive interventions to reduce their risk. Further prospective studies are needed to determine which criterion, or which combination of these criteria, is more accurate and clinically relevant for a more precise risk estimate of prediabetes and tailoring interventions (Mann et al., 2010).

Approximately 86 million people, or about 37% U.S. adults aged 20 years or older, are estimated to be prediabetic in 2012 (Centers for Disease Control and Prevention, 2014). The implication of this figure (86 million) for the future burden of diabetes is of particular concern. This figure is almost 3-fold greater than the number of individuals with diabetes (29.1 million, including both type 1 and type 2 diabetes) (Centers for Disease Control and Prevention, 2014). Each year, 11% of persons with prediabetes who do not lose weight and do not engage in moderate physical activity will progress to T2DM during an average 3 years of follow-up (Centers for Disease Control and Prevention, 2013a). Although the natural history of prediabetes varies considerably, without intervention, approximately one third of individuals with prediabetes are likely to convert to T2DM, one third will remain prediabetic, and one third will revert to normoglycemia (Garber, 2012). Applying this percentage to the estimated number of individuals with prediabetes would mean that about 28.7 million will become diabetic, and this is paramount to almost another 100% increase in the prevalence of T2DM in the

future. Therefore, interventions that prevent the progression from prediabetes to T2DM are essential.

Lifestyle Interventions and Type 2 Diabetes Mellitus Prevention

The alarming rise in the prevalence of T2DM is largely attributed to the epidemic of obesity and physical inactivity (Anselmino, Gohlke, Mellbin, & Ryden, 2008). In adults, a body mass index (BMI) of 18.5 to 24.9 kg/m^2 is considered normal. Currently, two thirds of the U.S. adult population are categorized as either overweight or obese, defined by BMI of 25 to 29.9, and 30 kg/m^2 or greater, respectively (Flegal, Carroll, Kit, & Ogden, 2012). Overweight or obese individuals with prediabetes are at a high risk for progression to T2DM and have been targeted for T2DM prevention. There is strong epidemiological evidence linking structured lifestyle interventions with T2DM prevention among overweight/obese adults with prediabetes.

Several landmark T2DM prevention clinical trials have provided robust evidence that participation in structured lifestyle interventions, focused on increased physical activity (2.5 to 4 hours/week), dietary modification (increased intake of whole grains, fiber, vegetables, and fruits; reduced intake of total and saturated fat, sugar, and refined grains), as well as weight reduction, improves blood glucose control and delays progression to T2DM among overweight/obese individuals with prediabetes (Knowler et al., 2002; Pan et al., 1997; Tuomilehto et al., 2001). A key component of prevention is to implement a comprehensive approach that addresses several risk factors together, such as overweight/obesity and physical inactivity, because each factor may not be independently associated with T2DM, but in combination, these risk factors strongly predict T2DM (Tuomilehto, Schwarz, & Lindström 2011). Furthermore, long-term follow-up studies of

structured lifestyle interventions have been shown to have a long-lasting effect on risk factors and diabetes incidence (Knowler et al., 2009; Li et al., 2014; Li et al., 2008; Lindström et al., 2006).

The Diabetes Prevention Program (DPP) clinical trial, one of the largest randomized controlled trials conducted to date, targeted overweight adults with IFG and IGT. A total of 3234 participants were enrolled in the program with a mean age 51 and the mean BMI 34 kg/m^2. In the DPP study, participants were randomly assigned to one of the three groups: lifestyle interventions, metformin, or to a non-intervention control group and followed over an average period of 2.8 years. Participants in the lifestyle intervention group were asked to eat a low-calorie, low-fat diet, participate in exercise for a minimum of 150 minutes/week, and lose 7% of their body weight. Those in the metformin group took 850 milligrams of metformin twice a day for the duration of the study. Participants in the control group received placebo 'sugar' tablets instead of metformin. The results showed that the lifestyle interventions reduced the incidence of T2DM by 58%, metformin by 31%, compared to controls (Knowler et al., 2002). The 10-year follow-up study of the DPP participants showed that T2DM incidence was reduced by 34% in the lifestyle intervention group, 18% in the metformin group compared to controls (Knowler et al., 2009). The cumulative incidence of T2DM remained lowest in the lifestyle intervention group, indicating that lifestyle interventions may be as effective as medications for prevention of T2DM and the effect remains significant over a long period of time (Knowler et al., 2009).

The Da Qing Study, conducted in China, was the one of the earliest randomized clinical trials of lifestyle interventions on T2DM incidence (Pan et al., 1997). This is also

the only study to date that systematically compared the efficacy of diet, exercise, and a combined approach on prevention of T2DM incidence. In the Da Qing Study, 577 participants with an IGT at baseline were recruited into the study and randomized into a control group and three lifestyle intervention groups consisting of diet, exercise, and the diet-plus-exercise group. The mean age of the participants was 45 years, and the mean BMI was 25.8 kg/m^2. After 6 years, the cumulative incidence of T2DM in the control group was 67.7%, 43.8% in the diet only group, 41.1% in the exercise only group, and 46% in the diet-plus-exercise group. The comparison between each intervention group and control group was significant ($p<0.05$), yet there were no significant differences between the three intervention group on incidence of T2DM, indicating that all 3 interventions had a similar influence on the prevention of T2DM. Although the active intervention was terminated after 6 years, the lifestyle interventions continued to prevent the onset of T2DM for up to 14 years, with 20-year cumulative incidence of 80% in the intervention groups and 93% in the control group (Li et al., 2008).

The Finnish Diabetes Prevention Study (FDPS) specifically examined the effect of lifestyle interventions on prevention of T2DM among overweight/obese subjects with IFG/IGT (Tuomilehto et al., 2001). In the FDPS, 522 middle-aged (mean age 55), obese (mean BMI 31 kg/m^2) subjects were randomized to either the intervention group or the control group. The subjects in the intervention group were provided with individualized counseling aimed at: (a) reducing weight, total intake of fat, and intake of saturated fat; (b) increasing intake of fiber; and (c) physical activity for a minimum of 4 hours/week. Subjects in the control group received only general information about diet and exercise at baseline and at subsequent annual visits. After 4 years, the cumulative incidence of

T2DM was 11% in the intervention group and 23% percent in the control group. The reduction in the incidence of T2DM was directly associated with lifestyle changes since no medications were used. Further, during the follow-up study of the FDPS, the risk of T2DM was reduced by 43% in the lifestyle intervention group compared to the control group (Lindström et al., 2006). The risk reduction in T2DM was related to number and magnitude that participants achieved the intervention goals of increased physical activity, dietary fiber intake, reduction in total and saturated fat, and weight loss (Lindström et al., 2006). These findings expanded prior studies of the benefits of lifestyle interventions alone in the prevention of T2DM.

More recently, Hooper and others (2011) reported a meta-analysis of prospective, randomized controlled trials that evaluated the effects of lifestyle interventions or pharmacological treatment on T2DM prevention among individuals with IGT and/or IFG (Hopper, Billah, Skiba, & Krum, 2011). This meta-analysis confirmed earlier data from the DPP clinical trial (Knowler et al., 2002; Orchard et al., 2005), showing the superiority of lifestyle interventions over drug-based treatment for T2DM prevention among prediabetic individuals. The meta-analysis included 10 randomized controlled trials with 23,152 patients. The average duration of the trials was 3.75 years. Overall, the interventions reduced the risk of T2DM by 17% (95% confidence interval [CI]: 14%-20%), with lifestyle interventions more effective than drug-based ones (risk ratio: 0.52; 95% CI: 0.46-0.58 vs 0.70; 95% CI: 0.58-0.85, $p<0.05$) (Hopper et al., 2011). Given the effectiveness and superiority of lifestyle interventions over drug-based treatment in T2DM prevention, lifestyle interventions have been recommended by the American

Diabetes Association (2015) as a primary intervention strategy among patients with prediabetes (American Diabetes Association, 2015).

Prediabetes and Cardiovascular Disease

Prediabetes as an Independent Risk Factor for Cardiovascular Disease

The close relationship between prediabetes and CVD is well established. The 10-year follow-up report of the Paris Prospective Study demonstrated that the annual mortality rates of coronary heart disease (CHD) were 1.4, 2.7, and 3.2 per 1000 for the 6055 normoglycaemic, 690 cases with IGT, and 293 new and known diabetic subjects ($p<0.01$), respectively (Eschwege et al., 1985). More recently, the results of this study have been replicated with similar findings. For example, in a cohort of more than 36,000 Taiwanese followed for an average of 11 years, those with an IFG between 110 to 125 mg/dl were at heightened risk for CVD-related mortality, compared to those with IFG below 110 mg/dl (relative risks: 4.4 and 1.5, respectively, $p<0.05$). The relationship between IFG and mortality remained significant even after adjusting for other cardiovascular risk factors, including systolic blood pressure (≥140 mm Hg), diastolic blood pressure (≥90 mm Hg), smoking, total serum cholesterol (≥240 mg/dl), and BMI (≥24 kg/m^2) (Wen, Cheng, Tsai, Hsu, & Wang, 2005). Using a database from the Emerging Risk Factors Collaboration that included 820,900 participants, another recently published study reported that for each 18 mg/dl increase in fasting glucose over 100 mg/dl, the risk of cardiovascular-related death grew by 13% (Seshasai et al., 2011).

Data from other longitudinal studies indicate that both IFG and IGT are associated with an increased hazard ratio (HR) for CVD, with IGT being a slightly stronger predictor (Balkau, Forhan, & Eschwège, 2002; M. Coutinho, Gerstein, Wang, & Yusuf,

1999; Levitan, Song, Ford, & Liu, 2004; Selvin et al., 2010; The DECODE Study Group & The European Diabetes Epidemiology Group, 2001, 2003). Furthermore, the most recent evidence available from the Strong Heart Study demonstrated that cardiac geometry and function were more severely altered among individuals with both IFG and IGT than those with IFG alone (Capaldo et al., 2013). The odds of left ventricular hypertrophy was 3.5 in those with isolated IFG (95% CI: 0.68-17.76; p=non-significant), and 9.76 (95% CI: 2.03-46.79; p=0.004) in those with both IFG and IGT, compared with participants with normal glucose tolerance, after controlling for age, gender, heart rate, waist circumference, and blood pressure (Capaldo et al., 2013). Compared with fasting glucose levels, combined postprandial hyperglycemia and fasting hyperglycemia prolongs the adverse effect of hyperglycemia (Monnier, Lapinski, & Colette, 2003), and is associated with fluctuations in glucose concentrations, which further increase vascular resistance and damage (Monnier et al., 2006).

Based on the observations of worsening cardiac function with higher aberration in glucose levels, the "ticking clock" hypothesis was formulated, which postulates that the clock for CVD starts ticking before the onset of clinical T2DM (Haffner, Stern, Hazuda, Mitchell, & Patterson, 1990). The findings of these studies provide strong evidence to support this hypothesis, showing that prediabetes increases the risk for CVD, independent of other risk factors (Ford, Zhao, & Li, 2010). This heightened risk for CVD is associated with hypertension, obesity (especially abdominal or visceral obesity), dyslipidemia with high triglyceride (TG) levels, high low-density lipoprotein cholesterol (LDL-C) levels, and low high-density lipoprotein cholesterol (HDL-C) levels, all of which are more prevalent among people with prediabetes than those with a normal glucose level, and

constitute the core characteristics of metabolic syndrome defined by the National Cholesterol Education Panel Adult Treatment Panel III (American Diabetes Association, 2014; Yang et al., 2011). However, it remains unclear whether the heightened CVD risk associated with IFG or IGT are more likely attributable to these other risk factors or progression to T2DM, where there is up to a four-fold increased risk of CVD if T2DM develops .

While there is a wealth of evidence suggesting that elevated blood glucose levels increase CVD risk and heighten cardiovascular events among prediabetics, there is little evidence indicating that a decline in blood glucose level would decrease cardiovascular events among persons with T2DM. The importance of preventing CVD among prediabetics is underscored by three recent clinical trials, all of which have demonstrated that in persons with T2DM, especially for older age with long term T2DM (8 to 10 years), intensive glycemic control may not reduce cardiovascular events (Duckworth et al., 2009; Gerstein et al., 2008; Patel et al., 2008), but rather increase mortality (Gerstein et al., 2008). The United Kingdom Prospective Diabetes Study (UKPDS) also showed that tight glycemic control could reduce the incidence of microvascular complications, but this did not result in a significant reduction in macrovascular disease ("Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group," 1998). Thus, these findings suggest that reversing the development of CVD at an early stage, such as observed in prediabetes, may be the most effective strategy for CVD risk reduction, morbidity, and mortality (Rijkelijkhuizen et al., 2007).

Mechanisms of Vascular Damage in Prediabetes

The processes by which prediabetes contributes to vascular damage are multiple and complex. In general, the mechanisms can be largely grouped into those mediated by insulin resistance, and those mediated by hyperglycemia (Milman & Crandall, 2011). Endothelial cells secrete substances that regulate relaxation of smooth muscle cells in the medial layer. Nitric oxide secreted by endothelial cells is one of the most important substances that exerts vascular protection because of vasodilation, anti-inflammation, permeability-reduction, inhibition of vascular smooth muscle proliferation and platelet and leukocyte aggregation that are involved in initiation of atherosclerotic plaque formation (Bian, Doursout, & Murad, 2008; Stehouwer & Smulders, 2006). In a normal vessel, the predominance of vasodilator substances results in net smooth muscle relaxation (Strom & Libby, 2010). The vascular nitric oxide is produced in part through the phosphatidylinositol 3-kinase-dependent insulin signaling pathway via stimulation of endothelial nitric oxide synthase activity (Milman & Crandall, 2011). This pathway however, is impaired in the state of insulin resistance, a hallmark of prediabetes, thus leading to reduced production of nitric oxide and its vascular protective effects (Milman & Crandall, 2011). For a full discussion of the pathophysiological mechanisms related to vascular damage in orediabetes and its relationship to CVD development refer to Appendix A.

Conceptual Framework

Overview

The conceptual framework for this study as shown in Figure 1 is adapted from Devereux and Alderman's schematic representation of the pathways from risk factor

exposure to preclinical disease and ultimate development of clinical morbid events with permission from Wolters Kluwer Health, Inc. (License Number 3662020335658) (Devereux & Alderman, 1993). Preclinical disease refers to the pathological changes in the heart and arteries that develop early in the course of CVD, before symptoms occur. Clinical morbid events is defined as symptomatic CVD with overt clinical manifestation, such as myocardial infarction, strokes, or arrhythmic sudden death (Devereux & Alderman, 1993). For the purposes of this study, prediabetes will be referred to as a preclinical condition in the conceptual framework instead of preclinical disease in the original model. The rationale for this change is that one of the health outcomes in this study is lowered cardiovascular risk rather than morbid events in the original model.

The original model postulates that at each step some individuals do not necessarily make the next transition, such that some patients with risk factors do not develop preclinical disease, and some patients with preclinical disease do not develop morbid events (Devereux & Alderman, 1993). Consistent with this assumption, the conceptual framework proposes that exposure to cardiovascular risk factors, including aging, gender, educational level, overweight/obesity, biological factors, physical factors, and psychological factors, may or may not predispose the person to develop prediabetes. It is not clear, however, whether overweight/obese adults without prediabetes have similar biological, physical, and psychological risks for CVD as those with prediabetes. As the specific aim, this study compared baseline biological, physical, and psychological risk factors in overweight/obese adults with and without prediabetes, controlling for age, gender, and educational level.

In general, the evolution of cardiovascular risk factors to morbid events may be regarded as proceeding in two stages: risk factors to preclinical disease, and then to morbid or clinical disease events, each of which may have naturally occurring "forward reactions" and "backward reactions" (Devereux & Alderman, 1993). The original model underscores the complex interplay between environmental and genetic factors that play an important role in determining whether forward reactions or backward reactions may occur at each step. The strength of the forward reactions is related to the power of underlying pathophysiologic changes and the unfavorable genotypes which may enhance adverse transitions, whereas the backward reactions may be induced by therapeutic interventions, counter-regulatory physiologic mechanisms, and favorable genotypes that may confer partial resistance to specific risk factors (Devereux & Alderman, 1993).

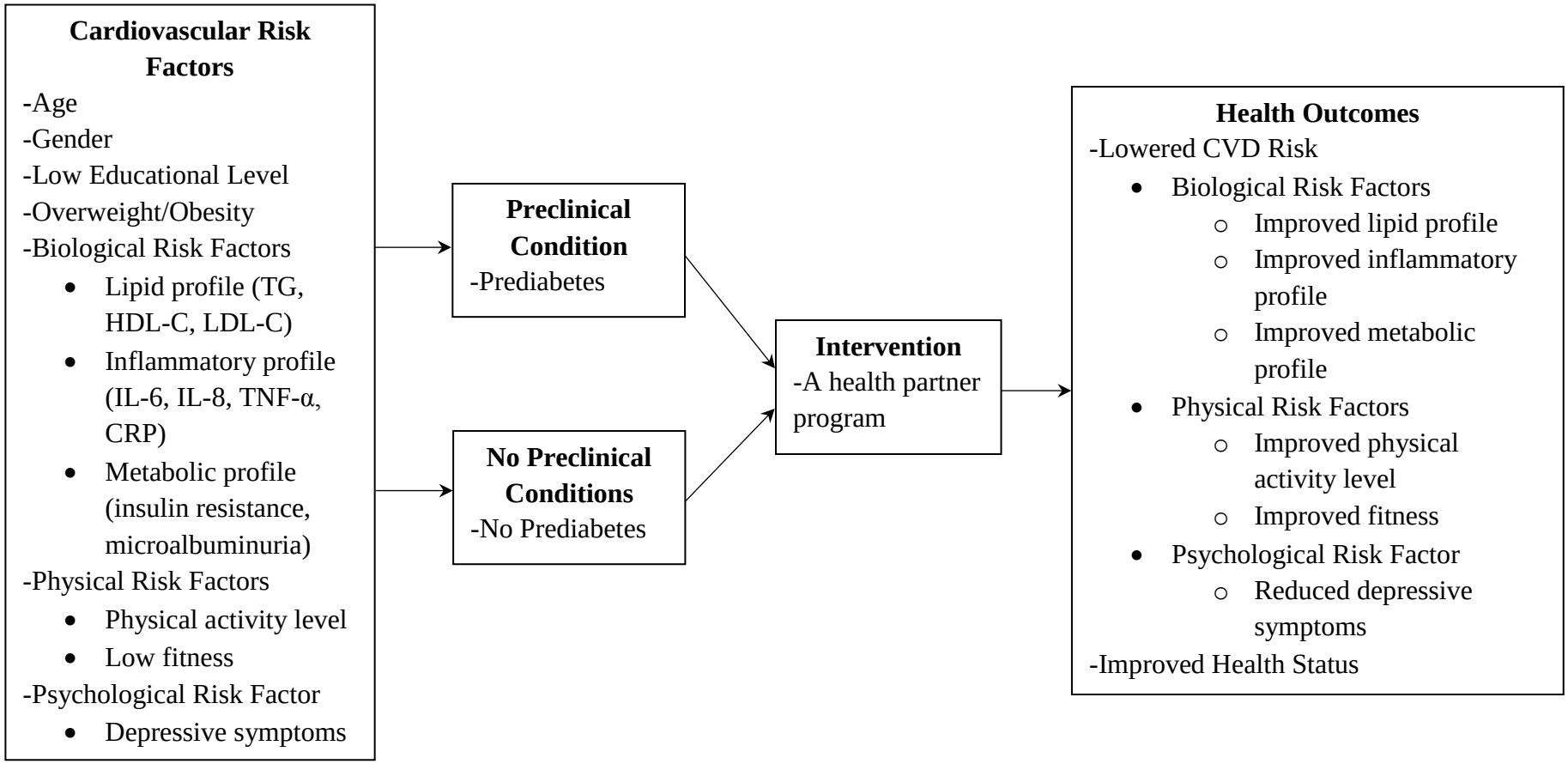
For purposes of this study, the health partner program is conceptualized as backward reactions insofar it may reverse the progression from prediabetes to development of CVD and thus lower CVD risk. The health partner program is a tailored program designed to meet the individual goals set by the participant. As part of the exploratory aim of this study, by employing positive lifestyle behaviors such as increased physical activity, healthier dietary choices, and weight loss, the health partner program may serves as backward reactions or intervention strategy that is anticipated to reduce the cardiovascular risk as exemplified by a reduction in biological risk factors (improved lipid profile, inflammatory profile, and metabolic profile); lower physical risk factors (improved physical activity level and fitness), and psychological risk factors (reduced depressive symptoms and improved health status) among individuals who are overweight/obese with and without prediabetes.

Theoretical Assumptions

The theoretical assumptions of the study include:

1. Adults have various cardiovascular risk factors that may predispose them to develop CVD. These risk factors include age, gender, low educational level, overweight/obesity, biological risk factors (lipid profile, inflammatory profile, metabolic profile), physical risk factors (physical inactivity, and cardiorespiratory fitness), and psychological risk factor (depressive symptoms and health status). The details of the risk factors are shown in the Figure 1.
2. Exposure to cardiovascular risk factors may or may not predispose the individual to development of prediabetes.
3. The presence of prediabetes is conceptualized as a preclinical condition, and the health partner program is conceptualized as backward reactions to offset or influence the adverse progression on health outcomes according to Devereux and Alderman (1993).
4. The effect of the health partner program may be influenced by the interaction between environmental and genetic factors, although it is not tested in the model.

Figure 1 Conceptual Framework



Note. The conceptual framework is adapted with permission from Wolters Kluwer Health, Inc. (License Number 3662020335658). TG=triglycerides; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; IL-6=interleukin 6; IL-8=interleukin 8; TNF-α =tumor necrosis factor-alpha; CRP=C-reactive protein; and fitness=cardiorespiratory fitness.

A comprehensive literature review of major concepts in the conceptual framework is provided below. A summary of study findings is available in Appendix B.

Age

Advancing age has been shown to increase the prevalence of prediabetes. Compared to young adults (ages 20 to 39 years), the likelihood of prediabetes was 2.7 times greater (95% CI: 2.1-3.4) in middle-aged adults (ages 40 to 59 years) and 4.6 times higher (95% CI: 3.5-6.0) in the older adults (≥60 years old) (Yang et al., 2011). Glucose tolerance progressively declines with advancing age, and this change is often accompanied by insulin resistance. In addition, when insulin sensitivity is controlled, insulin secretory defects have been consistently demonstrated in aging humans (Chang & Halter, 2003). These physiological changes may predispose older people to develop hyperglycemia and T2DM as a consequence of aging (Chang & Halter, 2003).

Age has also been found as an important risk factor for developing CVD. Data from the Seattle Longitudinal Study showed that using young adults (aged 25 to 44) as a referent, the odds ratio (OR) for CVD diagnosis was 4.355 (95% CI: 2.62-7.25, $p<0.05$), 11.358 (95% CI: 6.66-19.36, $p<0.05$), and 28.394 (95% CI: 15.33-52.58, $p<0.05$) for middle-aged adults (aged 45 to 64), young-old adults (aged 65 to 74), and old-old adults (aged 75 to 91), respectively (Cardi et al., 2009). It is estimated that approximately 82% of people who die of CHD are 65 or older (American Heart Association, 2013). Aging is associated with changes in the vascular wall which leads to the loss of arterial elasticity and reduced arterial compliance that may subsequently result in CVD (Jani & Rajkumar, 2006).

Gender

Gender differences in the prevalence of prediabetes were shown in the 2005-2006 National Health and Nutrition Examination Survey (NHANES). Male gender for example, was significantly associated with prediabetes compared to females. Thirty-three percent of male participants had prediabetes, while twenty-six percent of female participants had prediabetes ($p=0.0002$). Using men as the referent, the OR for prevalence of prediabetes was 0.57 (95% CI: 0.45-0.72) among women ($p<0.0001$) (Geiss et al., 2010; Yang et al., 2011). The reason for these gender differences is unclear. Lower rates of participation in the recommended health behaviors among men, such as weight loss, reduced fat intake and calories, and physical activity, are thought to explain some of differences (Geiss et al., 2010). Gender differences in the development of CVD are well established, with men having CVD on average 7 to 10 years younger than women, and estrogen plays an important cardio-protective role prior to menopause (Maas & Appelman, 2010). Postmenopausal women have similar or even higher rates of CVD reported as men (Maas & Appelman, 2010).

Educational Level

Cross-sectional data from the 2005-2006 NHANES showed lower educational attainment was linked with prediabetes (Geiss et al., 2010). The prevalence of prediabetes among people with less than high school education, those with high school diploma, and those above high school education was 36.9%, 31.0%, and 27.4%, respectively, and this trend was significant ($p=0.0156$) (Yang et al., 2011). The reason for this difference in prediabetes prevalence rates is not well understood. Lower rates of physical activity among those with less than a high school education, however, was thought to partially explain this difference (Geiss et al., 2010).

The Centers for Disease Control and Prevention has also released similar results from the Behavioral Risk Factor Surveillance System (BRFSS), a state-based system of ongoing telephone health surveys that collects information on health risk behaviors, preventive health practices, and health care access primarily related to chronic disease and injury. The results showed that educational level plays a significant role in CHD, with a lower educational level associated with a greater likelihood of being diagnosed with CHD. For example, CHD was more prevalent among people without a high school education (9.2%), compared to those with some college education (6.2%) or an undergraduate degree (4.6%) (Centers for Disease Control and Prevention, 2011). Higher educational levels are also associated with improved access to quality health care, which is also known to contribute to lower rates of CVD (Christensen, Mogelvang, Heitmann, & Prescott, 2011). In addition, those with more education are also more likely to be better informed about positive health practices and adopt healthier lifestyles that may lead to lower risk for CVD (Goyal et al., 2010).

Overweight/Obesity

Overweight/Obesity as a risk factor for cardiovascular disease.

Cross-sectional data from the 2005-2006 NHANES showed an increasing prevalence of prediabetes with increasing BMI. Using normal-weight individuals as the referent, the likelihood of having prediabetes was three times greater among obese individuals (95% CI: 2.0-3.6) and was twice as high among overweight individuals (95% CI: 1.3-2.1). Among overweight participants 33% experienced prediabetes while this number was approximately 10% higher among obese participants, compared to 16% of normal-weight participants ($p<0.0001$) (Yang et al., 2011). In addition, the DPP study also showed that losing a modest amount of body weight through dietary changes and

increased physical activity (7% of the original body weight) can prevent or delay the onset of T2DM among overweight/obese prediabetic individuals (Knowler et al., 2002).

Data from the Framingham Heart Study and from other studies show that the degree of body fat, particularly abdominal obesity, is related to the rate of development of CVD (Higgins, Kannel, Garrison, Pinsky, & Stokes, 1988; Pi-Sunyer, 1993). The Framingham Heart Study is a long-term, ongoing cardiovascular study with participants followed biennially for the development of CVD (Dawber, Meadors, & Moore, 1951). After 26 years of follow-up in the Framingham Heart Study, the risk for CHD, the most frequent manifestation of CVD in the Framingham cohort, increased proportionately in both men and women as BMI increased, and this association was more pronounced in those younger than 50 years of age. Among men younger than 50 years, the heaviest group was twice as likely to develop CHD as the leanest group. The risk for CHD was greater among women of similar age, with up to a 2.4 fold increased risk. Body weight was a significant predictor of total CVD in both genders after adjusting for other major cardiovascular risk factors, including age, systolic blood pressure, serum cholesterol, cigarettes smoked per day, left ventricular hypertrophy, and glucose intolerance (Hubert, Feinleib, McNamara, & Castelli, 1983). Furthermore, BMI at the upper end of normal range is associated with a more adverse cardiovascular risk profile compared to that at the lower end of normal range. After 8 years of follow-up in the Framingham Offspring Study, 40% to 70% of newly developing essential hypertension could be attributable to overweight, defined by BMI≥23 or a subscapular skinfold thickness of ≥1 cm (Garrison, Kannel, Stokes, & Castelli, 1987).

Most people (80%) who are overweight or obese display potentially unhealthy changes in metabolism (Karelis, St-Pierre, Conus, Rabasa-Lhoret, & Poehlman, 2004). These changes may include dyslipidemia, chronic, low-grade, systemic inflammation, insulin resistance, and components of metabolic syndrome, as discussed below, which put these individuals at a much higher risk for T2DM and CVD. In recent years, a novel concept of metabolically healthy obesity has been coined (Denis & Obin, 2013). Individuals with metabolically healthy obesity are a subgroup of obese individuals who meet the standard BMI cutoff point for obesity (BMI≥30), but are considered as metabolically healthy because they do not demonstrate the panoply of other major cardiovascular risk factors. However, metabolically healthy obesity is not a permanent state. Most likely, it is a transient state and is related to younger age (Appleton et al., 2013). Recent evidence from the North West Adelaide Health Study showed that one third of all individuals who were classified as metabolically healthy obese phenotype finally changed to a metabolically at-risk phenotype over a 5-to-10-year period (Appleton et al., 2013).

A consensus about the definition of metabolically healthy obesity has not been reached, although Stefan and associates (2013), upon reviewing previous studies, recommended the following criteria to define metabolically healthy obesity in epidemiological studies: absence of abdominal obesity and components of metabolic syndrome, being insulin sensitive, and having high levels of fitness (Stefan, Häring, Hu, & Schulze, 2013). This subgroup of obese people is thought to be at much lower risk for cardiovascular morbidity and mortality compared to those with major cardiovascular risk factors, who are judged as being metabolically unhealthy obesity (Stefan et al., 2013).

For the purpose of this study, the overweight/obese at-risk individuals are the focus of the study.

Measurement of overweight/obesity.

Since the epidemic of obesity threatens public health and contributes to the burden of disease (Caballero, 2007), clinical detection of overweight and obese individuals is critically important. Traditionally, for adults, BMI, calculated as weight in kilograms divided by height in meters squared, has been commonly used as an indicator of classifying underweight (BMI≤18.5 kg/m^2), healthy weight (BMI: 18.5-24.9 kg/m^2), overweight (BMI: 25-29.9 kg/m^2), and obesity (BMI≥30 kg/m^2). BMI is widely used in clinical practice, in part, because of its convenience, safety, and minimal cost.

However, BMI is a measure of excess weight rather than excess body fat. Recent studies found that BMI is an imprecise mathematical estimate of adiposity (Flegal et al., 2012; Razak et al., 2007; Q. Sun et al., 2010). One major limitation of BMI is that the use of BMI as a measure of body proportion does not indicate body fat distribution (Oza-Frank, Ali, Vaccarino, & Narayan, 2009). Waist circumference, or waist-hip ratio (WHR), in this case, allows better characterization of body fat accumulated in the abdominal region. Findings from several large prospective cohort studies showed that the association of risk for CVD and death with increasing waist circumference is stronger in non-obese individuals compared to obese individuals (Pischon et al., 2008; Staiano et al., 2012; Wormser et al., 2011).

Coutinho and associates (2013) reported that patients with coronary artery disease who had a normal BMI but with abdominal obesity had the worst long-term survival rate: a person with BMI of 22 kg/m^2 and WHR of 0.98 had higher mortality than a person with

similar BMI but WHR of 0.89 (HR=1.10; 95% CI: 1.05-1.17); than a person with BMI of 26 kg/m^2 and WHR of 0.89 (HR=1.20; 95% CI: 1.09-1.31), than in a person with BMI of 30 kg/m^2 and WHR of 0.89 (HR=1.61; 95% CI: 1.39-1.86), and a person with BMI of 30 kg/m^2 and WHR of 0.98 (HR=1.27; 95% CI: 1.18-1.39) ($p<0.0001$ for all) (T. Coutinho et al., 2013). This study adds to the literature that being overweight or obese by BMI criteria does not lead to higher mortality in the absence of abdominal obesity. This study also provides support to the use of BMI in combination with measures of abdominal obesity as a means to identify those at higher CVD risk and mortality, especially for normal weight abdominal obesity, whose adiposity-related risk may go unnoticed during clinical assessments due to the normal BMI.

Another limitation is that BMI does not distinguish between excess fat, muscle, or bone mass. In general, older adults tend to have more body fat than younger adults for an equivalent BMI. Women tend to have greater amount of total body fat than men with an equivalent BMI. Muscular individuals, or highly-trained athletes, may have a high BMI because of increased muscle mass. Because of this limitation, the term normal weight obesity (i.e., normal BMI but high body fat content) has been recently coined. Normal weight obesity has been shown to be associated with cardiovascular risk factors, and independently associated with increased risk for CVD mortality in women (Romero-Corral et al., 2010). BMI cannot be used to quantify visceral fat. Recently, it has been demonstrated that within abdominal obesity, it is visceral fat rather than subcutaneous fat, is the major predictor of adverse events, such as metabolic syndrome, CVD, and T2DM (Després & Lemieux, 2006). Conversely, techniques that accurately measure body fat such as dual-energy x-ray absorptiometry, hydrostatic weighing, and bioelectrical

impedance analysis are rarely used in clinical practice primarily due to costs, requiring specially trained personnel, or specialized laboratories (Okorodudu et al., 2010). Although it is beyond the scope of the current study to perform body fat measurement using these technological devices, dual-energy x-ray absorptiometry in particular may be beneficial for further studies as a method to examine the relationship between body fat and biological risk in the development of CVD. In this study, overweight/obesity is measured by both WHR and BMI.

Biological Risk Factors

Lipid profile.

