IDENTIFYING CLINICAL PHENOTYPES OF TYPE 1 DIABETES FOR THE CO-OPTIMIZATION OF WEIGHT AND GLYCEMIC CONTROL

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ABSTRACT

Anna R. Kahkoska: Identifying Clinical Phenotypes of Type 1 Diabetes for the Co-Optimization of Weight and Glycemic Control
(Under the direction of Elizabeth J. Mayer-Davis)

Obesity is an increasing concern in the clinical care of youth with type 1 diabetes (T1D). Standard approaches to co-optimize weight and glycemic control are challenged by profound population-level heterogeneity. Therefore, the goal of the dissertation was to apply novel analytic methods to understand heterogeneity in the co-occurrence of weight, glycemia, and underlying patterns of minute-to-minute dysglycemia among youth with T1D.

Data from the SEARCH for Diabetes in Youth study were used to characterize subgroups of youth with T1D showing similar weight status and level of glycemic control as distinct 'weight-glycemia phenotypes' of T1D. Cross-sectional weight-glycemia phenotypes were identified at the 5+ year follow-up visit (n=1,817) using hierarchical clustering on five measures summarizing the joint distribution of body mass index z-score (BMIz) and hemoglobin A1c (HbA1c), generated by reinforcement learning tree predictions. Longitudinal weight-glycemia phenotypes spanning eight years were identified with longitudinal k-means clustering using baseline and follow-up BMIz and HbA1c measures (n=570). Logistic regression modeling tested for differences in the emergence of early/subclinical diabetes complications across subgroups. Seven-day blinded continuous glucose monitoring (CGM) data from baseline of the Flexible Lifestyles Empowering Change randomized trial (n=234, 13-16 years, HbA1c 8-13%)

was clustered with a neural network approach to identify subgroups of adolescents with T1D and elevated HbA1c sharing patterns in their CGM data as ‘dysglycemia phenotypes.’

We identified six cross-sectional weight-glycemia phenotypes, including four normal-weight, one overweight, and one subgroup with obesity. Subgroups showed striking differences in other sociodemographic and clinical characteristics suggesting underlying health inequity. We identified four longitudinal weight-glycemia phenotypes associated with different patterns of early/subclinical complications, providing evidence that exposure to co-occurring obesity and worsening glycemic control may accelerate the development and increase the burden of co-morbid complications. We identified three dysglycemia phenotypes with significantly different patterns in hypoglycemia, hyperglycemia, glycemic variability, and 18-month changes in HbA1c. Patient-level drivers of the dysglycemia phenotypes appear to be different from risk factors for poor glycemic control as measured by HbA1c. These studies provide pragmatic, clinically-relevant examples of how novel statistics may be applied to data from T1D to derive patient subgroups for tailored interventions to improve weight alongside glycemic control.

To Augie

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Chapter 7 contains an essay co-written with Michael T. Lawson, a doctoral candidate in the UNC Department of Biostatistics.

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LIST OF ABBREVIATIONS

AOC	Area over the curve
ARI	Adjusted Rand Index
ATTD	Advanced Technologies & Treatments for Diabetes Congress
AUC	Area under the curve
BMI	Body mass index
BMIz	Body mass index z-score
CGM	Continuous glucose monitoring
$CONGA_n$	Continuous overlapping net glycemic action over an *n*-hour period
CV	Percent coefficient of variation
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DCCT	Diabetes Control and Complications Trial
DPV	Diabetes Prospective Follow-up Study
EDIC	Epidemiology of Diabetes Interventions and Complications
EHR	Electronic health record
FLEX	Flexible Living Empowering Change Randomized Trial
FWER	Family Wise Error Rate
GAD65	Glutamic acid decarboxylase 65-kilodalton isoform
HbA1c	Hemoglobin A1c
IA2	Islet tyrosine phosphatase 2
IQR	Interquartile range
MAGE	Mean amplitude of glucose excursion
MDI	Multiple daily injections

