The impact of modifiable lifestyle factors among individuals at high risk for cardiovascular disease due to prediabetes, the metabolic syndrome, or type 1 diabetes

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Abstract

Individuals with prediabetes, metabolic syndrome, or type 1 diabetes (T1D) are at increased cardiovascular disease risk. The American Heart Association's (AHA) cardiovascular health metrics framework offers an appealing approach to health promotion to minimize cardiovascular disease risk. This framework defines and quantifies cardiovascular health using seven metrics (total cholesterol, blood pressure, blood glucose, BMI, smoking, physical activity, diet), promoting progress toward ideal ranges of each. This dissertation expanded the application of these metrics by 1) measuring their improvement during the course of a behavioral lifestyle intervention among individuals with prediabetes and/or metabolic syndrome, and 2&3) among adults with T1D, establishing the predictive value of the AHA metrics scores for incident coronary artery disease (CAD) and exploring potential associations between TID-specific patterns of nutrient intake and CAD.

Cohorts from two Diabetes Prevention Program community-based behavioral lifestyle intervention studies (n=305) were used to address aim 1. Measures of cardiovascular health metrics across the 12-month intervention were evaluated and found to significantly improve. Not only was there a beneficial shift toward the ideal range in several of the metrics, but significant improvement was also seen in composite metric scores.

The Pittsburgh Epidemiology of Diabetes Complications cohort of individuals with childhood onset T1D was used to address aims 2 and 3. Among young adults (n=435), higher

composite cardiovascular health metrics scores were associated with lower CAD risk over 25 years of follow-up. Focusing on diet, (n=465), data derived patterns of nutrient intake were not significantly associated with CAD development over 30 years after adjusting for diabetes duration.

This effort demonstrated the value of the AHA cardiovascular health metrics in capturing improvement in risk factors among individuals with prediabetes and/or metabolic syndrome during the course of an effective and widely available behavioral lifestyle intervention. These metrics also provided support for developing cardiovascular risk factor targets for CAD prevention among young adults with T1D with additional research needed to understand the role of diet in this population. Overall, this body of work documents the public health relevance of the AHA cardiovascular health metrics in guiding health promotion for cardiovascular disease risk reduction in these high-risk populations.

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Preface

This dissertation effort marks the culmination of my doctoral work and is intended to inform approaches to cardiovascular health promotion among high risk groups. This work should be of interest to clinicians and public health professionals who interact with individuals with prediabetes, metabolic syndrome, or type 1 diabetes as a means of exploring targets for modifiable cardiovascular disease risk factor intervention. In particular, this work is intended to assist in identifying effective approaches to promote, assess, and monitor cardiovascular health.

This doctoral effort was inspired by my experience as a Registered Dietitian in clinical practice. Having witnessed the burden of cardiometabolic conditions occurring in concert and seeing the toll that these chronic health complications take on individuals and families, I felt the deep need to contribute to disease prevention. It is my sincere hope and ongoing motivation to help others to live a healthier and happier life. Through my studies and with the guidance of a village of accomplished and inspiring faculty and peers, I have gained the knowledge and skills to facilitate this journey toward health promotion research.

This work would not have been possible without the guidance of my advisor, Andrea Kriska, who has assisted me in every step along the way during my doctoral program. In addition, each member of my committee has provided patience, guidance, and invaluable input throughout the research process. Finally, I would like to thank my family, especially my husband Vivek who has been my rock during this process, and my daughter Sarla who is my inspiration. Thank you all for your unwavering support.

The first aim of this research was supported by the NIH-National Institute of Diabetes and Digestive and Kidney Diseases grants R18 DK081323-04 and 5R18DK100933-04 (Group Lifestyle Balance-Healthy and Group Lifestyle Balance-Moves.) The second and third aims were supported by NIH grant DK34818 and the Rossi Memorial Fund (the Epidemiology of Diabetes Complications study). I received additional support from the National Heart, Lung and Blood Institute Cardiovascular Disease Epidemiology T32 Training Grant (T32HL083825), As a final word of acknowledgement, this dissertation would also not be possible without the participants and community partners in these research efforts. To all who gave their time and energy to make this research possible, thank you.

1.0 Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the United States, with an estimated annual cost of over $351 billion each year. [1] Groups at higher risk for CVD could greatly benefit from approaches that identify intervention targets to promote cardiovascular (CV) health, a shift toward health promotion for CVD prevention early in or prior to the onset of the disease process. Individuals with glucose dysregulation, including prediabetes as well as types 1 and 2 diabetes, and metabolic syndrome are at higher risk for CVD.[1–3] Addressing CVD risk in individuals with glucose dysregulation must focus on modifiable factors that influence progression to type 2 diabetes and CVD, as well as development of CVD after diagnosis with non-preventable type 1 diabetes.

Prediabetes and metabolic syndrome are highly prevalent and known risk factors for the development of type 2 diabetes and CVD.[1] An estimated 84 million adults have prediabetes,[4] defined as fasting glucose 100 to 125 mg/dL or HbA_{1c} 5.7 to 6.4%. Metabolic syndrome is defined as three of the following five cardiometabolic risk factors: elevated fasting blood glucose, triglycerides, blood pressure or waist circumference, and low HDL cholesterol.[5] An estimated 34.3% of all US adults have metabolic syndrome according to National Health and Nutrition Examination Survey estimates from 2007-2014.[6] A focus on primary prevention of type 2 diabetes and CVD among individuals with prediabetes and metabolic syndrome is essential to decreasing the CVD burden.

A focus on secondary prevention can help to reduce CVD risk among individuals with type 1 diabetes (T1D). CVD is the leading cause of mortality in individuals with T1D, which constitutes 5-10% of diabetes in the United States.[1,7] Coronary artery disease (CAD), is the leading cause of

CVD mortality in the United States.[8] CAD occurs earlier and is more common in people with T1D, compared to people without diabetes.[2,9,10] Given the burden of CAD in the T1D population, early interventions that target the most influential CAD risk factors are imperative. A clear understanding of early predictors of CAD in those with T1D is needed to prevent CAD and its related complications and expenses in this population.

Straightforward approaches to improve modifiable risk factors that lead to CVD early in the disease process may help reduce the burden of CVD among individuals with prediabetes, metabolic syndrome and T1D. To promote CVD prevention, the American Heart Association (AHA) has developed a definition of CV health known as Life's Simple 7 (LS7) that has shown to predict CVD risk in the general population.[11–13] This concept was developed to promote primordial CVD prevention, providing clear goals defining and promoting optimal CV health.[14] LS7 is a composite of 7 modifiable metrics including four "health behaviors" (diet, physical activity, smoking and BMI), and three "health factors" (total cholesterol, blood pressure and fasting glucose), with criteria categorizing ranges within each metric as "ideal", "intermediate" or "poor".[14] Each additional CV health metric within the ideal range has shown to be associated with a 19% lower risk for CVD mortality in the general population.[11]

The AHA CV health metric approach has great potential for application in driving interventions with targeted goals to address CVD risk in a way that is easily interpretable and actionable.[15] However, the utilization of CV health metrics, especially among individuals at increased risk for CVD due to glucose and/or metabolic dysregulation, such as those with T1D, prediabetes and metabolic syndrome has not been thoroughly evaluated.

Using the AHA CV heath metrics in concert with behavioral lifestyle intervention programs may be an effective approach to CVD prevention among individuals with prediabetes

and/or metabolic syndrome. Behavioral lifestyle interventions, which usually promote weight loss through caloric restriction and balanced eating, increased physical activity and behavioral strategies to promote sustainable change, have shown to be effective in reducing the incidence of type 2 diabetes and reducing metabolic syndrome,[16–22] and in improving additional CVD risk factors.[23–43] Given their proven success, behavioral lifestyle interventions are an invaluable tool for the primary prevention of type 2 diabetes and CVD.

The landmark Diabetes Prevention Program (DPP) included a highly successful behavioral lifestyle intervention that is the platform for numerous intervention programs implemented across the United States. The National DPP, established by the US Centers for Disease Control and Prevention (CDC) for wide-scale delivery of the DPP lifestyle intervention with over 324,000 participants as of April of 2019,[44] is now reimbursable through the Centers for Medicare & Medicaid services (CMS; known as the Medicare-DPP).[45] These widely accessible DPP-based programs provide an ideal behavioral lifestyle intervention to explore the potential to improve CV health metrics.

Studies looking at improvement in CV health metrics as defined by the AHA during the course of behavioral lifestyle interventions are limited.[46–49] In addition, no studies to date have assessed the impact of widely implemented and accessible intervention programs on the AHA CV health metrics. Given the existing expansive impact and increasing availability of DPP-based behavioral lifestyle intervention programs nationwide, it is of interest to evaluate CV health metrics and their potential to capture meaningful progress toward clinically desirable values during the course of these programs.

The LS7 offers a straightforward and comprehensive approach to assessing health behaviors and health factors, capturing a picture of CVD risk that may also help identify and

monitor appropriate candidates for participation in DPP-based lifestyle intervention programs. Accessible and efficient tools for assessing health behaviors, in particular, are currently lacking in clinical and public health settings, and health behaviors are often not adequately addressed during routine care.[50–52] In addition, prediabetes itself is often under-diagnosed,[53] and current eligibility criteria for reimbursable DPP-based lifestyle intervention programs, including the Medicare-DPP, require that participants be overweight/obese and have prediabetes.[45] Using the CV health metrics would allow for the identification of appropriate lifestyle intervention participants based on existing DPP-based program eligibility criteria, and enriched with additional health behavior data. If found to capture change resulting from DPP-based programs, the AHA cardiovascular health metrics approach could offer an easy way to understand risk profiles, identify an effective lifestyle intervention referral option, and monitor change in key risk factors.

AHA defined CV health metrics have also not been well explored among individuals with T1D, an especially intriguing population due to its persistently high burden of CAD. A body of research continues to grow exploring CV risk factors in the high risk T1D population. Identifying appropriate goals for modifiable behaviors and factors that influence CAD risk among young adults with T1D could help to reduce the early onset and persistent burden of CAD in this population. The LS7 approach may, therefore, be valuable in the T1D population, however studies looking at the LS7 in individuals with T1D are lacking.[54,55]

To date, the AHA CV health metrics concept has not been explored in a cohort offering comprehensive CV health metric exposure data with a large enough sample and adequate follow up time to understand risk for development of CAD events. A cohort of individuals with T1D offering a rich selection of variables measured in early adulthood and a long follow up period with strong outcomes assessment are needed to clarify the role of CV health metrics in early adulthood

and CAD development over time. The Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort offers 30 years of prospectively collected data on individuals with childhood onset T1D, and the unique opportunity to explore AHA CV health metrics in relation to cardiovascular outcomes. The first step in exploring the AHA CV health metrics in the T1D population should be to explore the metrics as created by the AHA.

It is possible, however, that the existing AHA criteria for CV health metrics may not be directly applicable to T1D and may require population specific modifications. This may be most pertinent to the CV health definition of diet, which is not based on T1D specific patterns of intake or nutrient recommendations. For example, compared to the general population, individuals with T1D have a higher fat intake and low fiber intake due to the emphasis on limiting carbohydrate consumption for blood glucose control.[56,57] The existing LS7 diet criteria may not be realistically applicable to this population as the existing criteria do not take into account T1D specific intake in relation to CAD risk. The diet metric is also appealing because existing estimates in both the general and type 1 diabetes population show that achieving "ideal" status for this metric is rare,[55,58] thus a greater understanding of how best to focus attention on improving diet beyond the components captured by the current metric score is needed.

There is compelling new evidence that patterns of dietary intake influence CAD risk more than isolated nutrients.[59,60] Accordingly, population-specific patterns of nutrient intake could be especially valuable to understand CAD risk for adults with T1D. Exploring the potential to use the LS7 approach, enriched with population specific patterns of nutrient intake, could guide interventions to reduce or delay CAD in the high-risk T1D population.

1.1 Specific Aims

The first aim of this project is to determine the impact of a successful and accessible DPP-based lifestyle intervention on the AHA CV health metrics among individuals with prediabetes and/or metabolic syndrome. To address this aim, this project proposes the use of two cohorts of participants in a year-long DPP-based community intervention using a CDC recognized DPP translation curriculum known as Group Lifestyle Balance (DPP-GLB).

In addition, in aims 2 and 3, this project will explore the AHA CV health metrics with some T1D specific modifications, including deriving data driven patterns of nutrient intake in early adulthood and evaluating their impact on CAD risk in later adulthood. To address these objectives, this project proposes the use of a rich longitudinal data set, the Epidemiology of Diabetes Complications study cohort, which provides 30 years of follow up and allows for careful adjustment for potential confounding factors. The specific aims of this dissertation are:

Aim 1. To establish the utility of a successful DPP-based lifestyle intervention program, DPP-GLB, to improve the AHA CV health metrics among overweight or obese individuals with prediabetes and/or the metabolic syndrome.

Hypothesis: During the course of a yearlong DPP-based lifestyle intervention, improvement in individual AHA CV health metrics and composite metrics scores will be demonstrated after 6 months and maintained after 12 months of intervention.

Aim 2. To establish the predictive value of the AHA CV health metrics scores for risk of CAD among adults with T1D.

Hypothesis: Greater achievement of T1D specific ideal CV health metrics scores will protect against incident CAD and this relationship will persist with control for known confounders including renal function, increased albuminuria, triglycerides, duration of diabetes, inflammation, and depression.

Aim 3. To derive population-specific patterns of nutrient intake and explore their association with other CV risk factors and incident CAD in individuals with T1D.

Hypothesis: Patterns of nutrient intake that are lower in sodium and animal fat intake and higher in fiber, potassium, and vegetable fat will be associated with more favorable CV risk factors and lower risk for CAD.

The conceptual framework illustrating the potential associations of interest for these Aims are shown in the Conceptual Model (Figure 1, p.9).

The successful completion of these aims will help to determine whether the AHA concept known as LS7 can be effectively expanded to the high-risk prediabetes, metabolic syndrome and T1D populations.

Addressing aim 1 will establish the ability of the AHA CV health metrics, which offer simple and straightforward goals to reduce CVD risk, to capture cardiometabolic risk factor improvement during the course of a DPP-based lifestyle intervention. The DPP-GLB is an existing fully developed behavioral lifestyle intervention program with proven success. If found to improve CV health metrics, the straightforward LS7 approach could be used to identify appropriate

candidates for and monitor progress during these accessible and effective DPP-based lifestyle intervention programs.

In addition, completion of aims 2 and 3 will establish the potential for more favorable AHA CV health metrics in early adulthood to reduce CAD risk in individuals with T1D. Establishing patterns of nutrient intake will further inform the relationship between diet, other CV health risk factors, and CAD risk in individuals with T1D. Establishing these longitudinal associations will inform key targets for intervention to reduce CAD risk in the high risk T1D population.

Overall, building on the application of CV health metrics in the context of behavioral lifestyle interventions and among high-risk populations with prediabetes, metabolic syndrome and T1D could have the potential to advance translational efforts for reducing the CVD risk burden.

2.0 Conceptual Model

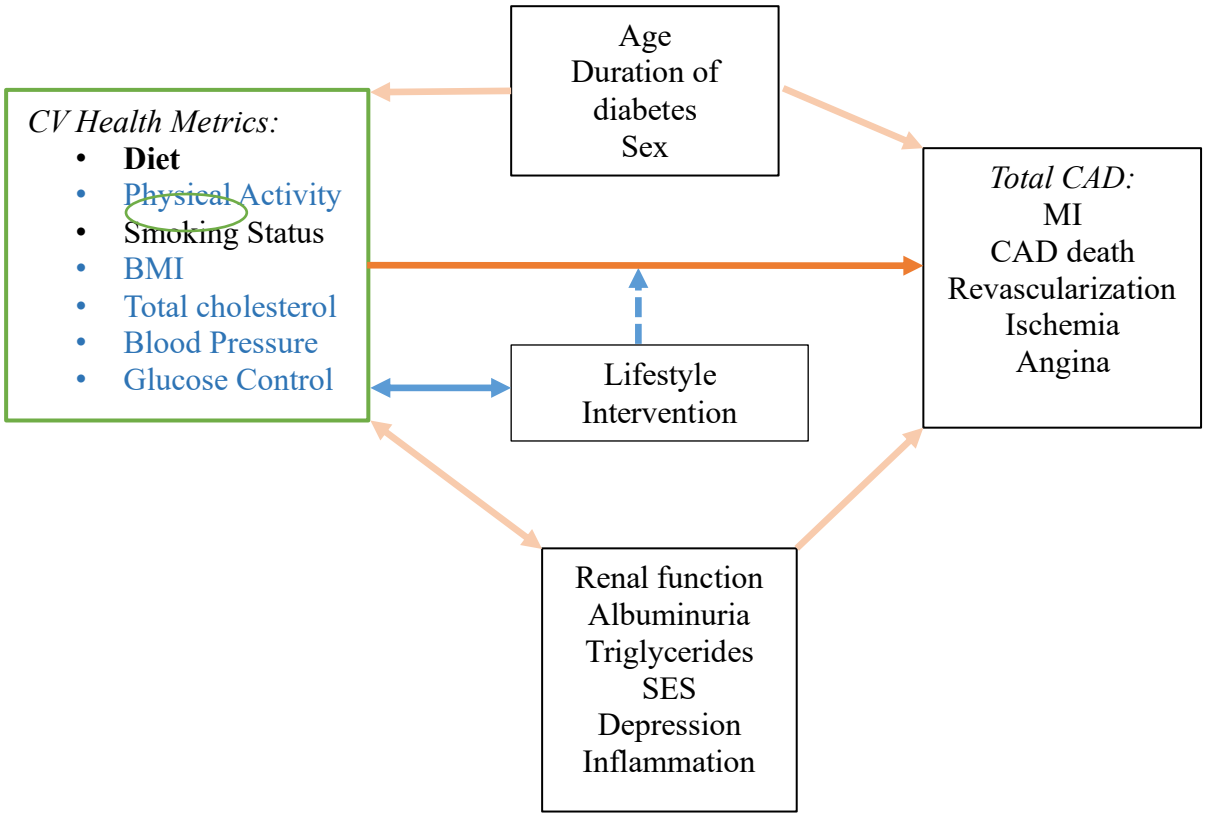

Figure 1 Conceptual Model
Aim 1: Blue, Aim 2: Orange, Aim 3: Green

3.0 Background and Significance

3.1 High Risk Populations and the Promise of the LS7 Approach

3.1.1 Cardiovascular Disease: A Pressing Health Concern

Despite declines in CVD mortality after it peaked in the 1970's,[1] CVD is a persistent health and economic burden in the United States. According to a 2016 estimate, 48% or about 121.5 million US adults age twenty and over, have CVD defined as coronary heart disease, heart failure, stroke and hypertension.[1] Excluding hypertension, the prevalence of heart disease, heart failure and stroke is about 9% of, or 23.1 million, US adults.[1] CVD is also a major contributor to mortality. While CVD deaths have decreased after peaking in about 1978, CVD remains the leading cause of death in the United States.[1,61] Coronary artery disease is the leading cause of CVD death[1] and the leading cause of death overall in the United States, accounting for about 166 deaths per 100,000 in 2016.[8] With the accumulation of risk factors over time, CVD prevalence and mortality increase for both males and females with age.[1,62] The high prevalence of CVD costs an estimated $351 billion dollars annually.[1] Addressing the burden of CVD is undoubtedly an ongoing public health priority.

3.1.2 Diabetes, Prediabetes, and Metabolic Syndrome Increase Risk for CVD

Diabetes is a risk factor for CVD, including CAD and stroke.[58] An extensive meta-analysis demonstrated that diabetes confers a two-fold greater risk for vascular disease, independent of

other traditional risk factors.[63] Diabetes is characterized by metabolic dysfunction, typically identified as elevated levels of blood glucose due to the inability to produce adequate insulin or utilize insulin effectively.[7] In general, varying degrees of metabolic dysfunction have been shown to increase CVD risk.[64,65] However, this dissertation effort focuses on T1D and those at risk for the development of type 2 diabetes (T2D). This is especially important as the prevalence of diagnosed diabetes, including both types 1 and 2, is increasing.[3]

T1D, about 5-10% of all cases of diabetes in the United States, is caused by an autoimmune condition leading to damage of the beta-cells of the pancreas and the inability to produce adequate insulin.[7] T1D is more likely to be diagnosed during childhood or adolescence.[7] There is no known intervention to prevent T1D, thus avoiding the development of its complications is a priority. CVD presents at an earlier age and is just as common among women as it is in men in the T1D population, both unique in comparison to the general population and in comparison to the T2D population.[9] As T1D itself usually presents at an earlier age compared to T2D,[7] duration of diabetes may also disproportionately contribute to increased risk for CVD at an earlier age among individuals with T1D.[66,67]

In T2D, which constitutes about 90% of all cases of diabetes, insulin resistance and inadequate insulin production lead to hyperglycemia.[7] T2D is characterized by progressive onset and is most often diagnosed in adulthood, thus intervention early in the disease process as soon as impaired glucose tolerance is identified may be an effective way to prevent or delay diabetes development and reduce CVD risk. T2D is thought to be caused by a multitude of genetic and environmental factors that influence beta-cell function and insulin resistance.[68] There are strong links between T2D and increasing age.[7] Several lifestyle factors are thought to greatly influence T2D development such as obesity, physical inactivity, sedentary lifestyle, and diet.[69]

Lifestyle interventions have shown to be effective in reducing CVD risk factors among individuals at risk for T2D.[16,70,71] These improvements in CVD risk factors do not always seem to translate to improvement in CVD outcomes,[72,73] however the longitudinal study of these associations is ongoing. The Da Qing Diabetes Prevention Study, one of the few lifestyle intervention studies that targeted individuals with impaired glucose tolerance and without T2D diagnosis with adequate follow up to ascertain CVD events, demonstrated reduced CVD mortality after 30 years of follow up in those who received the lifestyle intervention.[70] This indicates that it may be especially important to intervene early in the disease process to reduce CVD risk among individuals progressing toward the development of T2D.

Targeting intervention to capture individuals with impaired glucose tolerance, elevated fasting blood glucose or raised HbA_{1c} before it reaches the threshold for diabetes, is key to delaying or preventing progression to T2D, and as a result delaying or preventing the additional CVD risk that accompanies T2D development.[74,75] Prediabetes is the condition where blood glucose is above the normal range and below the diagnosable range for diabetes.[7] Specifically, prediabetes is often defined as a fasting glucose of 100 to 125 mg/dL or HbA_{1c} 5.7 to 6.4%.[4] People with prediabetes are at increased risk for developing T2D and CVD.[75,76] About 34% of adults in the United States have prediabetes,[1,4] presenting a substantial target population that would benefit from primary intervention to reduce risk for CVD.

Metabolic syndrome, the clustering of cardiometabolic risk factors, is also associated with the development of T2D and CVD.[58] Identifying and targeting individuals with metabolic syndrome presents the opportunity to intervene before these conditions develop. A harmonized definition of metabolic syndrome from the AHA, National Diabetes Federation, and National

Heart, Lung and Blood Institute specify metabolic syndrome as any three of these five criteria being present[1]:

- Elevated fasting blood glucose of ≥100mg/dL or treatment for elevated glucose
- HDL cholesterol of < 40mg/dL in males or < 50 mg/dL in females, or treatment for low HDLc
- Triglycerides of ≥ 150 mg/dL or treatment for elevated triglycerides
- Blood pressure of ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or treatment for hypertension
- Waist circumference of ≥ 102 cm (40 inches) in males and ≥ 89 cm (35 inches) in females

Recent analysis of National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2014 indicate that the prevalence of metabolic syndrome among US adults is around 34.3% and is relatively stable among males and females across age and racial/ethnic groups.[6]

Diabetes, prediabetes and metabolic syndrome are associated with increased CVD risk. In order to reduce the burden of CVD, it is important to understand how to best prevent complications among those at risk. Among individuals with prediabetes and/or metabolic syndrome, interventions to treat and prevent progression of these respective conditions are essential. Lifestyle modification is indicated as an effective means of preventing and treating prediabetes and metabolic syndrome.[16,17] As T1D is not preventable, reducing the burden of CVD among individuals with T1D requires identifying modifiable risk factors to prevent complications. This project explores the potential to reduce CVD risk through lifestyle intervention aimed at preventing or delaying CVD onset among individuals with prediabetes and/or metabolic syndrome.

Individuals at high risk for T2D who are overweight/obese and have prediabetes or metabolic syndrome are the focus of Aim 1 of this effort. This project also explores approaches to identify modifiable targets for CVD risk reduction in early adulthood among individuals with T1D. CVD risk among individuals with T1D is the focus of Aims 2 and 3 of this project.

3.1.3 AHA "Life's Simple Seven" to Reduce CVD: A Promising Approach

In 2010, the AHA was tasked with improving CV health in the general adult population by 20% by the year 2020.[14] Contrary to previous impact goals, this initiative marked a paradigm shift from reducing the burden of CAD and stroke through improved treatment alone toward an increased focus on prevention through health promotion.[14] This more expansive emphasis on prevention included three main concepts: *"(1) the power of primordial prevention; (2) evidence that CVD and risk factors for it develop early in life; and (3) the appropriate balance between population-level approaches for health promotion and disease prevention and individualized high-risk approaches."*[14] Primordial prevention refers to avoiding adverse risk factors, thus intervening before risk presents. Given that individuals with prediabetes, metabolic syndrome, and T1D are already at risk, primary and secondary prevention are the focus of this effort. The overall emphasis on expanding the application of CV health metrics in this dissertation effort aligns with this AHA initiative and goal of improving CV health.

In order to quantify improvement in CV health, the concept needed to be defined in a way that was measurable and actionable. The AHA wanted the definition of CV health to be simple and accessible to practitioners in providing guidance to patients while also providing easily digestible public health messaging to the lay person.[14] In addition, the definition of CV health was intended to contain actionable items that are readily measured and allow all subsets of the

population to make progress toward achieving or maintaining ideal CV health.[14] With these criteria in mind, the AHA defined CV health as a composite of modifiable metrics, known as "Life's Simple 7" (LS7), to create a clear idea of where to focus intervention efforts using easily interpretable goals at the individual, health system, and population level.[14,15] LS7 includes three "health factors": total cholesterol, blood pressure, and fasting blood glucose, and four "health behaviors": diet, physical activity, BMI and smoking. The AHA also defined set cut points to categorize all possible ranges for these seven metrics as poor, intermediate or ideal.[14]

These seven metrics were chosen based on an extensive review of literature and through consensus among the AHA Goals and Metrics Committee of the Strategic Planning Task Force.[14] Health factors were selected based on evidence demonstrating that untreated blood pressure <120/<80 mmHg, total cholesterol <200 mg/dL, and lack of diabetes, especially in combination, are associated with morbidity free survival, lower risk of CVD death, CVD events,[77–82] and additional benefits such as improved quality of life and lower healthcare costs.[83,84] Health behaviors were selected based on evidence indicating that being a nonsmoker and having a more favorable BMI, physical activity, and diet profile were associated with greater longevity and CVD-free survival, as well as lower incident diabetes, in men and women across the adult lifecourse.[85–92] Health factors and behaviors are highly correlated,[93,94] suggesting that lifestyle and environment play a substantial role in determining CV health and both behaviors and factors should be considered as contributors to CV health.

Cut points defining the ideal, intermediate, and poor categories for each CV health metric were based on a consensus in the literature, scientific statements and clinical practice guidelines.[5,95–104] Specifically, total cholesterol metric categories are based on the National Cholesterol Education Program Adult Treatment Panel III criteria,[101] the blood pressure metric

categories are based on those defined by the Joint National Committee on Prevention, 7th addition,[96] and fasting blood glucose categories are based on the ADA Standards of Medical Care in Diabetes, 2007.[104] The BMI categories are based on National Heart, Lung and Blood Institute definitions established in 1998,[105] physical activity on the 2008 Physical Activity Guidelines for Americans[106] and smoking cessation on an abundance of evidence and Surgeon General recommendations.[97] Dietary guidelines in relation to CVD risk remain nuanced, and the components chosen for inclusion in the AHA CV health metrics are based on a consensus between the 2005 Dietary Guidelines for Americans,[99] AHA recommendations[100,102,103] and a desire to focus on whole foods and a dietary pattern consistent with the Dietary Approaches to Stop Hypertension.[14] Ideal metric categories are meant to reflect optimal CV health, however ideal status for all metrics is rare, so intermediate and poor categories were developed to capture the full range of these metrics as they present in the general population, as shown in Table 1.[14]

Table 1 AHA Defined Cardiovascular Health Metrics, also known as "Life's Simple Seven"

Metric	**Ideal**	**Intermediate**	**Poor**
Total cholesterol	< 200 mg/dL	200-239 mg/dL or treated to the ideal range	≥ 240 mg/dL
Blood pressure	< 120 systolic, <80 mmHg diastolic	120-139 systolic or 80-89 mmHg or treated to the ideal range	≥ 140 systolic or ≥ 90 diastolic
Fasting Plasma Glucose	<100	7.0-8.9%	>9%
BMI	< 25 kg/m^2	25 - 29.9 kg/m^2	≥ 30 kg/m^2
Smoking status	Never or quit >12 months	Former ≤ 12 months	Current
Physical activity	≥ 150 minutes per week moderate to vigorous or ≥ 75 minutes vigorous	1-149 minutes per week moderate to vigorous or 1-74 min/wk vigorous or 1-149 min/wk moderate + vigorous	None
Healthy Diet Score: 1) Fruit and Vegetables ≥ 4.5 cups per day	4-5 components	2-3 components	0-1 component

2) Fish: two 3.5-oz servings per week (preferably oily fish) 3) Fiber-rich whole grains: ≥ three 1-oz-equivalent servings per day 4) Sodium: <1500 mg per day 5) Sugar-sweetened beverages: ≤ 450 kcal (36 oz) per week			

Studies looking at AHA CV health metrics in longitudinal cohorts have demonstrated an inverse linear dose response between higher ideal scores (sum of metrics in the ideal range) and mortality and cardiovascular mortality.[107–109] A dose-response meta-analysis found a pooled hazard ratio of 0.81 (95% confidence interval, 0.75–0.87) for cardiovascular mortality with each additional CV health metric within the ideal range.[11] A greater number of ideal metrics is also associated with less subclinical CVD and CVD development over time.[110–112] Similarly, studies looking at categories of ideal metrics found that achieving five or more ideal metrics was associated with a significantly lower CVD risk compared to zero or one ideal metric.[111,113] Achieving the highest total cardiovascular health metric score, quantified as a sum total score taking into account poor, intermediate or ideal status for each metric, has also been shown to significantly reduce CVD risk.[13,114]

The AHA released a new policy statement in March of 2020 reflecting on progress made over the past decade and setting goals for the decade to come.[115] With the recognition that few US adults meet the criteria for ideal CV health for all metrics, CV health promotion remains a fundamental part of the AHA 2030 impact goals.[1,115] Estimates based on historic trends in CV health metric progress predicted a 6% improvement in CV health by the year 2020, far short of the 20% improvement goal.[116] Building a greater understanding of the utility of these metrics among

higher risk populations is a priority given the importance of continued efforts to promote CV health.