Lipid abnormalities significantly contribute to increased risk of CVD and T2DM among prediabetics (Festa et al., 2005). The typical lipoprotein pattern in T2DM, also known as diabetes dyslipidemia or atherogenic dyslipidemia, consists of moderate elevation in TG levels, low HDL-C levels, and a shift in LDL-C to a more pro-atherogenic composition (small dense LDL particles) (Solano & Goldberg, 2006). This pattern of lipoprotein associated with insulin resistance and increased risk for CVD is present prior to the onset of T2DM (Gosavi, Flaker, & Gardner, 2006; Solano & Goldberg, 2006). One study found that the lipoprotein pattern in prediabetic individuals more clearly resembled diabetic patients compared to healthy nondiabetics with normal glucose tolerance (Festa et al., 2005). In addition, hyperglycemia and dyslipidemia are well established to increase CVD risk in prediabetics and diabetics (O'Keefe & Bell, 2007). Therefore, improved control of a lipid disorder may reduce cardiovascular complications among prediabetics.

Based on limited data available, however, dyslipidemia control among prediabetics is reported to be suboptimal. Cross-sectional data from the 2005-2006 NHANES showed that 34.4% of prediabetic patients had elevated TG (≥150 mg/dl or ≥1.70 mmol/l), and 28.3% had reduced HDL-C level (<40 mg/dl or <0.45 mmol/l in men and <50 mg/dl or <0.57 mmol/l in women) (Yang et al., 2011), placing them at a greater risk for CVD. At baseline of the DPP clinical trial, 21% of women and 29% of men had TG values ≥2.26 mmol/l and ≥1.69 mmol/l, respectively. Forty-one percent of women and 45% of men had elevated LDL-C levels (≥3.36 mmol/l). Low HDL-C concentrations were present in 60% of women (<1.29 mmol/l) and 52% of men (<1.03 mmol/l) (Diabetes Prevention Program Research Group, 2005). These studies suggest that interventions should be initiated to improve control of lipid abnormalities among prediabetic individuals.

Dyslipidemia is frequently associated with overweight/obesity (Franssen, Monajemi, Stroes, & Kastelein, 2011; Repas, 2011), with only 20% of the obese population not exhibiting typical metabolic lipid profile changes (Karelis et al., 2004). The typical dyslipidemia phenotype commonly associated with overweight/obesity is characterized by elevated TG concentrations, an excess of small dense LDL particles, and decreased HDL-C levels (Franssen et al., 2011), which are similar to those seen in patients with T2DM or prediabetes. This lipoprotein pattern is particularly atherogenic and, along with related comorbidities, contributes to an increased cardiometabolic risk associated with overweight/obesity (Repas, 2011).

A cross-sectional study of 9786 subjects found that the increased prevalence of dyslipidemia is parallel with increased BMI (Fu et al., 2010). The age-standardized

prevalence of dyslipidemia of normal, overweight, and obese population was 23.9%, 43.3% and 65.4% in men and 17.9%, 29.2% and 42.3% in women. Lipids abnormalities were also found to be positively related to BMI (r=0.17, 0.18, -0.26 and 0.35 between total cholesterol, LDL-C, HDL-C, TG and BMI, respectively, all $p<0.01$). Although overweight/obesity with and without prediabetes are both associated with similar lipoprotein pattern, evidence of which individuals present with greater biological CVD risk is currently lacking. This determination may become increasingly important to stratify individuals in the clinical treatment of overweight/obesity in order to develop effective screening tools aimed at identifying such risks. For a more complete description of the underlying pathophysiological mechanisms associated with dyslipidemia refer to Appendix C.

Inflammatory profile.

Adipose tissue is a major endocrine organ, secreting hormones that contribute to inflammation, atherogenesis, and insulin resistance, thus heightening the risk for T2DM and CVD (Galic et al., 2010). Notably, white adipose tissue secretes a diverse range of adipokines, a number of which are important inflammatory markers, such as TNF-α, interleukin-1beta (IL-1β), IL-6, monocyte chemoattractant protein-1, leptin, adiponectin, resistin, proteins of the renin-angiotensin system, and plasminogen activator inhibitor-1 (Galic et al., 2010; Kershaw & Flier, 2004; Wood, de Heredia, Wang, & Trayhurn, 2009). Overweight/Obesity has been frequently associated with low-grade, chronic, systemic inflammation, which is characterized by increased levels of inflammatory markers in the systemic circulation, including TNF-α, IL-6, IL-1β, IL-8, and CRP (Bastard et al., 2006; Berg & Scherer, 2005; Kershaw & Flier, 2004; Kim et al., 2006; Shoelson et al., 2006).

The increase in systemic inflammatory markers is modest, often less than two-fold above what is observed in healthy adults (Calder et al., 2011). Although diagnostic criteria for low-grade chronic inflammation have not been clearly defined, the phenotype is well recognized (Calder et al., 2011).

Elevated levels of inflammatory markers have been found in people with incident T2DM and with metabolic syndrome (Fernández-Real & Pickup, 2008; Kolb & Mandrup-Poulsen, 2010). However, prospective studies have demonstrated that increased circulating concentrations of inflammatory markers precede the development of T2DM by many years (Herder, Baumert, et al., 2006; Pradhan, Manson, Rifai, Buring, & Ridker, 2001; Schmidt et al., 1999; Thorand et al., 2005). Patients with prediabetes, in particular, those with IFG and IGT, are found to have elevated concentrations of inflammatory markers compared to normoglycemic healthy controls (Colak et al., 2013).

In a cross-sectional study by Colak and associates (2013), 165 participants were classified as those with newly diagnosed T2DM, those with IFG and IGT, and those with IFG. A control group consisted of age- and BMI-matched healthy subjects with a normal 75 g oral glucose tolerance test. There was no significant difference in terms of age, gender, or BMI between the patient group (those with IFG, IFG and IGT, and T2DM) and healthy controls. Concentrations of inflammatory markers were significantly elevated in patients with IFG and IGT compared to healthy controls and IFG patients (IFG and IGT vs control: $p<0.05$ for CRP, and IL-6; IFG and IGT vs IFG: $p<0.05$ for CRP and IL-6). Patients with IFG had similar concentrations of inflammatory markers (IL-6, IL-8, CRP) compared to healthy controls ($p>0.05$), and people with T2DM had similar concentrations of inflammatory markers (IL-6, IL-8, and CRP) compared to those with

IFG and IGT ($p>0.05$). Multiple regression analysis showed that both fasting and postload glucose concentration were independently associated with circulating CRP and IL-6 concentrations, controlling for age, gender, BMI, and lipid concentrations ($p<0.05$) (Colak et al., 2013). Postload glucose, but not fasting glucose, was independently associated with CRP levels greater than 3 mg/l (Colak et al., 2013), which is considered to indicate a high risk for CVD by the American Heart Association (Pearson et al., 2003). Colak et al. (2013) concluded that patients with prediabetes are accompanied by low-grade, systemic inflammation, which is independently of obesity and mostly driven by postload glucose concentrations.

Data from prospective studies support systemic elevation in inflammatory markers as a risk factor for T2DM. For example, CRP was associated with an increased risk of progression from prediabetes to T2DM in the absence of intensive lifestyle interventions (Herder, Peltonen, et al., 2006). In addition, low-grade, chronic inflammation has also been found as a risk factor for CVD. A meta-analysis of prospective studies investigating the relationship between chronic inflammatory markers and subsequent risk for CHD showed moderate but statistically significant associations between fibrinogen, CRP, albumin, and leukocyte count and the development of CHD (Danesh, Collins, Appleby, & Peto, 1998). In particular, in 7 studies with 1053 cases, people in the top tertile of CRP were 1.7 (95% CI: 1.4-2.1) times more likely to experience CHD compared to those in the bottom tertile, with a 1.4 mg/L difference in CRP between the two groups at baseline. Hence, the presence of low-grade, chronic, systemic inflammation among overweight/obese prediabetic individuals may put them at higher risk for both T2DM and CVD.

Although low-grade, chronic inflammation are found in both overweight/obesity with or without prediabetes, very few studies have compared the inflammatory levels between the two groups and indicate which group of patients are at a greater biological risk for CVD. In a cross-sectional study, 35 (27 women and 8 men) healthy, obese adults with a mean BMI 34.8 kg/m^2 were screened for anthropometric and laboratory measures (Gupta & Johnson, 2010). There was no significant difference in terms of age, weight, or waist circumference between healthy obese normoglycemic adults (n=24) and healthy obese prediabetic adults (n=11) ($p>0.05$). The latter group, however, had significantly higher levels of CRP (16.9 mg/l vs 3.7 mg/l; $p<0.0001$) and fibrinogen (599 mg/dl vs 472 mg/dl; $p<0.0002$) (Gupta & Johnson, 2010). It seems that overweight/obese adults with prediabetes are at a higher risk for CVD than their counterparts without prediabetes, since the CRP levels are significantly elevated. However, because of the small sample size, the study was not powered to evaluate any population differences in biological risks between the two groups. This study is proposed to fill this void by recruiting enough subjects to detect such differences.

In cardiovascular health, in particular, among the adipokines secreted by adipose tissue, the rise in circulating levels of IL-6, TNF-α, and CRP has been found to be associated with impaired cardiac morphology and function in obese subjects (Malavazos et al., 2007). These adipokines may contribute to endothelial dysfunction and potentially greater cardiovascular risk (Calabrò et al., 2009). Conversely, weight loss is associated with a reduction in the macrophage infiltration of white adipose tissue, and improvements of the inflammatory profile, insulin sensitivity, and lower CVD risk (Bastard et al., 2006; Poirier et al., 2006).

Metabolic profile.

Insulin resistance.

Insulin resistance is a pathophysiological condition in which cells fail to respond to the normal actions of insulin. In insulin resistance, skeletal muscle, fat, and liver cells do not respond properly to insulin and thus cannot easily absorb glucose from the bloodstream. In general, the strong positive relationship between BMI and insulin resistance is well documented in the literature (Qatanani & Lazar, 2007; Westphal, 2008), although in recent years, data from several small studies indicate that some obese individuals are not insulin resistant (McLaughlin, Abbasi, Lamendola, & Reaven, 2007; Reaven, 2005; Stefan et al., 2008), which support the novel concept of metabolically healthy obesity.

From the perspective of metabolic risk, the body fat distribution is important (Westphal, 2008). Although insulin resistance, as assessed by the homeostasis model assessment of insulin resistance (HOMA-IR), is positively associated with BMI, this association is much stronger among non-obese individuals compared to obese individuals (Stefan et al., 2013). As BMI increases, the variation of HOMA-IR among obese individuals becomes larger. This results in a group of individuals with insulin resistance below the population average (i.e., being insulin sensitive), although they are morbidly obese (Stefan et al., 2013). BMI measurement, therefore, may be more useful for identification of high metabolic risk for normal-weight and overweight individuals rather than for morbidly obese individuals. In contrast, waist circumference has been shown as the strongest predictor for insulin resistance in the multiple regression model (β=0.37), compared to log-plasma total cholesterol (β=0.23), systemic blood pressure (β=0.10),

HDL-C (β=-0.09), and BMI (β=0.15) among nondiabetic adults with BMI ranging from 18 kg/m^2 to 60 kg/m^2. It could explain over 50% of the variation in insulin resistance alone (Wahrenberg et al., 2005). The results showed that waist circumference, an indicator of abdominal obesity, is informative in qualifying metabolic risk in both non-obese and obese subjects.

Within abdominal obesity, liver fat content (Sung, Jeong, Wild, & Byrne, 2012), to a much greater extent than visceral fat accumulation (Klöting et al., 2010), is associated with metabolically unhealthy obesity (Stefan et al., 2013). Mounting evidence recently has shown that accumulation of fat in the liver, which are conditions commonly accompanied by inflammatory processes, are responsible for the genesis of insulin resistance (Fabbrini et al., 2009; Olefsky & Glass, 2010; Stefan et al., 2008). The use of WHR in this study allows better characterization of body fat distribution and distinguishes the location of body fat, thereby comparing baseline risk for CVD between overweight/obese individuals with prediabetes and overweight/obese at-risk individuals without prediabetes.

The pathophysiology of the prediabetic state is characterized by insulin resistance, β-cell dysfunction, and consequently, glucose dysregulation. However, IFG and IGT vary in the relative severity of hepatic versus skeletal muscle insulin resistance, with hepatic insulin resistance being worse in subjects with IFG, and skeletal muscle insulin resistance in subjects with IGT (Abdul-Ghani, Tripathy, & DeFronzo, 2006). In contrast to the daily glucose snapshot offered by IFG or IGT, HbA1c represents chronic exposure (over 2-3 months) to basal and postprandial hyperglycemia and reflects a combination of the pathophysiology (Goldstein et al., 2004). As a result of insulin resistance, the body needs

higher levels of insulin to help glucose transfer into cells. The increased fasting plasma insulin concentrations in individuals with prediabetes is indicative of an increased state of insulin resistance (Abdul-Ghani & DeFronzo, 2009). Insulin resistance places a high demand on the insulin-producing β cells in the pancreas, as the β cells try to keep up with this increased demand for insulin by producing more insulin. The normal β-cells function responding to increased insulin secretion in the presence of insulin resistance is an up-regulation of its set point: at each plasma glucose level absolute insulin secretion rates, both in the fasting state and throughout a 75 g oral glucose tolerance test, are higher among insulin-resistant individuals than their insulin-sensitive counterparts (Ferrannini, Gastaldelli, & Iozzo, 2011).

As long as β cells are able to produce enough insulin to fully compensate for the effect of insulin resistance, blood glucose levels would stay within the normal range. Once the β cells fail to keep up with the body's increased need for insulin, excess glucose builds up in the bloodstream, leading to prediabetes, T2DM, and other serious health problems. The cause of hyperglycemia, therefore, is not a deficiency in the absolute amount of secreted insulin, but the reduced ability of β cells to respond to increasing glucose concentrations in a timely manner during stimulation: for each increase in plasma glucose concentration during a 75 g oral glucose tolerance test, insulin secretion is less in prediabetic state than in normal-glucose-tolerance state (Ferrannini et al., 2011). Both IFG and IGT demonstrate impaired β cells dysfunction. However, the pattern of such dysfunction is different. Subjects with IFG have severe defects in the first-phase insulin secretion (0-30 minutes), but their second-phase insulin secretion (60-120 minutes) remains intact. Subjects with IGT have severe defects in both first- and second-phase

insulin secretion (Kanat et al., 2011). Although insulin resistance is demonstrated early in the natural history of T2DM, progressive β-cell dysfunction is the sine qua non responsible for the development of T2DM (DeFronzo & Tripathy, 2009). With the evolution from normoglycemia to T2DM, abnormalities in glucose control and insulin sensitivity occur continuously and insidiously over many years prior to T2DM diagnosis.

The importance of the effect of insulin resistance on the CVD risk profile among prediabetics is illustrated in the DPP study (Diabetes Prevention Program Research Group, 2005). Multiple regression analysis showed that the degree of insulin resistance, as measured by the HOMA-IR, had the strongest association with cardiovascular risk factors, including HDL-C, TG, and LDL particle size. Insulin resistance explained 3.4%, 8%, 3.1% of the variation of HDL-C, TG, and LDL particle size, respectively. Further scrutiny of the comparison between those in the upper half of the HOMA-IR distribution and those in the lower half of the HOMA-IR revealed TG, CRP, very low-density lipoprotein, fibrinogen, and tissue plasminogen activator were significantly higher and HDL-C and LDL particle size were significantly lower in those in the upper half of the HOMA-IR distribution than those in the lower half of the HOMA-IR. This did not appear to be influenced by whether they were in the upper or lower half of the range of an index of insulin secretion. The findings of this study support the importance of insulin resistance in the genesis of dyslipidemia in those with IFG/IGT (Diabetes Prevention Program Research Group, 2005), which put this patient population at a higher risk for CVD. However, the underlying mechanisms by which insulin resistance is associated with an increased risk of dyslipidemia in this patient population is still not clear and warrant further investigation.

Microalbuminuria.

Microalbuminuria is defined as levels of albumin ranging from 30 to 300 mg in a 24-hour urine collection (American Diabetes Association, 2015). Data from the Third NHANES indicated that the prevalence of microalbuminuria in U.S. adults aged 20 years and older was 8.8% (Coresh et al., 2005). Female gender, older age, and non-Hispanic Black ethnicity were associated with a higher prevalence (Coresh et al., 2005). Microalbuminuria is also more prevalent in hypertensive and diabetic populations, ranging from 10% to 40% (de Zeeuw, Parving, & Henning, 2006).

Prospective and epidemiologic studies have demonstrated that microalbuminuria is a predictive, independent risk factor for all-cause and cardiovascular mortality and adverse cardiovascular events among individuals with T2DM and hypertension (Basi, Fesler, Mimran, & Lewis, 2008; Gerstein et al., 2001; Viazzi et al., 2010). In the Heart Outcomes Prevention Evaluation (HOPE) study, microalbuminuria increased the adjusted relative risk of major cardiovascular events (relative risk: 1.83; 95% CI: 1.64-2.05), all-cause mortality (relative risk: 2.09; 95% CI: 1.84-2.38), and hospitalization for chronic heart failure (relative risk: 3.23; 95% CI: 2.54-4.10) (Gerstein et al., 2001). Increased cardiovascular mortality associated with microalbuminuria after adjusting for other risk factors has also been established in a population-based study of people aged 50 to 75 years (relative risk: 3.22; 95% CI: 1.28-8.06) (Jager et al., 1999). In the general population, heightened risk for poor cardiovascular outcomes however, has been observed below the conventionally accepted threshold of microalbuminuria. For example, in a 6-year longitudinal study with 1568 non-hypertensive, non-diabetic Framingham Offspring Study participants, those with urine albumin indexed to creatinine greater than

or equal to the gender-specific median (≥3.9 microg/mg for men, and ≥7.5 microg/mg for women) experienced a three-fold increase in CVD compared to those with urine albumin indexed to creatinine below the median. The increased CVD risk associated with urine albumin indexed to creatinine at or above the median remained robust in analyses restricted to adults without microalbuminuria (Arnlöv et al., 2005).

The mechanisms that link microalbuminuria and CVD together are poorly understood. Microalbuminuria is considered as a consequence of an increased albumin leakage though the glomerular capillary wall as a result of increased permeability of the wall, which is a marker of endothelial dysfunction (Ochodnicky et al., 2006). In view of this consideration, endothelial dysfunction has been hypothesized to explain the relationship between the two conditions (Ochodnicky et al., 2006; Stehouwer & Smulders, 2006). Many researchers have suggested that microalbuminuria is associated with generalized endothelial dysfunction (Ochodnicky et al., 2006), and generalized endothelial dysfunction is thought to play an important role in initiation and progression of atherosclerosis (Stehouwer & Smulders, 2006). However, which condition precedes the other is still not clear. Data from a population-based study with 645 individuals (mean age, 68 years; 248 with normal glucose metabolism, 137 with impaired glucose tolerance, and 260 with T2DM) showed endothelial nitric oxide synthesis was 0.12 mm in the presence of microalbuminuria (0.12 mm) (defined as urine albumin-to-creatinine ratio ≥ 2 mg/mmol), while it was 0.18 mm in its absence (p=0.002) (Stehouwer et al., 2004). After controlling for other risk factors, endothelial nitric oxide synthesis was still 0.038 mm (95% CI: 0.001 to 0.075) lower in the presence of microalbuminuria (p=0.04), and decreased linearly across microalbuminuria categories by 0.027 mm per category (<2, ≥2 to 5, ≥5 to

10, ≥10 mg/mmol). All results were similar among individuals with and without T2DM. These findings support that impaired endothelial nitric oxide synthesis plays a role in the association of microalbuminuria with CVD irrespective of the presence of T2DM.

Research on the prevalence of microalbuminuria among prediabetics is limited. Observational studies report that microalbuminuria is often present in prediabetes, suggesting that the microvascular complications occur even before the onset of T2DM. For example, at baseline of the DPP clinical trial, urine albumin-to-creatinine ratio was used to estimate 24-hour urinary albumin excretion and was calculated from untimed urine collection. Prevalence of albuminuria (≥30 mg/g, including both microalbuminuria and macroalbuminuria [urine albumin-to-creatinine ratio greater than 300 mg/g]) among three comparison groups was similar: 5.3% for the control group, 6.5% for the metformin group, and 6.8% for the lifestyle intervention group. One hundred and eighty-four (5.8%) out of 3188 study participants had microalbuminuria at baseline (Diabetes Prevention Program Research Group, 2009). The NHANES data from 1999 to 2006 revealed that the prevalence of chronic kidney disease (defined as urine albumin-to-creatinine ratio ≥30 mg/g or estimated glomerular filtration rate 15 to 59 ml/min per 1.73 m^2) was 17.1% in those with IFG compared to 11.8% in those without prediabetes, controlling for age, gender, and race (Plantinga et al., 2010). A cross-sectional study compared the prevalence of microalbuminuria among patients with newly diagnosed T2DM, IGT along with IFG, isolated IGT, isolated IFG, and normal glucose level and reported the prevalence was 20.7%, 13.1%, 11.1%, 5.8%, and 5.6%, respectively (X. L. Wang, Lu, Pan, & Tian, 2004). These findings are consistent with another cross-sectional study that found the prevalence of microalbuminuria increased with worsening glucose tolerance.

The prevalence of albuminuria among normal glucose level, IFG, IGT, and newly diagnosed T2DM was 5.1%, 9.3%, 11.0%, and 17.8%, respectively (Tapp et al., 2004). However, the underlying mechanisms by which prevalence of albuminuria increases with worsening glucose tolerance are poorly understood.

Physical Risk Factors

Physical activity level.

Exercise has been considered as a cornerstone of T2DM treatment for decades, along with diet, and medications. In addition, diet and physical activity are central to the management and prevention of T2DM, because they facilitate lowering of blood glucose and lipid levels, improve blood pressure control, as well as aid in weight loss and maintenance (Colberg et al., 2010). Moderate and vigorous exercise training improve insulin sensitivity (Bajpeyi et al., 2009; Galbo, Tobin, & van Loon, 2007), and lower intensity levels have been shown to increase insulin sensitivity to a lesser extent (Houmard et al., 2004). The effect of a single bout of aerobic exercise on increasing insulin sensitivity and glucose tolerance lasts about 24 to 72 hours (Boule, Haddad, Kenny, Wells, & Sigal, 2001). For this reason, the American Diabetes Association recommends that there should not be more than 2 consecutive days without aerobic physical activity among people with T2DM, and preferably, moderate physical activity (50% to 70% of maximum heart rate) should be performed at least 150 min/week and at least 3 days per week (American Diabetes Association, 2015). The effects of moderate aerobic exercise on glucose control are similar whether exercise is performed in a single session or divided into multiple bouts during the day (Baynard, Franklin, Goulopoulou, Carhart, & Kanaley, 2005).

Although weight loss was the predominant predictor of lower incidence of T2DM in the DPP clinical trial, those who met the goal of participating in moderate physical activity for 150 minute per week still reduced their risk for T2DM by 44%, independent of weight loss (Hamman et al., 2006). A systematic review and meta-analysis of 10 prospective cohort studies reported that the relative risk of T2DM was 0.69 for participation in moderate physical activity compared to being sedentary (Jeon, Lokken, Hu, & van Dam, 2007). Given the effectiveness of physical activity in prevention of T2DM, the American College of Sports Medicine and the American Diabetes Association jointly recommends 150 minute per week of moderate-intensity aerobic physical activity for prevention of T2DM in high-risk adult populations (Colberg et al., 2010). The preventive effect of resistance training has not been comprehensively studied so there are no current recommendations for this mode of exercise (Colberg et al., 2010).

Despite multiple health benefits of physical activity and the deleterious effects of remaining sedentary, less than half (48%) of the adult population in the U.S. meet the 2008 Physical Activity Guidelines to confer important health benefits (30-minute moderate physical activity on at least five days a week or equivalent and muscle-strengthening activities on 2 or more days a week that work all major muscle groups, including legs, hips, back, abdomen, chest, shoulders, and arms, or 75-minute vigorous-intensity aerobic activity every week and muscle-strengthening activities on 2 or more days a week that work all major muscle groups, or an equivalent mix of moderate- and vigorous-intensity aerobic activity and muscle-strengthening activities on 2 or more days a week that work all major muscle groups) (Centers for Disease Control and Prevention, 2013b). Among individuals with prediabetes, reported adherence to active lifestyle was

less than 70% (Yang et al., 2011). Exercise has to be performed regularly in order to maintain the positive health benefits. This is especially important for overweight/obese adults with prediabetes since physical activity has been promoted as an effective means to weight loss and promote CVD risk reduction.

One of the other major reasons to recommend regular physical activity for overweight/obese individuals with prediabetes is the potential to reduce the long-term increased risk of CVD associated with T2DM if it develops. The potential for achieving this goal can be assessed by evaluating two distinct outcomes: cardiovascular risk factors and clinically significant cardiovascular events. Prior studies suggest that higher levels of physical activity are associated with lower cardiovascular risk and mortality in both healthy and people with T2DM (Chudyk & Petrella, 2011; Kokkinos et al., 2009; Reddigan, Ardern, Riddell, & Kuk, 2011). Data from the Third NHANES demonstrated a significant beneficial effect of regular exercise on cardiovascular events in the general population. Engaging in light (HR: 0.72; 95% CI: 0.62-0.84) or moderate/vigorous physical activity (HR: 0.72; 95% CI: 0.61-0.84) was associated with a lower risk of CVD mortality compared to inactive subjects ($p<0.05$). Physical activity provided protective effects against CVD mortality in healthy subjects and those with metabolic risk factors (Reddigan et al., 2011). However, in a number of studies where a dose response is observed in preventing chronic disease such as CVD or reducing all-cause mortality, the relationship appears to be curvilinear. This means that the absolute increase in benefits becomes less and less for any given increase in the amount of physical activity ("Physical activity guidelines advisory committee report, 2008. To the Secretary of Health and Human Services. Part A: Executive Summary," 2009).

Cardiorespiratory fitness.

Maximum oxygen consumption (VO_{2max}) is the maximum amount of oxygen an individual can take in from inspired air while performing dynamic exercise involving a large part of total muscle mass (Fletcher et al., 2001). It is generally accepted as the best measure of functional limitation of the cardiovascular system and is commonly interpreted as an index of fitness (Howley, Bassett, & Welch, 1995). Data from a cross-sectional study indicated that VO_{2max} (absolute VO_{2max} & VO_{2max}/kg lean body mass) did not differ ($p>0.05$) in obese men and women compared to non-obese controls among young adults (Patkar & Joshi, 2011). In contrast, a prospective cohort study from a large, representative sample of Canadian general population found that moderate-to-high fitness was associated with substantially lower level of abdominal obesity, as measured by a lower waist circumference (main effect, $p=0.0001$ in men, $p=0.0009$ in women). The negative association between fitness and abdominal obesity is independent of BMI (Ross & Katzmarzyk, 2003). Furthermore, two cross-sectional studies found that fit men had lower visceral adipose tissue compared to unfit men for a given BMI, suggesting that the potential effect of cardiorespiratory fitness to ameliorate the health risks associated with obesity may be, in part, mediated through a less abdominal adiposity (Arsenault et al., 2007; Wong et al., 2004). This is especially important, given that abdominal obesity remains a significant predictor of prediabetes, T2DM, and CVD when compared to BMI (Freemantle, Holmes, Hockey, & Kumar, 2008; C. M. Lee, Huxley, Wildman, & Woodward, 2008; Yang et al., 2011).

Research on fitness among individuals with prediabetes, however, is sparse. Only one study suggests that fitness was reduced among high-risk individuals for T2DM,

defined as individuals aged 20 to 65 years, with a family history of T2DM or a history of gestational diabetes, and/or presence of one to three risk factors for T2DM, including obesity, hypertension, and dyslipidemia, but without all the major components of metabolic syndrome (Leite et al., 2009). After matching for sedentary behavior, age, gender, and BMI, compared to controls, those with fewer T2DM risk factors, individuals at high risk for T2DM had a 15% lower fitness than controls ($p<0.001$). Fitness also had a significant inverse relationship with insulin resistance ($r=-0.3$, $p<0.0001$) (Leite et al., 2009), and a significant positive relationship with insulin sensitivity ($r=0.25$, $p=0.005$) (Messier, Malita, Rabasa-Lhoret, Brochu, & Karelis, 2008). Therefore, the determination of fitness is of particular importance in overweight/obese adults with prediabetes since lower fitness level is associated with higher risk for CVD and insulin resistance.

Large prospective cohort studies of diverse populations have consistently shown that low fitness is associated with long-term cardiovascular events and all-cause mortality (Barlow et al., 2012; Lyerly et al., 2009; Rankinen et al., 2007). Fitness was determined by maximal graded exercise treadmill tests in all of these studies. Across 3 decades of follow-up in the general population, those in the 15% of low-fit (quintile 1) compared to 6% in the high-fit (quintile 5) individuals were significantly linked to experience death ($p<0.001$). High fitness is associated with a significant reduction in long-term CVD among individuals identified as low risk by the Framingham Risk Score. There was an incremental decrease in CVD risk with increasing fitness quintile, such that the high fit had the lowest adjusted 30-year CVD mortality rate (HR: 0.29 [95% CI: 0.16-0.51]) compared to the low fit (Barlow et al., 2012). Similar results of an inverse association between fitness and all-cause mortality risk have been reported among women with IFG.

In this study, fitness was defined categorically as low fitness (bottom 20%), moderate fitness (middle 40%), or high fitness (upper 40%) according to the previously published Aerobics Center Longitudinal Study guidelines (American College of Sports Medicine, 2013). Women with moderate or high fitness were at lower risk of mortality (moderate fitness, 35% lower; high fitness, 36% lower) than those with low fitness (Lyerly et al., 2009). Therefore, low fitness may be an independent predictor for long-term cardiovascular events and all-cause mortality.

Findings from several observational studies show that only obese, unfit individuals, but not obese, fit individuals, are at a higher risk for cardiometabolic disease and mortality than are normal weight fit individuals (Farrell, Fitzgerald, McAuley, & Barlow, 2010; S. Lee et al., 2005; McAuley et al., 2014; McAuley, Artero, et al., 2012; McAuley, Smith, Emerson, & Myers, 2012; Sui et al., 2007). For example, subjects were grouped by metabolic equivalents: unfit (lowest third) and fit (upper two-thirds), and by BMI: non-obese (BMI: 18.5-29.9 kg/m^2) and obese (BMI$\geq$30.0 kg/m^2). In multivariate analysis, mortality risk for obese/fit men did not differ significantly from non-obese/fit reference group, controlling for age, ethnicity, hypertension, hypercholesterolemia, family history of coronary artery disease, and cardiovascular medication use. However, compared to the reference group of non-obese/fit men, non-obese and obese unfit men were 2.2 ($p=0.01$) and 1.9 ($p=0.03$) times more likely to die, respectively (McAuley, Smith, et al., 2012). Evidence from these studies has shown that higher levels of fitness afford greater protection against morbidity and mortality attributable to obesity.

Methodological limitations among these studies preclude comparison of these study results. Although fitness can be measured in epidemiological research and clinical

practice, important differences exist in how fitness is defined and captured. Therefore, fitness has been defined with varying cutoff points based on different protocols to discriminate fit from unfit participants in these studies. In sum, previous studies showed that higher fitness may decrease the risk for long-term cardiovascular events and the premature mortality risk in both non-obese and obese individuals. However, an agreement on the cutoff values are needed to best discriminate the fit and unfit individuals and facilitate the comparisons of the study results.

Psychological Risk Factor

Depressive symptoms.

A growing body of research has indicated depression as a risk factor for the development of T2DM (Engum, 2007; Mezuk, Eaton, Albrecht, & Golden, 2008). A prospective population-based cohort study with a follow-up period of 10 years in Norway reported approximately 1.51 times ($p<0.001$) higher risk of developing T2DM among those with depression and anxiety compared to those without depression and anxiety (Engum, 2007). This relationship was consistent, independent of other established risk factors for T2DM, such as socioeconomic status, lifestyle factors, and markers of the metabolic syndrome (Engum, 2007). The results from this study have been consistently replicated in other investigations. For example, a recent meta-analysis of seven studies showed that depression was associated with a 60% elevated risk for T2DM over the lifespan (Mezuk, Eaton, Albrecht, et al., 2008). Based on 9 longitudinal studies, another meta-analysis concluded that compared with non-depressed controls, people with depression had a 37% increased risk of developing T2DM (Knol et al., 2006). In addition, the risk of developing T2DM associated with depression was higher for people who had

less than a high school education compared to those who had attended some college or vocational school (Mezuk, Eaton, Golden, & Ding, 2008). The underlying mechanism, such as socioeconomic status, that contributes to higher risk for T2DM with depression has not been well studied and warrant further investigation.

A meta-analysis of 28 longitudinal cohort and case-control studies found that depression was an independent risk factor for the onset of a wide range of CVDs, although this evidence is likely related to the high level of heterogeneity among the included studies. Among 8 studies that assessed the risk of depression and the onset of myocardial infarction, the results showed that individuals with depression were more 1.6 times more likely to develop myocardial infarction compared to individuals without depression. This meta-analysis concluded that clinically diagnosed major depressive disorder was the most important risk factor for developing subsequent CVD (OR=2.54; 95% CI: 2.07-3.10, I^2=0%) (Van der Kooy et al., 2007).

Only a paucity of studies has examined the prevalence of depression among prediabetic individuals, but the results have been mixed, depending on the study population. One cross-sectional study reported that the prevalence of depression in prediabetic participants varied by gender, with more prediabetic women being depressed (Adriaanse et al., 2008). There was a gradual rise in the prevalence of depression according to level of glucose intolerance. The prevalence of depression among urban residents of southern India was 13.1%, 15.7%, and 19.7% among those with normal glucose level, prediabetes, and T2DM, respectively (Poongothai et al., 2010). In contrast, a number of cross-sectional studies comparing the prevalence of depression along the continuum of glucose tolerance categories do not support these findings. Several

investigators have found the prevalence of depression not to differ significantly by level of glucose intolerance or diagnosis of T2DM (Icks et al., 2008; Knol et al., 2007; Mantyselka et al., 2011). Based on limited data available, it appears that prevalence of depression among patients with prediabetes is relatively low. At baseline, only 10.3% of DPP cohort participants had mild depression, and 2.7% of them had a moderate level of depression when measured by the Beck Depression Inventory-II (BDI-II) (Rubin et al., 2008). In another study, the reported prevalence of moderate-to-severe depressive symptoms was 7% (Rhee et al., 2008), which was similar to that (6.7%) in the general population (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Due to the varying methods to measure depression and the conflicting results, additional studies, especially those that are longitudinal, may help investigators understand these complex relationships between prediabetes, depression, and CVD risk.