MNAR	Missing not at random
MODD	Mean of daily differences
NHW	Non-Hispanic white
pFRD	Positive false discovery rate
SD	Standard deviation
SE	Standard error
SEARCH	SEARCH for Diabetes in Youth Study
SMART	Sequential multiple assignment randomized trial
SOM	Self-organizing map
T1D	Type 1 diabetes
US	United States
VI	Variable importance
ZnT8	Zinc Transporter 8

CHAPTER 1. INTRODUCTION AND RESEARCH AIMS

1.1 Introduction

The prevalence of obesity in youth and young adults with type 1 diabetes now parallels that of the general population, while the prevalence of overweight in type 1 diabetes is even higher.[1,2] Within this same population, adherence to the complex regimen required to achieve optimal blood glucose is challenging, resulting in various degrees of glycemic control[3-5] and dysglycemia[6,7] (i.e. glycemic variability). Both excess adiposity and poor glycemic control increase the risk of cardiovascular disease later in life.[8-11] Thus, there is a great need for new clinical strategies to co-optimize weight and glycemia among youth with type 1 diabetes to improve long-term cardiovascular outcomes in this heterogenous and high-risk population.

However, the goals and suitability of specific clinical strategies to mitigate cardiovascular disease risk may vary markedly across the spectrum of weight and glycemia seen day-to-day in clinical settings, as well as the specific patterns in dysglycemia that may underlie these outcomes. Thus, the type 1 diabetes patient population is a good candidate for precision medicine. Precision medicine is an emerging field that aims to support personalized medicine decisions with reproducible research, the goal of which is to match subgroups of patients to therapies based on the markers that indicate differential response.[12,13] Targeted application of interventions across population subgroups may increase efficiency and efficacy of prevention and treatment whilst reducing costs of care.[14,15] However, new data-driven approaches to

identify subgroups of type 1 diabetes based on heterogeneity in key clinical features are needed to pave the way for precision medicine interventions to optimize weight and glycemia in type 1 diabetes. Thus, the objective of the dissertation is to apply novel analytic methods to understand heterogeneity in the co-occurrence of weight, glycemia, and underlying patterns of minute-to-minute dysglycemia among youth with type 1 diabetes. There were two main goals: 1) use partially supervised and unsupervised machine learning approaches to identify clinically relevant patient phenotypes of type 1 diabetes; 2) evaluate the clinical utility of data-driven phenotypes to predict clinical outcomes.

1.2 Research Aims

In Aims 1 and 2, we use a data from a large, nationally-representative observational cohort to study a type 1 diabetes phenotype that is observed in the clinic but not well-characterized in epidemiological research**.** We identify subgroups of youth with type 1 diabetes who have a similar weight status and level of blood glucose control as distinct 'weight-glycemia phenotypes' of type 1 diabetes. It is likely that these subgroups with similar weight-status and blood glucose control would benefit from similar therapeutic strategies and can be targeted more efficiently as groups for clinical recommendations. In Aim 3, we shift to a smaller, high-dimensional dataset collected at baseline of a clinical trial to study heterogeneity underlying observed BMIz and HbA1c. We focus on a phenotype defined by shared patterns in measures of dysglycemia obtained from continuous glucose monitoring (CGM) data. We then test how 'dysglycemia' phenotypes of type 1 diabetes are associated with baseline and 18-month changes in BMIz and HbA1c.

Aim 1. To determine an optimal classification system for *cross-sectional* subgroups of youth who share clinical phenotypes based on body mass index z-score (BMIz) and hemoglobin A1c (HbA1c). Aim 1 uses cross-sectional data from the 5+ year follow-up visit of the large, nationally-representative SEARCH for Diabetes in Youth study (SEARCH, n=1,817, ages 7-30). There are three main components to the study.

1A: Cluster individuals in SEARCH by the joint distribution of BMIz and HbA1c and describe the relative prevalence of each subgroup.

1B: Examine aspects of type 1 diabetes and its clinical care, sociodemographic characteristics, and health behaviors/psychosocial features associated with **1A** subgroups.