The overarching goal of this project is to build on application of the AHA CV health metrics among high risk populations including individuals with prediabetes and/or the metabolic syndrome, and those with T1D. This will inform the value of using the AHA CV health metrics approach to monitor progress in a behavioral lifestyle intervention and provide direction on how to best direct interventions to reduce CVD among these high-risk populations. The diet component of the CV health metrics will receive additional consideration among individuals with T1D due to emerging compelling evidence for the role of patterns of nutrient intake in CVD risk.

3.2 The Potential for AHA CV Health Metrics to Capture Improvement During the Course of a Behavioral Lifestyle Intervention among Individuals with Prediabetes and/or Metabolic Syndrome

3.2.1 Lifestyle Intervention Reduces CVD Risk among Individuals with Prediabetes and Metabolic Syndrome

Interventions to improve risk factors for CVD are an essential step in prevention. Behavioral lifestyle interventions have gained popularity due to their success in reducing chronic disease risk, especially among adults who are overweight or obese and exhibit additional risk factors. In order to reduce risk, behavioral lifestyle interventions emphasize strategies to initiate and maintain changes such as weight loss, balanced eating, and adequate physical activity.

The goals promoted by these lifestyle intervention programs are supported by a considerable amount of published literature[23–43] including guidelines such as the Dietary Guidelines for Americans [117] and the Physical Activity Guidelines for Americans,[118] as well as scientific statements detailing diet, activity, and lifestyle recommendations to reduce CVD risk.[21,100,119] The strength of evidence for lifestyle interventions has led the United States Preventive Services Task Force to recommend "*offering or referring adults who are overweight or obese and have additional cardiovascular disease (CVD) risk factors to intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD prevention*."[120] This statement was given a B grade, meaning that there is high certainty that this recommendation will provide a moderate net benefit, there is moderate evidence that the net benefit is moderate or substantial, and implying that this service should be offered or provided.[121]

3.2.2 The Diabetes Prevention Program: A Successful Behavioral Lifestyle Intervention

The DPP was one of the first large scale randomized control trials to demonstrate that chronic conditions could be prevented or delayed through lifestyle changes.[17] The DPP was a landmark study among overweight or obese adults with prediabetes that demonstrated a 58% reduction in diabetes risk among those randomized to the lifestyle intervention compared to participants who received a placebo.[17] The goals of the lifestyle intervention were to achieve and maintain a seven percent weight reduction and to engage in 150 minutes or more per week of moderate intensity activity, similar to a brisk walk.[122] The structure of the lifestyle arm of the DPP involved one-on-one sessions utilizing a curriculum encouraging exercise, a balanced calorie restricted diet, and behavior modifications to help participants achieve program goals.[122]

In addition to reducing the risk of diabetes, the DPP also found that those in the lifestyle intervention arm were less likely to develop metabolic syndrome and more likely to see resolution of metabolic syndrome.[16] Also, participants in the lifestyle arm of the DPP were less likely to develop hypertension and dyslipidemia.[71] The lifestyle arm of the DPP has also shown to be cost-effective.[123] The reduced incidence of diabetes has been maintained in those who participated in the lifestyle intervention in the DPP through the course of 10 and 15 year outcomes studies.[124,125] As a demonstrably successful approach, the DPP was ideal for translation from efficacy to effectiveness.

A few additional large scale randomized trials designed primarily for diabetes prevention and promoting weight loss, adequate physical activity, and behavioral strategies to improve health among individuals at high risk for diabetes have been shown to be effective in delaying or decreasing diabetes and in improving other clinical metrics.[18–20,22] The Finnish Diabetes Prevention Study found a 43% reduction in diabetes risk with weight loss, reduced fat and saturated fat intake and increased physical activity.[22] The Da Qing Impaired Glucose Tolerance and Diabetes study found a lower cumulative incidence of diabetes with diet, exercise or diet+exercise compared to a control.[18] The Japanese DPP and Indian DPP also demonstrated decreases in diabetes incidence with lifestyle intervention promoting weight loss and adequate physical activity.[19,20] These studies have been especially influential in demonstrating the efficacy of lifestyle intervention approaches to reduce diabetes risk among individuals with impaired glucose tolerance. The approaches used in these programs have also helped to inform lifestyle interventions to reduce CVD risk.

3.2.3 The Diabetes Prevention Program Translation Efforts

A plethora of DPP translation efforts have adapted the lifestyle intervention from the DPP for use in a variety of settings.[44,126,127] The National DPP was established in 2010 by the CDC to build a delivery system for DPP programs.[44,128] Only a few versions of DPP lifestyle intervention translation efforts are available with CDC approved curriculum including the DPP-Group Lifestyle Balance (described in detail in Section 3.2.4, p.22), which was developed by members of the original DPP National Lifestyle Resource Core as a group-based format for use in community settings.[129] These CDC recognized programs have provided the framework for a variety of community studies. The National DPP includes four components: 1) training a workforce for effective delivery, 2) quality assurance, 3) intervention sites that provide infrastructure to deliver the program, and 4) health marketing, including program referral.[130]

The National DPP has significant reach and has shown to be effective. A 2017 study of 14,747 National DPP participants across 220 organizations found that average attendance was 14 out of 22 sessions with an average weight loss of 3.1% during the year-long program.[128] As of April of 2019, the National DPP has reached over 324,000 participants across over 3,000 organizations.[44] In 2018, CMS began offering reimbursement for participation in National DPP programs to eligible Medicare beneficiaries.[45] The significant step of achieving CMS reimbursement, alongside coverage offered by some private employers and commercial insurance plans,[44] have made the DPP lifestyle intervention one of the most accessible behavioral lifestyle intervention options available.

The success of DPP lifestyle intervention translation efforts has been demonstrated through consistent achievement of weight loss, however there are additional benefits to program participation that are less commonly identified. A systematic review and meta-analysis of 28

lifestyle interventions modeled on the DPP lifestyle intervention offered in real-world settings found that these programs were successful in achieving a clinically meaningful weight loss of about 4%.[127] While weight loss is one of the primary goals of the program, documentation of the other primary goal, physical activity, has shown to be less commonly reported.[131] Given the success of DPP translation efforts shown through meaningful weight loss, there are likely additional benefits achieved through participation in DPP lifestyle intervention translation efforts that have not yet been explored. Translation efforts, such as the DPP-GLB, that include more clinical measures offer the opportunity to explore novel approaches to understanding additional benefits of DPP participation.

3.2.4 The Group Lifestyle Balance Program: An Effective DPP Translation Effort

The Group Lifestyle Balance (DPP-GLB) program is an especially effective DPP translation effort that is not only CDC recognized but has also been shown to be effective in rigorous clinical trials.[132–147] The GLB program consists of 22 total sessions offered over 12 months. The intervention is led by lifestyle coaches who are certified in the DPP-GLB curriculum through a standard training provided by the Diabetes Prevention Support Center, an organization created and run by individuals involved in DPP lifestyle translation efforts.[129]

The DPP-GLB program has been evaluated in a number of diverse settings and has consistently found to be successful in achieving the primary goals of the intervention program (weight loss and physical activity) and shows good adherence.[129,133,140–143,148] Weight loss in DPP-GLB programs has been consistently reported to be around 5%, and the vast majority (>75%) of participants attended most sessions.[132,133,140–142] Showing effective weight loss and attendance is essential in DPP translation efforts as these are the criteria that CMS uses to justify coverage

eligibility for ongoing maintenance sessions.[45] Thus, GLB is an appealing option given its success in promoting weight loss and excellent attendance.

The DPP-GLB also shows the potential to impact on CVD risk as the intervention has been shown to improve other cardiometabolic measures. In studies offered in community settings measuring cardiometabolic risk factors including fasting blood glucose, blood pressure and BMI have shown improvement after intervention.[132,133] In the "Healthy Lifestyle Project", a yearlong GLB-DPP intervention this is part of this dissertation effort, weight, triglycerides, fasting blood glucose, systolic blood pressure, BMI, waist circumference, and physical activity improved significantly ($p<0.05$) after six and twelve months of intervention.[133] Total cholesterol also improved significantly after six months.[133] Improvement in BMI, blood pressure, fasting blood glucose, cholesterol and physical activity are notable as these are components of the AHA's CV health metrics. Looking at AHA CV health metrics specifically and composite CV health metrics scores has not yet been done in any DPP-based intervention studies.

3.2.5 Existing Lifestyle Interventions to Improve CV Health Metrics (The LS7 Approach): Limitations and Gaps in Knowledge

While more favorable AHA CV health metrics scores have been shown to be associated with lower CVD risk, recent evidence has demonstrated that the AHA CV health metrics are not improving among the general population. NHANES estimates showed no change in cardiovascular health metric scores in the general population from 1999 through 2016.[149] Thus, effective interventions to improve CV health metrics are needed. However, the body of literature exploring the potential to use behavioral lifestyle interventions to improve CV health metrics is small and has several key limitations.

A few behavioral lifestyle interventions have been tested for their ability to improve the AHA CV health metrics. These studies used a variety of approaches. The Fostering African-American Improvement in Total Health study, which used a culturally tailored 16-week education series using the LS7 framework offered through African-American churches in Rochester, MN, demonstrated feasibility (recruitment, attendance and retention) and improvement in cardiovascular health knowledge among its 37 participants.[47] Another community based pilot study offered by Nurse Practitioners in inner city Chicago demonstrated improvement in My Life Check, an interactive tool based on LS7, over six months among eight older adults, however improvement was not seen among ten homeless women.[49] These pilot studies were intended mainly to show the feasibility of their respective interventions and are limited by short duration and small sample size.

Two behavioral interventions with larger sample sizes and more outcomes measures have also been evaluated for their ability to improve CV health. The HeartSmarts study was a 12-week faith-based program completed by 199 participants through predominantly African American churches in New York City that significantly improved systolic and diastolic blood pressure and BMI, and improved CVD knowledge.[46] The largest intervention to date among 711 university employees utilized health-partners to offer an individual goal based intervention that showed improvement in systolic blood pressure, total cholesterol, BMI, smoking and a composite ideal CV health score over two years of follow up.[48] These results show promise for the feasibility and effectiveness of behavioral lifestyle interventions to improve CV health metrics. However, the potential impact on CV health metrics of a widely implemented and successful lifestyle intervention program has yet to be determined.

3.2.6 The Potential Value in Using the DPP Approach to Improve CV Health

Behavioral lifestyle interventions have been shown to be an effective approach to reducing risk factors for CVD.[23–29,31,33,35,38–43,73] The DPP lifestyle intervention was successful in reducing incidence of diabetes, metabolic syndrome, hypertension and dyslipidemia.[16,71] The behavioral lifestyle intervention used in the DPP has been modified for wide-scale implementation.[44,127] As of April of 2018, DPP programs are now reimbursable through CMS.[45] As a widely accessible program, the DPP approach has the potential for additional application to reduce CVD risk.

One of the most successful approaches to DPP lifestyle intervention translation is the DPP-GLB, as shown through consistently meeting weight loss goals, excellent adherence and improvement in cardiometabolic indicators.[132,133,141,150] The success and increasing availability of the DPP-GLB, along with the improvement in CVD risk factors demonstrated in the DPP and DPP-GLB, present an intriguing opportunity to consider the use of AHA CV health metrics as a means of capturing meaningful improvement during the course of a DPP lifestyle intervention-based program.

Improvement in AHA CV health metric scores during the DPP-GLB program would show the utility of these metrics in capturing beneficial changes in CV health and progress toward clinically desirable values during a widely accessible behavioral lifestyle intervention. If AHA CV health metrics show improvement during the course of the DPP-GLB, these metrics could be used as a clinical tool for screening, referral, and progress monitoring of appropriate candidates for DPP-based lifestyle intervention programs. **Aim 1 will establish the utility of a successful lifestyle intervention program (DPP-GLB) to improve CV health metrics among overweight or obese individuals with prediabetes and/or metabolic syndrome.**

3.3 The LS7 Approach as a Tool to Understand CVD Risk among Individuals with T1D

3.3.1 Coronary Artery Disease: An Outcome of Interest in T1D

Within the umbrella of CVD, CAD is of particular interest among individuals with T1D. It is well established that having T1D increases risk for developing CAD,[2,72,151] the most prevalent cause of CVD mortality in this population.[9] Not only are T1D individuals more likely to have CAD compared to similarly aged peers, they also experience earlier onset of CAD.[9] A landmark study from 1987 of premature CAD demonstrated that by age 55 about 35% of individuals with T1D experienced CAD mortality, compared to 8% of nondiabetic men and 4% of nondiabetic women.[10] More recent evidence has shown that increased premature CAD persists among individuals with T1D to this day.[66,152] As stroke has a relatively low incidence in the T1D population,[9] and may have a slightly different risk profile,[153] CAD is the primary outcome of interest in this dissertation effort. Given the disproportionate burden of CAD among individuals with T1D, identifying targets for intervention to decrease CAD risk in the T1D population is a priority.

3.3.2 What We Know about Risk Factors for CAD in T1D

The increased risk for CAD among individuals with T1D may be due to a variety of factors. As glycemic control is a unique consideration among individuals with diabetes, this factor has been implicated as a driver of greater atherosclerotic risk. However, the role of glycemic control is somewhat controversial, with some studies indicating that there is a relationship between poor glycemic control and CAD and/or CVD, [67,154,155] while some studies suggest little relationship.[156–158]

Previous studies in the Epidemiology of Diabetes Complications (EDC) cohort, an observational study of individuals with childhood onset T1D (the cohort of interest in this proposal, described in detail in Section 4.3.2, p.85), have historically not demonstrated that glycemic control is a major predictor of CAD.[156–158] The Diabetes Control and Complications Trial (DCCT), a clinical trial testing intensive blood glucose management compared to conventional therapy in a T1D cohort, found that intensive therapy delayed the onset of vascular complications.[159] An ongoing longitudinal study of the DCCT study cohort, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, found that the intensive therapy group displayed a 9% incidence of CVD compared to 14% in the conventional therapy group after 30 years of diabetes duration.[154]

Recent analyses of the DCCT/EDIC and EDC cohorts found that HbA_{1c} was a predictor of CVD, and was a much stronger predictor in DCCT/EDIC compared to EDC.[67,160] This difference may be due in part to a majority of participants in the EDC cohort having comparatively poor glycemic control, especially during the initial years of the study. In addition, the DCCT/EDIC excluded individuals with high blood pressure and with more than minimal albuminuria at baseline, which was not the case in the EDC cohort.[67,161] Some of the difference may also be attributed to the longer diabetes duration in the EDC cohort compared to the DCCT/EDIC cohort, and may imply that with longer duration, CVD risk associated with HbA_{1c} is mediated by other factors.[67]

Additional CAD risk factors have been proposed among individuals with T1D. Some of the factors found to be associated with CAD development in longitudinal analyses in the T1D population include traditional CVD risk factors such as hypertension, low HDL cholesterol, high non-HDL cholesterol, elevated triglycerides, high waist to hip ratio, elevated white blood cells, insulin resistance, and ever having been a smoker.[156,158,162]

More T1D population specific risk factors such as longer diabetes duration, as well as somewhat distinct pathophysiological factors such as overt nephropathy, and depressive symptomatology were also found to be associated with incident CAD.[156,158,162] Independent risk factors vary slightly by type of first CVD event, with hypertension, diabetes duration, white blood cells, HDL and non-HDL cholesterol, and smoking status found to predict total CAD in the EDC cohort.[156] Albumin excretion rate was found to be a strong risk factor for total CVD[67] and hard CAD[163] in the EDC cohort, and a strong predictor of CAD in a large sample of European T1D patients.[162] Interestingly, while risk factors may differ by sex,[157,162,163] CAD risk does not appear to differ by sex among individuals with T1D.[157,164] This is notable given the higher risk for CAD seen in males in the general population. The HP 2-2 genotype, which indicates inadequate antioxidant capacity and inefficient clearance of hemoglobin,[165,166] may also increase susceptibility to CAD in the T1D population,[167,168] a finding that has been shown in prospective studies of T2D complications as well.[169–172]

Lifestyle factors that contribute to CAD risk in the general population, such as diet and physical activity, may also be risk factors in the T1D population. Diet and physical activity in particular are of interest because individuals with T1D may make unique lifestyle choices, such as limiting activity or having a less balanced diet, due to diagnosis with a chronic condition during childhood.[9,173] While physical activity was found to be a risk factor for CAD and CVD in the EDC cohort,[67,156] studies including diet as a risk factor for CAD appear to be limited. Considering modifiable behaviors, including diet, alongside factors shown to be associated with CAD in individuals with T1D will be informative in understanding the full risk profile and potential for prevention.

As more people with T1D are living longer, they are at greater risk for developing CAD. Mortality from renal disease and other acute metabolic complications is falling, which has resulted in greater exposure to the cardiovascular risk factors associated with aging.[151,154] Diabetes duration also increases the risk for CAD,[156,158] with CVD as the leading cause of death 20 years after diagnosis.[174] A critical window of time to prevent CAD development is early adulthood due to the persistently high prevalence of CAD in mid to late adulthood.[66] An effective approach to reduce risk must therefore involve appropriately targeting health behaviors and factors in early adulthood that are most influential to CAD development.

It is likely that cumulative exposure to CAD risk factors starting with disease onset early in life plays a major role in the premature and more common development of CAD in T1D. This indicates an essential need to identify CAD risk factors and strategies for prevention in early adulthood. It is relevant, therefore, to determine if the AHA CV health metrics provide appropriate benchmarks to reduce the risk for CAD among young adults with T1D.

3.3.3 Cardiovascular Health in the T1D population: Limitations and Gaps in Knowledge

The LS7 approach creates a clear idea of where to focus intervention efforts using easily interpretable goals at the individual, health system, and population level.[15] This approach is highly desirable for individuals with T1D due to their high risk for CAD. A primary gap in knowledge among individuals with T1D is lack of application of approaches that define target values for modifiable risk factors in early adulthood to reduce risk for development of CAD.

The utility of the LS7 approach has yet to be fully explored in T1D with no existing studies ascertaining AHA CV health metrics in relation to CAD events. Among the limited studies that look at LS7 in T1D, a cross sectional study of six of the LS7 metrics in the T1D Exchange Clinic

Registry demonstrated low levels of ideal HbA_{1c} and physical activity, however it was not possible to evaluate CAD development.[54] The only longitudinal study of all factors among adults with T1D found that having more ideal CV health metrics was associated with decreased prevalence and progression of coronary artery calcification.[55] No studies to date have looked at all AHA CV health metrics longitudinally in relation to incident CAD.

If CV health metrics scores for T1D are as predictive of CV outcomes as the LS7 in the general population, they could be used to understand targets for improvement to reduce CAD in this high-risk population. CV health metrics could then become targets for intervention in T1D. However, some modifications to the AHA CV health metrics may be necessary for use in the T1D population.

An initial T1D specific modification to the AHA CV health metric of fasting plasma glucose is needed. Use of fasting blood glucose is inappropriate for those with T1D as fasting may be challenging given the need for regular use of exogenous insulin and fasting values may not be indicative of overall glucose control, however HbA_{1c} is an appropriate substitute. As previously discussed, some longitudinal analyses indicate HbA_{1c} as a particularly important predictor, second only to age (or diabetes duration) and alongside additional risk factors, for CAD development.[160]

While there is some agreement with the AHA in current T1D specific guidelines, additional modifications to the AHA cardiovascular health metrics may need to be the focus of future efforts. Per American Diabetes Association (ADA) guidelines, there is currently general agreement with the AHA on the recommended goals for individuals with T1D for blood pressure, physical activity, and smoking.[9,14,175,176] There is evidence suggesting that individuals with T1D may see an increase in risk for CVD at lower thresholds of blood pressure,[177–179] including new evidence from the EDC cohort suggesting that a lower blood pressure target may be needed to reduce CAD risk

among individuals with T1D.[180] There are not diabetes specific total cholesterol guidelines, with an emphasis instead on achieving LDLc <100mg/dL.[181] There are also not existing BMI criteria or dietary intake recommendations specific to CVD prevention in T1D, with a focus instead on individualized goals for maintaining a healthy body weight and dietary intake per risk profile and preferences.[176]

In order to determine the utility of CV health metrics among those with T1D, the logical next step is to evaluate LS7 in relation to CAD outcomes using criteria based on AHA and current T1D recommendations. These findings will then inform the potential need to further modify metrics for the high risk T1D population.

Additional discussion of how AHA metrics ranges and T1D specific guidelines have evolved over time can be found in Section 3.5 (p.39).

3.3.4 The EDC Cohort: Uniquely Suited to Explore CV Health in Individuals with T1D

The Pittsburgh EDC is a prospective cohort study of childhood onset T1D. Eligible participants were diagnosed, or seen within one year of diagnosis, before the age of 17 between 1950 and 1980 at the Children's Hospital of Pittsburgh.[182] Baseline data on 658 participants was collected in 1986-1988, with subsequent follow up roughly biennially since enrollment. The EDC has collected a rich amount of participant data using valid and reliable methods during clinical assessment visits and through surveys.[182] With the availability of 30 years of follow up data, the EDC has the strength of providing an adequate sample size and follow up time to ascertain CAD events as an outcome. In addition to the length of follow up time available, the EDC also uses strict protocols and physician adjudication to determine cardiovascular outcomes and mortality. The EDC cohort, with CV health metrics data available in early adulthood and extensive and carefully

monitored follow up data, is an invaluable resource in understanding CAD development in the high risk T1D population. **Aim 2 will establish the predictive value of CV health metrics for risk of CAD among adults with T1D over 25 years of follow up.**

3.4 Diet as a Uniquely Interesting Component of Cardiovascular Health Among Individuals with T1D

3.4.1 The relationship between diet and CVD risk

Within the CV health metrics, diet is an ongoing topic of interest. Diet influences risk for CVD. Early research concentrated mostly on individual nutrients, indicating that intake of certain nutrients is associated with increased risk of CVD while some nutrients may protect against CVD.[183] Dietary fat, for example, has received significant consideration due to its influence on serum cholesterol levels, with some types of fat, such as monounsaturated fat and polyunsaturated fat, seen as protective and others, such as saturated fat and trans-fat, seen as problematic.[184]

Trials aimed at modifying individual nutrients such as saturated fat, however, have not been effective in reducing CVD events.[183] One landmark large scale trial, the Multiple Risk Factors Intervention Trial (MRFIT), which randomized men at high risk for CVD to usual care or to receive an intervention promoting low saturated fat and cholesterol intake, found no significant differences in total mortality or coronary death after seven years of intervention.[185] As the men in MRFIT were successful in reducing saturated fat and cholesterol intake,[185] the lack of efficacy in this large scale trial indicates that the focus on intake of these individual nutrients did not appear to reduce risk.

More recently, diet research has moved toward looking at patterns of intake. This approach accounts for the effects of nutrients as they are consumed together in foods. Randomized control trials have demonstrated that patterns of intake may be related to improvement in CVD risk factors, as well as CVD events. The Dietary Approaches to Stop Hypertension trial found that a diet rich in fruits, vegetables, and low fat dairy, and low in saturated fat and cholesterol improved blood pressure.[186] Adding low sodium intake to this diet pattern may be even more effective in blood pressure reduction.[187] Additional meta-analyses of randomized trials indicate that saturated fat in place of carbohydrate[188] and trans-fat in place of saturated fat, polyunsaturated fat and monounsaturated fat may have a detrimental effect on serum lipid levels.[189] Randomized control trial evidence linking diet patterns and CVD events is less extensive. A key study known as PREvención con DIeta MEDiterránean in individuals at risk for CVD found that adherence to a Mediterranean diet pattern supplemented by olive oil or mixed nuts decreased the risk of stroke, myocardial infarction and cardiovascular death by about 30% compared to a control diet after about five years.[59]

Extensive research in prospective cohort studies has found additional associations with CVD development that have driven dietary recommendations for CVD prevention.[1,183,190] The 2015 US Dietary Guidelines for Americans recommend a healthy dietary pattern higher in fruit, vegetables, whole grains, low fat or nonfat dairy, seafood, legumes and nuts, and lower in red and processed meat, sugar-sweetened food and beverages and refined grain.[191] These recommendations are based on evidence that the overall composition of dietary intake helps to reduce risk for cardio-metabolic and other disease outcomes.[117] In summary, patterns of dietary intake are indicated as an effective modifiable risk factor for the development of CVD.

3.4.2 Diet as a predictor of CVD in T1D

Current dietary guidelines in T1D recommend an individualized approach to structuring dietary intake as opposed to providing generic nutrient goals, and there are not specific dietary guidelines for these individuals regarding CVD prevention.[176] Diet is central to management of T1D due to the need for exogenous insulin to aid in uptake of serum glucose after the consumption of meals. Carbohydrate intake in particular has historically been a more singular focus among individuals with T1D as it most directly influences blood glucose.[192] Regulating carbohydrate intake remains an important part of blood glucose management, and adequate dietary fiber in the form of complex carbohydrates is thought to be especially important in this population.[192–194] However, emphasis on carbohydrate alone may have led to inadequate emphasis on other nutrients that could influence CVD risk among individuals with T1D.[195]

Some literature suggests that nutrient intake among individuals with T1D is different than intake patterns in individuals without diabetes, and these differences may vary across countries.[56,196,197] Specifically, studies in the US and China found that the percentage of calories from carbohydrate was lower among individuals with T1D compared to individuals without diabetes, with an accordingly higher comparative intake of protein, and fat.[56,196] Interestingly, a recent study conducted in Spain found that compared to non-diabetic matched controls, individuals with type 1 diabetes had more favorable alternative Mediterranean diet and Healthy Eating Index scores.[197] These findings indicate that in some populations dietary intake is worse among individuals with T1D while in some populations dietary intake may actually be better among individuals with T1D compared to individuals without diabetes.

Several studies indicate that individuals with T1D have often not met recommended nutrient intake goals.[57,198–201] In particular, adults with T1D tend to consume more fat and saturated

fat than recommended.[198,199,201] Adults with T1D also often consume less carbohydrate[198,199] and fiber than has historically been recommended for people with diabetes.[199,201]

Additional research has explored individual nutrients in relation to CVD risk and risk factors among individuals with T1D. Excessive total fat and saturated fat intake have been found to be associated with higher total cholesterol, higher blood pressure, more adiposity and worse glucose control in T1D.[56,57,202] Total fat and saturated fat intake have also shown to be inversely associated with insulin sensitivity among those with T1D, and to be associated with more coronary artery calcium.[56] Endothelial dysfunction and low grade inflammation were greater among individuals with low soluble fiber and polyunsaturated fat intake in a longitudinal European cohort study of individuals with T1D.[203] Interestingly, another study in this same European cohort indicated that a positive association between saturated or total fat intake and LDL cholesterol disappears when accounting for fiber intake.[202] In addition, past research in the EDC cohort suggests that participants over thirty at baseline (1986-1988) who had low dietary cholesterol consumption had more desirable serum LDL cholesterol.[204]

The effect of diet in relation to CVD risk factors is suggested to extend beyond glycemic control, and nutrients other than carbohydrate are likely of interest.[57] With multiple nutrients found to be associated with CVD risk factors, more comprehensive T1D specific nutrient recommendations may be beneficial in reducing the burden of CVD in this population.

3.4.3 Patterns of Intake and CVD Risk in T1D: Limitations and Gaps in Knowledge

A limited number of studies have explored patterns of dietary intake among individuals with T1D, as detailed in Table 2 (p.37). No known studies have looked at patterns of nutrient intake.

Most T1D research looking at dietary patterns in relation to CVD risk have been conducted among a cohort of children with T1D. Studies from the SEARCH for Diabetes in Youth cohort found that adherence to the DASH diet pattern was associated with a more favorable LDLc/HDLc ratio, $HbA_{1c,}$[205] DBP and odds of hypertension[206] among youth with T1D. Higher Mediterranean Diet scores in the SEARCH cohort have also shown to be associated with lower HbA_{1c}, total cholesterol, and non-HDL cholesterol both cross sectionally and longitudinally.[60] Healthy Eating Index scores were also found to be inversely associated with microalbuminuria in youth and young adults with T1D in SEARCH, although no association was found with DASH and Mediterranean Diet scores.[207] Notably, adherence to both the DASH and Mediterranean diet patterns, as well as the Healthy Eating Index generally show room for improvement in this cohort.[207]

There are two known studies looking at data driven dietary patterns and vascular health in a cohort of adults with T1D. Both are cross sectional analyses in the Finnish Diabetic Nephropathy Study (FinnDiane) cohort, comprised of individuals with T1D in Finland, that used factor analysis to define dietary factors based on foods consumed and looked at these patterns in relation to vascular risk factors.[208,209] One study found that a diet pattern with abundant fruit, vegetables, fish and yogurt intake may benefit glycemic control and a diet pattern with fish and eggs may be beneficial for blood pressure.[208] Healthier diet patterns also were more common among participants with advanced chronic kidney disease (20% of cohort) and retinopathy (34% of cohort) in this study,[208] however these findings may imply potential reverse causation. The other study among a subsample of the FinnDiane cohort found that diet patterns characterized by intake of full fat cheese and eggs and by sweets were negatively associated with measures of arterial stiffness.[209] Again, the cross-sectional nature of this analysis indicates the need to interpret these

findings with caution given the high percentage of participants with other diagnosed health conditions.

Two clinical trials of patterns of intake have been conducted among adults with T1D. The first explored high versus low carbohydrate diets, and found less glycemic variability, less time in hypoglycemia, and less need for insulin, in the low carbohydrate diet but no influence on cardiovascular markers.[210] Another trial with a single arm following a very low carbohydrate diet found a reduction in weight, HbA_{1c}, and triglycerides and an increase in HDLc after 3 months.[211] Among young adults with T1D, data driven patterns of nutrient intake in relation to incident cardiovascular complications have not yet been explored.

