Prediabetes: Clinical Management and Nutrient Patterns Related to Diabetes Development

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Abstract

Background: Greater than one third of US adults have prediabetes, rising to nearly half of adults over the age of 65. Increased cardiometabolic health risks exist already in prediabetes and incur costs greater than $40 million per year. Less than 12% of individuals with prediabetes are aware of having increased risk of type 2 diabetes and infrequently receive resources to prevent the progression. Limited data exist regarding contributors to clinical decision-making when prediabetes develops. Diet is a modifiable risk factor influencing the risk of diabetes. Assessing patterns of intake enables the study of potential synergistic effects of habitual dietary consumption rather than studying individual nutrients in isolation. Previous methods to investigate the relationship between diet and diabetes risk are limited to deriving patterns that only describe intake among the group or outcomes related to diabetes, but not both. Little is known about nutrient intake of individuals with prediabetes that influence risk of diabetes development.

Methods: Two studies were conducted to investigate the research questions of this dissertation. In the first study, we performed a retrospective analysis of 3,675 adults with newly developed prediabetes (indicated by American Diabetes Association diagnostic criteria: hemoglobin A1c (HbA1c) 5.7-6.4%, fasting blood glucose 100-125 mg/dL, or 2-hour glucose following an oral glucose tolerance test 140-199 mg/dL) in two primary care clinics at the University of Kansas Health System. Clinical data entered into the EPIC electronic health record was captured using the i2b2-based clinical data repository tool, HERON. We assessed rates and predictors of prediabetes diagnosis, referrals to nutrition, weight management, or psychology, and prescriptions for

metformin or a weight loss medication that occurred within six-months of meeting prediabetes criteria. In the second study, we performed a tertiary analysis that included 1,674 participants enrolled in the Vitamin D and Type 2 Diabetes (D2d) study. Dietary intake was measured through food frequency questionnaire at baseline. Fasting glucose and fasting insulin were measured at baseline and used to calculate the homeostatic model assessment of insulin resistance (HOMA2-IR). We explored odds of one-year DM development according to low, medium, and high adherence to dietary patterns of nutrient intake using principal covariates regression (PCovR).

Results: In the first study, 40% of patients who developed prediabetes received documentation of a prediabetes diagnosis. Nutrition referrals were ordered in 6.6%, metformin prescriptions were made in 4.4%, psychology referrals were ordered in 2.4%, weight management referrals were ordered in 1.7%, and weight loss medications were prescribed in 1.5%. Lower age, female, and higher HbA1c values were frequent predicting variables of documentation for a six-month diagnosis, referral, or prescription. Receiving a clinical diagnosis increased the odds of receiving a referral to weight management and prescriptions for metformin or weight loss medications. In the second study, after accounting for the covariates, age, BMI, sex, education, smoking status, physical activity, race, and treatment group, we found high adherence to a nutrient pattern including intake of animal protein, cholesterol, and arachidonic acid to double the odds of DM development compared to medium adherence (OR 2.02, 95% CI=1.34, 3.04, p=<0.01). Additionally, high intake of total sugars associated with 57% higher odds of DM development compared to moderate intake (OR=1.57, 95% CI=1.02, 2.41, p=0.04).

Conclusion: In the clinical setting, patients with prediabetes are commonly not identified and, when identified, rarely referred to resources that help prevent the progression to DM. A nutrient intake pattern of high animal proteins, cholesterol, and arachidonic acid and a pattern of high total sugars was associated with increased odds of progression from prediabetes to DM.

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Chapter 1: Review of Literature

Introduction

Prediabetes is a stage in the continuum of metabolic dysfunction between normal glucose metabolism and the development of type 2 diabetes (DM) with its numerous downstream health complications (1). Prediabetes is characterized by insulin resistance (IR) and/or β-cell dysfunction which can occur 13 years prior to the diagnosis of DM (2). These underlying metabolic imbalances result in blood glucose values that are higher than normal but not high enough to diagnose DM. The American Diabetes Association (ADA) defines prediabetes as impaired fasting glucose (IFG) (100 – 125 mg/dL) and/or impaired glucose tolerance (IGT) (140 – 199 mg/dL). Prediabetes can also be classified by a hemoglobin A1c (HbA1c) of 5.7% - 6.4% (3).

The World Health Organization's Global Report on Diabetes states that the prevalence of DM worldwide has nearly quadrupled since 1980 (4) and could increase to more than 550 million people by 2030 (5). Up to 70% of individuals with prediabetes are projected to develop DM at rates of 5 – 10% conversion per year (6). In some countries, the prevalence of prediabetes is greater than 40% (7). In the US, more than one third of the population – approximately 84 million Americans – is estimated to have prediabetes (8). Nearly half of US adults aged 65 and older have prediabetes. Prediabetes was estimated to cost over $43 million in 2017 (9). The costs associated with DM reached $327 billion in the same year (10). Despite the widespread recognition of prediabetes in the US and worldwide, less than 12% of individuals with prediabetes are made aware by a health care provider (HCP) (8).

Risk Factors

Risk factors of prediabetes include having a first degree relative with DM, high-risk race/ethnicity (African American, Latino, Native American, Asian American, and Pacific Islander), cardiovascular disease (CVD), hypertension (HTN), low HDL cholesterol and/or high triglycerides, polycystic ovary syndrome (PCOS), physical inactivity, and clinical conditions associated with IR such as obesity and acanthosis nigricans (3). Women with a history of gestational diabetes (GDM) are also at increased risk for later development of DM (3).

Higher rates of depression and changes in brain structure have been shown in prediabetes. Middle and older-age adults with prediabetes and depression show increased risk of DM compared to those with prediabetes or depressive symptoms alone (11, 12). Depressive symptoms in prediabetes are more strongly associated with indices of obesity and are suggested to be potential barriers to weight management these individuals (13). Changes in brain structure have also been found in prediabetes compared to those with normal blood sugars. In middle age adults in the Maastricht Study, lunar infarcts, larger white matter hyperintensities, and smaller white matter volume were shown in prediabetes with further declines in DM (14). These authors suggest that early intervention in prediabetes may be an important strategy in reducing the risk of brain disease. The relationship between mental health and prediabetes is suggested to be reciprocal in that depressive symptoms may be risk factors for increased A1c, and in turn may be a risk factor for higher depressive symptoms (15). While many studies suggest depressive symptoms to be a risk factor involved in the progression of prediabetes to DM, the reverse has also been suggested as the clinical

identification of prediabetes and DM was shown to be associated with greater odds of depression compared to those whose prediabetes and DM were unrecognized (16).

Metabolic Imbalances

Insulin Resistance & β-Cell Dysfunction

Multiple sources of metabolic dysregulation have been identified in the development and progression of prediabetes. The etiology of prediabetes is multifactorial, with features acting in synergism. While the hallmark characteristics of prediabetes include IR and/or β-cell dysfunction (17), the progression in individuals is variable and depends upon genetics and environment. There is debate regarding the contribution of IR and β-cell dysfunction, though both clearly play important roles and already exist by the time glucose is abnormally elevated (18, 19). The British Whitehall II Study showed that both IR and β-cell dysfunction can be present many years prior to the development of DM (2). In this prospective cohort study of 6,538 healthy men and women, both fasting and post-load glucose increased linearly from baseline as many as 13 years before diagnosis of DM, with steeper increases in the last three to six years. Similarly, insulin sensitivity decreased gradually in all individuals but showed a steeper decline five years before diagnosis. In the last three to four years before conversion to DM, β-cell function increased in compensation for worsening IR followed by a sharp decrease. These findings agree with other reports that show rapid increases in fasting glucose in the years immediately preceding DM diagnosis (20-22). Similar trends in post-load glucose have been shown in Pima Indians (23).

5-Stage Model of Diabetes Progression

A five-stage model of DM progression has been proposed which originates with alterations in β-cell mass, phenotype, and function (24). *Stage 1* is a long period of IR matched with increased, compensatory insulin secretion and β-cell mass to maintain normoglycemia. In this stage, phenotype is unchanged and blood glucose remains within normal range. Stage 1 corresponds to the observable yet unnoticed period of subclinical elevations in fasting and post-load glucose (2). In *stage 2*, glucose levels begin to rise (FPG 89 – 130 mg/dL) as β-cell mass decreases with progressing IR. As fasting plasma glucose rises above 100 mg/dL, the threshold for prediabetes, changes in β-cell function are observed in acute glucose-stimulated insulin secretion, also known as first phase insulin secretion. Preclinical data suggest changes in β-cell phenotype occur in this stage with changes in gene and protein expression such as upregulation of glucose-6-phosphatase, fructose-1,6-bisphosphatase, and lactate dehydrogenase (25). *Stage 3* corresponds to the three to six-year period prior to DM diagnosis (2, 20, 21) and a rapid rise in glucose. In *stage 4,* β-cell mass is significantly reduced (≥40% compared to nonDM (26)), although insulin production is adequate to prevent diabetic ketoacidosis (DKA). In *stage 5*, there is severe loss of β-cells and risk of DKA (24). While these stages may vary in length for each individual, the development of DM may last longer than a decade.

Increased Lipolysis

Increased lipolysis is part of the pathophysiology of prediabetes (17, 27), leading to decreased insulin action (28). Both fasting and post prandial free fatty acids (FFA)

are higher among individuals with IFG (29, 30); and the increase is nearly three-fold in DM (31). Mensink and colleagues suggest that those with prediabetes and DM have matching defects in fatty acid utilization evidenced by lower rates of plasma FFA disappearance ($p<0.05$) and oxidation at rest ($p<0.01$) compared to controls (32).

Impaired Incretin Effect

Incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by L- and K-cells, respectively, located in the small intestine. They are released in response to food and are hypothesized to account for up to 70% of the postprandial secretion of insulin (known as the incretin effect) (33). The effect of these incretins is significantly lacking or deficient in those with DM, impairing first phase insulin secretion (33, 34). Decreases in incretin effects have been observed in women with prediabetes compared to controls ($p<0.01$) (35, 36) and decreases are negatively associated with HbA1c (37). Among participants in the Danish ADDITION-PRO study (n=1,462), men and women with prediabetes or DM showed 16-21% lower postprandial GLP-1 concentrations compared to those with normal glucose tolerance and the effect was independent of age and BMI ($p=0.041$) (38). Those with both IGT and IFG show greater impairments of incretin action compared to those with IGT or IFG alone ($p<0.005$) and may have weakened responses similar to those with DM (39).

Hepatic Glucose Overproduction

The liver is responsible for maintaining glucose homeostasis in the fasted state and suppresses glucose production in response to insulin production following a meal. In prediabetes, suppression of hepatic glucose is decreased resulting in excessive glucose production (40). Alatrach and colleagues showed that basal rates of hepatic glucose production were similar in IFG and NGT, however, suppression following a 75-gram oral glucose tolerance test (OGTT) was significantly weakened in IFG compared to normal glucose tolerance (NGT) ($p<0.05$) (41). Similar findings of reduced suppression of hepatic glucose production have been demonstrated in individuals with obesity and either IFG or normal fasting glucose (42). In individuals with IGT or IFG alone, both basal and post-OGTT glucagon levels are higher compared to NGT ($p\leq0.001$), suggesting an increased signal for hepatic glucose production. Similarly, in a study using a hyperinsulinemic-euglycemic clamp, increased gluconeogenesis resulted in higher fasting glucose production in IFG compared to normal fasting glucose ($p<0.0001$) while insulin action and postprandial glucose concentrations were similar between the two groups (43). In those with IFG and IGT, fasting glucose production was elevated ($p=0.0002$) while insulin action was weakened ($p=0.005$).

Visceral Adiposity

Body fat distribution is related to insulin sensitivity and risk of DM. Visceral adiposity index and waist circumference are independent risk factors for prediabetes (44, 45) and DM (45, 46) and are increased compared to individuals without prediabetes or DM (47, 48). In a multicenter, international cross-sectional study that included 2,515

participants with NGT, prediabetes, and newly diagnosed DM, visceral adiposity measured by computed tomography (CT) was associated with IFG, IGT, and DM (49). Visceral adiposity was also associated with liver fat which increased across the progression of IFG to DM. Visceral adiposity is positively associated with cardiovascular risk factors (higher triglycerides and total cholesterol, lower HDL) independent of subcutaneous adiposity and overall obesity in individuals with NGT, prediabetes, and DM (50). Inflammatory cytokines and FFAs produced by excess adipose tissue are released into the blood stream and contribute further to IR and metabolic stress (51).

Inflammation

Increased inflammation and oxidative stress are observed in individuals with prediabetes compared to those with normoglycemia (52-62). Cytokines in the interleukin family including IL-1β, IL-13, IL-18, IL-6, IL-4, IL-10, and IL-1RA are associated with prediabetes (52, 53, 56, 57, 59, 62) as are members of the tumor necrosis factor (TNF) family including osteoprotegerin and RANKL (54). E-selectin in endothelial cells is elevated in the progression from normoglycemia to DM (57, 58). Higher arterial stiffness in prediabetes (58) suggests endothelial inflammation and dysfunction prior to established DM and predict future cardiovascular events. C-reactive protein (CRP), a hepatic acute phase protein and a common marker of systemic inflammation, is elevated in prediabetes (53, 56, 60, 61, 63-65) and may be elevated further by poor vitamin D status (63) and postprandial hyperglycemia (66). Oxidative damage, a trigger of inflammation, is increased in prediabetes (52, 55, 67). Elevated inflammation and oxidative stress in prediabetes are associated with IR (68-70), and contribute to the

interconnected nature of metabolic dysregulation that occurs even before development of DM.

Complications

Prediabetes is identified as either IGT, IFG, or both; however, the presence of both IGT and IFG represents a greater risk of developing DM and other chronic health conditions (71). The overlapping of hypertension, visceral adiposity, and dyslipidemia with the key characteristics of prediabetes and are classified as Metabolic Syndrome (MetS), a high-risk state for developing DM and CVD (72). Identifying and treating patients with prediabetes not only aims to prevent progression to DM and its long-term complications but also the health risks associated with prediabetes itself. The long-term complications of prediabetes include increased risk of DM as well as microvascular and macrovascular complications.

As IR and β-cell dysfunction can be present as much as 13 years prior to the diagnosis of DM (2), higher rates of microvascular and macrovascular complications, typically only considered in established DM, are also found in prediabetes. Many studies describe microvascular and macrovascular complications in prediabetes (17, 27, 71, 73, 74). Retinopathy (75-77), neuropathy (78, 79), and nephropathy (80, 81) have been identified in prediabetes. Assessment of microvascular function of the retina and skin in the Maastricht Study cohort (82) showed significantly lower function of both measures in prediabetes compared to normal glucose metabolism ($p=0.001$). Those with prediabetes have higher odds of developing chronic kidney disease (CKD) (83), and early stages of CKD found in prediabetes is associated with a 67% higher risk of myocardial infarction,

nonfatal stroke, and CV death (80). Prediabetes is associated with subclinical myocardial damage (84) and a three-fold increase in unrecognized myocardial infarction (MI) (85).

People with prediabetes are at increased risk of macrovascular complications such as endothelial dysfunction (58, 67, 86), stroke (87-89), and MI (85, 90-92). Positive associations are found between HbA1c and both CVD and all-cause mortality, with each 1% increase in HbA1c associated with 24% and 28% increases in risk of all-cause death in men and women, respectively (93). It has been suggested that hyperglycemia paired with IR expedites the atherosclerotic changes and promotion of macrovascular complications (94). Oxidative stress is elevated in prediabetes compared to controls in multiple studies (52, 55, 67) and are similar to the oxidative stress found in DM and CVD (95). Ischemic stroke and CVD events have been associated with 2-hour glucose (96) and more highly correlated with CVD risk than IFG (94). Coronary flow reserve, a prognostic marker of CAD, is also impaired in prediabetes (97).

Treatment / Interventions

Diabetes Prevention Program

It is well known that prevention of DM is possible through modification of reversible risk factors. Multiple studies demonstrate the benefit of lifestyle intervention to reduce the risk of developing DM in both the short and long term. In the Diabetes Prevention Program (DPP) study (98), 3,234 participants with prediabetes (IFG + IGT) were randomized to a structured lifestyle-modification program (six months of curriculum-based sessions, additional six months maintenance), 850 mg metformin

twice daily, or placebo. The lifestyle-modification program targeted at least 7% weight loss and 150 minutes of physical activity (moderate intensity, i.e. brisk walk) per week. Weight loss through diet was recommended through a caloric deficit (500 – 1,000 less calories/day) via reduction of dietary fat intake. After three years, those in the lifestyle intervention group resulted in a 58% reduced incidence of DM while there was a 31% reduction in the metformin group compared to placebo (98). Lower DM incidence persisted in the 10-year DPP Outcomes Study (DPPOS) with a 34% reduction in the lifestyle group and 18% reduction in the metformin group compared to placebo (99). The 15-year follow up of the DPPOS found a sustained 27% reduction in the lifestyle group and 18% in the metformin group compared to placebo (100). Further, participants who did not develop DM showed 28% lower prevalence of microvascular complications from nephropathy, retinopathy, and neuropathy. A national effort was initiated by the CDC in 2010 to provide evidence-based, structured lifestyle change programs modeled after interventions used in the DPP study. Currently there are over 1,500 CDC-recognized sites across the US offering these programs to individuals with prediabetes. Other DM prevention studies in populations worldwide using lifestyle intervention with or without metformin have also shown significant risk reductions (up to 43% reduced risk after 20 years) (101, 102) (103-106) with beneficial effects lasting up to 30 years following the intervention (103). Risk of CV events were also reduced (103).

Medications

Currently there are no medications approved by the FDA for the prevention of DM, although several may be effective at reducing risk and/or risk factors in patients

with consideration of factors such as comorbidities, cost, and associated side effects (107). There is robust evidence that metformin is effective and safe long-term for those with prediabetes, particularly for individuals with BMI ≥35, less than 60 years of age, and women with a history of gestational diabetes (108). While it was not more effective than the lifestyle intervention in the DPP (98, 109), higher metformin adherence reduced risk of DM by 38.2% compared to placebo ($p<0.0003$). Effectiveness of metformin compared to placebo persisted for over 15 years resulting in an 18% reduction in incidence and cost savings (108). Other medications that have reduced or delayed conversion to DM include thiazolidinediones (110-115), GLP-1 receptor agonists (116), alpha-glucosidase inhibitors (117, 118), and a novel dual peroxisome proliferator-activated receptor alpha/gamma agonist (119).

Exercise

There is strong evidence that physical activity can improve of β-cell function (120-122) and promote DM prevention (123). Effectiveness in the DPP lifestyle intervention targeted at least 150 minutes of moderate-intensity physical activity per week (98). Exercise training improves both peripheral and hepatic insulin sensitivity (121), reduces the odds of MetS (124), and reduces levels of pancreatic fat (125) in those with prediabetes and is suggested to outperform medication (126). With exercise, glucose tolerance may improve in the absence of significant weight loss (127). Improved glycemic measures can be achieved by increasing total leisure-time physical activity (128) or increasing upper body activity while seated (129).

Screening / Management Gaps

The ADA recommends prediabetes screening for all adults age 45 and older and anyone with a BMI ≥25 kg/m^2 (≥23 kg/m^2 in Asian Americans) and at least one other risk factor for DM (107). A one-page risk-assessment tool has been created by the ADA to assist providers in decisions for further screening and early identification of DM risk. Diagnostic methods for screening include either FPG, 2-hour glucose following a 75-gram OGTT, or elevated HbA1c. If these measures are normal, re-screening at least every three years is suggested. If individuals meet the criteria for prediabetes, follow up testing should occur yearly.

Following the identification of prediabetes, evidence-based interventions are crucial to reduce risk of downstream health complications. The short- and long-term benefits from lifestyle and pharmaceutical interventions are well recognized in the prevention of DM and improvement of overall public health (130). However, there are gaps in delivery of this evidence into clinical practice (107). There are more than 84 million Americans, one third of the adult population, living with prediabetes; nearly half of adults over the age of 65 (8). However, almost 90% of these individuals are unaware they have prediabetes (8). Studies show that opportunities are often missed to screen individuals at risk for diabetes (131, 132) and even among those meeting prediabetes criteria based on lab values, very few have the diagnosis in their medical record (133, 134). The National Ambulatory Medical Care Survey found that while 33.6% of patients met criteria for prediabetes, the number who were given a prediabetes diagnosis was too low for a reliable population estimate (133). Similarly, data collected through electronic health records (EHR) found that in the six months following identification of

prediabetes, only 13% had the diagnosis in their EHR (134). These findings may be influenced by a loss of follow up (135), HCP attitude towards prediabetes (136) or a discrepancy between the HCP report and objective assessment of practices (137). Knowledge of ADA-defined parameters for diagnosing and treating prediabetes may also influence management. A survey of physician referral practices found that many physicians correctly identified the risk factors suggesting the need to screen for prediabetes and diabetes, however, 17% correctly identified the lab parameters for diagnosing prediabetes (138).

When patients are identified as having prediabetes, evidence-based interventions to reduce conversion to DM are noted infrequently by physician report and measurement in the EHR. In a survey of 155 primary care physicians (PCPs), 11% reported referral to a weight loss program as the initial treatment for prediabetes (138). Another study found that while weight loss and increased physical activity were recommended by 58% of PCPs, none recommended a DPP or metformin for patients with prediabetes (139). Further, in a survey of screening, testing, and referral practices among PCPs, 38% said they were aware of the CDC-recognized DPP (132). Data collected from EHRs and national medical surveys show similar underutilization of interventions. Lifestyle counseling and/or metformin were documented in less than a quarter of prediabetes patients in the National Ambulatory Medical Care Survey (133), while NHANES data found metformin prescription in less than 1% of patients with prediabetes (140). Similarly, in two EHR queries, less than one third of patients had lifestyle counseling documented in the office visit note (134, 141), while metformin was prescribed in less than 0.1% (134). Zimmerman et al. and Tseng et al. found higher

counseling rates among those with higher baseline BMI values (138, 141) while Hooks-Andersen et al. showed higher prevalence of referral to diabetes education among African American patients compared to Caucasian (142). Patient-related factors are recognized as barriers in treatment for prediabetes. Barriers reported by HCPs to utilize interventions for prediabetes include patient economic resources (136), motivation (136, 138, 143), ability to modify lifestyle (136, 138), lack of support services (138, 143), and limited time to educate the patients (136, 143).