A potential association between depression and overweight/obesity is supported by data primarily from cross-sectional studies. A recent systematic review reported a weak association between obesity and incidence of depression, especially in women (Atlantis & Baker, 2008). Another recent meta-analysis of 17 community-based cross-sectional studies in the general population demonstrated a significant association between depression and obesity (OR=1.26, 95% CI: 1.17-1.36, $p \leq 0.001$) (de Wit et al., 2010). A systematic review and meta-analysis of 15 longitudinal studies found that obesity and overweight at baseline increased the risk of depression at follow-up, with unadjusted OR 1.55 ($p<0.001$) and 1.27 ($p<0.01$), respectively. Depression at baseline increased the odds for obesity (OR=1.58, $p<0.001$) but not overweight (Luppino et al., 2010). Although overweight/obesity with and without prediabetes are both associated with depression,

evidence on which patients present with greater psychological CVD risk is currently lacking. The current study will help address this gap.

Although some meta-analyses and systematic reviews provide firm evidence of a reciprocal relationship between depression and obesity, the mechanisms that link the two conditions are complex and elusive. Evidence from prior research supports inflammatory markers as a possible mediator between overweight/obesity and depression (Luppino et al., 2010). As previously noted, overweight/obesity has been frequently associated with low-grade, chronic systemic inflammation, with elevated levels of inflammatory markers (Bastard et al., 2006), which in turn have been associated with an increase in depression incidence in a number of observational studies (Bremmer et al., 2008; Miller, Stetler, Carney, Freedland, & Banks, 2002; Penninx et al., 2003). Significantly higher concentrations of CRP, TNF-α, and IL-6 were found in patients with major depressive disorder than normal, non-depressed subjects in two recent meta-analyses (Dowlati et al., 2010; Liu, Ho, & Mak, 2012). Remission from depressive episode is associated with decreased levels of inflammatory markers. The serum concentrations of interleukin-1beta and IL-6 decreased in response to selective serotonin reuptake inhibitors in a meta-analysis of 22 studies (Hannestad, DellaGioia, & Bloch, 2011). In this study, the relationship between depressive symptoms, biological factors, and obesity in prediabetic individuals will be studied over time which may provide greater insight into these complex relationships in this population.

Health Outcomes

Lowered CVD Risk.

Biological risk factors.

Improved lipid profile.

The similar lipoprotein pattern seen in overweight/obesity and in overweight/obesity with prediabetes suggests that the possibility of applying similar preventive interventions to reduce the cardiometabolic risk for both patient populations. Weight loss and long-term maintenance of a reduced body weight are important but difficult objectives to achieve for most overweight/obese patients (Tonstad & Després, 2011). Of particular note is the moderate weight loss achievable through intensive, structured lifestyle modifications, which are associated with improvements in lipids and lipoproteins (Lindström et al., 2003; Orchard et al., 2013). The following paragraphs now focus on approaches to treatment and reduction of cardiovascular risk by lifestyle interventions.

Despite the high number of lipid abnormalities among overweight/obese adults with prediabetes, very limited studies have investigated the long-term effects of CVD risk reduction achieved by lifestyle interventions. At the 3 year follow-up of the DPP clinical trial, total cholesterol and LDL-C levels were similar among the three comparison groups in the DPP study. Significantly lower TG levels, however, were found in the intensive lifestyle group (-0.296 mmol/l [-25.4 mg/dl]) than in the controls (-0.13 mmol/l [-11.9 mg/dl]) and metformin (-0.08 mmol/l [-7.4 mg/dl]) group. The HDL-C levels were also significantly increased in the lifestyle group (+0.026 mmol/l [+1.0 mg/dl]) compared with the metformin (+0.008 mmol/l or [+0.3 mg/dl]) and control (-0.002 mmol/l [-0.1 mg/dl]) groups. Consistent with reduction in lipid levels, the need for hypolipidimic medications was the lowest among subjects assigned to the intensive lifestyle arm (12%) compared to

those assigned to metformin (16%) and placebo (16%) groups at year 3 (Ratner et al., 2005).

In addition to the DPP clinical trial, the FDPS Research Group also reported changes in lipid profiles in response to lifestyle interventions in a 3-year follow-up report (Lindström et al., 2003). There were significantly greater improvements in serum total cholesterol-to-HDL-C ratio (-0.4 vs -0.1), and TG levels (-0.2 vs -0.0 mmol/l) in the intervention group compared to controls at year 3. The findings of both the DPP and the FDPS clinical trials (Lindström et al., 2003; Ratner et al., 2005) provide evidence of the favorable effects structured lifestyle interventions may have on lipid profiles among overweight/obese prediabetics in the short-term.

The Diabetes Prevention Program Outcomes Study (DPPOS) was designed as a follow-up study of the original participants enrolled in the DPP clinical trial. The DPPOS followed the DPP subjects in their original groups and examined the impact of long-term risk reduction on diabetes-related complications. The DPPOS protocol provided quarterly group lifestyle sessions to all participants and an additional two group classes annually to the original DPP intensive lifestyle intervention participants. Those randomly assigned to metformin continued taking 850 mg of the medication twice a day unless T2DM occurred (Orchard et al., 2013).

A recent study using the DPPOS data with 2766 out of 3234 DPP enrollees reported that all three treatment groups experienced significant improvements in LDL-C, TG, and HDL-C from DPP baseline to 10-year follow-up (i.e., year 5 of the DPPOS), with serum LDL-C, TG concentrations decreased 0.51 to 0.6 mmol/l, 0.23 to 0.25 mmol/l, respectively, and HDL-C levels increased 0.14 to 0.15 mmol/l. However, there were no

differences among all three treatment groups, indicating each had a similar effect in lipid levels (Orchard et al., 2013). Consistent with the previous report in the DPP clinical trial (Ratner et al., 2005), at year 5 of follow-up, lipid-lowering (p=0.01) and antihypertensive medication (p=0.09) use were the lowest in the lifestyle group compared to metformin and control groups (Orchard et al., 2013).

Similar results have also been reported among overweight/obese adults with or without associated comorbidities. A meta-analysis of 30 randomized controlled trials concluded that at an average of 3-year follow up, compared with standard care, lifestyle interventions significantly reduced body weight, waist circumference, blood pressure, blood lipids, and blood glucose in overweight/obese individuals. A subgroup analysis performed in overweight people with cardiovascular risk factors found that compared with standard care, lifestyle interventions improved lipid profile with the exception of TG and HDL-C. The difference in means was -0.35 mmol/l in total cholesterol (p<0.0001), 0.01 mmol/l in HDL-C (p=0.798), -0.27 mmol/l in LDL-C (p=0.001), -0.24 mmol/l in TG (p=0.087) (Galani & Schneider, 2007). Although these studies provide robust evidence to support lifestyle interventions as an effective means for lipid management in overweight/obese individuals, whether the positive changes would translate into clinically meaningful reductions in cardiovascular events remains to be determined. It is also not clear whether overweight/obese individuals with prediabetes or without prediabetes would experience similar beneficial changes in lipid profile after enrolling in a health partner program. This study will help fill this gap by examining the longitudinal effects of such a program on lipid abnormalities associated with overweight/obesity in these people as an exploratory aim.

Improved inflammatory profile.

The potential to lower the risk profile of inflammatory markers among overweight/obese adults with prediabetes by lifestyle interventions have been demonstrated in the DPP clinical trial. In men, lifestyle interventions reduced CRP by 33% from baseline to 1 year, compared with only 7% in the metformin group. In women, changes in CRP from baseline to follow-up were -29% in the lifestyle group, compared with -14% in the metformin group. A modest decrease in fibrinogen (-2%) was also observed in the lifestyle intervention group, compared with -0.3% in the metformin from baseline to 1 year (Haffner et al., 2005). Based on limited data, lifestyle interventions appear to be equally effective as medication for reducing inflammatory risk profile among prediabetics (Haffner et al., 2005). The decrease in CRP in response to lifestyle interventions in the DPP was similar to the effects observed in the FDPS (Herder et al., 2009). In the FDPS, there was a significant decrease in CRP in the intervention group from baseline to 1 year compared to control group, with mean change -1.24 mg/l ($p<0.001$) and -0.38 mg/l ($p=0.12$), respectively. Likewise, lifestyle interventions reduced IL-6 levels in the intervention group (mean change: -0.4 pg/ml, $p=0.06$), while IL-6 levels increased in the control group (mean change: +0.22 pg/ml, $p=0.27$) from baseline to 1 year (Herder et al., 2009). However, the short-term follow-up of both studies precluded any further observation and analyses on how inflammatory markers would change in response to the interventions.

In another randomized controlled trial with 120 healthy, obese, premenopausal women (BMI≥30), marked reductions in circulating levels of IL-6 (-1.1 pg/ml; $p=0.009$), IL-18 (-57 pg/ml; $p=0.02$), and CRP (-1.6 mg/l; $p=0.008$), as well as a significant

increase in adiponectin (2.2 μg/ml; p=0.01) have been observed at the 2-year follow-up in the intervention group receiving detailed weight loss advice compared to a control group receiving general information about healthy food choices and exercise (Esposito et al., 2003). Weight loss has been found to be a strong predictor of reduced level of CRP. A systematic review based on 33 studies showed that for each kilogram of weight loss, there was a mean decline in CRP by 0.13 mg/l (Selvin, Paynter, & Erlinger, 2007). Although weight loss was related to a decline in CRP across all types of interventions, the relationship between weight loss through lifestyle interventions alone and changes in CRP level was only 0.30, a relatively small effect size. In contrast, weight loss induced by other means, such as bariatric surgery, which was the most pronounced weight change, typically -30 kg to -45kg, are more likely to produce the highest magnitude of change in CRP level (-5 to -10 mg/l) (Selvin et al., 2007). Further research is needed, however, to determine if intensive lifestyle interventions can be generalized to routine community settings as well as the benefits of these programs on inflammatory markers known to enhance disease progression and heighten future CVD risk among overweight/obese individuals with and without prediabetes.

Improved metabolic profile.

Insulin resistance

Since insulin resistance is a major hallmark of prediabetes, a number of clinical trials have examined the changes in insulin resistance in response to structured, intensive lifestyle interventions. At baseline, the mean insulin resistance, as assessed by the HOMA-IR, was 7.1, 7.2, and 7.0 for placebo, metformin, and lifestyle intervention groups, respectively. After 1-year post-intervention, HOMA-IR increased by 5.1% in

placebo group, while it decreased by 15.3% and 22.7% in metformin and lifestyle intervention groups, respectively ($p<0.001$) (Haffner et al., 2005). Similar results have also been reported in the FDPS over four years of treatment, with the magnitude of improvement strongly related to changes in body weight (Uusitupa et al., 2003). Although there was no significant difference in changes in insulin sensitivity between treatment groups, insulin sensitivity tended to be higher in the intervention group than in the control group (the difference between the mean values 36%; $p=0.067$). Further scrutiny of the data revealed that improvement in insulin sensitivity strongly related to the weight loss ($r=-0.628$ and $r=-0.710$ for intervention and control groups, respectively, $p<0.001$ for both groups) (Uusitupa et al., 2003).

In addition, findings from the Chinese Da Qing Study not only confirmed the data from the DPP and the FDPS clinical trials (Haffner et al., 2005; Uusitupa et al., 2003), showing the beneficial effects of lifestyle interventions on improving insulin sensitivity among prediabetic individuals, but also demonstrated that the potential to delay the onset of T2DM by lifestyle interventions differed according to the degree of both insulin resistance and insulin sensitivity at baseline (Li et al., 2002). The greatest effects were found among those with less insulin resistance at baseline, as evidenced by an approximately 50% decrease in the incidence of T2DM among this group of people, whereas an approximately 30% decrease in incidence of T2DM among those with higher insulin resistance, compared to that in the control group (Li et al., 2002). This study suggests that in addition to lifestyle interventions, other strategies aimed to improve insulin sensitivity, such as pharmacological interventions, may be required for prediabetic individuals with higher degree of insulin resistance at baseline. Because the DPP, the

FDPS, and the Chinese Da Qing Study were not designed to examine CVD outcomes, the effects on some hard endpoints, such as cardiovascular events and death, cannot be assessed. Nevertheless, given the importance of the effect of insulin resistance on the cardiovascular risk profile among prediabetics, which is illustrated in the DPP study (Diabetes Prevention Program Research Group, 2005), one can assume that effects of lifestyle interventions on insulin resistance are likely to be important for CVD prevention.

Lifestyle interventions are the first-line treatment in obese people to reduce body weight and risk for adiposity-related disorders. So far, four studies have investigated the effectiveness of lifestyle interventions in individuals with different risks for metabolic disorder, and the results are mixed. In a study by Gilardini and colleagues (2012), 263 obese women and 93 obese men underwent 3 month lifestyle interventions with hypocaloric low fat/high protein diet and physical activity 30 min/day. Although an increase in insulin sensitivity was observed among insulin-resistant, obese patients, a decrease in insulin sensitivity was found in the insulin-sensitive phenotype of obesity (Gilardini et al., 2012). Similar results were also reported by Karelis and colleagues (2008). However, the reason is not well understood and requires further investigation of the possible mechanism(s) involved (Gilardini et al., 2012; Karelis, Messier, Brochu, & Rabasa-Lhoret, 2008).

In a study by Kantartzis and coworkers (2011), a total of 103 non-diabetic obese individuals, who were stratified as having metabolically healthy obesity (upper quartile of insulin sensitivity) or as being insulin-resistant obesity (lower three quartiles of insulin sensitivity), participated in a 9-month lifestyle intervention program. Although a decrease in visceral fat was found in both groups and insulin sensitivity improved significantly

only among insulin-resistant, obese patients, insulin sensitivity did not change in metabolically healthy obese men and women (Kantartzis et al., 2011). In a study by Janiszewski and Ross (2010), improvement in insulin sensitivity was observed in metabolically healthy obese adults (defined in this study as the presence of abdominal obesity but no more than one component of the metabolic syndrome) and in the obese at-risk individuals (defined as the presence of abdominal obesity and more than one components of metabolic syndrome) receiving a 3 to 6 month lifestyle intervention ($p<0.05$), but the improvement was greater in the obese at-risk individuals ($p<0.05$) (Janiszewski & Ross, 2010). Post-intervention insulin sensitivity was lower among obese at-risk individuals than that found among participants with metabolically healthy obesity in some studies (Janiszewski & Ross, 2010; Kantartzis et al., 2011; Karelis et al., 2008), but not others (Gilardini et al., 2012).

Taken together, these lines of evidence suggest that the metabolic benefits from weight loss vary depending on the metabolic phenotype of obesity. However, researchers have used different criteria to define metabolically healthy individuals and obese at-risk individuals, which complicates the comparison and interpretation of the study results. Future studies are needed to investigate the long-term effects of lifestyle interventions on insulin sensitivity and cardiovascular events among both metabolic phenotypes of obesity.

Microalbuminuria

Studies examining the effect of structured lifestyle interventions to lower microalbuminuria among overweight/obese individuals with prediabetes are very limited. After a mean of 3.4 years of the DPP clinical trial, of the 2802 participants had urine albumin-to-creatinine ratio measurement at both baseline and the end of study, the

percentage of albuminuria declined from 6.2% at baseline to 6.1% at the end of the study, with no significant differences between the treatment groups. There were minimal but not significant differences in the frequency of albuminuria among the groups: 6.3%, 6.7%, and 5.4% for control, metformin, and lifestyle intervention group, respectively. Low statistical power, shorter follow-up period, and relatively small numbers of individuals who had microalbuminuria at baseline precluded the researchers to detect small changes in the lifestyle intervention group. Further analysis of change in albuminuria for each group showed that the net change from normal to albuminuria were 9, 0, and -12 for control, metformin, and lifestyle intervention group, respectively. Although this difference was not statistically significant ($p=0.07$), the results showed that there were greater improvements in the lifestyle intervention group compared to metformin and control groups (Diabetes Prevention Program Research Group, 2009). It is unclear however, whether the results of the DPP clinical trial can be replicated with a health partner program among overweight/obese prediabetics in community settings. An exploratory aim of the current study will provide greater insight of the feasibility and effectiveness of such a program.

A similar study was conducted in overweight/obese individuals without prediabetes. A 12-month combined lifestyle modification and metformin intervention was effective in decreasing urinary albumin excretion that was below the conventionally accepted threshold of microalbuminuria in obese non-diabetic subjects (Cubeddu, Alfieri, & Hoffmann, 2008). Both groups received the lifestyle modification and metformin intervention. Group I consisted of people with urinary albumin excretion of less than 10 mg/day, and group II consisted of people with urinary albumin excretion of 10-29 mg/day.

Although the intervention induced comparable reductions in obesity, blood pressure, lipids, and insulin levels in both groups, urinary albumin excretion was significantly reduced in group II (N=18) (9.1+/-1.8 mg/24 h; 60% reduction; $p<0.001$), and non-significantly in group I (N=23) (0.75+/-0.5 mg/day; 12% reduction; $p>0.1$). Although this study shed lights on the promising strategy to reverse urinary albumin excretion among healthy overweight/obese individuals without prediabetes, the quasi-experimental design without randomization provides little basis for inference about the impact of lifestyle modification and metformin intervention on the beneficial changes in urinary albumin excretion. Furthermore, the small sample size precluded meaningful subgroup analysis, which was important, given that other factors might have contributed to the change.

Physical risk factors.

Improved physical activity level.

Large prospective cohort studies of diverse population have clearly shown that an energy expenditure of approximately 1000 kcal/week of moderate-intensity physical activity for about 150 minutes/week is associated with lower rates of CVD and premature mortality (I. M. Lee, Rexrode, Cook, Manson, & Buring, 2001; Manson et al., 2002; Sesso, Paffenbarger, & Lee, 2000; Tanasescu et al., 2002). However, significant risk reductions for CVD and premature mortality begin to be observed at volumes below the recommended amount of energy expenditure, starting at approximately 500 kcal/week (Manson et al., 2002; Sesso et al., 2000; Tanasescu et al., 2002).

The impact of physical activity on traditional risk factors for CVD has been well studied among adults with T2DM. A meta-analysis of 34 studies concluded aerobic exercise alone or combined with resistance training significantly reduced systolic blood

pressure by 6.08 mm Hg and 3.59 mm Hg, respectively (95% CI: -10.79 to -1.36 mm Hg and -6.93 to -0.24 mm Hg, respectively), and TG by 0.3 mmol/l (95% CI: -0.48 to -0.11 mmol/l and -0.57 to -0.02 mmol/l, respectively) among patients with T2DM. Waist circumference was also significantly improved -3.1 cm (95% CI: -10.3 to -1.2 cm) with combined aerobic and resistance exercise (Chudyk & Petrella, 2011). Research on the effects of physical activity on CVD risk among prediabetics is very limited and yielded inconsistent findings. Significantly lower systolic, diastolic blood pressures, and body weight was reported in one randomized controlled trial (Wu, Hwang, Chen, & Chuang, 2011), but not others (Yates, Davies, Gorely, Bull, & Khunti, 2009). Data on the influence of physical activity on risk factors for CVD among prediabetics are lacking. The proposed study will help fill this gap by examining the longitudinal effects of lifestyle interventions on CVD risk in overweight/obese individuals with and without prediabetes as an exploratory aim.

Improved cardiorespiratory fitness.

Despite the importance of fitness in affording greater protection against morbidity and mortality attributable to obesity, no studies have examined the potential benefits of structured lifestyle interventions on improving fitness among overweight/obese adults with prediabetes and without prediabetes. Similar studies however, have been conducted among overweight/obese adults with T2DM reported in the Look AHEAD (Action for Health in Diabetes) clinical trial (Jakicic et al., 2009). In the Look AHEAD trial, 5145 overweight or obese people with T2DM were recruited from 16 centers in the U.S. (Ryan et al., 2003). The mean age of the participants was 58.7 years, and the mean BMI was 36 kg/m^2. Within each center, the participants were randomly assigned to an intensive

lifestyle intervention program or to diabetes support and education group. Participants in the intensive lifestyle intervention group received a calorie-controlled diet and were asked to participate in moderate-intensity physical activity for 175 minutes/week over a four-year period. The diabetes support and education participants were given three educational sessions related to diet/nutrition, exercise, and social support each year for four years after randomization and they served as an attention control group for the study.

Fitness was significantly improved in overweight diabetic adults in the lifestyle intervention group compared to diabetes support and education group in the Look AHEAD clinical trial (20.9% vs 5.7%; $p<0.0001$). However, structured lifestyle interventions may have varying effects on improvement in fitness among adults with different BMI categories. The differences achieved in fitness was lower in individuals with higher baseline BMI, individuals with class II (BMI: 35-39.9 kg/m^2) and III (BMI$\geq$40 kg/m^2) obesity had significantly lower improvement in fitness compared to overweight counterparts (BMI: 25-29.9 kg/m^2) after 1-year follow-up.

The Look AHEAD Research Group also reported beneficial effects on fitness by structured, intensive lifestyle interventions in the 4-year follow-up research report (Jakicic et al., 2013). At the 4-year follow-up, the difference in percent fitness change between lifestyle intervention group and diabetes support and education group was significant after adjustment for baseline fitness and change in weight (3.70% vs 0.94%; $p<0.01$). The improvement in fitness was inversely related to change in HbA1c after adjustment for clinical site, treatment, baseline HbA1c, prescribed diabetes medication, baseline fitness, and weight change ($p<0.01$). Nevertheless, because physical activity is primarily a non-genetic determinant of fitness (American College of Sports Medicine,

2013), one can assume that a health partner program aimed at increasing physical activity is likely to increase fitness and be important for CVD prevention among overweight/obese individuals with and without prediabetes.

Psychological risk factor.

Reduced depressive symptoms.

Despite the potential association between depression and overweight/obesity, few studies have examined the potential benefits of structured, intensive lifestyle interventions on alleviating depressive symptoms among overweight/obese adults with prediabetes, and the results are contradictory. On the one hand, in the DPP clinical trial, participation in the structured, intensive lifestyle interventions was not associated with changes in depressive symptoms. Depression was measured in terms of BDI scores ≥11, which was used as a threshold for mild depression, current use of antidepressant medications, and either BDI scores ≥11 or current use of antidepressant medications. On study entry, 10.3% of participants had BDI scores ≥11, 5.7% took antidepressant agents, and 0.9% had both indicators. After an average follow-up of 3.2 years, while the prevalence of elevated depressive symptoms reduced from 10.3% to 8.4%, the proportion of antidepressant agent users increased from 5.7% to 8.7%, leaving the proportion with either marker unchanged. The time trends were not significantly associated with the DPP treatment arms for either men or women, indicating that the trends were similar for the three treatment arms. However, at annual visit of year 2 and 3, the proportion of participants in the intensive lifestyle intervention arm with either depression marker was still lower than that in the placebo arm. Weight loss was associated with a small but

significant reduction in elevated depressive symptoms (OR=0.975 kg, 95% CI: 0.960-0.990) (Rubin et al., 2005).

On the other hand, the FDPS Research Group demonstrated the beneficial effects of structured, intensive lifestyle interventions on improvement in depressive symptoms among middle-aged study participants, who were overweight or obese and had IFG/IGT. After 3-year follow-up, favorable changes in depressive symptoms, as measured by the Finnish version of the BDI, were observed in the intervention group. Although there was no significant difference in changes of the BDI scores between the study groups (p=0.965), BDI scores decreased more in the lifestyle intervention group (0.90±4.54; 95% CI:-1.99 to -0.19) than in in the control group (0.75±4.47; 95% CI: -1.80 to 0.31). With the same cutoff (BDI≥11) that was used in the DPP clinical trial, the prevalence of depressive symptoms was higher both at baseline (21.4%) and at year 3 (15.7%) compared to the DPP. However, the use of antidepressants was uncommon both at baseline (2.3%) and at 3-year visit (3.6%). This was because during the FDPS in the 1990s, it was not common to treat mild depression with medications in Finland. Therefore, the use of antidepressants was not likely to affect study outcomes, so the change in depression was most likely can be attributed to lifestyle interventions alone. Consistent with the prior studies of the reciprocal relationship between depression and obesity and the findings of the DPP clinical trial, multivariate regression analysis showed that weight loss was one of the strongest predictors for the decrease in BDI scores (Ruusunen et al., 2012).

Similar to the FDPS, results from the Look AHEAD clinical trial have also provided provisional support for the additional benefits lifestyle interventions have on

depressive symptoms among 5145 overweight T2DM adults. A greater decrease in depressive symptoms measured by the BDI-II measured was observed in the lifestyle intervention group (-0.83±4.86, $p<0.001$) compared to the diabetes support and education group (-0.23±4.63, $p<0.001$) after 1-year follow-up. In line with the reciprocal relationship between depression and obesity, in this study, the improvement associated with structured lifestyle interventions in these subjects was mediated by weight loss (Williamson et al., 2009). Longer follow-up is required to evaluate the longitudinal effects of lifestyle interventions on depression level in this population.

The difference in measures of depression might explain the different results of these studies. If only depressive symptoms measured by the BDI were considered in the DPP clinical trial, the researchers might have concluded that lifestyle interventions would result in decreased depressive symptoms, which was consistent with the findings from the FDPS and the Look AHEAD clinical trials. However, including antidepressant medication use as another depression marker suggested no effect of the intervention on the prevalence of depression in the DPP clinical trial. In conclusion, evidence to support the use of structured, intensive lifestyle interventions as an effective strategy to alleviate depressive symptoms among overweight/obese adults with prediabetes is inconsistent, and this warrants further investigation.

An accumulating body of research suggests that depressive symptoms can be alleviated with regular exercise in the general population. A recent meta-analysis synthesizing the effect of 70 physical activity intervention studies on depressive symptom outcomes found that the standardized effect size between intervention versus control group was 0.372 among 38 supervised physical activity studies and 0.522 among 22

unsupervised physical activity studies (Conn, 2010). Physical activity interventions reduced mild to moderate depressive symptoms among adults without clinical depression (Conn, 2010). Three earlier systematic reviews of clinically depressed men and women of all age groups found a substantial decrease in depressive symptoms following short and long-term courses of physical activity (Craft & Perna, 2004) and reduced depressive symptoms among the aged (Blake, Mo, Malik, & Thomas, 2009). Based on these studies, a health partner program aimed at increasing physical activity may alleviate depressive symptoms among overweight/obese individuals without prediabetes.

Improved Health Status.

A major limitation of prior diabetes prevention clinical trials is a lack of reports on health status, with the exception of the DPP study. One cross-sectional study reported that there was a gradual decrease in the mean scores on health status measured by the Medical Outcomes Study Short Form (SF-36), indicating worse health status across those with normal blood glucose, prediabetes, and T2DM (Tapp et al., 2006). Individuals with IGT and T2DM were 44% and 46% more likely respectively, to report a reduced health status on physical and social functioning compared to those with normal blood glucose. Another cross-sectional study found that individuals with IFG scored statistically lower compared to those with normal blood glucose in the SF-36 on the bodily pain and the physical functioning subscales (Chittleborough, Baldock, Taylor, Phillips, & North West Adelaide Health Study Team, 2006). Based on limited existing evidence, these findings indicate that health status may begin to decline at the prediabetic stage and support an important need for further study of health status in this population.

After adjusting for established risk factors that influence health status, obesity has been shown to be a strong predictor of worse health status in the general population. Health status decreases with increasing BMI, with those with severe obesity having the lowest health status (Jia & Lubetkin, 2005). One study using cross-sectional data from a national representative sample found that compared to normal-weight respondents, individuals with severe obesity had significantly lower scores on the 12-item Short Form physical and mental summary scores, EuroQol EQ-5D index, and visual analogue scale. Persons with moderate obesity or overweight also had significantly lower health status scores on the 12-item Short Form physical summary scores and EuroQol EQ-5D index (Jia & Lubetkin, 2005).

Similar findings of a negative association between BMI and health status have also been reported in another cross-sectional study (Hassan, Joshi, Madhavan, & Amonkar, 2003). Morbidly obese (OR=1.87, 95% CI: 1.64-2.12) and obese (OR=1.21; 95% CI: 1.09-1.33) were more likely to experience greater than 14 unhealthy days that negatively affected the physical health domain compared with normal-weight respondents. In addition, morbidly obese (OR=1.41; 95% CI: 1.26-1.59) and obese (OR=1.17; 95% CI: 1.07-1.28) were also more likely to experience greater than 14 unhealthy days that negatively influenced the mental health domain compared with normal-weight individuals. Finally, morbidly obese (OR=1.73; 95% CI:1.50-1.99) and obese (OR=1.22; 95% CI: 1.08-1.37) individuals were more likely to experience greater than 14 days with activity limitations compared to those of normal-weight. Notably, the greater is the weight, the poorer the health status is among obese individuals. Lifestyle interventions used by obese individuals to lose weight was associated with improved

health status scores across all three domains (Hassan et al., 2003). Although overweight/obesity with and without prediabetes are both associated with a reduced health status, it is not clear which patients present with greater psychological risk.

Studies examining health status in prediabetics are very limited. The DPP clinical trial is one of the first to evaluate the potential treatment effects of structured, intensive lifestyle interventions or metformin on health status in those with prediabetes (Florez et al., 2012). After a mean follow-up of 3.2 years, compared to placebo group, there were significant improvements in the health utility index (+0.008, $p=0.04$) and physical component score of the SF-36 (+1.57, $p<0.0001$) in the lifestyle intervention group but not in the metformin group (+0.002 and +0.15, respectively, $p=0.6$). Participants in the lifestyle intervention group showed improvements in general health (+3.2, $p<0.001$), physical function (+3.6, $p<0.001$), bodily pain (+1.9, $p=0.01$), and vitality (+2.1, $p=0.01$) domain scores as measured by the SF-36 (Florez et al., 2012). The DPP Research Group concluded that lifestyle interventions that resulted in intentional weight loss and increased physical activity had an independent but small to modest association with better health status in overweight/obese participants with prediabetes. In agreement with findings that overweight and obesity are associated with lower health status, the DPP study participants in both intervention groups who experienced weight gain had significant lower scores on physical function, general health, body pain, and vitality domains of the SF-36 compared to those who achieved major weight loss. Weight loss was found to be the most important factor associated with improvement in health status among participants in the DPP clinical trial (Florez et al., 2012).

Similar results of the potential benefits of structured, intensive lifestyle interventions on health status in overweight/obese adults with T2DM were reported in the Look AHEAD clinical trial. Health status was significantly improved in overweight diabetic adults; the largest effect was observed in the SF-36 physical component score (difference=-2.91, 99% CI: -3.44 to -2.37) between the lifestyle intervention group and the diabetes support and education group after 1-year follow-up. Further analyses showed that the improvement associated with structured lifestyle interventions in subjects with T2DM was partially mediated by weight loss, improved physical fitness, and reduction in physical symptoms (Williamson et al., 2009). However, evidence on the potential to improve health status by lifestyle interventions among overweight/obese individuals without prediabetes is scarce. The current study is designed to compare the differences in health status among overweight/obese participants with prediabetes who were enrolled in a health partner program at one year compared to overweight/obese participants without prediabetes.

In summary, the emerging body of evidence from clinical trials suggests that the benefits of structured, intensive lifestyle interventions may not be limited to T2DM prevention only. It is possible that people with prediabetes and T2DM may improve their health status by enrolling in a structured, intensive lifestyle intervention program that results in significant weight loss, which was shown in the DPP and Look AHEAD clinical trials (Florez et al., 2012; Williamson et al., 2009). Data from previous studies suggest that structured, intensive lifestyle interventions can be used to achieve multiple benefits for overweight/obese adults with prediabetes. However, studies integrating the DPP and the Look AHEAD lifestyle interventions to diverse community settings are

limited and few have used a longitudinal design. This study will provide greater insight of the feasibility and effectiveness of similar interventions to enhance health status in community settings.

Summary

The epidemic of T2DM in the U.S. and globally has made diabetes prevention important, despite the fact there continues to be no agreed upon consensus or established, formal guidelines for screening or the treatment of prediabetes (American Diabetes Association, 2014; Grundy, 2012). Prediabetes and overweight/obesity are the leading risk factors for T2DM and CVD and as such are major targets for interventions to reduce the progression to T2DM and subsequent CVD. Although clinical trials of lifestyle interventions have been shown to delay or prevent the onset of T2DM in persons with prediabetes who are overweight or obese, the beneficial effects of such interventions to reduce the biological risk factors that contribute to CVD in prediabetes has not been as well established compared to T2DM. Moreover, the physical and psychological risks and outcomes associated with prediabetes related to CVD development is currently lacking. Because changes in the underlying biological risk factors may precede clinical changes, this has important implications for detecting prediabetes sooner and slowing the progression to T2DM and subsequent CVD. Finally, although structured, intensive lifestyle interventions have brought about substantial changes in a variety of health outcomes related to prediabetes and risk for developing future CVD, the influence on biological risk factors has been modest and inconsistent. The proposed secondary analysis will help fill this void by examining the biological risk factors in a comprehensive database of overweight and obese individuals with and without prediabetes. This analysis is anticipated to clarify the incremental effect of prediabetes

above that observed in overweight/obesity alone on biological factors, physical, and psychological health outcomes that contribute to overall CVD risk.