Table 2 T1D Diet Pattern Studies with Cardiovascular Outcomes

Publication	**Study Sample**	**Study Design**	**Findings**
Observational Studies			
Liese AD, et al. *Circulation*. 2011;123(13):1410-1417.	SEARCH; Youth with physician diagnosed diabetes, age <20 at diagnosis, DM prevalent in 2001 or incident in 2002-2005; n=1810 T1DM, n=320 T2DM	Self-administered FFQ consisting of 85 food lines, adherence to DASH diet assessed with overall score (range 0-80); cardiometabolic indicators measured during clinic visits	Among T1D: Increased adherence to DASH (by tertile) associated with decreasing LDLc, LDL/HDL ratio, A1c, total cholesterol, apoB and BMI z score
Zhong VW, et al. Eur. J. Clin. Nutr. 2016;70:802–807.	SEARCH; Incident T1D, age <20 at diagnosis between 2002-2005; n=793 at baseline, n=512 at 1 year, n=501 at 5 years	Diet assessed at baseline, 1-year, 5 years using modified KIDMED; multiple linear regression to look at diet score and logA1c, lipids, BP, obesity	Low % with high KIDMED score at all time points. At baseline and longitudinally, 2 pt higher diet score a/w lower A1c, lower total cholesterol, LDLc, non-HDLc; A1c mediated 20% of med diet effect on lipids
Guenther AL, et al. Hypertension. 2009; *53*:6–12.	SEARCH; n=2830 for this	Block Kid's Food Questionnaire at study visits for participants ≥	In the T1D sample, mean DBP and odds of HTN

	analysis (2440 T1DM)	10 years of age, DASH score assigned (range 0-80); height, weight, BP collected at clinic visits, PA assessed with YRBSS	decreased across tertiles of DASH adherence
Costacou T, et al. *Diabetes Care*. 2018;41(8):1615–1622	SEARCH: Youth with incident diabetes 2002-2006, or 2008; visits at 12, 24, 60 months; those with 5 years duration and age 10 and over; n=461 T1D with all measures of interest	FFQ at baseline, 12, mo, 60 mo, 2012-15 visit; adherence to DASH, HEI and Mediterranean diet assessed in relation to microalbuminuria status and hyperfiltration	Adherence to DASH and Med. diet poor, HEI "in need of improvement"; habitual intake of higher quality diet assessed with HEI inversely associated with microalbuminuria, though no longer sig. when adjusting for A1c and SBP; no patterns a/w hyperfiltration
Ahola AJ, et al. *J Diabetes Complications*. 2016;30(6):1144-1150.	FinnDiane; Diabetes onset <35 years of age & insulin initiated within 1 year of diagnosis; n=874 who filled in diet questionnaire within 2 years of visit	Cross sectional, diet questionnaire including FFQ of most popular foods in Finland; intake scored 0-22 based on compliance with dietary recs; FFQ data used for factor analysis	7 factors created; "healthy" correlated with high diet score and a/w better glycemic control, BP (also sweet and egg/fish); "traditional" a/w higher WHR; pattern that more closely adhered to diet recommendations a/w better glycemic control, BP; CKD and retinopathy tended to have healthier diet
Ahola AJ, et al. *Nutr Metab Cardiovasc Dis*. 2018; 28(11):1166-1172.	FinnDiane subgroup, n=612; eGFR $\geq$ 30, completed dietary questionnaire or food record with plausible intake; measures of arterial stiffness at Helsinki University Hospital	Cross sectional; FFQ data used for factor analysis and 3-day food records used for macronutrient substitution analysis; arterial stiffness measured using pulse wave velocity	Factors for "full fat cheese and eggs" and "sweets" diet patterns negatively associated with aortic pulse pressure and aortic mean arterial pressure (sweets also augmentation index); favoring carb over fat or protein a/w greater arterial stiffness, protein instead of alcohol beneficial
Clinical Trials			

Ranjan, A. et al. Diabetes Obes Metab. 2017.Oct; 19 (10):1479-1484.	Danish; clinic based, 10 patients (age 48 +/- 10, 4 women), insulin pump treated	Followed isocaloric high carbohydrate diet for 1 week and isocaloric low carbohydrate diet for 1 week, in random order. Diet plans created by dietitian. Participants wore insulin pumps and blood glucose sensors, and had weekly BP measures and fasting blood draws	Low carbohydrate diet intake associated with less glucose variability, more time in euglycemia, less time in hypoglycemia. No difference in BP, total chol, HDLc, LDLc, VLDLc
Neilson JJV, et al. Diabetol Metab Syndr. 2012; 4: 23.	Sweden, clinic based, single arm; 48 participants (average DM duration 24 +/- 12 years, 31 women)	Participants attended educational course detailing a carbohydrate restricted diet regimen (<75 g/day); followed in clinic up to 4 years	Weight, BMI, HDLc, triacylglycerol, HbA_{1c} improved after 3 months; participants who remained adherent to the diet for 2 years achieved stable lowering of A1c

3.4.4 Utilizing the EDC Cohort to Explore Patterns of Nutrient Intake among Young Adults with T1D

It appears there are differences in nutrient intake among individuals with T1D compared to individuals without diabetes. Research has also suggested that individuals with T1D have room for improvement in regard to diet quality. With patterns of dietary intake showing the potential to influence CVD risk, there is a need to further explore patterns of intake in the T1D population. Utilizing data driven approaches will allow for the identification of nutrient intake patterns as they present in the T1D population, as opposed to trying to fit the intake in this population into predefined patterns of intake. Understanding patterns of nutrients that present together will give some idea of where to best focus prevention efforts. Again, given the extensive data collected, the

EDC cohort provides the unique opportunity to explore nutrient data, alongside additional CVD risk factors, and CAD risk. **Aim 3 will identify patterns of nutrient intake in young adults with T1D and explore their association with other CV risk factors and incident CAD.**

3.5 Comment on Changes in CV Health Recommendations Over Time

CV health metrics measures from the EDC baseline and first follow up visit, which took place in the years 1986-1990, were used in this effort, as detailed in Section 4.3.2 (p.85). The AHA CV Health Metrics were developed in 2010. It is worth considering guidelines and recommended standards of care at the time of EDC baseline and how they have changed over the course of the EDC cohort's follow up until the creation of the AHA CV Health Metrics. The AHA LS7 was created based on guidelines for the general population. General population recommendations have changed relatively little, although more specific guidelines have been developed over time. Changes over time in guidelines specific to the T1D population have varied somewhat compared to those in the general population. Trends and notable changes in general population and T1D specific guidelines over the past 30 years are discussed in this section.

3.5.1 Health Behaviors

With regard to health behaviors, smoking cessation was a recommendation prior to the EDC cohort baseline, and remained consistent throughout follow up.[97] Per BMI, goal weight ranges based on height were promoted in the Dietary Guidelines for Americans[212–215] prior to the development of more specific BMI ranges for overweight and obesity in the year 1998.[105] These

ranges have not changed meaningfully since that time. Among individuals with diabetes, achieving and maintaining reasonable individual body weight goals, as acknowledged by a health care provider, was historically encouraged in ADA nutrition recommendation position statements and remains part of the ADA Standards of Medical Care.[176,216,217]

Prior to the establishment of the physical activity guidelines in 2008,[106] physical activity was promoted through the Dietary Guidelines for Americans.[99,212–215,218] Physical activity was initially mainly encouraged as a means of promoting weight management, with the first quantifiable recommendation of "30 minutes or more of moderate physical activity on most—preferably all—days of the week" starting in 1995[215] and a recognition of the importance of physical activity in disease prevention starting in 2000.[218] The ADA promotes activity among individuals with diabetes including adults with T1D, although T1D specific activity guidelines were not issued until 2016, and also promotes additional consideration for carbohydrate intake and insulin dosage to maintain glycemic balance during activity. [219]

Due to the type of nutrient data readily available for analysis in the EDC cohort, diet components included in Aim 2 of this effort include limiting sodium and saturated fat and promoting fiber intake. These components have been promoted as part of the Dietary Guidelines since they were created in 1980,[99,212–215,218,220] although more specific goal ranges were added over time, with <10% of calories from saturated fat added in 1990,[214] consuming <2,300mg/day of sodium added in 2005[99] and fiber intake of 25 g/day for women and 38 g/day for men added in 2010.[220]

Aim 3 addresses patterns of intake at study baseline and first visit in relation to CAD development over time. Understanding changes over time in recommended dietary intake is important to interpreting this association. The ADA has released a number of nutrition

recommendation policy statements over time specific to individuals with diabetes, providing some nutrient specific recommendations though always with the caveat that it is appropriate to individualize care. An ADA statement from 1979 recommended percent caloric intake as follows: 12-20% protein, 50-60% carbohydrate, <10% saturated fat.[217] These recommendations were updated to allow for slightly more liberal carbohydrate intake of 55-60% and limiting total fat to <30% of total caloric intake, and protein modified to reflect the Recommended Dietary Allowance of 0.8 g/kg body weight in 1986.[216] Specific recommended ranges for carbohydrate intake were removed starting in 1994.[221] All diabetes specific caloric intake ranges were removed from ADA position statements over time with general agreement with the Dietary Guidelines for Americans often acknowledged, and in favor of more individualized approaches to structuring diet.[193,222–225] Monitoring carbohydrate intake and adjusting rapid acting insulin administration to maintain glycemic control has been a consistent recommendation for individuals with T1D.[193,217,221–225]

3.5.2 Health Factors

The health factors have followed a similar course of providing general guidance that has become more specific over time. Recommendations for total cholesterol were first detailed by the National Cholesterol Education Program Adult Treatment Panel in 1988.[226] Their statement recommended that in individuals free of CHD, a total cholesterol level below 200mg/dL was desirable, 200-239 was borderline, and ≥240 was considered high.[226] These categories have not changed meaningfully over time, although recommended treatment for hypercholesterolemia has evolved.[5,226,227] Use of statins has notably increased since they were approved for commercial use in the late 1980s.[228] The American Heart Association incorporated medication treatment into the

categories of the Life's Simple Seven, with being treated to the ideal goal range falling into the "intermediate" status category.[14]

Blood pressure recommendations have shifted toward lower thresholds for hypertension over time. The 1984 and 1988 Joint National Committee on Prevention (JNC) defined normal blood pressure as a DBP <85 mmHg and normal high 85-89 as well as SBP <140 (if DBP <90), with SBP 140-159 considered borderline and >160 hypertension.[226,229] In the fifth JNC report in 1993, the definition of normal SBP shifted lower to <130mm/Hg, high normal 130-139, and anything 140 or higher was considered hypertension.[230] The sixth JNC in 1997 saw a shift lower in the definition of normal blood pressure for both SBP (<120) and DBP (<80) with hypertension cutpoints remaining at 140/90,[231] which remained consistent in the seventh JNC though terminology for the middle ranges moved from "borderline" to "prehypertension".[96] Treatment of hypertension has evolved over time with consideration to various classes and combinations of hypertensive therapies. Like total cholesterol, the Life's Simple Seven incorporates blood pressure medication into metric categories, with treatment to goal falling in the "intermediate" range.[14]

Goal ranges for total cholesterol and blood pressure have been somewhat less definitive for individuals with T1D. A study from the DCCT in 1992 suggested that lipid levels among individuals with well-controlled T1D were generally similar to levels among individuals without diabetes.[232] There do not appear to be T1D specific goal ranges for total cholesterol, with an emphasis instead on reducing LDLc and somewhat controversial indications for HDLc.[179,233] As with the general population, recommended use of lipid medication has increased over time for T1D, although earlier statin initiation may be indicated compared to the general population.[66] Existing EDC studies have considered appropriate goal ranges for blood pressure.[179,180] A goal blood pressure range of <120/80 mmHg (SBP/DBP) was suggested, although the ADA suggests a

goal range of <140/90 mmHg for individuals with diabetes, or 130/80 mmHg with high risk for CVD.[234] Given the importance of hypertension as a risk factor for CVD in the T1D population more aggressive blood pressure goals may be indicated to initiate treatment,[9] as previously discussed in Section 3.3.3 (p.29).

Finally, glycosylated hemoglobin is used in this effort instead of fasting blood glucose to more accurately capture the influence of blood glucose management in the T1D population. The first "Classification and Diagnosis of Diabetes Mellitus and Other Categories of Glucose Intolerance" was published in 1979 and defined blood glucose ranges for classifying "normal", "diabetes" and "impaired glucose tolerance".[235] The landmark DCCT, discussed previously, with findings published in 1993 demonstrating reduced complications with intensive blood glucose management,[159] helped to establish goal ranges for HbA_{1c} to reduce CVD risk. As a result, standards of care for blood glucose management among the T1D population became more stringent in the mid-nineties, with a consistent recommended goal HbA_{1c} of <7.0 since that time.

Overall, changes in guidelines for all CV health metrics over time provide context to our interpretation of the association between CV health metrics and CAD development in the EDC cohort. The context of these changes will be discussed further in the Aim 2 manuscript (Section 4.3.5.5, p.104), and in the overall implications (Section 5.0, p.142).

3.6 Background Summary and Overall Significance

In summary, individuals with prediabetes, metabolic syndrome, and T1D are at increased CVD risk and would benefit from ongoing efforts to identify and reduce risk factors. The AHA has pioneered an initiative to promote prevention by improving CV health metrics. This approach,

which provides straightforward goals promoting "ideal" ranges of achievement of seven key health behaviors and factors, has shown to predict CVD risk in the general population. Application of the AHA CV health metrics approach among individuals with prediabetes, metabolic syndrome and T1D has significant potential to decrease CVD risk.

Demonstrated progress toward meaningful CV health metric goal ranges during successful and accessible behavioral lifestyle intervention programs could meaningfully reduce CVD risk among individuals with prediabetes and/or metabolic syndrome. The DPP-GLB lifestyle intervention, based on the highly successful DPP lifestyle intervention, has been shown to be effective in achieving the program goals of weight loss and improved physical activity, and demonstrates excellent adherence as well as the potential to improve cardiometabolic risk factors.[133,140,141] Improvement in AHA CV health metrics during the course of the DPP-GLB intervention would show that these programs drive change in CVD risk factors toward meaningful goal ranges, and that the metrics tool could help to facilitate referral to and monitoring of progress in these programs. Capturing these changes is especially valuable in a successful, widely implemented, increasingly more accessible, CDC recognized and CMS reimbursable DPP-based lifestyle intervention.

Identifying appropriate targets for CAD risk reduction in T1D early in adulthood could have significant implications for reducing incident CAD later in life. CAD prevalence is high among those with T1D and is a persistent complication and cause of mortality as life expectancy has increased in this population.[66,152] The LS7 approach to prevention could be effective among those with T1D, however the relationship between AHA CV health metrics and CAD outcomes needs to be explored due to the unique pathology of this population. Exploring AHA CV health metrics in early adulthood relative to incident CAD over time can inform the most influential areas

to focus early intervention efforts in the T1D population. Measures of AHA CV health metrics in young adults with T1D with adequate follow up to assess CAD outcomes have not previously been explored. The availability of 25-30 years of follow up data in this project allows for the unique approach to capturing a cohort of individuals with T1D who are experiencing the trend of increased life expectancy and greater likelihood of developing CAD.

One of the most unique areas of influence among individuals with T1D may be diet composition, which will likely be a more appropriate predictor of CVD risk with modifications reflecting patterns of intake seen in the T1D population. Diet is also particularly interesting to consider with regard to CVD risk because diet analysis has shifted toward looking at patterns of intake as a more valuable indicator of diet related risk compared to previous approaches looking at isolated nutrients. Using a data driven approach to find patterns in diet will allow for the identification of nutrient patterns specific to the T1D population, and to determine the association between these patterns and other CV health metrics and incident CAD.

As shown through the implementation of LS7 thus far, identifying a short list of modifiable factors allows for effective public health and clinical messaging, as well as straightforward targets that could drive interventions on individual and systems levels. Extending the application of LS7 to individuals at higher risk due to prediabetes, metabolic syndrome or T1D could have broad implications for CVD prevention.

4.0 Approach and Findings

4.1 Overview

This project utilized three study cohorts. To address Aim 1, where the population of interest is individuals with prediabetes or the metabolic syndrome who participate in a lifestyle intervention, two DPP-GLB translation study cohorts were used. The exposure was participation in a yearlong behavioral lifestyle intervention, and the outcome of interest was change in CV health metrics. To address Aims 2 and 3 where the population of interest is adults with type 1 diabetes, the Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort, comprised of 658 individuals with T1D diagnosed before the age of 17 who have been providing data for 30 years, was used. The main predictor for Aim 2 was CV health metrics, measured using behavioral and clinical data during the first two clinic assessments and the outcome was development of CAD over the course of the 25 year follow up using patient reported status at clinic visits, medical records, and mortality reports. Aim 3 looked at cross-sectional associations between patterns of nutrient intake and other CV health metrics and longitudinal associations between nutrient patterns and CAD development over 30 years among individuals with T1D in the EDC cohort.

4.2 Change in CV Health Metrics Over the Course of the DPP-GLB (Aim 1)

The DPP lifestyle intervention has shown to be effective in reducing risk factors for CVD, including type 2 diabetes, metabolic syndrome, dyslipidemia and hypertension.[16,17,71] The DPP

lifestyle intervention has been translated to be more widely accessible in a variety of settings and is now CDC recognized and CMS reimbursable, further increasing its availability.[44] One of the most effective DPP translation lifestyle interventions is the DPP-GLB, which has demonstrated success in achieving weight loss and physical activity goals and good adherence, as well as improvement in cardiometabolic risk factors.[133,140,141] However, the potential to improve CV health metrics during a DPP-based intervention has yet to be explored. Aim 1 sought to establish the utility of a successful DPP-based lifestyle intervention program to improve CV health metrics among overweight or obese individuals with prediabetes and/or metabolic syndrome, with use of two DPP-GLB cohorts.

4.2.1 Parent Cohorts

GLB-Healthy: The Healthy Lifestyle Project (GLB-Healthy) was conducted from March 2010 through February 2014.[133] This study was primarily intended to test the framework for translation of the DPP lifestyle intervention into the "real world" in a variety of settings among diverse communities. The program was offered through community and worksite locations, with a total of 223 enrolled participants across sites. The program was also offered in a military setting, however these participants are not included in this dissertation effort due to unique considerations for program participation such as the site not wishing to have a delayed intervention arm, and the potential need for participants to travel/deploy. The primary goals of the GLB-Healthy intervention were the same as those in the DPP lifestyle intervention: to achieve a 7% weight loss and to reach at least 150 minutes per week of moderate intensity physical activity.

GLB-Moves: The Physical Activity and Sedentary Behavior Change study (GLB-Moves) was conducted from September 2014 through July 2019. This study built on the findings of GLB-

Healthy and utilized the same DPP lifestyle intervention translation approach. The primary aims of this study were to ascertain change in physical activity using objective measures and to examine the impact of replacing a moderate intensity activity goal with a goal to break up and decrease sedentary time. Participants were randomized to receive either an intervention with the same goals as the DPP lifestyle intervention and GLB-Healthy, (to achieve a 7% weight loss and to reach at least 150 per week of moderate intensity physical activity), or to an intervention where the activity goal was to reduce and replace time spent sitting. All intervention sites used in the GLB-Moves study were community based. A total of 308 participants were enrolled in this study.

For the purpose of this project, only participants who received the traditional DPP-GLB curriculum with the primary movement goal of 150 minutes or more of moderate intensity aerobic physical activity were included from both studies. Those who received intervention in the military arm of GLB Healthy or intervention goals to reduce sedentary time were not included. Both studies had almost identical eligibility and study design, as described in section 4.2.3 (p.51).

Analyses indicate that the community participants in the GLB Healthy and GLB Moves cohorts showed similar success in achieving program goals and improving additional clinical characteristics. Attendance was excellent across both cohorts with median attendance of 14 sessions in GLB-Healthy[133] and 16 session in GLB-Moves during the first 16 sessions of the intervention. The average percentage weight loss was about 5% in both cohorts, and average moderate intensity leisure physical activity increased significantly across cohorts after both six and twelve months of intervention compared to intervention baseline. Both cohorts also demonstrated improvement in additional cardiometabolic outcomes. Due to the comparable success in achieving program goals and excellent program attendance demonstrated in both the GLB-Moves and GLB-Healthy cohorts, the combined sample of participants as described above

was the population of interest in this effort. A comparison of demographic characteristics across studies showed that a higher percentage of GLB-Moves participants were female, and this cohort was more diverse compared to the GLB-Healthy participants. There was no statistically significant difference in age despite the difference in eligibility criteria, detailed in the next section and as shown in Table 20 (p.148).

4.2.2 Study Population

Specific eligibility criteria for both studies included age ≥ 18 years of age (GLB-Healthy) and ≥ 40 years of age (GLB-Moves) , BMI >24 kg/m^2 (>22 kg/m^2 for Asian persons consistent with the DPP BMI eligibility criteria[17]), evidence of prediabetes defined as fasting glucose ≥100 to <126 and/or HbA_{1c} 5.7-6.4%, and/or metabolic syndrome defined by National Cholesterol Education Program Adult Treatment Panel III criteria or hyperlipidemia and 1 component of metabolic syndrome.[236] Participants were ineligible if they had ever had diagnosed diabetes, planned to move away in the 18 months following screening, were taking metformin, or had recently (within the past 3 months) had an initiation or change in blood pressure or lipid medication. Women who were pregnant or breast feeding at the time of screening were not eligible. Recruitment and screening efforts were conducted for the community sites in GLB-Healthy from September 2011 to November 2011 and for GLB-Moves from October 2014 through March 2017.

In both study efforts, investigators partnered with community organizations in Allegheny County, Pennsylvania (i.e., the greater Pittsburgh area) to recruit at community centers and, in GLB-Healthy, with the Bayer Corporation, which has a worksite in the Pittsburgh metropolitan area, to recruit employees.[133,141] Recruitment efforts included direct mailings to households located near the community centers and of Bayer employees, email blasts to worksite employees and

community center members, posters at community centers, and information sessions at the worksite and community centers, as well as health fairs in the community.[133,141] The lifestyle intervention and clinic assessment visits were conducted at the community centers and worksite.

A two-step screening process was used. Potential participants were first screened over the phone for basic eligibility criteria. Those found eligible through the phone screening were invited to in-person screening. Informed consent was obtained before conducting each stage of screening. Those found eligible through the in-person screening were invited to enroll in the study and to attend an information session providing an overview of the study that covered background about the DPP, and a general outline of the structure of the intervention in order to give people an idea of what to expect. These information sessions are believed to be beneficial in improving intervention attendance and retention.

As detailed in Figure 2 (p.53), over one thousand participants were screened for participation in worksite and community-site based intervention across both studies. A total of 223 participants were enrolled in the worksite and community sites of the GLB-Healthy study, and a total of 308 participants were enrolled in the GLB-Moves study. For the purpose of this project, only participants who have complete data on CV health metrics at baseline and follow up assessment visits were included in the analysis.

4.2.3 Study Design

Both studies had a nearly identical randomized 6-month delayed intervention control design. In GLB-Healthy, participants were randomized to begin the program immediately or after a 6-month delay in a 2:1 ratio stratified by site location.[133] In GLB-Moves, participants were randomized to begin the program immediately as part of either a group receiving the traditional

moderate or greater intensity activity goal or as part of a sedentary intervention arm, or to begin the program after a 6-month delay, again stratified by site location. Basic sampling was used to balance randomization by site using a SAS program.[133] Participants who were randomized to the delayed intervention arm received the exact same yearlong intervention program but starting 6 months later. One of the intervention arms in GLB-Moves involved an alternate intervention and is not included as part of this analysis. Of note, half of the participants randomized to the delayed arm in GLB-Moves were later assigned to this alternative intervention and are not included in this analysis. Screening, enrollment and randomization are detailed in Figure 2 (p.53). In both studies participants were given randomization assignments in sealed envelopes at the end of the baseline assessment visit.[133] Participants and lifestyle coaches could not be blinded to randomization assignment due to the nature of the intervention, however lifestyle coaches were not involved in assessing study outcomes.

The most important question for this project was change in CV health metrics during the course of a DPP-GLB intervention. Therefore, change in CV health status from intervention baseline (which is the six-month assessment visit for delayed participants) through six and twelve months of intervention was the primary outcome of interest.

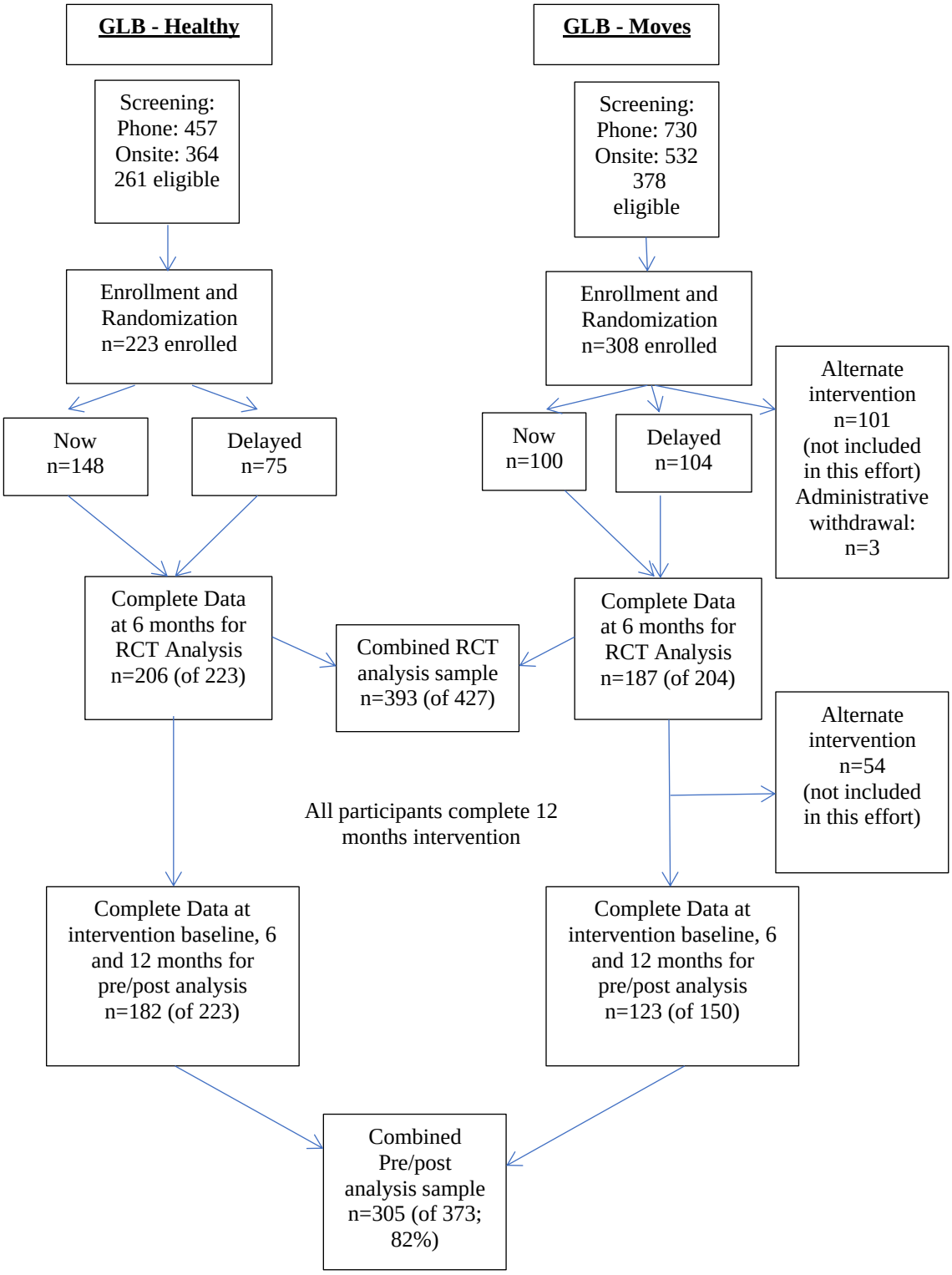

Figure 2 Community Based GLB Intervention Recruitment, Enrollment and Study Participation Flow Chart

4.2.4 Intervention

The DPP-GLB intervention used in both studies was developed by members of the original DPP Lifestyle Resource Core adapted from the lifestyle arm of the DPP to be a group based program.[129] The GLB program consists of 22 total sessions offered over 12 months. The first 12 sessions occur weekly, followed by four biweekly sessions and six monthly sessions. All lifestyle coaches were certified in the DPP-GLB curriculum through a standard training provided by the Diabetes Prevention Support Center, an organization created and run by individuals involved in DPP lifestyle translation efforts.[129]

The primary goals of the DPP-GLB lifestyle intervention were to achieve and maintain a 7% weight loss and to safely progress to 150 minutes per week of moderate intensity physical activity, similar to a brisk walk. The program curriculum consisted of group discussion and education surrounding topics promoting activity, balanced diet and caloric restriction to promote weight loss, and behavioral strategies to support program goals. Program sessions were supported by the use of handouts, a fat gram and calorie counter, self-monitoring booklets, a pedometer, exercise bands, and weigh-ins at each in-person meeting. Delayed participants received the same program starting 6 months after randomization. During the delay, those participants randomized to this arm received occasional health-related handouts to promote retention.

4.2.5 Outcomes Measures

The outcomes of interest in this dissertation effort were the AHA cardiovascular health metrics. While the AHA defines criteria for seven metrics[14], direct measures of diet were not available in these studies and smoking prevalence was low (4.9%). Remaining metrics (BMI,

physical activity, blood pressure, fasting plasma glucose, total cholesterol) were measured and quantified in accordance with AHA criteria (Table 3). All metric calculations are based on measures taken at clinic assessment visits which took place at baseline, 6 months, and 12 months. Participants randomized to the delayed arm had an additional clinic visit at 18 months to capture change after the year-long intervention. The protocols for outcome measures were the same for both study cohorts. All CV health metric measures and category criteria are described in detail in the manuscript *"The Impact of a Yearlong Diabetes Prevention Program-based Lifestyle Intervention on Cardiovascular Health Metrics"* (Section 4.2.9.3, p.64).

Table 3 DPP-GLB Measures of Interest and CV Health Categories

Measures	Method of Measurement	Ideal	Intermediate	Poor
BMI	Measured height and weight	< 25 kg/m^2 (< 23 kg/m^2 Asian)	25- < 30 kg/m^2 (23- < 27.5 kg/m^2 Asian)	≥ 30 kg/m^2 (≥ 27.5 kg/m^2 Asian)
Physical activity	Modifiable Activity Questionnaire	≥ 7.5 MET hours/week	> 0 to < 7.5 MET hours/week	0 MET hours/week
Blood pressure	Sphygmomanometer using an average of 2 measures after a 5 minute rest period	< 120 systolic, < 80 mmHg diastolic	120-139 systolic or 80-89 mmHg or treated to ideal range	≥ 140 systolic or ≥ 90 diastolic
Fasting Plasma Glucose	Fasting blood draw	< 100 mg/dL	100-125 mg/dL or treated to ideal range	≥126 mg/dL
Total cholesterol	Fasting blood draw	< 200 mg/dL	200-239 mg/dL or treated to ideal range	≥ 240 mg/dL

4.2.6 Analytic Methods

Hypothesis: During the course of a yearlong lifestyle intervention, improvement in individual CV health metrics and composite metrics scores will be demonstrated at 6 months and maintained at 12 months.