Diet

Nutritional recommendations can require lengthy conversation and education. In addition to patient motivation and having time required to provide the education as noted above, understanding the most effective yet personalized evidence-based recommendations can be challenging. Observational studies show associations between risk of DM and multiple foods and nutrients. Foods associated with reductions in risk include whole grains, unsaturated fatty acids, polyphenols (144), coffee (145), nuts and nut butter (146), low-fat fermented dairy/yogurt (147, 148) olive oil (149, 150), and green leafy vegetables (151). Foods associated with increased risk of DM include refined grains (151), animal products and red or processed meat (152, 153) and sugar-sweetened beverages (144, 153, 154). There is inconclusive evidence regarding artificially sweetened beverage consumption as both positive (155-157) and lack of (154) associations have been observed between its consumption and DM or prediabetes risk. Diet soda was associated with 67% increased relative risk of DM independent of baseline and change in adiposity (158). Conversely, others have found

no association with prediabetes risk, claiming reverse causality that those consuming artificially sweetened beverages may have overweight BMIs and are already at increased risk of DM (154). In a systematic review and meta-analysis that found a positive association between artificially sweetened beverages and DM risk, authors caution about publication bias and residual confounding. However, these and other authors conclude that artificially sweetened beverages are improbable healthy alternatives to sugar-sweetened beverages (157, 159).

Quality of food is proposed to be more influential on health outcomes than quantity of food consumed (151). Schulze et al. showed that the glycemic index (GI) was significantly associated with increased DM risk while cereal fiber (lower GI) was associated with a decreased risk among women (160). Similarly, Alessa et al. found no association between total carbohydrate intake and DM risk, an increased association with starch intake, and a decreased risk associated with total, cereal, and fruit fiber (161). However, higher carbohydrate consumption and higher glycemic load were associated with increased DM risk in the Nurses' Health Study cohort (162).

An assessment of overall dietary intake, rather than single foods or nutrients, may provide greater understanding of the cumulative effects of diet on DM risk. While dietary indices such as the Healthy Eating Index (HEI), Alternative HEI (aHEI), and Dietary Approach to Stop Hypertension (DASH) have all shown observational evidence of reducing diabetes risk (107, 163), both observation and intervention studies support the effectiveness of the Mediterranean diet in DM risk reduction (164). Multiple studies show significant benefit in both reduction of DM and related cardiometabolic health measures in those following a Mediterranean diet pattern (165-169). Filippatos and

colleagues found that those having medium to high adherence to a Mediterranean diet had a lower 10-year incidence of DM compared to those with low adherence (166). Low adherence to the Mediterranean diet was found to be associated with higher homeostatic model assessment for insulin resistance (HOMA-IR) and hsCRP levels (170). Bioactive food components prevalent in the Mediterranean eating style such as polyphenols found in olive oil, nuts, and wine are inversely associated with IR and DM risk (165). Further, improved endothelial function was observed in individuals with prediabetes who followed a 1.5-year Mediterranean diet intervention (167). The Mediterranean diet may improve risk of DM through anti-inflammatory and antioxidative effects (171).

Diet as an Inflammatory Modulator

Diet is a modulator of chronic, low-grade, systemic inflammation (172), and inflammation is a major underlying factor in the development of DM. Dietary fatty acids are important modulators of the inflammatory response (173) and act synergistically to influence inflammatory status (174). While total fat intake has not been association with risk of DM (175-179), evidence regarding individual fatty acids remains inconclusive (177, 178). Mirmiran et al. assessed the associations of fatty acid quality and quantity among 2,139 Iranian participants in the Tehran Lipid and Glucose Study and found lower risk of DM was associated with dietary cholesterol, monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), and omega-3 (n-3) fatty acids (all $p \leq 0.04$) (180). Additionally, omega-6 (n-6):n-3, and total fat:n-3 ratios were positively associated with DM risk ($p=0.04$ and 0.05, respectively). Liu et al. found no association

between total saturated fatty acids (SFA) and DM, however, they found higher risk with soft and liquid fatty acids (178). Studies in women show reduced risk of DM from dietary PUFAs (175, 181) and olive oil (149), neutral effects from total fat and SFA (175), and increased risk from trans-fat (175), high intake of marine omega-3 (≥0.20 g/day) and more than 2 servings/day of fish (182).

Dietary Patterns

Health outcomes are related to long term, habitual food intake. Meal patterns involve consumption of numerous foods and nutrients multiple times per day, representing a complex variable influencing overall health. Foods and their nutrients interact synergistically rather than in isolation (183) and can be measured cumulatively through statistical analyses of dietary patterns. Dietary patterns are suggested to better represent overall diet and prediction for risk of chronic disease (184) than food components alone. Patterns can be assessed using *a priori* and *a posteriori* methods. *A priori* methods are based on previous evidence, such as assessing adherence to a specific pre-defined diet (183). For example, individuals with high adherence to patterns of intake including the aHEI (185, 186), Mediterranean Diet (166, 186-189), and DASH diet (186), are associated with a 19-57% lower DM risk compared to those with low adherence. *A posteriori* methods are exploratory and data-driven, describing patterns of intake representative of the population being studied (190) rather than conformance to a predefined diet. They are dimension-reduction techniques, taking multiple food variables or groups of foods and reducing them into a few primary patterns of foods explaining the greatest variability of intake. Commonly used methods in nutrition research are principle

components analysis (PCA) and reduced rank regression (RRR). PCA is purely data-driven and explains the maximum variance of dietary intake within the group, which is beneficial for capturing actual intake of the population being studied (191). RRR explains the maximum variance of an outcome, such as disease-related biomarkers. It derives patterns in an exploratory way but uses *a priori* knowledge (e.g. biomarker known to be linked to disease) which may help to understand connections between diet and disease (190).

Exploratory studies of dietary patterns and DM risk using PCA show intake of prudent (192) and plant-based (193-196) patterns are associated with lower risk of DM, while Western diet patterns are associated with higher DM risk (192, 197, 198). Foods prevalent in the prudent/healthy dietary patterns include vegetables and fruits (196, 199-202), fish (199, 201), poultry (201), legumes (196), and whole grains (196, 198, 201, 202), while Western/unhealthy patterns consist of red and processed meat (201, 202), fried foods (200-203), sugar-sweetened beverages (200, 201, 203), and refined grains (201). A recent systematic review and meta-analysis found “mainly unhealthy” patterns to be positively associated with DM (RR 1.44; 95% CI: 1.27,1.62) while “mainly healthy” patterns were inversely associated with DM (RR: 0.84; 95% CI: 0.77,0.91). Previous systematic reviews and meta-analyses similarly found highest adherence to prudent or “healthy dietary patterns” reduced DM risk by 14 – 21%, while highest adherence to Western or “unhealthy dietary patterns” increased risk by 30 – 44% (201, 202, 204). One study has investigated PCA-derived fatty acid intake patterns on DM risk. In the Tehran Lipid and Glucose Study cohort, three patterns of dietary fat intake were identified. While a pattern of high dietary cholesterol and SFAs approached a significant

negative association with DM (HR=0.56, 95% CI=0.29, 1.07), no significant associations were found among any of the three patterns (179). Further, no significant associations were shown between total, animal, or plant-based fats and DM risk.

Patterns of nutrient intake related to biomarkers have been studied in other disease states to learn potential mechanisms in which nutrients affect pathogenesis (205, 206). Exploratory analyses of nutrient patterns related to cardiometabolic health have been assessed in South African (207), Iranian (208), and Chinese (209) cohorts and show associations of a number of nutrients with fasting glucose and HbA1c (207) and risk of MetS (208, 209). Among women in the E3N-EPIC cohort, a positive association was found between DM and a pattern of intake including vitamins B2 and B5 (HR 1.34; 95% CI 1.16, 1.56) (210). In addition, an increased risk was found with a pattern characterized by high intakes of vitamin B12 and retinol, and a low intake of vitamin C (HR 1.30; 95% CI 1.15, 1.48). Inverse associations were found in patterns of magnesium and vitamin B3 (HR 0.75; 95% CI 0.66, 0.86) as well as manganese (HR 0.82; 95% CI 0.72, 0.94) (210). To date, no studies have investigated the relationship of nutrient patterns related to risk of diabetes in a US cohort.

Studies using RRR to investigate dietary patterns related to DM have used outcomes such as inflammatory markers, IR, and nutrients associated with DM. Multiple studies generated patterns related to inflammation that were associated with DM (211-214). Patterns associated with three to four-fold higher risk of DM include high intakes of sugar-sweetened beverages, refined grains, processed and red meats, low and high fat dairy, and fried foods, and low intakes of wine and coffee (211, 212). Patterns showing a protective effect on DM included high intakes of whole grains, fruit, colorful

vegetables, and low-fat dairy with low intakes of processed and red meat, sugar-sweetened beverages, artificially-sweetened beverages, beer, and white rice (213, 214). A similar pattern was related to IR and with additional influences from dressing (low intake) and snacks (high intake), both associated with increased DM risk (215). Heterogeneity between populations and response variables limit the generalizability of these findings as patterns of intake vary greatly across ethnicities and may generate different patterns based on the type and number of disease-related biomarkers used (216).

Methodologies in Dietary Pattern Analysis

Principal components analysis and RRR complement each other such that PCA is a behaviorally meaningful method to explain actual intake of the group being studied while RRR allows greater disease prediction based on dietary patterns associated with a disease-related outcome (217). Alone PCA is weaker in predicting disease risk compared to RRR, while RRR has limited ability to capture actual patterns of food intake (217). Principal covariates regression (PCovR) is a statistical analysis with incorporating strengths of both PCA and RRR (218). It's use in the statistical R package (R Foundation, Vienna, Austria) is described by Vervloet and colleagues (219). In linear regression analysis of a high number of predictor (e.g. dietary intake) variables (>10), PCovR reduces predictor variables to a small number of components (like PCA and RRR). Dependent (e.g. biomarker) variables are regressed on the component(s). A weighting parameter (α) is used to allow simultaneous and optimal prediction of the dependent variable(s) and explanation of the greatest variability of predictor variables

(219). The PCovR patterns that are generated show the ranges of high-positive to high-negative variable loadings (i.e. high-positive and negative loadings represent high intake of nutrients). Adherence to the PCovR-generated pattern can then be calculated for each individual based on the observed data. While many studies have used PCA and RRR to assess relationships between dietary patterns and risk of DM, none to date have used PCovR to maximize the strengths and minimize limitations of PCA and RRR using nutrients as predicting variables.

Gaps in Literature

There are gaps in clinical practice to intervene in patients with prediabetes. Barriers are recognized in primary care which may contribute to these gaps; however, it is not known if patient characteristics predict who will receive clinical recognition (e.g. documented diagnosis or intervention). Gaps also exist in understanding the mediating effects of nutrient patterns on diabetes risk. It is known that diet is a modifiable risk factor involved in the progression of prediabetes to DM. It is also known that dietary patterns are related to DM risk, however, commonly used methodologies have limited the ability to derive patterns related to both dietary intake and the outcome of interest. Studies to investigate the effect of nutrient patterns on DM risk could advance the knowledge of how diet drives DM development and specific nutrients that may play key roles. Further, by studying intervention practices among primary care clinics and patient-characteristics that support their use, strategies can be created to increase utilization and better prevent DM in those most at risk.

Justification

The prevalence of prediabetes in United States adults is nearly three times that of type 1 and type 2 diabetes combined (8). One out of every three adults has prediabetes, and the prevalence increases to one in every two individuals above the age of 65. Dietary intake is a significant determinant of DM development and interventions have proven to delay or prevent progression from prediabetes to diabetes. Multiple studies have investigated *a priori* (185, 188) and *a posteriori* (192, 195) dietary patterns and their relation to DM. Most studies derive patterns of food intake using methodologies that may limit either behavioral or biological relevance. Limited evidence is available describing patterns of nutrient intake and their relationship with DM development. Despite our awareness of the consequences and reversibility of prediabetes, very few individuals are aware they have prediabetes (8), and even fewer receive the appropriate interventions to treat it (141). In order to provide evidence-based treatment to individuals with prediabetes, we must first be able to identify and connect them with available resources. Exploring and translating interventions from research to the real-world clinical environment is imperative in advancing the field of DM prevention.

Statement of Problem

We know little about how nutrient intake patterns that predict DM development. Moreover, barriers exist in informing patients with prediabetes of their health risk and evidence-based interventions as well as connecting patients with prediabetes to effective resources. Knowledge of nutrient factors involved in the progression to DM must be gained to better understand the role of diet in DM development and to

effectively utilize dietary modifications as interventions to prevent it. In understanding the importance of and benefits to intervening early in the progression of prediabetes, is it critical to bridge the gap between the evidence of lifechanging interventions and the patients in need of them most.

Statement of Purpose

The purpose of this study is to identify nutrient patterns that predict DM development and explain maximal variation of intake. Additionally, this study aims to assess the identification and clinical recognition rates of patients with prediabetes and explore factors that may influence the probability of receiving a clinical response. The results of this study will advance knowledge of nutritional factors which influence progression from prediabetes to DM and inform future dietary interventions to prevent development of DM. Further, results of this study will provide guidance for strategies of quality improvement in the identification and intervention for patients with prediabetes managed in primary care clinics.

Aims of Study

1. Assess prediabetes clinical recognition rates among primary care clinics at The University of Kansas Health System and significant patient characteristics that influence the presence of clinical recognition. Incident prediabetes cases during 2016-2019 will be identified through the Epic electronic health record using the i2b2-based clinical repository tool, HERON. Rates of 6-month prediabetes diagnosis, referral to a dietitian, referral to weight management, referral to psychology, metformin prescription, or weight loss medication prescription will be assessed. Odds ratios will be

assessed to determine likelihood of age, sex, race, weight category, HbA1c, diagnosis, insurance payer, and presence of comorbidities: hypertension, hyperlipidemia, or depression to influence clinical response rates. I hypothesize that clinical recognition rates will be higher in those with higher HbA1c and BMI values.

2. Derive nutrient patterns related to insulin resistance and investigate their relationships between the nutrient pattern and odds of DM development at one year. Nutrient patterns related to baseline insulin resistance will be derived by principal covariates regression analysis (PCovR) from baseline food frequency questionnaires completed by participants with prediabetes enrolled in the Vitamin D and Type 2 Diabetes (D2d) study. The derived nutrient patterns will be assessed for their relationship with risk of DM development at one year. I hypothesize that a nutrient pattern predicting DM development will have higher loadings of trans fatty acids, animal proteins, and total sugars with lower loadings of MUFA and n-3 fatty acids. High adherence to the nutrient pattern is associated with increased risk of conversion to DM at one year.

Chapter 2: Methods

Overview

This research is composed of two studies, each with a different study design. Both studies will contribute to the knowledge of how nutritional factors may influence the progression from prediabetes to DM and the avenues in which awareness and lifestyle resources are offered to individuals with prediabetes in the primary care setting of a large academic medical center.

Study 1 (Aim 1)

General Study Design

This retrospective review assesses incident cases of prediabetes from June 2016 to June 2019 and subsequent clinical recognition rates measured by prediabetes diagnosis, referral to a dietitian, referral to weight management clinic, referral to psychology, prescription for metformin, or prescription for a weight loss medication (FDA-approved medications included: Orlistat, Lorcaserin, Phentermine-topiramate, Naltrexone-bupropion, Liraglutide). The review includes two primary care clinics at the University of Kansas Health System. Age, sex, race, BMI category, HbA1c value, prediabetes diagnosis, insurance payer, and comorbidity (diagnosis of or prescription for hypertension, hyperlipidemia, or depression) were considered as predicting variables influencing clinical responses. Data from Health System's Epic EHR was collected using the University of Kansas Medical Center (KUMC) i2b2-based clinical data repository, HERON and organized using the software, SQLite Studio.

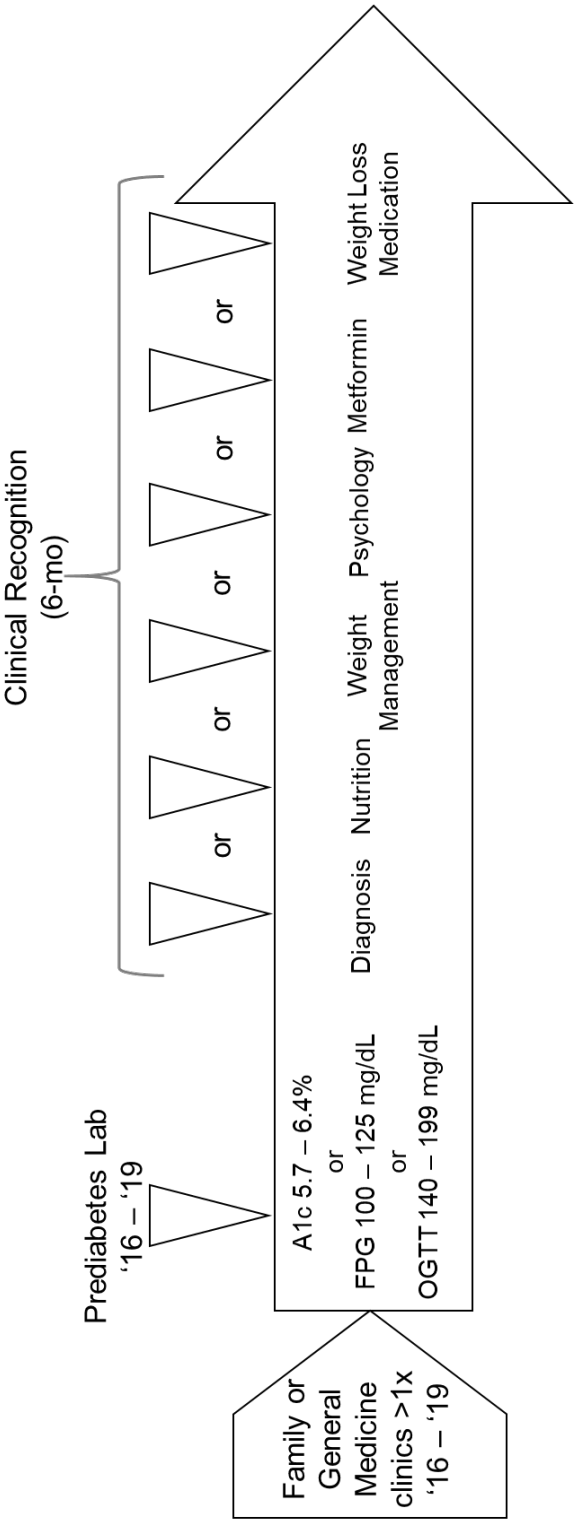

Figure 1: Study Timeline

Eligibility

Eligible patients were adult (> 18 y/o) male and female patients with established care (visited clinic > 1x) in either the Family Medicine or General Medicine clinics at the University of Kansas Health System seen between June 1 2016 and June 1 2019 and who met at least one laboratory criteria for prediabetes for the first time during this two-year period. Qualifying laboratory criteria included: FPG 100-125 mg/dL, 2-hour glucose 140-199 mg/dL following OGTT, or hemoglobin HbA1c 5.7-6.4%.

Patients were excluded if they were < 18 y/o, had previous (prior to June 1 2016) diagnostic codes indicative of prediabetes or DM (prediabetes: ICD-9 790.2, ICD-10 R73.03; DM: ICD-9 790.2, ICD-10 R73.03), record of glucose regulation agents (prior to June 1 2016), record of prediabetes diagnostic laboratories (FPG, 2-hour glucose, HbA1c, prior to June 1 2015), or record of pregnancy/gestational DM (ICD-9: 648, ICD-10: O24) during the three-year investigational window.

HERON

HERON (Healthcare Enterprise Repository for Ontological Narration) is the University of Kansas Medical Center's (KUMC) i2b2-based clinical data repository tool for de-identified searches of multiple healthcare-related sources (220, 221). Part of the 12-site Greater Plains Collaborative network, KUMC's HERON was developed through support from the NIH Clinical and Translational Science Award (CTSA) (#UL1TR002366). Three criteria must be met to access the HERON data repository: 1) faculty member status or sponsorship, 2) current CITI training, and 3) a signed System Use Agreement.

A hierarchical structure is used to navigate through available HERON data. Queries built from variables including, but not limited to, Demographics (e.g. age, gender, race/ethnicity, marital status), Diagnoses (ICD-9, ICD-10 codes), Laboratory Tests (hemoglobin HbA1c), Medications (inpatient, outpatient), Orders (referral to dietitian), and Visit Details (BMI). Queries can be used to identify a unique and specific cohort of patients meeting certain inclusion and exclusion criteria. A “drag and drop” feature allows categories of variables to be used in building a query. Logical conditions “OR” and “AND” are used to narrow or broaden searches. Conditional parameters are used to specify variables such as date ranges, laboratory values of a specified number or range, a clinical order placed during the same financial encounter (e.g. events which happen at the same time), or number of encounters occurring in a clinical department. Once the query is built, HERON returns the number of patients meeting the defined search criteria.

Once the query is finalized and requested, the data are uploaded in a REDCap project for access. Raw data are available and organized into csv files including patient (age, sex, race, etc.), data (variable, units, start date, etc.), code-info (code label, code path, etc.), and variable (name, counts, etc.) information. These raw data are then uploaded to a software to organize and prepare for analysis.