Chapter Three

Methodology

Introduction

This chapter describes the research design and methodology including a description of the original parent study. This is followed by the current secondary data analysis, sample description, and recruitment strategies that were used. The study procedures are described and a description of the study instruments is provided. In addition, the data analysis techniques used for the primary aim and the exploratory aim are also described.

Research Design

Design

Study design.

A secondary analysis was conducted using the Center for Health Discovery and Well Being (hereafter referred to as "the Center") database at Emory University.

Parent study overview.

The parent study was a quasi-experimental study conducted by the Center. The Center is a clinical site for predictive health care delivery as well as a clinical laboratory for the testing of health-focused care. Participants in the parent study were employees of Emory University in Atlanta, Georgia for a minimum of 2 years. By participating in the study, all participants were eligible to have a health partner to help them achieve their self-directed goals. The Center collected a wide range of biological, physical and psychological variables on all participants at baseline, 6 months and annually thereafter that are available to researchers upon request.

At baseline, participants completed a self-report demographic form, individual and family health history, social/family/spiritual profile, health literacy form, lifestyle profile form, Cross-Cultural Activity Participation Study (CAPS) Typical Week Physical Activity Questionnaire (Ainsworth et al., 1993), Beck Depression Inventory-II (BDI-II) (Beck, Brown, & Robert, 1996), Medical Outcomes Study Short Form (SF-36) (Ware & Sherbourne, 1992), body composition (i.e., height, weight, waist circumference, hip circumference), random urine, maximal oxygen consumption (VO_{2max}), and laboratory blood work for a variety of biological biomarkers, including triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and insulin resistance. At 1 year, participants completed body composition measures, CAPS Typical Week Physical Activity Recall Questionnaire, blood work, VO_{2max}, BDI-II, and SF-36. The time of evaluation for measuring these factors is presented in Table 2.

Upon completing the baseline testing at the Center, each participant was provided the opportunity to collaborate with a health partner who reviewed, interpreted, and advised them about their health status report and goals. The health status report was a summation of their personal data, and both conventional and research-based health data were included. Based on the health status report, the participant had the opportunity to articulate their vision for optimal health and wellness, describing specific goals and strategies they would like to achieve. The health partner and the participant collaborated to establish a tailored health action plan with defined goals and strategies that were achievable and practical for the participants' home and work situation. The health action

plan included interventions chosen by the participant that best addressed their personal needs and lifestyle. Plans were individualized but might include changes in diet or exercise, modification of risk-related behaviors (e.g., tobacco use, alcohol use), and stress reduction techniques such as yoga, interactions with religious leaders, meditation, or other alternative approaches. Although different action plans might yield different results, action plans addressing unhealthy lifestyles and stress reduction may reduce the risk of cardiovascular disease (CVD).

When a health action plan was selected, the health partner interacted by email or telephone with the participant at mutually agreed-upon times to discuss their progress in meeting their health action goals. Modifying the health action plan was an option for participant's who may have had difficulty meeting their goals or those who wanted to try a different approach. The health partner was available as frequently as needed to help the participant achieve or modify their goals throughout the duration of their program. The Center health partners did not provide medical care and participants who required a physician's care, including psychological counseling, were referred to an appropriate medical professional. In addition to their bachelor's or master's degree in a health science or related field, the health partners were required to undergo a customized training curriculum by the professional staff of the Center. Details of this health partner training were not made available in the protocol, so details regarding the length and content of the training are unclear. Upon completing training, health partners had the requisite skills and knowledge to explain the health status report and were taught to employ empathetic and active listening as well as motivational interviewing to help participants identify and achieve their health action goals.

The concept of involving health care professionals other than physicians and nurses in aiding patients' management of chronic diseases has been driven by the recognition that time constraints in a traditional medical care settings do not permit adequate interactions for optimal outcomes (Bodenheimer & Laing, 2007; Handley et al., 2006). The most common term used to describe these care givers uses a sports metaphor, "health coach". Studies indicate that involving a health coach either in the setting of a physician's office (Handley et al., 2006) or in other settings can improve T2DM and hypertension management (Annesi & Unruh, 2007; Hohenadel et al., 2007). In this secondary analysis study, a similar program was used, but the term health partner was chosen to signify mutual collaboration with the participant and a joint effort to alter behaviors in ways that enhance and maintain improvements in health.

Secondary analysis.

At the time the secondary analysis was proposed, the largest amount of data collected was at baseline and at the one-year follow-up period. For these reasons, these two time points, baseline and one year follow-up were selected for the secondary analysis study. Given the study aims for the current study, only the following risk factors were included for the secondary analysis: biological risk factors, including lipid profile (TG, LDL-C, and HDL-C), inflammatory profile (IL-6, IL-8, TNF-α, and CRP), and metabolic profile (insulin resistance and microalbuminuria), physical risk factors (cardiorespiratory fitness and physical activity level), psychological risk factor (depressive symptoms), and health status. The secondary analysis compared the baseline biological, physical and psychological risk factors of overweight/obese adults with and without prediabetes to determine the risk for CVD. Fasting blood glucose (100-125 mg/dl) was used to detect

people with prediabetes. Data were extracted from the de-identified Center dataset based on available fasting blood glucose. Fasting blood glucose was not available for every participant however, and there were some missing data. The reasons participants did not have their blood glucose levels drawn were unclear, but may reflect some limitations in the data. In addition, this study used a quasi-experimental design to examine the effects of a health partner program on biological, physical, and psychological risk factors associated with CVD among overweight/obese adults with and without prediabetes. The Center's standardized collection of biomarkers, lifestyle, and psychological profiles allowed for examination of the biological, physical and psychological risk factors that contribute to CVD risk and whether a health partner program reduced risk in overweight/obese adults with and without prediabetes at 1 year.

Setting and Sample

Parent study.

Data were derived from a de-identified Center database of all active participants provided by the Center coordinator. The Center participants were healthy subjects who were employees of Emory University for a minimum of 2 years at the time of enrollment and were identified by the human resource department for study eligibility. To be eligible, participants had to be free of any acute or life-threatening illness and had to be considered normal for age and gender in relation to their physical performance status. The sampling strategy was a systematic sampling plan where faculty and staff were randomly selected to obtain a representative sample. An alphabetic list of employees was generated and every 10th employee was invited to participate. Identified employees were sent an email invitation to participate as well as information about the Center program. Approximately 30% of solicited employees agreed to be contacted for screening, and

approximately 10% were ultimately enrolled in the Center cohort (Rask, Brigham, & Johns, 2011). In addition, the general public was also invited to participate in the Center program if they met eligibility criteria (detailed below) and maintained their membership. The recruitment strategy, consent forms, and data collection protocols were approved by the Emory University Institutional Review Board (IRB). Informed consent was obtained from all participants prior to enrolling in the Center program as part of the parent study.

Secondary analysis (current) study.

The target population for current study was overweight/obese adults (body mass index [BMI]≥25) with and without prediabetes. The inclusion criteria for Center eligibility were: (a) age 18 and older; (b) no history of hospitalization due to an acute or chronic disease within the previous year (with exception of hospitalization for treatment of accidental trauma); (c) no history of severe Axis 1 psychological disorders within the previous year (e.g., delirium, dementia, schizophrenia, depression, bipolar disorder, hypochondriasis, dissociative disorder); (d) no history of addition of new prescription medications to treat a chronic disease condition (with exception of changes in anti-hypertensive or anti-diabetic agents) within the previous year; (e) no history of substance/drug abuse or alcoholism within the previous year; and (f) employed at Emory University at least part-time for at least two years.

The exclusion criteria were: (a) current active malignant neoplasm; history of malignancy other than localized basal cell cancer of skin during previous 5 years; (b) uncontrolled or poorly controlled autoimmune, cardiovascular, endocrine, gastrointestinal, hematologic, infectious, inflammatory, musculoskeletal, neurologic, psychiatric or respiratory disease; (c) any acute illness (such as viral infection) in previous 12 weeks

before baseline studies; (d) inability to give informed consent. Because all participants were enrolled in the Center health partner program rather than randomization to different treatment arms, it was not possible to compare different intervention strategies or goals (e.g., exercise or weight loss goals) on the outcomes of interest. Therefore, the data analysis included a longitudinal analysis of how the health partner program influenced the health outcomes of interest. The secondary analysis did not require an IRB approval because only de-identified data were used for the analysis (See Appendix D).

Sample Size and Power Calculation

The Power Analysis and Sample Size software was used for sample size calculation. Given the sample size of 625 in January 2011 and current proportions of BMI categories in the dataset (1.5% underweight BMI<18.5, 35.8% normal weight BMI 18.5 to 24.9; 35.3% overweight BMI 25 to 29.9 and 28.9% obese BMI of 30 or greater), it was estimated that there would be approximately 401 overweight/obese subjects (64.2% of 625). Further, according to the findings from the 2005-2006 National Health and Nutrition Examination Survey (NHANES), the crude prevalence of IFG was estimated to be 25.7% and IGT was estimated to be 13.8%, with approximately 30% having either condition (Cowie et al., 2009). Based on the literature and the population in the Center database at the time the secondary analysis was performed, of 401 overweight/obese participants, approximately 120 participants were anticipated to be prediabetic (30%), with the remaining 281 without prediabetes. For these anticipated sample sizes, a small effect size of d=0.31 (Cohen's d) would be detectable at 80% power and at a 5% significance level (Cohen, 1992). However, the actual sample size for individuals with and without prediabetes in the current study was 44 and 297, respectively, in the current

study due to missing blood glucose levels on a number of participants. The reasons participants did not have their blood glucose levels drawn were unclear. Given the sample sizes for the two groups, the effect size possible for a two-group t-test was d=0.45 which is considered a moderate effect size. The Chi-square goodness of fit test showed that the prediabetic group of 44 was unexpectedly small in this sample, relative to the expected population prevalence proportion reported by the NHANES (p=0.001). The unequal sample size greatly limited the ability to accurately estimate power in the sample.

Similarly, for the longitudinal models which considered the 246 subjects who had completed both baseline and 1-year evaluations, 74 were expected to be overweight/obese and prediabetic and 172 were expected to be overweight/obese and non-prediabetes. For these expected sample sizes at 80% power and 5% significance level, it was estimated to detect a small-to-moderate effect size d=0.36 for the group effect and a moderate effect size d=0.42 for the time and group-by-time effects. The actual sample size however, for individuals with and without prediabetes in the current study was 30 and 216, respectively. This presents a lower bound sample size of a minimum of 60 with 30 in each group (assumed equal sample sizes for computing power in a repeated-measures ANOVA model for the group-by-time effect), which increases the detectable effect size to a large d=0.74, which is unlikely for the outcomes evaluated here. Thus, as previously mentioned, the ability to calculate power was also greatly limited by the unequal sample sizes and low sample size of only 30 prediabetics with data at both time points, which led to being underpowered to detect any significant group-by-time effects for the exploratory aim.

Variables, Definitions, and Measures

Overview

The data collection instruments are described, and the relevant reliability and validity information are presented. Variables, instruments, and the time of evaluation are described below in Table 2.

Table 2

Variables, Instruments, and Time of Evaluation

Variables	Measure/Instrument	Number of Items	Time of Evaluation
Participant demographic and clinical information	Age, gender, educational level, marital status, vital signs, health behaviors	15 (10 min)	Baseline only
Overweight/obesity	Height, weight, waist circumference, hip circumference	N/A	Baseline and 1 year
IL-6, IL-8, TNF-α, CRP, TG, LDL-C, HDL-C, insulin resistance microalbuminuria	Serum samples Random urine sample	N/A	Baseline and 1 year
Cardiorespiratory fitness Physical activity	Maximal oxygen consumption (Modified Balke protocol) CAPS Typical Week Physical Activity Recall Questionnaire	N/A Physical activity recall	Baseline and 1 year Baseline and 1 year
Depressive symptoms	BDI-II	21 (10 min)	Baseline and 1 year
Health status	SF-36	36 (10 min)	Baseline and 1 year

Conceptual and Operational Definitions (Instruments)

Age, gender, and educational level were obtained from the standardized self-report demographics, individual and family health history, social/family/spiritual profile,

and health literacy form, to determine adults eligible to participate in the study. These data will be used to fully describe the characteristics of the sample.

BMI was calculated by dividing weight in kilograms by the square of height in meters, kg/m^2. In adults, a BMI of 18.5 kg/m^2 to 24.9 kg/m^2 is considered normal. Overweight is defined as a BMI of 25 kg/m^2 to 29.9 kg/m^2. Obesity is defined as a BMI of 30 kg/m^2 or greater. Weight was measured to nearest 0.1 kilogram and height was measured in centimeters. Body weight and height measures were taken at baseline and annually.

Abdominal obesity was measured by waist-hip ratio (WHR). WHR is the ratio of the circumference of the waist to that of the hips. Abdominal obesity is further defined as WHR above 0.90 for males and above 0.85 for females, or a BMI above 30.0 kg/m^2 (World Health Organization, 2011). According to the World Health Organization (2011), waist circumference should be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, with a stretch-resistant tape that provides a constant 100 g tension. Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor (World Health Organization, 2011). These procedures were used to collect WHR at the Center.

Prediabetes was defined as blood glucose levels higher than normal but not high enough to be diagnosed as T2DM (American Diabetes Association, 2014). In this secondary analysis, presence or absence of prediabetes was determined by fasting blood glucose. An elevated fasting blood glucose level of 100 to 125 mg/dl was considered as a prediabetic state in this study.

Lipid profile (TG, LDL-C, and HDL-C) was measured using commercially available assays (Quest Diagnostics, Madison, New Jersey) at baseline and 1 year for all Center participants. Fasting blood serum samples were collected in the morning after 8 hours fasting. The American Diabetes Association (2015) has set guidelines for TG, LDL-C, and HDL-C levels: TG levels<150 mg/dl (1.7 mmol/l), LDL-C<100 mg/dl (2.6 mmol/l), and HDL-C>40 mg/dl (1.0 mmol/l) in men and>50 mg/dl (1.3 mmol/l) in women as desirable (American Diabetes Association, 2015).

Inflammatory profile (IL-6, IL-8, TNF-α, and CRP) was measured using commercially available assays (Quest Diagnostics, Madison, New Jersey) at baseline and 1 year for all Center participants. IL-6 (<7 pg/ml) (Ravishankaran & Karunanithi, 2011), IL-8 (<8.7 pg/ml) (A. Sun, Wang, Chia, & Chiang, 2005), and TNF-α (1.2 and 15.3 pg/ml) (Elias, Nanda, & Pandian, 2004) are present in a healthy individual in small amounts. In 2003, the American Heart Association and the Centers for Disease Control and Prevention recommended that CRP be regarded as an element of global coronary risk assessment in adults without known CVD. In that recommendation, a CRP cutoff value lower than 1.0 mg/l, between 1.0 and 3.0 mg/l, and higher than 3.0 mg/l was considered to indicate a low risk, average risk, and high risk for CVD, respectively (Pearson et al., 2003). The same cutoff values were applied in the current study. Results of the blood tests were downloaded at the time data were collected into the Center database.

Insulin resistance and microalbuminuria were included as measures of metabolic profile. Insulin resistance was measured by the homeostasis model assessment of insulin resistance (HOMA-IR). HOMA-IR was calculated as fasting plasma glucose (mg/dl)×fasting plasma insulin (μU/ml)/405 (Matthews et al., 1985). A HOMA-IR value

above 2.5 was used to indicate insulin resistance in previous studies in diverse populations (da Silva, Miranda, Chacra, & Dib, 2005; Yamada et al., 2011).

Microalbuminuria is defined as levels of albumin ranging from 30 to 300 mg in a 24-hour urine collection (American Diabetes Association, 2015). In this study, urine albumin-to-creatinine ratio was used to estimate 24-hour urinary albumin excretion and was calculated from a random urine sample that was collected at baseline and annually for all Center participants.

Physical activity level is defined as any bodily movement produced by the skeletal muscle contractions that result in energy expenditure above basal requirements (Caspersen, Powell, & Christenson, 1985). Routine physical activity was measured using the CAPS Typical Week Physical Activity Level Questionnaire (Ainsworth et al., 1993). The CAPS Typical Week Activity Recall Questionnaire was used to measure physical activity level. Specific categories of physical activities (i.e., light, moderate, or vigorous effort) are listed and the participant selected which of these they had performed in the past 7 days in terms of duration, frequency, and intensity. The responses provided are then compared to a Compendium of Physical Activities to determine metabolic equivalents (METs) (Ainsworth et al., 1993). One MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 ml O_2 uptake/kg/min (Jette, Sidney, & Blumchen, 1990).

The CAPS Typical Week Physical Activity Recall Questionnaire has lower than desired reliability (r=0.51) for moderate intensity activities when compared with other physical activity records. Test-retest intra-class coefficients for the CAPS Typical Week Physical Activity Recall Questionnaire are reported to range between 0.55 to 0.75

(Ainsworth, 2000). Vigorous intensity physical activity are associated with higher fitness levels which provides construct validity (r=0.45) (Ainsworth, 2000). The criterion-related validity for this questionnaire was considered poor, with the Spearman correlation coefficient 0.16 between energy expenditures obtained from the doubly labeled water method and those obtained from the CAPS Typical Week Physical Activity Recall Questionnaire among 65 postmenopausal women (Mahabir et al., 2006).

Cardiorespiratory fitness (hereafter referred to as "fitness") is viewed as a health-related component of physical fitness, which is defined as the ability of the circulatory, respiratory, and muscular systems to supply oxygen during sustained physical activity (D. C. Lee, Artero, Sui, & Blair, 2010). Fitness is usually expressed in METs of task or maximal oxygen uptake (VO_{2max}) measured by exercise tests such as treadmill or cycle ergometer (D. C. Lee et al., 2010). In this study, fitness was expressed in VO_{2max} and was measured using the GE T2100 treadmill modified Balke protocol. During the modified Balke protocol, the treadmill speed is initially set at 2.0 miles/hour and the incline by 3.5% and increased in increments until the participant reaches volitional fatigue (Brown, Miller, & Eason, 2006). The treadmill test was used to determine VO_{2max}, for fitness levels based on age, gender, and BMI, identify target heart rate for an exercise prescription if desired by the participant and to screen for cardiac contraindications to exercise according to the American Heart Association and the American College of Cardiology guidelines (Gibbons et al., 2002). Expired gas analysis and measurement procedures followed manufacturer specifications. A certified exercise physiologist administered the test and the results were interpreted by a Center physician who supervised the test.

Depressive symptoms refer to thoughts, feelings, and behaviors demonstrating sadness, loss of interest in life, and negative perception of self or the future (Beck, Steer, Ball, & Ranieri, 1996; Steer, Ball, Ranieri, & Beck, 1999). Depressive symptoms were measured using the BDI-II (Beck, Brown, et al., 1996). The 21-item scale is one of the most widely used self-report measures of depressive symptoms (Beck, Brown, et al., 1996). The BDI-II was designed to assess the cognitive and somatic symptoms as indicated by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (American Psychiatric Association, 1994). Most of the items assess depressive symptoms on a Likert scale of 0 to 3. A total score of 0-13 is considered minimal depression, 14-19 is mild depression, 20-28 is moderate depression, and 29-63 is severe depression (Beck, Brown, et al., 1996).

When used in the general population, the BDI-II has been shown to have excellent test-retest reliability (r=0.93) and inter-item correlations (ranging from r=0.91-0.95) (Beck, Brown, et al., 1996). BDI-II total scores have been correlated with scores on other psychological tests. The BDI-II was positively related to the Scale for Suicide Ideation (r=0.37, n=158) as well as the Beck Hopelessness Scale (r=0.68, n=158) (Beck, Brown, et al., 1996). The BDI-II was shown to be a reliable and valid measure of depressive symptoms among overweight/obese individuals with prediabetes in the Diabetes Prevention Program (Rubin et al., 2005; Rubin et al., 2008), but was not reported in the parent study.

Health status is a broad multidimensional concept that usually includes domains related to physical and mental health perceptions. Health status was measured using the SF-36 (Ware & Sherbourne, 1992). The SF-36 is a multi-purpose, short-form health

survey with 36 items that evaluates eight areas of health status subscales (i.e., vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health) focusing on both physical and mental health (Ware & Sherbourne, 1992). It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Five items are included in a Likert style format, ranging from poor health to excellent health, are used to measure the persons' appraisal of general health. The reliability of the eight subscales and two summary measures has been estimated using both internal consistency and test-retest methods (Ware & Gandek, 1998). In more than 25 studies, published reliability statistics have exceeded the minimum standard of 0.70 recommended for measures used in group comparisons (Manocchia et al., 1998). Reliability estimates for physical and mental summary scores usually exceed 0.90 (Ware, Kosinski, & Keller, 1994). A review of the first 15 published studies revealed that the median reliability coefficients for each of the eight scales was equal or greater than 0.80 except for social functioning, which had a median reliability across studies of 0.76 (Ware, Snow, Kosinski, & Gandek, 1993). Convergent validity was supported with a significant correlation (r=0.96) with the 22-item General Health Rating Index (Ware & Sherbourne, 1992).

Statistical Analysis

This secondary analysis examined the baseline biological, physical, and psychological risk factors among overweight/obese adults with and without prediabetes for CVD risk. In addition, the study explored whether a health partner program reduced biological, physical, and psychological risk factors in overweight/obese adults with and without diabetes at the 1 year follow-up period.

Descriptive analyses were used to initially examine sample characteristics and psychometrically evaluate all scored instruments to determine the distributions of the variables, identify any unusual data values or entry errors, and evaluate any predictors of missing data (i.e. missing data bias and checking assumptions of missing completely at random or missing at random). All variables were reviewed to ensure they meet the assumptions for inferential testing procedures (e.g. normality) and whether transformations may be required. If the variables were normally distributed, the mean and standard deviation were presented. If the variables were non-normally distributed, the median and interquartile range (25th to 75th percentiles) were presented in the original units. If a variable was mathematically transformed in addition to the median and IQR in the original units, the median and IQR in the transformed units were listed. For any variables that cannot be normalized using square root or log transformations, data were dichotomized based on clinical cut-points or natural split points, or broken into the recognized clinical categories (depressed/not depressed, weight categories, etc.). For dichotomized or categorical variables, Chi-square tests or logistic regression was used when applicable. All the analyses were conducted using the SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

RQ1a: First, the normality of the variables, TG, LDL-C, HDL-C, IL-6, IL-8, TNF-α, CRP, blood glucose and microalbuminuria, were examined using frequency distributions, QQ plots, Shapiro-Wilk test as well as statistical indices of mean, media, skewness and kurtosis. T-tests were used to compare normally distributed continuous variables between those with and without prediabetes, and Wilcoxon two-independent group tests were used to compare non-normally distributed continuous variables between

those with and without prediabetes. Chi-square tests were conducted to compare differences between those with and without prediabetes for categorical variables. Necessary transformation (for example, logarithm transformation) was applied to variables when normality was violated. Second, a linear or logistic regression model was built for each outcome variable based on prediabetic status, controlling for age, gender, and educational level.

RQ1b: First, outcome variables for physical activity level (the maximum amount of oxygen in milliliters [VO_{2max}] from the modified Balke treadmill test and energy expenditures calculated from the CAPS Typical Week Physical Activity Recall Questionnaire) and psychological measurement (BDI-II score and SF-36 score) were checked for normality using frequency distributions, QQ plots, Shapiro-Wilk test as well as statistical indices of mean, media, skewness and kurtosis. T-tests were used to compare normally distributed continuous variables between those with and without prediabetes, and Wilcoxon two-independent group tests were used to compare non-normally distributed continuous variables between those with and without prediabetes. Chi-square tests were conducted to compare differences between those with and without prediabetes for categorical variables. Necessary transformations were applied to those variables when there was a violation of normality. Second, a linear or logistic regression model was built for each outcome variable based on prediabetic status, controlling for age, gender, and educational level.

RQ2a and 2b: Changes for the risk factors were computed by subtracting one-year from baseline values. The descriptive statistics (mean, standard deviation, median, minimum, and maximum) for these changes were also calculated for the total sample and

by prediabetic status. Paired t-tests were conducted to compare these changes from baseline to one-year follow-up within prediabetics and non-prediabetics for normally distributed continuous variables, and non-parametric tests were applied to compare changes within prediabetics and non-prediabetics for non-normally distributed continuous variables. Chi-square tests were conducted to compare changes between those with and without prediabetes for categorical variables. Non-normally distributed changes in risk factors were normalized using logarithm transformations. Cohen's d effect sizes were calculated to examine the within-group differences. Although it was underpowered to detect any group-by-time effects for the exploratory aim, multiple linear regression models were applied to compare changes in risk factors between those with and without prediabetes controlling for important covariates, including age in model 2 and age, gender, and education in model 3. For the comparison of changes in categorical variables between those with and without prediabetes, generalized estimating equation models were conducted in the model, controlling for important covariates, including age in model 2 and age, gender, and education in model 3. Multicollinearity assumptions were checked and reported whether or not each regression model met those assumptions, and variance inflation factors<10, tolerance>0.2 or condition index<30 was considered no multicollinearity among independent variables (Kleinbaum, Kupper, Nizam, & Muller, 2007).

Summary

This is a secondary analysis of the Center database at Emory University which compared the baseline biological, physical and psychological risk factors of overweight and obese adults with and without prediabetes. In addition, this study also examined the

effects of a health partner program on biological, physical, and psychological risk associated with CVD among overweight/obese adults with and without prediabetes at one-year follow-up. The sample size of 341 (44 for prediabetics and 297 for nonprediabetics) participants enrolled in the Center was used for testing the primary aim. There were 246 (30 for prediabetics and 216 for non-prediabetics) participants enrolled at baseline and 1 year for testing the exploratory aim. The reasons for the smaller than estimated sample size and missing data for pre-diabetics were unclear, but this limited the power and ability to draw any inferences from this secondary analysis.

Data were analyzed by using the SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina). For the primary aim, linear or logistic regression models were used to evaluate the association between prediabetes and biological, physical, and psychological risk factors, controlling for age, gender, and educational level. For the exploratory aim, changes of the risk factors were computed by subtracting the one-year values from baseline values. Paired t-tests were conducted to compare these changes from baseline to one-year follow-up within prediabetics and non-prediabetics for normally distributed continuous variables, and non-parametric tests were applied to compare changes within prediabetics and non-prediabetics for non-normally distributed continuous variables. Chi-square tests were conducted to compare these change scores between those with and without prediabetes for categorical variables. Multiple linear regression models were applied to compare changes in risk factors between those with and without prediabetes controlling for important covariates, including age in model 2 and age, gender, and education in model 3.

Chapter Four

Results

Baseline Sample Characteristics

This was a secondary data analysis using the Center database at Emory University. The baseline sample (N=341) characteristics are presented in Table 3. The mean age of the participants was 48.92 (standard deviation [SD]=10.9) years. The study sample was predominately Caucasian, female, college-educated and employed full-time. Median income level was $100,000-$150,000 (interquartile range [IQR]=50,000-200000), indicating that participants were high in socioeconomic status.

Table 3

Baseline Sample Characteristics

Variables	Mean or median or n	% or IQR or SD
Gender		
• Female	219	63.11%
• Male	128	36.89%
Race		
• Black	99	28.53%
• White	241	69.45%
• Other	7	2.02%
Age, years	48.92	SD=10.93
Income, $	100,000-150,000	IQR=50,000-200,000
Education, years	18	IQR=16-22

Baseline Sample Characteristics by Prediabetic State

Baseline sample characteristics by prediabetic state are presented in Table 4. A total of 341 participants were free of type 2 diabetes and were included in the baseline analyses. The mean age of participants with and without prediabetes was 55 (SD=10.7)

and 48 years (SD=10.4; p<0.0001), respectively. Median education level and household income was similar among participants with and without prediabetes.

Table 4

Baseline Sample Characteristics by Prediabetic State

Variables	Non-prediabetics (n=297)	Prediabetics (n=44)	p	Statistical test
Age, years, mean (SD)	48 (10.7)	55.3 (10.4)	**<0.001**	T-test
Gender				Chi-square
• Male, n (%)	104 (35.02)	19 (43.18)	0.293	Chi-square
• Female, n (%)	193 (64.98)	25 (56.82)		
Race, %				
• Black	29.29	20.45	0.248	Chi-square
• White	68.35	79.55		
• Other	2.36	0.00		
Income, $, median (IQR)	100,000-150,000 (75,000-200,000)	100,000-150,000 (75,000-250,000)	0.377	Wilcoxon two-independent group test
Education, years, median (IQR)	17 (16-22)	18 (15.5-22)	0.981	Wilcoxon two-independent group test

Note. SD=standard deviation. If variables are normally distributed, the mean and standard deviation are presented. If variables are non-normally distributed, the median and IQR are presented in the original units.

Baseline Characteristics of Biological, Physical, and Psychological Risk Factors

Question RQ1a: Baseline Characteristics of Biological Risk Factors

Compared to participants without prediabetes, participants with prediabetes had much higher fasting blood glucose levels (104.8 vs 86.3 mg/dl, p<0.0001). Participants with prediabetes were also significantly heavier than those without prediabetes, with a median body mass index (BMI) of 31.2 kg/m^2 (IQR=27.4-36.9) versus 28.8 kg/m^2 (IQR=26.8-32.7) (p<0.017), respectively. Similarly, participants with prediabetes had significantly higher waist-hip ratio (WHR) than those without prediabetes (p=0.014), and

this was particularly pronounced in women (p=0.020). Participants with prediabetes had significantly higher median triglyceride (TG) levels compared to participants without prediabetes (111 vs 91 mg/dl, p=0.0002). In addition, a significantly higher number of participants with prediabetes were insulin resistant compared to those without prediabetes (47.7% vs 14.1%, p<0.0001). Finally, there was a trend for prediabetic participants to have microalbuminuria (7.3% vs 3.1%, p=0.178). None of the additional biological factors between groups were significant as shown in Table 5.

Table 5

Baseline Characteristics of Biological Risk Factors by Prediabetic State

Variables	Non-prediabetics (n=297)	Prediabetics (n=44)	p	Statistical test
BMI, kg/m^2, median (IQR)	28.8 (26.8-32.7)	31.2 (27.4-36.9)	**0.017**	Wilcoxon two-independent group test
WHR, mean (SD)				T-test
• Total	0.8 (0.1)	0.9 (0.1)	**0.014***	
• Male	0.92 (0.01)	0.93 (0.01)	0.485*	
• Female	0.8 (0.00)	0.83 (0.01)	**0.020***	
Fasting blood glucose, mg/dl, mean (SD)	86.33 (6.6)	104.82 (4.7)	**<0.0001**	N/A
HOMA-IR >2.5, %	14.1	47.7	**<0.0001**	Chi-square
LDL-C, mg/dl, mean (SD)	114.62 (31.7)	108.00 (30.6)	0.199*	t-test
HDL-C, mg/dl, median (IQR)	56 (48-69)	56 (43-66)	0.314	Wilcoxon two-independent group test
TG, mg/dl, median (IQR)	91 (69-125)	111 (89-191)	**0.0002**	Wilcoxon two-independent group test
IL-6, pg/ml, median (IQR)	1.11(0.5-2.3)	1.42 (0.7-2.2)	0.558	Wilcoxon two-independent group test
Elevated IL-6 greater than	7.50	0	0.093	Fisher's

7 pg/ml, %				exact test
IL-8, pg/ml, median (IQR)	8 (5.8-11.4)	7.6 (5-11.4)	0.528	Wilcoxon two-independent group test
Elevated IL-8 greater than 8.7 pg/ml, %	44.6	38.6	0.460	Chi-square
TNF-α, pg/ml, median (IQR)	3.9 (2.5-5)	3.7 (2.5-4.5)	0.391	Wilcoxon two-independent group test
CRP, mg/l, median (IQR)	0.2 (0.1-0.4)	0.3 (0.2-0.5)	0.109	Wilcoxon two-independent group test
Abnormal CRP greater than 1.0 mg/l, %	7.1	2.3	0.332	Chi-square
UACR, median (IQR)	5 (3.5-7)	6 (3-8)	0.423	Wilcoxon two-independent group test
Abnormal UACR>30.0 mg/g, %	3.1	7.3	0.178	Chi-square

Note. TNF-α=tumor necrosis factor-alpha; HOMA-IR=homeostasis model assessment of insulin resistance; UACR=urine albumin-to-creatinine ratio. *indicates t-test p value, otherwise, p values are calculated from non-parametric tests.

Differences in Biological Risk Factors Between Participants With and Without Prediabetes at Baseline

Since age was the only baseline sample characteristic that differed between the two grops (Table 4), gender and educational level were not controlled or adjusted for in the linear or logistic regression model, depending on continuous or dichotomous variables. Controlling for age, differences in biological risk factors between participates with and without prediabetes at baseline are shown in Table 6. The biological differences between the two groups at baseline remained significant after controlling for age (BMI, blood glucose, TG, and insulin resistance), using non-prediabetics as a reference group.

Compared to non-prediabetics, prediabetics were heavier, more likely to be insulin resistant, and had higher fasting blood glucose and TG levels.

Table 6

Differences in Biological Risk Factors Between Participants With and Without Prediabetes at Baseline, Controlling for Age

Outcomes	Group effect (adjusting for age) Betas/ OR (95% CI)	Group effect (adjusting for age) p
BMI, kg/m^2	2.261 (1.163-4.399)	**0.016**
Log-WHR	0.079	0.148
LDL-C, mg/dl	-0.091	0.104
Log-HDL-C, mg/dl	-0.100	0.071
Abnormal CRP>1, mg/l *	0.431 (0.055-3.382)	0.423
Log-TG, mg/dl	0.179	**0.001**
Abnormal UACR	2.166 (0.527-8.906)	0.284
Log-IL-6, pg/ml	0.010	0.862
HOMA-IR>2.5*	5.426 (2.689-10.948)	**<0.001**
Log-IL-8, pg/ml	-0.071	0.195
Log-TNF-α, pg/ml	-0.076	0.171
Fasting blood glucose, mg/dl	0.653	**<0.001**

Note. SE=standard error; *indicates dichotomous variables.