1C: Compare data-driven weight-glycemia subgroups against *a-priori* classifications based on clinical cut-points[3,16-18] and determine the extent to which simple classifications adequately characterize the heterogeneity in weight and glycemia across the population.

Aim 2: To test how *longitudinal* clinical phenotypes based on weight and glycemia are susceptible to different early or subclinical diabetes complications. Aim 2 uses data from the baseline visit and the 5+ year follow-up visit of the SEARCH study (n=570, diabetes duration>12 months at the baseline visit). There are two main components to the study.

2A: Identify subgroups in SEARCH sharing patterns in BMIz and HbA1c from baseline through the follow-up visit.

2B: Compare the prevalence of early and subclinical complications of diabetes (hyperlipidemia, arterial stiffness, hypertension, diabetic kidney disease, retinopathy, peripheral neuropathy, and cardiovascular autonomic neuropathy) across subgroups at the follow-up visit.

Aim 3: To identify subgroups of youth who share 'dysglycemia phenotypes' based on shared patterns derived from CGM measures at baseline of a clinical trial and test how subgroups differ in terms of baseline and 18-month changes in BMIz and HbA1c. Aim 3 uses data from the Flexible Lifestyles Empowering Change trial (FLEX, n=257, ages 13-16), an NIH-funded 18-month randomized clinical trial testing the efficacy of an adaptive behavioral intervention to promote self-management and improve glycemic control[19]. Participants wore a blinded CGM for 7 days at baseline, at 6 mo-, and at 18-mo visits. There are three main components to the study.

3A: Assess how baseline CGM measures of glucose exposure, hyperglycemia, hypoglycemia, and glycemic variability cluster and how participants can be grouped within these dysglycemia phenotypes.

3B: Characterize dsglycemia clusters according to their baseline sociodemographic, clinical, and psychosocial characteristics.

3C: Test how dysglycemia phenotypes are associated with longitudinal BMIz and HbA1c, accounting for FLEX study site and randomization assignment.

Together, these studies leverage high-dimensional data from two contemporary studies of youth with type 1 diabetes, including a population-based cohort study and a randomized clinical trial, to discover and understand clinically important patient phenotypes and the clinical implications of each. Early recognition of these phenotypes

in youth and adolescents will allow clinicians to offer a tailored care plan that appropriately integrates glycemia and weight-oriented recommendations and strategies. This dissertation provides pragmatic, clinically-relevant examples of how novel statistics and analytic methods may be applied to data from T1D to derive patient subgroups that are sufficiently different to warrant tailored and targeted interventions. Giving voice to the emerging yet vague notion of precision medicine in chronic disease, these results are intended to propel the field to realize the potential of this paradigm for diabetes care.

CHAPTER 2. BACKGROUND AND MOTIVATION

Chapter 2 first provides an overview of type 1 diabetes, including the pathophysiology and etiology, epidemiology, its presentation and clinical care, and key glycemic control outcomes. The chapter then provides an overview of obesity in the setting of type 1 diabetes, including the epidemiology, proposed mechanisms and clinical significance, and the current approaches to clinical management. An overview of precision medicine follows. The chapter concludes with a discussion of the identified clinical needs and research priorities, current gaps in the literature, and key research questions that serve as motivation for the dissertation studies.

2.1 Background on Type 1 Diabetes

2.1.1 Pathophysiology and etiology

Type 1 diabetes is an autoimmune disease that is characterized by an absolute insulin deficiency caused by T-cell–mediated autoimmune destruction of pancreatic β-cells.[20] Defects in insulin secretion result in chronic hyperglycemia and lead to abnormalities of carbohydrate, fat, and protein metabolism.[21] Prior to disease onset, the rate of autoimmune-mediated pancreatic β-cell destruction is variable.[20,22] It has been proposed that youth progress through three distinct stages.[22] Stage 1 is characterized by the presence of β-cell autoimmunity with normoglycemia and a lack of clinical symptoms that lasts from months to years, Stage 2 progresses to measurable dysglycemia, but remains asymptomatic, and Stage 3 is defined as the onset of

symptomatic disease.[22] Individuals become clinically symptomatic when approximately 90% of pancreatic β-cells are destroyed.[22]