Building blocks of the query to be used for this project are shown below. Group 1 establishes the primary care clinical departments in which patients will be searched. Group 2 sets exclusion criteria for the cohort. Group 3 specifies laboratory criteria used to identify only patients with incident prediabetes during the defined timeline. Group 4 is the “shopping cart” which gathers all variables of interest for the cohort. Total patient

number is not limited by this selection due to inclusion of the gender variable which is linked with each patient. By including gender, patients lacking in one or more variables (e.g. patients who without outpatient metformin orders) are guaranteed to be included. Group 5 excludes patients who are not adults at the time of their visit(s) to the primary care clinics.

Table 1: Building the HERON Query

Group 1 *Occurs >1x* *One or more of these*	**Group 2** *Exclude* *None of these*	**Group 3** *One or more of these*	**Group 4** *One or more of these* *"Shopping Cart"*	**Group 5** *Occurs in Same Encounter* *Exclude* *None of these*
• Family Medicine (6/1/16-6/1/19) • General Internal Medicine (6/1/16-6/1/19)	• Codes o ICD-9: 250, 648, 790.2; o ICD-10: E08-E13, O24, R73 • Blood glucose regulation agents (<5/31/16) • Glucose, 2hr (140-199 mg/dL <5/31/16) • Glucose, fasting (100-125 mg/dL <5/31/16) • Hemoglobin HbA1c (5.7-6.4% <5/31/16)	• Glucose, 2hr (140-199 mg/dL 6/1/16-6/1/19) • Glucose, fasting (100-125 mg/dL 6/1/16-6/1/19) • Hemoglobin HbA1c (5.7-6.4% 6/1/16-6/1/19)	• Metformin and Metformin Extended Release Oral Tablet (outpatient medication orders) • Ambulatory referral to dietitian, medical nutrition therapy, weight management program, KU weight management program, psychology • orlistat Oral Capsule • Bupropion / Naltrexone Extended Release Oral Tablet • CENTRALLY-ACTING APPETITE SUPPRESSANTS • liraglutide Pen Injector • Codes: 272 (ICD-9), E78 (ICD-10) • Codes 311 (ICD-9), F32 (ICD-10) • Codes: 401 (ICD-9), I10 (ICD-10) • Codes: 790.2 (ICD-9), R73 (ICD-10) • Antidepressant, antihypertensive, and antilipemic medications • Payer • Gender • Body mass index • Glucose, 2hr • Glucose, fasting • Hemoglobin A1c	• 0-17 years old at visit

SQLite Studio

SQLite Studio (Structured Query Language) was used to clean and organize databases using standard language commands. Raw data from the HERON were uploaded to SQLite Studio and organized to enable statistical analysis. Cleaned data were exported to a csv file and sent to the SAS ® statistical program.

Ethics

No patient-identifiers were used in this study and the study is considered non-human subjects research. The de-identified HERON queries remove 18 patient-identifiers in compliance with HIPAA Safe Harbor De-identification requirements. Further measures of de-identification included date-shifting up to 365 days prior to the actual date of data capture. IRB approval was not required for this limited dataset request.

Analysis of Data

Aim 1

Statistical analyses were performed in SAS ® 9.4. Stepwise logistic regression was performed to create models for each outcome variable (diagnosis, nutrition/weight management/psychology referral, metformin/weight loss medication prescription) using the predictor variables (age, sex, race, weight category, HbA1c, diagnosis, insurance payer, and presence of comorbidities). The significance level to enter was set at p-value < 0.15 and the significance level to stay was set at p-value < 0.05.

Study 2 (Aim 2)

General Study Design

This was a tertiary analysis of the Vitamin D and Type 2 Diabetes (D2d) study, a multicenter, randomized, double-blinded, placebo controlled, parallel group, primary prevention clinical trial (NCT01942694, U01DK098245) (222). Participants with prediabetes were randomized to a) an oral daily vitamin D_3 (4,000 IU soft-gel) or b) placebo and followed for a median of two and half years for incident DM. Recruitment began in October 2013, end of study visits were completed in Fall 2018. Analysis of the primary study outcomes began in early 2019 and the results were presented at the annual American Diabetes Association (ADA) Scientific Sessions meeting in June 2019 (223).

Eligibility and Recruitment

Sample and inclusion/exclusion criteria have been described in detail (222). The D2d cohort was appropriate for this research due to large sample size and as eligibility based on meeting at least two ADA-defined criteria for prediabetes: fasting plasma glucose (FPG) 100-125 mg/dL, 2-h postload glucose after 75-g glucose load (OGTT) 140-199 mg/dL, hemoglobin HbA1c (HbA1c) 5.7-6.4%. Participants were recruited from 22 US collaborating sites to ensure diversity in geographic location (varying latitudes producing low to high ultraviolet B exposure) and race. Targeted enrollment aimed for 100-150 participants per site, with 2,423 total participants enrolled and 99% retained for duration of the trial.

Ethics

After final study protocol was approved by the D2d data and safety monitoring board (DSMB), steering committee, and select members of the D2d Research Group, each study site's local institutional review board (IRB) granted approval to begin recruitment.

Assessment of Dietary Intake

A validated multicultural self-administered semi-quantitative food frequency questionnaire (FFQ) (224) was collected at baseline, month 12, and month 36 in participants free of DM (if DM was diagnosed after baseline, subsequent FFQs were not collected). Data from the cohorts' baseline FFQs were used to assess the relationship between diet and one-year diabetes development.

The FFQ was adapted from the original National Cancer Institute (NCI)/Block FFQ (225) to include additional foods of ethnic minority groups prevalent in the general US population as well as expand portion size options and food preparation techniques (226). To complete the FFQ, participants answered 125 questions regarding their usual frequency of consumption of a list of food items over the past 12 months (e.g. with which frequency do you eat cantaloupe or honeydew melon: never, less than once per month, 1 time per month, 2-3 times per month, etc.) and estimated portion sizes (e.g. if you eat cantaloupe or honeydew melon, your portion is usually closest to: ½ wedge or ½ cup, 1 wedge or ¾ cup, 1 ½ wedge or 1 cup, etc.). Completed FFQ booklets were sent to the Dietary Assessment Center at Northeastern University (https://bouve.northeastern.edu/dac/), processed using an OpScan 6 Scanner optical

mar reader (OMR) from Pearson Assessments and linked to the Nutrition Data System for Research (NDSR) software program (http://www.ncc.umn.edu/products/) to analyze nutrient data. The NDSR software bases its food and nutrient composition on the USDA National Nutrient Database for Standard Reference, which expands and revises nutrient composition annually based on continued analysis of foods in the US food supply. The software converts to nutrient intake totals by a description of the food, a food code, and the nutrient composition per 100 grams of the food. To calculate the individual's intake per nutrient, the software converts the food amount reported into a multiple of 100 grams, multiplies by that nutrient's composition factor (per 100 grams), and sums across all foods for each nutrient for each individual (227).

Recommendations of Healthy Lifestyle

Standards of care provided to both arms included written information detailing the 2010 Standards of Medical Care in Diabetes (228) guidelines for DM prevention. These recommendations encourage at least a 5% weight loss and 150 minutes of physical activity per week. Letters were sent to participants primary care providers to further support healthy lifestyle changes. Additionally, participants were invited to join the D2d Support and Education Program biannually at study sites where specific topics in nutrition and physical activity were discussed.

Laboratory Collection/Analysis

Fasting glucose and fasting insulin (used for baseline HOMA2-IR calculation) were collected at baseline after an overnight fast of at least 8 hours. Laboratory

samples were collected and processed at each study site and sent to the D2d Central Laboratory for storage and analysis. The Homeostasis Model Assessment (HOMA) is one of the most commonly used clinical and epidemiological calculations for the assessment of IR (229). The HOMA2 Calculator by the University of Oxford (https://www.dtu.ox.ac.uk/homacalculator/) was used to calculate HOMA2-IR and includes measures of beta cell function (%B) and insulin sensitivity (%S).

Acquisition of Data for Tertiary Analysis

The proposal for this tertiary analysis was submitted to the D2d Publication & Presentation Proposal Subcommittee detailing the intended aims and analysis plan in January 2019. The proposal was reviewed by the committee, which voted to consider pending our responses to their suggestions. A revised proposal was submitted to the Publication & Presentation Proposal Subcommittee meeting in March 2019 and final approval occurred in May 2019 with data received in January 2020.

Deriving Nutrient Patterns

Nutrient patterns were derived using principal covariates regression (PCovR). Our aim was to derive nutrient patterns which correlate to DM and we used HOMA2-IR to derive the patterns. We checked for patterns using DM development as the dependent variable and these patterns were identical to patterns derived using HOMA2-IR. As a continuous variable, HOMA2-IR enabled easier interpretability compared to the binomial variable of DM development.

Total nutrient intake was reduced to patterns that explained variance in nutrient intake and baseline HOMA2-IR. Forty commonly consumed nutrients were chosen from the FFQ nutrient variables. Nutrient values were standardized into Z-scores and centered to a mean of 0 and scaled to an SD of 1 to be used for derivation of the nutrient patterns. The nutrient variables were included as the independent variables and baseline HOMA2-IR was used as the dependent variable. Pertinent nutrient patterns were automatically retained based on eigenvalues. Adherence to the nutrient pattern (e.g. score of nutrient consumption on derived nutrient pattern; level at which the diet is consumed according to the pattern) was calculated for each individual (higher absolute value scores/loadings indicate stronger adherence to the nutrient pattern). Adherence scores were divided into low, medium, and high adherence groups. The relationship between adherence to the nutrient pattern and risk of development of DM at one year was investigated.

Analysis of Data

Aim 2

To investigate whether different levels of adherence to the nutrient patterns were related to risk of conversion to DM, pattern adherence was divided into equally distributed tertiles of low, medium, and high adherence groups. As nutrient pattern adherence does not relate to specific quantities or portions of nutrient intake, adherence groups were used for improved interpretability. Binary logistic regression was applied to assign odds ratios (OR) and 95% confidence intervals for conversion to DM by nutrient pattern adherence group (the medium intake group was assigned OR=1.0). Analyses

were controlled for age, gender, race, BMI, smoking status, physical activity, and study treatment group (Vitamin D or placebo). To determine R square values for assessing variance in HOMA2-IR explained by each nutrient pattern, a simple linear regression was performed with the pattern adherence scores as the independent variable and HOMA2-IR scores as the dependent variable. ANOVA as a special case of ordinary least squares regression was performed to assess differences in demographics and nutrient intakes between pattern adherence tertiles. Simple linear regression was performed to assess the relationship between glycemic load and both pattern adherence and HOMA2-IR.

Chapter 3: Prediabetes Management in Primary Care

Abstract

Objective: To determine diagnosis rates, frequency of lifestyle and prescription interventions among patients with newly developed prediabetes and assess characteristics of patients most likely to be clinically identified or treated.

Methods: Data from the EpicCare EHR were analyzed using the University of Kansas Medical Center i2b2-based clinical data repository (HERON). Data were collected for 75,857 patients established in academically affiliated primary care clinics between 2016 and 2019. After excluding for previous diabetes/prediabetes diagnoses or use of glucose lowering agents, 49,485 patients remained to assess for incident prediabetes (ADA criteria). Stepwise logistic regression was used to assess patient variables predicting the clinical recognition of a prediabetes diagnosis, nutrition, weight management, or psychology referral, metformin, or weight loss medication prescriptions within six months of meeting prediabetes criteria.

Results: Prediabetes was observed for 3,675 patients. Forty percent of those received a charted prediabetes diagnosis, 6.6% referred to nutrition, 4.4% prescribed metformin, 2.4% referred to psychology, 1.7% referred to weight management, and 1.5% were prescribed a weight loss medication. Younger age, higher HbA1c, and being female were associated with higher probability of receiving a diagnosis or other form of prediabetes treatment. There were significant interactions between some races and ages.

Conclusion: Relatively few people with prediabetes are clinically noted and even fewer receive interventions that may reduce the conversion to DM. Differences in race, age, and sex suggest specific populations that may be overlooked for prediabetes

interventions. These low rates of recognition and treatment are likely to be similar among health care systems across the country. The low rates of recognizing, documenting, and intervening are opportunities to better utilize the EMR and reduce conversion to DM.

INTRODUCTION

Insulin resistance and progressive β-cell dysfunction are characteristics of prediabetes that can occur up to 13 years prior to the development of DM (2). Compared to the 34 million Americans with DM (90-95% type 2 vs 5-10% type 1), 88 million have prediabetes (230) and convert to DM at rates of 5-10% per year (6).

Microvascular and macrovascular complications most often associated with long term DM have been identified in prediabetes (17), with a 20-30% increased risk of CVD and all-cause mortality with increasing HbA1c in the prediabetes range (5.7 – 6.4%) (93). Higher rates of depression are also found in prediabetes compared to the general population (231) and the combination of prediabetes and depression is associated with increased risk of DM compared to either prediabetes or depression alone (11, 12).

The success of lifestyle interventions on diabetes prevention is evidenced by multiple diabetes prevention studies (100, 101, 103, 105, 106). The well-known National Diabetes Prevention Program (DPP) was initiated in 2010 following evidence of a 58% reduction of diabetes incidence in participants with prediabetes randomized to a structured lifestyle intervention (98). In addition, while no medications are FDA-approved for the prevention of diabetes, the ADA recommends the consideration of metformin for those with prediabetes (232) and is cost-saving for direct and indirect medical costs, especially in those with BMI values above 30 kg/m^2 (233).

Despite the widespread prevalence and known health risks of prediabetes, fewer than 16% of individuals with prediabetes are aware (230). Physician surveys and data collection through the EHR show infrequent screening for prediabetes and limited use of evidence-based interventions (131-135, 138, 139). These findings may be related to

contrasting prediabetes management beliefs (136), limited awareness of DPPs (132), and patient-related factors such as economic resources, motivation, and time (136, 138, 143). Studies suggest patient-related factors including BMI (138, 141) and race (142) influence the counseling and education referral rates observed in prediabetes management, respectively, though it is unknown if and how other factors may influence clinical decision-making.

The purpose of this study was to better understand clinical management strategies used for prediabetes in academically affiliated primary care clinics and to determine if the odds of receiving a diagnosis or intervention within six months of developing prediabetes is related to patient characteristics.

METHODS

Data Repository and Population

Electronic health record (EHR, Epic©) data were collected using the i2b2-based Healthcare Enterprise Repository for Ontological Narration clinical data repository (HERON). HERON is a tool of the Greater Plains Collaborative network developed through support from the NIH Clinical and Translational Science Award (#UL1TR002366) which enables deidentified searches of multiple healthcare-related sources. Raw data are generated by a query built from variables of interest to identify a cohort of patients meeting specified inclusion and exclusion criteria. The raw data were uploaded to a REDCap project as four csv files and exported to SQLite Studio (Structured Query Language) to organize into a single csv file of one row per patient for analysis. This cohort received care from two primary care clinics at The University of

Kansas Health System (TUKHS), a nationally ranked academic hospital serving greater than 222,000 patients annually across Kansas and the Kansas City metro area with over 1 million outpatient encounters.

This was a de-identified search with 18 patient-identifiers removed and date-shifting up to 365 days prior to the actual date of data capture. HIPAA Safe Harbor De-identification requirements were fulfilled and thus is considered non-human subjects research. IRB approval is not required for limited dataset views.

Measures

Data were collected between June 1 2016 and June 1 2019 in established (visited clinic >1x) patients of two primary care clinics at TUKHS (Figure 1). Inclusion criteria consisted of adults (>18 y/o) who met ADA-defined criteria for prediabetes (fasting plasma glucose (FPG) 100-125 mg/dL, 2-hour glucose tolerance 140-199 mg/dL, or HbA1c 5.7-6.4%) for the first time during the data collection window. Those <18 years old, with prior (before June 1 2016) diagnostic codes indicating prediabetes (ICD-9 790.2, ICD-10 R73.03) or DM (ICD-9 250, 648, ICD-10 E08-E13), previous record of glucose regulation agents, previous ADA prediabetes diagnostic laboratories (above), or current diagnostic codes for pregnancy or gestational diabetes (ICD-9: 648, ICD-10: O24) were excluded. Extreme BMI values (<15 or >80 kg/m^2) were also excluded. Documentation of a prediabetes diagnosis, nutrition/dietitian referral, weight management referral, psychology referral, metformin prescription, or FDA-approved weight loss medication prescription were collected in the six months following prediabetes development.

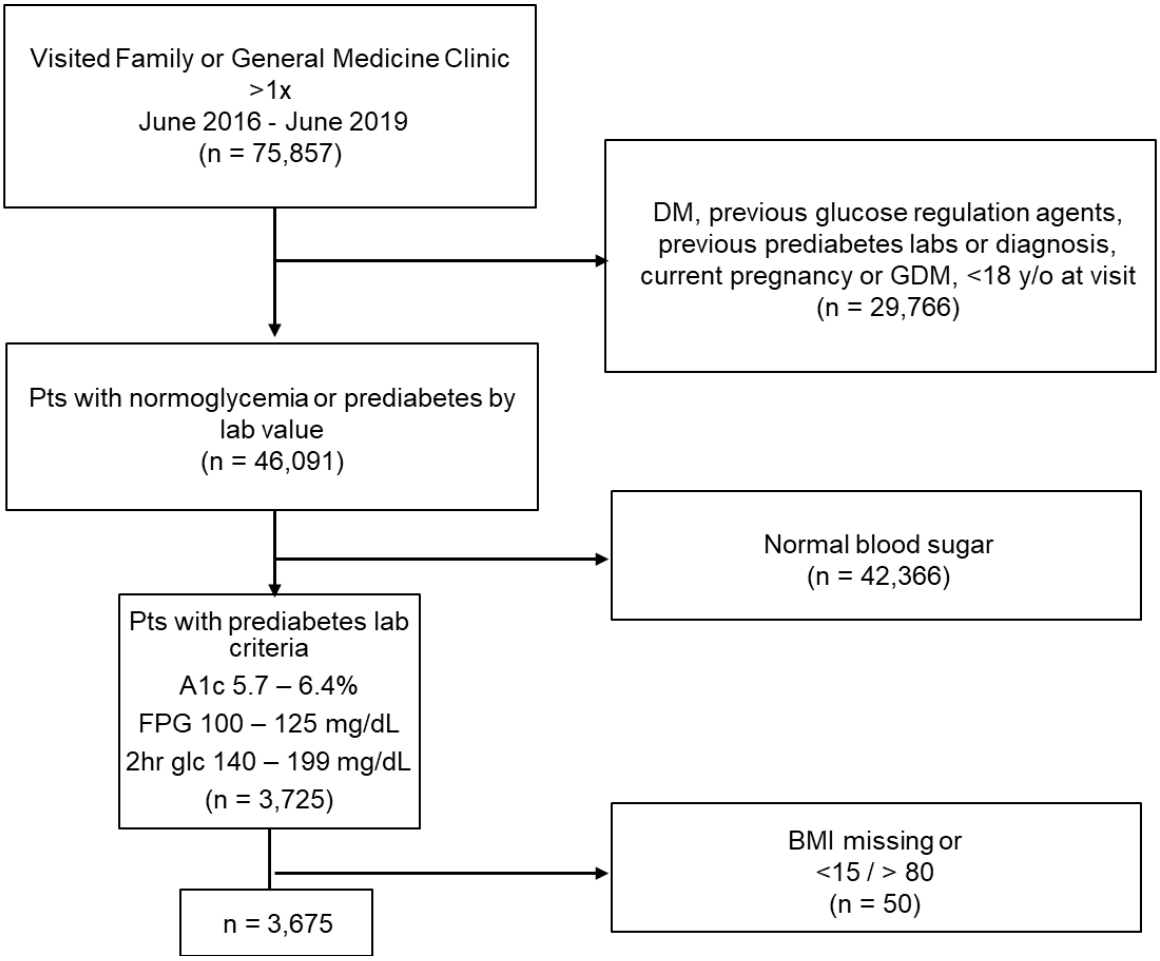

Figure 2: CONSORT Diagram

Statistical Analyses

Data were analyzed using SAS ® 9.4. Stepwise logistic regression was performed to determine significant patient characteristics (age, sex, race, BMI category, HbA1c, diagnosis, insurance payer, and presence of comorbidities: hypertension, hyperlipidemia, or depression) and two-way interactions for each outcome variable (diagnosis, nutrition/weight management/psychology referral, metformin/weight loss medication prescription). Models for each outcome variable were created with a

significance level to enter set at p-value <0.15 and significance level to stay set at p-value <0.05 including main effects and all two-way interactions.

RESULTS

Of 46,091 eligible patients without a history of diabetes, 3,675 (8%) met criteria for incident prediabetes during the three-year study window. Fifty-five percent were female, 58% with obese BMI values, 55% white, and 51% had at least one of the three assessed comorbidities. The average age was 55 ± 15 (mean ± standard deviation) years, average BMI was 32.6 ± 8.0, and average HbA1c was 5.9 ± 0.2%.

Fifty-six percent were privately insured and 55% were seen in Family Medicine versus 45% in General Internal Medicine (Table 2). Within 6 months of meeting prediabetes criteria, 40.4% received documentation of a prediabetes diagnosis, 6.6% had documentation of a nutrition referral, 4.4% were prescribed metformin, 2.4% were referred to psychology, 1.7% were referred to weight management, and 1.5% were prescribed a weight loss medication (Figure 4). Stepwise logistic regression was performed to determine significant main effects and two-way interactions which influenced the documented clinical recognition within 6 months following the date of meeting prediabetes criteria (Table 3).