RQ1b: Baseline Characteristics of Physical Risk Factors

Participants with prediabetes had poorer cardiorespiratory fitness as evidenced by a lower performance on the modified Balke maximal treadmill test (Table 7). The median cardiorespiratory fitness level (VO_{2max}) was significantly lower among prediabetic participants compared to those without prediabetes (28.5 vs 32 ml/kg/min, p=0.03). In addition, prediabetics self-reported poorer physical functioning on the Medical Outcomes Study Short Form (SF-36) physical component score; 53.8 (SD=6) versus 49.9 (SD=8.1) (p=0.003), respectively. Participants with prediabetes were also more sedentary as evidenced by lower total, moderate and vigorous activity levels on the Cross-Cultural

Activity Participation Study (CAPS) Typical Week Physical Activity Recall Questionnaire, but these differences were not significant as shown in Table 4.

Table 7

Baseline Characteristics of Physical Risk Factors by Prediabetic State

Variables	Non-prediabetics (n=297)	Prediabetics (n=44)	p	Statistical test
VO_{2max}, ml/kg/min, median (IQR)	32 (26-38)	28.5 (24-34)	**0.029**	Wilcoxon two-independent group test
CAPS Typical Week Physical Activity Recall Questionnaire				
• Daily living activity, MET-hours/week, median (IQR)	23.4 (66-98.4)	21.37 (68.4-91.5)	0.459	Wilcoxon two-independent group test
• Moderate + vigorous activity, MET-hours/week, median (IQR)	18 (9.6-32.8)	14.5 (9.3-25.1)	0.105	Wilcoxon two-independent group test
• Total activity, MET-hours/week, median (IQR)	28.74 (86.9-120.4)	26.09 (82-106.6)	0.062	Wilcoxon two-independent group test
SF-36 physical component score, mean (SD)	53.8 (6)	49.9 (8.1)	**0.003**	T-test

Note. MET=metabolic equivalent; CAPS=Cross-Cultural Activity Participation Study.

Baseline Characteristics of Psychological Risk Factors

Among those without prediabetes, there was a trend for poorer mental health functioning on the SF-36 and the percentage of people with depressive symptoms was almost as twice as that in people with prediabetes.

Table 8

Baseline Characteristics of Psychological Risk Factors by Prediabetic State

Variables	Non-prediabetics (n=297)	Prediabetics (n=44)	p	Statistical test
BDI score, median (IQR)	4 (1-9)	5 (2-8)	0.775	Wilcoxon two-

				independent group test
Depressive symptoms (BDI II≥11), %	9.7	5.4	0.396	Chi-square
SF-36 mental component score, median (IQR)	53 (47-57)	55.5 (51-57.5)	0.080	Wilcoxon two-independent group test

Note. BDI= Beck Depression Index.

Differences in Physical and Psychological Risk Factors Between Participants With and Without Prediabetes at Baseline

Since age was the only baseline sample characteristic between those with and without prediabetes (Table 4), gender and educational level were not controlled for in the linear or logistic regression model, depending on continuous or dichotomous variables. Controlling for age, differences in physical and psychological risk factors between participates with and without prediabetes at baseline are shown in Table 9. Compared to participants without prediabetes, participants with prediabetes were more likely to be at lower levels of physical functioning and had lower fitness levels at baseline. There were no significant differences in other physical risk factors outcome variables.

Since data from the 1999-2004 NHANES found that individuals who were obese had approximately 10% to 15% lower fitness level than non-obese individuals (C. Y. Wang et al., 2010), prediabetics were significantly heavier than non-prediabetics at baseline (Table 5) in the current study. Age and BMI were controlled in the linear regression model (Table 10) to see whether there was still a significant difference in cardiorespiratory fitness between those with and without prediabetes. Compared to participants without prediabetes, participants with prediabetes had lower fitness levels at baseline.

Table 9

Differences in Physical and Psychological Risk Factors Between Participants With and Without Prediabetes at Baseline, Controlling for Age

Outcomes	Group effect (adjusting for age) Betas / OR (95% CI)	Group effect (adjusting for age) p
Log-VO_{2max}, ml/kg/min	-0.128	**0.026**
Log-daily living activity	0.003	0.952
Log-moderate+vigorous activity	-0.086	0.123
Log-total activity	-0.069	0.215
SF-36 physical component score	-0.019	**0.001**
Log-SF-36 mental component score	-0.061	0.264
BDI-II≥11*	1.435 (0.311-6.619)	0.644

Note. SE=standard error; *indicates dichotomous variables.

Table 10

Differences in Fitness Levels Between Participants With and Without Prediabetes at Baseline, Controlling for Age and BMI

Outcome	Group effect (adjusting for age and BMI) Betas	Group effect (adjusting for age and BMI) p
Log-VO_{2max}, ml/kg/min	-0.128	**0.026**

Changes in Biological, Physical, and Psychological Risk Factors At One-Year Follow-up Visit

RQ2a: Changes in Biological Risk Factors at One-Year Follow-up Visit: Total Sample

Changes in biological risk factors at one-year follow-up among the total sample are presented in Table 11. These changes were calculated by subtracting one-year values from baseline. Thus, positive change scores indicate subjects whose values at 1 year were less than they were at baseline. Significant tests for the paired t-tests (or signed rank test)

indicate that there were significant changes from baseline to 1 year. At one-year follow-up, the total sample, both prediabetics and those without prediabetes, had significant improvements ($p<0.05$) in BMI, WHR, LDL-C, IL-6, CRP, and microalbuminuria. The p values for CRP and UACR are different in paired t-test and signed rank test due to skewness in the change scores. The most change for the biological risk factors was LDL-C which was reduced by 6.172 mg/dl at one-year follow-up. However, changes in other biological factors, including levels of fasting glucose, HDL-C, TG, IL-8, TNF-α, and HOMA-IR were not significant. Means and standard deviations were used to calculate effect sizes (Cohen's d). Cohen (1988) gave the following rough guidelines for interpreting the effect size: d=0.3 depicted a small effect size, d=0.5 depicted a moderate effect size, and d=0.8 a large effect size (Cohen, 1988). Based on these guidelines, Cohen's d effect size in Table 11 indicated that the effect sizes for changes in these biological risk factors were considered small.

Table 11

Average Changes in Biological Risk Factors at One-Year Follow-up Among Participants With and Without Prediabetes

Variables	N	Mean (SD)	Median (IQR)	Min	Max	Paired t-test p	Signed rank test p	Cohen's d effect size
BMI, kg/m^2	245	0.542 (2.066)	0.286 (1.837)	-7.502	13.983	**<0.000**	**<0.001**	0.262
WHR	238	0.012 (0.061)	0.011 (0.042)	-0.218	0.431	**0.002**	**<0.001**	0.197
Fasting glucose, mg/dl	245	-0.212 (9.913)	0 (11)	-68	33	0.738	0.692	-0.021
LDL-C, mg/dl	244	6.172 (24.063)	4 (23.5)	-75	141	**<0.000**	**0.001**	0.256
HDL-C, mg/dl	245	0.869 (7.736)	1 (9)	-22	29	0.080	0.070	0.112
TG, mg/dl	244	0.795 (47.449)	2 (37.5)	-219	191	0.794	0.680	0.017
IL-6, pg/ml	239	0.474 (2.211)	0.36 (1.85)	-4.780	22.134	**0.001**	**0.000**	0.214
IL-8, pg/ml	240	0.057 (6.801)	0 (5.695)	-48.931	33.261	0.897	0.847	0.008
TNF-α, pg/ml	240	0.216 (2.882)	0.16 (3.217)	-9.792	22.172	0.248	0.303	0.075
CRP, mg/dl	243	0.025 (0.242)	0 (0.13)	-1.473	1.232	0.105	**0.014**	0.103
UACR	231	-0.974 (13.758)	0 (5)	-100	64	0.283	**0.032**	-0.071
HOMA	245	-0.252 (6.536)	0.005 (0.793)	-99.084	17.121	0.546	0.549	-0.039

Changes in Biological Risk Factors at One-Year Follow-up Visit: Prediabetics

Changes in biological risk factors at one-year follow-up among participants with prediabetes are presented in Table 12. These changes were calculated using the same technique as described above. At one-year follow-up, participants with prediabetes had significant improvements in some of the biological risk factors, including BMI, fasting blood glucose, and insulin resistance. The p values for HOMA are different in paired t-test and signed rank test due to skewness in the change scores. In addition, although not significant, TG levels decreased by 9.828 mg/dl with a trend for significance (p=0.077). However, changes in other biological factors were not significant as shown in Table 11. It is noted that with a sample size of 30 prediabetics we were only powered to detect effect sizes of d=0.53 and larger for paired t-tests to test for changes scores significantly different from 0 (no change). Cohen's d effect sizes were calculated using the same technique as described above. Based on rough guidelines for interpreting the effect size (Cohen, 1988), the Cohen's d effect size for changes in BMI was considered moderate, and for changes in fasting blood glucose were considered small to moderate, but for changes in other biological risk factors were considered small.

Table 12

Average Changes in Biological Risk Factors at One-Year Follow-up among Participants With Prediabetes

Variables	N	Mean (SD)	Median (IQR)	Min	Max	Paired t-test p	Signed rank test p	Cohen's d effect size
BMI, kg/m^2	29	1.685 (3.248)	0.968 (1.992)	-2.026	13.983	**0.009**	**0.002**	0.519
WHR	29	-0.004 (0.046)	0.002 (0.049)	-0.162	0.062	0.664	0.975	-0.087
Fasting glucose,	30	7.867	9.5 (11)	-68.000	33.000	**0.018**	**<0.000**	

mg/dl		(17.212)						0.457
LDL-C, mg/dl	29	4.414 (21.921)	5 (30)	-41.000	57.000	0.288	0.339	0.201
HDL-C, mg/dl	30	0.167 (6.778)	1.5 (8)	-20.000	10.000	0.894	0.461	0.025
TG, mg/dl	29	9.828 (64.224)	8 (26)	-219.000	161.000	0.417	0.077	0.153
IL-6, pg/ml	30	0.389 (1.424)	0.655 (1.93)	-2.400	3.430	0.146	0.147	0.273
IL-8, pg/ml	30	-1.863 (6.222)	-1.745 (7.24)	-16.480	9.340	0.112	0.144	-0.299
TNF-α, pg/ml	30	-0.252 (2.098)	-0.534 (3.78)	-3.320	4.440	0.516	0.312	-0.120
CRP, mg/dl	30	0.014 (0.242)	0 (0.14)	-0.780	0.460	0.760	0.310	0.058
UACR	27	0.074 (6.961)	0 (5)	-13.000	24.000	0.956	0.553	0.011
HOMA	30	1.521(18.750)	0.794 (1.622)	-99.084	17.121	0.660	**0.001**	-0.081

Changes in Biological Risk Factors at One-Year Follow-up Visit: Non-Prediabetics

Changes in biological risk factors at one-year follow-up among participants without prediabetes are presented in Table 13. At one-year follow-up, participants without prediabetes had significant improvements in some of the biological risk factors, including BMI, WHR, LDL-C, IL-6, and microalbuminuria levels. However, fasting glucose level increased by 1.343 mg/dl at 1 year follow-up (p=0.013). Changes in other biological factors were not significant. The p values for CRP and UACR are different in paired t-test and signed rank test due to skewness in the change scores. All Cohen's d effect sizes for changes in these biological risk factors were considered small.

Table 13

Average Changes in Biological Risk Factors at One-Year Follow-up among Participants Without Prediabetes

Variables	N	Mean (SD)	Median (IQR)	Min	Max	Paired t-test p	Signed rank test p	Cohen's d effect size
BMI, kg/m^2	216	0.388 (1.808)	0.251 (1.682)	-7.502	8.984	**0.002**	**0.001**	0.215
WHR	209	0.014 (0.061)	0.011 (0.042)	-0.218	0.431	**0.001**	**<0.001**	0.230
Fasting glucose, mg/dl	215	-1.343 (7.841)	-1 (9)	-20.000	23.000	**0.013**	**0.016**	-0.171
LDL-C, mg/dl	215	6.409 (24.375)	4 (22)	-75.000	141.000	**0.000**	**0.009**	0.263
HDL-C, mg/dl	215	0.967 (7.871)	1 (9)	-22.000	29.000	0.073	0.092	0.123
TG, mg/dl	215	-0.423 (44.769)	1 (38)	-184.000	191.000	0.890	0.870	-0.009
IL-6, pg/ml	209	0.486 (2.304)	0.363(1.84)	-4.780	22.100	**0.003**	**0.009**	0.211
IL-8, pg/ml	210	0.331 (6.849)	0.175 (5.33)	-48.930	33.260	0.485	0.387	0.048
TNF-α, pg/ml	210	0.282 (2.975)	0.21 (3.1)	-9.790	22.170	0.171	0.152	0.094
CRP, mg/dl	213	0.027 (0.243)	0 (0.12)	-1.470	1.200	0.107	**0.027**	0.111
UACR	204	-1.113 (14.425)	0 (5)	-100.000	64.000	0.272	**0.037**	-0.077
HOMA	215	-0.075 (0.904)	-0.009 (0.664)	-4.052	2.603	0.223	0.243	-0.083

Compare Changes in Biological Risk Factors at One-Year Follow-up Visit Between Those With and Without Prediabetes

Changes in biological risk factors were compared between those with and without prediabetes. There were significant differences in changes from baseline to one year, including BMI, fasting blood glucose, and insulin resistance between the two groups as shown in Table 14 for three models: group differences unadjusted (no covariates), or after adjusting for age, or after adjusting for age, gender, and education. Compared to non-prediabetics, prediabetics had significant improvements in BMI, fasting blood glucose, and insulin resistance at the one-year follow-up. Both prediabetics and non-prediabetics had similar changes in other biological factors over the one-year follow-up period.

Table 14

Compare Changes in Biological Risk Factors at One-Year Follow-up Visit Between Those With and Without Prediabetes

Variables	Model 1: No covariates, Group only		Model 2: Group adjusted for age		Model 3: Group adjusted for age, sex, and education	
	Betas Group	p	Betas Group	p	Betas Group	p
BMI, kg/m^2	0.203	**0.001**	0.192	**0.003**	0.181	**0.007**
WHR*	-0.106	0.104	-0.101	0.131	-0.107	0.121
Fasting glucose, mg/dl	0.305	**<0.001**	0.320	**<0.001**	0.327	**<0.001**
LDL-C, mg/dl	-0.027	0.676	-0.049	0.460	-0.046	0.450
HDL-C, mg/dl	-0.034	0.596	-0.036	0.584	-0.031	0.651
TG*, mg/dl	0.054	0.399	0.058	0.380	0.055	0.415
IL-6*, pg/ml	-0.004	0.948	-0.005	0.945	0.004	0.952
IL-8*, pg/ml	-0.106	0.100	-0.078	0.241	-0.076	0.265
TNF-α*, pg/ml	-0.052	0.424	-0.046	0.493	-0.043	0.532
Abnormal CRP>1 (logit) [§], mg/dl	0.6752	0.189	0.7105	0.186	0.7182	0.215
Abnormal UACR>30 (logit) [§]	-0.2329	0.595	-0.2301	0.591	-0.1521	0.748

HOMA-IR>2.5 (logit) §	-0.6067	**0.007**	-0.6073	**0.006**	-0.6257	**0.007**

Note. Regression coefficients and p-values for the group variables (i.e., prediabetics versus non-prediabetics) are presented in the table. *=log transformed variable; §The interaction term between time and prediabetes in a GEE model.

RQ2b: Changes in Physical Risk Factors at One-Year Follow-up Visit: Total Sample

Changes in physical risk factors among the overall participants are shown in Table 15. At one-year follow-up, both participants with and without prediabetes had higher moderate and vigorous activity levels and improved physical function. However, cardiorespiratory fitness, daily living activity, and total activity levels were decreased from baseline to one-year follow-up in both groups. All Cohen's d effect sizes for changes in these physical risk factors were considered small.

Table 15

Average Changes in Physical Risk Factors at One-Year Follow-up among Participants With and Without Prediabetes

Variables	Mean (SD)	Median (IQR)	Min	Max	Paired t-test p	Signed rank test p	Cohen's d effect size
VO_{2max}, ml/kg/min	1.745 (8.573)	0 (7.5)	-21	43	**0.003**	0.059	0.203
CAPS Typical Week Physical Activity Recall Questionnaire, MET-hours/week							
• Daily living activity	5.048 (22.826)	4.125 (22.625)	-29.286	26.143	**0.001**	**0.001**	0.221
• Moderate + vigorous activity	-0.746 (18.685)	-0.250 (12.375)	-22.428	41.371	0.551	0.143	-0.040
• Total activity	4.302 (32.783)	3.625 (26.000)	-42.514	39.429	0.051	**0.022**	0.131
SF-36 physical component score	-0.996 (5.708)	-1 (6)	-19	22	**0.010**	**0.009**	0.174

Changes in Physical Risk Factors at One-Year Follow-up Visit: Prediabetics

At the one-year follow-up, cardiorespiratory fitness, moderate and vigorous activity levels, and physical functioning were improved among participants with prediabetes. However, only improvement in physical functioning was significant (p=0.010). Daily living activity and total activity levels were slightly decreased as depicted in Table 16. All Cohen's d effect sizes for changes in these physical risk factors were considered small except for changes in the SF-36 physical component score.

Table 16

Average Changes in Physical Risk Factors at One-Year Follow-up among Participants With Prediabetes

Variables	Mean (SD)	Median (IQR)	Min	Max	Paired t-test p	Signed rank test p	Cohen's d effect size
VO_{2max}, ml/kg/min	-1.039 (6.076)	-1.5 (7)	-15.000	13.000	0.392	0.219	-0.171
CAPS Typical Week Physical Activity Recall Questionnaire, MET-hours/week							
• Daily living activity	4.129 (22.792)	1.5 (13)	-40.500	21.285	0.338	0.533	0.181
• Moderate + vigorous activity	-3.172 (11.514)	0.25 (13)	-30.000	18.750	0.149	0.297	-0.275
• Total activity	0.957 (26.813)	4 (20)	-45.250	23	0.849	0.650	0.036
SF-36 physical component score	-2.693 (5.265)	-1 (4)	-17.000	5.000	**0.010**	**0.006**	-0.511

Changes in Physical Risk Factors at One-Year Follow-up Visit: Non-Prediabetics

Changes in physical risk factors at one-year follow-up among participants without prediabetes are presented in Table 17. At the one-year follow-up, participants without prediabetes had very slight improvements in moderate and vigorous activity and physical functioning. Cardiorespiratory fitness, daily living activity, and total activity levels were

decreased as evidenced by a significant decrease in the treadmill test and CAPS Typical Week Physical Activity Recall Questionnaire among participants without prediabetes. All Cohen's d effect sizes for changes in these physical risk factors were considered small.

Table 17

Average Changes in Physical Risk Factors at One-Year Follow-up among Participants Without Prediabetes

Variables	Mean (SD)	Median (IQR)	Min	Max	Paired t-test p	Signed rank test p	Cohen's d effect size
VO_{2max}, ml/kg/min	2.134 (8.809)	1(8)	-21.000	43.000	**0.001**	**0.014**	-0.242
CAPS Typical Week Physical Activity Recall Questionnaire, MET-hours/week							
• Daily living activity	5.184 (22.886)	4.750 (23.750)	-29.286	26.143	**0.002**	**0.001**	0.227
• Moderate + vigorous activity	-0.385 (19.523)	-0.250 (12.750)	-22.429	41.371	0.784	0.227	-0.020
• Total activity	4.800 (33.611)	3 (27.250)	-42.514	39.428	**0.048**	**0.021**	0.143
SF-36 physical component score	-0.745 (5.74)	0 (6)	-19.000	22.000	0.071	0.060	-0.130

Compare Changes in Physical Risk Factors at One-Year Follow-up Visit Between Those With and Without Prediabetes

The three models for physical risk factors were also built to compare changes in physical factors over the 1 year follow-up period between prediabetic and non-prediabetic groups. As shown in Table 18, prediabetic participants had higher increase in cardiorespiratory fitness and physical functioning, and the differences were significant in the model controlling for age. Difference in cardiorespiratory fitness was also significant when additionally controlling for gender and education as shown in model 3. Changes in

physical functioning was marginal significant in model 3. Changes in physical activity level however, were not significantly different between the two groups.

Table 18

Compare Changes in Physical Risk Factors at One-Year Follow-up Visit Between Those With and Without Prediabetes

Variables	Model 1: No covariates, group only		Model 2: Group adjusted for age		Model 3: Group adjusted for age, sex, and education	
	Betas	p	Betas	p	Betas	p
VO_{2max}*, ml/kg/min	-0.124	0.071	-0.14	**0.049**	-0.146	**0.043**
CAPS Typical Week Physical Activity Recall Questionnaire, MET-hours/week						
• Daily living activity*	-0.015	0.820	-0.008	0.912	-0.007	0.916
• Moderate and vigorous activity*	-0.042	0.534	-0.021	0.762	-0.022	0.748
• Total activity	-0.039	0.557	-0.022	0.750	-0.023	0.740
SF-36 physical functioning	-0.114	0.087	-0.137	**0.047**	-0.132	0.058

Note. *=log transformed variable.

Changes in Psychological Risk Factors at One-Year Follow-up Visit: Total Sample

At one-year follow-up, participants with and without prediabetes had improvements in depressive symptoms and the SF-36 mental component score. The mean BDI depression score decreased by 1.829, and the mean mental function score increased by 1.889 from baseline to one-year follow-up. Both changes were statistically significant. The Cohen's d effect size for changes in BDI depression score was considered small to moderate.

Table 19

Average Changes in Psychological Risk Factors at One-Year Follow-up among Participants With and Without Prediabetes

Variables	Mean (SD)	Median (IQR)	Min	Max	Paired t-test p	Signed rank test p	Cohen's d effect size
BDI Score	1.829 (4.251)	1 (4)	-15	21	**<0.000**	**<0.001**	0.430
SF-36 mental component score	-1.889 (7.867)	-1 (7)	-32	24	**0.000**	**0.000**	-0.240

Changes in Psychological Risk Factors at One-Year Follow-up Visit: Prediabetics

Similar to the overall participants, at one-year follow-up, the mean BDI depression score significantly decreased by 1.724 from baseline to one-year follow-up. Mental functioning slightly increased by 0.966 in the SF-36 mental component score among participants with prediabetes. However, the change was not significant. The Cohen's d effect size for changes in BDI depression score was considered small to moderate.

Table 20

Average Changes in Psychological Risk Factors at One-Year Follow-up among Participants With Prediabetes

Variables	Mean (SD)	Median (IQR)	Min	Max	Paired t-test p	Signed rank test p	Cohen's d effect size
BDI score	1.724 (3.524)	1 (5)	-4	9	**0.014**	**0.018**	0.489
SF-36 mental component score	-0.966 (6.936)	-1 (5)	-15	24	0.460	0.153	-0.139

Changes in Psychological Risk Factors at One-Year Follow-up Visit: Non-Prediabetics

The changes in psychological risk factors among non-prediabetes participants are shown in Table 21. At one-year follow-up, participants without prediabetes had significant improvements in depressive symptoms as measured by BDI depression score and mental functioning as measured by the SF-36 mental component score. The Cohen's d effect size for changes in BDI depression score was considered small to moderate.

Table 21

Average Changes in Psychological Risk Factors at One-Year Follow-up among Participants Without Prediabetes

Variables	Mean (SD)	Median (IQR)	Min	Max	Paired t-test p	Signed rank test p	Cohen's d effect size
BDI score	1.845 (4.357)	1 (4)	-15	21	**<.001**	**<0.001**	0.423
SF-36 mental component score	-2.026 (8.003)	-1 (8)	-32	21	**0.001**	**0.000**	-0.253

Compare Changes in Psychological Risk Factors at One-Year Follow-up Visit Between Those With and Without Prediabetes

Changes in psychological risk factors were compared between those with and without prediabetes. There were no significant differences in changes in depressive symptoms and mental functioning between those with and without prediabetes in all three models.

Table 22

Compare Changes in Psychological Risk Factors at One-Year Follow-up Visit Between Those With and Without Prediabetes

Variables	Model 1: no covariates, group only		Model 2: Group adjusted for age		Model 3: Group adjusted for age, sex, and education	
	Betas	p	Betas	p	Betas	p
BDI score*	-0.005	0.939	-0.008	0.907	-0.003	0.962
SF-36 mental functioning	0.045	0.500	0.070	0.309	0.065	0.353

Note. *=log transformed variable.

Checking for Multicollinearity Assumptions

Multicollinearity assumptions were checked and the results were shown in Table 23. Variance inflation factors<10, tolerance>0.2 or condition index<30 was considered no multicollinearity among independent variables (Kleinbaum et al., 2007). All models were reviewed and none had a Condition Index greater than 30, and this indicated that each regression model met those assumptions. The results are presented in Appendix E.

Chapter Five

Discussion

Introduction

This final chapter presents a summary of principal findings, discusses the major strengths and limitations of this study, and concludes with a discussion of the recommendations for future research and implications of the study and clinical practice.

Summary of Major Findings

The findings from this study showed that healthy overweight/obese participants with prediabetes were likely at higher biological and physical risk for cardiovascular disease (CVD) at baseline compared to those without prediabetes. Biological risk factors among prediabetics that increased CVD risk included higher fasting blood glucose, body mass index (BMI), total waist-hip ratio (WHR), insulin resistance, and triglycerides (TG). Among the physical risk factors examined, prediabetic participants had lower cardiorespiratory fitness, self-reported poorer physical function and were more sedentary. Participants in the study were predominately female and high in socioeconomic status (SES) and they participated in a health partner program, which varied in structure, goals, and intensity of interaction.

At the one-year follow-up visit, compared to participants without prediabetes, participants with prediabetes had the greatest improvements in body weight, fasting blood glucose, cardiorespiratory fitness, and physical functioning levels. In addition, a greater number of participants with prediabetes were no longer insulin resistant compared to those without prediabetes, while some of those without prediabetes increased in insulin resistance. Despite the non-structured and participant-driven health partner program,

there were improvements in biological and physical risk factors for CVD in this population among those with prediabetes and fewer changes were observed among non-prediabetics.

Comparison to Findings of Previous Literature/Research

Baseline Characteristics of Biological Risk Factors

The current study reported biological risk factors and their relation to CVD risk among overweight/obese adults with and without prediabetes. Participants with prediabetes were at higher biological risk for CVD than those without prediabetes. For example, compared to participants without prediabetes, those with prediabetes were heavier and predictably, more likely to be insulin resistant. In addition, they had elevated fasting blood glucose, higher TG levels, and higher WHR, all of which heightens CVD risk (Czernichow, Kengne, Stamatakis, Hamer, & Batty, 2011; de Koning, Merchant, Pogue, & Anand, 2007; Laakso & Kuusisto, 2014; Sarwar et al., 2007; Seshasai et al., 2011). The findings of this study are consistent with previous observational studies, (Seshasai et al., 2011; Wen et al., 2005) which support prediabetes increases the risk for CVD, independent of other risk factors (Ford et al., 2010).

Although overweight/obese individuals with prediabetes had heightened biological risk for CVD compared to those without prediabetes, this risk appears to be less than those with type 2 diabetes mellitus (T2DM) as previously reported. For example, in the current study the median BMI among prediabetics was 31.2 kg/m^2 (interquartile range [IQR] 27.4-36.9 kg/m^2), while BMI averaged 36 ± 5.9 kg/m^2 at baseline in the Look AHEAD (Action for Health in Diabetes) Research Study (Bray et al., 2006). Although elevated TG levels are common among individuals with T2DM and

prediabetes (Ginsberg, Zhang, & Hernandez-Ono, 2005; Yang et al., 2011), the median TG levels were 111 (IQR: 89-191) mg/dl in the current study, which was much lower than the average TG (180.95 mg/dl) reported in the Look AHEAD Research Study (Bray et al., 2006). Notably, the median TG levels in this study were within the range of the current guidelines recommended for lipid control (TG<150 mg/dl) by the American Diabetes Association (2015). Fasting blood glucose averaged 104.8 mg/dl among overweight/obese prediabetics in this study, which was much lower than that reported in the Look AHEAD Research Study (153.12 mg/dl) (Bray et al., 2006). In addition, only male participants with prediabetes were "borderline" abdominally obese, with WHR 0.93, which is slightly above the recommended range (<0.9) (World Health Organization, 2011), and among women, WHR was within the normal range (0.83).

Cross-sectional data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES) were also used to compare the current study participants with the characteristics of 2005-2006 NHANES participants, a representative sample of the U.S. adult population. This comparison was limited to the 2005-2006 NHANES participants (n=996) with prediabetes (Yang et al., 2011). Serum lipid profiles were lower in the current study compared to the NHANES participants. For example, low-density lipoprotein cholesterol (LDL-C) (108 vs 118.4 mg/dl, respectively) and TG levels (111 vs 141.8 mg/dl, respectively) were lower in the current study participants compared to 2005-2006 NHANES participants with prediabetes. In contrast to current study where WHR was 0.83 among female participants, women with prediabetes in the 2005-2006 NHANES had a much higher average waist circumference (101.0 cm) (Yang et al., 2011). Fasting plasma glucose concentrations (104.8 vs 103.7 mg/dl, respectively) and

BMI (31.2 vs 30.3 kg/m^2, respectively) were similar to those in 2005-2006 NHANES. In summary, the current study participants with prediabetes had higher biological risk for CVD than those without prediabetes. When compared to other populations with prediabetes reported in the literature however, the current participants appeared to be at lower biological risk for CVD, which may be the result of differences in SES than prior research.

Participants in the current study were higher in socioeconomic status (SES) compared to 2005-2006 NHANES participants with prediabetes. In the NHANES study, approximately 68% had received a high school education or below compared to the college level or higher educational levels achieved by participants in the current study. There were a large number of participants in the current study who were non-Hispanic White (69.45%) compared to 29.8% in the NHANES study. In addition, there may be some interaction effects between race/ethnicity and SES. The non-Hispanic Whites and African Americans in the current study may have had different characteristics than their counterparts in the NHANES. In addition, the lifestyle habits may have differed between the two groups due to social norms and environment that resulted in less association on biological risk factors.

A large body of epidemiologic data showed that lifestyle habits follow a SES gradient (Darmon & Drewnowski, 2008; Gidlow, Johnston, Crone, Ellis, & James, 2006). For example, a review concluded that consumption of lean meats, whole grains, fish, low-fat dairy products, and fresh vegetables and fruits was consistently associated with higher SES groups, whereas consumption of refined grains, fatty meats, and added fats was associated with lower SES groups (Darmon & Drewnowski, 2008). This difference

in SES gradient and lifestyle factors related to nutritional intake may in part explain the differences in the biological characteristics of the current study participants compared to those enrolled in the NHANES cohort.

Several cross-sectional and longitudinal studies have consistently shown that low SES characteristics (e.g., household income, education level) are associated with a large increase in CVD and CVD risk factors, especially higher BMI, smoking and lower HDL-C levels (Clark, DesMeules, Luo, Duncan, & Wielgosz, 2009; Franks, Winters, Tancredi, & Fiscella, 2011; Pollitt et al., 2007). The difference in SES between the current study participants and the 2005-2006 NHANES may explain in part, disparities in the CVD risk profiles between the two studies. In addition, social disadvantages and adversity in childhood may have lasting adaptations to stress that take a heavy toll on the cardiovascular system (Shonkoff, Boyce, & McEwen, 2009). Moreover, the cumulative effects of social disadvantages and challenges throughout the lifespan could also negatively influence risk factors and the development of CVD as research has shown in the literature (Pollitt, Rose, & Kaufman, 2005).

Baseline Characteristics of Physical Risk Factors

Compared to participants without prediabetes, those with prediabetes had poorer cardiorespiratory fitness levels and had decreased physical activity, both of which increases risk for CVD (Barlow et al., 2012; McAuley et al., 2014; Reddigan et al., 2011). Moderate to high levels of cardiorespiratory fitness may play a protective role in prediabetics, as individuals with low cardiorespiratory fitness are more likely to be insulin resistant (Leite et al., 2009; Totsikas et al., 2011). Cross-sectional data from the 1999-2004 NHANES showed that among individuals with diabetes, participants who sat

during the day and were sedentary had lower average cardiorespiratory fitness (26.1 ml/kg/min [95% CI: 18.9-33.4]) than those doing heavy work or carrying heavy loads (34.6 ml/kg/min [95% CI: 30.2-39.1]) (Loprinzi & Pariser, 2013). Fitness was defined categorically as low fitness (bottom 20%), moderate fitness (middle 40%), or high fitness (upper 40%) according to the previously published Aerobics Center Longitudinal Study guidelines (American College of Sports Medicine, 2013), and most (55.1%) participates from the 1999-2004 NHANES cohort had low to moderate levels of fitness (Loprinzi & Pariser, 2013). Similar results were also reported in the Look AHEAD clinical trial. Participants with T2DM in the intensive lifestyle intervention group who were more physically active had higher cardiorespiratory fitness levels compared to those in the control group (Jakicic et al., 2009). In the current study, participants with prediabetes had a median fitness level of 28.5 ml/kg/min (8.14 metabolic equivalents [METs]; 1 MET=3.5 ml O_2 uptake/kg/min) (IQR: 24-34 ml/kg/min), which was similar to those in 1999-2004 NHANES with diabetes. These findings suggest that the current study participants may have similar physical activity levels than persons with diabetes.