The etiology of type 1 diabetes is multifactorial.[21] However, the specific roles for genetic susceptibility, environmental factors, immune response, and β-cell physiology in the pathogenic processes underlying type 1 diabetes remain unclear.[21] In general, individuals at increased risk of developing type 1 diabetes can be identified by a combination of diabetes associated autoantibodies, genetic markers, intravenous glucose tolerance test and/or oral glucose tolerance test.[23-27] Diabetes associated autoantibodies are serological markers of β-cell autoimmunity and include antibodies to GAD65, IA2, ZnT8, and insulin.[28] HLA genotype confers approximately 30-50% of risk for type 1 diabetes.[22,29-31] Genome-wide association studies have also identified numerous non-HLA genes or loci that contribute small to moderate effects on disease risk.[32,33] Environmental triggers of type 1 diabetes are under study and may include infectious diseases such as enterovirus infection[34,35] or other nutritional and chemical exposures months to years before the manifestation of clinical symptoms.[25,36,37]

Of note, the pathophysiology and etiology of type 1 diabetes is distinct from type 2 diabetes, which is characterized by resistance to insulin action and defective tissue response, as well as an inadequate compensatory insulin secretory response for the degree of insulin resistance;[21] type 2 diabetes has only recently emerged among youth and the prevalence is highest among children with obesity and in high risk ethnic populations.[38,39] Autoimmune type 1 diabetes is also distinct from monogenic forms of diabetes, which result from genetic mutations in key genes for the development or function of β-cells.[40,41] The latter is marked by the presentation of mild diabetes with a

significant family history during late youth or adolescence and accounts for less than 4% of pediatric diabetes cases.[42-45]

2.1.2 Epidemiology

The incidence and prevalence of type 1 diabetes varies greatly between different countries, and within countries, between different ethnic populations.[21] Approximately 80,000 children under the age of 15 years are estimated to develop type 1 diabetes annually worldwide.[46] An increase in incidence of type 1 diabetes has been observed globally in recent decades,[39,47-63] with a disproportionately greater increase in those under the age of 5 years[47,64] and in developing countries or those undergoing recent economic transition.[47,55] In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, while across the lifespan, type 1 diabetes accounts for 5-10% of individuals with diabetes.[21]

In the United States, recent data show that the incidence of type 1 diabetes is increasing.[39] The rate of increase is higher among non-Hispanic white youth compared to non-Hispanic white youth (4.2% vs. 1.2%).[39] The prevalence of type 1 diabetes in the United States was highest among white youth and lowest in American Indian youth, with prevalence rates of 2.55 per 1000 (95% CI, 2.48-2.62) versus 0.35 per 1000 (95% CI, 0.26-0.47), respectively.[65]

2.1.3 Presentation and clinical care

Type 1 diabetes in childhood typically presents with characteristic symptoms including polyuria, polydipsia, nocturia, enuresis, weight loss, which may be accompanied by polyphagia, behavioral disturbances, and blurred vision.[20] In advanced cases, diagnosis may present with diabetic ketoacidosis and coma.[20] Impairment of

growth and susceptibility to certain infections may also accompany chronic hyperglycemia.[21] Diagnostic criteria for diabetes are based on laboratory-based blood glucose measurements and the presence or absence of symptoms.[66,67]