Table 2: Patient Characteristics

Demographic / Anthropometric	Mean ± SD or Frequency
N Total	3,675
Sex, %	
Female	55
Male	45
Age	55 ± 15
BMI (kg/m^2)	32.6 ± 8.0
BMI Category, %	
Underweight	1
Normal	14
Overweight	27
Obese	58
A1c (%)	5.9 ± 0.2
Race, %	
Asian	4
Black	28
White	55
Other/declined	13
Comorbidities, %	
Hypertension	51
Hyperlipidemia	26
Depression	17
Insurance Provider, %	
Private	56
No Pay/Self Pay	16
Medicare	15
Medicaid	8
Other	5
Clinical Service Department, %	
Family Medicine	55
General Internal Medicine	45

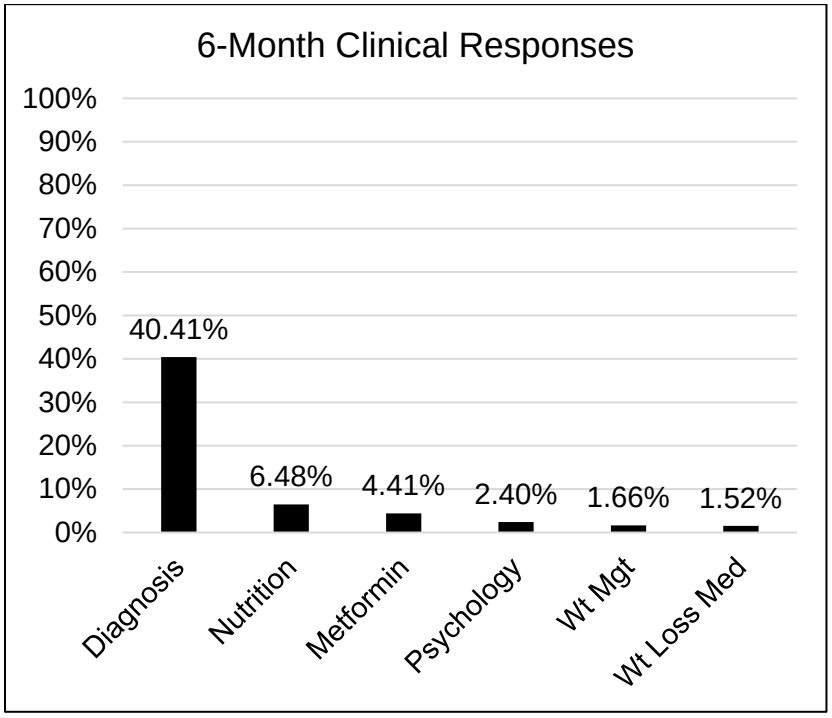

Figure 3: Frequency of Clinical Response Outcomes

Diagnosis

The initial model for diagnosis showed a significant interaction between sex and race, suggesting females in the Asian race category had lower odds of receiving a diagnosis of prediabetes compared to males in the white race category (not shown). Upon further investigation and adjustment for multiple comparisons of sex and race categories, the interaction term was not nonsignificant. Model fitness was similar when removing the interaction term and provided a more meaningful interpretation, thus it was removed for the final model. Variables significantly influencing the odds of receiving a prediabetes diagnosis were sex, race, HbA1c, age, and insurance provider. Females were 20% more likely to receive a prediabetes diagnosis compared to males (OR=1.20, 95% CI=1.04, 1.38, p=0.01). Those in the black race category showed 22% lower odds

compared to the white race (OR=0.78, 95% CI=0.66, 0.92, p=<0.01). The impact of HbA1c was influenced by age. As HbA1c and age increased, odds of receiving a diagnosis decreased. Generally, increasing HbA1c showed higher odds of a diagnosis, however this trend weakened as age increased (Table 3). Lastly, compared to privately insured patients, those with Medicaid or Other insurance categories were 30% and 53% less likely to receive a prediabetes diagnosis, respectively (OR=0.70, 95% CI=0.53, 0.92, p=0.01; OR=0.47, 95% CI=0.33, 0.68, p<0.01).

Nutrition Referral

A 0.5% increase in HbA1c was associated with 1.66 times greater odds of receiving a nutrition referral (95% CI=1.66, 2.37, p=<0.01). For every five-year increase in age, odds of receiving a nutrition referral decreased 12% (OR=0.88, 95% CI=0.83, 0.92, p<0.01). Black and other/declined races were 1.57 and 1.74 times more likely, respectively, to be referred to nutrition compared to the white race (95% CI=1.14, 2.17, p=0.01; 95% CI=1.16, 2.60, p=0.01). An interaction was observed between sex and diagnosis, suggesting the effect of sex was dependent on whether a diagnosis was present. Upon multiple comparisons between pairs, it was shown that females with or without a diagnosis were more than three and two times more likely, respectively, to receive a nutrition referral compared to men without a diagnosis (OR=3.42, 95% CI=1.87, 6.25, p<0.01; OR=2.44, 95% CI=1.35, 4.44, p=<0.01). Further, men with a diagnosis were greater than three times more likely to receive a nutrition referral compared to men without a diagnosis (OR=3.14, 95% CI=1.64, 6.01, p<0.01). The difference between females and males with a diagnosis was not significant (not shown).

Patients with obese and underweight BMIs were 1.81 and 4.16 times more likely, respectively, than those with normal BMIs to receive a nutrition referral (95% CI=1.04, 3.16, p=0.04; 95% CI=1.37, 12.65, p=0.01).

Metformin Prescription

The impact of sex on the odds of being prescribed metformin varied by age. Generally, the odds of receiving a metformin prescription were higher in females compared to males; however, this effect weakened as age increased. Having a diagnosis of prediabetes resulted in more than 8 times higher odds of a metformin prescription than if lacking a diagnosis (OR=8.16, 95% CI=5.18, 12.87, p<0.01). A 0.5% increase in HbA1c resulted in 20 times higher odds of receiving a metformin prescription (OR=21.71, 95% CI=9.56, 49.30, p<0.01). Those with obese BMI values were more than 4.5 times more likely to be prescribed metformin compared to those with normal BMI values (OR=4.59, 95% CI=1.65, 12.72, p=<0.01).

Psychology Referral

Odds of being referred to psychology decreased 18% with each five-year increase in age (OR=0.82, 95% CI=0.77, 0.88, p<0.01). Females were nearly 3 times more likely to be referred compared to males (OR=2.89, 95% CI=1.74, 4.80, p<0.01).

Weight Management Referral

For every five-year increase in age, odds of a referral to weight management decreased 12% (OR=0.88, 95% CI=0.81, 0.96, p=0.01). Females had two times higher odds of a referral compared to males (OR=2.04, 95% CI=1.14, 3.64, p=0.02). Those who received a prediabetes diagnosis also had two times higher odds of a weight management referral than those without a diagnosis (OR=2.14, 95% CI=1.27, 3.62, p=<0.01).

Weight Loss Medication

For every five-year increase in age, odds of being prescribed a weight loss medication decreased by 28% (OR=0.72, 95% CI=0.65, 0.79, p<0.01). Females had 6.27 times higher odds compared to males (95% CI=2.65, 14.80, p<0.01). Those who received a prediabetes diagnosis had 2.82 times higher odds compared to those without a diagnosis (95% CI=1.57, 5.05, p=<0.01).

Table 3: Predictors of 6-month clinical recognition of prediabetes

Outcome	OR (95% CI)	P value
Diagnosis		
Sex		
Female	1.20 (1.04, 1.38)	0.01
Race		
Black	0.78 (0.66, 0.92)	<0.01
HbA1c*age		
Age=25	4.46 (2.07, 9.61)	<0.01
Age=35	3.75 (2.11, 6.66)	<0.01
Age=45	3.16 (2.10, 4.75)	<0.01
Payer		
Medicaid	0.70 (0.53, 0.92)	0.01
Other	0.47 (0.33, 0.68)	<0.01
HbA1c, hemoglobin A1c; Rx, prescription; unit of measure: age, 5 years; HbA1c, 0.5% Stepwise logistic regression including age, sex, race, BMI category, HbA1c, diagnosis, insurance payer, comorbidities		

(Table 3 continued: Predictors of 6-month clinical recognition of prediabetes)

Outcome	OR (95% CI)	P value
Nutrition Referral		
HbA1c	1.66 (1.16, 2.37)	0.01
Age	0.88 (0.83, 0.92)	<0.01
Race		
Black	1.57 (1.14, 2.17)	0.01
Other/declined	1.74 (1.15, 2.60)	0.01
Sex*diagnosis		
Female (yes) vs Male (no)	3.42 (1.87, 6.25)	<0.01
Female (no) vs Male (no)	2.44 (1.35, 4.44)	<0.01
Male (yes) vs Male (no)	3.14 (1.64, 6.01)	<0.01
BMI category		
Obese	1.81 (1.07, 3.28)	0.04
Underweight	4.16 (1.24, 12.00)	0.01
Metformin Rx		
Age*sex		
Female (age=25)	3.34 (1.59, 7.01)	<0.01
Female (age 35)	2.39 (1.40, 4.07)	<0.01
Female (age=45)	1.70 (1.02, 2.84)	0.01
Diagnosis		
Yes	8.16 (5.18, 12.87)	<0.01
HbA1c	4.66 (3.09, 7.02)	<0.01
BMI category		
Obese	4.59 (1.65, 12.72)	<0.01
Psychology Referral		
Age	0.82 (0.77, 0.88)	<0.01
Sex		
Female	2.89 (1.74, 4.8)	<0.01
Weight Management Referral		
Age	0.88 (0.81, 0.96)	<0.01
Sex		
Female	2.04 (1.14, 3.64)	0.02
Diagnosis		
Yes	2.14 (1.27, 3.62)	<0.01
Weight Loss Medication Rx		
Age	0.72 (0.65, 0.79)	<0.01
Sex		
Female	6.27 (2.65, 14.80)	<0.01
Diagnosis		
Yes	2.82 (1.57, 5.05)	<0.01

HbA1c, hemoglobin A1c; Rx, prescription; unit of measure: age, 5 years; HbA1c, 0.5%
Stepwise logistic regression including age, sex, race, BMI category, HbA1c, diagnosis, insurance payer, comorbidities

DISCUSSION

Most patients with incident prediabetes were undiagnosed and did not receive treatment referrals or prescriptions within 6 months of developing prediabetes. Diagnosis rates in this study were higher than what has been found in other studies. We found 40% of patients with incident prediabetes receive a diagnosis while Schmittdiel et al. found a 13% diagnosis rate (134) and Mainous et al. found a rate too low for a reliable population estimate (133). Metformin prescriptions were higher in our cohort (4.4%) compared to other studies that reported < 0.1 (134) and 0.7% (140). Tseng et al. found metformin use to be associated with higher BMI and glucose values (140) similar to our study, We also found that those with higher HbA1c values and with BMIs values in the obese category were more likely to be prescribed metformin. Lifestyle changes are the first-line recommendation for diabetes prevention, which may be responsible for the limited use of metformin within the six months following prediabetes development. PCPs may provide patients a window of opportunity to make lifestyle changes on their own before deciding to pursue pharmacologic intervention(s).

While some PCPs report follow up for patients with prediabetes within six months (138), recent national trends found a 6% reduction in PCP follow up, suggesting there are missed opportunities to reevaluate the effectiveness of lifestyle changes and the potential need for escalation of care during the often-short period between prediabetes and DM development.

In this study documentation of prediabetes was less likely in males, blacks, with increasing age, and when Medicaid or Other insurance was indicated. Naz and colleagues found higher odds of diagnoses among those who were female, middle

aged, higher BMI, previous diagnosis of hypertension or high cholesterol, and having a family member with diabetes (234). Interactions were not assessed in the Naz et al. study, while ours found an interaction between HbA1c and age suggesting higher age reduced the odds of a diagnosis despite a higher HbA1c. Having a diagnosis of prediabetes was more commonly associated with documentation of additional interventions which may indicate that awareness/recognition of prediabetes increases the likelihood of additional efforts to prevent diabetes or, alternatively, that a medical diagnosis is required to order referrals or prescribe medications.

Increasing age was consistently associated with reduced or weakened odds of documentation of a diagnosis, referral, or prescription for prediabetes. It is known that prevalence of prediabetes increases with age, however, the therapeutic approach to DM care in older adults is dependent on regular assessment of the patients' medical complexity, functional status, and personal values (235, 236). Providers may choose not to inform elderly patients they have prediabetes to avoid confusion in the diagnostic labeling of the person while downplaying the urgency to treat their glycemic control (237). Personalized glycemic goals may be relaxed in older individuals with diabetes and may be reflected in generally less-aggressive interventions for prediabetes in this cohort. Metformin was safe (238) though not significantly more effective than the placebo at reducing diabetes risk for those aged >60 years during initial follow up of the DPP study (98) and its use, especially in older individuals, may be limited by gastrointestinal side effects (239).

Subgroup differences have been noted in the literature and found in this study. Females are shown to have higher rates of health care utilization compared to males

(240) and similarly in this study females were more likely to receive a diagnosis and other care resources (psychology, weight management, weight loss medication) following prediabetes development. Other studies have reported race-related disparities with higher diabetes education rates shown in African Americans (142). Similarly, in our cohort those whose races were black or “other/declined” were more than 1.5 times more likely to be referred to nutrition compared to those whose race was white, though those in the black race were less likely to receive a prediabetes diagnosis compared to those in the white race.

Physician surveys show that lifestyle intervention is the preferred treatment for prediabetes compared to medications (133, 241). However, it is noted that provider confidence in patient’s ability to achieve significant lifestyle improvements are weakened based on previous experiences (241, 242). While limitations are noted in providers’ own abilities to counsel patients in the visit due to a lack of time (241), this study did not find higher use of outside resources including referrals to an outpatient dietitian or weight management program. We were unable to assess use of local DPPs through our EHR system as currently there is no electronic referral capability in place. This may also be a barrier in referring patients to these programs as a 2016 national survey shows very few of those at risk for diabetes report ever being referred (243, 244). Additional efforts are needed to foster relationships between health care systems and community centers offering DPPs (245).

It should be noted that the perceived usefulness of clinical diagnosis and treatment of prediabetes varies greatly across providers. While some feel addressing prediabetes presents an opportunity to educate patients on diabetes prevention, others

view it as a “waste of time or resources” or more beneficial to address in patients who are younger and with fewer comorbidities (241). This study may reflect similar thoughts as patients who were older tended to be less-frequently diagnosed, referred, or prescribed. Further, we found management practices to vary between clinical service departments (not shown), suggesting inconsistencies or disagreements even across a Health System sharing the same resources.

To our knowledge, this is the first study to investigate patient characteristics that influence the likelihood of interventions for prediabetes documented in the EHR. This study has several strengths. It involved a sample of more than 3,500 patients established with a primary care provider who develop prediabetes based on ADA standard criteria. The exclusion of those with previous DM diagnostic codes and glucose regulation agents allow for a more reliable inclusion of incident prediabetes cases and understanding of what electronically documented resources are provided to patients in the first six months of developing prediabetes. An additional strength of this study was the assessment of data collected through the EHR. Assessing these data allows for the collection of what is documented in the patients’ EHR rather than reliance on self-reported practices that may be discordant with EHR documentation (137). Use of EHR data promotes the exploration of relevant and clinically meaningful investigations that can be easily replicated in an inexpensive and timely manner. Finally, investigating patient factors that influence the likelihood of prediabetes interventions can help uncover unmet needs of specific populations being overlooked upon prediabetes development, such as racial minorities or men. Opportunities may exist in decision-

support technologies embedded within the EHR (244, 246) which could enhance the integration of prediabetes identification and intervention electronically.

There are limitations that should be considered. This was a retrospective study, thus data are limited to what has been documented in the EHR. As observed in previous studies and this analysis, there are differing management practices across and within departments of a single health system. Inconsistencies and inaccuracies in diagnosing parameters (138) suggests interventions may be made prior to or later in the continuum of dysglycemia. This study did not assess interventions that may have been made prior to or beyond six months of developing prediabetes. Free-text word searches of prediabetes or lifestyle terminology were not measured which could indicate diabetes risk reduction advice that is often more common than referring to a weight loss DM prevention program (244).

In conclusion, waiting for diabetes development is too late to address potential complications from long-term metabolic imbalances present in prediabetes. This study supports other reports of infrequent diagnosis rates and underutilized interventions in the management of prediabetes and adds patient-related factors that may influence the likelihood of interventions documented in the EHR. Education of both providers and at-risk patients is needed to improve the awareness of prediabetes and its health risks, knowledge of evidence that diabetes can be prevented, and access of potentially life-changing resources within the community. Thus, this study can serve as a call to action for health care systems to develop and implement initiatives that target apparent gaps in care for patients with prediabetes. While prediabetes and diabetes are large-scale

global health problems, we must recognize the immediate need to intervene within our own practices and support the individuals trusting us with their health.

Chapter 4: Nutrient Patterns Predicting Diabetes Development

Abstract

Objective: To describe the relationship between adherence to nutrient intake patterns and risk of type 2 diabetes (DM) development among adults with prediabetes.

Methods: We used principal covariates regression (PCovR) to derive nutrient patterns that best explained variance in nutrient intake and insulin resistance (HOMA2-IR) in 1,674 adults with prediabetes enrolled in the Vitamin D and Type 2 Diabetes (D2d) trial. We conducted binary logistic regression to calculate odds ratios (OR) and 95% confidence intervals of DM development at one year across low, moderate, and high nutrient pattern adherence tertiles for each nutrient pattern.

Results: Three energy-adjusted patterns of nutrient intake were identified. The second nutrient pattern from the PCovR was a unique factor that described bipolar nutrient consumption patterns within the factor. High positive loadings indicated consumption of animal proteins, cholesterol, and arachidonic acid while high negative loadings indicated consumption of total sugar. The nutrient pattern explained 14% of variance in nutrient intake and 0.1% of variance in HOMA2-IR. After accounting for age, sex, BMI, education level, smoking status, physical activity, race, and treatment group, the OR for the high animal proteins group was two times higher compared to the moderate (reference) group (OR=2.02, 95% CI=1.34, 3.04, p=0.001) while the OR for the high sugar group was 57% higher than the moderate group (OR=1.57, 95% CI=1.02, 2.41, p=0.041). Every one-year increase in baseline age decreased the odds of DM development by 2% (OR=0.98, 95% CI=0.97, 0.99, p=0.037).

Conclusion: Patterns of nutrient intake with high consumption of animal proteins and dietary fats as well as high sugar intake were predictive of DM development. These

findings support further investigation of nutrition interventions that may reduce risk of prediabetes conversion to DM.

INTRODUCTION

Type 2 diabetes (DM) is a chronic disease affecting nearly 10% of the US population that impacts both individuals and their families as well as national healthcare spending. It can lead to multiple burdens including those that are mental/emotional, physical, and financial. Prediabetes is the state of higher than normal blood sugars but not high enough to diagnose DM; however, carries higher risk of health burdens similar to DM. Evidence supports that DM can be prevented with lifestyle changes such as nutritional modification (98). Observational studies show association of single foods/nutrients and diabetes risk (145, 146, 149, 152, 154); however, foods are eaten in combination and work synergistically to influence health benefit or detriment.

Patterns of dietary intake have been measured as a cumulative way to explain common “themes” of intake (183) that may predict chronic disease (184). Studying the diet in this way provides a more meaningful explanation of how foods commonly consumed together influence health, rather than looking at how an individual food or nutrient acts in isolation. Data-driven, as opposed to *a priori,* methods such as principal components analysis (PCA), explains maximal variation of intake within a group, and reduced rank regression (RRR), explains maximal variation of a biomarker of interest. PCA is beneficial for deriving patterns based on data collected from a cohort’s dietary assessment (191), while RRR draws in addition on *a priori* knowledge by using a biomarker related to the disease of interest as well as the diet to generate the dietary pattern(s) (190). PCA explains the actual intake of a cohort as it derives patterns only using dietary input data. As it does not include a biomarker to inform the patterns, it’s use in relating to biologically relevant mechanisms by which diet impacts disease is

limited. In contrast, RRR derives patterns that are related to a biomarker and thus provides more biologically meaningful patterns of dietary intake. Though, as the patterns relate to a biomarker related to the disease of interest, RRR less optimally explains the actual intake of the cohort. Alternatively, principal covariates regression (PCovR) is a method that maximally explains variance in intake while best predicting variance in the biomarker of interest (218, 219). This method incorporates strengths of both PCA and RRR while minimizing their limitations.

Most exploratory studies of dietary intake have included food variables to derive the patterns. Prudent (fruits, vegetables, fish, poultry, legumes, whole grains) and plant-based food patterns associate with lower DM risk (192, 195-197) while Western (red and processed meat, fried foods, sugar sweetened beverages, refined grains) associate with increased risk (211, 213, 215). Studies of nutrient intake patterns and their association with DM development are lacking.

While many studies in those at risk for DM have assessed food intake patterns through methods of PCA and RRR, no studies to date have investigated nutrient intake patterns derived by PCovR. Further, no studies have included only individuals with documented prediabetes who have a high probability of converting to DM within one year. The purpose of this study is to determine if there are nutrient factors related to conversion of prediabetes to DM.

METHODS

Study Population

This was a tertiary analysis of the Vitamin D and Type 2 Diabetes (D2d) study (NCT01942694, U01DK098245) which was a randomized, double-blind, placebo controlled trial across 22 US collaborating sites investigating the efficacy of vitamin D_3 supplementation for preventing conversion from prediabetes to DM (222). The proposal for this tertiary analysis was submitted to the D2d Publication & Presentation Proposal Subcommittee detailing the intended aims and analysis plan in January of 2019 and final approval granted in May of 2019.

Inclusion and exclusion criteria have previously been described in detail (224). Briefly, the cohort comprised 2,423 adult men (55%) and women (45%) at risk for DM defined by 2010 ADA criteria for prediabetes. Eligible participants met at least two criteria at baseline: FPG 100-125 mg/dL, 2-h post-load glucose after 75-g OGTT 140-199 mg/dL, or HbA1c 5.7-6.4%. Participants were randomized to 4,000 IU vitamin D_3 or placebo daily and followed for a median of two and a half years. Participants had the option to attend group meetings held twice yearly to discuss topics in nutrition and exercise. To enable detection of the hypothesized treatment effect, 508 DM conversions were required among the study sample before conclusion of the trial. Recruitment began in October 2013 and the final trial encounter was in November 2018.