Although cardiorespiratory fitness is an important marker for cardiorespiratory risk for individuals with prediabetes, very few studies have examined fitness in this population (Gatterer, Ulmer, Dzien, Somavilla, & Burtscher, 2011; McAuley et al., 2014). Baseline average maximal oxygen uptake (VO_{2max}) was 7 METs among 72 individuals with prediabetes in a study by Gatterer and colleagues (2011), which is equivalent to 24.5 ml/kg/min. In a study by McAuley and coworkers (2014), baseline average VO_{2max} was 11.9 METs (41.65 ml/kg/min) for men and 9.4 METs (32.90 ml/kg/min) for women in a cohort of 17,044 participants (89% men) with impaired

fasting glucose. In the current study, participants with prediabetes had a total median fitness level of 28.5 ml/kg/min (8.14 METs) (IQR: 24-34 ml/kg/min), and was comparable to persons with prediabetes reported by Gatterer et al. (2011), but it was lower than persons with prediabetes reported by McAuley et al. (2014). The younger participants (mean age 45.9 for men and 47.6 for women) in McAuley et al (2014) study may partly explain higher levels of cardiorespiratory fitness reported in that study.

Data from the 2005-2006 NHANES showed that individuals with prediabetes had fewer steps each day (9,145 vs 10,000) and less total, moderate and vigorous physical activity (minutes/week) than those without prediabetes (Yang et al., 2011). Consistent with these findings, data from the current study also showed that participants with prediabetes were more sedentary as evidenced by lower total, daily living, moderate and vigorous activity levels on the Cross-Cultural Activity Participation Study (CAPS) Typical Week Physical Activity Recall Questionnaire than those without prediabetes. In the NHANES study, those with a sedentary lifestyle had a greater likelihood (ranging from 19% to 35%) of being prediabetic than those with an active lifestyle (p values ranging from 0.018 to 0.061) (Yang et al., 2011). The results from the current study support previous findings that low physical activity levels are associated with greater numbers of experiencing prediabetes, which in turn may increase the probability of developing future CVD. However, in the current study, although total physical activity level in individuals with prediabetes (26.09 METs-hours/week) was lower than individuals without prediabetes (28.74 METs-hours/week), these people were still considered physically active. Previous research has shown that 10000 steps are close to 23 METs-hours/week (Tudor-Locke et al., 2011). Thus, this may partly explain lower

cardiometabolic risk of participants with prediabetes in the current study compared to other populations with prediabetes reported in the literature (Yang et al., 2011).

A negative relationship between levels of physical activity and risk for CVD has been well documented in the literature among both healthy individuals and those with metabolic risk factors (Reddigan et al., 2011). In a number of studies however, there is a dose response in preventing chronic disease such as CVD or reducing all-cause mortality, and this relationship is curvilinear with increasing levels of physical activity. Investigators have shown that the benefits of higher levels of physical activity does not necessarily equate to higher health benefits ("Physical activity guidelines advisory committee report, 2008. To the Secretary of Health and Human Services. Part A: Executive Summary," 2009). Additionally, while intensive lifestyle interventions may prevent the progression from prediabetes to diabetes, once T2DM develops, interventions such as diet, exercise, and weight loss have not resulted in lower rates of adverse cardiovascular events in overweight or obese adults with T2DM (Wing et al., 2013). Therefore, early lifestyle interventions, such as participation in regular moderate physical activity, may represent a window of opportunity for reducing CVD risk among overweight/obese individuals with prediabetes as well prevent or delay the onset of T2DM.

Compared to participants without prediabetes, participants with prediabetes self-reported poorer physical functioning on the Medical Outcomes Study Short Form (SF-36) physical component score (53.8 vs 49.9, p=0.003). The physical component score in the current study was comparable to that in the Diabetes Prevention Program (DPP) study. The baseline physical component scores across the three treatment groups in the DPP

study were 50.6, 50.0, and 50.3 for lifestyle intervention group, metformin group, and placebo group, respectively (Florez et al., 2012). Future studies are needed that address low physical activity levels and this represent an area of opportunity for intervention in this population.

Baseline Characteristics of Psychological Risk Factors

Participants without prediabetes were more likely to self-report poorer mental health functioning on the SF-36 mental component score and higher levels of depressive symptoms. At baseline, 9.7% of participants without prediabetes had Beck Depression Inventory-II (BDI-II) scores indicating mild depressive symptoms (≥11), which is higher than that (6.7%) in the general population (Kessler et al., 2005). In comparison, participants with prediabetes reported better mental functioning on the SF-36 (55.5 vs 53) and had lower depressive symptoms (5.4% vs 9.7%). A recent meta-analysis of 17 community-based cross-sectional studies in the general population demonstrated a significant association between obesity and depressive symptoms. Individuals with obesity were 1.26 times (95% CI: 1.17-1.36, $p \leq 0.001$) more likely to have depressive symptoms than individuals without obesity, and this association was stronger among females (odds ratio [OR]=1.31) than in males (OR=1.12) (de Wit et al., 2010). In the current study, the sample was predominately female, so this is consistent with these findings. The reasons for greater depressive symptoms among those without prediabetes compared to those with prediabetes were unclear, but might reflect the unequal sample size of participants without prediabetes.

The prevalence of depressive symptoms was 5.4% among participants with prediabetes in the current study, which was lower than in the DPP (10.7%). Because the

BDI-II was the instrument used to measure depressive symptoms in the current and DPP study, the conflicting results were not likely due to instrumentation. Other reasons however, may explain the inconsistent findings between studies. Elevated BDI-II scores at baseline and over time during the DPP study were associated with female gender, race/ethnicity (other than non-Hispanic White), less education, higher BMI, fasting insulin levels, and lower physical activity (Rubin et al., 2008). Compared to the DPP cohort (Knowler et al., 2002), participants with prediabetes in the current study were predominately Caucasian (54.7% [DPP study] vs 69.45% [current study], respectively), less heavier in weight (BMI=34 [DPP study] vs 31.2 [current study] kg/m^2, respectively), and more physically active (16.3 [DPP study] vs 26.09 [current study] METs-hours/week, respectively). These important differences in baseline sample characteristics may in part explain the lower levels of depressive symptoms in the current study.

A large body of epidemiologic evidence has shown that low SES is generally associated with higher psychiatric morbidity and disability. A meta-analysis of 51 observational studies concluded that lower-SES individuals had higher odds of being depressed (OR=1.81, $p<0.001$) compared with higher-SES individuals. Once depressive symptoms occurred, lower-SES individuals were more likely to continue to experience these symptoms for longer periods of time compared to those individuals with higher-SES (OR=2.06) due to poorer access to healthcare and fewer resources (Lorant et al., 2003).

A dose-response relationship has also been reported for education and income. For example, one study showed that for each additional year of education, the log odds ratio of being depressed decreased by 3%, and for each 1% increase in relative ranking in

income, the log odds ratio of being depressed decreased by 0.74% (Lorant et al., 2003). Other findings have shown that economic stress is one of several possible explanations for the correlation between low SES and risk of mental illness. Factors that contributed to this effect included how much the local income was below the federal poverty level, the rate of unemployment, and rental housing unaffordability. These three indicators had the most dramatic impact among those with lower SES (Hudson, 2005). These findings suggest that because participants in the current study were predominantly high in SES, their likelihood of being depressed or experiencing depressive symptoms may have been lower than in prior research on similar populations. Thus, the findings from this study suggest that participants with prediabetes were at lower psychological risk for CVD than in prior studies of similar populations.

Compared to participants without prediabetes, participants with prediabetes self-reported better mental functioning on the SF-36 mental component score (53 vs 55.5, p=0.080). A 3% difference between groups on health status scores has been reported as clinically meaningful (Florez et al., 2012). In the current the interpretation of differences in mental health scores is difficult because of the high sociodemographic profile of the current sample and unequal sample sizes, but a difference in 2.5 on scores may not reflect clinically meaningful differences. The mental component score in the current study was comparable to that in the DPP study. The baseline physical component scores across the three treatment groups in the DPP study were 53.8, 54.1, and 54.1 for lifestyle intervention group, metformin group, and placebo group, respectively (Florez et al., 2012). The mental component score in the current study were also comparable to that in the Look AHEAD study. The baseline mental component scores across the two treatment

groups in the Look AHEAD study were 54.1, and 53.7 for diabetes support and education group (control group) and intensive lifestyle intervention group, respectively (Rubin et al., 2014).

Changes in Biological Risk Factors: One-Year Follow-Up Visit

The current findings showed that at one-year follow-up, participants with prediabetes had the most improvements in fasting blood glucose, BMI, and insulin resistance. Participants without prediabetes had improvements in BMI, WHR, LDL-C, IL-6, and microalbuminuria levels. In addition, fasting blood glucose levels (increased by 1.343 mg/dl) and insulin resistance (increased by 0.075) increased among participants without prediabetes, but these were not clinically meaningful changes. The reasons for greater improvements in fasting blood glucose, BMI, and insulin resistance were unclear but this may reflect higher deviation from normal biological values and therefore, these may be more likely to improve with intervention. In addition, participants with prediabetes may have been more motivated to improve their abnormal laboratory values since they were at greater risk for progressing to T2DM.

The findings of this study support that a health partner intervention strategy lowered the biological risk factors among overweight/obese adults with prediabetes. Other studies which are similar using lifestyle interventions have also shown improvements in biological risk factors. For example, at baseline, the mean insulin resistance, as assessed by the homeostatic model assessment-insulin resistance (HOMA-IR), was 7.1, 7.2, and 7.0 for placebo, metformin, and lifestyle intervention groups, respectively. After 1-year post-intervention, HOMA-IR increased by 5.1% in placebo group, while it decreased by 15.3% and 22.7% in metformin and lifestyle intervention

groups, respectively ($p<0.001$) (Haffner et al., 2005). Significant improvements were also reported in the Finnish Diabetes Prevention Study (FDPS) at year one in fasting plasma glucose (-0.2 vs. 0.0 mmol/l) and 2-hour plasma glucose (-0.9 vs. -0.3 mmol/l) in the intervention group compared with the control group (Lindström et al., 2003). By receiving intensive training in diet and physical activity, 50% of the DPP enrollees in the lifestyle intervention group had achieved the goal of weight loss of 7% or more by the end of the study (Knowler et al., 2002). These studies provide robust evidence of the favorable effects of structured lifestyle interventions may have on plasma glucose, body weight, and insulin sensitivity among overweight/obese individuals with prediabetes. The current study adds to the literature by suggesting that a less structured health partner strategy may also have beneficial effects on biological risk factors in overweight/obese persons with prediabetes.

Similar results of reductions in biological risks were also observed among overweight/obese individuals without prediabetes. For example, a meta-analysis of 30 randomized controlled trials conducted over an average of 3 years found that among those in the lifestyle interventions there was improved BMI, waist circumference, and lipid profile, with the exception of TG and HDL-C, among overweight people with cardiovascular risk factors compared to those receiving usual care (Galani & Schneider, 2007).

The findings from the current study indicate that those with prediabetes and without prediabetes benefited from the health partner program in relation to reducing biological risk for CVD. The pattern between the two groups was different however, with prediabetics experiencing the greatest improvements in BMI, fasting blood glucose, and

insulin resistance compared to non-prediabetics. A particularly encouraging finding was the improvements in fasting blood glucose and insulin resistance among overweight/obese individuals with prediabetes. Not so encouraging however, was the increase in fasting blood glucose and insulin resistance among those without prediabetes during the one-year follow-up period.

Comparisons with previous studies that used more structured interventions with the current study that used a less structured health partner approach are problematic and require further discussion. Although participants with prediabetes improved on a number of biological risk factors in the current study, a structured lifestyle intervention was not administered. The participant self-selected and set individual goals for areas of health improvement they would like to accomplish with assistance from a health partner. The frequency of contact with the health partner also varied depending on the preferences of the participant. One plausible explanation for improved biological risks among those with prediabetes is that they may have perceived greater health risks based on their individual test results and counseled from the health partner. As a consequence, those with prediabetes may have desired higher levels of physical activity and weight management to reduce these biological risk factors compared to those without prediabetes who may have had less perceived risk. The health partner program used in the current study was a weaker intervention design than studies using a structured and well-defined lifestyle intervention. In addition, because the current study was not a randomized controlled trial, other alternative explanations may have accounted or influenced the biological changes that occurred in both groups. Future well designed studies using innovate lifestyle interventions are needed to address this problem.

Changes in Physical Risk Factors at One-Year Follow-up Visit

At the one-year follow-up, participants with prediabetes had greater improvements in cardiorespiratory fitness and physical functioning compared to those without prediabetes. Findings from the study using a participant-driven health partner program suggests that improvements in physical functioning and cardiorespiratory fitness may be achieved using less rigorous designs and methods. Studies using a more rigorous structured lifestyle intervention strategy however, often show greater improvement in physical functioning. For example, after a mean follow-up of 3.2 years in the DPP study, compared to placebo group, there was modest but significant improvement in the physical component score of the SF-36 (+1.57, $p<0.0001$) in the lifestyle intervention group. No significant changes were observed in the metformin group (+0.002 and +0.15, respectively, $p=0.6$). The DPP Research Group concluded that lifestyle interventions that resulted in intentional weight loss and increased physical activity had an independent but small to modest association with better health status in overweight/obese participants with prediabetes (Florez et al., 2012).

Studies examining physical functioning in overweight/obese individuals without prediabetes are very limited. This study adds to the current literature to evaluate the potential effects of a health partner program on physical functioning among those without prediabetes. Although both prediabetics and non-prediabetics had improvement in physical functioning, the response to behavioral interventions is inconsistent among different populations. In the current study, prediabetics had the most change in physical functioning at one-year follow-up. The effect of the health partner program was likely influenced by participant's baseline physical functioning levels. Participants with

prediabetes had significantly worse physical functioning at baseline than those without prediabetes, as indicated by the baseline SF-36 physical component score (49.9 vs 53.8, p=0.003). This finding is consistent among other studies across different populations that those with actual or perceived lower physical functioning levels often have the greatest improvement from intervention (Williamson et al., 2009).

The potential benefits of a health partner program on cardiorespiratory fitness among overweight/obese adults with prediabetes have not been previously reported. The current study showed that in response to a health partner program, cardiorespiratory fitness slightly increased among those with prediabetes, while it decreased among those without prediabetes at the one-year follow-up period. Studies have evaluated similar outcomes among overweight/obese adults with T2DM (Jakicic et al., 2009). In the Look AHEAD trial for example, cardiorespiratory fitness was significantly improved in overweight diabetic adults in the lifestyle intervention group compared to the diabetes support and education group (20.9% vs 5.7%; p<0.0001). In addition, structured lifestyle interventions may have varying effects on improvement in fitness among adults with different BMI categories. For example, the differences achieved in fitness were lower in individuals with higher baseline BMI. Individuals with class II (BMI: 35-39.9 kg/m^2) and III (BMI≥40 kg/m^2) obesity had significantly lower improvement in cardiorespiratory fitness compared to overweight counterparts (BMI: 25-29.9 kg/m^2) after 1-year follow-up. In the current study, the median BMI among those with prediabetes at baseline was 31.2 kg/m^2, and on average, they reduced their BMI by 1.685 kg/m^2 at one-year follow-up visit. The weight loss achieved by participants with prediabetes may be one reason to explain for the increase in cardiorespiratory fitness. The other reason may be individuals

with prediabetes exercised more because of their baseline lower cardiorespiratory fitness levels. However, why there was a decrease in cardiorespiratory fitness among those without prediabetes remains unclear, especially given that these participants had lower baseline weight, and they also achieved weight loss during the course of the health partner program. Gender and age differences in fitness level have well documented in the literature. Absolute VO_{2max} is, on average, 40 percent greater in a man than a woman (Brooks, Fahey, & Baldwin, 2004). Cardiorespiratory fitness declines with aging in the general population. A decrement in VO_{2max} of about 1.6% per year in both men and women has been described (Hakola et al., 2011). Therefore, the fact that the majority of the sample was older and female may also explain why there was less change over time in cardiorespiratory fitness in both groups. In addition, although both groups had weight loss, it remains less clear how much weight loss is required to show a significant improvement in cardiorespiratory fitness, and this needs to be addressed in a future study.

Changes in Psychological Risk Factors at One-Year Follow-up Visit

The study findings revealed that at one-year follow-up, participants with prediabetes had the most improvement in depressive symptoms. Participants without prediabetes had improvements in both depressive symptoms and mental functioning. However, there were no significant differences in changes in depressive symptoms and mental functioning between those with and without prediabetes.

This study has shown the potential beneficial effects of a health partner program on alleviating depressive symptoms among overweight/obese individuals without prediabetes, which are consistent with previous studies. For example, after a 3-year follow-up, favorable changes in depressive symptoms were observed in the intervention

group in the FDPS. Although there was no significant difference in changes of the BDI-II scores between the study groups (p=0.965), BDI-II scores decreased more in the lifestyle intervention group (0.90±4.54; 95% CI:-1.99 to -0.19) than in in the control group (0.75±4.47; 95% CI: -1.80 to 0.31) (Ruusunen et al., 2012). Similar to the FDPS, results from the Look AHEAD clinical trial have also provided support for the additional benefits lifestyle interventions have on depressive symptoms among 5145 overweight T2DM adults. A greater decrease in depressive symptoms measured by the BDI-II measured was observed in the lifestyle intervention group (-0.83±4.86, p<0.001) compared to the diabetes support and education group (-0.23±4.63, p<0.001) after 1-year follow-up. In line with the reciprocal relationship between depression and obesity in the literature, the Look AHEAD Research Group concluded that the improvement associated with structured lifestyle interventions in these subjects was mediated by weight loss (Williamson et al., 2009).

A paucity of studies has examined changes in mental functioning in response to lifestyle interventions among overweight/obese individuals without prediabetes. This study evaluated the potential treatment effects of the health partner program on mental functioning among those without prediabetes. Similar studies were conducted among individuals with prediabetes and reported in the DPP study. Participants in the lifestyle intervention group showed improvement in mental component score of the SF-36 (Florez et al., 2012). The current study used a non-structured, participant-driven health partner approach, so direct comparisons with other structured, randomized lifestyle interventions are not possible. In the DPP trial however, compared to those who experienced weight gain, health status scores in three physical domains (physical function, general health,

and body pain) and in one mental domain (vitality) reached a significant difference in those who achieved moderate (3.7%-7%) or major (>7 %) weight loss. Weight loss was found to be the most important factor associated with improvement in mental functioning among participants in the DPP clinical trial (Florez et al., 2012). The lack of change in BMI and WHR between baseline and the one-year follow-up in the health partner program may in part explain why mental functioning showed no improvement over time. As indicated earlier, the methodological limitations of the parent study not using standardized program may have contributed to the lack of change in these outcome variables. A more intensive lifestyle intervention may be needed to achieve greater weight loss and improve mental health component score of the participants.

Diabetes Phenotype and Lifestyle Interventions

Amongst the 387 million people with diabetes worldwide in 2014, over 200 million came from Asia, with China and India having the most cases of diabetes (International Diabetes Federation, 2014). Compared to Western populations, the prevalence of overweight and obesity in Asia is relatively low, but Asians are more likely to develop T2DM even with a lower BMI (Chan et al., 2009; Hu, 2011). In addition, even a modest amount of weight gain substantially increases the risk of T2DM in susceptible Asian subjects (Hu, 2011). Several studies in Asian populations, especially in Asian Indians, have highlighted the "metabolically obese" phenotype among high-risk normal-weight individuals (Hu, 2011; J. W. Lee, Brancati, & Yeh, 2011; Ramachandran, Ma, & Snehalatha, 2010). This phenotype is characterized by greater abdominal obesity despite a normal BMI, less muscle mass, 3% to 5% higher total body fat, and increased propensity for insulin resistance than in Western populations (Hu, 2011; Mehta, Mahajan,

Steinbeck, & Bermingham, 2002; Ramachandran, Snehalatha, Shetty, & Nanditha, 2012). This phenotype may explain why Asians are at higher risk of developing T2DM despite a lower BMI, when compared with Western populations.

Similar to other multifactorial diseases, T2DM is considered a product of the interplay between genetic and environmental factors (Hu, 2011). On the one hand, it is possible that genetic factors that underlie one's susceptibility to T2DM are amplified in the presence of certain environmental triggers (Hu, 2011). On the other hand, given the relatively stability of DNA sequence within populations over decades, recent increases in T2DM prevalence may largely be attributed to environmental changes (Abdullah, Attia, Oldmeadow, Scott, & Holliday, 2014). The rapid increase in the Western-style fast food outlets has had a huge impact on the T2DM epidemic in Asia. For example, traditional Chinese dietary patterns, characterized by high consumptions of fruits, vegetables, whole grains, and limited consumption of animal products, are shifting towards Western dietary patterns, characterized by high intakes of processed red meats, polished rice, refined wheat, and sugar-sweetened beverages (Hu, 2011). Habitual Western-style fast food consumption is positively associated with a higher risk of cardiometabolic disease in Asian countries. A large prospective cohort study found that Chinese Singaporeans who had Western-style fast foods more than twice a week had a 27% increased risk of developing T2DM and a 56% increased risk of dying from coronary heart disease, compared to their counterparts who reported little or no intake (Odegaard, Koh, Yuan, Gross, & Pereira, 2012).

Very few studies have examined gene-environment interactions in the context of T2DM risk. In the Health Professionals' Follow-up Study, Qi and associates (2009)

found a significant interaction between a Western-style dietary pattern and a genetic risk score of T2DM based on 10 single nucleotide polymorphisms (p=0.02). The Western-style dietary pattern was associated with an increased risk of T2DM among those with a greater genetic risk score (≥12 risk alleles; p for trend=0.01), but not those with a lower genetic risk score (Qi, Cornelis, Zhang, van Dam, & Hu, 2009). Other studies have also reported an interaction between transcription factor 7-like 2 variants and the quality and quantity of ingested carbohydrates in the context of T2DM risk, and a stronger association was observed in those with a high-risk genetic profile (Qi & Liang, 2010). These studies suggest that the detrimental effects of environmental factors on T2DM risk may be enhanced by unfavorable genotypes. However, no studies have been conducted in Asia, and gene-environment interactions in T2DM risk among Asians require more investigation.

Even with a focus on the "metabolically obese" phenotype among high-risk normal-weight Asians, lifestyle interventions to prevent T2DM among high-risk Asian individuals should not differ significantly from those conducted in Western populations. Large randomized controlled trials conducted in China (Pan et al., 1997), India (Ramachandran et al., 2006), and Japan (Kosaka, Noda, & Kuzuya, 2005) provided robust evidence that lifestyle interventions are effective for T2DM prevention among high-risk Asian populations. Although these T2DM prevention programs differ in details, those that are the most successful share some common components with the DPP: a low-fat, reduced-calorie diet and weight loss for overweight or obese individuals, increasing intake of fibers, avoidance of sugar, and an increase in leisure-time physical activity for all participants (Kosaka et al., 2005; Pan et al., 1997; Ramachandran et al., 2006). All

programs provide structured lifestyle interventions and utilize risk identification, risk communication, and motivate participants to change lifestyle behaviors (Weber, Oza-Frank, Staimez, Ali, & Narayan, 2012). In addition, a key component of these programs is to implement a comprehensive approach that addresses Westernized lifestyles adopted by Asian populations, such as physical inactivity and unhealthy dietary patterns. Since recent increases in T2DM prevalence may largely be attributed to environmental changes (Abdullah et al., 2014), lifestyle interventions that address Westernized lifestyles as those conducted in Western populations have been shown to be equally effective in T2DM prevention among Asian populations, despite differences in diabetes phenotype.

Strengths of the Study

There are several strengths of this secondary analysis study. First, this study reported biological, physical, and psychological risk factors and their relation to CVD risk among overweight/obese adults with and without prediabetes. It was also designed to determine if there are differences in biological, physical, and psychological risk factors among overweight/obese adults with and without prediabetes. Although there were many methodological issues, the findings that a participant-driven, non-structured health partner program influenced biological and physical outcomes are important. The use of highly structured lifestyle programs has been found to decrease in effectiveness over time (Orchard et al., 2013). The less structured interventions and goals set by participants may have same benefits over time for maintaining lifestyle changes associated with less CVD risk and improved health outcomes. Well-designed studies that compare the two approaches are needed on short and long term outcomes in this population. Another strength of the study was the dataset, which was comprehensive. In addition, a number of

biological risk factors were available for analysis that contributed to a comparison and greater understanding of the biological risk and differences associated in these two study groups that often are not available in other clinical studies.

Secondary data analyses are limited by which variables are selected for outcome measurement, the instruments employed, how data are collected, analyzed and interpreted. The quality of the secondary analysis therefore, depends on the quality of the data collected. Meticulous examination of the data set and obtaining all documentation of instruments and procedures that accompany the database was completed prior to initiating the secondary analysis. The supporting documentation, for example, included: procedures for coding missing data, codebooks to identify variables, research proposals, any publications, formula for weighting variables, frequency tables of the original items, and copies of the instruments (Garmon Bibb, 2007; Jacobson, Hamilton, & Galloway, 1993). In the proposed secondary analysis, the researcher was provided the opportunity to meet with the original Center investigators to discuss the study design, procedures, and information required to conduct the analysis.

Limitations of the Study

This secondary analysis has several limitations that are associated with the larger Center study. First, those who participated in the Center program were predominately White, female, middle-aged, well educated, healthy, and had high income levels. In addition, given the missing data for fasting blood glucose, the resulting sample was only 13% prediabetic which is well below the expected 37% prevalence rate in the general population (Centers for Disease Control and Prevention, 2014). The sample characteristics may have influenced external validity of the study. Therefore, it is unclear

to what extent the sample is representative of others overweight/obese with and without prediabetes and therefore must be interpreted with caution. Future studies are needed in a larger, more diverse prediabetic population to longitudinally and more comprehensively examine the biological, physical, and psychological risk factors for CVD in this dramatically increasing population.

Second, only 10% of the 30% of solicited employees who agreed to be contacted for screening enrolled in the study. The reasons for non-participation of the solicited employees were not made available and it was unclear to what extent those who enrolled and did not enroll in the Center were similar or differed in characteristics. For example, participants who wanted to achieve self-directed health goals may have been more likely to enroll in the study, which contributed to selection bias. In addition, it is unclear to what extent the Center population reflected Emory University since there was no attempt to stratify recruitment by employment status, ethnicity, or gender. The high cost of the Center program to the general public implied that only high income individuals likely joined and may have further contributed to selection bias. The Center recruitment process may have been strengthened by a different sampling strategy such as stratification by employment status, gender, or ethnicity in order to ensure a more representative sample. In addition, the ability to determine differences in employees who joined or did not join the Center would help identify specific strategies to encourage participation in future similar employee health programs.

Third, there was no information on medications in the de-identified data, so the number of participants who took lipid lowering statins was not clear. Statins are often prescribed for people with high cholesterol to lower their total cholesterol and LDL-C to

reduce their risk of a heart attack or stroke. However, a review of findings from observational studies and meta-analyses showed that statins can modestly raise blood glucose levels, and an association of incident diabetes with statin use in patients with concomitant risk factors for diabetes (Park, Juska, Dyakov, & Patel, 2014). This may in part, explain the close-to-optimal LDL-C levels in the current study participants with prediabetes.

Fourth, fasting blood glucose was only available on approximately 50% of participants, which was a threat to internal validity of the study. The reasons participants did not have their blood glucose levels drawn were unclear, since documentation was not available. Because missing blood glucose data could not be controlled as part of a secondary analysis, it is possible that that we did not include subjects who were prediabetic in the analysis. In addition, some individuals may have been reluctant to have their blood glucose drawn for a number of reasons, including requirement for fasting, lack of time for an early morning laboratory visit and fear of what the blood test may reveal. The likelihood that the fasting blood glucose data were not randomly missing may have introduced bias.

Another major limitation in the study design of the parent study is the lack of a control group to compare the effects of the health partner program. The major threat to internal validity associated with single-group time-series quasi-experimental design is history (Cook & Campbell, 1979; Shadish, Cook, & Campbell, 2001). It is impossible, for example, to rule out the possibility that other extraneous factor may have influenced health outcomes measures (Cook & Campbell, 1979). Adding a non-equivalent, non-treatment time series control group that has similar sociodemographic characteristics

would have reduced this threat. A medical record sample would enable comparison of some risk factors over time, but controlling for all potential confounders would be difficult. The reasons for not including a control group or adding a more stringent intervention design were unclear. Despite these limitations, the Center provided a comprehensive battery of data for analysis that did advance the knowledge about biological, physical and psychological risk factors in this population and use of non-structured programs in a predominately White and female population.

Recommendations for Future Research

Future studies are needed to replicate this study in a sample more representative of the general population of overweight/obese individuals with and without prediabetes. Specifically, participants in this study were predominately female, Caucasian, college-educated, employed full-time, and most were high SES level, which limits external validity. In addition, the significant amount of missing blood glucose data threatened internal validity, since it is unclear how many participants had prediabetes. As a result, the findings of this study need to be interpreted with caution, and future studies with a more diverse and representative population is essential to better understand the biological, physical and psychological risk for CVD in a more representative sample.

Most interventions, such as the one used in the DPP, FDPS, and Chinese Da Qing Study, focused on weight loss rather than strategies to maintain weight reduction. Because many of the beneficial effects of lifestyle changes accrue over time, long-term adherence maximizes individual and population benefits. While weight loss is important, future studies are also needed to examine strategies to prevent weight gains after weight loss among high-risk populations. Wing and Hill (2001) proposed that individuals with

successful weight maintenance of weight loss be defined as those who have intentionally lost at least 10% of their body weight and maintain the loss at least 1 year (Wing & Hill, 2001). The latest evidence on long-term weight loss success from a 10-year observational study of self-reported weight loss and behavior change in 2886 participants (78% female; mean age 48 years) in the National Weight Control Registry suggests that decreases in leisure-time physical activity, calorie restrictions, and frequency of self-weighing and increases in energy intake from fat and disinhibition were associated with long-term weight regain (Thomas, Bond, Phelan, Hill, & Wing, 2014). However, these strategies were not examined in the Diabetes Prevention Program Outcomes Study. Interventions that combine these strategies should be tested in the future studies to prevent weight gain among overweight/obese individuals with prediabetes.

Given the difficulties of losing weight and maintaining weight loss over the long term (Wing & Phelan, 2005), it is important to identify methods other than weight loss for risk reduction among overweight/obese individuals with prediabetes. Since high cardiorespiratory fitness is a strong and independent predictor of lower all-cause and CVD mortality (Barlow et al., 2012; Lyerly et al., 2009; Rankinen et al., 2007), and may attenuate the higher risk of morbidity and mortality associated with obesity (McAuley et al., 2014; Sui et al., 2007), improving cardiorespiratory fitness levels among this population is especially important. Individual level of fitness is dependent on those modifiable (physical activity, smoking, obesity, medical condition) and non-modifiable (age, gender, and genotype) factors, but it is primary determined by regular physical activity (American College of Sports Medicine, 2013; D. C. Lee et al., 2010). A dose-response relationship between regular physical activity and improvement in fitness levels

has been demonstrated from several randomized controlled trials, suggesting that increasing either intensity or volume of physical activity appears to have additional effects on fitness levels after controlling for each other (Church, Earnest, Skinner, & Blair, 2007; Duscha et al., 2005; O'Donovan et al., 2005). Even moderate intensity physical activity at 40-55% of peak VO_{2max} intensity is sufficient to improve cardiorespiratory fitness level (Church et al., 2007; Duscha et al., 2005).

The low cardiorespiratory fitness and levels of physical activity at baseline suggest that exercise may be particularly beneficial in persons with prediabetes for lowering CVD risk factors. Similar lifestyle interventions aimed at increasing even moderate intensity physical activity is likely to increase fitness levels and be important for CVD prevention among overweight/obese individuals with prediabetes. It is not clear, however, whether such lifestyle interventions may have any effect on T2DM prevention among overweight/obese individuals with prediabetes. The failure to demonstrate a significant improvement in overall fitness by the health partner program may be partly attributed to the limitation of the study design. In addition, since the health partner program is individualized rather than structured, not every intervention mutually agreed upon by the health partner and the participant is targeted in improving regular exercise. Future studies with a more rigorous study design and longer follow-up are needed to examine the effects of lifestyle interventions aiming at improving physical activity on changes in overall fitness level, CVD and T2DM prevention among overweight/obese individuals with prediabetes.

In addition to regular physical activity, data from the 1999-2004 NHANES found that individuals who were obese had approximately 10% to 15% lower fitness level than

non-obese individuals (C. Y. Wang et al., 2010). Similar findings have also been reported among individuals with prediabetes. Overweight and obese prediabetics had approximately 10% to 23% lower fitness level than normal-weight prediabetics, respectively (McAuley et al., 2014). Findings from the Aerobics Center Longitudinal Study show that engaging in physical activity, maintaining a normal weight, and not smoking were associated with substantially higher levels of cardiorespiratory fitness across the adult life span in both men and women (Jackson, Sui, Hebert, Church, & Blair, 2009). Taken together, these studies suggest that a combined strategy is needed to improve cardiorespiratory fitness levels among overweight/obese individuals with prediabetes. The combined strategy should include weight loss and regular moderate intensity physical activity, and should be tested in the future studies to improve fitness levels among overweight/obese individuals with prediabetes.

Implications for Clinical Practice

The findings from the current study have several implications for clinical practice with overweight/obese individuals with prediabetes. First, since healthy overweight/obese participants with prediabetes were likely at higher biological and physical risk for CVD at baseline compared to those without prediabetes, it is necessary for clinicians to develop and test a screening tool, such as biochemical tests, aimed at identifying these risks in this population. Second, the highest risk of mortality and cardiometabolic disease is observed in those who are both obese and unfit (McAuley et al., 2014; Sui et al., 2007). The low cardiorespiratory fitness and physical activity levels at baseline suggest that exercise may be particularly beneficial in persons with prediabetes for lowering these cardiovascular risk factors. Therefore, clinicians should encourage patients to actively engage in regular

moderate intensity physical activity on most days of the week to develop and maintain higher levels of cardiorespiratory fitness, whether or not weight loss is achieved.