The primary outcome of interest was change from baseline to after receiving the intervention (6 and 12 months pre/post analysis). Pre/post assessment was of primary interest in order to understand the value of the CV health metrics in capturing change during the DPP-GLB as currently offered in the real-world setting, and as reimbursable by CMS. For this analysis, baseline was the clinic visit immediately preceding the start of the lifestyle program sessions (ie. month 6 for delayed participants). Additional analysis considered comparison between the intervention arm and the delayed arm (RCT analysis), which was only possible at 6 months as delayed group participants received the intervention after that assessment. RCT findings are of interest as a secondary analysis in informing how the DPP-GLB intervention influences CV health in participants randomized to receive the intervention compared to not receiving an intervention at that time period.

Significant continuous change in each metric at 6 and 12 months was tested using Wilcoxon signed-rank tests due to the non-normal distribution of change variables. Since study participants were heterogeneous in their cardiometabolic risk profile, for any one health metric some participants were in need of improvement while others may have already been ideal for that metric. For that reason, additional separate analyses were done for continuous change for each metric, limited to only those participants at "high risk" for that metric (defined as having baseline values falling within the intermediate or poor range for each metric).

Differences in the proportion of metrics within each category (ideal, intermediate, and poor) were determined using a marginal homogeneity test of symmetry to assess whether there was a significant shift in off-diagonal terms from baseline to 6 months and from baseline to 12 months. A "total metric score" was calculated as the sum of the categories of each metric (poor=0, intermediate=1, ideal=2; possible "total metric score" range 0-10). "Ideal metric score" was

calculated as a count of metrics falling within the ideal range (possible "ideal metric score" range 0-5). Within group change for all participants from baseline to 6 and baseline to 12 months was determined using the Wilcoxon signed-rank test, again due to the non-normal distribution of pairwise differences between timepoints.

Two sensitivity analyses were conducted. In the first, the GLB-Healthy and GLB-Moves data were analyzed separately. In the second, participants who received community-based intervention and those who received intervention in the worksite were analyzed separately. Additionally, we assessed the impact of restricting our analyses to those with complete data by repeating our analyses using last observation carried forward (LOCF). The LOCF is an imputation method that can be used when repeated measures have been taken per subject by time point. This is a method in which the last observed nonmissing value is used to fill in missing values.

The two-sample T-test or Wilcoxon rank sum test was used to determine between group differences in change variables in the RCT analysis, depending on the distribution of the data.

StatXact version 11.1 (Cytel Inc.) will be used for the marginal homogeneity test. All other analyses will be conducted in SAS version 9.4 (SAS Institute, Inc.).

4.2.7 Findings

Full results of the proposed analysis for Aim 1 are included in the manuscript, "*The Impact of a Yearlong Diabetes Prevention Program-based Lifestyle Intervention on Cardiovascular Health Metrics*" (Section 4.2.9.4, p.69). Briefly, the results show that CV health metrics generally improved over the course of the DPP-GLB intervention. A total of 305 participants (82%) had complete metrics data at intervention baseline and follow up assessments. When measured continuously (Table 5, p.76), each CV health metric showed significant improvement ($p<0.01$) at

6 and 12 months with the exception of total cholesterol at 12 months. When analyses were restricted to only participants with values outside of the ideal range for each metric, all metrics including total cholesterol showed significant improvement. The proportion of participants across CV health metric categories significantly shifted in a more favorable direction (i.e. more participants within the ideal range and fewer within the poor range) for BMI, physical activity and blood pressure at 6 and 12 months (Figure 3, p. 77). The total metric score and ideal metric score improved significantly after both 6 months [median (IQR) change: +1.0 (0 - +1.0), p<0.01; median (IQR) change: 0.0 (0 - +1.0), p<0.01, respectively] and 12 months of intervention [median (IQR) change: 0.0 (0 - +1.0), p<0.01; median (IQR) change: 0.0 (0 - +1.0), p<0.01, respectively] (Table 6, p. 78).

4.2.8 Implications

A more detailed discussion of the implications of this work is included in the Aim 1 manuscript, Section 4.2.9.5 (p.71). In short, the DPP-GLB behavioral lifestyle intervention was successful in improving CV health metrics based on the AHA LS7 concept. Among the five metrics that were evaluated during the course of the DPP-GLB intervention, improvement was shown in composite ideal and total metric scores. All metrics improved when measured continuously with the exception of total cholesterol at 12 months, and significant shifts toward the ideal range were seen in BMI, physical activity and blood pressure. These findings indicate that the AHA cardiovascular health metrics approach has great potential to capture the reduction in CVD risk resulting from participation in the DPP-GLB. The AHA cardiovascular health metrics captured improvement toward meaningful cut points, demonstrating the potential utility of this approach in screening for program referral and monitoring program success. In addition, effective

approaches to improving the AHA CV health metrics are appealing because national estimates show that CV health metrics show room for improvement, and that more favorable CV health metrics are associated with reduced risk of CVD and other chronic disease outcomes. The DPP-GLB is especially appealing given the fact that it is accessible due to CDC recognition and CMS reimbursement.

Additional RCT results and implications can be found in the Appendix, p. 147.

4.2.9 Aim 1 Manuscript: The Impact of a Yearlong Diabetes Prevention Program-based Lifestyle Intervention on Cardiovascular Health Metrics

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4.2.9.1 Introductory Section

The American Heart Association (AHA) created "Life's Simple Seven" metrics to standardize estimations of improvements in US cardiovascular health. Given widespread use of Diabetes Prevention Program (DPP) translated lifestyle interventions such as the Group Lifestyle Balance (DPP-GLB), evaluation of change in health metrics in these programs is critical. This effort examined change in five AHA health metrics (BMI, physical activity, blood pressure, total cholesterol, fasting plasma glucose) within a yearlong community-based DPP-GLB intervention among overweight individuals with prediabetes and/or metabolic syndrome. Pre/post intervention changes in the health metrics were examined at 6 and 12 months. Among 305 participants with complete data (81.8%), significant improvements were demonstrated in all five risk factors measured continuously at both time points mirrored by beneficial shifts ($p<0.05$) in the proportion of participants across categories for BMI, activity, and blood pressure. Likewise, AHA-defined "ideal" (sum of metrics in the ideal range) and "total" metric scores (metric sum where ideal=2, intermediate=1 and poor=0 for each metric) improved significantly at 6 and 12 months. In conclusion, the AHA health metrics appear to have clinical utility in estimating an individual's cardiovascular health status and may also be useful for capturing improvement in cardiometabolic and behavioral risk factors as a result of participation in community-based translations of the DPP lifestyle intervention.

4.2.9.2 Introduction

The American Heart Association (AHA) set a goal of improving the cardiovascular health of all Americans by 20% by the year 2020 in an effort to reduce the burden of cardiovascular disease (CVD).[14] In order to measure progress toward this goal, the AHA created Life's Simple Seven (LS7) metrics to estimate cardiovascular health status. These 7 metrics include BMI, physical activity, diet, smoking, blood pressure, total cholesterol, and fasting plasma glucose.[14] The AHA established criteria classifying each metric as "ideal", "intermediate" or "poor" based on evidence in line with clinical practice and public health guidelines for promoting CVD free survival.[14] By including both behavioral and cardiometabolic factors, the LS7 concept captures a comprehensive picture of modifiable CVD risk while providing straightforward standardized definitions of optimal status. The LS7 could be a useful approach to identifying individuals who may be appropriate candidates for intervention programs promoting cardiovascular health, and monitoring progress resulting from program participation.

A growing body of evidence indicates that more favorable LS7 metric profiles are associated with decreased CVD,[110,111] mortality,[11,109,237] and other non-CVD outcomes, including type 2 diabetes.[238–240] Studies to date have demonstrated that lifestyle intervention programs specifically designed to improve cardiovascular health metrics by the AHA definition are feasible,[47,49] and show potential for improvement in individual metrics.[46,48] Unfortunately, these studies are limited by small sample size or interventions designed for use in specific settings.

Currently, there are a multitude of lifestyle intervention efforts underway that are based on the US Diabetes Prevention Program (DPP) lifestyle intervention.[44] The landmark DPP study demonstrated that those who participated in the lifestyle intervention had a 58% reduction in

diabetes risk.[17] DPP lifestyle intervention participants were also less likely to develop metabolic syndrome, more likely to see metabolic syndrome resolve[16] and were less likely to develop hypertension and dyslipidemia.[71] Building on the findings of the DPP, the lifestyle intervention program was translated to be more widely available in the public health arena.[44,127] The success of this program has led to the US Centers for Disease Control and Prevention (CDC) overseeing wide-scale delivery of the DPP-based intervention, with CDC approved DPP-based lifestyle intervention now reimbursable through the Centers for Medicare & Medicaid services (CMS).[45] CDC recognition and CMS reimbursement have had significant implications for increasing access to DPP-based interventions, with over 324,000 individuals having participated in DPP-based programs to date.[44]

The Group Lifestyle Balance (DPP-GLB) is an intervention program translated from the DPP lifestyle intervention that is CDC-recognized and has been shown to be effective in improving CVD and diabetes risk factors in rigorous clinical trials offered across a variety of diverse community settings.[132,133,140–142] Given the increasing reach of DPP-based programs and the proven success of the DPP-GLB lifestyle intervention in improving behavioral and cardiometabolic risk factors, the DPP-GLB provided a unique opportunity to evaluate for the first time in a DPP translation effort the AHA-defined health metrics based on LS7 and their ability to capture improvements in risk factors in a population at high cardiometabolic risk. If effective, this approach would be a standardized and simple way to report change in CVD risk factors in widely utilized DPP-based lifestyle intervention programs.

Available data from two large scale DPP-GLB translation efforts completed over the past ten years allowed an opportunity to assess changes in cardiovascular health metrics based on AHA criteria resulting from participation in this yearlong CDC-recognized intervention program. It was

hypothesized that participants of the DPP-GLB would demonstrate an improvement in cardiovascular health metrics after 6 months and improvement would be maintained after 12 months of intervention.

4.2.9.3 Methods

This project is a secondary data analysis of two NIH funded intervention trials evaluating the DPP-GLB in the community setting with almost identical eligibility criteria and study design. The Healthy Lifestyle Project (GLB-Healthy) was conducted from March 2010 through February 2014.[133] The Physical Activity and Sedentary Behavior Change study (GLB-Moves) was conducted from September 2014 through July 2019. Both studies received University of Pittsburgh Institutional Review Board approval and all subjects provided written informed consent.

Study Population

Eligibility criteria for these studies included age ≥18 years of age (GLB-Healthy) or ≥40 years of age (GLB-Moves), BMI >24 kg/m^2 (>22 kg/m^2 for Asian persons, consistent with the DPP BMI eligibility criteria[17]), evidence of prediabetes defined as fasting glucose ≥100 to <126 and/or hemoglobin A1c 5.7-6.4%, and/or metabolic syndrome defined by National Cholesterol Education Program Adult Treatment Panel III criteria or hyperlipidemia and 1 component of metabolic syndrome.[236] Participants were ineligible if they had ever had diagnosed diabetes, planned to move away in the 18 months following screening, were taking metformin, had an initiation or change in blood pressure or lipid medication within the past 3 months, or were pregnant or breastfeeding. Recruitment and screening efforts were conducted for GLB-Healthy

from September 2010 to November 2011, and for GLB-Moves from October 2014 through March 2017.

In both study efforts, investigators partnered with community organizations in Allegheny County, Pennsylvania (i.e., the greater Pittsburgh area) to recruit in the geographic area around community centers. In GLB-Healthy, investigators also partnered with the Bayer Corporation, which had a worksite in the Pittsburgh metropolitan area, to recruit employees.[133,141] The lifestyle intervention and clinic assessment visits were conducted at the community centers and worksite.

Study Design

Both studies had a randomized controlled design with participants assigned to begin the intervention program immediately or after a 6-month delay with randomization stratified by site location. Participants who were randomized to the delayed intervention arm received an identical yearlong intervention program but started 6 months later (Figure 2, p.53). Baseline was considered to be the clinic visit immediately preceding the start of the lifestyle program sessions (i.e., month 6 for delayed participants).

The focus of this analysis is change during the course of a yearlong DPP-GLB intervention that is currently widely used in community settings. For this reason, pre/post intervention assessments were examined to capture the time period of interest for these national programs. Randomized controlled trial results for DPP-GLB have been published previously.[133,141]

One of the intervention arms in the GLB-Moves study involved an alternative intervention with a focus on reducing time spent sitting. Participants from that study arm were excluded from this analysis due to the experimental nature of that intervention, and because it is a significant departure from the current CDC-recognized GLB curriculum. Although participants and lifestyle

coaches could not be blinded to randomization assignment due to the nature of the intervention, lifestyle coaches were not involved in any outcome assessments.

Program Structure

The DPP-GLB lifestyle intervention used in both studies was adapted from the lifestyle intervention of the DPP to be a 22 session, year-long, group-based program, developed by individuals who helped direct both the DPP lifestyle intervention and the resulting translation efforts.[129] The first 12 sessions occurred weekly, followed by four biweekly sessions and six monthly maintenance sessions. All lifestyle coaches received standard training in the DPP-GLB curriculum.

The primary goals of the DPP-GLB lifestyle intervention were to achieve and maintain a 7% weight loss and to safely progress to 150 minutes per week of moderate physical activity, with an intensity similar to a brisk walk. The program curriculum consisted of group discussion and education surrounding topics encouraging activity, balanced diet and caloric restriction to promote weight loss, and behavioral strategies to support program goals. Delayed participants received the same program starting 6 months after randomization. During the delay, those participants randomized to this arm received occasional health-related handouts to promote retention. Attendance included both in-person small group sessions and make-up sessions, which were completed as needed.

Outcomes

Five of the seven AHA cardiovascular health metrics were available to analyze in this study. Direct measures of diet were not collected in these two studies, and smoking prevalence

was rare (4.9%) at baseline and therefore not collected beyond that point. All metric calculations are based on measures taken at clinic assessment visits that took place at intervention baseline, and after 6 months, and 12 months of intervention. The protocols for outcome measures were the same in both study cohorts.

Body mass index (BMI) was determined by measured height and weight. A BMI below 25 was considered ideal, 25 to <30 intermediate and ≥30 poor, in accordance with AHA criteria.[14] Asian participants with a BMI <23 were classified as ideal, 23-27.5 intermediate and ≥27.5 poor, per the greater risk associated with lower BMI cut points in this demographic.[241,242]

Leisure physical activity was assessed using a past month version of the Modifiable Activity Questionnaire, which has been shown to be reliable and valid in adults,[243,244] and quantified as Metabolic Equivalent of Task (MET) hours per week. Activity of ≥7.5 MET hours/week was considered ideal, >0 to <7.5 MET hours/week intermediate, and no reported activity poor. The ideal cut point is roughly equivalent to the AHA criteria promoting 150 minutes or more of moderate intensity or 75 minutes or more of vigorous intensity activity each week. [14,245]

Blood pressure was measured using the average of two readings taken after a five-minute rest with an automatic digital sphygmomanometer. If measures differed by greater than 5 mmHg, a third measure was taken. Ideal blood pressure was defined as <120/80 mmHg without treatment, intermediate as 120-139 systolic or 80-89 mmHg diastolic or treated to ideal range, and poor as ≥140 systolic or ≥90 mmHg diastolic, as outlined by AHA criteria.[14]

Total cholesterol and fasting plasma glucose were determined using a fasting blood draw. Ideal total cholesterol was defined as <200 mg/dL (<5.18 mmol/L), intermediate as 200-239 mg/dL (5.18-6.21 mmol/L) or treated to ideal range and poor as ≥240 mg/dL (≥6.22 mmol/L). Fasting plasma glucose was considered ideal with a level of <100 mg/dL (<5.6 mmol/L), intermediate with

100-125mg/dL (5.6-6.9 mmol/L) or treated to ideal range, and poor was ≥126 mg/dL (≥6.9 mmol/L). Blood value cut points were consistent with AHA criteria.[14] Treatment for blood pressure, total cholesterol and fasting plasma glucose was ascertained using a medication questionnaire.

Analysis

Differences in demographic characteristics between those who were included in the analysis and those who were excluded were tested using chi-square, Fisher's exact, and t-tests.

Significant continuous change in each metric at 6 and 12 months was tested using Wilcoxon signed-rank tests due to the non-normal distribution of change variables. Since study participants were heterogeneous in their cardiometabolic risk profile, for any one health metric some participants were in need of improvement while others may have already been ideal for that metric. For that reason, additional separate analyses were done for continuous change for each metric, limited to only those participants at "high risk" for that metric (defined as having baseline values falling within the intermediate or poor range).

Differences in the proportion of metrics within each category (ideal, intermediate, and poor) were determined using a marginal homogeneity test of symmetry to assess whether there was a significant shift in off-diagonal terms from baseline to 6 months and from baseline to 12 months. A "total metric score" was calculated as the sum of the categories of each metric (poor=0, intermediate=1, ideal=2; possible "total metric score" range 0-10). "Ideal metric score" was calculated as a count of metrics falling within the ideal range (possible "ideal metric score" range 0-5). Within group change for all participants from baseline to 6 months and baseline to 12 months

was determined using the Wilcoxon signed-rank test, again due to the non-normal distribution of pairwise differences between timepoints. StatXact version 11.1 (Cytel Inc.) was used for the marginal homogeneity test. All other analyses were conducted in SAS version 9.4 (SAS Institute, Inc.).

Two sensitivity analyses were conducted to examine outcomes for stratified groups 1) study cohort: GLB-Healthy and GLB-Moves and 2) delivery site type: community center and worksite. Additionally, we assessed the impact of restricting our analyses to those with complete data by repeating our analyses using last observation carried forward (LOCF), an imputation method that can be used when repeated measures have been taken per subject by time point in which the last observed nonmissing value is used to fill in missing values.

4.2.9.4 Results

Of the 373 participants eligible for this analysis in the combined cohorts, 305 participants (81.8%) had data available for 6 and 12-month pre/post intervention comparison (182 of 223 in GLB-Healthy, 123 of 150 in GLB-Moves). Screening and enrollment in both studies is shown in Figure 2 (p.53) but was described previously for the GLB-Healthy study only.[133,141] Median participant attendance was 21 out of 22 sessions.

Demographic characteristics for the combined cohorts used in pre/post analysis are shown in Table 4 (p.75). The majority of participants were female (74.3%), and the mean age was 60.4 years. Nearly half of the participants indicated they were working full time (48.9%) and more than half had completed at least some college education. Participants identifying as Black were slightly more likely to have incomplete data than individuals self-identifying as White, Asian, or another race. When comparing the study cohorts (data not shown), the GLB-Moves study had significantly

more females (82.1% vs 60.1%), was more diverse (87.0% White vs 92.9% White), had a higher percentage with some college education and a lower percentage with graduate degrees, and had more retired participants compared to GLB-Healthy.

Confirmation of Lifestyle Intervention Success

When measured continuously, all of the outcome variables that form the basis of the cardiovascular health metrics for this study (Table 5, p.76) demonstrated significant improvement at 6 and maintenance at 12 months ($p<0.01$), with the exception of total cholesterol at 12 months. When examining total cholesterol continuously among those at "high risk" (i.e., with baseline values falling within the intermediate or poor range for each metric), there was a significant improvement ($p<0.01$) at both 6 and 12 months [n=127, median (IQR): -11.5 mg/dL (-28.5, 5.5) and -4.0 (-24.0, 10.0), respectively]. All other metrics also demonstrated a greater magnitude of improvement when measured continuously for those at "high risk" (data not shown). Participants with medication changes related to a metric over the course of the intervention study were excluded from the continuous change analysis of that metric, although all significant changes remained consistent when these participants were included.

Examining the Impact of the Intervention on the AHA Cardiovascular Health Metrics

The percentages of participants within each metric category (poor, intermediate, ideal) showed improvement over the course of the intervention, as shown in Figure 3 (p.77). Shifts in the ordered proportion of participants across categories for BMI, physical activity and blood pressure were statistically significant from baseline to 6 months and from baseline to 12 months ($p<0.05$), with a higher percentage of participants moving into the ideal range and a lower percentage of

participants in the poor range after receiving the intervention. A favorable, but not statistically significant, shift was seen with the fasting plasma glucose metric. The proportion of participants within each category of total cholesterol did not change significantly.

"Total" and "ideal" metric scores at each time point, and changes in metric scores are shown in Table 6 (p.78). The "total metric score" improved significantly at 6 [median (IQR) change: +1.0 (0, +1.0), $p<0.01$] and 12 months [median (IQR) change: 0.0 (0, +1.0), $p<0.01$]. The "ideal metric score" also improved significantly at 6 [median (IQR) change: 0.0 (0, +1.0), $p<0.01$] and 12 months [median (IQR) change: 0.0 (0, +1.0), $p<0.01$].

These findings were largely consistent when looking at the two study cohorts separately, and when examining all community sites and the worksite setting separately (not shown). While results were generally similar to those observed overall, the smaller sample sizes in the subgroup analysis led to reduced power, thus continuous change in fasting plasma glucose did not reach statistical significance in the worksite only sample. Also, the shift in the percentage of participants within each blood pressure category did not reach statistical significance at either time point at the worksite and community sites when analyzed separately. All findings for LOCF analysis were consistent with the complete case analysis.

4.2.9.5 Discussion

American Heart Association–defined health metrics captured improvement in behavioral and cardiometabolic risk factors that occurred as the result of the effective DPP-GLB behavioral lifestyle intervention. This improvement was of substantial public health significance as it indicated that several metrics reached clinically meaningful cut points associated with lower CVD

risk. In addition, it demonstrated the potential utility of the AHA-defined approach for monitoring progress during and after lifestyle intervention participation.

In this effort, continuous measures of the CVD risk factors of interest improved significantly at both 6 and 12 months, although total cholesterol change was only significant for "high risk" participants at the 12-month assessment. Continuous change in CVD risk factors was mirrored by beneficial shifts toward ideal metric status for BMI, blood pressure and physical activity and significant improvement in "total" and "ideal" composite scores.

Positive changes in BMI, physical activity, and blood pressure appeared to contribute most to the shifts toward more favorable "total" and "ideal" composite scores of cardiovascular health metrics. Although the metrics of total cholesterol and glucose levels appeared to be less influenced by the intervention in this cohort, it should be noted that the lack of a visible significant change in the total cholesterol metric may be due to the high percentage (44%) of participants reporting use of medication for lipid management, which could mask the effects of the program on lipid levels. Additionally, we had a low prevalence of individuals with poor and intermediate glucose status which may account for the relatively lower impact of the intervention on changes in glucose as measured by the metric scores. However, in general, the beneficial impact of this DPP-based lifestyle intervention on cardiovascular risk factors in need of change specific to this cohort of individuals with prediabetes and/or metabolic syndrome as quantified by the AHA cardiovascular health metrics is encouraging.

Assessment and promotion of health behaviors and approaches to identifying appropriate lifestyle intervention candidates remain limited in clinical care,[50,51,53,246] making screening tools desirable. The AHA metrics provides both a standard assessment tool and goal-based guidance in addressing health behaviors and associated cardiometabolic risk, serving as a natural complement

to a lifestyle intervention program. In addition, prevalence estimates of cardiovascular health metrics in the general population show room for improvement,[58,247] with projections suggesting a relative increase in cardiovascular health metric scores of about 6% in 2020, far lower than the 20% goal.[247] Given the improvement in AHA metrics demonstrated in the current analysis, referral to and coverage for DPP-GLB programs based on initial cardiovascular health metric score status could meaningfully improve risk profiles in those in need of change.

Without direct diet measures and with a low prevalence of smokers, this effort was limited in the ability to capture change in the entire AHA cardiovascular health metrics framework which includes seven components. Changes in diet quality were not primary behavioral goals of these DPP-GLB study efforts, which focused primarily on weight loss and physical activity. In general, diet quality is not typically measured in these community-based programs. However, balanced heart healthy eating was discussed and encouraged during the course of the intervention. In a post-intervention survey conducted in the GLB-Moves study, 94% of participants said they made healthier food choices as a result of the program. In addition, while significant effort was made to sample communities to maximize diversity, participation by non-white individuals was constrained by the fact that the greater Pittsburgh area has limited racial/ethnic diversity[248]. Although the more recent community study (GLB-Moves) was able to relatively improve its racial/ethnic diversity, future studies should focus on other geographic regions with more diverse populations.

A notable strength of this study is the consistent findings across two different study cohorts, spanning a period of eight years, and across worksite and community settings. The consistency of the results across studies and sites justified the combination of these cohorts, in turn providing a more robust sample to examine effectiveness of the DPP-GLB program in improving

cardiovascular health factors. In addition, the DPP-GLB programs demonstrated excellent adherence, with median attendance of 21 out of 22 sessions. Finally, post-intervention surveys reflected positive perceptions of the program among participants, with 95% of community participants and 99% of worksite participants surveyed in GLB-Healthy reporting they would recommend the DPP-GLB program to others.[133,141] Similarly, 94% of GLB-Moves participants surveyed reported that the program helped them achieve a healthier lifestyle.

Conclusion

Participation in the highly successful, CDC-recognized and CMS funded, DPP-GLB resulted in improvement in several of the AHA cardiovascular health metrics, a composite of behavioral and cardiometabolic CVD risk factors. Each of the included AHA metrics improved significantly when measured continuously, confirming previous findings regarding participation in the DPP-GLB and benefits to the cardiovascular risk profile. Improvement in "ideal" and "total" composite metric scores, as well as shifts toward more favorable individual cardiovascular health metric categories, mirrored this continuous change, signifying risk factor progression towards clinically desirable values. Given these metric improvements, the AHA metrics approach could have great utility in streamlining referral to and monitoring of success in behavioral lifestyle interventions, all of which would have important implications for CVD prevention.

Table 4 Demographic Characteristics of Combined GLB Cohort Pre/Post Analysis Sample [(n (%) or mean (SD), Samples with Complete Metric Data vs. Missing Metric Data

	Complete Data (n=305)	Missing Metric Data (n=68)	Between Group p-value
Female	165 (74.3)	49 (72.1)	0.68
Age	60.4 (10.3)	57.9 (11.4)	0.08
Race/ethnicity			
White	276 (90.5)	57 (83.8)	0.04
Black	17 (5.6)	10 (14.7)	
Asian	7 (2.3)	0 (0)	
Other	5 (1.6)	1 (1.5)	
Spanish/Hispanic/Latino	5 (1.6)	1 (1)	0.99
Smoking Status			
Current	15 (4.9)	2 (2.9)	0.78
Former	101 (33.1)	23 (33.8)	
Never	189 (62.0)	43 (63.2)	
Employment			
Working full-time	149 (48.9)	44 (64.7)	0.19
Working part-time	33 (10.8)	5 (7.4)	
Unemployed	6 (2.0)	0 (0)	
Homemaker	8 (2.6)	2 (2.9)	
Retired	102 (33.4)	14 (20.6)	
Disabled/unable to work	7 (2.3)	3 (4.4)	
Education			
8th Grade or less	1 (0.3)	0 (0)	0.06
Some high school	1 (0.3)	1 (1.5)	
High school graduate	29 (9.5)	7 (10.3)	
Some college	92 (30.2)	28 (41.2)	
College graduate	98 (32.1)	11 (16.2)	
Graduate degree	84 (27.5)	21 (30.9)	

Allegheny County, PA. USA. Study date: 2010-2019. Eligible population: overweight with prediabetes and/or metabolic syndrome

Table 5 Continuous Change in CVH Metrics of Combined GLB Cohort Pre/Post Analysis Sample as median (25th, 75th percentile), n=305

Metric	Baseline	6 months	12 Months	6-month Change	12-Month Change
BMI (kg/m^2)	33.4 (29.9, 37.9)	31.4 (27.6, 35.9)	31.6 (27.9, 35.9)	-1.8 (-2.6, -0.8)[a]	-1.4 (-3.1, -0.3)[a]
Physical Activity (leisure MET-h/wk)	10.4 (3.0, 20.8)	19.7 (9.1, 33.2)	14.6 (7.2, 26.8)	6.9 (-2.1, 19.5)[a]	2.2 (-2.8, 10.8)[a]
Blood Pressure					
SBP (mmHg)	120.0 (112.0, 129.0)	116.0 (107.0, 124.0)	116.6 (107.0, 126.5)	-4.0 (-12.0, 3.0)[a]	-3.0 (-12.0, 5.0)[a]
DBP (mmHg)	75.5 (69.0, 81.0)	73.0 (66.0, 79.0)	72.5 (66.3, 80.0)	-3.2 (-7.5, 2.0)[a]	-2.7 (-8.3, 4.0)[a]
Total Cholesterol					
(mg/dl)	193.0 (169.0, 217.0)	188.0 (164.0, 213.0)	195.0 (172.0, 219.0)	-4.5 (-21.0, 9.0)[a]	1.0 (-11.0, 15.0)
(mmol/L)	4.99 (4.37, 5.61)	4.86 (4.24, 5.51)	5.04 (4.45, 5.66)	-0.12 (-0.54, 0.23)[a]	0.03 (-0.28, 0.39)
Fasting Plasma Glucose (mg/dl)	92.0 (86.0, 98.0)	90.0 (86.0, 96.0)	90.0 (85.0, 98.0)	-1.5 (-6.0, 3.0)[a]	-1.0 (-7.0, 3.0)[a]
(mmol/L)	5.11 (4.77, 5.44)	5.00 (4.77, 5.33)	5.00 (4.72, 5.44)	-0.08 (-0.33, 0.17)[a]	-0.06 (-0.39, 0.17)[a]

Allegheny County, PA. USA. Study date: 2010-2019. Eligible population: overweight with prediabetes and/or metabolic syndrome; a: p-value for change <0.05 using Signed Rank test. Participants with medication changes related to the variable examined were excluded from analysis.