For this analysis, 37 of the 2,423 randomized participants were excluded due to missing baseline FFQs. We calculated modified z-scores for energy (caloric) intake and removed participants with an absolute value greater than 1.5 to exclude implausible over and under-report of dietary intake (N=391). Individuals included in the analyses

reported consuming 500-4,000 calories per day. Implausible low report ranged from 120-500 calories and implausible high report ranged from 4,000-7,000 calories. Baseline HOMA2-IR values were absent in 321 participants due to missing fasting insulin measures. There were 1,674 participants included in our analyses (Figure 5).

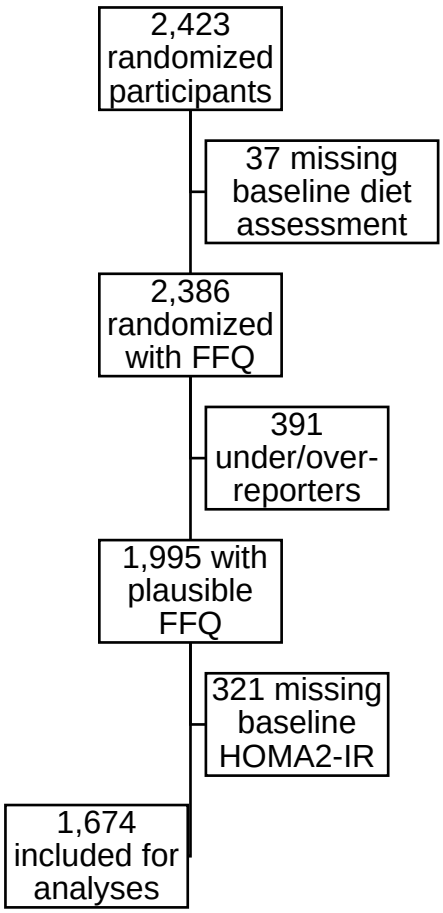

Figure 4: CONSORT Diagram

Dietary Assessment

Dietary data were collected using a validated 125-item multicultural self-administered semi-quantitative food frequency questionnaire (FFQ) designed to include

foods prevalent in both the general population and ethnic minorities among the US population (226). FFQs were administered at baseline and at months 12 and 36 in participants free of DM. Subjects were instructed to record their usual intake over the previous year. For this analysis, we used only baseline dietary data. Once completed, FFQ booklets were sent to the Dietary Assessment Center of Northeastern University and analyzed with the Nutrition Data System for Research (NDSR) software to estimate nutrient intake.

Laboratory Measures

HOMA2-IR was determined from baseline fasting glucose and fasting insulin using the HOMA2 Calculator (https://www.dtu.ox.ac.uk/homacalculator/). Samples were processed locally at each study site and shipped frozen to the D2d central laboratory at the University of Vermont Laboratory for Clinical Biochemistry Research (Colchester, VT) where they were stored and analyzed.

Covariate Assessment

Age, gender, race, education, and BMI (kg/m^2) were collected at the screening visit. Smoking status, physical activity (calculated into METS per week) (247), and vitamin D status (25OHD) were collected at the baseline visit.

Pattern Derivation

For the principal covariates regression (PCovR) analysis, we used two different approaches to derive nutrient intake patterns related to DM development. First, we used

nutrients as the independent variable and DM development (0=no, 1=yes) as the dependent variable. Second, we used nutrients as the independent variable and baseline HOMA2-IR, a known biomarker associated with prediabetes and DM pathophysiology (19), as the dependent variable. The nutrient patterns derived using DM development as the outcome variable were identical to those derived using HOMA2-IR. As HOMA2-IR is a continuous variable, and the regression analysis is modeled after a linear relationship, it provided numerical variance needed compared to categorical variance of DM development. Therefore, HOMA2-IR was used to derive the nutrient patterns.

We included output from the FFQ consisting of 40 nutrient variables. By default, nutrient variables were output from the FFQ assessment analysis, as opposed to food variables, which would have given clear insight into actual foods consumed and avoided the risk of collinearity between related nutrients. However, the PCovR analysis inherently minimizes collinearity as it considers all nutrient variables to be independent of each other. We created an artificial sweetener variable by combining the following non-nutritive sweeteners: aspartame, acesulfame potassium (K), and sucralose. We included fatty acid variables consisting of total monounsaturated fatty acids (MUFA), total trans fatty acids (TFA), total saturated fatty acids (SFA), individual polyunsaturated fatty acids (arachidonic acid, linoleic acid, α-linolenic acid), and the sum of the two primary dietary long chain n-3 fatty acids (eicosapentaenoic acid or EPA and docosahexaenoic acid or DHA). A list of the nutrient variables included in the analyses is provided in **Table 3**.

Table 3: List of Nutrient Variables

Nutrient Variables	
Animal protein	Folate
Vegetable protein	Vitamin B12
Alcohol	Calcium
Cholesterol	Phosphorus
Total SFA	Magnesium
Total MUFA	Iron
Starch	Zinc
Soluble fiber	Copper
Insoluble fiber	Selenium
Vitamin A	Sodium
Vitamin D	Potassium
Vitamin E	Caffeine
Vitamin K	Total TFA
Vitamin C	Total sugars
Thiamin	Manganese
Riboflavin	Total CLA
Niacin	Artificial sweeteners
Pantothenic acid	Linoleic acid
Vitamin B6	Alpha linolenic acid
EPA + DHA	Arachidonic acid
SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; TFA, trans fatty acid; CLA, conjugated linoleic acid; EPA eicosapentaenoic acid; DHA, docosahexaenoic acid	

Principal Covariates Regression

Nutrient intake patterns were derived using the [PCovR] package for R version 3.6.1 (R Foundation, Vienna, Austria). We first derived patterns using standardized intake scores for each nutrient variable. The derived patterns were highly influenced by energy intake and overwhelmed the contribution of nutrient variability to the patterns; thus, we adjusted the nutrient variables for each participant based on an energy intake of 1,000 calories. We rotated the factor loadings using the varimax rotation method to scale factor loading values between -1 and 1. [PCovR] automatically retained relevant components based on eigenvalues. Following derivation of the nutrient patterns, we calculated individual adherence scores to measure the degree to which their intake compared to the nutrient pattern. Adherence was calculated from the equation of a

linear combination of nutrient coefficients for that pattern. Every nutrient is assigned a coefficient number, and each person's raw nutrient intake was multiplied by that nutrient's coefficient; the products were then summed together to total the individual's adherence score for each nutrient pattern (**Equation 1**).

Equation 1. Example calculation of nutrient pattern adherence scores with magnesium (Mg) and zinc (Zn) (real equation includes all 40 nutrient variables).

Adherence Score = Mg coefficient*Mg raw value + Zn coefficient*Zn raw value + etc.

Statistical Analysis

Statistical analyses to generate the nutrient patterns were performed using R version 3.6.1. The relationships between pattern adherence scores and risk of DM development at one year were assessed using the SPSS statistical software. Assumptions of normality were tested and indicated usage of parametric statistical analyses. ANOVA as a special case of ordinary least squares regression was performed to assess differences in demographics and nutrient intakes between pattern adherence tertiles. Simple linear regression was performed to assess the relationship between glycemic load and both pattern adherence and HOMA2-IR. Binary logistic regression was performed to calculate odds ratios and 95% confidence intervals (CI) for conversion to DM (0=no, 1=yes) by nutrient pattern adherence group (low, moderate, high) with the moderate group serving as the reference group and assigned an OR of 1.0. Two models were assessed: Model 1 included only the nutrient pattern adherence groups and Model 2 included the predefined covariates of interest: age, BMI, sex, race,

education, smoking status, physical activity, and treatment group in the primary D2d trial (vitamin D or placebo). The statistical significance level was set at $p < 0.05$. The R statistical analysis code is included in Appendix 2.

RESULTS

Demographics

Participant characteristics are presented in **Table 4**. Most participants were male (54%), received post-high school education or higher, Caucasian (72%), non-smokers (94%), and had an average BMI value of 32 kg/m^2. At one year following randomization, 10% of the cohort had developed DM.

Table 4: Participant characteristics

Demographic / Anthropometric	Mean ± SD or Frequency (%)
Total	N = 1,674
Age	61 ± 10
Sex (female/male), n	735/897
Female/male, %	44/54
BMI (kg/m^2)	31.8 ± 4.4
Education level, n %	
No schooling	3 (<1)
High school or less	250 (15)
Some post-high school	541 (32)
Bachelor's degree	447 (27)
Graduate or professional degree	426 (26)
Prefer not to answer	7 (<1)
Race, n %	
American Indian/Alaska Native	6 (<1)
Asian	86 (5)
Black or African American	346 (21)
Native Hawaiian or Pacific Islander	3 (<1)
Caucasian	1,200 (72)
Other	33 (2)
Smoking status, n %	
No	1,581 (94)
Yes	87 (5)
Prefer not to answer	2 (<1)
Vitamin D (25OHD, ng/mL)	
Baseline	29 ± 10
12-month	40 ± 17
Insulin resistance	
HOMA2 %B	92 ± 41
HOMA2 %S	83 ± 58
HOMA2 IR	1.7 ± 1.1
Macronutrient intake	
Energy (kcal)	2,175 ± 758
Fat (%)	36 ± 6
Carbohydrate (%)	45 ± 7
Protein (%)	16 ± 3
1-year diabetes incidence, n %	171 (10)

Principal Covariates Regression

We derived nutrient intake patterns using nutrient variables unadjusted and adjusted for 1000 calories. The three patterns derived before adjusting for energy were overwhelmingly influenced by total energy intake as factor scores loaded in a manner that best explained energy variance (r^2=0.92 – 0.96) and minimized explanation of

variance in HOMA2-IR. Total energy was regressed on 12-month DM development and showed no association (p=0.66). Pattern loadings and results tables for the energy-unadjusted analyses can be found in Appendices 3 and 4. We proceeded with the three derived nutrient patterns using energy-adjusted nutrient variables. Nutrient pattern factor loading scores with absolute values greater than or equal to 0.3 are presented in **Table 5**.

The first pattern explained 20% of nutrient variance and 0.4% of variance in HOMA2-IR. We named this the “Plant-Based Nutrient Pattern” because it resulted in high positive loadings of insoluble fiber, vegetable protein, and folate with high negative loadings of dietary fats including total CLA, SFA, and MUFA (**Figure 5)**. The second pattern presented unique binary factor loading scores that included two polar nutrient patterns within the same factor. At one end (represented by high positive adherence scores), high consumption of animal protein, cholesterol, n-6 arachidonic acid (primarily found in meats and poultry) was indicated while the opposite end (represented by high negative adherence scores) indicated high sugar consumption (**Figure 6**). This pattern suggested that the cohort generally consumed either a high meat diet, a moderate diet, or a high sugar diet. Thus, we named this the “Meat or Sugar Pattern” and it explained 14% of nutrient variance and 0.1% of HOMA2-IR variance. A third pattern was named the “Dairy and Caffeine Pattern” as it resulted in high positive loadings of nutrients rich in milk (riboflavin, pantothenic acid, magnesium, potassium, phosphorus, calcium) and caffeine (**Figure 7**). This pattern explained 9% of nutrient variance and 0.2% of HOMA2-IR variance.

Table 5: Nutrient pattern loading scores

Nutrient	Plant-Based	Meat or Sugar	Dairy and Caffeine
Animal protein	-	0.82	-
Vegetable protein	0.71	-	-
Alcohol	-	-	-
Cholesterol	-	0.75	-
Total SFA	-0.56	0.46	-
Total MUFA	-0.33	0.68	-
Starch	0.59	-	-
Soluble fiber	-	-	0.87
Insoluble fiber	0.76	-	-
Vitamin A	-	-	-
Vitamin D	-	0.46	-
Vitamin E	0.38	-	-
Vitamin K	-	-	-
Vitamin C	0.44	-	-
Thiamin	0.50	-	0.51
Riboflavin	-	-	0.90
Niacin	0.45	0.40	0.49
Pantothenic acid	-	-	0.89
Vitamin B6	0.41	-	-
Folate	0.66	-	0.35
Vitamin B12	-	0.61	-
Calcium	-	-	0.39
Phosphorus	-	0.67	0.36
Magnesium	0.51	-	0.67
Iron	0.72	0.31	-
Zinc	-	0.58	0.36
Copper	-	0.34	-
Selenium	0.32	0.68	-
Sodium	-	0.58	-
Potassium	0.31	-	0.78
Caffeine	-	-	0.87
Total TFA	-0.31	0.35	-
Total sugars	-	-0.45	-
Manganese	0.31	-	0.35
Total CLA	-0.53	0.34	-
Artificial sweeteners	-	-	-
Linoleic acid	-	-	-
Alpha linolenic acid	-	0.41	-
Arachidonic acid	-	0.73	-
EPA + DHA	-	0.36	-

Loading scores with absolute values ≥ 0.3.
SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; CLA, conjugated linoleic acid; EPA eicosapentaenoic acid; DHA, docosahexaenoic acid

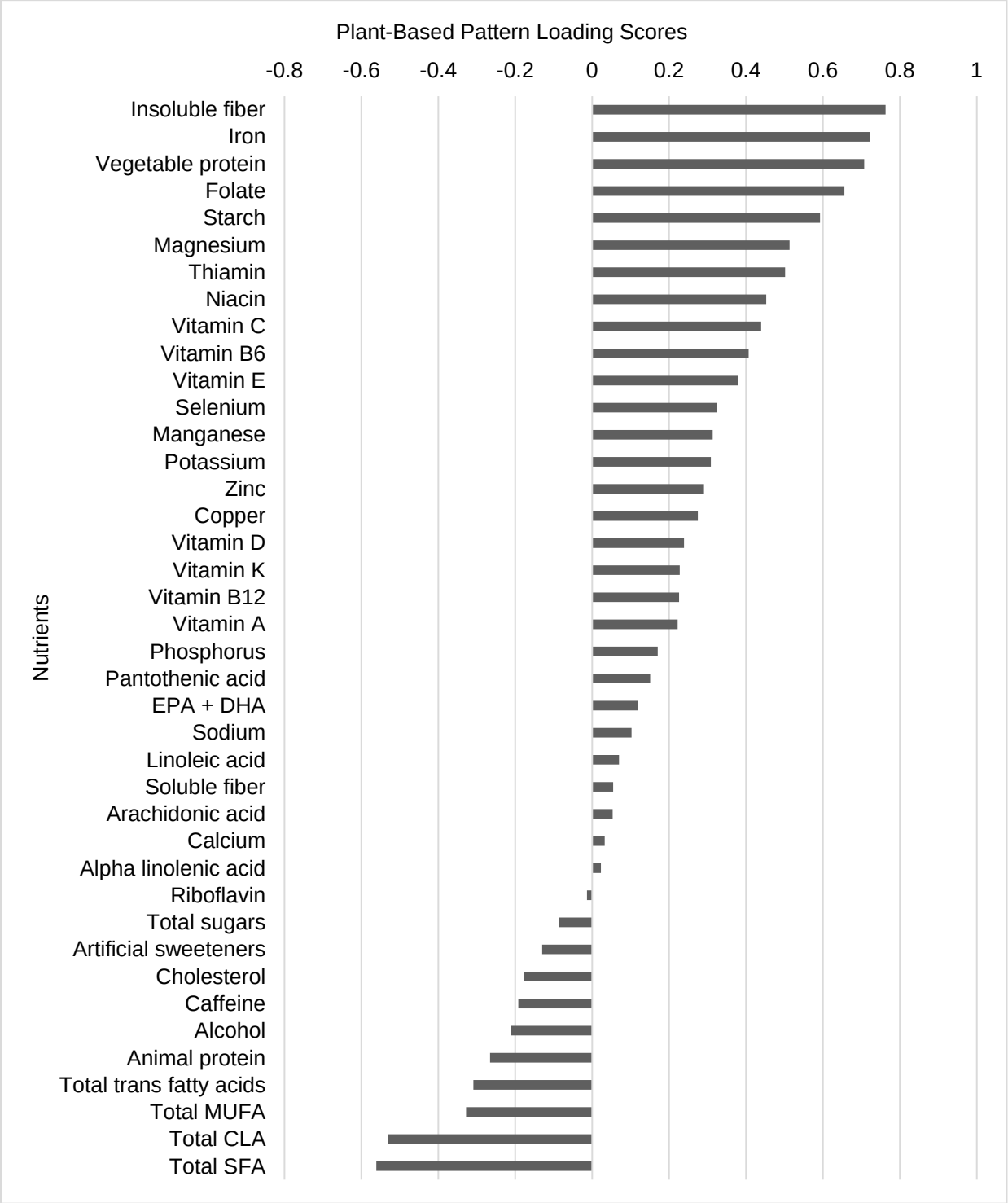

Figure 5: Plant-Based pattern factor loadings for all nutrients
The Plant-Based pattern explains 20% of nutrient intake variance and 0.4% of variance in HOMA2-IR. Factor loadings are represented by horizontal bars. Wider bars indicate nutrients with greatest variability in the pattern. Intake of nutrients with high positive loadings resulted in high plant-based pattern adherence. Intake of foods with high negative loadings resulted in higher dietary fat adherence.

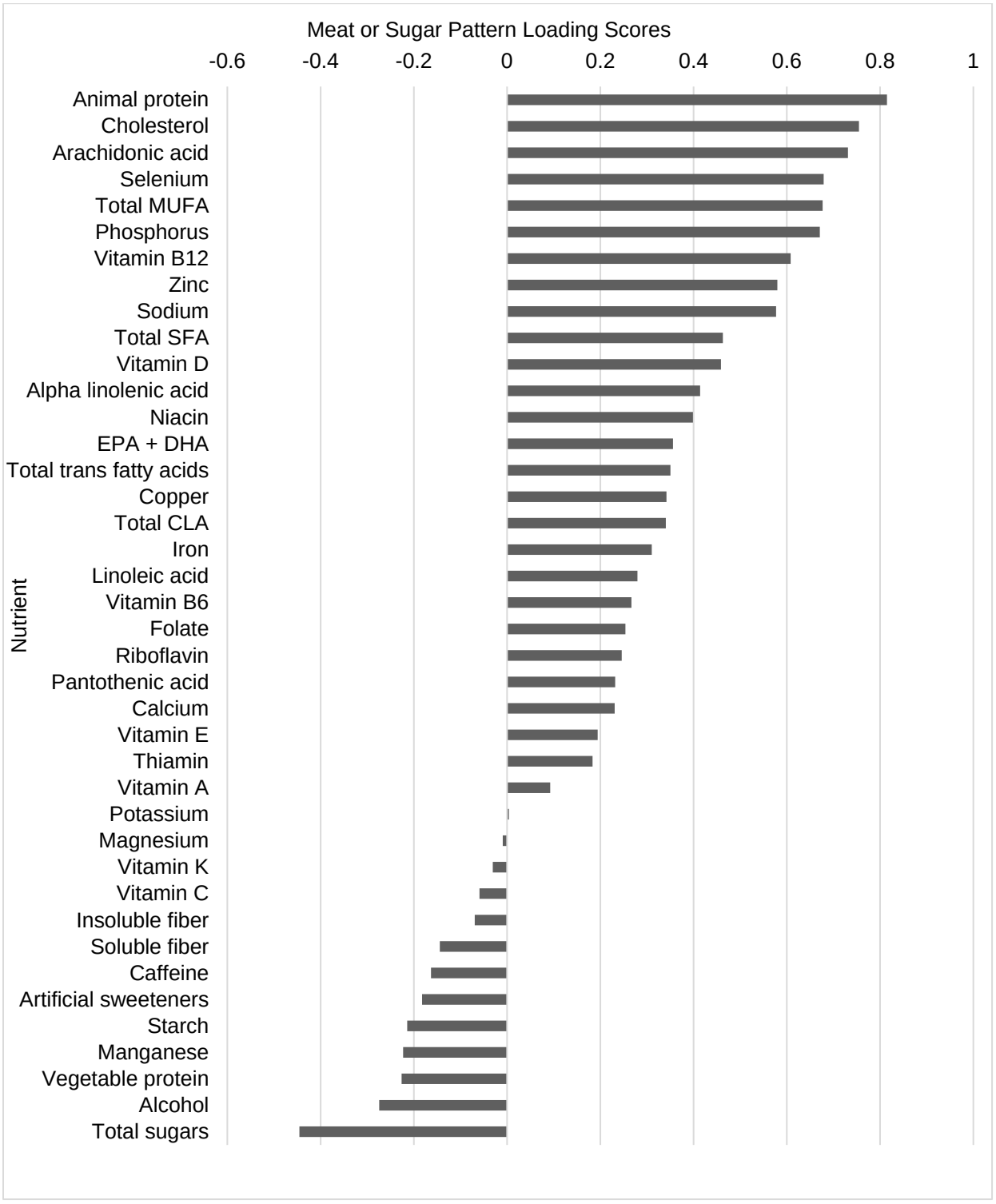

Figure 6: Meat or Sugar pattern loadings for all nutrients
The Meat or Sugar pattern explains 14% of nutrient intake variance and 0.1% of variance in HOMA2-IR. Factor loadings are represented by horizontal bars. Wider bars indicate nutrients with greatest variability in the pattern. Intake of nutrients with high positive loadings resulted in high meat pattern adherence. Intake of foods with high negative loadings resulted in high sugar pattern adherence.