Third, provider advice and preventive measures aimed at reducing CVD risk should be proactively incorporated into clinical practice. Data from the 2005-2006 NHANES showed that after practicing weight control suggested by the providers, patients demonstrated a significantly lower prevalence of obesity and a higher prevalence of lower LDL-C and higher high-density lipoprotein levels (Yang et al., 2011). Studies have shown however, that only one third to two fifths of individuals with prediabetes have been advised by their clinician to take any steps to reduce their cardiovascular risk with lifestyle changes (Dorsey & Songer, 2011; Geiss et al., 2010; Yang et al., 2011). Therefore, it is important for clinicians to raise the awareness of high risk for CVD and T2DM and to provide clear advice on methods to reduce this risk among overweight/obese individuals with prediabetes.

Fourth, it is important for clinicians to help patients identify specific and appropriate goals for weight loss, and clinicians and patients should discuss and adjust those goals on a regular basis. These discussions will provide valuable feedback to patients as well as clinicians about the progress of weight loss. Finally, clinicians must recognize that it is not sufficient to educate patients about weight loss, and that it is important to increase focus on preventing weight gain in the long-term. In particular, encouraging patients to continue to adhere to dietary restrictions, engage in high levels of physical activity, and self-monitor weight is important to prevent weight gains and achieve better health outcomes.

Conclusions

The purpose of this study was to compare the baseline biological, physical, and psychological risk factors in overweight/obese adults with and without prediabetes, and determine if a health partner program reduced biological, physical, and psychological factors in overweight/obese adults with and without prediabetes at 12 months. The findings of this study indicate that healthy overweight/obese participants with prediabetes were likely at higher biological and physical risk for CVD at baseline compared to those without prediabetes. Although the risk is lower than those with T2DM, early intervention to improve CVD risk progression is essential. There is a lack of clear evidence on the best strategy to prevent the progression of prediabetes to T2DM. The evidence that weight loss or dietary restrictions prevent the onset of T2DM has not been fully elucidated. The presence of diabetes phenotypes and their differing characteristics and therapeutic responses suggest that targeting the specific phenotype of the individual with prediabetes may be key to developing effective interventions to prevent the onset of T2DM in the future.

The low cardiorespiratory fitness and physical activity levels suggest that exercise may be particularly beneficial in persons with prediabetes for lowering these CVD risk factors. Again, the identification of phenotypes and response to exercise is an area of future study that may shed light on the most appropriate strategy for optimizing outcomes in prediabetes and prevention of T2DM. Although positive benefits were achieved using the health partner program, the considerable limitations of the sample and missing data prevent definitive conclusions and generalizations. Future studies are needed in a larger, more diverse prediabetic population to longitudinally and more comprehensively

examine the biological, physical, and psychological risk factors for CVD in this dramatically increasing population.

Appendices

Appendix A. Mechanisms of Vascular Damage in Prediabetes

Small-vessel complications may also occur due to tissue ischemia as a consequence of a failure of reactive vasodilation, which is mediated by availability of nitric oxide (Hanna-Moussa, Gardner, Kurukulasuriya, & Sowers, 2009; Singleton, Smith, Russell, & Feldman, 2003). The mitogen-activated protein kinase signaling pathway, in contrast, remains unaffected in an insulin-resistant state. As compensatory hyperinsulinemia develops, this signaling pathway promotes endothelial proliferation (Groop, Forsblom, & Thomas, 2005; Milman & Crandall, 2011). Insulin-sensitizing medications, in particular the thiazolidinedione class of drugs, such as rosiglitazone (Avandia) and pioglitazone (Actos), have a major impact on improvement of endothelial dysfunction (DeFronzo & Abdul-Ghani, 2011).

Although many different pathways have been involved in mediating the vascular injuries of hyperglycemia, a unifying theory proposed by Brownlee (2005) indicated that hyperglycemia promotes overproduction of reactive oxygen species, notably, superoxide anion, by the mitochondrial electron transport chain (Brownlee, 2005). This has been proposed as the key and first process in the vascular damage associated with hyperglycemia (Brownlee, 2005; Ceriello, 2005). Although these mechanisms have been shown to occur in T2DM, they also have relevance to vascular dysfunction in the prediabetic state that are characterized by mild and/or transient hyperglycemia (Milman & Crandall, 2011). In addition to being directly injurious to vasculature, reactive oxygen species act to bind nitric oxide and convert it to peroxynitrite, which causes damage to

the endothelial cells. Increased production of reactive oxygen species also leads to oxidation of LDL-C, making it more atherogenic (Hanna-Moussa et al., 2009).

Chronic and acute hyperglycemia confers an increased risk for vascular damage in part through alteration in the activity of protein kinase C, which, in turn, increases secretion of endothelin, type IV collagen, and fibronectin. These biologically active substances enhance expression of adhesive molecules in endothelial cells and activate macrophage migration process (Bianchi, Miccoli, Penno, & Del Prato, 2008). In such an environment, the endothelial cells promote local inflammation (Strom & Libby, 2010). In addition, hyperglycemia activates the enzyme aldose reductase, which converts excess glucose to sorbitol. Sorbitol is then metabolized by sorbitol dehydrogenase to fructose. Glucose, and especially sorbitol and fructose, reacts nonenzymatically with proteins, lipids, and nucleic acids to produce advanced glycation end products, which further increase reactive oxygen species production that consumes the availability of nitric oxide (Hanna-Moussa et al., 2009).

Interventions to Prevent the Development/Worsening of Prediabetes-Related Cardiovascular Risk Factors

Prevention of CVD should be pursued with the same vigorous effort when prediabetes develops as in T2DM, since prediabetes carries a significant risk of CVD. The demonstration that T2DM is preventable as shown in the landmark T2DM prevention studies (Knowler et al., 2002; Pan et al., 1997; Tuomilehto et al., 2001) suggests the possibility of concomitant prevention of CVD morbidity and mortality associated with prediabetes, since T2DM and CVD share common genetic and environmental antecedents, known as the ‘common soil’ hypothesis (Stern, 1995). The

potential for preventing CVD can be assessed by evaluating three distinct outcomes: cardiovascular risk factors, surrogate markers of atherosclerosis, or clinically significant cardiovascular events (Nathan et al., 2007). Both lifestyle interventions and pharmacological agents have been used to achieve this goal.

The DPP Research Group demonstrated the effects of intensive lifestyle interventions, metformin (Glucophage), and placebo on cardiovascular risk factors among subject with prediabetes (Ratner et al., 2005). In the DPP clinical trial, the prevalence of hypertension was 30% at baseline in the three comparison groups. At the 3-year follow-up, the hypertension prevalence increased to 40% in the metformin and control arms, but it remained at 30% in the lifestyle intervention group, accompanied by significantly decreased systolic and diastolic blood pressures ($p<0.001$) (Ratner et al., 2005). In the lifestyle intervention group, the need for antihypertensive agents was also significantly reduced. For example, 17% of the participants reported the use of antihypertensive medications at baseline in three comparison groups.

At the 3 year follow-up, the prevalence of antihypertensive pharmacologic therapy was significantly lower (27%-28%) in the lifestyle modification group than in control (31%) or metformin (32%) groups ($p<0.001$). Total cholesterol and LDL-C levels were similar among the three comparison groups in the DPP study. Significantly lower TG levels, however, were found in the intensive lifestyle group (-0.296 mmol/l [-25.4 mg/dl]) than in the controls (-0.13 mmol/l [-11.9 mg/dl]) and metformin (-0.08 mmol/l [-7.4 mg/dl]) group. The HDL-C levels were also significantly increased in the lifestyle group (+0.026 mmol/l [+1.0 mg/dl]) compared with the metformin (+0.008 mmol/l or [+0.3 mg/dl]) and control (-0.002 mmol/l [-0.1 mg/dl]) groups. Consistent with reduction

in lipid levels, the need for lipid lowing medications was the lowest among subjects assigned to the intensive lifestyle arm (12%) compared to those assigned to metformin (16%) and placebo (16%) groups at year 3 (Ratner et al., 2005). These findings provide compelling evidence of the positive influence of lifestyle modification which reduced multiple risk factors associated with CVD. The failure to demonstrate cardiovascular protective effects by metformin may be partly attributed to the very low (<5%) prevalence of documented cardiovascular events at baseline, because subjects who had a recent cardiovascular events within the previous 6 months were excluded from the DPP study.

In addition to metformin, other pharmacological agents have also been used. The results are inconsistent, depending on the medications prescribed. Pioglitazone (Actos), an insulin-sensitizing medication, has been used to reduce cardiovascular risk factors among individuals with prediabetes in a randomized, double-blind, placebo-controlled trial (DeFronzo et al., 2011). A total of 602 participants with a mean age 52.3 and a mean BMI 34.5 were enrolled. The intervention group received pioglitazone (30 mg once daily for the first month and 45 mg once daily thereafter) and the control group received matching placebo. After a median follow-up period of 2.4 years, although systolic blood pressure did not differ between the groups, a decreased in diastolic blood pressure was associated with pioglitazone therapy (-2 mm Hg vs 0.0 mm Hg, p=0.03). A significantly higher HDL-C levels were also found in the pioglitazone group (+0.4 mmol/l [7.35 mg/dl]) compared to control group (+0.3 mmol [4.5 mg/dl]).

In the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial (Gerstein et al., 2006), 5269 adults with IGT, or IFG, or both, who had

no previous CVD were randomly assigned to receive rosiglitazone (4 mg once daily for the first 2 months and then 8 mg once daily) or placebo and followed for a median of 3 years. The study showed that rosiglitazone (Avandia) decreased the development of T2DM and reduced blood pressure, with mean systolic and diastolic blood pressure being 1.7 mm Hg and 1.4 mm Hg lower, respectively, in the rosiglitazone group than in the placebo group ($p<0.0001$).

Of the usual surrogate measures of atherosclerosis, only carotid intima-media thickness has been studied in T2DM prevention trials. Carotid intima-media thickness is highly correlated with cardiovascular events, and changes in this measure over time have predictive value beyond that of standard markers of risk, such as lipid profile (Crouse, 2006; Hodis et al., 1998). In a subgroup of patients (n=115) with both IFG and IGT from the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, acarbose (Precose), an intestinal alpha glucosidase inhibitor, was associated with by a 50% decrease in the progression of carotid intima-media thickness compared to placebo (Hanefeld et al., 2004). In another clinical trial, pioglitazone (Actos) slows the progression of carotid intima-media thickness by 31.5% ($p=0.047$) compared to placebo in subjects with prediabetes (DeFronzo et al., 2011). Based on limited data available, pharmacological agents seem to be effective in reducing the progression of carotid intima-media thickness among adults with prediabetes. However, the effectiveness of achieving this goal by lifestyle interventions remains to be determined in future studies in this population.

Often, time is a necessary cofactor that allows transmutation of risk factors, such as lipid profile shown in the DPP study (Ratner et al., 2005), to clinical cardiovascular

events. Strategies aimed at reducing cardiovascular risk factors therefore should lead to low cardiovascular events and mortality in the long-term. However, previous data from published trials were not available to determine whether this occurs due to low statistical power to detect small differences between intervention and control groups (Li et al., 2008; Orchard et al., 2013; Uusitupa et al., 2009). More recently, after 23-year follow-up, the Chinese Da Qing Study was the first randomized controlled trial to show that lifestyle interventions aimed at changing diet and physical activity reduced all-cause and CVD mortality among individuals with IGT (Li et al., 2014).

The 20-year follow-up study of the Chinese Da Qing Study and the 10-year follow-up study of the FDPS were two of the limited studies to assess whether lifestyle interventions had a long-term effect on cardiovascular events and CVD mortality over the 20-year follow-up period (Li et al., 2008). The results showed no statistically significant differences in cardiovascular events (HR=0.98), CVD mortality (HR=0.83), or all-cause mortality (HR=0.96) between the control group and the three intervention groups, although a non-significant 17% reduction in CVD mortality was reported in the combined (diet-plus-exercise) intervention group. Secondary analysis of the FDPS showed that after a median follow-up period of 10.2 years, there were 57/257 new cardiovascular events in the intervention group and 54/248 in the control group, which did not differ significantly between the intervention and control groups (Uusitupa et al., 2009). The limited statistical power and an initial lower CVD risk profile precluded a reliable conclusion of whether lifestyle interventions led to reduced cardiovascular events and mortality (Li et al., 2008; Uusitupa et al., 2009). However, particularly encouraging was the finding that each of these outcomes (i.e., cardiovascular events, CVD mortality, and all-cause

mortality) was lower for people who received an intervention, which may be interpreted as a beneficial effect of lifestyle interventions over the long-term.

More recently, the 23-year follow-up study of the Chinese Da Qing Study showed that cumulative CVD incidence was 11.9% (95% CI: 8.8%-15.0%) in the intervention group versus 19.6% (95% CI: 12.9%-26.3%) in the control group (hazard ratio [HR]=0.59, 95% CI: 0.36-0.96; p=0.033). All-cause mortality was 28.1% in the intervention group versus 38.4% in the control group (HR=0.71, 95% CI: 0.51-0.99; p=0.049) (Li et al., 2014). A key difference between this study and previous studies (Li et al., 2008; Orchard et al., 2013; Uusitupa et al., 2009) is the length of follow-up. A short length of follow-up may not be sufficient to detect any significant effects of lifestyle interventions on CVD mortality. In the Chinese Da Qing Study, a difference in CVD mortality between the intervention and control groups started to emerge 12 years after the study began, slowly increased to a 17% difference at the 20-year follow-up (Li et al., 2008), and was statistically significant at the 23-year follow-up (Li et al., 2014). Another key difference between this study and the 20-year follow-up study of the Chinese Da Qing Study (Li et al., 2008) is that the original three intervention groups in the Da Qing Study were combined a priori to increase the statistical power to detect any mortality difference attributable to the intervention in this study. This may partly explain the different findings between the two study reports.

Pharmacological agents have also been employed to prevent cardiovascular events among prediabetics and have shown mixed results, depending on the medications prescribed. In the STOP-NIDDM trial, prevention of T2DM among people with both IFG and IGT by acarbose (Precose) was associated with a 49% relative risk reduction in the

development of cardiovascular events (HR: 0.51; 95% CI: 0.28-0.95; p=0.03) and a 34% relative risk reduction in the incidence of new cases of hypertension (HR: 0.66; 95% CI: 0.49-0.89; p=0.006). The reduced risk of cardiovascular events (HR: 0.47; 95% CI: 0.24-0.90; p=0.02) and hypertension (HR: 0.62; 95% CI: 0.45-0.86; p=0.004) associated with acarbose treatment remained statistically significant even after adjusting for major risk factors (Chiasson et al., 2003). The results were limited, however, given the relatively small number of cardiovascular events in both comparison groups (15 in the acarbose group and 32 in the placebo group). Besides relatively small numbers of cardiovascular events, short follow-up periods (average duration was only 3.3 years) may have also led to inadequate power and limited ability to interpret findings.

In contrast, the DREAM Trial showed conflicting results (Gerstein et al., 2006). Despite a potent reduction in T2DM incidence among individuals with either IFG, or IGT, or both who received rosiglitazone (Avandia) compared to placebo ($p<0.0001$), both treatment groups had a similar frequency of composite cardiovascular outcomes with the exception of heart failure: 14 (0.5%) participants in the rosiglitazone group and two (0.1%) in the placebo group developed heart failure (p=0.01).

The combined use of both lifestyle modification and pharmacological agents in lowing cardiovascular risk was examined in a large, prospective clinical trial, called the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study. The NAVIGATOR study was designed to evaluate whether nateglinide (Starlix), a blood glucose-lowering drug in the meglitinide class, or valsartan (Diovan), an angiotensin-receptor blocker, would reduce the risk of T2DM and cardiovascular events among patients with both IFG and IGT and established CVD or

cardiovascular risk factors (Holman et al., 2010; McMurray et al., 2010). In this double-blind, randomized clinical trial with a two-by-two factorial design, a total of over 9000 subjects at 806 centers from 40 countries were assigned to receive valsartan (up to 160 mg daily) or placebo (and nateglinide or matching placebo) in addition to lifestyle modification. The patients were followed up for a median of 5 years for occurrence of three co-primary outcomes: development of T2DM; an extended cardiovascular outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina; and a core composite outcome that excluded unstable angina and revascularization.

The cumulative incidence of T2DM was 33.1% in the valsartan group, as compared with 36.8% in the placebo group (HR=0.86 in the valsartan group; 95% CI=0.80 to 0.92; $p<0.001$). Valsartan, as compared with placebo, did not significantly reduce the incidence of either the extended cardiovascular outcome (14.5% vs 14.8%; HR=0.96; 95% CI: 0.86-1.07; p=0.43) or the core cardiovascular outcome (8.1% vs 8.1%; HR=0.99; 95% CI: 0.86-1.14; p=0.85). In conclusion, when added to a lifestyle intervention, valsartan at a daily dose of 160 mg reduced the risk of T2DM but did not affect cardiovascular outcomes in patients with IGT (McMurray et al., 2010). Patients with established CVD were extensively treated at baseline and treated with other non-study therapies during follow-up. In addition, during the course of the study, 556 patients (12.0%) in the valsartan group discontinued the study drug because of an adverse event. These factors may have masked any beneficial effects of valsartan (McMurray et al., 2010).

The cumulative incidence of T2DM was 36% in the nateglinide group, as compared with 33.9% in the placebo group (HR=1.07; 95% CI: 1.00-1.15; p=0.05). Nateglinide, as compared with placebo, did not significantly reduce the incidence of either the core composite cardiovascular outcome (7.9% and 8.3%, respectively; HR=0.94, 95% CI: 0.82-1.09; p=0.43), or the extended composite cardiovascular outcome (14.2% and 15.2%, respectively; HR=0.93, 95% CI: 0.83-1.03; p=0.16). The NAVIGATOR Research Group concluded that when added to a lifestyle intervention, nateglinide at a daily dose of up to 60 mg three times did not reduce the incidence of T2DM or the coprimary composite cardiovascular outcomes (Holman et al., 2010).

In conclusion, both lifestyle modification and pharmacological interventions have been shown to reduce the progression from IFG/IGT to T2DM, but likely have different mechanisms for improving cardiovascular risk factors and cardiovascular events. For example, due to few cardiovascular events that occurred in the DPP study, current evidence is not sufficient to draw any reliable conclusions with regard to the cardiovascular effects of the prescribed interventions, such as metformin and lifestyle interventions on cardiovascular risk reduction. On the other hand, despite limitations imposed by the small cases of cardiovascular events at baseline, the modest effect of lifestyle interventions on improvements in cardiovascular risk factors in the DPP clinical trial is noteworthy (Ratner et al., 2005). Particular encouraging was the finding that the considerable cost savings of less medication use was achieved in the lifestyle intervention group compared to metformin group and controls.

Previous randomized clinical trials however, have predominantly focused on the changes in biological risk factors related to CVD. Far less is known on the physical and

psychological risk factors of persons with prediabetes and how these risk factors change in response to interventions. Using a research database that includes biological, physical, and psychological risk factors related to CVD will allow the current study to examine the impact of a health partner program, as contrast to structured lifestyle interventions in the above mentioned clinical trials, on cardiovascular risk factors in a more comprehensive manner than previously reported as an exploratory aim.

Appendix B. Literature Review Table

A Description of Studies on Effects of Lifestyle Interventions on Cardiovascular Risk Factors Among Overweight/Obese Adults With and Without Prediabetes

Improved Lipid Profile

Study (author, date)	Purpose	Design	Sample	Variables/ Measures	Significant findings	Strengths/Weaknesses
The DPP clinical trial (Ratner et al., 2005)	To compare the impact of intensive lifestyle interventions or metformin therapy with that of a placebo on improving the lipid profile among patients with IFG/IGT.	Randomized controlled trial with 3-year follow-up	Overall, 3234 overweight/obese individuals with IFG/IGT were randomly assigned to one of the three groups: 1082 to placebo, 1073 to metformin, and 1079 to the intensive lifestyle intervention group.	Hypertension, LDL-C, TG, total cholesterol	At the 3-year follow-up, the hypertension prevalence increased from 30% to 40% among metformin and control arms. But it remained 30% in the lifestyle intervention group. Significantly lower serum TG levels and higher levels of HDL-C were observed in the lifestyle intervention group sustained over the course of the study. The need for antilipemic and antihypertensive	Random assignment of patients to treatments provides the strongest possible basis for inference about the significant impact of structured, intensive lifestyle interventions on the favorable changes in lipid profile among adults with prediabetes. However, the results of the DPP may be difficult to be translated into community settings, because the lifestyle interventions used in the DPP clinical trial was not designed to be used in community settings (Knowler et al., 2002). Furthermore, the short follow-up period precluded evaluation of the any favorable changes in the lipid profile in the long-term.

					medications was the lowest among subjects assigned to the lifestyle intervention group.	
The FDPS (Lindström et al., 2003)	To evaluate the effect of the lifestyle interventions on lipid metabolism among adults with IFG/IGT.	Randomized controlled trial with 3-year follow-up	Middle-aged, overweight/obese people with IFG/IGT (n = 522) were randomized into intensive lifestyle intervention group, which included physical activity, weight reduction, and dietary counseling, or control group, which received only general information about diet and exercise at baseline and at subsequent annual visits.	Lipid profile	There were significantly greater improvements in serum total cholesterol-to-HDL-C ratio (-0.4 vs -0.1), and TG (-0.2 vs -0.0 mmol/l) in the intervention group compared to controls at year 1.	Random assignment of patients to treatments provides the strongest possible basis for inference about the significant impact of structured, intensive lifestyle interventions on the beneficial changes in lipid profile. In addition, the intervention tested in the FDPS is practical, and can be implemented in primary health care, since one of the main objectives in the FDPS was to test an intervention feasible in primary health care settings (Lindström et al., 2003). However, the intervention program was most intensive during the first year. The effect of intervention was somewhat attenuated at 3 years, but this result may be biased due to the study design. Subjects who developed T2DM during the first 2 years of the trial did not have a 3-year examination, and the majority of them were in the

						control group. Furthermore, the control group subjects were actually provided information on diet and exercise. Therefore, they were not considered as a true non-treatment group (Lindström et al., 2003). Finally, the short follow-up period precluded evaluation of the any favorable changes in the lipid profile in the long-term.
The DPPOS (Orchard et al., 2013)	To determine the long-term differences in cardiovascular risk factors and the use of lipid and blood pressure medications by the original Diabetes Prevention Program intervention groups.	Randomized controlled trial with 10-year follow-up of the DPP clinical trial baseline (year 5 of the DPPOS)	Eighty-eight percent (2766) of all surviving DPP participants were eligible for the DPPOS. The DPPOS protocol provided quarterly lifestyle sessions to all participants and an additional two group classes annually to the original DPP	Blood pressure and lipoprotein levels	The highly significant lower blood pressure seen at the end of the DPP clinical trial (Ratner et al., 2005) in the lifestyle intervention group were no longer apparent at DPPOS year 5. Blood pressure decreased remarkably in all groups from DPP baseline, with mean levels approximating 121 mmHg systolic and 73 diastolic mmHg by DPPOS year 5. All three	Random assignment of patients to treatments provides the strongest possible basis for inference about the significant impact of structured, intensive lifestyle interventions on the beneficial changes in blood pressure and lipoprotein control among adults with prediabetes in the long-term. However, since these data are from a clinical trial, they may not be generalizable to all those with IGT/IFG. Furthermore, the limited number of CVD events in the three comparison groups precluded further analyses on evaluation of the potential to lowing CVD morbidity/mortality by the DPP interventions in the long-term (Orchard et al., 2013).

	intensive lifestyle intervention participants. Those randomly assigned to metformin continued taking 850 mg of the drug twice a day unless T2DM developed. Those assigned to placebo stopped taking the placebo.	treatment groups experienced significant improvements in LDL-C, TG, and HDL-C from DPP baseline to 10-year follow-up (i.e., year 5 of the DPPOS), with serum LDL-C, TG levels decreased 0.51 to 0.6 mmol/l, 0.23 to 0.25 mmol/l, respectively, and HDL-C levels increased 0.14 to 0.15 mmol/l. However, there were no differences among all three treatment groups. Consistent with the previous report in the DPP clinical trial, at year 5 of the DPPOS follow-up, lipid-lowering (p=0.01) and antihypertensive medication (p=0.09) use were the lowest	Finally, the control group subjects were actually provided information on diet and exercise. Therefore, they were not considered as a true non-treatment group in the DPPOS. It is difficult to separate out the DPP interventions per se from the impact of follow-up in the DPPOS (Orchard et al., 2013).

					in the lifestyle group compared to metformin and control groups.	

Improved Inflammatory Profile

Study (author, date)	Purpose	Design	Sample	Variables/ Measures	Significant findings	Strengths/Weaknesses
The DPP clinical trial (Haffner et al., 2005)	To examine the effects of intensive lifestyle interventions and metformin on levels of CRP and fibrinogen.	Randomized controlled trial with 1-year follow-up.	Overall, 3234 overweight/obese individuals with IFG/IGT were randomly assigned to one of the three groups: 1082 to placebo, 1073 to metformin, and 1079 to the intensive lifestyle intervention group.	CRP, fibrinogen, and insulin resistance	In men, the median changes in CRP from baseline to 1 year were -33% in the lifestyle group, -7% in the metformin group, and +5% in the placebo group. In women, the changes in CRP from baseline to follow-up were -29% in the lifestyle group, -14% in the metformin group, and 0% in the placebo group. A modest decrease in fibrinogen (-2%)	Random assignment of patients to treatments provides the strongest possible basis for inference about the significant impact of structured, intensive lifestyle interventions on the beneficial changes in CRP and fibrinogen. However, the short-term follow-up precluded any further observation and analyses on how inflammatory markers would change in response to the interventions. In addition, the results of the DPP may be difficult to be translated into community settings.

		was also observed in the lifestyle intervention group, compared with -0.3% in the metformin from baseline to 1 year. At baseline, the mean insulin resistance, as assessed by the HOMA-IR, was 7.1, 7.2, and 7.0 for placebo, metformin, and lifestyle intervention groups, respectively. After 1-year post-intervention, HOMA-IR increased by 5.1% in placebo group, while it decreased by 15.3% and 22.7% in metformin and lifestyle intervention groups, respectively ($p<0.001$).

The FDPS (Herder et al., 2009)	To determine whether lifestyle interventions affected subclinical inflammatory markers	Randomized controlled trial with 1-year follow-up	A subsample of 406 of 522 FDPS participants were analyzed on the research report.	CRP and IL-6	There was a significant decrease in CRP in the intervention group from baseline to 1 year compared to control group, with mean change -1.24 mg/l ($p<0.001$) and -0.38 mg/l ($p=0.12$), respectively. Likewise, lifestyle interventions reduced IL-6 levels in the intervention group (mean change: -0.4 pg/ml, $p=0.06$), while IL-6 levels increased in the control group (mean change: +0.22 pg/ml, $p=0.27$) from baseline to 1 year.	Random assignment of patients to treatments provides the strongest possible basis for inference about the significant impact of structured, intensive lifestyle interventions on the beneficial changes in CRP and fibrinogen. However, the short-term follow-up precluded any further observation and analyses on how inflammatory markers would change in response to the interventions.
Esposito et al., 2003	To determine the effect of a program of changes in lifestyle designed to obtain a sustained	Randomized controlled trial with 2-year follow-up	A total of 120 healthy, obese, premenopausal women were randomly assigned to lifestyle intervention	IL-6, IL-18, CRP, and adiponectin	Significant reductions in circulating levels of IL-6 (-1.1 pg/mL; $p=0.009$), IL-18 (-57 pg/ml; $p=0.02$), and CRP (-1.6 mg/l; $p = 0.008$), as well as a	Random assignment of patients to treatments provides the strongest possible basis for inference about the significant impact of structured, intensive lifestyle interventions on the beneficial changes in inflammatory markers. However, the short-

	reduction of body weight on markers of systemic vascular inflammation and insulin resistance		group through a low-energy Mediterranean-style diet and increased physical activity, or a control group receiving general information about healthy food choices and exercise.		significant increase in adiponectin (2.2 μg/ml; p=0.01) have been observed at the 2-year follow-up in the intervention group compared to control group.	term follow-up precluded any further observation and analyses on how inflammatory markers would change in response to the interventions. In addition, the control group is considered as a true non-treatment group.

Improved Metabolic Profile

Study (author, date)	Purpose	Design	Sample	Variables/ Measures	Significant findings	Strengths/Weaknesses
The DPP clinical trial (Diabetes Prevention Program Research Group, 2009)	To describe the baseline prevalence and effect of DPP interventions on the development and reversal of elevated albumin excretion.	Randomized controlled trial with 3.4 years	A subsample of 2802 DPP participants	urine albumin-to-creatinine ratio	There were minimal but not significant differences in the frequency of albuminuria among the groups: 6.3%, 6.7%, and 5.4% for control, metformin, and lifestyle	Random assignment of patients to treatments provides the strongest possible basis for inference about the significant impact of structured, intensive lifestyle interventions on the beneficial changes in urine albumin-to-creatinine ratio. However, low statistical power,

					intervention group, respectively. Further analysis of change in albuminuria for each group showed that the net change from normal to albuminuria were 9, 0, and -12 for control, metformin, and lifestyle intervention group, respectively, but this difference was not statistically significant (p=0.07).	shorter follow-up period, and relatively small numbers of individuals who had microalbuminuria at baseline precluded the researchers to detect small changes in the lifestyle intervention group.
Cubeddu et al., 2008	To determine whether urinary albumin excretion below the conventionally accepted threshold of microalbuminuria (<30 mg/day) are sensitive to correction of obesity and obesity-related risk factors.	Quasi-experimental design with 1-year follow-up.	A total of 41 overweight/obese healthy adults received the lifestyle modification and metformin intervention: Group I (23 participants) consisted of people with urinary albumin	Urinary albumin excretion	Urinary albumin excretion was significantly reduced in group II (N=18) (9.1+/-1.8 mg/24 h; 60% reduction; p < 0.001), and non-significantly in group I (N=23) (0.75+/-0.5 mg/day; 12% reduction; p>0.1).	Quasi-experimental design is relatively easy to conduct. However, the quasi-experimental design without randomization provides little basis for inference about the impact of lifestyle modification and metformin intervention on the beneficial changes in urinary albumin excretion. Furthermore, the small sample size precluded meaningful subgroup analysis, which is important, given that other factors may have contributed to the change.

			excretion of less than 10 mg/day, and group II (18 participants) consisted of people with urinary albumin excretion of 10 - 29 mg/day.			
Wu, Hwang, Chen, & Chuang, 2011	To evaluate short- (3 months) and long-term (9 months) effects of home-based exercise on adiponectin, exercise behavior and metabolic risk factors in middle-aged adults at diabetic risk.	Randomized controlled trial with 9-month follow-up	One hundred and thirty-five middle-aged adults (38 men, 97 women) with at least one diabetic risk factor were randomly assigned to either a home-based exercise group or a control group.	Plasma insulin levels, HOMA-IR, physical fitness, and components of metabolic syndrome	Significantly lower BMI was observed in exercise group after 3 and 9 months compared with the baseline, while BMI remained unchanged in the control group. At 3-month follow-up, both groups had significantly lower systolic and diastolic blood pressures and higher HDL-C compared with the baseline. Systolic and diastolic pressures remained lower at 9-month follow-up	Random assignment of patients to treatments provides the strongest possible basis for inference about the significant impact of physical activity on the beneficial changes in BMI, blood pressure. This study demonstrates the benefits of home-based exercise for community residents and the general population. However, the control group is not considered as a true non-treatment group. Finally, the short-term follow-up precluded any further observation and analyses on how inflammatory markers would change in response to the interventions

					compared to the baseline. TG and HOMA-IR remained unchanged for all participants.	
Gilardini et al., 2012	To investigate the effects of 3-month lifestyle interventions on insulin sensitivity and its related cardiometabolic factors in obese patients.	Quasi-experimental design with 3-month follow-up	A total of 263 obese women and 93 obese men were recruited into the study	Anthropometry, body composition, 75 g oral glucose tolerance test, lipids, alanine aminotransferase, insulin sensitivity (insulinogenic index, HOMA-IR, and β-cell performance	Patients were divided into 3 groups according to the intervention-induced changes in insulinogenic index: group 1 (decrease), group 2 (stability) and group 3 (increase). Insulin sensitivity and the disposition index were significantly higher before the intervention in group 1 than in group 3. BMI, waist circumference, and fat mass significantly decreased in groups 1 and 3 in both sexes. β-cell performance decreased in group 1 and increased in group 3. Metabolic variables improved in	Quasi-experimental design is relatively easy to conduct. However, the quasi-experimental design without randomization provides little basis for inference about the impact of lifestyle modification on the changes in insulin resistance among both metabolically healthy obese patients and obese at-risk individuals. Longer follow-up is required to assess some hard endpoint, such as cardiovascular events and death.

					group 3, whereas glucose levels increased in women of group 1. The post-intervention insulin sensitivity was lower in group 1 than in group 3.	
Kerelis et al., 2008	To investigate the effect of a 6 month energy-restricted diet on insulin sensitivity using the euglycemic-hyperinsulinemic clamp technique in a sample of metabolically health obese postmenopausal women.	Quasi-experimental design with 6-month follow-up	60 obese postmenopausal women	Body weight, insulin sensitivity	Participants were divided into metabolically healthy obesity and obese at-risk individuals, using the euglycemic-hyperinsulinemic clamp technique. No significant differences between groups were observed for body weight or fat mass before or after the diet. By the end of the diet, insulin sensitivity levels had significantly increased ($p<0.01$) by 26.1% in at-risk participants, but it decreased significantly by 12.8% in	Quasi-experimental design is relatively easy to conduct. However, the quasi-experimental design without randomization provides little basis for inference about the impact of lifestyle modification on the changes in insulin resistance among both metabolically healthy obese patients and obese at-risk individuals. Longer follow-up is required to assess some hard endpoint, such as cardiovascular events and death.

					metabolically healthy obese women.	
Kantartzis et al., 2011	To investigate whether a lifestyle intervention is sufficient to place obese insulin-resistant individuals in a position where the possible metabolic consequences are similar to those for metabolically healthy obese individuals.	Quasi-experimental design with 9-month follow-up	A total of 103 non-diabetic individuals	Total body , visceral fat, and insulin sensitivity	During the intervention, visceral fat decreased significantly in insulin-resistant, obese and metabolically healthy obese adults, ($p \leq 0.009$), whereas total body and liver fat decreased only in the insulin-resistant, obese individuals ($p<0.0001$). Insulin sensitivity improved in the insulin-resistant, obese individuals ($p<0.0001$), but remained essentially unchanged in the metabolically healthy obese individuals ($p=0.30$).	Quasi-experimental design is relatively easy to conduct. However, the quasi-experimental design without randomization provides little basis for inference about the impact of lifestyle modification on the changes in insulin resistance among both metabolically healthy obese patients and obese at-risk individuals. Longer follow-up is required to assess some hard endpoint, such as cardiovascular events and death.
Janiszewski and Ross (2010)	To examine the effects of exercise- or diet-induced weight loss on	Quasi-experimental design with 3-to-6-month follow-up	63 metabolically healthy obese and 43 metabolicall	Body weight, waist circumference, total abdominal ,	Improvement in insulin sensitivity was observed in metabolically healthy obese adults and in	Quasi-experimental design is relatively easy to conduct. However, the quasi-experimental design without randomization provides little basis for inference

	cardiometabolic risk among metabolically healthy obese and metabolically abnormal obese adults.		y abnormal obese adults	visceral adipose tissue, and insulin sensitivity	the obese at-risk individuals receiving a 3 to 6 month lifestyle intervention ($p<0.05$), but the improvement was greater in the obese at-risk individuals ($p<0.05$). Body weight, waist circumference, and total abdominal and visceral adipose tissue were reduced in all subjects ($p<0.05$).	about the impact of lifestyle modification on the changes in insulin resistance among both metabolically healthy obese patients and obese at-risk individuals. Longer follow-up is required to assess some hard endpoint, such as cardiovascular events and death.