Sustained hyperglycemia in type 1 diabetes is linked to the development of chronic complications of the disease, which represent the major source of morbidity and mortality. Complications associated with type 1 diabetes include including microvascular disease (i.e. retinopathy, diabetic kidney disease, neuropathy) and macrovascular disease (i.e. cardiovascular disease).[68] Cardiovascular disease risk is elevated up to 10-fold in type 1 diabetes,[10,11,69] as compared to individuals without type 1 diabetes, and cardiovascular disease is currently the leading cause of death in type 1 diabetes.[70] The benefits of intensive insulin therapy for the prevention of long-term microvascular and microvascular complications of diabetes were demonstrated by the Diabetes Control and Complications Trial (DCCT),[71,72] with persistent benefit over 30 years later.[73,74] In the DCCT, intensive insulin therapy consisted of multiple daily injections or continuous subcutaneous insulin infusion therapy aimed at normal or near-normal blood glucose levels based on frequent self-monitoring and intensified patient education and follow-up.[75] In youth and adolescents, multiple studies have shown that the risk for these outcomes is associated with glycemic control as measured by hemoglobin A1c (HbA1c).[10,74,76,77] Therefore, the daily management of type 1 diabetes is centered on intensifying insulin therapy and engaging patients to maintain blood glucose levels in near-normal ranges to delay or prevent the development of cardiovascular disease risk factors and diabetes-related complications.[78]

To this end, the type 1 diabetes self-management regime includes monitoring blood glucose, dosing insulin, measuring and regulating carbohydrates, and responding to episodes of hypoglycemia with appropriate intake of rapid-acting carbohydrate.[79] Major aspects of clinical care include blood glucose monitoring, which can be accomplished with frequent blood glucose checks or use of newly-developed continuous glucose monitoring systems, and insulin replacement, which is typically accomplished with multiple daily injections or insulin infusion (i.e. insulin pumps).[80] Current American Diabetes Association Standards of Care recommend intensive insulin therapy that consists of multiple-dose insulin injections (3-4 injections/day of basal and prandial insulin) or insulin pump therapy.[81] Optimal nutrition is an important component of the recommended treatment plan for individuals with diabetes,[80,82] although literature on specific diets for type 1 diabetes, including low and very low carbohydrate diets, is mixed and lacking in rigorous, randomized studies.[83] Non-insulin adjuvants have recently been evaluated in combination with insulin to improve glycemic control in the setting of type 1 diabetes, including amylin analogues, metformin, sodium–glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists.[84]

Overall, medical standards of care acknowledge the profound inter-individual differences and suggest individualized care considering patient factors and preferences in the selection of clinical goals, glycemic targets, and therapeutic approach.[80,85] Specific aspects of the type 1 diabetes care plan that can be individualized include insulin regimen, the degree of meal-planning and carbohydrate restriction, physical activity routines, and other supportive aspects of care including psychosocial support and self-management strategies. Within any given self-management strategy, there is

potential for high variability in effect size due to multifactorial, patient-specific characteristics, preferences, values, and abilities.[86] Other key components of the medical management of type 1 diabetes includes the regular screening for subclinical or early complications of diabetes and prompt intervention upon positive findings.[80,85]

2.1.4 Glycemic control outcomes

Glycemic control is a complex clinical outcome related to physiological factors such as insulin sensitivity[87] and residual beta cell function,[88] as well as diabetes treatment regimens and self-management strategies,[89] psychosocial well-being,[90] and behavioral factors.[91,92] Glycemic control is assessed *via* laboratory measures, which capture sustained exposure to hyperglycemia, and continuous glucose monitoring systems, which capture more transient features of hyperglycemia, hypoglycemia, and glycemic variability.

2.1.4.1 Hemoglobin A1c

Hemoglobin A1c (HbA1c) is the most widely used measure of medium-term glycemic control in type 1 diabetes.[78] As the 'gold-standard' clinical assay, HbA1c shows high within-person reliability, is standardized internationally, and represents approximately 8-12 weeks of glucose control in individuals with normal hematological profiles.[93] As described in Section 2.1.3, HbA1c has been directly associated with the risk for long-term diabetic complications in large trials and cohort studies such as the DCCT/EDIC study.[94,95]

The youth and adolescent type 1 diabetes population is characterized by variable degrees of suboptimal glycemic control as measured by HbA1c.[3,4,96] Glycemic control can vary considerably from diabetes onset through adolescence,[97-99] where fluctuations

are known to occur during puberty[77,97,100-106] and during early adulthood. Recent data demonstrate elevated HbA1c levels that peak to >9.0% in 17-year-olds and remain elevated >8.0% until a mean age of 30 years.[107] Poorer glycemic control during early adulthood or from childhood to young adulthood has been attributed to a lack of continuity in diabetes-related clinical care[97,105,106] as well as changes in self-care as children and adolescents with type 1 diabetes grow into adulthood.[102-104]