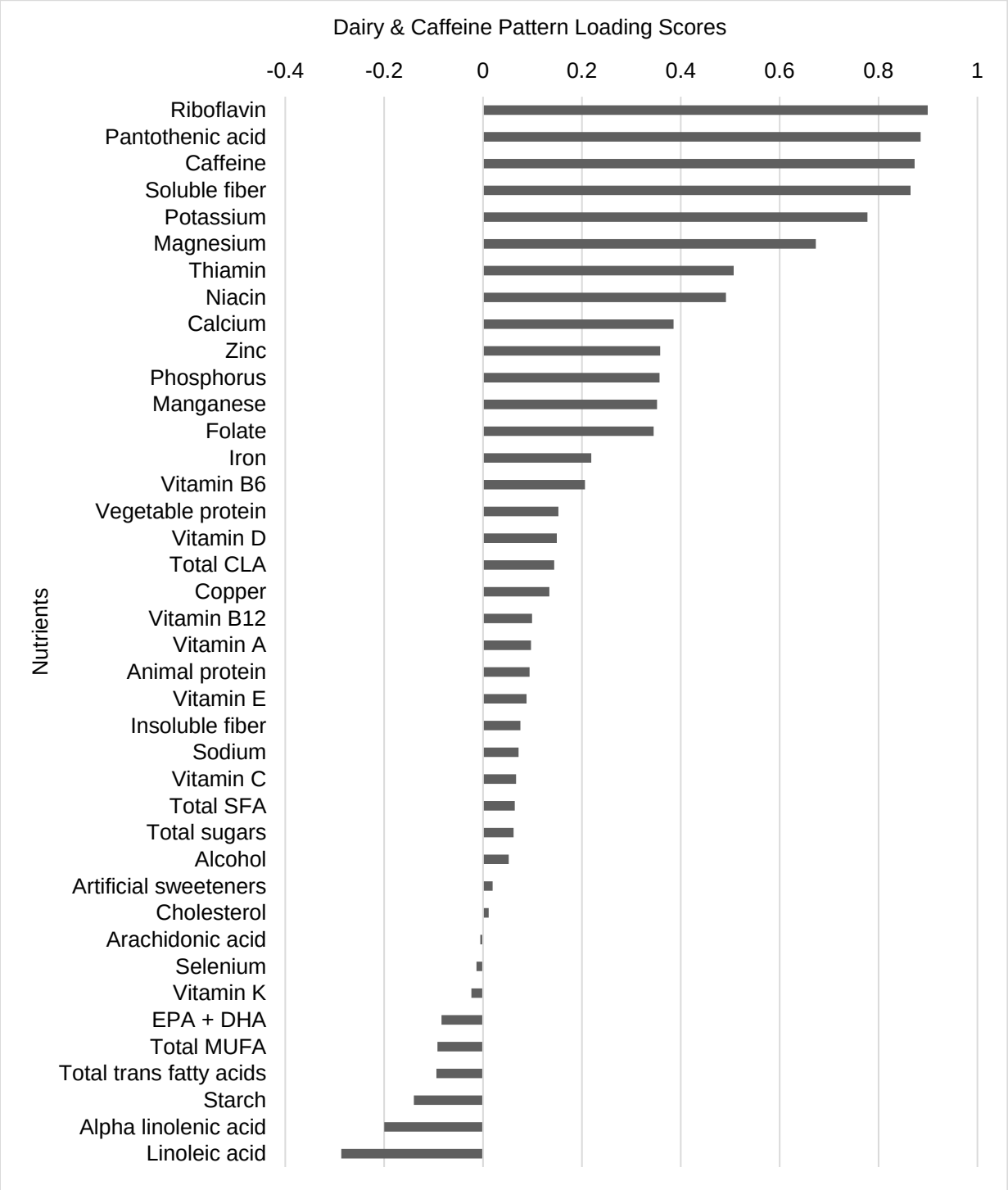

Figure 7: Dairy and Caffeine pattern loadings for all nutrients
The Dairy and Caffeine pattern explains 9% of nutrient intake variance and 0.2% of variance in HOMA2-IR. Factor loadings are represented by bars. Wider bars indicate nutrients with greatest variability in the pattern. Intake of nutrients with high positive loadings resulted in high dairy and caffeine pattern adherence.

We further explored the unique nature of the Meat or Sugar pattern which presented interesting contrasts in nutrient intake. Differences in participant characteristics and raw nutrient intakes between tertile groups of the Meat or Sugar pattern are shown in **Table 7**. Total caloric intake did not differ between groups; however, the high meat group contained a greater proportion of females (51%) and consumed an average of 21 grams more total fat, 26 grams more total protein, 30 grams more animal protein, and 259 grams more cholesterol per day compared to the high sugar group. Conversely, the high sugar group contained a greater proportion of males (60%) and consumed 60 grams more total carbohydrate and 38 grams more total sugar per day compared to the high meat group. As total sugar comprised both added sugars and natural sugars (e.g. sugar from fruits, yogurt, etc.), we were interested to better understand the types of sugars consumed and if they related to HOMA2-IR. Thus, we assessed the relationship between glycemic load (GL), a quantification of the glycemic effect of food portions, and HOMA2-IR. A significant positive relationship was found ($p<0.01$, $\beta=0.08$ for glucose and bread references) indicating that as a person's GL increased so did their HOMA2-IR. Additionally, adherence to the high sugar end of pattern 2 (i.e. higher negative adherence scores) was associated with GL ($p<0.01$, $\beta=-0.31$ for glucose and bread references) suggesting the stronger a person's adherence to total sugar consumption, the higher their GL.

Table 6: Descriptive summary by groups of Meat or Sugar pattern

	ALL N=1674	High Sugar N=558	Moderate N=558	High Meat N=558	p-value
Treatment group:					0.96
Placebo	835 (49.9%)	278 (49.8%)	276 (49.5%)	281 (50.4%)	
Vitamin D	839 (50.1%)	280 (50.2%)	282 (50.5%)	277 (49.6%)	
Sex:					<0.01
F	735 (43.9%)	210 (37.6%)	241 (43.2%)	284 (50.9%)	
M	897 (53.6%)	337 (60.4%)	300 (53.8%)	260 (46.6%)	
Age	61.1±9.5	62.3±9.5	60.4±9.8	60.5±9.2	<0.01
BMI	31.8±4.4	31.2±4.4	31.8±4.2	32.3±4.4	<0.01
Total calories	2175.2±757.6	2163.3±756.6	2197.0±744.1	2165.2±772.8	0.71
Fat:					
(g)	89.5±35.5	78.1±31.6	91.5±33.8	98.8±37.7	<0.01
(%)	36.1±6.0	31.6±5.4	36.5±4.2	40.2±4.7	<0.01
Carbohydrate:					
(g)	249.1±92.6	277.8±99.6	251.5±86.1	218.1±81.4	<0.01
(%)	45.1±7.5	50.6±7.5	45.1±4.9	39.7±5.2	<0.01
Protein:					
(g)	87.6±33.8	73.7±26.6	89.0±31.2	100.1±37.3	<0.01
(%)	15.8±2.8	13.4±1.9	15.9±1.6	18.2±2.3	<0.01
Animal Pro	60.6±27.6	45.4±19.2	61.1±23.5	75.3±30.4	<0.01
Vegetable pro	27.0±10.8	28.3±11.7	27.8±10.6	24.8±9.7	<0.01
Cholesterol	451.5±232.8	324.3±151.1	446.8±189.6	583.4±265.2	<0.01
Total SFA	30.1±13.2	25.9±11.1	30.8±12.8	33.6±14.3	<0.01
Total MUFA	31.1±12.2	27.1±10.8	31.8±11.5	34.5±13.0	<0.01
Starch	100.7±44.4	106.0±48.9	104.8±43.3	91.3±39.0	<0.01
Soluble fiber	8.9±5.9	9.6±7.0	9.0±5.8	8.3±4.8	<0.01
Insoluble fiber	14.6±6.3	14.8±6.8	15.1±6.2	13.8±5.7	<0.01
Riboflavin	3.0±1.4	2.7±1.4	3.0±1.3	3.3±1.3	<0.01
Pantothenic acid	8.7±4.2	7.8±4.3	8.5±4.0	9.6±4.1	<0.01
Sodium	4167.7±1656.6	3629.5±1441.4	4248.1±1604.4	4625.4±1756.3	<0.01
Linoleic acid	17.9±8.4	16.4±8.5	18.4±8.1	19.0±8.3	<0.01
α linolenic acid	1.7±0.8	1.5±0.6	1.8±0.7	1.9±0.8	<0.01
Arachidonic acid	0.2±0.1	0.1±0.1	0.2±0.1	0.3±0.1	<0.01
EPA	0.1±0.1	0.1±<0.1	0.1±0.1	0.1±0.1	<0.01
DHA	0.2±0.1	0.1±0.1	0.2±0.1	0.2±0.2	<0.01
Caffeine	320.7±470.2	381.9±589.1	307.7±438.5	272.6±344.1	<0.01
Total sugar	108.9±56.1	129.1±68.9	106.6±45.6	91.0±43.4	<0.01
Total CLA	0.2±0.1	0.2±0.1	0.2±0.1	0.2±0.1	<0.01
Artificial sweetener	35.6±118.3	62.4±175.9	27.3±80.1	17.1±59.7	<0.01

Pattern Adherence and DM Development

Odds ratios and 95% confidence intervals calculated from binary logistic regression for development of DM across nutrient pattern intake tertiles are presented in **Table 6.** Model 1 includes only the nutrient pattern adherence groups as the independent variable. Model 2 includes the nutrient pattern adherence group variable and all covariates of interest. After accounting for all covariates of interest, Pattern 2, the Meat or Sugar pattern, was significantly related to DM development as, relative to the moderate adherence group, those with higher sugar consumption had OR (95% CI) of 1.57 (1.02 – 2.14) and those with higher animal protein, cholesterol, and arachidonic acid consumption had 2.02 higher OR (1.34 – 3.04). Including 12-month change in BMI as a covariate was considered, but it had no effect on the associations of Model 2 and therefore was not included. Age predicted one-year DM development indicating lower baseline age was associated with higher odds of development (OR=0.98, 95% CI=0.97, 0.99). There was no association between DM development and adherence to either the Plant-Based or Dairy and Caffeine patterns.

Table 7: DM odds by energy-adjusted pattern adherence

Odds of DM Development					
Pattern Adherence		**Model 1[a]**		**Model 2[b]**	
		OR (95% CI)	**p**	**OR (95% CI)**	**p**
Plant-Based	Low Moderate High	0.98 (0.68, 1.43) - 0.75 (0.51, 1.12)	0.92 0.16	0.91 (0.62, 1.34) - 0.77 (0.51, 1.15)	0.63 0.20
Meat or Sugar	Low Moderate High	1.47 (0.97, 2.25) - 1.98 (1.32, 2.97)	*0.07* **0.01**	1.57 (1.02, 2.41) - 2.02 (1.34, 3.04)	**0.04** **0.01**
Dairy and Caffeine	Low Moderate High	0.80 (0.54, 1.19) - 0.98 (0.67, 1.43)	0.27 0.92	0.80 (0.53, 1.20) - 0.95 (0.64, 1.40)	0.27 0.79

[a] Binary logistic regression of 12-month DM development predicted by nutrient pattern adherence.
[b] Binary logistic regression of 12-month DM development predicted by nutrient pattern adherence and all covariates of interest (age, BMI, sex, education, smoking status, physical activity, race, and treatment group).

The relationship between the Meat or Sugar pattern and one-year DM development is displayed in **Figure 8.** A curvilinear, rather than linear, relationship was apparent as higher odds of DM development associated in both high sugar and high meat groups compared to the moderate group.

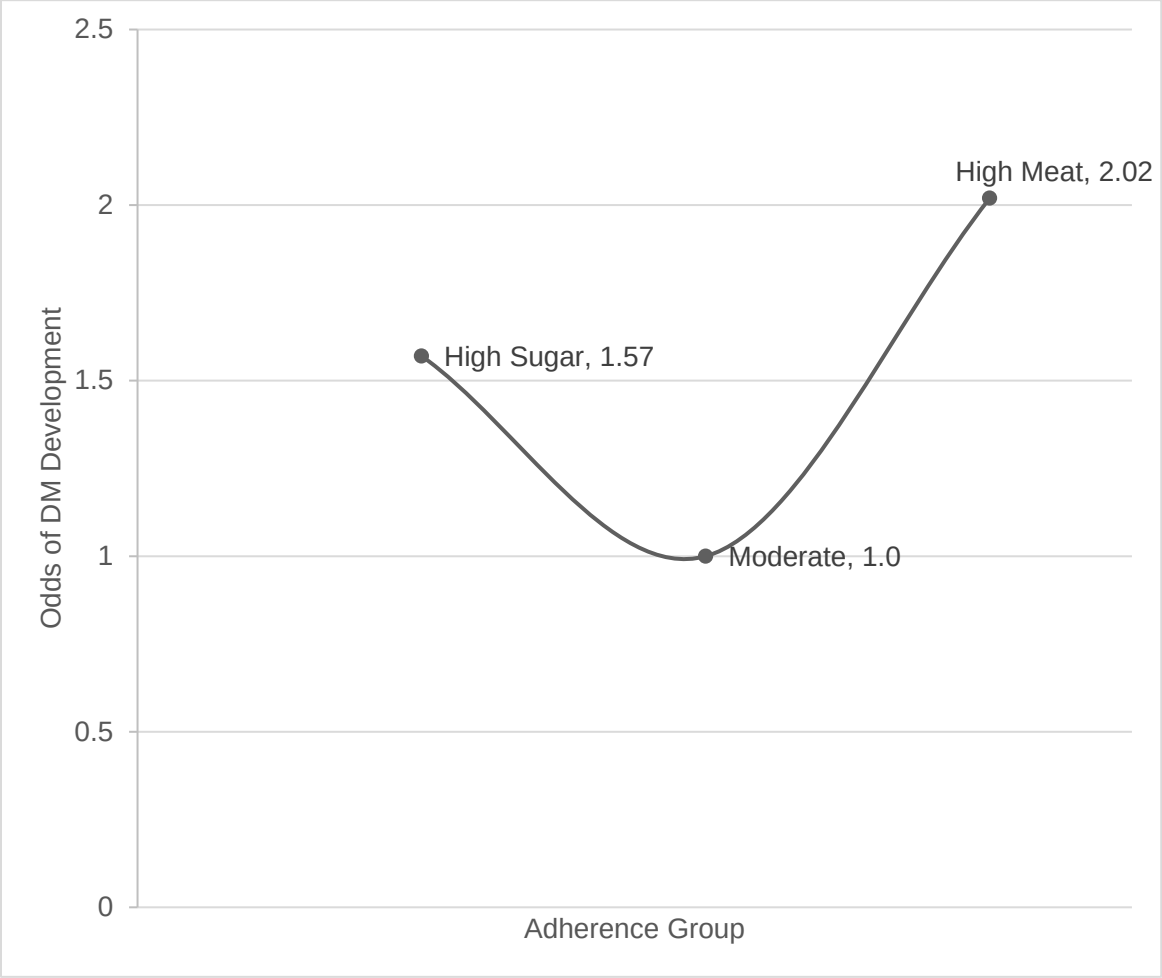

Figure 8: Odds of DM development across Meat or Sugar pattern adherence groups
The high sugar group had OR (95% CI) of 1.57 (1.02 – 2.14) and the high meat group had OR 2.02 (1.34 – 3.04) compared to the moderate group.

DISCUSSION

The current study is the first to evaluate nutrient patterns in relation to one-year DM conversion in adults at high risk of DM. We used a biologically relevant biomarker associated with prediabetes (HOMA2-IR) and identified 3 nutrient patterns using PCovR. The patterns we derived each explained less than 1% of variance in HOMA2-IR; however, our goal was to identify nutrients that explain conversion to DM using a

marker with biological relevance. Using HOMA2-IR, we found a nutrient intake pattern that associated with DM conversion within the short timeframe of one year.

We found that Pattern 2 was uniquely loaded with two polar patterns of intake, with each terminal end associating with higher odds of DM conversion compared to those with moderate adherence. At one end, higher consumption of animal proteins, cholesterol, and arachidonic acid resulted in twice the odds of one-year DM development compared to moderate intake. At the opposing end, higher intake of total sugars increased the odds of DM development more than 50% compared to moderate intake. Lowest odds of DM conversion were among those with modest intake of animal-based nutrients and total sugars, suggesting that, in this cohort, a health-protective way of eating was inclusive of moderate intake of all nutrients.

Our findings concur with multiple exploratory dietary pattern studies that associate higher intakes of both meats, animal products, and sources of sugar with DM or the risk of DM development (211-215). While previous studies identified patterns that included both meat and sugar within the same pattern (211, 213-215), our PCovR analysis identified the unique variation of intake within this cohort that differentiated between those who were high sugar consumers, high meat consumers, or moderate consumers of all nutrients.

We divided the total polyunsaturated fatty acid (PUFA) variable into five primary fatty acids due to their presence in a variety of foods with different biological effects and nutritional requirements (248). Linoleic acid and arachidonic acid are omega-6 fatty acids and α-linolenic acid, DHA, and EPA are omega-3 fatty acids. Both omega-6 and omega-3 are essential for human life; however, an overabundance in intake of omega-6

compared to omega-3, common to Western dietary habits, is associated with higher risk of obesity (249) and many chronic diseases (250). Due to the contrasting health effects and food sources of PUFAs, grouping them together would risk missing meaningful differences in nutrient patterns. We found that a nutrient pattern including higher intake of arachidonic acid (n-6) was associated with nearly two-fold greater odds of DM development. Meats, poultry, and eggs are common dietary sources of arachidonic acid which are also sources of the other nutrients with high loadings in this pattern including animal proteins, cholesterol, selenium, and vitamin B12.

The total MUFA variable loaded highly positive in the Meat or Sugar pattern which predicted significantly higher risk of DM development. Greater than 90% of dietary MUFAs come from oleic acid (18:1), primarily found in olive oil. While positive health effects are often attributed to dietary MUFA as a whole, isocaloric replacements of SFA, TFA, and refined carbohydrates with plant MUFA was found to be protective against cardiovascular outcomes while replacing with animal MUFA was not (251). Our findings suggest contributions of animal based dietary MUFA to the pattern as its theme clearly indicated intake of animal containing nutrients.

Nearly 45% of total sugars in the US diet is attributed to beverages, half of which come from sugar sweetened beverages (252). Following beverages, snacks and sweets largely contribute to total sugar consumption. While our study did not assess specific food groups to indicate sources of total sugars, we speculate that high GL foods/beverages such as sugar sweetened beverages and energy-dense carbohydrate snacks may substantially contribute to our findings as GL associated with both HOMA2-IR and adherence to total sugar consumption. Sweetened beverages and refined

carbohydrate foods are repeatedly found in empirically derived dietary patterns that associated with increased risk of DM (211, 213, 215). While self-report of sugar consumption from sweetened beverages among adults has declined over the last decade (253), overall consumption remains largely above the dietary guidelines (254). Carbohydrate intake, particularly refined carbohydrate found in sweetened beverages and processed foods, produces a rapid influx blood glucose. In the setting of impaired insulin production and/or action distinctive of prediabetes, hyperglycemia in response to habitual dietary intake serves as a constant insult to the body's already weakened ability to maintain glycemic homeostasis. Our study emphasizes the harmful effects of high sugar consumption as odds of one-year DM development were nearly 60% higher in the high sugar group compared to the moderate group.

A strength of this tertiary analysis is that the nutrient intake used came from a well-controlled, well-characterized double-blind RCT. Our cohort represented a specific population or adults at very high risk of DM as only those meeting at least two ADA-defined criteria for prediabetes were included in the study. The large sample size contributed to the power to detect meaningful relationships. Laboratory measures of fasting glucose and insulin were stored and analyzed at a single site minimizing potential analysis inconsistencies across local laboratories. The HOMA2-IR measurement is a valid and reliable model of steady-state IR that accounts for variations in hepatic and peripheral glucose resistance, and it is appropriate for large epidemiological studies compared to the gold standard insulin clamp which is more labor intensive, expensive, and requires intravenous infusion (255).

The study also has several limitations. We were forced to exclude 391 participants because of a high degree of implausible dietary report; and even among the participants included, we adjusted nutrient intake to a common energy intake and were forced to make the assumption that the balance of foods consumed (and, therefore, the intake of individual nutrients) was not changed in the process. This was a retrospective analysis and was not designed to study the effect of diet on DM development. Dietary intake was collected at baseline and it is unknown if participants changed their dietary intake during the 1-year trial duration.

Actual foods consumed were not available and the analysis by nutrients risks multiple collinearity because some foods are good sources of many nutrients. We do not know the exact foods consumed in this population which poses a challenge when making inferences about the nutrient intake patterns. However, the PCovR method considers all nutrients independent of each other, and we further adjusted nutrient output for a standard energy intake to reduce collinearity. The presence of related nutrients in an intake pattern, such as animal proteins, cholesterol, and arachidonic acid, allowed us to confidently translate the nutrient intake patterns into habitual dietary consumption in this cohort.

There are limitations in the generalizability of dietary pattern analyses across different populations. A pattern predicting DM in one population are not necessarily generalizable to another (216). However, food pattern components associated with DM risk show overlap in several studies (163). Common predictive components across the NHS, EPIC, and Whitehall studies included meat products, refined grains, and caloric and non-caloric soft drinks (216). Our study similarly found high intake of meat proteins,

animal-based nutrients (cholesterol, arachidonic acid), and total sugars to be associated with increased odds of DM.

In conclusion, we identified a polar nutrient intake pattern that was predictive of one-year DM development with high consumption of animal proteins and dietary fats at one end and high sugar intake at the opposing end. We used a novel method in nutrition research that complements the assessment of total nutrient intake with relation to disease progression. Further exploring the relationship between PCovR-derived diet patterns specifically using food variables and DM development may improve the translation of direct dietary sources associated with progression from prediabetes to DM. Further assessing if temporal changes in dietary pattern intake can alter the development of DM is crucial to inform future DM prevention interventions.