BMI 12-month n=304; SBP/DBP 6-month n=285, 12-month n=272; Total cholesterol 6-month n=278, 12-month n=262; Glucose 6-month n=304, 12-month n=303

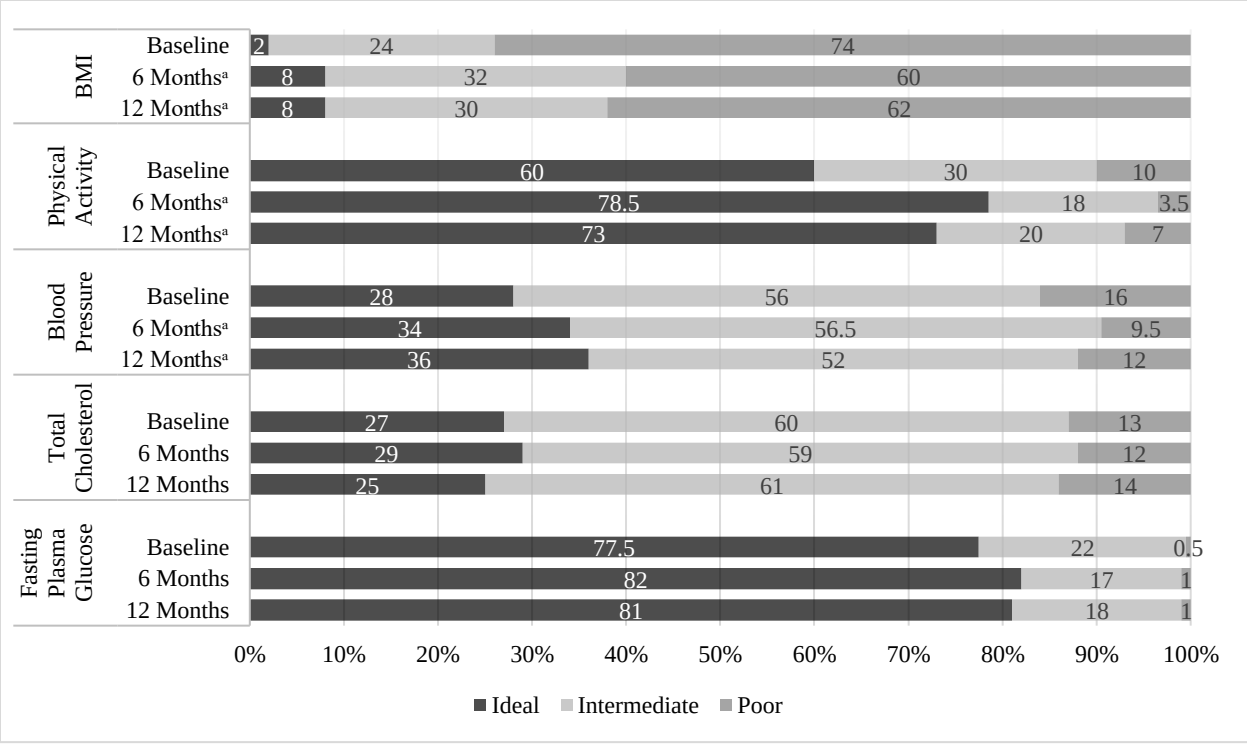

Figure 3 Individual Metric Category Percentages at Baseline, 6 and 12 months in Combined GLB Cohort Pre/Post Analysis Sample, n=305

Allegheny County, PA. USA. Study date: 2010-2019. Eligible population: overweight with prediabetes and/or metabolic syndrome. a: p-value <0.05 using Marginal Homogeneity Test for shift in ordered proportion of participants within metric category compared to baseline.

Ideal / intermediate / poor categories: BMI (kg/m2) <25 / 25-30 / >30; Physical Activity (MET hr/wk) none / >0 to <7.5 / ≥7.5; Blood pressure (mmHg) ≤120 SBP, 80 DBP / 120-139 SBP, 80-89 DBP and/or treated to ideal range / ≥140 SBP and/or ≥90 DBP; Total cholesterol (mmol/L): <5.18 / 5.18-6.21 or treated to ideal range/ >6.22; Fasting Plasma Glucose (mmon/L) <5.6 / 5.6-6.9 or treated to ideal range / ≥6.9

Table 6 Total Metric and Ideal Metric Scores and Changes at 6 and 12 months in Combined GLB Cohort

Pre/Post Analysis Sample, n=305

Composite Metric Score	Baseline Mean (SD) Median (IQR)	6 months Mean (SD) Median (IQR)	12 months Mean (SD) Median (IQR)	6 M Change Mean (SD) Median (IQR)	12 M Change Mean (SD) Median (IQR)
Total Metric Score	5.80 (1.41) 6.0 (5.0, 7.0)	6.43 (1.42) 6.0 (5.0, 7.0)	6.28 (1.43) 6.0 (5.0, 7.0)	0.59 (1.11) +1.0 (0.0, +1.0)[b]	0.48 (1.22) 0.0 (0.0, +1.0)[b]
Ideal Metric Score	1.94 (0.94) 2.0 (1.0, 3.0)	2.30 (1.01) 2.0 (2.0, 3.0)	2.23 (1.01) 2.0 (2.0, 3.0)	0.36 (0.95) 0.0 (0.0, +1.0)[b]	0.29 (0.93) 0.0 (0.0, +1.0)[b]

Allegheny County, PA. USA. Study date: 2010-2019. Eligible population: overweight with prediabetes and/or metabolic syndrome; b: P-value <0.01 using Signed-Rank test to assess change

4.3 Cardiovascular Health and CAD Development Among Individuals with Type 1 Diabetes in The Epidemiology of Diabetes Complications Study Cohort

CAD is persistently more prevalent in the T1D population than the general population.[10,66,152] Several risk factors have been implicated as increasing CAD risk among those with T1D.[157,158,163] AHA CV health metrics scores in early adulthood as a predictor of incident CAD have not yet been fully explored in the T1D population.[54,55] As previously described, the EDC is uniquely situated to study exposures in early adulthood and the development of complications over time among individuals with T1D. The EDC cohort also provides the opportunity to explore T1D specific nutrient intake patterns in relation to other CV risk factors as well as CAD risk.

4.3.1 Parent cohort

The Pittsburgh EDC study is a prospective cohort study of childhood onset Type 1 Diabetes. Eligible participants were diagnosed, or seen within one year of diagnosis, before the age of 17 between 1950 and 1980 at the Children's Hospital of Pittsburgh. Hospital records were used to identify potential participants based on clinical diagnosis of T1D. After identification through medical record review, eligible participants provided informed consent and were enrolled in the study. While this study sample was enrolled from a single clinic center, it has been shown to be representative of the T1D population of Allegheny County at the time of enrollment.[249] A total of 658 participants were seen at the baseline visit in 1986-1988 and have been prospectively followed through clinic examinations occurring biennially for the first 10 years and at years 18, 25 and 30. In addition, surveys were conducted biennially throughout the study.

4.3.2 Cardiovascular Health Metrics and CAD Development Among Individuals with T1D (Aim 2)

4.3.2.1 Study sample

For the purposes of this project, an average of measures taken at the first and second visit will be used in order to provide more robust measures and account for some variability. The use of the average of measures taken two years apart is desirable due to the inclusion of self-reported behavioral measures, specifically diet and physical activity. Participants below the age of 20 (n=111) at baseline or with prevalent CAD by the second visit (n=68) were excluded, leaving an eligible sample of 478. The age cut point of 20 was used in order to target early adulthood, and to be consistent with the AHA defined cut point for use of LS7 metrics in adults.[14]

4.3.2.2 Measures

Timing of all measures is detailed in Figure 4 (p.82). All measures of interest, methods of measurement, and the role of each variable are detailed in Table 7 (p.83). Components of the CV health metrics were determined as the mean of first and second visit measures in order to provide more robust estimates and account for variability in self-reported measures. If a measure was missing at one of the two visits, the measure from the other visit was used. Observations with missing measures at both visits for any metric were excluded. All measures of interest for Aim 2 are summarized in Tables 7 and 8 (p.83-84) and described in detail in the manuscript, "*Cardiovascular Health in Early Adulthood Predicts the Development of Coronary Heart Disease in Individuals with Type 1 Diabetes: 25 year Follow Up from the Pittsburgh Epidemiology of*

Diabetes Complications Study" (Section 4.3.5.3, p.91). Categories of ideal, intermediate, and poor cardiovascular health metrics were defined using AHA criteria [14], with some necessary modifications as shown in Table 8 (p.84).

The primary outcome of interest was time to development of total CAD, as described in detail in the accompanying manuscript. Secondary outcomes of Hard CHD (defined as CHD, but excluding angina and ischemia), and Major Adverse Cardiovascular Events (MACE, defined as the first instance of myocardial infarction, stroke, or cardiovascular mortality), were also examined.

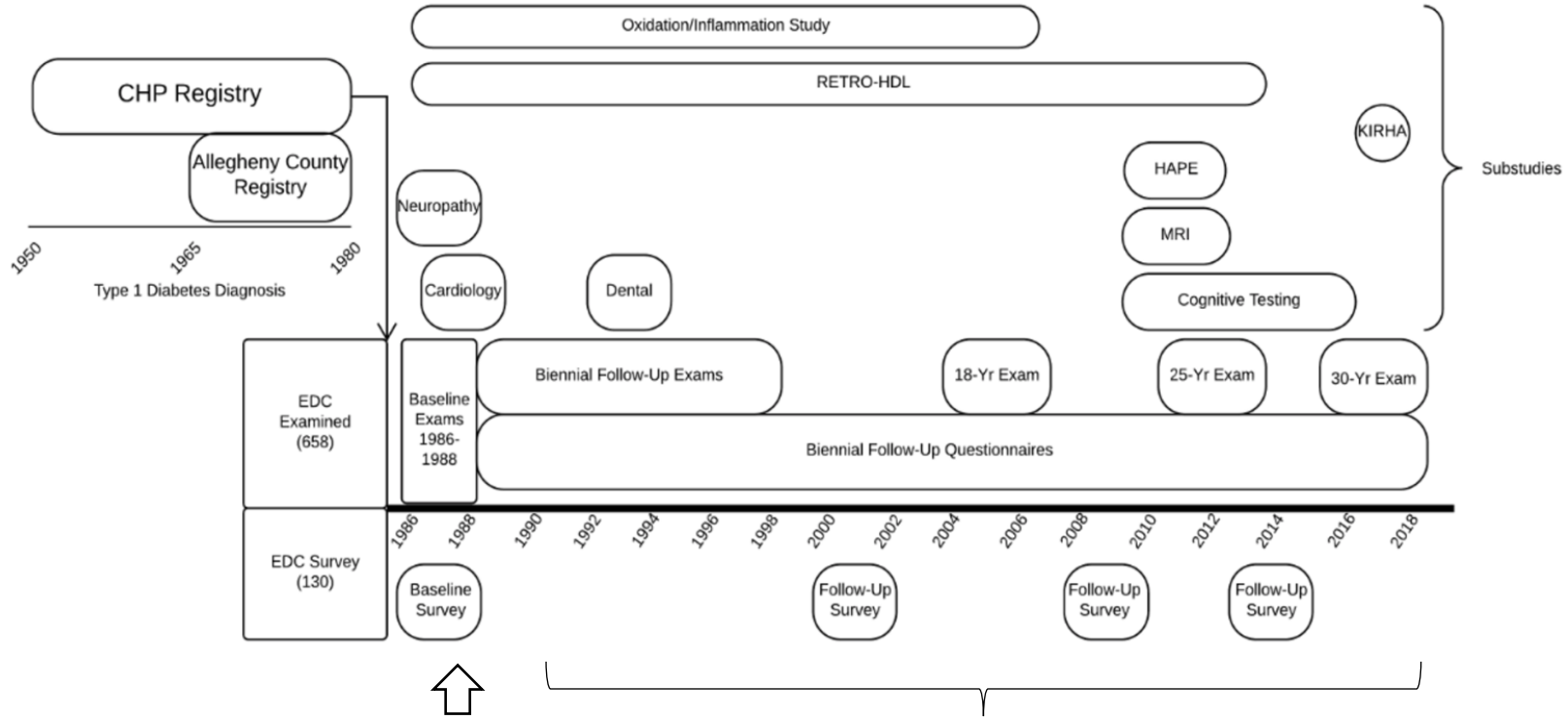

Figure 4 EDC Study Timeline

Table 7 EDC Measures of Interest

Domain and Timing	Measures	Method of Measurement	How Measure was Used in Analysis
CVH Metrics Composite Score *Measures taken 1986-1990*	*Health Factors:*		Primary predictor All metrics categorized into poor, intermediate and ideal status (per Table 11). "Ideal score" was a sum of metrics within the ideal range (possible range 0-7). "Total score" was the sum total for each participant of all metrics across categories where poor=0, intermediate=1 and ideal=2 (possible range of 0-14).
	Total cholesterol	Fasting blood draw	
	Blood pressure	Sphygmomanometer using an average of 2 measures after a 5 minute rest period	
	Hemoglobin A_{1c}	Fasting blood draw	
	Health Behaviors:		
	BMI	Height and weight	
	Smoking status	Demographic and medical history questionnaire	
	Physical activity	Paffenbarger Physical Activity Questionnaire	
	Diet	Harvard Willet Food Frequency Questionnaire	
Other variables of interest *Measures taken 1986-1990*	Sex	Demographic questionnaire	Potential confounder
	Duration of diabetes	Medical records from Children's Hospital of Pittsburgh	Potential confounder
	Triglycerides	Fasting blood draw	Potential confounder
	Albumin Excretion Rate	24 hours urine collection, immunonephelometric analysis	Potential confounder
	Estimated Glomerular Filtration Rate	Chronic Kidney Disease Epidemiology Collaboration creatinine equation	Potential confounder
	White Blood Cells	Fasting blood draw, Counter S-plus IV	Potential confounder
	Depression	Beck Depression Inventory	Potential confounder
	Household Income	Demographic questionnaire	Potential confounder
Measures taken 1992-2013	Lipid and Blood Pressure Medication Use Over Time	Medical history questionnaire	Potential confounder
CAD *Time to event measure starting at second follow up visit*	CAD Events: Total CAD, Hard CAD	Self-report, medical records; physician adjudicated	Outcome
	CAD Mortality	Death certificates, autopsy reports, and coroner reports	

Table 8 Cardiovascular Health Metrics and Modifications from LS7

Metric	Ideal	Intermediate	Poor	Modifications
"Health Factors"				
Total cholesterol	< 200 mg/dL	200-239 mg/dL or treated to the ideal range	≥ 240 mg/dL	None
Blood pressure	< 120 systolic, <80 mmHg diastolic	120-139 systolic or 80-89 mmHg or treated to the ideal range	≥ 140 systolic or ≥ 90 diastolic	None
Hemoglobin A_{1c}	<7%	7.0-8.9%	>9%	Use of HbA_{1c} instead of fasting blood glucose
"Health Behaviors"				
BMI	< 25 kg/m^2	25 - 29.9 kg/m^2	≥ 30 kg/m^2	None
Smoking status	Never or quit >12 months	Former ≤ 12 months	Current	Use of "former" at any time instead of former ≤ 12 months due to availability of data
Physical activity	≥ 150 minutes per week moderate to vigorous or ≥ 75 minutes vigorous	1-149 minutes per week moderate to vigorous or 1-74 minutes vigorous	None	None
Nutrition Components	3 components: 1) Fiber intake >25g women, >38g men 2) Sodium intake <2,300mg 3) Percent Calories from Saturated Fat <10%	2 components	0-1 component	Use of individual nutrients and 3 criteria instead of 5 criteria based on ADA and USDA/HHS recommendations

4.3.2.3 Analytic Methods

Hypothesis: Greater achievement of T1D-specific ideal CV health metrics will protect against incident CAD.

All continuous variables were examined for normality, trends and potential outliers. Variables were transformed if appropriate for analysis. Baseline characteristics, including prevalence of CV health metrics, were described using means or medians for continuous variables and frequencies and percentages for categorical variables. Baseline characteristics represent an average of variables from the first visit and second visit, with the exception of age and duration of diabetes, which were first visit values. All analyses were performed in SAS 9.4 (SAS Inc., Cary, NC).

CV health metrics were quantified as "ideal score", indicating the total number of metrics out of seven within the ideal range (possible range 0-7). In addition, a "total score" was determined representing the sum of all seven metrics where each metric with poor status was assigned a value of 0, intermediate a value of 1 and ideal a value of 2 (possible range 0-14). Additional analyses evaluated ideal and total "health behavior" and "health factor" scores separately as predictors of CAD. Cox proportional hazards analysis models were used to explore total ideal and total score as predictors of CAD. Potential covariates including sex, diabetes duration, triglycerides, BDI, WBC, household income, AER and eGFR were included based on stepwise selection at the level of $p<0.25$ for entry and 0.15 to stay.

Two sensitivity analyses were conducted, 1) including repeated assessments of lipid and blood pressure medication use during follow up in models and 2) including only participants who indicated that their reported activity reflected their usual activity level.

4.3.3 Findings

Results of the analysis for Aim 2 are included in the manuscript "*Cardiovascular Health in Early Adulthood Predicts the Development of Coronary Heart Disease in Individuals with Type*

1 Diabetes: 25 year Follow Up from the Pittsburgh Epidemiology of Diabetes Complications Study" (see Section 4.3.5.4, p. 98). The results of this study indicate that higher ideal and total CV health scores in early adulthood were associated with lower risk for CAD development over time among individuals with T1D. Among 435 adults without CAD at baseline (90.8% of eligible sample), each additional CV health metric within the ideal range and each unit increase in total metric score decreased the incidence of CAD determined over a 25-year follow-up period (19%, $p<0.01$ and 17%, $p<0.01$ respectively) adjusting for duration of diabetes, albumin excretion rate, estimated glomerular filtration rate, triglycerides, depression, and white blood cell count (Table 11, p.108). Each unit increase in total "health behavior" score decreased adjusted rate of developing CAD by 13% ($p<0.01$), and each unit increase in total "health factor" score decreased the adjusted rate of CAD by 21% ($p<0.01$) (Table 11, p.108).

4.3.4 Implications

These findings indicate that a modified LS7 approach may be a valuable goal setting tool to reduce CAD risk among individuals with T1D. A greater number of metrics within the ideal range and increases in total metric score were associated with reduced risk for incident CAD. Prevalence estimates of the CV health metrics give an idea of where efforts to improve these metrics may be best directed. Diet, in particular, shows room for improvement. The findings from the EDC cohort indicate that the LS7 approach has the potential for use in clinical and public health intervention to potentially reduce the burden of CAD in the high risk T1D population. Additional discussion is included in the "Aim 2" manuscript (see Section 4.3.5.5, p.100).

4.3.5 Aim 2 Manuscript: Cardiovascular Health in Early Adulthood Predicts the Development of Coronary Heart Disease in Individuals with Type 1 Diabetes: 25 year Follow-Up from the Pittsburgh Epidemiology of Diabetes Complications Study

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4.3.5.1 Introductory Section

Aims/Hypothesis: Type 1 diabetes increases CHD risk. We examined the use of the American Heart Association's (AHA) cardiovascular health metrics (blood pressure, total cholesterol, glucose/HbA_{1c}, BMI, physical activity, diet, smoking) to predict incidence of CHD among individuals with type 1 diabetes, with the hypothesis that a better AHA health metric profile would be associated with lower incident CHD.

Methods: Prevalence of the seven cardiovascular health metrics was determined using first and second visits from adult participants (average age 28.6 years) in the Epidemiology of Diabetes Complications (EDC) prospective cohort study of childhood-onset type 1 diabetes. An ideal metric score (0-7) was defined as the sum of all metrics within the ideal range, and a total metric score (0-14) was calculated based on poor, intermediate and ideal categories for each metric. Incident CHD development (medical record confirmed CHD death, myocardial infarction, revascularization, ischemic electrocardiogram changes, or EDC physician determined angina) over 25 years of follow-up was examined by metric scores.

Results: Among 435 participants, BMI, blood pressure, total cholesterol and smoking demonstrated the highest prevalence within the ideal range, while diet and HbA_{1c} demonstrated the lowest. During 25 years of follow-up, 177 participants developed CHD. In Cox models, each additional metric within the ideal range was associated with a 19% lower risk ($p=0.01$), and each unit increase in total metric score was associated with a 17% lower risk ($p<0.01$) of CHD, adjusting for diabetes duration, estimated glomerular filtration rate, albumin excretion rate, triglycerides, depression, and white blood cell count.

Conclusion/Interpretation: Among individuals with type 1 diabetes, higher cardiovascular health metric scores were associated with lower risk of incident CHD. The AHA defined cardiovascular health metrics provide straightforward goals for health promotion that may reduce CHD risk in the type 1 diabetes population.

4.3.5.2 Introduction

Cardiovascular disease is the leading cause of mortality in individuals with type 1 diabetes.[174] CHD, the most prevalent form of CVD, develops at an earlier age and is disproportionately burdensome among individuals with type 1 diabetes compared with the general population.[9,10] Since the incidence of type 1 diabetes is increasing worldwide [7] without a known intervention that is effective in preventing it, measures to delay or decrease diabetes complications are essential. Early prevention of CHD to offset earlier development and greater prevalence with aging [66,151] has therefore become a priority.

In 2010, the American Heart Association (AHA) created a framework for assessing and promoting cardiovascular health using seven simple metrics, known as Life's Simple Seven (LS7). These metrics include four "health behaviors" (smoking, BMI, physical activity, and diet), and three "health factors" (total cholesterol, blood pressure, and glucose).[14] AHA also created ideal, intermediate, and poor categories for each metric using criteria in line with clinical practice and public health guidelines.[14] Longitudinal studies demonstrated an inverse linear dose response between a greater number of metrics within the ideal range and cardiovascular mortality [11,108] and CVD development over time.[110,111] The LS7 is meant to reduce CVD burden by offering a straightforward, simple way to quantify important health behaviors and health factors to provide clear, actionable change goals. This framework has potential utility in public health messaging and as an assessment and goal setting tool in clinical practice.[15]

The composite of modifiable metrics that comprise the LS7 has not yet been explored in relation to CHD in the type 1 diabetes population. Traditional risk factors such as blood pressure, blood lipids, waist to hip ratio, and smoking have been shown to be related to CHD risk in type 1

diabetes, while population specific risk factors such as diabetes duration and overt nephropathy also influence risk.[67,156,158,162] A small body of research examined the prevalence of ideal cardiovascular health metrics in type 1 diabetes [54,55] and found an association between cardiovascular health and development of coronary artery calcium,[54] although the prospective association between the LS7 metrics and CHD development has not yet been determined.

The Pittsburgh Epidemiology of Diabetes Complications (EDC) is a prospective study of individuals with childhood-onset type 1 diabetes with over 25 years of follow-up. The availability of extensive longitudinal data in this cohort allowed for the opportunity to describe baseline measures of ideal, intermediate, and poor cardiovascular health metrics based on LS7, and to determine the association between these cardiovascular health metrics and future CHD. It was hypothesized that a greater number of baseline cardiovascular health metrics within the ideal range and a higher total cardiovascular health metric score would be associated with lower CHD incidence.

4.3.5.3 Methods

Study design and subjects

EDC study participants were identified based on clinical diagnosis of type 1 diabetes before the age of 17 between 1950 and 1980 at Children's Hospital of Pittsburgh.182 A total of 658 participants were seen at the baseline visit (1986-1988) and have been prospectively followed through clinic examinations occurring biennially for the first 10 years and at years 18, 25 and 30. In addition, surveys were conducted biennially throughout the study. Outcome data collected through the 2013-2015 (25-year) visit were used for this analysis. As separate LS7 cut-points were developed for use in adults (defined as ≥20 years of age by AHA) and children, participants <20

years of age at baseline risk factor assessment were excluded (n=111, 12 of whom developed CHD during follow-up), as were those with prevalent CHD by the second visit (years 1988-1990, n=68). Thus, the total eligible sample for this analysis was 479 individuals. All participants provided written informed consent and all protocols were approved by the Institutional Review Board at the University of Pittsburgh.

Cardiovascular Health Metrics

Components (i.e., health behaviors and health factors) of the cardiovascular health metrics scores were based on the mean of measures taken at first and the second visit to provide more robust estimates. If a measure was only available at one visit, then that value was used. Participants with missing data at both visits for any variable were excluded. Categories of ideal, intermediate, and poor cardiovascular health metrics were defined using AHA criteria [14], with some necessary modifications as indicated below and shown in Table 9 (p.105).

Four "Health Behaviors"

1) BMI

BMI (kg/m^2) was calculated using height and weight measured at clinic visits. The ideal BMI range was defined as <25, intermediate as 25-30 and poor as $\geq$30 kg/m^2.

2) Smoking

Smoking status was self-reported using a demographic/medical history questionnaire. In this analysis, consistent with the approach taken previously,[55] ideal was defined as never smoker,

intermediate as former smoker and poor as current smoker. Never smokers were defined as those who stated at both the first and second visit that they had never smoked 100 or more cigarettes. Former smokers indicated that they were former smokers at both visits or that they were smokers at the first visit and no longer smoked at the second visit. Current smokers indicated current smoker status at the second visit.

3) Physical Activity

Physical activity status was assessed using the Paffenbarger Physical Activity Questionnaire,[250] whose validity in assessing moderate or greater (moderate+) intensity physical activity was previously shown.[251] The following question was used to determine minutes of activity per week: "List any sports or recreation you have participated in during the past week. Please include only the time you were physically active," which then included prompts for time and frequency. An added question to the Paffenbarger Questionnaire asked if the reported level of activity reflected the participant's usual activity over the past week. Activity intensity was determined using metabolic equivalents of task (METs) according to the 2011 Compendium of Physical Activity.[252] Activities of ≥3.0 METs were considered moderate+ and counted toward activity time per week, in line with the AHA criteria for this metric.[14] The ideal range for physical activity was defined as ≥150 minutes per week of moderate+ intensity activity. Intermediate was defined as 1-149 minutes per week of moderate+ intensity activity and poor as no physical activity.

4) Nutrition

Diet was assessed using the Harvard/Willet Food Frequency Questionnaire, which was shown to be a valid method for collecting nutrient intake data.[253] Participants indicated how

frequently 116 food/drink items were consumed on average over the past year. Questionnaires were optically processed at the Harvard Medical School (Channing Laboratory, Boston, MA 02115) to produce daily nutrient consumption data. Unfortunately, food group data were not available. Nutrient components included in determining cardiovascular health metrics score were chosen from a consensus between the rationale for the AHA LS7, Dietary Reference Intakes, and ADA recommendations for dietary intake for people with diabetes. Components of the score include 1) sodium intake of <2,300 mg/day, 2) saturated fat intake of <10% of total calories, and 3) fiber intake of ≥25 g/day for females and 38 g/day for males. The sodium criterion is consistent with the ADA recommendations for individuals with diabetes and Dietary Reference Intake.[117,193] The fiber criteria are intended to reflect ADA and AHA LS7 recommendations for greater intake of whole grains, fruits and vegetables,[14,193] with sex-specific intake cut points based on Dietary Reference Intake values.[117] The saturated fat criterion is explicit in ADA guidelines for recommended intake for individuals with diabetes, and restricting saturated fat intake is mentioned in the LS7 strategic plan.[14,193] Ideal status was defined as meeting all three criteria, intermediate as meeting two and poor as meeting one or none.

Three "Health Factors"

1) Total cholesterol

Serum total cholesterol was determined enzymatically from blood drawn after fasting.[254] Per AHA LS7 ranges, ideal total cholesterol was defined as <5.18 mmol/L, intermediate as 5.18-6.21 or treated to ideal range and poor as ≥6.22.[14] Lipid medication use, which was self-reported

using a medical history questionnaire, at either first or second visit was considered when determining categories.

2) Blood pressure

Blood pressure was measured with a random zero sphygmomanometer; the mean of the last two of three readings taken after a 5-minute rest were used. In accordance with the AHA LS7 status ranges, ideal blood pressure was defined as systolic blood pressure (SBP) <120 mmHg and diastolic blood pressure (DBP) <80 mmHg, intermediate as SBP 120-139 or DBP 80-89 or treated to ideal range, and poor as SBP ≥140 or DBP ≥90.[14] Self-reported antihypertensive medication use at either visit was considered when determining categories.

3) Glycosylated hemoglobin

Glycosylated hemoglobin (HbA_{1c}), a more appropriate indicator of overall glucose management in the type 1 diabetes population, was used instead of the LS7 metric of fasting blood glucose. Stable glycosylated hemoglobin (HbA_1) was measured by ion-exchange chromatography (Isolab, Akron, OH), for the first 18 months of EDC, and subsequently by automated high-performance liquid chromatography (Diamat; Bio-Rad, Hercules, CA). The two assays were highly correlated (r=0.95). HbA_1 values were converted to Diabetes Control and Complications Trial-aligned HbA_{1c} values using a regression equation derived from duplicate assays (DCCT HbA_{1c} = 0.14 + 0.83 [EDC HbA_1]). Consistent with the current ADA guidelines for glycemic targets, the ideal range for HbA_{1c} was <53 mmol/mol (<7%) [255], intermediate was 53-75 mmol/mol (7-8.9%) and poor was ≥75 mmol/mol (≥9%).

CHD Outcomes

The primary outcome of interest was time to development of CHD, defined as the first instance of CHD death, myocardial infarction confirmed by Q-waves on electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records, angiographic stenosis ≥50 percent, revascularization, ischemic electrocardiogram changes (Minnesota codes 1.3, 4.1-4.3, 5.1-5.3, 7.1) or EDC study physician diagnosed angina. Self-reported CHD events were confirmed using medical records. CHD as either the primary cause or a contributing cause of death was determined using death certificates, autopsy reports, and coroner reports and reviewed in accordance with the Diabetes Epidemiology Research International mortality protocol.[256] Secondary outcomes of Hard CHD (defined as CHD, but excluding angina and ischemia), and Major Adverse Cardiovascular Events (MACE, defined as the first instance of myocardial infarction, stroke, or cardiovascular mortality), were also examined.

Other measures of interest

Potential confounding variables were considered based on previous research looking at CHD [156,158] and cardiovascular health metrics [54,55] in type 1 diabetes. Duration of diabetes was determined using date of diagnosis. Sex, race/ethnicity, and household income were specified in a demographic questionnaire administered at first visit. All additional covariates used the mean of first and second visit measures. The Beck Depression Inventory (BDI) questionnaire was used to ascertain depressive symptoms.[257,258] Triglycerides were obtained enzymatically using fasting blood draw.[182,259] White blood cell count (WBC) was measured using a counter S-plus IV (Coulter Electronics, Hialeah, FL). Urinary albumin was measured by immunonephelometry in three timed

urines.[260] Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[261]

Analysis

Cardiovascular health metrics were quantified as "ideal score", indicating the sum of the seven metrics within the ideal range (possible range 0-7). In addition, a "total score" was determined representing the sum across all seven metrics where each metric with poor status was assigned a value of 0, intermediate a value of 1, and ideal a value of 2 (possible range 0-14). Ideal score and total score were used as continuous predictors of time from cardiovascular health metric assessment (i.e., starting from the date of the second clinic visit) to first CHD event using Cox Proportional Hazard models. Models were adjusted for potential confounders, including sex, diabetes duration at visit 1, and the mean of visit 1 and 2 triglycerides, BDI, WBC, household income, AER and eGFR. AER and triglycerides were log transformed and quartiles of BDI were used to reduce skewness. Covariates were included based on stepwise selection at the level of $p<0.25$ for entry and $p<0.15$ to retain.