Among adolescents and young adults, there is evidence of health inequity that affects glycemic control outcomes. Mean HbA1c levels differs by racial and ethnic subgroups.[108] African-American, American Indian, Hispanic, and Asian/Pacific Islander youth with type 1 diabetes are more likely to have higher HbA1c levels compared with non-Hispanic white youth.[3,109] Our research group reported that compared to non-Hispanic white youth, youth with black race or Hispanic ethnicity were at higher risk of being in the highest and most rapidly increasing HbA1c trajectory group over 9 years after diabetes diagnosis; these associations persisted among males and those with diagnosis at age under 9 years.[109] Individual, community, and societal level factors have been posited to drive disparity in diabetes outcomes, such as socioeconomic status or other barriers to health care access[3,96,110] which may result in complex patterns in healthcare utilization and inconsistences in the availability of resources or support for glucose management.[111,112]

There is a substantial body of literature that describes the clinical care and behavioral correlates of HbA1c. Decreasing HbA1c has been associated with insulin pump therapy[4,113,114] and increased frequency of blood glucose monitoring.[89] Among youth, higher diet quality is associated with better glycemic control measured by

HbA1c.[115,116] The association between HbA1c and physical activity is controversial;[117] multiple reports among youth suggest that physical activity generally does not lead to significant reductions in HbA1c,[118,119] which may be attributable to increased food consumption to avoid hypoglycemia or rebound hyperglycemia following exercise.[118] HbA1c is correlated with measures of psychosocial well-being;[120] HbA1c levels have been shown to be positively associated with depressive symptoms[121] and negatively associated with perceived quality of life[122-127] among youth with type 1 diabetes. In addition, disturbed eating behaviors in type 1 diabetes occur at a higher prevalence than in the general population and are associated with suddenly increasing or very high HbA1c levels.[128-131]

The validity of HbA1c as a measure of average glycemic control is affected by co-occurring conditions or drugs that change the glycation of hemoglobin or red blood cell lifespan and turnover, such as anemia and hemoglobinopathies.[93,132] Moreover, there are known racial and ethnic differences in the validity of HbA1c as a measure of average glycemia, presumably owing to racial differences in the glycation of hemoglobin or other factors affecting red blood cell turnover and iron status.[133-135]

2.1.4.2 Continuous Glucose Monitoring

Aside from sustained, chronic hyperglycemia, dysglycemia can manifest as acute glucose fluctuations[93] and glycemic variability;[136] yet HbA1c reflects average glucose level rather than these transient glycemic excursions.[136] Continuous glucose monitoring (CGM) collects and displays measurement of interstitial glucose in an ongoing fashion, providing high amounts of information relating to real-time blood glucose approximately every five minutes for optimal treatment decisions throughout the day and night.[137] CGM

studies have shown that youth with type 1 diabetes may have significant glycemic variability, even at 'well-controlled' HbA1c levels.[138] Moreover, even at the same HbA1c level, individuals may show vastly different measures of short-term dysglycemia measured by CGM.[139]

In particular, CGM data capture two key aspects of dysglycemia that are not represented by HbA1c, including hypoglycemia and glycemic variability. Hypoglycemia is the major barrier to achieving tight glucose control in type 1 diabetes and has been linked to anxiety, decreased quality of life, and excessive morbidity and mortality.[140] Youth with type 1 diabetes are particularly vulnerable to hypoglycemia due to unpredictable food consumption, erratic activity, and problems with accurate insulin dosing and detecting hypoglycemia.[3,7] Glycemic variability quantifies variation in blood glucose levels over time.[139] Multiple measures have been proposed to quantify glycemic variability using CGM data, including standard deviation (SD), percentage coefficient of variation (CV), interquartile range (IQR), mean amplitude of glucose excursion (MAGE), mean of daily differences (MODD), and continuous overlapping net glycemic action over an *n*-hour period ($CONGA_n$).[141] Futher, there may be within-day variability that is depdendent on the time of day[141] as well as between-day variability within one individual.