Chapter 5: Discussion and Conclusions

Summary of Findings

This dissertation revealed multiple important factors related to the progression of DM. Among greater than 3,500 patients with newly established prediabetes, 40% were clinically recognized and even fewer referred or provided evidence-based interventions to help prevent DM. Differences in patient-related factors, such as HbA1c level, BMI, and age impact the odds of receiving clinical recognition or intervention. The presence of a prediabetes diagnosis frequently increased the odds of receiving additional DM prevention interventions, which be a meaningful predictor indicating providers' increased awareness of DM risk. This lack of recognition and intervention in crucial stages prior to DM development is a concern as rates of prediabetes continue to increase, rising above one third of the US adult population (230). In a separate analysis, we identified themes of nutrient intake among a sample of 1,674 individuals who were recognized to have prediabetes and enrolled in a trial to determine if vitamin D could reduce the number of persons who converted to DM within 12 months. Using PCovR, and after normalizing energy intake and adjusting for covariates, a higher intake of animal proteins, cholesterol, and arachidonic acid as well as total sugars were associated with a significant increase in the risk of DM development at one year.

Limitations

Findings from both studies provide valuable advancements in the study of prediabetes. Predictors of various DM prevention interventions had not previously been identified and important considerations in the study of nutrient intake related to DM development were uncovered. Nevertheless, there are limitations to these studies that

must be noted. Both studies were retrospective analyses and allow poor control of exposure and confounding variables. Retrospective analyses are not designed to establish cause and effect relationships. Project 1 relied upon previously documented data with potential inaccuracies in the patients' medical record. Further, free-text documentation was not collected for this study and limits the measure of verbal recommendations provided during the visit. Project 2 used FFQs to measure usual dietary intake. FFQs are subject to significant bias due to self-report of dietary intake. Lastly, dietary and other lifestyle habits may have changed throughout the period of study related to general advice provided as the standard of care.

Future Directions

The prevalence of prediabetes continues to grow despite national efforts to support prevention programs and increase awareness among the public and healthcare settings. Better understanding of barriers in identifying and treating patients at greatest risk of DM and potential nutritional mechanisms in which to intervene is crucial to slow the progression and potentially prevent DM from developing.

Using a clinical data repository, important research questions related to prediabetes identification, management, and progression to DM can be investigated that otherwise may take years to learn through prospective cohort studies. Future studies should investigate documentation within the clinical note to determine extent and influence of HCP counseling. Formal survey of HCPs caring for those with prediabetes is valuable to learn individual philosophies and management to compliment the EHR data. Interventions to alert HCP when someone meets criteria for prediabetes can

increase awareness and promote interventions to prevent DM. Beyond this study, it is vital to intervene in the period of prediabetes that is well-supported in the literature to be neglected. To reduce the burden of DM, improvement in healthcare delivery and patient access to evidence-based interventions is critical. Continued and regular use of the HERON tool for prediabetes research can promote more rapid changes to healthcare systems as this research can be investigated in and applied to local practices. Further, this tool reveals gaps in reliable and worthwhile data to be collected for nutritional research.

Investigations of dietary intake patterns related to progression from prediabetes to DM are important to better understand the cumulative influence of overall dietary intake rather than isolated nutrients or foods. We can better identify meaningful patterns of intake using novel statistical methods such as PCovR that explain both dietary intake and biologically relevant disease factors. Future PCovR dietary pattern studies using food variables is valuable to provide greater insight into actual dietary consumption and its relationship with DM conversion.

Closing Statement

As the path to DM development is an often unrecognized and highly influenced by habitual dietary intake, the purpose of this research was to better understand clinical management practices and nutritional factors related to DM development. The findings of my dissertation suggest that individuals with prediabetes are often unrecognized and under-supported in their path towards DM, and dietary nutrients play a role in the protective and promotive modulators of prediabetes. This study serves as both a light shed on areas of improvement in the clinical management of prediabetes and a

magnifying glass to help identify nutrient intake patterns associated with the conversion to DM.

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Appendices

Appendix 1: SQLite Studio Code

```
select COUNT (distinct patient_num)
from data_view
;
--3725 total patients

create table Demographics as
select patient_num, age, sex, race
from patient_view
order by patient_num
;
select *
from Demographics
;
create table First_A1c as
select patient_num, nval as A1c, min(start_date) as A1c_date
from data_view
where data_view.variable in ('HEMOGLOBIN A1C (#2034)', 'POC HEMOGLOBIN A1C
(#2893)') and modifier = '@'
and nval >= 5.7 and nval <= 6.4
group by patient_num /*group by pt number to have one lab per pt rather than only 1
row*/
order by patient_num, start_date
;
--returns 3681 patients
select*
from First_A1c
;
create table First_labdate as
select distinct patient_num, nval as first_labvalue, min(start_date) as first_labdate,
variable as first_lab
from data_view
where (data_view.variable = 'GLUCOSE, 2 HR. (#2041)' and modifier = '@' /*4 pts*/
and nval >= 140 and nval <= 199)
OR
(data_view.variable in ('HEMOGLOBIN A1C (#2034)', 'POC HEMOGLOBIN A1C
(#2893)') and modifier = '@'
and nval >= 5.7 and nval <= 6.4)
OR
(data_view.variable = 'GLUCOSE, FASTING (#2035)' and modifier = '@' /*44 pts*/
and nval >= 100 and nval <= 125)
group by patient_num
order by variable, patient_num, start_date
;
select*
```

```
from First_labdate
;
--returns 3725 patients

create table labdate_enc_num as
select distinct patient_num, nval as first_labvalue, min(start_date) as first_labdate,
variable as first_lab, encounter_num
from data_view
where (data_view.variable = 'GLUCOSE, 2 HR. (#2041)' and modifier = '@' /*4 pts*/
and nval >= 140 and nval <= 199)
OR
(data_view.variable in ('HEMOGLOBIN A1C (#2034)', 'POC HEMOGLOBIN A1C
(#2893)') and modifier = '@'
and nval >= 5.7 and nval <= 6.4)
OR
(data_view.variable = 'GLUCOSE, FASTING (#2035)' and modifier = '@' /*44 pts*/
and nval >= 100 and nval <= 125)
group by patient_num
order by variable, patient_num, start_date
;
select*
from labdate_enc_num
;
--returns 3725 patients

select * from variable_view
;
create table dept_date as
select patient_num, variable as Department, start_date
from data_view
where variable in ('ZZUKP-LCOA FAM MED', 'ZZUKP-KU FAM MED', 'ZZUKP-FM',
'ZZUKP FAMILY MED', 'ZZJPC SPRINT CENTER FM', 'ZZJPC MISSION FAMILY'
, 'ZZJPC KUMW FM', 'ZZJPC CREEKWOOD FAMILY', 'ZZJPC BLUE RIDGE FAM',
'ZZC-CREEKWOOD FAMILY', 'SCA1 FAMILY CL', 'MSN1 FAMILY CL'
, 'MPA1 FAMILY MED CL', 'LCOA FAMILY MED CL', 'KUMW FAMILY CL', 'JPC-STATE
AVENUE-HC', 'IM GENERAL MEDICINE KU 38', 'General Internal Medicine'
, 'FM FAMILY MEDICINE KU 31', 'FM FAMILY MED LANDON CENTER 31', 'CWA1
FAMILY CL', 'BRA FAMILY CL')
and start_date between ('2016-06-01') and ('2019-06-01')
order by patient_num
;
select * from dept_date
;
create table dept_days as
select dept_date.*, First_labdate.first_labdate,
julianday(dept_date.start_date) - julianday(First_labdate.first_labdate) as days_btw
```

```
from dept_date
join First_labdate
on dept_date.patient_num = First_labdate.patient_num
;
select * from dept_days
;
create table abs_dept_days as
select patient_num, Department, abs(days_btw) as abs_dept_days
from dept_days
;
select * from abs_dept_days
;
create table closest_dept as
select patient_num, Department, min(abs_dept_days)
from abs_dept_days
group by patient_num
;
select * from closest_dept
;
create table PreDM_dept as
select patient_num, Department
from closest_Dept
;
select *
from PreDM_dept
;
create table Dept as
select PreDM_dept.*,
case
when PreDM_dept.Department is 'IM GENERAL MEDICINE KU 38' then 'General
Internal Medicine'
when PreDM_dept.Department is 'General Internal Medicine' then 'General Internal
Medicine'
when PreDM_dept.Department is 'ZZUKP-LCOA FAM MED' then 'Family Medicine'
when PreDM_dept.Department is 'ZZUKP-KU FAM MED'then 'Family Medicine'
when PreDM_dept.Department is 'ZZUKP-FM' then 'Family Medicine'
when PreDM_dept.Department is 'ZZUKP FAMILY MED' then 'Family Medicine'
when PreDM_dept.Department is 'ZZJPC SPRINT CENTER FM' then 'Family Medicine'
when PreDM_dept.Department is 'ZZJPC MISSION FAMILY' then 'Family Medicine'
when PreDM_dept.Department is 'ZZJPC KUMW FM' then 'Family Medicine'
when PreDM_dept.Department is 'ZZJPC CREEKWOOD FAMILY' then 'Family
Medicine'
when PreDM_dept.Department is 'ZZJPC BLUE RIDGE FAM' then 'Family Medicine'
when PreDM_dept.Department is 'ZZC-CREEKWOOD FAMILY' then 'Family Medicine'
when PreDM_dept.Department is 'SCA1 FAMILY CL' then 'Family Medicine'
when PreDM_dept.Department is 'MSN1 FAMILY CL' then 'Family Medicine'
```

```
when PreDM_dept.Department is 'MPA1 FAMILY MED CL' then 'Family Medicine'
when PreDM_dept.Department is 'LCOA FAMILY MED CL' then 'Family Medicine'
when PreDM_dept.Department is 'KUMW FAMILY CL' then 'Family Medicine'
when PreDM_dept.Department is 'JPC-STATE AVENUE-HC' then 'Family Medicine'
when PreDM_dept.Department is 'FM FAMILY MEDICINE KU 31' then 'Family
Medicine'
when PreDM_dept.Department is 'FM FAMILY MED LANDON CENTER 31' then
'Family Medicine'
when PreDM_dept.Department is 'CWA1 FAMILY CL' then 'Family Medicine'
when PreDM_dept.Department is 'BRA FAMILY CL' then 'Family Medicine'
end as Dept
from PreDM_dept
;
select * from Dept
;
create table BMI as
select patient_num, nval as BMI, start_date
from data_view
where variable LIKE 'Body Mass Index'
;
select *
from BMI
;
create table BMI_near_labdate as
select BMI.patient_num, BMI.BMI, BMI.start_date as BMI_date,
First_labdate.first_labdate,
julianday(First_labdate.first_labdate) - julianday(BMI.start_date) as
days_btw_lab_and_BMI
from BMI
join First_labdate
on First_labdate.patient_num = BMI.patient_num
where BMI.start_date between date(First_labdate.first_labdate, '-90 day') /*three month
window rather than one to increase totals*/
and date(First_labdate.first_labdate, '+90 day')
;
select *
from BMI_near_labdate
;
create table abs_val_BMI_days as
select patient_num, BMI, abs(days_btw_lab_and_BMI) as abs_val_BMI_days
from BMI_near_labdate
;
select *
from abs_val_BMI_days
;
create table closest_BMI as
```

```
select patient_num, BMI, min(abs_val_BMI_days)
from abs_val_BMI_days
group by patient_num
;
select *
from closest_BMI
;
--BMIs for 3683 pts

create table preDM_BMI as
select patient_num, BMI
from closest_BMI
;
select *
from preDM_BMI
;
create table BMI_category as
select *
, CASE
when BMI >= 30 then 'OBESE'
when BMI >= 25 and BMI <= 29.99 then 'OVERWEIGHT'
when BMI >= 18.5 and BMI <= 24.99 then 'NORMAL'
when BMI < 18.5 then 'UNDERWEIGHT'
END as wt_category
from preDM_BMI
;
select *
from BMI_category
;
--BMIs for 3683 pts

create table Nutr_referral as
select data_view.patient_num, data_view.start_date as nutr_ref,
First_labdate.first_labdate, First_labdate.first_labvalue
from data_view
join First_labdate
on First_labdate.patient_num = data_view.patient_num
where variable in ('AMB REFERRAL TO DIETICIAN', 'AMB REFERRAL TO MEDICAL
NUTRITION THERAPY', 'AMB REFERRAL TO NUTRITION')
order by data_view.patient_num
;
select *
from Nutr_referral
;
--returns 740 rows, multiple rows per pt
```

```
create table Nutr_ref_1 as
select *
from Nutr_referral
where Nutr_referral.nutr_ref between date(Nutr_referral.first_labdate)
and date(Nutr_referral.first_labdate, '+180 day')
group by Nutr_referral.patient_num
;
create table Metformin as
select data_view.patient_num, data_view.start_date as Metformin,
First_labdate.first_labdate, First_labdate.first_labvalue
from data_view
join First_labdate
on First_labdate.patient_num = data_view.patient_num
where variable in ('Metformin Extended Release Oral Tablet', 'Metformin Oral Solution',
'Metformin Oral Tablet')
and modifier not like 'Surescripts%'
order by data_view.patient_num
;
select * from Metformin
;
select * from data_view
where variable in ('Metformin Oral Tablet')
;
create table Metformin_1 as
select *
from Metformin
where Metformin.Metformin between date(Metformin.first_labdate)
and date(Metformin.first_labdate, '+180 day')
group by Metformin.patient_num
;
select *
from Metformin_1
;
--returns 165 patients

create table Metf_final as
select Metformin_1.*,
case
when Metformin_1.Metformin is not null then 'Y'
end as Met_referral
from Metformin_1
;
select *
from Metf_final
;
drop table Metf_final
```

```
;
create table Metformin as
select Demographics.*, Metf_final.Met_referral
from Demographics
left join Metf_final
on Demographics.patient_num = Metf_final.patient_num
;
select * from Metformin
;
create table Metf_final as
select Metformin.*,
case
when Met_referral is null then 'N'
when Met_referral is 'Y' then 'Y'
end as Metformin
from Metformin
;
create table Psychology as
select data_view.patient_num, data_view.start_date as Psych_ref,
First_labdate.first_labdate, First_labdate.first_labvalue
from data_view
join First_labdate
on First_labdate.patient_num = data_view.patient_num
where variable in ('AMB REFERRAL TO PSYCHOLOGY')
order by data_view.patient_num
;
create table Psychology_1 as
select *
from Psychology
where Psychology.Psych_ref between date(Psychology.first_labdate)
and date(Psychology.first_labdate, '+180 day')
group by Psychology.patient_num
;
select *
from Psychology_1
;
--returns 88 patients

create table Psych_final as
select Psychology_1.*,
case
when Psychology_1.Psych_ref is not null then 'Y'
end as Psych_referral
from Psychology_1
;
select *
```

```
from Psych_final
;
create table Psychology as
select Demographics.*, Psych_final.Psych_referral
from Demographics
left join Psych_final
on Demographics.patient_num = Psych_final.patient_num
;
select * from Psychology
;
create table Psych_final as
select Psychology.*,
case
when Psych_referral is null then 'N'
when Psych_referral is 'Y' then 'Y'
end as Psychology
from Psychology
;
create table Wt_mgt as
select data_view.patient_num, data_view.start_date as wtmgt_ref,
First_labdate.first_labdate, First_labdate.first_labvalue
from data_view
join First_labdate
on First_labdate.patient_num = data_view.patient_num
where variable in ('AMB REFERRAL TO WEIGHT MANAGEMENT', 'KU WEIGHT
MANAGEMENT PROGRAM')
order by data_view.patient_num
;
create table Wt_mgt_1 as
select *
from Wt_mgt
where Wt_mgt.wtmgt_ref between date(Wt_mgt.first_labdate)
and date(Wt_mgt.first_labdate, '+180 day')
group by Wt_mgt.patient_num
;
select *
from Wt_mgt_1
;
--returns 61 patients

create table WM_final as
select Wt_mgt_1.*,
case
when Wt_mgt_1.wtmgt_ref is not null then 'Y'
end as WM_referral
from Wt_mgt_1
```

```
;
select *
from WM_final
;
create table WM as
select Demographics.*, WM_final.WM_referral
from Demographics
left join WM_final
on Demographics.patient_num = WM_final.patient_num
;
select * from WM
;
create table WM_final as
select WM.*,
case
when WM_referral is null then 'N'
when WM_referral is 'Y' then 'Y'
end as WtMgt
from WM
;
create table Wt_loss_med as
select data_view.patient_num, data_view.start_date as wtloss_med,
First_labdate.first_labdate, First_labdate.first_labvalue
from data_view
join First_labdate
on First_labdate.patient_num = data_view.patient_num
where variable in ('orlistat Oral Capsule', 'Bupropion / Naltrexone Extended Release
Oral Tablet', '[GA751] CENTRALLY-ACTING APPETITE SUPPRESSANTS', 'liraglutide
Pen Injector')
and modifier not like 'Surescripts%'
order by data_view.patient_num
;
select * from Wt_loss_med
;
create table Wtloss_med_1 as
select *
from Wt_loss_med
where Wt_loss_med.wtloss_med between date(Wt_loss_med.first_labdate)
and date(Wt_loss_med.first_labdate, '+180 day')
group by Wt_loss_med.patient_num
;
select *
from Wtloss_med_1
;
--returns 56 patients
```

```
create table WLmed_final as
select Wtloss_med_1.*,
case
when Wtloss_med_1.wtloss_med is not null then 'Y'
end as WL_med
from Wtloss_med_1
;
select *
from WLmed_final
;
create table wt_loss_med as
select Demographics.*, WLmed_final.WL_med
from Demographics
left join WLmed_final
on Demographics.patient_num = WLmed_final.patient_num
;
select * from wt_loss_med
;
create table WLmed_final as
select wt_loss_med.*,
case
when WL_med is null then 'N'
when WL_med is 'Y' then 'Y'
end as Wt_med
from wt_loss_med
;
create table PreDM_dx as
select data_view.patient_num, data_view.start_date as diagnosis,
First_labdate.first_labdate, First_labdate.first_labvalue
from data_view
join First_labdate
on First_labdate.patient_num = data_view.patient_num
where variable in ('790.2 Abnormal glucose', 'R73 Elevated blood glucose level')
order by data_view.patient_num
;
create table PreDM_dx_1 as
select *
from PreDM_dx
where PreDM_dx.diagnosis between date(PreDM_dx.first_labdate)
and date(PreDM_dx.first_labdate, '+180 day')
group by PreDM_dx.patient_num
;
select *
from PreDM_dx_1
;
--returns 1507 patients
```

```
create table Dx_final as
select PreDM_dx_1.*,
case
when PreDM_dx_1.diagnosis is not null then 'Y'
end as dx
from PreDM_dx_1
;
select *
from Dx_final
;
create table Diagnosis as
select Demographics.*, Dx_final.dx
from Demographics
left join Dx_final
on Demographics.patient_num = Dx_final.patient_num
;
select * from Diagnosis
;
create table DX_final as
select Diagnosis.*,
case
when dx is null then 'N'
when dx is 'Y' then 'Y'
end as Diagnosis
from Diagnosis
;
--HYPERLIPIDEMIA
create table HLD as
select patient_num, encounter_num, start_date, variable
from data_view
where variable in ('E78 Disorders of lipoprotein metabolism and other lipidemias', '272
Disorders of lipoid metabolism')
;
create table HLD_1 as
select HLD.*, First_labdate.first_labdate
from HLD
join First_labdate
on HLD.patient_num = First_labdate.patient_num
where HLD.start_date between date('2016-06-01') and First_labdate.first_labdate
group by HLD.patient_num
;
--returns 1410 patients
select *
from HLD_1
;
```

```
create table HLDdx_final as
select HLD_1.*,
case
when HLD_1.variable is not null then 'Y'
end as HLD_dx
from HLD_1
;
select *
from HLDdx_final
;
/*ANTILIPEMIC AGENTS*/
Select * from code_info_view
Where code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257602\%"
;
Select * from data_view
Where code in (Select code from code_info_view
Where code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257602\%"
)
;
create table HLD_meds as
select patient_num, encounter_num, start_date, variable
from data_view
where code in (select code from code_info_view
where code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257602\%")
and modifier not like 'Surescripts%'
;
select * from HLD_meds
;
create table HLD_meds_1 as
select HLD_meds.*, First_labdate.first_labdate
from HLD_meds
join First_labdate
on HLD_meds.patient_num = First_labdate.patient_num
where HLD_meds.start_date between date('2016-06-01') and First_labdate.first_labdate
group by HLD_meds.patient_num
;
select * from HLD_meds_1
;
--returns 1059 patients
create table HLDmed_final as
select HLD_meds_1.*,
case
when HLD_meds_1.variable is not null then 'Y'
end as HLD_Rx
from HLD_meds_1
;
```

```
select *
from HLDmed_final
;
--DEPRESSION
create table Depression as
select patient_num, encounter_num, start_date, variable
from data_view
where variable in ('311 Depressive disorder, not elsewhere classified', 'F32 Major
depressive disorder, single episode')
;
select * from Depression
;
create table Depression_1 as
select Depression.*, First_labdate.first_labdate
from Depression
join First_labdate
on Depression.patient_num = First_labdate.patient_num
where Depression.start_date between date('2016-06-01') and First_labdate.first_labdate
group by Depression.patient_num
;
select * from Depression_1
;
--returns 468 patients
create table Depr_final as
select Depression_1.*,
case
when Depression_1.variable is not null then 'Y'
end as Depr_Dx
from Depression_1
;
select *
from Depr_final
;
create table Antidepr as
select patient_num, encounter_num, start_date, variable
from data_view
where variable in ('[CN600] ANTIDEPRESSANTS')
and modifier not like 'Surescripts%'
;
create table Antidepr_1 as
select Antidepr.*, First_labdate.first_labdate
from Antidepr
join First_labdate
on Antidepr.patient_num = First_labdate.patient_num
where Antidepr.start_date between date('2016-06-01') and First_labdate.first_labdate
group by Antidepr.patient_num
```

```
;
select * from Antidepr_1
;
--returns 1039 patients

create table Antidep_final as
select Antidepr_1.*,
case
when Antidepr_1.variable is not null then 'Y'
end as Antidep_Rx
from Antidepr_1
;
select *
from Antidep_final
;
--HYPERTENSION
create table HTN as
select patient_num, encounter_num, start_date, variable
from data_view
where variable in ('401 Essential hypertension', 'I10 Essential (primary) hypertension')
;
create table HTN_2 as
select HTN.*, First_labdate.first_labdate
from HTN
join First_labdate
on HTN.patient_num = First_labdate.patient_num
where HTN.start_date between date('2016-06-01') and First_labdate.first_labdate
group by HTN.patient_num
;
select * from HTN_2
;
--returns 1824 patients

create table HTN_final as
select HTN_2.*,
case
when HTN_2.variable is not null then 'Y'
end as HTN_Dx
from HTN_2
;
select *
from HTN_final
;
/*ANTIHYPERTENSIVES*/
Select * from data_view
Where code in (Select code from code_info_view
```

```
Where code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257597\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257598\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257599\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257603\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257604\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257607\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257605\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257613\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257614\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257615\%")
;
create table HTN_meds as
select patient_num, encounter_num, start_date, variable
from data_view
Where code in (Select code from code_info_view
Where code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257597\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257598\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257599\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257603\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257604\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257607\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257605\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257613\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257614\%"
or code_path like "\i2b2\Medications\RXAUI:3257595\RXAUI:3257615\%")
and modifier not like 'Surescripts%'
;
select * from HTN_meds
;
create table HTN_meds_1 as
select HTN_meds.*, First_labdate.first_labdate
from HTN_meds
join First_labdate
on HTN_meds.patient_num = First_labdate.patient_num
where HTN_meds.start_date between date('2016-06-01') and First_labdate.first_labdate
group by HTN_meds.patient_num
;
select * from HTN_meds_1
;
--returns 1898 patients

create table HTNmed_final as
select HTN_meds_1.*,
case
when HTN_meds_1.variable is not null then 'Y'
end as HTN_Rx
```

```
from HTN_meds_1
;
select *
from HTNmed_final
;
create table Comorbidity as
select HTNmed_final.patient_num, HTNmed_final.HTN_Rx, HTN_final.HTN_Dx,
HLDdx_final.HLD_dx, HLDmed_final.HLD_Rx, Depr_final.Depr_Dx,
Antidep_final.Antidep_Rx
from HTNmed_final
left join HTN_final
on HTNmed_final.patient_num = HTN_final.patient_num
left join HLDdx_final
on HTNmed_final.patient_num = HLDdx_final.patient_num
left join HLDmed_final
on HTNmed_final.patient_num = HLDmed_final.patient_num
left join Depr_final
on HTNmed_final.patient_num = Depr_final.patient_num
left join Antidep_final
on HTNmed_final.patient_num = Antidep_final.patient_num
;
select * from Comorbidity
;
create table Comorbidity_final as
select Comorbidity.*,
case
when HTN_Rx is not null then 'Y'
when HTN_Dx is not null then 'Y'
when HLD_dx is not null then 'Y'
when HLD_Rx is not null then 'Y'
when Depr_Dx is not null then 'Y'
when Antidep_Rx is not null then 'Y'
end as Any_Comorb
from Comorbidity
;
select * from Comorbidity_final
;
--Any HTN
create table HTN as
select HTNmed_final.patient_num, HTNmed_final.HTN_Rx, HTN_final.HTN_Dx
from HTNmed_final
left join HTN_final
on HTNmed_final.patient_num = HTN_final.patient_num
;
create table HTN_1 as
select HTN.*,
```

```
case
when HTN_Rx is not null then 'Y'
when HTN_Dx is not null then 'Y'
end as Any_HTN
from HTN
;
select * from HTN_1
;
--Any HLD
create table HLD as
select HLDdx_final.patient_num, HLDdx_final.HLD_dx, HLDmed_final.HLD_Rx
from HLDdx_final
left join HLDmed_final
on HLDdx_final.patient_num = HLDmed_final.patient_num
;
select * from HLD
;
create table HLD_1 as
select HLD.*,
case
when HLD_dx is not null then 'Y'
when HLD_Rx is not null then 'Y'
end as Any_HLD
from HLD
;
--Any Depression
select * from Depr_final
;
select * from Antidep_final
;
create table Any_depr as
select Antidep_final.patient_num, Antidep_final.Antidep_Rx, Depr_final.Depr_Dx
from Antidep_final
left join Depr_final
on Antidep_final.patient_num = Depr_final.patient_num
;
select * from Any_depr
;
create table Depr_1 as
select Any_depr.*,
case
when Antidep_Rx is not null then 'Y'
when Depr_Dx is not null then 'Y'
end as Any_Depr
from Any_depr
;
```

```
select * from Depr_1
;
select * from HTN_1
;
select * from HLD_1
;
create table HTN_HLD_DEPR as
select HTN_1.patient_num, HTN_1.Any_HTN, HLD_1.Any_HLD, Depr_1.Any_Depr
from HTN_1
left join HLD_1
on HTN_1.patient_num = HLD_1.patient_num
left join Depr_1
on HTN_1.patient_num = Depr_1.patient_num
;
select * from Comorbidities_final
;
create table Comorb as
select Demographics.*, Comorbidities_final.Any_Comorb,
from Demographics
left join Comorbidities_final
on Demographics.patient_num = Comorbidities_final.patient_num
;
select * from Comorb
;
create table Comorbidities_final as
select Comorb.*,
case
when Any_Comorb is null then 'N'
when Any_Comorb is 'Y' then 'Y'
end as Comorbidity
from Comorb
;
-- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- --
/*...PAYER...*/
select * from data_view
where variable_index = 40
order by data_view.patient_num
;
--taking closest recorded payer to lab date

select *
from Payer
where Payer.Payer_start_date /*or Payer.Payer_end_date*/ between ('2016-06-01') and
('2019-06-01')
group by Payer.patient_num
```

```
order by Payer.patient_num
;
create table Payer_near_labdate as
select Payer.patient_num, Payer.Payer, Payer.Payer_start_date,
Payer.Payer_end_date, First_labdate.first_labdate,
julianday(First_labdate.first_labdate) - julianday(Payer.Payer_start_date) as
days_btw_lab_and_Payer
from Payer
join First_labdate
on First_labdate.patient_num = Payer.patient_num
where Payer.Payer_start_date between date(First_labdate.first_labdate, '-5475 day')
/*minus 10 years, plus 3 years*/
and date(First_labdate.first_labdate, '+1095 day')
;
select *
from Payer_near_labdate
;
create table abs_val_Payer_days as
select patient_num, Payer, abs(days_btw_lab_and_Payer) as abs_val_Payer_days
from Payer_near_labdate
;
select *
from abs_val_Payer_days
;
create table closest_Payer as
select patient_num, Payer, min(abs_val_Payer_days)
from abs_val_Payer_days
group by patient_num
;
select *
from closest_Payer
;
--Payer for 3502 pts

select *
from Payer_map
;
create table Payer_DT as
select closest_Payer.patient_num, closest_Payer.Payer as map_payer, DT_adjusted as
Payer
from closest_Payer
left join payer_map
on closest_Payer.Payer = payer_map.payer_name
;
select * from Payer_DT
;
```

```
select count (distinct patient_num)
from Payer_DT
where Payer_DT.Payer = 'PRIVATE HEALTH INSURANCE'
;
--1936

select count (distinct patient_num)
from Payer_DT
where Payer_DT.Payer = 'NO PAY_SELF PAY'
;
--553

select count (distinct patient_num)
from Payer_DT
where Payer_DT.Payer = 'MEDICARE'
;
--501

select count (distinct patient_num)
from Payer_DT
where Payer_DT.Payer = 'MEDICAID'
;
--293

select count (distinct patient_num)
from Payer_DT
where Payer_DT.Payer = 'GOVT'
;
--45

select count (distinct patient_num)
from Payer_DT
where Payer_DT.Payer = 'OTHER'
;
--134

create table Payer_final as
select Payer_DT.*,
case
when Payer_DT.Payer is 'GOVT' then 'Other'
when Payer_DT.Payer is 'PRIVATE HEALTH INSURANCE' then 'Private'
when Payer_DT.Payer is 'NO PAY_SELF PAY' then 'No Pay_Self Pay'
when Payer_DT.Payer is 'MEDICARE' then 'Medicare'
when Payer_DT.Payer is 'MEDICAID' then 'Medicaid'
When Payer_DT.Payer is 'OTHER' then 'Other'
```

```
end as Payer_final
from Payer_DT
;
select *
from Payer_final
;
select *
from Nutr_final
;
create table Nutrition as
select Demographics.*, Nutr_final.N_referral
from Demographics
left join Nutr_final
on Demographics.patient_num = Nutr_final.patient_num
;
select * from Nutrition
;
create table Nutr_final as
select Nutrition.*,
case
when N_referral is null then 'N'
when N_referral is 'Y' then 'Y'
end as Nutrition
from Nutrition
;
-- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- -- --

select *
from HTN_HLD_DEPR
;
--FINAL ANALYTIC DATASET IN PROGRESS--

create table Final_analytic_set as
select Demographics.*, Dept.Dept
, First_A1c.A1c, BMI_category.BMI, BMI_category.wt_category, Payer_final.Payer_final
as Payer
, HTN_HLD_DEPR.Any_HTN, HTN_HLD_DEPR.Any_HLD,
HTN_HLD_DEPR.Any_Depr, Comorbidities_final.Comorbidity
, Nutr_final.Nutrition, Metf_final.Metformin, Psych_final.Psychology
, WM_final.WtMgt, WLmed_final.Wt_med, Dx_final.Diagnosis
from Demographics
left join Dept
on Demographics.patient_num = Dept.patient_num
left join First_A1c
on Demographics.patient_num = First_A1c.patient_num
left join BMI_category
```

```
on Demographics.patient_num = BMI_category.patient_num
left join Payer_final
on Demographics.patient_num = Payer_final.patient_num
left join HTN_HLD_DEPR
on Demographics.patient_num = HTN_HLD_DEPR.patient_num
left join Comorbidities_final
on Demographics.patient_num = Comorbidities_final.patient_num
left join Nutr_final
on Demographics.patient_num = Nutr_final.patient_num
left join Metf_final
on Demographics.patient_num = Metf_final.patient_num
left join Psych_final
on Demographics.patient_num = Psych_final.patient_num
left join WM_final
on Demographics.patient_num = WM_final.patient_num
left join WLmed_final
on Demographics.patient_num = WLmed_final.patient_num
left join Dx_final
on Demographics.patient_num = Dx_final.patient_num
;
select *
from Final_Analytic_Set
;
```