As renal disease is a strong risk factor for CHD risk in type 1 diabetes, effect modification of the association between total metric score and CHD by eGFR was assessed by including a metric score x eGFR interaction term in Cox models. All Cox models were confirmed to meet the proportional hazards assumption by assessing that interaction terms between the metric score variables and time were not statistically significant. Additional analyses evaluated ideal and total "health behavior" and "health factor" scores separately as predictors of CHD, hard CHD and MACE outcomes. Two sensitivity analyses were conducted, 1) including repeated assessments of

lipid and blood pressure medication use during follow-up in models and 2) including only participants who indicated that their reported activity reflected their usual activity level. Absolute risk was calculated using Kaplan Meier survival probabilities for high vs. low scores based on the score midpoint (>3 vs. ≤3 ideal and >7 vs. ≤7 total). All analyses were conducted using SAS version 9.4 (SAS Institute, Inc.).

4.3.5.4 Results

Of 479 eligible participants, 43 were excluded due to missing cardiovascular health metric or covariate data and 1 had unknown CHD status through 25 years of follow-up, leaving a final sample of 435 (90.8%). Median participant age at the first visit was 28.6 years, median diabetes duration was 19.8 years, males and females were evenly represented, and the sample was 97.9% White (Table 10, p.106). At baseline, three participants reported taking lipid medications and 57 reported taking blood pressure medications. During the 25-year follow-up, 177 (40.7) participants had an incident CHD event (fatal CHD: 18, non-fatal MI: 47, revascularization: 36, ischemic electrocardiogram: 25, angina: 50).

At baseline (Figure 5, p.107), the majority of participants were in the ideal range for total cholesterol (64.4%), blood pressure (64.4%), BMI (64.6%), and smoking status (58.2%). Only 7.4% had ideal HbA_{1c} and 1.2% had ideal nutrition component status. The ideal physical activity goal was met by 39.4% of participants.

The median number of ideal metrics was 3 (IQR: 2-4; minimum: 0, maximum: 6). The median total metrics score was 8 (IQR: 6-9; minimum: 2, maximum: 13). No participants achieved ideal status for all seven metrics.

Ideal Metric Score: In unadjusted models, each additional ideal metric was associated with a 38% decreased risk of CHD ($p<0.01$) (Table 11, p.108). This association was attenuated to 32% ($p<0.01$) adjusting for diabetes duration; it was further attenuated to 24% ($p<0.01$) with additional adjustment for eGFR, and AER, and to 19% ($p=0.01$) in the final multivariable model adding triglycerides, WBC, and depression (no significant eGFR effect modification found). Each additional ideal "health factor" metric was associated with a 26% decreased risk ($p<0.01$) in final models with adjustment for the same covariates as the full score plus cardiovascular health behaviors. Risk reduction with each additional ideal health behavior was significant in unadjusted models (HR: 0.68, $p<0.01$) and no longer significant in fully adjusted models.

Total Metric Score: Each unit increase in total cardiovascular health metric score was associated with a 27% decreased risk of CHD ($p<0.01$) which was attenuated to 26% ($p<0.01$) in models adjusted for diabetes duration alone, 21% ($p<0.01$) when adjusting for diabetes duration, eGFR, and AER, and 17% in final models with additional adjustment for triglycerides, WBC, and BDI (Table 11, p.108). Each unit increase in total "health behavior" score was associated with a 13% decreased adjusted risk of CHD ($p=0.04$), and each unit increase in total "health factor" score with a 21% decreased risk ($p<0.01$).

Similar results were obtained when examining hard CHD (*i.e.*, excluding angina and ischemic electrocardiogram, n=475, events=166; Table 11, p.108). Results were also similar with MACE as the outcome of interest (n=477, events=133), with a slightly stronger 26% decreased risk ($p<0.01$) associated with each unit increase in ideal metric score, in the fully adjusted model. Sensitivity analysis found no difference in time to event models when including repeated assessments of medication use, which increased over time (Table 23, p.151), and, separately, when restricted to those who reported that their activity level reflected their usual level of activity

(n=368). After 25 years, the absolute risk reduction for total CHD for high vs. low ideal scores was 0.498 (95% CI: 0.415-0.581) and for high vs. low total metric scores was 0.153 (95% CI: 0.122-0.184).

4.3.5.5 Discussion

A carefully designed longitudinal study of a large cohort of individuals with childhood-onset type 1 diabetes allowed for the examination of the relationship between measures of a modified version of AHA's cardiovascular health metrics in early adulthood and incident CHD. Each additional cardiovascular health metric within the ideal range and each unit increase in total metric score was associated with a lower incidence of CHD (19%, $p=0.01$ and 17%, $p<0.01$, respectively) over a 25-year follow-up. These findings support the hypothesis that a more favorable cardiovascular health metrics profile in early adulthood is associated with a lower incidence of CHD in type 1 diabetes, showing the potential utility of the AHA LS7 as a tool to identify and promote improvement in health behaviors and health factors in this population.

This is the first known report of the association between cardiovascular health metrics and incident CHD in type 1 diabetes and was done in the EDC study with data on all seven metrics over 25 years of follow-up. Measures from the first two clinic assessment visits (young adulthood) were considered for all metrics as the time of exposure of interest due to risk for earlier development of CHD among individuals with type 1 diabetes. Granted, physical activity and nutrient intake were self-reported and diet could not be characterized using the same criteria outlined by LS7 due to the availability of nutrient intake data. Also, repeated measures of diet data were limited, not allowing the assessment of repeated measures of the full LS7 profile. Finally, while the EDC cohort is representative of baseline type 1 diabetes prevalence in the geographic

area at the time,[249] the lack of racial/ethnic diversity is a limitation in this study, especially given an increased incidence among Black individuals.[262]

The current analysis builds on existing literature exploring the prevalence of cardiovascular health metrics in individuals with type 1 diabetes. In comparison with the EDC cohort, the Type 1 Diabetes Exchange Clinic registry (years 2010-2012) and the Coronary Artery Calcification in Type 1 Diabetes (CACTI, years 2000-2002) cohort found that a greater percentage of their study samples met the HbA_{1c} goal, but a lower percentage met the ideal criteria for blood pressure and BMI.[54,55] The CACTI study also demonstrated a similar prevalence of individuals meeting the ideal criteria for diet, total cholesterol, and smoking, and a lower prevalence of ideal physical activity when compared to EDC.[55] Differences in prevalence may be due to an older average age of 37 years in both the Diabetes Exchange and CACTI cohorts compared to the EDC cohort, differences in years when measures were taken (1986-90 vs 2000-02 and 2010-12), [54,55] and differences in activity assessment across studies.[55] In addition, EDC participants were not directly treated by research staff, while "Exchange" members were seen in the reporting clinics and about half of the CACTI participants were treated by study personnel. The lack of guidelines for blood glucose management and dietary intake among the type 1 population in the 1986-1990 time period may have further contributed to lower prevalence of ideal HbA_{1c} and diet in the EDC cohort. However, more contemporary estimates in type 1 diabetes youth in the SEARCH study [263] and adults in the "Exchange" (years 2016-2018) [264] have demonstrated similar mean levels of HbA_{1c} compared to similarly aged EDC participants in the mid/late 1980s. Also, the comparably low prevalence of ideal diet in CACTI is noteworthy, indicating that perhaps components of the risk profile have remained somewhat unchanged over time.

There are inconsistencies in studies of cardiovascular health metric prevalence in the general population compared to those among individuals with type 1 diabetes. The Framingham Offspring study from a similar time period to EDC demonstrated a comparatively lower prevalence versus EDC of ideal smoking status, total cholesterol, and blood pressure. [110] NHANES metric estimates among a comparable age range to EDC baseline also demonstrated lower prevalence of ideal BMI.[265] In contrast, the CACTI study, which compared all seven cardiovascular health metrics in a type 1 diabetes population to individuals without diabetes, found that blood pressure was significantly *less* favorable among the former.[55] In summary, CACTI found less favorable while EDC found more favorable metrics profiles in their cohorts with type 1 diabetes compared to individuals without diabetes. Possible reasons for these discrepancies include the fact that the CACTI study was initiated over fifteen years after EDC baseline and involves a control group comprised primarily of family and friends of enrolled individuals with type 1 diabetes.

Longitudinal examination of cardiovascular health metrics and future atherosclerotic outcomes in type 1 diabetes has only been done previously in the CACTI study, which found that a higher number of ideal cardiovascular health metrics was associated with decreased coronary artery calcium progression.[55]. The current analysis from the EDC study demonstrated that each unit increase in ideal and total cardiovascular health metric scores was associated with a lower risk for CHD and MACE. This EDC study also looked at "health behaviors" and "health factors" as independent predictors of CHD. Ideal health behaviors were not associated with CHD in fully adjusted models, which may speak to the influence of depression on health behavior and the overall health profile of participants in the ideal range for BMI. Also, it is important to note that adjustment for post baseline lipid medication use did not eliminate the value of LS7 as a predictor of CHD in the EDC. This further underscores the utility of LS7 as a predictor, given that young adults with

20 years type 1 diabetes duration commonly reach risk levels meriting statin use under current guidelines.[66]

Our findings in the EDC cohort are in line with findings in the general population demonstrating a dose response relationship between the number of ideal cardiovascular health metrics and CVD risk. In the Framingham Offspring study, for each unit increase in the ideal cardiovascular health metric score (range 0-7), CVD incidence decreased by 23%.[266] Similarly, others reported that achieving five or more ideal metrics was associated with a significantly lower CVD risk compared to zero or one ideal metric.[111,113] Achieving the highest total cardiovascular health metric score, quantified in the same way as in the EDC study, significantly reduced CVD risk.[13,114] Finally, in the limited literature looking at CHD in the general population, self-reported CHD has been shown to be lower among individuals with more ideal cardiovascular health metrics.[267]

The fact that a similar or more favorable cardiovascular health risk profile in type 1 diabetes compared to the general population occurs despite a relatively higher burden of CHD, as shown in the EDC, warrants further consideration. For example, previous EDC findings indicate that treatment guidelines may need to consider lower blood pressure goals in individuals with type 1 diabetes in order to decrease CHD risk.[180] While the current analysis was intended to evaluate the AHA LS7 criteria with only minimal necessary changes, future analyses could consider additional modifications to create a more population specific LS7.

A potential limitation to the LS7 approach is that it does not provide information on the relative importance of each component and is not meant to serve as a risk prediction model. Consistent with other studies,[11,13] the current findings indicate that any improvement in LS7 metrics scores is associated with decreased CVD risk. Future research can investigate the

utilization of LS7 in children and further explore the relative importance of CVD risk factors and resulting LS7 metrics in the type 1 diabetes population.[268] Additional studies of the impact of interventions designed to improve cardiovascular health on the LS7 are also needed.

In conclusion, cardiovascular health metrics shows promise for use in type 1 diabetes as a clinical and public health promotion tool and provides insight into areas of greatest need of intervention to improve cardiovascular health in specific type 1 diabetes cohorts. In the EDC cohort, diet had an ideal prevalence of 1.1%, making it a first line intervention target. Extending the application of the LS7 approach, which allows for easy assessment and sets straightforward goals for modifiable risk factors, to the high-risk type 1 diabetes population, has great potential to promote cardiovascular health.

Table 9 Cardiovascular Health Metrics Categories

Metric	Ideal	Intermediate	Poor
Total cholesterol	< 5.18 mmol/L	5.18-6.21 mmol or treated to the ideal range	≥ 6.22 mmol/L
Blood pressure	< 120 systolic, <80 mmHg diastolic	120-139 systolic or 80-89 mmHg or treated to the ideal range	≥ 140 systolic or ≥ 90 diastolic
Hemoglobin A_{1c}	<53 mmol/mol (<7%)	53-75 mmol/mol (7.0-8.9%)	≥75 mmol/mol (>9%)
BMI	< 25 kg/m^2	25 - 29.9 kg/m^2	≥ 30 kg/m^2
Smoking status	Never	Former	Current
Physical activity	≥ 150 minutes per week moderate+	1-149 minutes per week moderate+	None
Nutrition	3 components: 1) Fiber intake >25g women, >38g men 2) Sodium intake <2,300mg 3) Percent Calories from Saturated Fat <10%	2 components	0-1 component

Ideal metric scores: sum count for each participant of metrics in the ideal range (possible score 0-7)

Total metric scores: sum of each participant's metrics across all ranges where ideal=2, intermediate=1, poor=0 (possible score 0-14)

Table 10 Participant Characteristics [Average of first visit (1986-1988) and second visit (1988-1990); n=435]

Characteristic	Median (25^{th} and 75^{th} percentile) or N(%)
Age (years, at first visit)*	28.6 (24.5, 33.3)
Diabetes duration (years, at first visit)*	19.8 (15.2, 26.0)
Sex (male)	217 (49.9%)
Triglycerides (mmol/L)	0.94 (0.69, 1.39)
Total Cholesterol (mmol/L)	4.78 (4.29, 5.56)
HDLc (mmol/L); n=434	1.35 (1.17, 1.57)
LDLc (mmol/L); n=428	2.93 (2.46, 3.50)
Race: White	426 (97.9%)
Albumin excretion rate (µg/min)	18.3 (8.3, 213.2)
Estimated GFR (ml/min/1.73m^2)	109.5 (91.6, 121.0)
Blood Pressure (mm/Hg)	112.5 (105.0, 122.0)/ 72.5 (66.5, 79.0)
HbA_{1c} (mmol/mol), [(%)]	67 (62, 81) [8.7 (7.8, 9.6)]
White Blood Cells (10^9/L)	6.4 (5.6, 7.7)
BMI (kg/m^2)	23.9 (21.8, 25.8)
Physical Activity (min/week moderate+)	90 (0, 255)
Beck Depression Inventory	5.5 (2.5, 9.5)

*Only baseline data used for age and diabetes duration

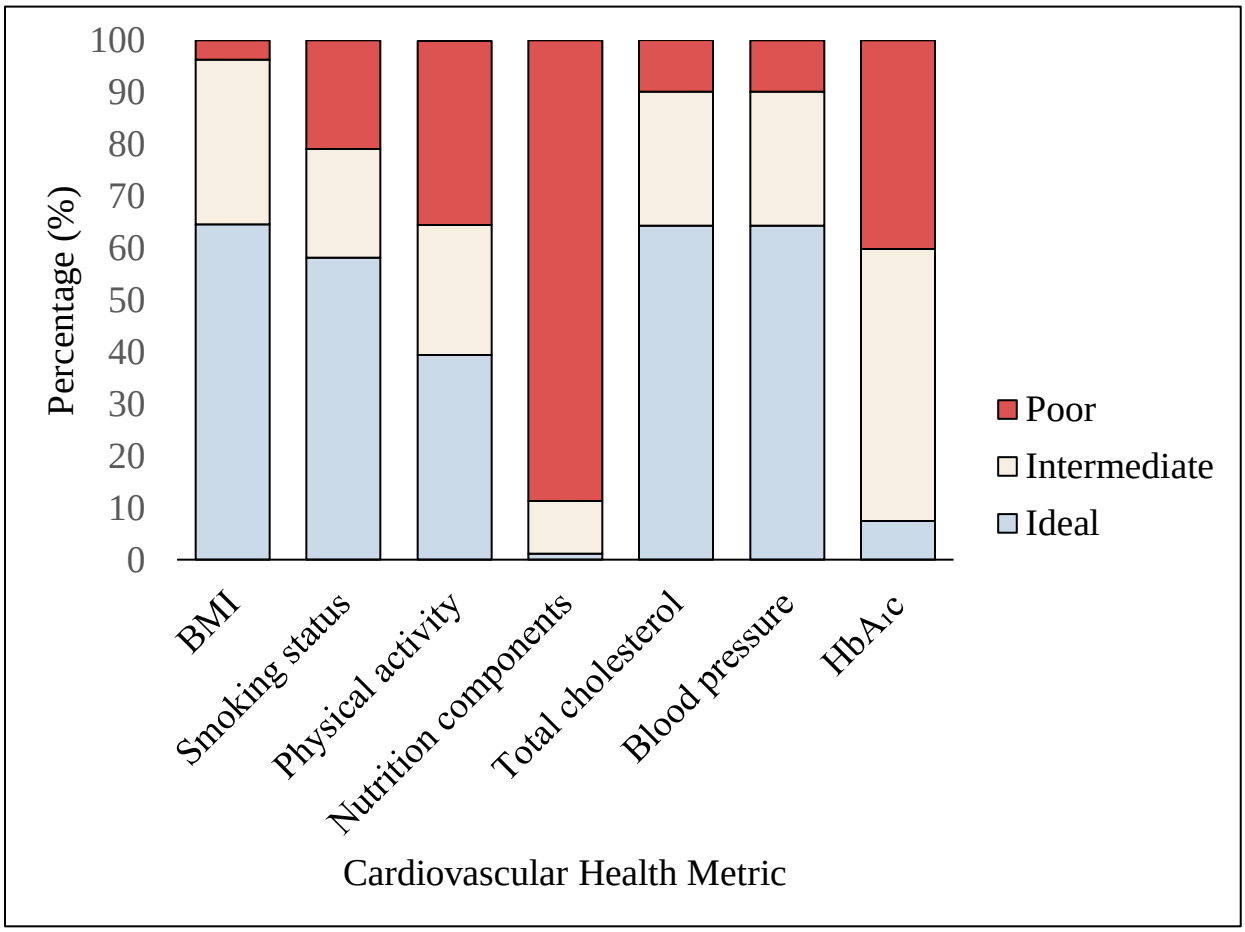

Figure 5: Prevalence of Cardiovascular Health Metrics [Average of first visit (1986-1988) and second visit (1988-1990); n=435]

Prevalence estimates are the mean of measures taken at first and the second visit. If a measure was missing at one of the two visits, the measure from the other visit was used

Table 11 Cox Proportional Hazards Outcome Analysis of Ideal Score or Total Score and CHD, Hard CHD and MACE as HR (95% Confidence Interval)

Cox Proportional Hazard Ratio	Unadjusted	p-value	Adjusted for Diabetes Duration	p-value	Adjusted for Duration, AER, log eGFR	p-value	Fully Adjusted*	p-value
Total CHD (n=435, events = 177)								
Ideal Score	0.62 (0.55, 0.71)	<0.01	0.68 (0.60, 0.77)	<0.01	0.76 (0.66, 0.87)	<0.01	0.81 (0.70, 0.94)	0.01
Ideal "Health Behaviors" only[ɪ]	0.68 (0.54, 0.86)	<0.01	0.76 (0.61, 0.96)	0.02	0.79 (0.62, 1.00)	0.05	0.88 (0.69, 1.12)	0.28
Ideal "Health Factors" only[ɪ]	0.60 (0.52, 0.70)	<0.01	0.65 (0.56, 0.76)	<0.01	0.75 (0.64, 0.88)	<0.01	0.78 (0.66, 0.93)	0.01
Total score	0.73 (0.67, 0.79)	<0.01	0.74 (0.69, 0.81)	<0.01	0.79 (0.72, 0.86)	<0.01	0.83 (0.75, 0.92)	<0.01
Total "Health Behaviors" Only[ɪ]	0.76 (0.67, 0.86)	<0.01	0.80 (0.71, 0.91)	<0.01	0.82 (0.72, 0.93)	<0.01	0.87 (0.76, 0.99)	0.04
Total "Health Factors" Only[ɪ]	0.70 (0.64, 0.77)	<0.01	0.71 (0.64, 0.78)	<0.01	0.77 (0.68, 0.86)	<0.01	0.79 (0.70, 0.90)	<0.01
Hard CHD [n = 475 (92% of 519 eligible), events = 166]								
Ideal Score	0.59 (0.51, 0.67)	<0.01	0.65 (0.57, 0.75)	<0.01	0.75 (0.64, 0.87)	<0.01	0.80 (0.68, 0.93)	0.01
Total score	0.69 (0.64, 0.75)	<0.01	0.72 (0.67, 0.79)	<0.01	0.78 (0.72, 0.86)	<0.01	0.82 (0.74, 0.90)	<0.01
MACE [n = 477 (92% of 518 eligible), events = 133]								
Ideal Score	0.52 (0.45, 0.61)	<0.01	0.59 (0.51, 0.68)	<0.01	0.67 (0.57, 0.79)	<0.01	0.74 (0.62, 0.88)	<0.01
Total score	0.68 (0.62, 0.74)	<0.01	0.72 (0.66, 0.79)	<0.01	0.78 (0.71, 0.86)	<0.01	0.85 (0.77, 0.94)	<0.01

*Adjusted for duration of diabetes, albumin excretion rate, estimated glomerular filtration rate, triglycerides, depression, white blood cells.

[ɪ] Adjusted for factors or behaviors.

Participants censored at time of first event or at last follow-up.

4.3.6 Patterns of Nutrient Intake and CAD Risk Among Individuals with T1D (Aim 3)

4.3.6.1 Study Sample

The parent EDC cohort was described in Section 4.3.1 (p.79). For Aim 3, anyone below the age of 18 (n=66) at baseline or with prevalent CAD by the second visit (n=73) was excluded. The age cut point of 18 is in line with the age at which individuals with T1D are considered adults and is a more appropriate cut point for analysis that may inform nutrient guidelines specific to this population. The eligible sample for this analysis was 521 participants. Due to the age cut point of 18 instead of 20, the eligible sample was larger for Aim 3 than it was for Aim 2. Also of note, 30 years of follow up were available for time to event Aim 3 analyses.

The sample included in creating nutrient PCs was further limited by excluding participants with missing nutrient data (n=2) and with implausible total caloric intake values (n=4). In determining implausible values, the general approach of Willet and others was used, i.e. to exclude individuals with caloric intake <500 kcal/day or >3,500 kcal/day for women, and <800 kcal/day or >4,000 kcal/day for men.[269,270] In addition to considering these values, individuals just outside of suggested ranges were included, as appropriate, with consideration given to physical activity level, age, BMI, and glycemic control. One individual with missing CAD status during follow up was also excluded from PC analysis, leaving a total sample included in creation of the PCs of n=514.

4.3.6.2 Measures

Nutrient data were collected using the Harvard/Willet Food Frequency Questionnaire, as previously described in the measures for Aim 2 (Section 4.3.5.3, p.93). Dietary intake alone was considered in cases where nutrient intake from supplements may have contributed to total nutrient intake. Supplement use was accounted for during analysis using a calculated variable.

A total of 45 dietary intake nutrient variables were considered for inclusion in nutrient pattern components, and ultimately 29 nutrients were included. Variables that had overlap in the nutrients they captured were excluded. Only animal and vegetable fat appeared to capture the full energy intake indicated from fat, thus these variables were used instead of saturated fat, monounsaturated fat, polyunsaturated fat, trans fat, and additional fatty acids. A few amino acids (tryptophan, methionine), carbohydrates (fructose, sucrose), and forms of Vitamin A (retinol, carotene) were also excluded for this reason. In addition, on manual inspection, selenium and iodine appeared to have a high frequency of zero values, which did not seem plausible, thus these nutrients were excluded as well.

Additional measures of interest included incident CAD and other potential CAD risk factors, as previously described (Section 4.3.5.3, p.91) and detailed in Table 12 (p.111) and the manuscript *Data Driven Patterns of Nutrient Intake and Coronary Artery Disease Risk in Adults with Type 1 Diabetes* (Section 4.3.7.3, p.121).

Table 12 Nutrient Principal Component Measures of Interest

Domain and Timing	Measures	Method of Measurement	How Measure was Used in Analysis
Nutrient Principal Components *Measures taken 1986-1990*	*Dietary Intake*	Harvard Willet Food Frequency Questionnaire	Primary predictor
Other variables of interest *Measures taken 1986-1990*	Total cholesterol HDLc, non-HDLc	Fasting blood draw	Cross-sectional correlation analysis Exposure in multiple regression analysis in relation to each Principal Component Covariate for longitudinal analysis
	Blood pressure	Sphygmomanometer using an average of 2 measures after a 5 minute rest period; hypertension yes/no variable includes use of antihypertensives	
	Hemoglobin A_{1c}	Fasting blood draw	
	BMI	Height and weight	
	Smoking status	Demographic and medical history questionnaire	
	Physical activity	Paffenbarger Physical Activity Questionnaire	
	Sex	Demographic questionnaire	
	Duration of diabetes	Medical records from Children's Hospital of Pittsburgh	
	Triglycerides	Fasting blood draw	
	Albumin Excretion Rate	24 hours urine collection, immunonephelometric analysis	
	Estimated Glomerular Filtration Rate	Chronic Kidney Disease Epidemiology Collaboration creatinine equation	
	White Blood Cell Count	Fasting blood draw, Counter S-plus IV	
	Depression	Beck Depression Inventory	
	Household Income	Demographic questionnaire	
CAD *Time to event measure starting at second follow up visit*	CAD Events	Self-report, medical records; physician adjudicated	Outcome
	CAD Mortality	Death certificates, autopsy reports, and coroner reports	

4.3.6.3 Analytic Methods

Hypothesis: Patterns of nutrient intake that are lower in sodium and animal fat intake and higher in fiber, potassium, and vegetable fat will be associated with more favorable CV risk factors and lower risk for CAD.

All continuous variables were examined for normality, trends and potential outliers. Variables were transformed as appropriate for analysis. Again, all baseline characteristics were the mean of measures from the first visit and second visit in order to provide more robust estimates and account for variability in self-reported measures, with the exception of age and duration of diabetes, which were first visit values.

Nutrients are highly correlated due to multiple nutrients coming from the same foods and the likely grouping of nutrients within patterns of dietary behavior. Principal component analysis is a useful tool in instances where several independent continuous variables of interest are correlated, making it an ideal approach for looking at nutrient intake. This approach is appealing because it flattens the data and accounts for collinearity between variables. In this context, this type of approach allows us to understand how nutrients present together while accounting for collinearity between nutrient variables.

An average of nutrient data obtained at the first and second visits was calculated to account for variability in self-reported dietary intake. Prior to inclusion in PC analysis, nutrients were transformed to account for variability in energy needs and nutrient scale. Nutrients were log transformed to account for differences in units of measure. In order to account for confounding by total energy intake, nutrient values were regressed on total energy intake to compute residuals of nutrient intake.[269]

Statistical software was used to orthogonally transform nutrient data into principal components, with patterns that explain the greatest percentage of variance considered in further analysis. The covariance matrix was used to create PCs. PCs were retained based on total variance explained, inflections in scree plot, eigenvalues, and interpretation of patterns.

Nutrient pattern components determined by PC analysis were analyzed for association with other CV health risk factors, also determined as the average of first and second visit values. These cross-sectional analyses were conducted using Spearman correlation and Wilcoxon or Kruskall-Wallis tests as appropriate and using multiple linear regression, with nutrient PCs as the outcome, to determine independent associations. In addition, nutrient PCs were tested for association with development of CAD using Cox proportional hazard time to event models, with control for potential confounding variables consistent with the analysis used in Aim 2. All analyses were performed in SAS 9.4 (SAS Inc., Cary, NC).

4.3.6.4 Findings

Main results are presented in Section 4.3.7.4 (p.125). Additional detail on rationale behind retaining PCs for this analysis is provided here. As shown in the scree plot below (Figure 6, p.114), there is a notable inflection and leveling off at about 5 components. However, eigenvalues less than 1 may not be worth retaining.[271] Eigenvalues drop below 1 after 3 components, as shown in Table 13 (p.115). Also, the difference between cumulative variance explained seems to be much smaller after about 3 components. Ultimately, 3 PCs were retained for analysis.

To provide more context to the terminology:

- Each PC is a linear combination of variables that describes variation in the data. The first PC always describes the most variance, with each subsequent PC

describing less than the PC that precedes it. Variables are not mutually exclusive within components, and each variable has some contribution to each component.

- The eigenvector is a best fit line for each PC scaled to be 1 unit long. The loading matrix is calculated relative to the eigenvector and provides an idea of how each variable used to create the PCs contributes to that PC.
- Eigenvalues are the sum of squares of the distance from the origin of the best fit line to each variable. A greater distance to the origin implies a shorter distance between each variable and the best fit line, thus a higher eigenvalue is desirable.