Improved Physical Risk Factors

Study (author, date)	Purpose	Design	Sample	Variables/ Measures	Significant findings	Strengths/Weaknesses
The PREPARE program (Yates, Davies, Gorely, Bull, & Khunti,	To investigate whether a pragmatic structured education program with and without	Randomized controlled trial with 12-month follow-up	A total of 87 participants were randomly assigned to one of three groups.	75 g oral glucose tolerance test, standard anthropometri c measures, ambulatory	There was no difference in measured blood lipids, body weight, waist circumference, or blood pressure in either of the	First, the small sample size precluded meaningful subgroup analysis, which is important, given the heterogeneity of the study sample. Second, the study was conducted in a single center. This limits the generalizability of

2009)	pedometer use is effective for promoting physical activity and improving glucose tolerance in overweight/obese individuals with IGT.	Group 1 received a 3-h group-based structured education program designed to promote walking activity using personalized steps-per-day goals and pedometers. Group 2 received a 3-h group-based structured education program designed to promote walking activity using generic time-based goals. Group 3 received a brief information leaflet	activity, and psychological variables	intervention groups compared with that in the control group at 3, 6 12-month follow-up. At 12 months, significant decreases in 2-h postchallenge glucose and fasting glucose of -1.31 mmol/l and -0.32 mmol/l, respectively, were seen in the pedometer group compared with the control group. No significant improvement in glucose control was seen in those given the standard education program.	the findings. These limitations notwithstanding, this study is the first randomized controlled trial to demonstrate behavioral change and improved glucose tolerance in individuals with IGT after a pragmatic structured education program.

			(control condition).			
The Look AHEAD clinical trial (Jakicic et al., 2009).	To examine the effect of an intensive lifestyle interventions compared to diabetes support and education on changes in CRF and physical activity.	Randomized controlled trial with 12-month follow-up	A subsample of 4376 overweight /obese adults with T2DM	Cardiorespiratory fitness (CRF), physical activity	Change in CRF was statistically greater in intervention group compared to control group after adjustment for baseline fitness (20.9% vs 5.7%; $p<0.0001$). Multivariate analysis showed that change in fitness was greater in overweight versus obese Class II and III ($p<0.05$). Changes in fitness ($r=0.41$) were significantly correlated with weight loss ($p<0.0001$). Physical activity increased by 892+/-1694 kcal per week in intervention group versus 108+/-1254 kcal per week in control group ($p<0.01$).	Strengths of this study include the ability to recruit and prospectively assess CRF in a large cohort of diabetics, the randomized nature of the study design, and the ability to objectively assess CRF in this cohort. Weakness may include the use of a submaximal rather than a maximal graded exercise test to assess the change in CRF. This may have influenced the precise assessment of fitness in this study. The subjective assessment of physical activity on a subsample of the subjects using a questionnaire may not be accurate.

The Look AHEAD clinical trial (Jakicic et al., 2013).	To examine the effect of an intensive lifestyle intervention compared to diabetes support and education (control group) on changes in CRF and physical activity.	Randomized controlled trial with 4-year follow-up	A subsample of 3,942 overweight /obese adults with T2DM (76.6% of the randomized subjects)	CRF, physical activity	At the 4-year follow-up, the difference in percent CRF change between lifestyle intervention group and diabetes support and education group was significant after adjustment for baseline CRF and change in weight (3.70% vs 0.94%; p<0.01). Physical activity increased by 348 (1,562) kcal/week in intervention group versus 105 (1,309) kcal/week in control group (p<0.01).	Strengths of this study include the ability to recruit and prospectively assess CRF in a large cohort of diabetics, the randomized nature of the study design, and the ability to objectively assess CRF in this cohort. However, CRF measures were obtained from 76.6% of the randomized sample, and there were differences in baseline demographic characteristics between subjects providing and not providing fitness data. This pattern of findings may affect the generalizability of the results.

Improved Depressive Symptoms

Study (author, date)	Purpose	Design	Sample	Variables/ Measures	Significant findings	Strengths/Weaknesses
The DPP clinical trial	To assess depression markers	Randomized controlled trial with 3.2-	A subsample of 3187 DPP participants	Depressive symptoms measured by	After an average follow-up of 3.2 years, while the	Strengths of the current study include the large multiethnic population, the randomized

(Rubin et al., 2005)	(symptoms and antidepressant medicine use) in DPP enrollees and to determine whether changes in depression markers during the course of the study were associated with treatment arm, weight change, physical activity level, or participant demographic characteristics.	year follow-up	BDI and reported use of antidepressant medicines	prevalence of elevated depressive symptoms reduced from 10.3% to 8.4%, the proportion of antidepressant agent users increased from 5.7% to 8.7%, leaving no significant change in the proportion with either marker. These depression marker time trends were not significantly associated with the DPP treatment arms for either men or women. However, at annual visit of year 2 and 3, the proportion of participants in the intensive lifestyle intervention arm with either depression marker was still lower than that in the placebo arm.	nature of the study design and the fact that data were collected regarding antidepressant medication and depression symptoms. Limitations include the fact that the study cohort was probably not representative of all individuals with IFG/ IGT because self-selection and screening procedures made it very likely that severely and even moderately depressed individuals were under-represented. Also, the investigators did not confirm that all patients using antidepressants were taking them for depression than for other conditions.

The FDPS clinical trial (Ruusunnen et al., 2012)	To assess the effect of lifestyle interventions on depressive symptoms.	Randomized controlled trial with 3-year follow-up	A subsample of 140 out of the FDPS enrollees middle-aged overweight/obese participants with IFG/IGT were analyzed on the research report.	Depressive symptoms measured by the BDI and reported use of antidepressant	After 3-year follow-up, favorable changes in depressive symptoms, as measured by the Finnish version of the BDI, were observed in the intervention group. Although there was no significant difference in changes of the BDI scores between the study groups (p=0.965), BDI scores decreased more in the lifestyle intervention group (0.90±4.54; 95% CI:-1.99 to -0.19) than in in the control group (0.75±4.47; 95% CI: -1.80 to 0.31). With the same cutoff (BDI≥11) that was used in the DPP, in the FDPS, the prevalence of depressive	Strengths of this study include the long duration of the intervention, the randomized nature of the study design, fact that data were collected regarding antidepressant medication and depression symptoms, and the low dropout from the follow-up in the FDPS (9% for the intervention group and 7% for the control group). The most important weakness of the study is the limited number of study participants with BDI scores available. Another limitation is that the study had no clinical interview-based diagnosis of depressive symptoms available. It is also possible that severely or moderately depressed individuals may be under-represented because of the self-selection and screening procedures of intervention study.

					symptoms was higher both at baseline (21.4%) and at year 3 (15.7%) and use of antidepressants was uncommon both at baseline (2.3%) and at 3-year visit (3.6%).	
The Look AHEAD clinical trial (Williams on et al., 2009)	To examine the efficacy of a weight management program for improving depressive symptoms and health status in overweight or obese adults diagnosed as having T2DM.	Randomized controlled trial with 1-year follow-up	A total of 5145 overweight or obese persons with T2DM	Depressive symptoms, health status	A greater decrease in depressive symptoms measured by the BDI-II measured was observed in the lifestyle intervention group (-0.83±4.86, $p<0.001$) compared to the diabetes support and education group (-0.23±4.63, $p<0.001$) after 1-year follow-up. Health status was significantly improved in overweight diabetic adults; the largest effect was observed in the SF-36	Strengths of this study include the ability to recruit and prospectively assess depression in a large cohort of diabetics and the randomized nature of the study design. The primary limitations of the study are the relatively short duration of the study (i.e., 1 year) and the focus upon a highly selected population. These findings should not be generalized to other (less highly selected) populations. Future studies on this patient population are needed to determine if these changes in depressive symptoms and health status persist over much longer periods of time.

					physical component score (difference =2.91, 99% CI: -3.44 to -2.37) between the lifestyle intervention group and the diabetes support and education group after 1-year follow-up.	

Improved Health Status

Study (author, date)	Purpose	Design	Sample	Variables/ Measures	Significant findings	Strengths/Weaknesses
The DPP clinical trial (Florez et al., 2012)	To assess changes in health status after interventions aimed at diabetes risk reduction.	Randomized controlled trial with 3.2-year follow-up	A subsample of 3,206 of the DPP participants were analyzed in the research report	Health status	After a mean follow-up of 3.2 years, compared to placebo group, there were significant improvements in the health utility index (+0.008, p=0.04) and physical component score of the SF-36 (+1.57, p <0.0001) scores in	Strengths of this study include the long duration of the intervention and the randomized nature of the study design. The primary limitations of the study are the focus upon a highly selected population. These findings should not be generalized to other (less highly selected) populations. Second, health status measurements used were not disease-specific. It is

	the lifestyle intervention group but not in the metformin group (+0.002 and +0.15, respectively, p=0.6). Participants in the lifestyle intervention group showed improvements in general health (+3.2, p<0.001), physical function (+3.6, p<0.001), bodily pain (+1.9, p=0.01), and vitality (+2.1, p=0.01) domain scores as measured by the SF-36.	also possible that the results would have differed if a disease-specific health status measurement other than SF-36 were used. Finally, it is possible that the health status benefits resulted from the so-called "regression to the mean," where individuals with worse health status at baseline got the greatest benefits from the weight management intervention.

Appendix C. Underlying Pathophysiological Mechanisms Associated With Dyslipidemia

The central pathological mechanisms in macrovascular disease is the process of atherosclerosis (Fowler, 2008). The intima of an artery consists of endothelial cells, which are thought to be the key to atherosclerosis and the underlying endothelial dysfunction is a central feature of CVD. In a healthy artery, the tightly adjoined endothelial cells form a barrier to keep the passage of large molecules, such as lipoprotein, from the circulation into the subendothelial space (Strom & Libby, 2010). Injury to the endothelium represents a primary event in atherosclerosis and it may result from abnormal circulating lipid concentrations, diabetes, and smoking (Strom & Libby, 2010). These states interrupt normal endothelial hemeostasis, manifested by increased endothelial permeability that allows deposits of lipids, notably LDL-C, within the subendothelial space, where they serve as pro-inflammatory markers that initiate leukocyte recruitment and foam cell formation (Strom & Libby, 2010).

Once inside the vessel wall, LDL-C molecules become susceptible to oxidation by free radicals. Oxidation, in turn, occurs with the LDL-C trapped in the subendothelial space (Strom & Libby, 2010). Small dense LDL-C particles are highly atherogenic because of their enhanced susceptibility to oxidative modification and enhanced uptake by the arterial wall (Solano & Goldberg, 2006). In sustained hyperglycemia, as is present in T2DM and prediabetic state, glycated LDL-C can occur, which may ultimately render LDL-C pro-inflammatory (Strom & Libby, 2010). The oxidized LDL-C molecules can trigger a cascade of immune responses which over time initiate leukocyte recruitment. Monocytes then penetrate into the intima and differentiate into macrophages, which

accumulate and immobile oxidized LDL-C to form foam cells (Solano & Goldberg, 2006; Strom & Libby, 2010). The formation of foam cells is considered as the first hallmark of an atherosclerotic lesion (van Tits et al., 2011).

In normal individuals, approximately 60% to 70% of LDL-C can be metabolized by LDL-receptors (Gosavi et al., 2006). In prolonged hyperglycemia, however, oxidized LDL-C cannot be recognized by LDL-C receptors. Instead, it is engulfed by macrophage scavenger receptors, which evades negative feedback inhibition and permits engorgement of the macrophages with cholesterol and cholesterol ester, resulting in the typical appearance of foam cells (Strom & Libby, 2010). Once formed, foam cells produce several factors such as platelet-derived growth factor that induce smooth muscle migration and proliferation into the arterial intima (Strom & Libby, 2010). The net result of this process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Most acute coronary syndrome, i.e., acute myocardial infarction and unstable angina pectoris, result when the fibrous cap ruptures, exposing prothrombotic molecules within the lipid core and precipitating an acute thrombus that suddenly occludes the arterial lumen (Strom & Libby, 2010).

Appendix D. Study Approval from the Institutional Review Board

EMORY UNIVERSITY

Institutional Review Board

July 23, 2013

Tingting Liu
PhD Student/Graduate Assistant
Nell Hodgson Woodruff School of Nursing, Emory University
1520 Clifton Road NE., Room 130
Atlanta, GA, 30322-4201

RE: Determination: No IRB Review Required
Running head: Biological, Physical and Psychological risks for Cardiovascular Disease among Overweight/Obese Individuals with and without Prediabetes

Dear Ms. Liu:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition of "research" involving "human subjects" as set forth in Emory policies and procedures and federal rules. Specifically, the review of existing de-identified data from thr Center for Health Discovery and Well Being at Emory University for the purpose of comparing baseline biological, physical and psychological status in overweight/obese adults with and without prediabetes, controlling for age, gender, educational level and marital status/social support does not meet the criteria of being "generalizable" in the definition of research as stated in 45 CFR 46.102(d).

As such, this project fall outside of the purview of the IRB, though we thank you for consulting us.

Sincerely,

Andrea Goosen

Andrea Goosen, MPH, CIP
Research Protocol Analyst
Institutional Review Board
Emory University

Appendix E. Checking for Multicollinearity Assumptions

Model	Dependent	Number	Eigenvalue	Condition index	Intercept	Age	Gender	Education	Prediabetes
MODEL1	VO_{2max}*	1	3.650	1	0.002	0.003	0.023	0.003	0.014
MODEL1	VO_{2max}*	2	0.824	2.105	0.000	0.000	0.013	0.001	0.926
MODEL1	VO_{2max}*	3	0.469	2.790	0.004	0.006	0.864	0.003	0.004
MODEL1	VO_{2max}*	4	0.043	9.252	0.001	0.413	0.042	0.567	0.039
MODEL1	VO_{2max}*	5	0.015	15.741	0.993	0.578	0.057	0.425	0.016
MODEL1	Daily activity*	1	3.627	1	0.002	0.003	0.024	0.003	0.015
MODEL1	Daily activity*	2	0.811	2.115	0.001	0.001	0.006	0.002	0.925
MODEL1	Daily activity*	3	0.503	2.686	0.004	0.006	0.881	0.003	0.000
MODEL1	Daily activity*	4	0.043	9.217	0.000	0.461	0.062	0.578	0.044
MODEL1	Daily activity*	5	0.017	14.816	0.993	0.530	0.028	0.415	0.016
MODEL1	M+V	1	3.627	1	0.002	0.003	0.024	0.003	0.015
MODEL1	M+V	2	0.811	2.115	0.001	0.001	0.006	0.002	0.925
MODEL1	M+V	3	0.503	2.686	0.004	0.006	0.881	0.003	0.000

MODEL1	M+V	4	0.043	9.217	0.000	0.461	0.062	0.578	0.044
MODEL1	M+V	5	0.017	14.816	0.993	0.530	0.028	0.415	0.016
MODEL1	Total activity	1	3.627	1	0.002	0.003	0.024	0.003	0.015
MODEL1	Total activity	2	0.811	2.115	0.001	0.001	0.006	0.002	0.925
MODEL1	Total activity	3	0.503	2.686	0.004	0.006	0.881	0.003	0.000
MODEL1	Total activity	4	0.043	9.217	0.000	0.461	0.062	0.578	0.044
MODEL1	Total activity	5	0.017	14.816	0.993	0.530	0.028	0.415	0.016
MODEL1	BMI	1	3.617	1	0.002	0.003	0.024	0.003	0.015
MODEL1	BMI	2	0.821	2.099	0.001	0.000	0.005	0.002	0.925
MODEL1	BMI	3	0.503	2.681	0.004	0.006	0.877	0.003	0.000
MODEL1	BMI	4	0.043	9.173	0.001	0.449	0.061	0.580	0.043
MODEL1	BMI	5	0.016	14.880	0.993	0.541	0.033	0.412	0.017
MODEL1	WHR*	1	3.630	1	0.002	0.003	0.023	0.003	0.015
MODEL1	WHR*	2	0.817	2.108	0.001	0.000	0.007	0.002	0.927
MODEL1	WHR*	3	0.493	2.713	0.004	0.006	0.869	0.003	0.000

MODEL1	WHR*	4	0.044	9.112	0.001	0.436	0.056	0.566	0.041
MODEL1	WHR*	5	0.016	15.159	0.993	0.554	0.045	0.427	0.018
MODEL1	Glucose	1	3.619	1	0.002	0.003	0.023	0.003	0.015
MODEL1	Glucose	2	0.818	2.103	0.001	0.000	0.008	0.001	0.929
MODEL1	Glucose	3	0.503	2.681	0.004	0.006	0.874	0.003	0.000
MODEL1	Glucose	4	0.043	9.180	0.001	0.448	0.061	0.581	0.042
MODEL1	Glucose	5	0.016	14.893	0.993	0.542	0.033	0.411	0.014
MODEL1	LDL-C	1	3.613	1	0.002	0.003	0.023	0.003	0.014
MODEL1	LDL-C	2	0.824	2.094	0.001	0.000	0.011	0.001	0.919
MODEL1	LDL-C	3	0.505	2.675	0.004	0.006	0.868	0.003	0.002
MODEL1	LDL-C	4	0.043	9.168	0.001	0.436	0.060	0.583	0.043
MODEL1	LDL-C	5	0.016	15.011	0.993	0.554	0.037	0.409	0.021
MODEL1	HDL-C	1	3.619	1	0.002	0.003	0.023	0.003	0.015
MODEL1	HDL-C	2	0.818	2.103	0.001	0.000	0.008	0.001	0.929
MODEL1	HDL-C	3	0.503	2.681	0.004	0.006	0.874	0.003	0.000

MODEL1	HDL-C	4	0.043	9.180	0.001	0.448	0.061	0.581	0.042
MODEL1	HDL-C	5	0.016	14.893	0.993	0.542	0.033	0.411	0.014
MODEL1	TG*	1	3.607	1	0.002	0.003	0.024	0.003	0.014
MODEL1	TG*	2	0.827	2.089	0.001	0.000	0.010	0.001	0.937
MODEL1	TG*	3	0.507	2.666	0.004	0.006	0.874	0.003	0.001
MODEL1	TG*	4	0.043	9.129	0.001	0.436	0.062	0.581	0.039
MODEL1	TG*	5	0.016	15.049	0.993	0.555	0.030	0.412	0.009
MODEL1	IL-6*	1	3.626	1	0.002	0.003	0.023	0.003	0.015
MODEL1	IL-6*	2	0.815	2.109	0.001	0.000	0.009	0.002	0.926
MODEL1	IL-6*	3	0.499	2.695	0.004	0.006	0.872	0.003	0.000
MODEL1	IL-6*	4	0.044	9.129	0.001	0.451	0.062	0.580	0.044
MODEL1	IL-6*	5	0.017	14.773	0.993	0.539	0.034	0.413	0.015
MODEL1	IL-8*	1	3.626	1	0.002	0.003	0.023	0.003	0.015
MODEL1	IL-8*	2	0.815	2.109	0.001	0.000	0.009	0.001	0.926
MODEL1	IL-8*	3	0.499	2.695	0.004	0.006	0.872	0.003	0.000

MODEL1	IL-8*	4	0.044	9.129	0.001	0.451	0.062	0.580	0.044
MODEL1	IL-8*	5	0.017	14.773	0.993	0.539	0.034	0.413	0.015
MODEL1	TNF-α*	1	3.626	1	0.002	0.003	0.023	0.003	0.015
MODEL1	TNF-α*	2	0.815	2.109	0.001	0.000	0.009	0.002	0.926
MODEL1	TNF-α*	3	0.499	2.695	0.004	0.006	0.872	0.003	0.000
MODEL1	TNF-α*	4	0.044	9.129	0.001	0.451	0.062	0.580	0.045
MODEL1	TNF-α*	5	0.016	14.773	0.993	0.539	0.033	0.413	0.015
MODEL1	CRP	1	3.623	1	0.002	0.003	0.023	0.003	0.015
MODEL1	CRP	2	0.817	2.105	0.001	0.000	0.009	0.001	0.928
MODEL1	CRP	3	0.500	2.691	0.004	0.006	0.873	0.003	0.000
MODEL1	CRP	4	0.043	9.165	0.001	0.439	0.063	0.586	0.045
MODEL1	CRP	5	0.016	14.947	0.993	0.551	0.032	0.406	0.015
MODEL1	SF-36 PCS	1	3.635	1	0.002	0.003	0.023	0.003	0.015
MODEL1	SF-36 PCS	2	0.812	2.115	0.001	0.000	0.007	0.002	0.926
MODEL1	SF-36 PCS	3	0.494	2.714	0.004	0.007	0.874	0.003	0.000

MODEL1	SF-36 PCS	4	0.043	9.217	0.000	0.463	0.065	0.573	0.044
MODEL1	SF-36 PCS	5	0.017	14.834	0.993	0.527	0.030	0.419	0.015
MODEL1	SF-36 MCS	1	3.635	1	0.002	0.003	0.023	0.003	0.015
MODEL1	SF-36 MCS	2	0.812	2.115	0.001	0.000	0.007	0.002	0.926
MODEL1	SF-36 MCS	3	0.494	2.714	0.004	0.007	0.874	0.003	0.000
MODEL1	SF-36 MCS	4	0.043	9.217	0.000	0.463	0.065	0.573	0.044
MODEL1	SF-36 MCS	5	0.017	14.834	0.993	0.527	0.030	0.419	0.015
MODEL1	BDI-II*	1	3.631	1	0.002	0.003	0.023	0.003	0.015
MODEL1	BDI-II*	2	0.810	2.117	0.001	0.001	0.006	0.002	0.926
MODEL1	BDI-II*	3	0.450	2.696	0.004	0.006	0.878	0.003	0.000
MODEL1	BDI-II*	4	0.043	9.226	0.000	0.458	0.066	0.584	0.043
MODEL1	BDI-II*	5	0.017	14.778	0.993	0.532	0.027	0.409	0.016

Note. *=log transformed variable. M+V=moderate and vigorous activity; SF-36 PCS=SF-36 physical component score; SF-36 MCS= SF-36 mental component score.

Appendix F. Copies of the Study Instruments

Beck Depression Inventory-II

Instructions: This questionnaire consists of 21 groups pf statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describe the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all of the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism
0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my fortune is hopeless and will get only worse.

3. Past Failure
0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure
0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty most of the time.

6. Punishment Feelings
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.

3 I feel I am being punished.

7. Self-dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-criticisms

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11. Agitation

0 I am no more restless or would up than usual.
1 I feel more restless or would up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than usual.
3 I have trouble making any decision.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy
0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Patterns
0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability
0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite
0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than usual.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty
0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue
0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

CAPS Typical Week Physical Activity Questionnaire

Think about the types of activities you did in a **typical week in the past month** (see calendar provided). For each activity, note which of these activities you did by checking a box for YES or NO. Then, for each item you marked as YES, write the number of days you did the activity Monday to Friday and Saturday to Sunday, and the AVERAGE TIME in hours and minutes that you did these activities. Refer to the following INTENSITY levels before responding to each question:

Intensity levels:
Light → easy or no effort at all
Moderate → harder than light, some increase in breathing or heart rate
Vigorous → all-out effort, large increase in breathing or heart rate

***Example*:**

Conditioning Activities

Moderate Effort
Low impact aerobics
health club machines
bicycling, Tai Chi

	Monday-Friday			Saturday-Sunday		
	#of days	Hours/day	Minutes/day	#of days	Hours/day	Minutes/day
☒1. Yes	3	0	30	0	0	0
☐2. No						

During a typical week in _____ , did you do
Month

Household Activities		Monday-Friday			Saturday-Sunday		
		#of days	Hours/day	Minutes/day	#of days	Hours/day	Minutes/day
1. Light Effort: Cooking, Cleaning up, laundry, shopping, dusting	☐1. Yes → ☐ / ☐2. No	☐	☐	☐	☐	☐	☐
	SUP0501	SUP0501A	SUP0501B	SUP0501C	SUP0501D	SUP0501E	SUP0501F
2. Moderate or Vigorous Effort: Scrubbing, vacuuming, repairs, mopping, washing car	☐1. Yes → ☐ / ☐ 2. No	☐	☐	☐	☐	☐	☐
	SUP0502	SUP0502A	SUP0502B	SUP0502C	SUP0502D	SUP0502E	SUP0502F
Lawn/Yard/Garden/Farm							
3. Moderate Effort: Weeding, sweeping, Mowing, raking	☐1. Yes → ☐ / ☐2. No	☐	☐	☐	☐	☐	☐
	SUP0503	SUP0503A	SUP0503B	SUP0503C	SUP0503D	SUP0503E	SUP0503F
4. Vigorous Effort: Shoveling, pruning, chopping wood	☐1. Yes → ☐ / ☐2. No	☐	☐	☐	☐	☐	☐
	SUP0504	SUP0504A	SUP0504B	SUP0504C	SUP0504D	SUP0504E	SUP0504F

During a typical week in _____ , did you do
Month

Caring of Children /Adults/Animals		**Monday-Friday** #of days	Hours/day	Minutes/day	**Saturday-Sunday** #of days	Hours/day	Minutes/day
5. Light Efforts: Bathing, feeding, playing with child or animal	☐1. Yes ☐ 2. No SUP0505	→ ☐ SUP0505A	☐ SUP0505B	☐ SUP0505C	☐ SUP0505D	☐ SUP0505E	☐ SUP0505F
6. Moderate Effort: Lifting and carrying, Pushing wheelchair or stroller	☐1. Yes ☐2. No SUP0506	→ ☐ SUP0506A	☐ SUP0506B	☐ SUP0506C	☐ SUP0506D	☐ SUP0506E	☐ SUP0506F
Transportation							
7. Light Effort: Drive or ride a car, ride the bus or subway, include travel to work	☐1. Yes ☐2. No SUP0507	→ ☐ SUP0507A	☐ SUP0507B	☐ SUP0507C	☐ SUP0507D	☐ SUP0507E	☐ SUP0507F
Walking (not at work)							
8. Moderate Effort: Walking to get places, to the bus, car, or work	☐1. Yes ☐2. No SUP0508	→ ☐ SUP0508A	☐ SUP0508B	☐ SUP0508C	☐ SUP0508D	☐ SUP0508E	☐ SUP0508F
9. Moderate Effort: Walking for exercise or social, walking your dog, during work breaks	☐1. Yes ☐2. No SUP0509	→ ☐ SUP0509A	☐ SUP0509B	☐ SUP0509C	☐ SUP0509D	☐ SUP0509E	☐ SUP0509F
Dance and Sports							
10. Moderate Effort: Dancing in church, ceremonies, or for pleasure	☐1. Yes ☐2. No SUP0510	→ ☐ SUP0510A	☐ SUP0510B	☐ SUP0510C	☐ SUP0510D	☐ SUP0510E	☐ SUP0510F

During a typical week in _____ , did you do
Month

		Monday-Friday			**Saturday-Sunday**		
		#of days	Hours/day	Minutes/day	#of days	Hours/day	Minutes/day
11. Moderate or Vigorous Effort: Sports-golf, soccer, softball, tennis, racquetball, basketball	☐1. Yes ☐2. No SUP0511 →	☐ SUP0510A	☐ SUP0510B	☐ SUP0510C	☐ SUP0510D	☐ SUP0510E	☐ SUP0510F
Conditioning Activities							
12. Moderate Effort: Low impact aerobics, health club machines, bicycling, Tai Chi	☐1. Yes ☐2. No SUP0512 →	☐ SUP0512A	☐ SUP0512B	☐ SUP0512C	☐ SUP0512D	☐ SUP0512E	☐ SUP0512F
13. Vigorous Effort: Step aerobics, running/jogging, karate, swim training	☐1. Yes ☐2. No SUP0513 →	☐ SUP0513A	☐ SUP0513B	☐ SUP0513C	☐ SUP0513D	☐ SUP0513E	☐ SUP0513F
14. Light Effort: Stretching and flexibility exercises	☐1. Yes ☐2. No SUP0514 →	☐ SUP0514A	☐ SUP0514B	☐ SUP0514C	☐ SUP0514D	☐ SUP0514E	☐ SUP0514F
15. Moderate effort: Lifting weights, strength training	☐1. Yes ☐2. No SUP0515 →	☐ SUP0515A	☐ SUP0515B	☐ SUP0515C	☐ SUP0515D	☐ SUP0515E	☐ SUP0515F
Leisure Activities							
16. Light Effort: Watching TV and doing nothing else	☐1. Yes ☐2. No SUP0516 →	☐ SUP0516A	☐ SUP0516B	☐ SUP0516C	☐ SUP0516D	☐ SUP0516E	☐ SUP0516F
17. Light Effort: Reading, sewing, or using a computer (not at work)	☐1.Yes ☐2. No SUP0517 →	☐ SUP0517A	☐ SUP0517B	☐ SUP0517C	☐ SUP0517D	☐ SUP0517E	☐ SUP0517F

During a typical week in _____ , did you do
Month

Occupational Activities

18. Do you work to earn money? ☐1. Yes → ***Continue to #19***
☐2. No → ***Go to VOLUNTEER ACTIVITIES***
SUP0518

How many hours/week do you work to earn money in all jobs?
_____hrs/week [SUP0518a]

How many days/week in all jobs?
_____hrs/week [SUP0518b]

At work do you do:		**Monday-Friday**			**Saturday-Sunday**		
		#of days	Hours/day	Minutes/day	#of days	Hours/day	Minutes/day
19. Light Effort–Sitting (e.g., office/lab work)	☐1. Yes ☐2. No SUP0519 →	☐ SUP0519A	☐ SUP0519B	☐ SUP0519C	☐ SUP0519D	☐ SUP0519E	☐ SUP0519F
20. Light Effort-Standing or walking (nursing, custodial, making deliveries)	☐1. Yes ☐2. No SUP0520 →	☐ SUP0520A	☐ SUP0520B	☐ SUP0520C	☐ SUP0520D	☐ SUP0520E	☐ SUP0520F
21. Moderate Effort-Standing or walking (nursing, custodial, making deliveries)	☐1. Yes ☐2. No SUP0521 →	☐ SUP0521A	☐ SUP0521B	☐ SUP0521C	☐ SUP0521D	☐ SUP0521E	☐ SUP0521F
22. Vigorous Effort-Manual labor, ranch or farm labor, loading trucks	☐1. Yes ☐2. No SUP0522 →	☐ SUP0522A	☐ SUP0522B	☐ SUP0522C	☐ SUP0522D	☐ SUP0522E	☐ SUP0522F

Volunteer Activities

23. Do you work as a volunteer in activities you have not yet mentioned on this survey?

☐1. Yes → ***Continue to #24***
☐2. No → ***End***

SUP0523

During a typical week in _____ , did you do
Month

Does your volunteer work include:		**Monday-Friday** #of days	Hours/day	Minutes/day	**Saturday-Sunday** #of days	Hours/day	Minutes/day
24. Light Effort- Sitting or standing	☐1. Yes ☐2. No SUP0524	☐ SUP0524A	☐ SUP0524B	☐ SUP0524C	☐ SUP0524D	☐ SUP0524E	☐ SUP0524F
25. Moderate Effort- Standing or walking	☐1. Yes ☐2. No SUP0525	☐ SUP0525A	☐ SUP0525B	☐ SUP0525C	☐ SUP0525D	☐ SUP0525E	☐ SUP0525F
26. Vigorous Effort- Pushing, lifting carrying, climbing	☐1. Yes ☐2. No SUP0526	☐ SUP0526A	☐ SUP0526	☐ SUP0526C	☐ SUP0526D	☐ SUP0526E	☐ SUP0526F

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