Appendix 2: R Statistical Analysis Code

```
BL.FFQ <- read.csv(file.choose())
ID.DF <- read.csv(file.choose())
BL.CRP <- read.csv(file.choose())

### Data Wrangling ###
# Create new DF with only randomized participants
ID.Rand <- ID.DF[ which(ID.DF$rand_assign != ''), ]

# Merged randomized IDs with BL FFQ data #
FFQ.Rand <- merge(ID.Rand, BL.FFQ, by.x = 'Subject', by.y = 'ID')

colnames(FFQ.Rand)[colnames(FFQ.Rand) == ''] <- 'Subject'

DP.DF <- merge(FFQ.Rand, BL.CRP, by = "Subject")

# Modified z-scores for outliers #
library(spatialEco)
DP.DF <- DP.DF[-167]
DP.DF$energy.outliers <- outliers(DP.DF$rfkcal)
DP.DF$crp.outliers <- outliers(DP.DF$BL.CRP)
range(DP.DF$crp.outliers)
range(DP.DF$energy.outliers)
range(DP.DF$rfkcal)

# Remove energy outliers
DP.DF1 <- DP.DF[ which(DP.DF$energy.outliers <= 1.25), ]
DP.DF1 <- DP.DF1[ which(DP.DF1$energy.outliers >= -1.25), ]
range(DP.DF1$rfkcal)


# Mutate dx #
dx <- D2D[c('Subject', 'diag_dt_M12')]

library(dplyr)
library(plyr)

dx <- mutate_all(dx, list(~na_if(.,"")))
dx$diag_dt_M12 <- ifelse(dx$diag_dt_M12 == '', 0, 1)


# merge conversion data into dp.df2 #
DP.DF2 <- merge(DP.DF1, dx, by = 'Subject')
```

```
# merge homa-ir scores calculated in excel
homa <- read.csv(file.choose())
DP.DF2 <- merge(DP.DF2, homa, by = 'Subject')


### DP Derivation ###

# Make Artificial Sweetener Variable #
DP.DF1$art.sw <- FFQ.Rand$rfaspt + FFQ.Rand$rfacesk + FFQ.Rand$rfsucl

# Determine Diet Pattern Variables (including energy for adjustment)
dp.vars <- DP.DF2[c(11, 15:21, 28, 30:31, 33, 36, 38, 42:59, 102, 113, 125:127, 156,
165, 76:77, 79, 80, 82)]
dp.vars <- dp.vars[-c(8, 36)]
dp.vars$epa.dha <- dp.vars$rfp20_5 + dp.vars$rfp22_6
dp.vars <- dp.vars[-c(41, 42)]
# Unadjusted diet pattern variables (excludig energy)
dp.vars1 <- dp.vars[-c(1)]
# Create energy adjusted variables for PCovR
dp.vars2 <- dp.vars / (dp.vars$rfkcal/1000)
dp.vars2 <- dp.vars2[-c(1)]

# merge covariates into data frame
covariates <- D2D[c(1,56:89)]
DP.DF2 <- merge(DP.DF2, covariates, by = 'Subject')

# create homa variable for PCovR
homa.bl <- DP.DF2$HOMA2_IR_BASE
homa.bl <- data.frame(homa.bl)


library(PCovR)
homa.bl.pattern.unadjusted <- pcovr(dp.vars1, homa.bl, prepX = 'stand', prepY =
'stand')
summary(homa.bl.pattern.unadjusted)
unadj.homa.loadings <- homa.bl.pattern.unadjusted$Px
unadj.homa.loadings <- t(unadj.homa.loadings)
unadj.homa.loadings <- as.data.frame(unclass(unadj.homa.loadings))
write.csv(unadj.homa.loadings, file = 'Unadjusted HOMA Nutrient Pattern Loadings.csv')

homa.bl.pattern.adjusted <- pcovr(dp.vars2, homa.bl, prepX = 'stand', prepY = 'stand')
summary(homa.bl.pattern.adjusted)
adj.homa.loadings <- homa.bl.pattern.adjusted$Px
adj.homa.loadings <- t(adj.homa.loadings)
adj.homa.loadings <- as.data.frame(unclass(adj.homa.loadings))
```

```
write.csv(adj.homa.loadings, file = 'Adjusted HOMA Nutrient Pattern Loadings.csv')

hdiet <- homa.bl.pattern.adjusted$Te
DP.DF2$HOMA.Nutr1.Unadjusted <- hdiet$component1
DP.DF2$HOMA.Nutr2.Unadjusted <- hdiet$component2
DP.DF2$HOMA.Nutr3.Unadjusted <- hdiet$component3

summary(lm(DP.DF2$HOMA2_IR_BASE ~ DP.DF2$HOMA.Nutr1.Unadjusted))
summary(lm(DP.DF2$HOMA2_IR_BASE ~ DP.DF2$HOMA.Nutr2.Unadjusted))
summary(lm(DP.DF2$HOMA2_IR_BASE ~ DP.DF2$HOMA.Nutr3.Unadjusted))


library(dplyr)
library(plyr)
#Tertiles by adherence
DP.DF2 <- mutate(DP.DF2, HOMA.Nutr1.Unadj.Tertile =
ntile(DP.DF2$HOMA.Nutr1.Unadjusted,3))
DP.DF2$HOMA.Nutr1.Unadj.Tertile <- factor(DP.DF2$HOMA.Nutr1.Unadj.Tertile)
DP.DF2$HOMA.Nutr1.Unadj.Tertile <- revalue(DP.DF2$HOMA.Nutr1.Unadj.Tertile, c('1'
= 'Low', '2' = 'Medium', '3' = 'High'))

DP.DF2 <- mutate(DP.DF2, HOMA.Nutr2.Unadj.Tertile =
ntile(DP.DF2$HOMA.Nutr2.Unadjusted,3))
DP.DF2$HOMA.Nutr2.Unadj.Tertile <- factor(DP.DF2$HOMA.Nutr2.Unadj.Tertile)
DP.DF2$HOMA.Nutr2.Unadj.Tertile <- revalue(DP.DF2$HOMA.Nutr2.Unadj.Tertile, c('1'
= 'Low', '2' = 'Medium', '3' = 'High'))

DP.DF2 <- mutate(DP.DF2, HOMA.Nutr3.Unadj.Tertile =
ntile(DP.DF2$HOMA.Nutr3.Unadjusted,3))
DP.DF2$HOMA.Nutr3.Unadj.Tertile <- factor(DP.DF2$HOMA.Nutr3.Unadj.Tertile)
DP.DF2$HOMA.Nutr3.Unadj.Tertile <- revalue(DP.DF2$HOMA.Nutr3.Unadj.Tertile, c('1'
= 'Low', '2' = 'Medium', '3' = 'High'))


# Preliminary Visualization of Data Prior to Writing Final CSV for SPSS Statistical
Analysis
library(oddsratio)
library(jtools)
DP.DF2$HOMA.Nutr2.Unadj.Tertile <- factor(DP.DF2$HOMA.Nutr2.Unadj.Tertile, levels
= c('Medium', 'Low', 'High'))

log.reg <- glm(Diagnosis ~ HOMA.Nutr3.Unadj.Tertile, family = "binomial", data =
DP.DF2)
summ(log.reg)
OR <- or_glm(data = DP.DF2, model = log.reg, incr = list(Tertile))
OR
```

```
## Write DF with all the new HOMA nutrient pattern variables #
# Add physical activity data
pa.df <- read.csv(file.choose())
DP.DF2 <- merge(DP.DF2, pa.df, by = 'Subject')
write.csv(DP.DF2, file = 'New D2D Data.csv')

## Write characteristics table
library(compareGroups)
DP.DF5$HOMA.Nutr2.Tertile
char <- compareGroups(HOMA.Nutr2.Tertile ~ ., data = DP.DF5)
chartab <- createTable(char, type = 2, digits = 1, digits.p = 2, sd.type = 2,
                       hide.no = "no", show.n = F, show.all = T)
export2word(chartab, file = "Demos by Pattern 2 Tertile.docx", header.labels =
c(p.overall = "p-value"))
```

Appendix 3: Energy-Unadjusted Nutrient Pattern Loadings

Nutrient	Kcal & Animal	Caffeine & Soluble Fiber	Plant-Based
Animal protein	**0.93**	-	-
Vegetable protein	0.33	-	**0.83**
Alcohol	-	-	-
Cholesterol	**0.87**	-	-
Total SFA	**0.80**	-	0.30
Total MUFA	**0.83**	-	0.40
Starch	0.37	-	**0.76**
Soluble fiber	-	**0.89**	-
Insoluble fiber	-	-	**0.86**
Vitamin A	0.39	-	0.36
Vitamin D	0.64	-	0.31
Vitamin E	0.42	-	0.57
Vitamin K	-	-	0.50
Vitamin C	-	-	0.59
Thiamin	0.59	0.37	0.61
Riboflavin	0.56	**0.77**	-
Niacin	0.67	0.41	0.45
Pantothenic acid	0.46	**0.80**	-
Vitamin B6	0.57	-	0.46
Folate	0.51	0.31	0.62
Vitamin B12	0.69	-	-
Calcium	0.63	-	0.45
Phosphorus	**0.80**	-	0.46
Magnesium	0.46	0.50	0.67
Iron	0.60	-	0.63
Zinc	0.78	-	0.45
Copper	0.53	-	-
Selenium	**0.80**	-	0.44
Sodium	0.76	-	0.49
Potassium	0.44	0.63	0.55
Caffeine	-	**0.95**	-
Total trans fatty acids	0.72	-	0.34
Total sugars	0.33	-	0.40
Manganese	-	0.40	0.55
Total CLA	0.72	-	-
Artificial sweeteners	-	-	-
Linoleic acid	0.62	-	0.49
Alpha linolenic acid	0.71	-	0.41
Arachidonic acid	**0.81**	-	-
EPA + DHA	0.49	-	-

Appendix 4: DM Development by Energy-Unadjusted Pattern Adherence

Odds of DM Development					
Pattern Adherence		**Model 1[a]**		**Model 2[b]**	
		OR (95% CI)	**p**	**OR (95% CI)**	**p**
Kcal & Animal	Low				
	Medium	0.81 (0.55, 1.21)	0.31	0.83 (0.55, 1.25)	0.40
	High	1.08 (0.74, 1.57)	0.70	1.00 (0.68, 1.47)	0.99
Caffeine & Soluble Fiber	Low				
	Medium	1.23 (0.83, 1.84)	0.31	1.20 (0.79, 1.81)	0.39
	High	1.40 (0.95, 2.08)	0.09	1.29 (0.86, 1.94)	0.22
Plant-Based	Low				
	Medium	1.47 (0.99, 2.16)	*0.05*	1.45 (0.98, 2.15)	*0.07*
	High	1.09 (0.73, 1.64)	0.68	1.15 (0.76, 1.74)	0.50

[a] Binary logistic regression of 12-month DM development predicted by nutrient pattern adherence.

[b] Binary logistic regression of 12-month DM development predicted by nutrient pattern adherence and all covariates of interest (age, BMI, sex, education, smoking status, physical activity, race, and treatment group).

Pattern	Variance in Nutrient Intake	Variance in HOMA2-IR
Kcal & Animal	52%	0.6%
Caffeine & Soluble Fiber	7%	0.1%
Plant-Based	5%	0.1%