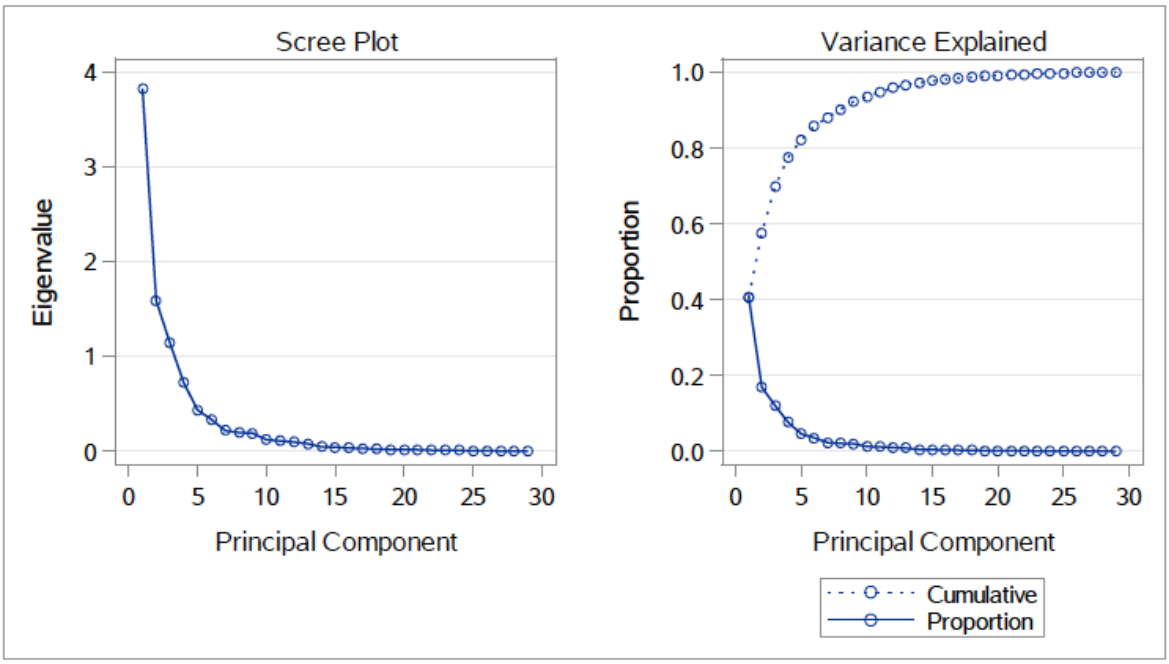

Figure 6 Scree Plot of Eigenvalues and Plot of Variance Explained in PC Analysis

Table 13 Nutrient PC Eigenvalues

Eigenvalues of the Covariance Matrix				
	Eigenvalue	Difference	Proportion	Cumulative
1	3.82881953	2.23792450	0.4074	0.4074
2	1.59089503	0.44824496	0.1693	0.5767
3	1.14265007	0.41794825	0.1216	0.6982
4	0.72470182	0.28800066	0.0771	0.7753
5	0.43670116	0.09827356	0.0465	0.8218
6	0.33842761	0.11807687	0.0360	0.8578
7	0.22035074	0.02104895	0.0234	0.8813
8	0.19930178	0.00639645	0.0212	0.9025
9	0.19290534	0.06911368	0.0205	0.9230
10	0.12379166	0.01184865	0.0132	0.9362
11	0.11194301	0.01266592	0.0119	0.9481
12	0.09927709	0.01731901	0.0106	0.9586
13	0.08195808	0.03336011	0.0087	0.9674
14	0.04859797	0.00305105	0.0052	0.9725

Visual representations of these components are shown in the Table 14 (p.116) and Figure 7 (p.134). These components can be described as follows:

- PC1 - all essential nutrients have a slightly positive or negligible contribution; relatively high intake of saccharin and caffeine
- PC2 - high caffeine intake, fairly high alcohol and copper intake, low vitamin D, low saccharin, all essential nutrients other than copper and vitamin D fairly negligible
- PC3 - higher intake of fiber and generally all micronutrients, very low alcohol intake

Table 14 Eigenvectors for Nutrient Controbutions to Each PC

Nutrient	PC1	PC2	PC3
Macronutrients			
Carbohydrate	-0.011	-0.021	0.037
Fiber	0.025	-0.033	**0.123**
Veg Fat	0.024	0.009	-0.023
An Fat	0.002	-0.005	0.016
Cholesterol	-0.0003	0.004	0.050
Protein	0.011	-0.030	0.071
Micronutrients			
Sodium	0.026	-0.006	0.043
Calcium	0.006	-0.047	**0.135**
Iron	0.028	-0.032	0.087
Magnesium	0.011	0.042	**0.120**
Phosphorus	0.024	-0.032	0.087
Potassium	0.011	0.011	**0.115**
Zinc	0.052	-0.016	0.055
Manganese	-0.002	0.059	**0.237**
Copper	0.050	**0.342**	**0.300**
Vit C	0.001	-0.086	**0.113**
Vit B1	0.019	-0.050	0.085
Vit B2	0.005	-0.041	**0.122**
Niacin (B3)	0.032	0.070	**0.204**
Vit B6	0.015	-0.034	0.091
Folate (B9)	0.020	-0.047	**0.103**
Vit B12	0.006	-0.047	**0.168**
Pantothenic Acid (B5)	0.008	-0.010	**0.302**
Vit A	0.011	-0.077	**0.247**
Vit D	-0.005	**-0.130**	**0.214**
Vit E	0.016	-0.016	0.072
Other			
Ethanol	-0.019	**0.481**	**-0.576**
Caffeine	**0.134**	**0.763**	**0.308**
Saccharin	**0.985**	**-0.107**	**-0.101**

Bold if factor loading is >0.1

The implications of the full results are discussed in the manuscript, *Data Driven Patterns of Nutrient Intake and Coronary Artery Disease Risk in Adults with Type 1 Diabetes,* Section 4.3.7.5 (p. 127).

4.3.7 Data Driven Patterns of Nutrient Intake and Coronary Artery Disease Risk in Adults with Type 1 Diabetes

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4.3.7.1 Introductory Section

Background: Individuals with type 1 diabetes experience a disproportionately high burden and earlier age of onset of coronary artery disease (CAD). Dietary intake provides a potential intervention target to reduce CAD risk. This effort aimed to identify patterns of nutrient intake in young to middle aged adults with type 1 diabetes and explore those patterns in association with development of CAD.

Methods: Participants in the Pittsburgh Epidemiology of Diabetes Complication cohort of individuals with childhood onset type 1 diabetes who were age 18 and older at baseline and free of CAD by the first follow up visit (n=521) were included in this effort. Principal component analysis was used to derive patterns of nutrient intake using the mean of nutrient intake values from the first two visit (years 1986-1988 and 1988-1990). Cross-sectional associations between nutrient patterns and other CAD risk factors and demographic characteristics were examined. Cox proportional hazard models were used to evaluate associations between nutrient patterns and incident CAD over 30 years of follow-up.

Results: Among 514 participants, three nutrient principal components (PC) were identified as meaningful. PC1, characterized by high caffeine and saccharin intake and negligible contributions from other essential nutrients, was associated with shorter diabetes duration and more physical activity. PC2, driven by high alcohol and caffeine intake and relatively lower intake of most essential nutrients, was associated with longer diabetes duration, and not smoking. PC3, defined by low alcohol, high caffeine, and relatively higher intake of most essential nutrients, was associated with being a current smoker. In unadjusted Cox models, PC1 was associated lower CAD

risk and PC2 with higher CAD risk, however these associations were no longer significant when adjusting for diabetes duration.

Conclusion: Our data suggest that there may not be enough meaningful variability in nutrient intake to discern differences in CAD risk in this type 1 diabetes cohort, independent of other CAD risk factors. Important dietary components underlying the three patterns identified may have been influenced by duration of diabetes or age. Future research can continue to explore patterns of nutrient intake over time in relation to CAD in the type 1 diabetes population.

4.3.7.2 Introduction

The incidence of type 1 diabetes is increasing with no known means of prevention.[7] Cardiovascular disease (CVD) remains disproportionately high among individuals with type 1 diabetes and presents at an earlier age.[9,66] Coronary artery disease (CAD) is especially burdensome among young adults with type 1 diabetes compared to the general population.[66,152] Identifying and addressing modifiable risk factors for CAD early in the disease process is, therefore, essential in this population.

Dietary intake is a modifiable factor that influences CVD risk and may be a meaningful target for risk reduction.[58] Following a healthy diet pattern is recommended as part of the American Heart Association's initiative to promote cardiovascular health.[14] While certain nutrients are generally recognized as beneficial and others as harmful, emphasizing modification to the intake of individual nutrients has demonstrated little influence on CVD outcomes.[82,183] Over time, promoting beneficial patterns of intake has shown to be a more effective approach to reducing CVD risk.[206,272] A variety of recommended patterns of intake have shown to be associated with lower risk for the development of CVD.[190]

Diet may be a uniquely interesting CVD risk factor among individuals with type 1 diabetes given the central role of diet in blood glucose management and potential for unique intake patterns in this population. Research has indicated that a low percentage of individuals with type 1 diabetes met recommended nutrient intake goals.[57,198–201] An atherogenic diet that is high in fat and saturated fat has shown to be more common among type 1 diabetes compared to individuals without diabetes.[56] This may be due in part to an emphasis on carbohydrate intake in order to manage blood glucose in type 1 diabetes. While carbohydrate monitoring is important,[192] this

emphasis may have led to inadequate consideration for other aspects of the diet that influence CVD risk.[195] A handful of studies have considered the influence of patterns of intake on CVD risk factors in type 1 diabetes,[60,205,206,208,209,211] with some protective associations indicated for intake aligning with DASH and Mediterranean diet patterns. However, no study to date has evaluated patterns of intake among individuals with type 1 diabetes in relation to development of CAD.

Principal component (PC) analysis offers an *a posteriori* approach to capturing patterns of intake based on existing data for the diet consumed while accounting for the interactive effects of multiple nutrients occurring together. This approach is appealing in the type 1 diabetes population as it will identify patterns of nutrient intake as they present in this population, as opposed to fitting nutrient intake into predetermined nutrient intake patterns.

The Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort is a prospective cohort study of childhood onset type 1 diabetes with thirty years of follow up. This cohort offers the unique opportunity to explore dietary exposures in young adulthood in relation to subsequent CAD development. The aim of this study was to derive patterns of nutrient intake, using PC analysis, among young adults with type 1 diabetes and explore the association of these patterns with CAD risk factors and development of CAD.

4.3.7.3 Methods

Study population

The Pittsburgh EDC cohort enrolled 658 individuals with childhood onset (before the age of 17) type 1 diabetes diagnosed or seen within one year of diagnosis at Children's Hospital of Pittsburgh between the years 1950-1980.[182] Baseline visits occurred in 1986-1988 and participants have been followed since then, with in person clinical visits occurring biennially for the first 10

years and at years 18, 25, and 30. Surveys have been collected biennially throughout the follow up period. Due to recommendations for adults with type 1 diabetes generally starting at age 18, anyone below 18 years of age at baseline was excluded from this effort (n=66). Nutrient data from the first and second clinic visits were used as the exposure of interest in this investigation, thus anyone with CAD before the second visit was also excluded (n=71), leaving an eligible sample size for this analysis of 521.

Nutrient measures

Nutrient data were collected using the Harvard/Willet Food Frequency Questionnaire (FFQ)[273] during the first (1986-1988) and second (1989-1990) clinic visits. Questionnaires were optically processed at the Harvard Medical School (Channing Laboratory, Boston, MA 02115) to produce daily nutrient intake data. Participants with missing nutrient data at both visits were excluded from the analysis (n=2). All nutrients were evaluated for realistic ranges of values. Participants with implausible caloric intake were excluded (<500kcal/day, >3,500/kcal day for women and <800kcal/day, >4,000/day for men[270]) with some flexibility based on individual inspection of activity level, BMI, and glucose control (n=4). A total of 29 nutrition variables were included in this analysis, as detailed in Table 16 (p.133). An average of intake from visit 1 and visit 2 was calculated and used for all nutrient values.

A dichotomous variable was created to indicate nutrient supplement use based on reported supplement use on the FFQ at visit 1 and/or visit 2.

CAD Risk Factors

CAD risk factors were selected based on previous literature among individuals with type 1 diabetes looking at CAD risk. Diabetes duration was calculated based on the date of diagnosis. Sex, race/ethnicity, household income, and smoking status were collected using a demographic questionnaire. Smoking was classified as current, former, or never (<100 cigarettes in lifetime) as of the second clinic visit. Household income was standardized at age 28, or as close to this age as possible, in order to capture socioeconomic status during a comparable point in life, as has been previously described in detail.[274]

An average of first and second visit values was calculated for all additional risk factors. Physical activity was measured using the Paffenbarger Physical Activity Questionnaire using a question about past week leisure activity and quantified as minutes per week of moderate or greater intensity activity (moderate+).[251] The Beck Depression Inventory (BDI) was used to measure depressive symptoms.[257,258] BMI (kg/m2) was calculated from clinic visit measured height and weight. Blood pressure was measured using with random a zero sphygmomanometer after 5 minutes of rest as the mean of the last two of three readings. The presence of hypertension was defined as SBP ≥140 or DBP ≥90 or use of antihypertensive medication.

A fasting blood draw was used for measures of triglycerides, total cholesterol and HDL-cholesterol,[182,254] and non-HDL was calculated as the difference between total and HDL-cholesterol. White blood cell count (WBC) was measured using a counter S-plus IV (Coulter Electronics, Hialeah, FL). Urinary albumin was measured by immunonephelometry in three timed urines[260] and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[261] Stable glycosylated hemoglobin (HbA_1) was measured by ion-exchange chromatography (Isolab, Akron, OH), for the first 18 months of EDC, and subsequently by automated high-performance liquid chromatography

(Diamat; Bio-Rad, Hercules, CA). The two assays were highly correlated (r=0.95). HbA_1 values were converted to Diabetes Control and Complications Trial-aligned HbA_{1c} values using a regression equation derived from duplicate assays (DCCT HbA_{1c} = 0.14 + 0.83 [EDC HbA_1]).

CAD

Time to first CAD event was the primary outcome of interest. Total CAD was defined as CAD death, myocardial infarction confirmed by Q-waves on electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records, angiographic stenosis ≥50 percent, coronary artery bypass surgery, angioplasty, ischemic electrocardiogram changes (Minnesota codes 1.3, 4.1-4.3, 5.1-5.3, 7.1) or EDC study physician diagnosed angina. A secondary outcome of hard CAD was defined using the same criteria but excluding angina and ischemia.

Analysis

After exclusions for implausible nutrient intake (as previously described, n=4) and missing nutrient data (n=2), and missing CAD status (n=1), 514 of the 521 eligible participants were included in PC analysis. In order to account for scale differences in how nutrients are measured, the means of all nutrients were log transformed.[275] These variables were then regressed on total caloric intake to account for differences in total energy intake.[269]

Diet patterns were extracted with PC analysis using the PRINCOMP command in SAS (version 9.4, Cary, NC) and covariance matrix. The number of PCs retained was based on eigenvalues >1.0 and total variance explained, as well as inflections in the Scree plot and meaningful differences in the interpretation of patterns of nutrients created. The loading matrix for

nutrient PCs was examined to determine which nutrients meaningfully contributed to the patterns derived.

Cross-sectional correlations between nutrient PCs and CAD risk factors were calculated using Spearman correlation coefficients for continuous variables. Wilcoxon or Kruskall-Wallis tests were used to evaluate associations between categorical factors and nutrient PCs. Multiple regression models were fitted with principal component as the dependent variable and CAD risk factors as independent variables. To account for skewed distribution, prior to inclusion in models, AER and triglycerides were log transformed, BDI was categorized by quartile, and physical activity was categorized as none, up to 150 minutes per day, and ≥150 minutes per day of moderate+ activity. Participants with missing data for any CAD risk factor were excluded (n=49) from regression models.

Finally, time to first CAD event was calculated using Cox Proportional Hazard models for each PC. Covariates were subsequently added to models, first including nutrient supplement use (model 2), then adding diabetes duration (model 3), then adding all additional covariates as appropriate per stepwise selection with the criteria of 0.25 to enter, 0.15 to stay. Covariates considered for inclusion in model 4 include duration, sex, smoking status, physical activity, hypertension (yes/no), HbA_{1c}, total cholesterol, triglycerides, WBC, AER, eGFR, BDI, household income, nutrient supplement use, and total caloric intake.

4.3.7.4 Results

Of the 514 participants included in creating nutrients PCs, the median age at baseline was 27.6 years (25^{th}, 75^{th} percentile: 22.8, 33.0)), with a median diabetes duration of 19.0 years (25^{th}, 75^{th} percentile: 14.6, 25.5). The sample was evenly split by sex (256 female, 258 male), and 97.5%

of participants identified as white, as shown in Table 15 (p.132) alongside remaining average first and second visit participant characteristics.

Median nutrient intake values for the 29 nutrients included in creating the PCs are shown in Table 16 (p.133). Total caloric intake and the percentage of caloric intake from total fat, saturated fat, protein and carbohydrate and recommended nutritional goals based on Recommended Dietary intakes and 2015-2020 Dietary Guidelines for Americans recommendations, where established, are also shown in Table 16 (p.133). Compared to recommended intake, percent intake from saturated fat was high and fiber, magnesium, potassium, folate, vitamin D and vitamin E intake low. Calcium and iron intake were low among females and sodium intake high among males.

A total of 3 nutrient PCs were retained for additional analysis. Contributions of each nutrient to each of the nutrient PCs is shown in Figure 8 (p.134), and can be summarized as follows:

PC1 - all essential nutrients have a slightly positive or negligible contribution; relatively high intake of saccharin and caffeine

PC2 - high caffeine intake, fairly high alcohol and copper intake, low vitamin D, low saccharin, all essential nutrients other than copper and vitamin D fairly negligible

PC3 - higher intake of fiber and generally all micronutrients, very low alcohol intake

Cross sectional correlations between potential CAD risk factors and nutrient PCs are shown in Table 17 (p.135). Younger age, shorter duration, more physical activity, lower blood pressure and non-HDL cholesterol, higher eGFR, and being female were correlated with PC1. Older age, longer diabetes duration, higher BMI, and lower HDL cholesterol and eGFR were correlated with

PC2. PC3 was also correlated with older age and longer diabetes duration, and with lower BMI, higher AER and lower eGFR, and being a current or former smoker.

Multiple regression and time to event analyses were restricted to only those participants who had complete data for all covariates included in models (n=465, 89% of the full eligible sample).

Multiple linear regression models (Table 18, p.136) demonstrated independent associations between shorter diabetes duration, being female, being more active, and using nutrition supplements with PC1. Longer diabetes duration, not being a current smoker, and using nutrition supplements were independently associated with PC2, while being male and being a current smoker were associated with PC3.

Unadjusted time-to-event Cox models of nutrient components and CAD development showed a lower risk of CAD (HR 0.92, 95% CI: 0.85, 0.99) with the PC1 diet pattern and a higher risk of CAD with PC2 (HR 1.14, 95% CI: 1.06, 1.23), Table 19 (p.137). These associations remained significant in models adjusted for nutrient supplement use (PC1 HR: 0.91, 95% CI: 0.84, 0.97; PC2: 1.11, 95% CI: 1.01, 1.21). When duration was added to the models, these associations were no longer significant. This lack of significant association remained in models fully adjusted for covariates chosen using stepwise selection, including AER, hypertension (yes/no), total cholesterol, triglycerides, WBC, AER, and BDI. No significant associations were found between PC3 and CAD in any model. These associations were consistent when restricting the definition of CAD to hard outcomes only. Additional analysis of PCs across quartiles of duration showed an inverse relationship between PC1 and increasing categories of duration, flipping from positive to negative PC values after 19 years of duration, while PCs 2 and 3 had the opposite trend (data not shown).

Notably, lipid medication use was minimal at the first two visits in this cohort (1986-1990, n=4 participants using lipid medication), thus it was not included in models. Given that medication use increased during follow up, a sub-analysis using the same Cox models was done in order to better understand the association between nutrient PCs and CAD independent of lipid medication by excluding all participants who started using lipid medication over the course of follow up. This analysis, final sample n=217, yielded similar results, with the exception of PC1 no longer being significantly associated with CAD in the crude model.

4.3.7.5 Discussion

Three data-driven patterns of nutrient intake were identified among young adults with type 1 diabetes and found to be associated with other CAD risk factors. The nutrient PC characterized by higher intake of caffeine and saccharin was associated with younger age, shorter diabetes duration, being female, and a generally more favorable cardiovascular risk profile. Another pattern characterized by high alcohol and caffeine intake, and relatively lower intake of some micronutrients was associated with older age and longer diabetes duration. The third pattern, characterized by higher intake of most micronutrients and low alcohol intake, was associated with being male and being a smoker. Associations between these nutrient PCs and development of CAD, however, were not significant after accounting for diabetes duration.

The fact that adjusting for diabetes duration, which is highly correlated with age, led to longitudinal findings no longer being significant may have implications for nutrient patterns in this type 1 diabetes cohort. It is possible that intake of the nutrients that may most influence CAD risk did not vary enough within this cohort. Findings from previous observational studies in type 1 diabetes indicate that higher fat and saturated fat and lower fiber are associated with more adverse

CAD risk profiles.[56,57,194,201,203] While fiber intake was a stronger contributor to PC3, intake of animal and vegetable fats were not much different across nutrient PCs. In general, PC3 seemed to represent the most desirable nutrient intake pattern, however analysis of PC values across categories of duration indicated that participants with longer duration/older age were likely to have this pattern of intake, which may explain the lack of association between PC3 and CAD development.

The nutrients that showed the most variability across the patterns derived included caffeine, alcohol, and saccharin. Looking first at saccharin, non-nutritive sweeteners such as saccharin may in theory be most influential to type 1 diabetes complications through their use in place of carbohydrate intake.[276] However, carbohydrate intake did not appear to be meaningfully variable across these nutrient components. High saccharin intake occurring alongside higher caffeine intake in PC1 may indicate consumption of these nutrients together, such as through sweetening coffee, which may not meaningfully influence overall macronutrient intake. Looking next at caffeine and alcohol, in the general population, moderate consumption of alcohol and caffeine is generally thought not to increase CVD risk, however excessive intake of either has the potential to be harmful.[277,278] There is some evidence that caffeine and alcohol may be associated with type 1 diabetes complications,[279,280] however patterns characterized by these nutrients were not found to be associated with CAD development in this analysis after accounting for diabetes duration.

Age and diabetes duration are correlated in this childhood-onset type 1 diabetes cohort, and it is possible that intake of alcohol, caffeine, and saccharin vary in relation to age and/or duration. For example, older age and longer duration are associated with PC2 which is also characterized by higher alcohol and caffeine intake. Future research efforts that measure changes

in nutrient intake over time may further clarify our finding of loss of significance between diet patterns and CAD when controlling for diabetes duration.

A combination of *a priori* and *a posteriori* defined patterns of dietary intake have been found to be associated with CVD risk factors in existing type 1 diabetes studies. Among youth with type 1 diabetes, dietary intake that better aligns with the Mediterranean diet pattern was found to be associated with lower HbA_{1c}, total cholesterol, and non-HDL cholesterol.[60] Within this same youth with type 1 diabetes cohort, closer adherence to the Dietary Approaches to Stop Hypertension style of eating was associated with a more favorable LDL/HDL cholesterol ratio, $HbA_{1c,}$[205] DBP and odds of hypertension.[206] Food group based data driven patterns of dietary intake in a large cohort of Finnish individuals with type 1 diabetes found that a diet pattern with abundant fruit, vegetables, fish and yogurt intake may benefit glycemic control and a diet pattern with fish and eggs may be beneficial for blood pressure.[208] Our findings show that a diet with relatively higher intake of caffeine and saccharin was correlated with more favorable blood pressure, and total and non-HDL cholesterol, though these associations were not significant in multivariable models.

The EDC type 1 diabetes cohort demonstrated some high and some low intake relative to established nutrient recommendations for the general population. As there are not type 1 diabetes specific recommended nutrient intake values, the 2015-2020 Dietary Guidelines for Americans[117] were used to provide context for the median nutrient intake values in this population. This comparison to contemporary guidelines provides an idea of how intake at the 1986-1990 visits in this cohort compares to our current understanding of optimal nutrient consumption. Participants in this type 1 diabetes cohort had higher intake of saturated fat, and lower intake of fiber, magnesium, potassium, folate, vitamin D and vitamin E than recommended in the general population. Current

recommendations for individuals with diabetes suggest that nutrient intake goals should be individualized,[281] however these findings may help to inform aspects of the diet that might be worth further assessing.

This study is not without limitations. The primary exposure of interest, diet, is subject to self-reported measurement error. However, measures from the first two visits occurring two years apart were used to more accurately capture dietary data. Additional dietary intake measures over time were limited in this population, and an inherent limitation in PC analysis is that, as a data driven method, components would be different at each time period where data are collected. Future studies can continue to explore how patterns of nutrient intake change over time in the type 1 diabetes population. In addition, animal and vegetable fat appeared to most completely capture total caloric intake from fat in these data, thus saturated, mono- and polyunsaturated fat were not included in the PC analysis. However, fat intake did not appear to vary much across the nutrient PCs. Lastly, while the EDC cohort was representative of individuals with type 1 diabetes in the geographic area at the time of enrollment,[249] the sample has limited diversity. Future efforts can focus on exploring dietary data in more diverse cohorts of individuals with type 1 diabetes. Future efforts can also continue to explore data driven patterns of intake in other cohorts of individuals with type 1 diabetes across different ages and geographic locations.

This effort has the notable strength of offering 30 years of follow up with an extensive amount of data for a large type 1 diabetes cohort. Dietary data were available for the majority of individuals in this cohort, with measures from two visits that occurred only two years apart allowing for more robust measures of nutrient intake. In addition, this is the first known data-driven analysis of nutrient intake in the type 1 diabetes population. This approach is helpful in

providing a picture of dietary intake as it presents in this population as opposed to fitting dietary intake into a pre-established pattern.

In summary, there are several potential explanations for the lack of significant associations between nutrient patterns and CAD after accounting for other CAD risk factors. There may not be meaningful variability in the nutrients most associated with CAD development. Caffeine, alcohol, and non-nutritive sweeteners accounted for the most variability in diet, with little meaningful variation in intake of most essential nutrients. In addition, diabetes duration and/or age, in particular, are strong drivers of CAD risk and may also influence differences in intake of the nutrients that drove the identified PCs. Overall, given that diet is central to managing type 1 diabetes, future efforts exploring patterns of intake should continue to be a focus in this high-risk population. Exploring changes in intake over time and potentially identifying more heterogeneity in nutrients that may meaningfully influence CAD risk in other type 1 diabetes cohorts would be of particular interest in future research efforts.

Table 15 Participant Characteristics [Average of first visit (1986-1988) and second visit (1988-1990), n=514

Characteristic	**Median (25^{th}, 75^{th}) or n (%)**
Age, years	27.6 (22.8, 33.0)
Duration, years	19.0 (14.6, 25.5)
Race, white	501 (97.5)
BMI (n=511), kg/m^2	23.7 (21.8, 25.8)
Physical Activity (n=505), min/wk moderate+	105 (0, 272)
SBP, mmHg	112.0 (105.0, 121.0)
DBP, mmHg	72.5 (66.5, 79.0)
HbA1c (n=511), %	8.5 (7.7, 9.7)
Total Cholesterol, mg/dL	185.5 (166.5, 215.0)
HDLc (n=513), mg/dL	51.9 (45.1, 60.6)
nonHDLc (n=513), mg/dL	132.8 (110.9, 161.5)
Triglycerides (n=504), mg/dL	84.8 (62.8, 123.5)
WBC (n=512), (10^9/L)	6.4 (5.6, 7.7)
AER (n=512), (µg/min)	17.1 (8.2, 176.7)
eGFR, (ml/min/$1.73m^2$)	110.3 (91.7, 123.2)
BDI (n=484)	5.5 (2.5, 9.5)
Household income* (n=406)	5 (3, 6)
Female (n=257)	257 (49.8)
Smoking status	
Never smoker	297 (57.8)
Former smoker	114 (22.2)
Current smoker	103 (10.0)
Nutrition Supplement Use	252 (49.0)

Age and duration are baseline visit values; Household income is an ordinal variable scaled to the income at the visit where the participant was closest to age 28

Table 16 Median Nutrient Intake of Adult Males and Females and Nutritional Goals based on Recommended Dietary Intakes and Dietary Guidelines Recommendations

Nutrient*	Men (n=258)		Women (n=256)	
	Median (IQR)	Goal	Median (IQR)	Goal
Total calories	2307 (1917, 2798)	-	1727 (1404, 2404)	-
% calories from fat	35 (31, 38)	20-35	34 (31, 38)	20-35
% calories from SFA	12 (11, 14)	<10	12 (11, 14)	<10
% calories from CHO	48 (44, 52)	45-65	49 (43, 52)	45-65
% calories from protein	17 (16, 19)	10-35	18 (16, 20)	10-35
CHO (g)	272 (227, 339)	130	201 (165, 253)	130
Fiber (g)	22 (17, 28)	30.8, 33.6✢	19 (14, 24)	28, 25.2✢
Vegetable Fat (g)	37 (28, 48)	-	29 (21, 36)	-
Animal Fat (g)	50 (40, 64)	-	35 (28, 46)	-
Cholesterol (mg)	326 (261, 442)	-	265 (200, 324)	-
Protein (g)	96 (81, 117)	56	75 (63, 93)	46
Sodium (mg)	2618 (2147, 3347)	2300	2067 (1663, 2469)	2300
Calcium (mg)	1213 (853, 1598)	1000	858 (647, 1194)	1000
Iron (mg)	15 (12, 19)	8	13 (10, 15)	18
Magnesium (mg)	372 (300, 457)	400, 420✢	285 (226, 363)	310, 320✢
Phosphorus (mg)	1670 (1369, 2063)	700	1281 (1044, 1647)	700
Potassium (mg)	3799 (3063, 4603)	4700	2948 (2456, 3711)	4700
Zinc (mg)	16 (13, 19)	11	13 (11, 16)	8
Manganese (mg)	3.5 (2.5, 5.0)	2.3	3.0 (2.1, 4.0)	1.8
Copper (mg)	2.9 (1.8, 4.4)	0.9	2.2 (1.6, 4.0)	0.9
Vit C (mg)	157 (117, 221)	90	132 (104, 178)	75
Vit B1 (mg)	1.8 (1.4, 2.2)	1.2	1.4 (1.1, 1.7)	1.1
Vit B2 (mg)	2.6 (2.0, 3.2)	1.3	1.9 (1.5, 2.4)	1.1
Niacin (mg)	30 (24, 39)	16	25 (18, 33)	14
Vit B6 (mg)	2.3 (1.9, 2.8)	1.3	1.9 (1.5, 2.3)	1.3
Folate (mcg)	350 (290, 446)	400	280 (176, 350)	400
Vit B12 (mcg)	7.8 (6.0, 11.2)	2.4	6.2 (4.3, 9.9)	2.4
Pantothenic Acid (mg)	6.8 (5.1, 10.6)	5	5.1 (3.8, 8.7)	5
Vit A (IU)	9941 (6918, 14690)	3000	9577 (6650, 13216)	2333
Vit D (IU)	326 (195, 422)	600	223 (141, 327)	600
Vit E (mg)	9 (7, 11)	15	7 (6, 9)	15
Ethanol (g)	2.1 (0.0, 7.3)	≤ 28g	0.5 (0, 2.3)	≤ 14g
Caffeine (mg)	274 (125, 445)	-	226 (127, 411)	-
Saccharin (mg)	95 (24, 229)	-	138 (50, 295)	-

*Total calories and percent calorie variables not included in nutrient PC creation

✢ Recommended intake for age 19-30, 30-50; SFA: Saturated fat; CHO: carbohydrate; vit: vitamin

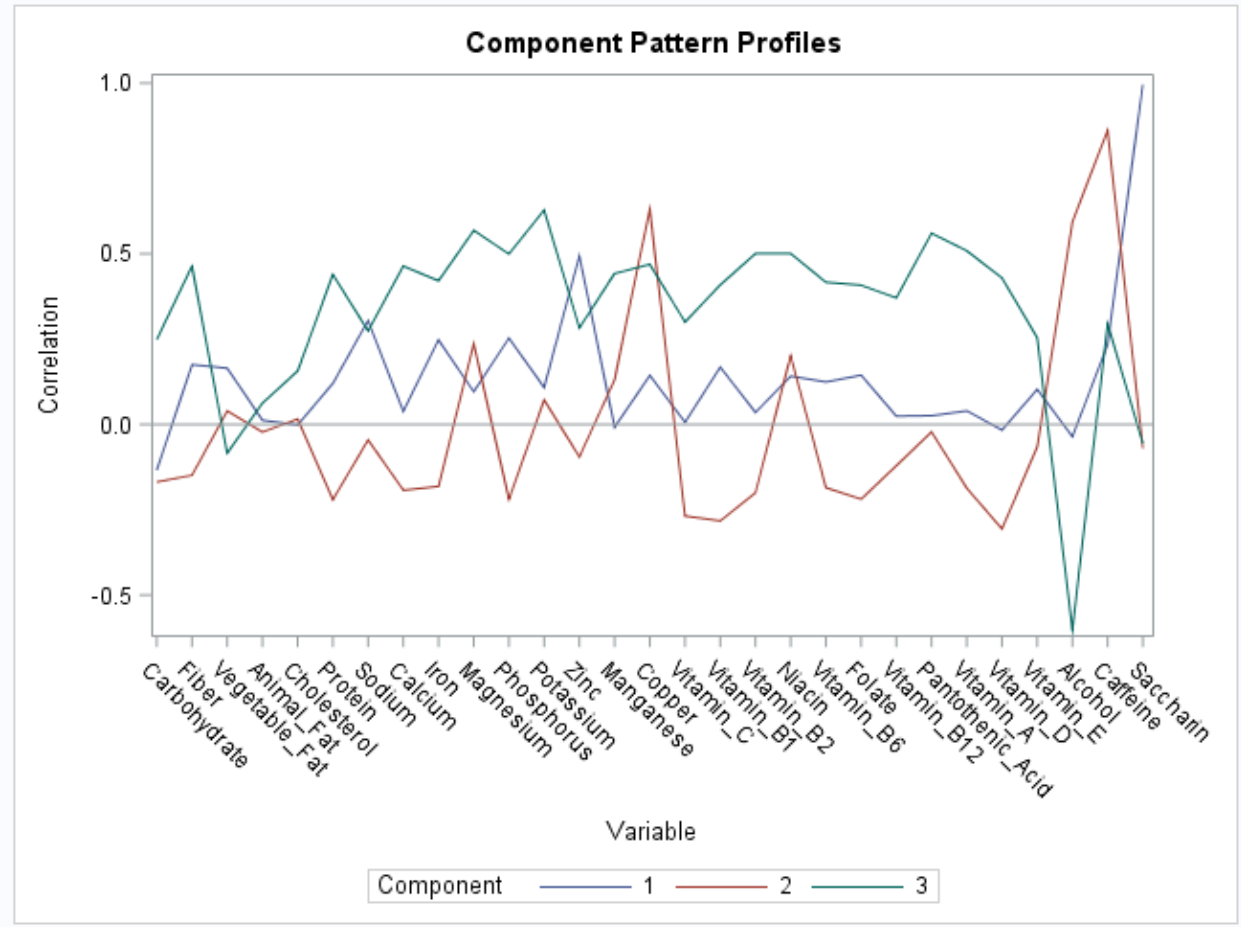

Figure 7 Nutrient Contributions to Each Principal Component

Table 17 Correlation coefficients and nonparametric tests of association between cardiovascular risk factors and nutrient principal components (n=514 unless otherwise indicated)

	PC1	P value	PC2	P value	PC3	P value
Age	-0.153	**<0.001**	0.217	**<0.001**	0.250	**<0.001**
Duration	-0.189	**<0.001**	0.184	**<0.001**	0.179	**<0.001**
BMI (n=511)	0.073	0.101	0.093	**0.036**	-0.097	**0.029**
Physical Activity (n=505)	0.138	**0.002**	-0.012	0.781	-0.074	0.098
SBP	-0.148	**0.001**	0.056	0.201	-0.010	0.820
DBP	-0.095	**0.032**	0.030	0.497	-0.029	0.517
HbA_{1c} (n=511)	0.029	0.510	-0.023	0.600	0.019	0.663
Total Cholesterol	-0.113	**0.010**	-0.001	0.977	0.078	0.075
HDLc (n=513)	0.025	0.567	-0.089	**0.044**	0.053	0.231
nonHDLc (n=513)	-0.104	**0.019**	0.028	0.524	0.062	0.155
Triglycerides (n=504)	-0.037	0.403	0.083	0.062	0.069	0.120
WBC (n=512)	-0.032	0.474	0.056	0.206	0.033	0.455
AER (n=512)	-0.053	0.232	0.073	0.097	0.114	**0.010**
eGFR	0.111	**0.012**	-0.122	**0.006**	-0.104	**0.019**
BDI (n=484)	0.008	0.855	0.007	0.878	0.042	0.361
Household income at age ~28 (n=406)	0.028	0.572	0.089	0.072	0.083	0.094
Female* (n=257)	0.660	**0.019**	-0.451	0.618	-0.126	0.072
Male* (n=258)	0.337		-0.435		0.113	
Never smoker* (n=297)	0.597	0.056	-0.367	0.145	-0.265	**<0.001**
Former smoker* (n=114)	0.108		-0.556		0.116	
Current smoker* (n=103)	0.363		-0.448		0.676	

*Wilcoxon or Kruskal-Wallis Test, median PC values

SBP: systolic blood pressure; DBP: diastolic blood pressure; WBC: white blood cell count; AER: albumin excretion rate; eGFR: estimated glomerular filtration rate; BDI: Beck depression inventory

Table 18 Multiple linear regression derived beta coefficient and standard errors of cardiovascular risk factors and nutrient principal components (n=465)

	PC1		PC2		PC3	
Characteristic	Coeff (SE)	p-value	Coeff (SE)	p-value	Coeff (SE)	p-value
Duration	**-0.04 (0.01)**	**<0.01**	**0.03 (0.01)**	**<0.01**	0.02 (0.01)	0.06
Female	**0.44 (0.21)**	**0.04**	0.01 (0.16)	0.94	**-0.27 (0.13)**	**0.05**
BMI	0.03 (0.03)	0.39	0.02 (0.02)	0.28	-0.03 (0.02)	0.10
Smoking						
Never	Ref	-	Ref	-	Ref	-
Former	-0.17 (0.22)	0.45	-0.11 (0.17)	0.53	**0.54 (0.14)**	**<0.01**
Current	-0.28 (0.24)	0.25	**-0.39 (0.18)**	**0.04**	**0.93 (0.15)**	**<0.01**
Physical Activity						
None	Ref	-	Ref	-	Ref	-
1 - <150 min/wk	0.33 (0.23)	0.15	-0.02 (0.17)	0.93	0.25 (0.15)	0.09
≥ 150 min/wk	**0.61 (0.21)**	**<0.01**	0.23 (0.16)	0.14	-0.05 (0.13)	0.73
HTN (yes)	-0.08 (0.27)	0.77	0.12 (0.20)	0.55	-0.05 (0.17)	0.78
HbA_{1c}	0.04 (0.07)	0.58	0.02 (0.05)	0.65	0.02 (0.04)	0.64
Total Cholesterol	-0.01 (0.003)	0.05	-0.002 (0.002)	0.31	-.0002(.002)	0.91
Log Triglycerides	0.09 (0.20)	0.66	0.12 (0.15)	0.43	-0.05 (0.12)	0.67
WBC	-0.02 (0.05)	0.70	0.03 (0.04)	0.53	-0.02 (0.03)	0.66
eGFR	0.004 (0.004)	0.32	$9.7x10^{-6}$ (0.003)	0.85	-0.003 (0.003)	0.26
Log AER	0.02 (0.06)	0.70	0.01 (0.04)	0.76	0.004 (0.04)	0.90
BDI						
< 2.5	Ref	-	Ref	-	Ref	-
2.5- <5.5	-0.23 (0.24)	0.35	0.23 (0.18)	0.20	0.27 (0.15)	0.07
5.5-9.5	0.24 (0.25)	0.36	-0.16 (0.19)	0.39	-0.02 (0.16)	0.90
≥ 9.5	-0.08 (0.25)	0.74	-0.09 (0.19)	0.62	0.06 (0.16)	0.71
Nutrition supplement use (y)	**0.51 (0.18)**	**<0.01**	**1.94 (0.13)**	**<0.01**	0.03 (0.11)	0.82
Total Calorie Intake	$1.6x10^{-5}$ ($1.5x10^{-4)}$	0.92	$1.2x10^{-5}$ (.0001)	0.37	$9.4x10^{-5}$ ($9.8x10^{-5}$)	0.34

WBC: white blood cell count; AER: albumin excretion rate; BDI: Beck depression inventory.

Models run with each PC as the outcome and all risk factors included as predictors in each model.

Table 19 Nutrient Components and CAD over 30 years of follow up using Cox Proportional Hazards

Outcome Analysis as HR (95% Confidence Interval) n=465

	Model 1		**Model 2**		**Model 3**		**Model 4**	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Total CAD								
PC1	0.92 (0.85, 0.99)	**0.02**	0.91 (0.84, 0.97)	**0.01**	0.94 (0.87, 1.01)	0.09	0.96 (0.89, 1.03)	0.25
PC2	1.14 (1.06, 1.23)	**<0.01**	1.11 (1.01, 1.21)	**0.03**	1.03 (0.94, 1.13)	0.47	1.04 (0.95, 1.15)	0.42
PC3	1.09 (0.98, 1.22)	0.12	1.10 (0.98, 1.23)	0.11	1.01 (0.91, 1.13)	0.82	0.96 (0.84, 1.09)	0.50
Hard CAD								
PC1	0.92 (0.85, 0.99)	**0.04**	0.91 (0.84, 0.98)	**0.01**	0.94 0.87, 1.02)	0.15	0.97 (0.84, 1.12)	0.66
PC2	1.15 (1.07, 1.25)	**<0.01**	1.11 (1.01, 1.22)	**0.03**	1.03 (0.94, 1.14)	0.50	1.04 (0.94, 1.16)	0.43
PC3	1.11 (0.98, 1.26)	0.09	1.12 (0.99, 1.26)	0.08	1.02 (0.91, 1.15)	0.70	0.99 (0.87, 1.13)	0.99

Model 1: crude

Model 2: adjusted for nutrient supplement use

Model 3: model 2 + duration

Model 4: model 3 + AER, HTN, total cholesterol, triglycerides, WBC, AER, BDI, smoking (per stepwise selection)

5.0 Overall Implications

This dissertation effort sought to explore modifiable lifestyle related CVD risk factors through extension of the AHA CV health metrics framework in individuals with prediabetes and/or metabolic syndrome, and individuals with T1D, all of whom are at increased CVD risk. Among individuals with prediabetes and/or metabolic syndrome, this effort looked at possible beneficial changes in CV health metrics due to a successful and accessible behavioral lifestyle intervention. Among individuals with T1D, the association between AHA CV health metrics profiles and incident CAD, as well as dietary patterns in relation to CAD, were examined. This dissertation effort was accomplished through the pursuit of three aims.

The first aim was to establish the utility of a successful DPP-based lifestyle intervention program, DPP-GLB, to improve the AHA CV health metrics among overweight or obese individuals with prediabetes and/or metabolic syndrome. Aim 1 results showed that CV health metrics improved during the course of the DPP-GLB behavioral lifestyle intervention. This improvement was captured through beneficial shifts toward ideal status for blood pressure, physical activity, and BMI, and resulting significant improvement in composite metrics scores. These findings demonstrate that the AHA CV health metrics can capture meaningful improvement during the course of DPP-based lifestyle interventions.

Limitations to addressing Aim 1 include the lack of detailed measures of dietary intake. In addition, diversity in this cohort is somewhat limited, due in part to lack of diversity in the greater Pittsburgh area. This approach also had notable strengths, including excellent attendance and positive participant feedback regarding perceived benefits of being part of the intervention. These CDC recognized DPP-based lifestyle interventions are CMS reimbursable and widely

implemented, with over 324,000 participants across over 3,000 organizations to date[44] taking part in these interventions. The fact that these DPP-based lifestyle intervention programs have a growing record of use and success makes them an appealing intervention option to improve CV health metrics, especially among high-risk populations including individuals with prediabetes and metabolic syndrome who have great potential to benefit from risk reduction approaches.

The successful completion of Aim 1 also suggests the potential for use of the AHA CV health metrics to facilitate coordination of behavioral lifestyle interventions with clinical care. The AHA has already created an online interactive tool for assessment of CV health metrics status called "My Life Check".[282] Healthcare providers and/or potential behavioral lifestyle intervention candidates could use this tool to screen for and monitor CV health, with DPP-based lifestyle interventions suggested as an appropriate referral option based on at-risk CV health metric profiles.

Future research can focus on the use of a healthcare system integrated assessment of AHA CV health metrics as a screening, monitoring, and behavioral lifestyle intervention referral tool, thus potentially increasing the recommended use of lifestyle intervention programs as a treatment option. The use of AHA CV health metrics as a healthcare system integrated tool could assist in creating sustainable approaches to offering lifestyle intervention programs to individuals with poor CV health metrics profiles as well as those with prediabetes. These intervention programs could be offered through the healthcare system itself or through collaboration with community sites. Implementing healthcare systems integrated CV health metrics monitoring and referral could continue to increase behavioral lifestyle intervention engagement and, in turn, have an even greater population impact on reducing CVD risk. Findings from the DPP outcomes study indicated that the lifestyle intervention was cost effective when compared to placebo.[123] Thus streamlining approaches to offering lifestyle intervention to address the CV health profile could make economic

sense. Increased utilization of behavioral lifestyle interventions would also offer the benefit of risk reduction for other adverse health outcomes that are influenced by a similar risk profile. Overall, there is great potential to use this AHA framework to promote CVD prevention through behavioral lifestyle intervention among individuals with prediabetes and/or metabolic syndrome.

The second aim of this dissertation effort was to establish the prospective association between AHA CV health metrics scores and risk of CAD among adults with T1D. Aim 2 findings showed that among young adults with T1D in the Pittsburgh EDC cohort, more favorable composite CV health metrics scores were associated with less incident CAD over 25 years of follow-up. This suggests that promoting ideal CV health metrics among young adults with T1D would be beneficial in reducing the burden of CAD in this population.

Measures of CV health metrics were taken between the years 1986 and 1990 for Aim 2 in this effort. As previously discussed in Section 3.5 (p.40), the guidelines used as the basis for the AHA CV health metrics have evolved over time, generally becoming more refined. One notable change in the standard of care to reduce CVD risk during the time of follow up in this cohort is increased use of lipid medication.[228] Analysis in the EDC cohort as part of this dissertation effort found that controlling for repeated measures of lipid medication, as well as antihypertensive medication, over time did not meaningfully change the strong independent association between CV health metrics and incident CAD. This is notable because anti-hypertensive and lipid medication use increased during the 25-year follow up, suggesting that perhaps initiation of these medications may not negate the influence of the CV health profile in early adulthood. It would be of interest to see if CV health metrics profiles look different in current estimates among young adults with T1D given this increase in medication use.

Potential limitations of the approach to Aim 2 include the inability to use diet criteria as defined by the AHA due to the lack of available food group data. In addition, the EDC cohort has limited diversity. Strengths of this approach include the use of a large cohort of individuals with T1D with a vast amount of data and over 25 years of follow up.

Future efforts can also consider the impact on CVD risk of promoting CV health using the AHA metric approach among young adults with T1D. This could potentially be accomplished by using a behavioral lifestyle intervention approach, as shown to be effective in improving CV health metrics in Aim 1, but with T1D specific modifications. However, a lifestyle intervention approach in this population would likely need to be more specialized to consist of individuals with T1D working with a health professional with expertise in the activity and diet management needs of T1D, such as a Certified Diabetes Educator.

The findings of Aim 2 demonstrate that the AHA CV health metrics, a simple and straightforward goal-setting tool, may be useful in addressing the disproportionately high burden of CAD in TID. Just as the AHA CV health metrics are intended to be health promoting in the general population, this approach to public health messaging may also be meaningful in the T1D population. By providing straightforward and easy to understand goals, this approach can help to make health promotion more digestible in a population that may already be overwhelmed with the need to manage care. This approach also includes some guidance on health behaviors such as diet quality and physical activity, which may not be prioritized or given sufficient attention during clinical interactions. While not meant to take the place of individualized approaches to care, the AHA CV health metrics may help to at least start the conversation around potential modifications to help reduce CVD risk in the T1D population. These conversations would allow the provider and patient to review the complete risk profile and discuss appropriate goals and intervention options.

The final aim of this dissertation was to derive population-specific patterns of nutrient intake and explore their association with other CV risk factors and incident CAD in individuals with T1D. Aim 3 findings identified three distinct data-driven patterns of nutrient intake among young-middle aged adults with T1D in the EDC cohort. The nutrients that most contributed to these different patterns were alcohol, caffeine, and saccharin, while consumption of most micronutrients was also generally negligible in one pattern, low in another, and high in the last. The diet pattern characterized by higher intake of caffeine and saccharin was associated with less incident CAD while the pattern characterized by higher intake of alcohol and caffeine and lower intake of most micronutrients was associated with higher risk of CAD in crude models. However, these associations were no longer significant after controlling for diabetes duration, which was shorter with the diet pattern associated with less CAD risk and longer in the pattern associated with higher CAD risk. These findings indicate that there may not be meaningful variability in intake among young-middle age adults with T1D in the nutrients that most influence CAD development in this population independent of diabetes duration. These findings emphasize the strength of diabetes duration and/or age as a risk factor for CAD. In addition, the nutrients that are most variable in this cohort may differ by diabetes duration, which would explain why the associations found in crude models disappeared when controlling for duration. Analytical approaches that can account for variability in nutrient intake over time would be of interest in the T1D population given the potential role of diabetes duration in the relationship between nutrient intake and CAD development found in this effort.

The pursuit of Aim 3 was a useful compliment to and expanded on the findings of Aim 2, which showed that only 1.2% of EDC participants had ideal nutrient component status. A comparison of median nutrient intake in the Aim 3 sample to the most recent Dietary Guidelines

for Americans recommended intake goals[117] showed that intake of sodium (among males) and saturated fat was high, while fiber intake was low – all of which were included as nutrients of interest in addressing Aim 2. This indicates that the nutrients selected for inclusion in the LS7 in Aim 2 may be capturing some of the nutrients with the most potential to improve in this cohort. The median intake falling outside of the recommended range, for the general population, for these nutrients may indicate that diet quality in relation to CVD risk shows room for improvement in this population. These findings are consistent with previous studies in the T1D population suggesting intake of a diet that is high in fat and saturated fat[56,57,201] and low in fiber,[201] may be the product of the emphasis on lower carbohydrate intake in T1D.[173] This reinforces the need to continue to encourage balanced intake alongside blood glucose management in this population.

The main limitation to Aim 3 was the inability to account for changes in dietary intake over time. Understanding change in intake over time relative to CAD development using this type of data driven analysis would be complicated as the data used to establish patterns of intake would change, thus the patterns themselves would change. In addition, nutrient data were only available at one additional time point in this cohort among a smaller sample size. As in Aim 2, limited diversity is a limitation in this aim as well. However, this effort also boasts the strength of being able to use a rich data set from a large T1D cohort with 30 years of follow up. In addition, this data driven approach to defining nutrient patterns provides a picture of what these T1D individuals actually consume, as opposed to how their intake might compare to predetermined patterns of intake.

Future efforts can consider whether these patterns of intake influence any other complications in this cohort as well as appropriate approaches to looking at change in dietary intake using the additional measures available. Additional research can also consider alternative

approaches to assessing patterns of intake among adults with T1D in relation to CAD risk. The influence of nutrition counseling received from healthcare professionals on dietary intake in relation to CAD risk would also be of interest in future research. Overall, efforts looking at dietary intake in the T1D population in relation to long-term CV complications should continue to be an area of emphasis in this high-risk group given the lack of existing research in this area. Individualized approaches to diet management, per the current ADA guidelines, continue to be an appropriate approach to accommodate the needs of individuals with T1D. However, additional nutrition research will help to inform appropriate recommendations to structure balanced dietary intake to reduce the risk for complications in the T1D population.

In summary, the AHA CV health metrics show promise as an approach to capturing modifiable CVD risk factors among individuals with prediabetes, metabolic syndrome, and T1D. Use of the AHA metrics may help to simplify the assessment of changes in health behaviors and cardiometabolic indicators while assisting in promoting success during DPP-based behavioral lifestyle intervention programs. Given that these CDC recognized, CMS funded, and widely implemented intervention programs show the potential to improve CV health metrics, they are a desirable treatment option for overweight/obese individuals with prediabetes and/or metabolic syndrome to reduce CVD risk. Many of these overweight/obese individuals with prediabetes may already qualify for participation in these DPP-based programs. Future efforts could consider whether it would be appropriate to expand coverage based on a poor CV health profile.

Among individuals with T1D, the AHA metrics may also serve as a health promotion tool in young adulthood to reduce the burden of CAD, with a more desirable metrics profile shown here to be associated with decreased CAD risk. Patterns of nutrient intake in young adults with T1D were not associated with CAD independent of other CAD risk factors in this effort. However,

these patterns demonstrated strong associations with diabetes duration, and either were not meaningfully variable independent of duration or were driven by duration. Future research should continue to explore patterns of intake over time in the T1D population in order to inform recommendations for structuring intake patterns to reduce CAD risk. Overall, these findings can help to guide future CV health promotion efforts, in turn contributing to a reduction in the burden of CVD among these high-risk populations.

A logical next step to build from the findings of this dissertation effort would be to build and evaluate health systems integrated tools to assess CV health based on the AHA LS7. A health system integrated approach would provide several benefits. The first would be creating a means of patient self-assessment using a combination of electronic health record data and self-report, thus allowing for assessment of these lifestyle factors while minimizing time taken away from in-person clinical interaction. The provider could have access to the assessment results, and together the patient and provider could discuss appropriate treatment options. This would provide the opportunity to normalize discussion of health behavior during clinical interaction using a standardized approach. Providers would then be able to address health behaviors as part of the full risk profile, while also identifying at-risk individuals who may benefit from referral to lifestyle intervention or other treatment options. Finally, patients could then monitor their health status, need for intervention, and success in maintaining the changes resulting from intervention.

There is great potential to build on effective approaches to reducing diabetes risk and associated CVD complications through lifestyle intervention. Use of the CV health metrics, including a focus on the nutrition component in particular, could help to facilitate meaningful approaches to lifestyle modification.

Appendix A

Appendix A.1 Supplemental DPP-GLB RCT Analysis – Not Included in Aim 1 Manuscript

The primary question of interest in Aim 1 is change resulting from participation in DPP-GLB intervention efforts as this reflects the effect of these programs as they are currently implemented across the country. Therefore, the pre/post analysis was given priority in the manuscript. Including the RCT analysis may take away from the impact of the pre/post findings given the need to discuss the RCT results and the implications of their findings. However, for the purpose of this dissertation, all analyses have been made available. This supplement includes additional analytic methods and results of the RCT analysis that are intentionally not included in the manuscript.

Appendix A.1.1 Supplemental Analytic Approach

Additional analysis considered comparison between the intervention arm and the delayed arm (RCT analysis), which was only possible at 6 months due to the 6-month delay study design. The Wilcoxon two-sample test was used to determine between group differences in change variables in the RCT analysis.

Appendix A.1.2 Results of Supplemental Analysis

In the combined cohort sample, 393 participants (91%) had data available for 6-month comparison between intervention and delayed control. Consistent with differences across cohorts described in the pre/post analysis, comparable similarities and significant differences across study cohorts were seen in the sample included in the RCT analysis (Table 7, p.81).

Additional analyses looked at change in individual metric frequencies in the delayed versus intervention arm at 6 months (Table 8, p.82) and found significant improvement in BMI ($p<0.01$), physical activity ($p<0.01$) and blood pressure ($p=0.02$) in the intervention arm. Physical activity also improved significantly in the delayed arm ($p<0.01$). Change in total and ideal metric scores were also considered using RCT analysis, with both arms showing significant improvement. Changes in total and ideal metric scores were greater in the intervention arm [median change (IQR): 0 (0, +1) total score delayed, 1 (0, +1) total score intervention; 0 (0, +1) ideal score delayed, 0 (0, +1) ideal score intervention], however the difference between arms was not statistically significant (Table 9, p.83).

Appendix A.1.3 Discussion of Supplemental Findings

The primary outcomes of interest in this dissertation effort were changes in CV health metrics during the course of the DPP-GLB to mimic the intervention program as it is currently widely offered nationwide. Discussion of the results of the pre/post analysis have been discussed (Section 4.2.9.5, p.71), and generally show that the AHA CV health metrics improved during the course of the DPP-GLB.

An additional RCT analysis was done and also showed significant improvement in AHA CV health improved toward meaningful cut points during the DPP-GLB intervention. A noted beneficial shift in physical activity was found in the delayed group as well, likely due to seasonal

change in activity. With this change in the delayed group, the composite cardiovascular health metrics scores were not statistically significantly different. Future studies need to account for the role of season in these behavioral lifestyle interventions.

Table 20 Appendix: Demographic Characteristics by Cohort and Combined Sample [(n (%) or mean (SD)]

	Pre/post Analysis			RCT Analysis			
	Healthy (n=182)	Moves (n=123)	Between Group p-value	Healthy (n=206)	Moves (n=187)	Between Group p-value	Combined (n=393)
Female	111 (60.1)	101 (82.1)	<0.01	127 (61.7)	151 (80.8)	<0.01	278 (70.7)
Age	59.1 (11.3)	62.4 (8.4)	0.18	60.4 (10.4)	62.8 (8.9)	0.99	60.4 (10.4)
Race							
White	169 (92.9)	107 (87.0)	<0.01	193 (93.7)	160 (86.0)	<0.01	353 (90.0)
Black	3 (1.7)	14 (11.4)		3 (1.5)	23 (12.4)		26 (6.6)
Other	10 (5.6)	2 (1.6)		10 (4.9)	3 (1.6)		10 (2.5)
Spanish/Hispanic/Latino	4 (2.2)	1 (0.8)	0.65	4 (1.9)	2 (1.1)	0.69	6 (1.5)
Smoking Status							
Current	14 (7.7)	1 (0.8)	0.01	14 (6.8)	2 (1.1)	0.01	16 (4.1)
Former	59 (32.4)	42 (34.2)		67 (32.5)	60 (32.1)		127 (32.3)
Never	109 (60.0)	80 (65.0)		125 (60.7)	125 (66.8)		250 (63.6)
Employment							
Working full-time	102 (56.0)	47 (38.2)	<0.01	121 (58.7)	70 (37.4)	<0.01	191 (48.6)
Working part-time	14 (7.7)	19 (15.5)		15 (7.3)	23 (12.3)		38 (9.7)
Unemployed	4 (2.2)	2 (1.6)		4 (1.9)	3 (1.6)		7 (1.8)
Homemaker	6 (3.3)	2 (1.6)		7 (3.4)	6 (3.2)		13 (3.3)
Retired	52 (28.6)	50 (40.7)		55 (26.7)	77 (41.2)		132 (33.6)
Disabled/unable to work	4 (2.2)	3 (2.4)		4 (1.9)	7 (3.7)		11 (2.8)
Other	0 (0)	0 (0)		0 (0)	1 (0.5)		1 (0.3)
Education							
8th Grade or less	0 (0)	1 (0.8)	0.01	0 (0)	1 (0.5)	0.02	1 (0.3)
Some high school	1 (0.6)	0 (0.0)		1 (0.5)	3 (1.6)		4 (1.0)
High school graduate	19 (10.4)	10 (8.1)		22 (10.7)	19 (10.2)		41 (10.4)
Some college	43 (23.6)	49 (39.8)		51 (24.8)	72 (38.5)		123 (31.3)
College graduate	60 (31.0)	38 (30.9)		65 (31.6)	53 (28.3)		118 (30.0)
Graduate degree	59 (32.4)	25 (20.3)		67 (32.5)	39 (20.9)		106 (27.0)

Wilcoxon two-sample tests used to test between group difference

Table 21 Appendix: Comparison of Individual Metric Frequencies at Baseline and 6 months, Intervention vs Delayed in Combined GLB Cohort RCT Analysis Sample

		Delayed (n=162)			Intervention (n=231)		
Metric	Category	Baseline N (%)	6 months N (%)	p-value*	Baseline N (%)	6 months N (%)	p-value*
BMI	Ideal	1 (1)	2 (1)	0.21	3 (1.5)	19 (8)	<0.01
	Intermediate	34 (21)	38 (23.5)		56 (24)	73 (32)	
	Poor	127 (78)	122 (75.5)		172 (74.5)	139 (60)	
Physical Activity	Ideal	81 (50)	116 (72)	<0.01	126 (55)	195 (84.5)	<0.01
	Intermediate	54 (33)	35 (22)		79 (34)	31 (13.5)	
	Poor	27 (17)	11 (11)		26 (11)	5 (2)	
Blood Pressure	Ideal	40 (25)	50 (31)	0.06	64 (28)	74 (32)	0.01
	Intermediate	94 (58)	89 (55)		128 (55)	130 (56)	
	Poor	28 (17)	23 (14)		39 (17)	27 (12)	
Total Cholesterol	Ideal	45 (28)	47 (29)	0.43	58 (25)	69 (30)	0.15
	Intermediate	90 (55.5)	92 (57)		144 (62)	133 (57.5)	
	Poor	27 (16.5)	23 (14)		29 (13)	29 (12.5)	
Fasting Plasma Glucose	Ideal	120 (74)	126 (78)	0.33	179 (77)	188 (81)	0.52
	Intermediate	40 (25)	34 (21)		52 (23)	39 (17)	
	Poor	2 (1)	2 (1)		0 (0)	4 (2)	

*Marginal Homogeneity Test for ordered frequency compared to baseline

Table 22 Appendix: Total Metric and Ideal Metric Scores and Changes at 6 months, Delayed vs Intervention in Combined GLB Cohort RCT Analysis Sample

	Delayed (n=162)			Intervention (n=231)			Between Arm p-value
	Baseline Mean (SD) Median (IQR)	**6 months** Mean (SD) Median (IQR)	**6 M Change** Mean (SD) Median (IQR)	**Baseline** Mean (SD) Median (IQR)	**6 months** Mean (SD) Median (IQR)	**6 M Change** Mean (SD) Median (IQR)	
Total Metric Score	5.47 (1.33) 5 (5-6)	5.99 (1.33) 6 (5-7)	0.52 (1.21) 0 (0 - +1)**	5.71 (1.43) 6 (5-7)	6.48 (1.42) 7 (5-7)	0.77 (1.23) 1.0 (0-2)**	0.14
Ideal Metric Score	1.77 (0.93) 2 (1-2)	2.10 (0.92) 2 (2-3)	0.33 (0.86) 0 (0 - +1)**	1.86 (0.95) 2 (1-2)	2.35 (0.98) 2 (2-3)	0.49 (0.96) 0 (0 - +1)**	0.07

Within arm p-value determined using signed rank test; between arm p-value determined using Wilcoxon two-sample test; ** within arm p-value <0.01

Appendix A.2 EDC Medication Use Data

Table 23 Appendix: The proportion of participants using blood pressure and lipid medication of those with available data at each biennial follow-up

Year of follow-up	Proportion using lipid medication	Proportion using blood pressure medication
Baseline	0.7%	13.5%
1990-1992	2.8%	18.0%
1992-1994	3.8%	21.0%
1994-1996	4.1%	22.1%
1996-1998	7.0%	26.2%
2000-2002	17.3%	27.6%
2002-2004	25.3%	28.4%
2004-2006	48.8%	26.9%
2006-2008	47.8%	34.3%
2008-2010	54.6%	34.3%
2010-2012	52.1%	30.5%
2012-2014	50.9%	33.8%

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