Emerging evidence suggests that glycemic variability may be a stronger predictor of diabetes complications than sustained hyperglycemia,[93] consistent with findings from the DCCT study showing that patients with same HbA1C levels in the intensive and conventional arms of therapy had differing rates of microvascular complications.[95] The

mechanism for the link between glycemic variability and cardiovascular disease has been proposed as increased oxidative stress[93,142] and vascular damage.[136]

In scientific literature, it has been proposed that incorporating new glucose sensing technologies and metrics of glycemia will be important to better understand the dynamic nature of glucose, which may ultimately help to decrease complications and the burden of type 1 diabetes management on patients.[6] In clinical practice, there is a call to use HbA1c in combination with other metrics of dysglycemia to ultimately tailor an individualized approach that will result in better outcomes and patient empowerment.[6] With wider adoption of continuous glucose monitoring[143] and an increase in the availability of this type of data,[144] recent research has focused on reconciling CGM measures with HbA1c, yielding formulas for converting CGM-derived mean glucose values to a glucose management indicator (CGMI) measure for use in diabetes care and research.[145]

2.2 Background on Obesity in the Setting of Type 1 Diabetes

2.2.1 Epidemiology

In the past, children with type 1 diabetes were thin or normal weight due to impaired glucose utilization associated with insufficient tools and therapies for management and restricted diets to facilitate glucose management.[146] Since the widespread adoption of intensified insulin therapy for the prevention of complications in 1993 based on evidence from the DCCT, the technologies meant to keep blood glucose normal have also promoted weight gain.[146-149]

Today, approximately 36% of adolescents with type 1 diabetes are overweight/obese.[2,150] The prevalence of obesity in youth and young adults with type 1

diabetes parallels that of the general population at approximately 12.6%.[151] The prevalence of overweight is even higher than the general population: 22.1% of adolescents with type 1 diabetes are overweight.[151] Similar prevalence rates have been reported in other US-based cohorts and registries, Canada,[152] and Europe.[2,153-155] The prevalence of obesity increases in people with type 1 diabetes as they age[107,156,157] and has been reported as high as 50% in adults with type 1 diabetes.[107,156-158] For example, the T1D Exchange found that 50% of adults with type 1 diabetes are overweight/obese,[159] consistent with other large scale studies.[160,161]

Multiple studies have shown that females with type 1 diabetes are more likely to be overweight and/or obese than males.[153,162-164] The highest prevalence of overweight and obesity in the setting of type 1 diabetes has been reported among those of Hispanic/Latino descent at approximately 46.1%.[163] Additional socioeconomic predictors of overweight/obese status in type 1 diabetes include lower household income[163] and lower parental education level,[162] although these associations are stronger in females than males.[165]

Epidemiologic correlates of overweight and obesity in type 1 diabetes also include longer type 1 diabetes duration[162,163], higher HbA1c[163,166], and higher insulin dose.[163,164]. Studies investigating insulin pump use and weight gain are mixed; some studies have demonstrated that insulin pump use and higher basal rates lead to overweight/obese status,[164,167] whereas others have not.[168-170]. A physically active lifestyle has been associated with lower BMI and percentage of body fat in type 1 diabetes[171]. Similarly, increased sedentary time is associated with increased adiposity[172,173]. Psychosocial aspects that are associated with overweight or obese

status among individuals with type 1 diabetes include higher depressive symptoms,[174,175] lower quality of life,[162,173,176] and decreased social support, self-esteem, and body image.[177]

2.2.2 Proposed mechanisms and clinical significance

Obesity is a heterogeneous disease that is driven by many factors.[178,179] In a given individual, weight status represents a complex interaction of biological, behavioral, and cultural factors.[180] Among individuals with type 1 diabetes, there are diabetes-specific and non-diabetes specific mechanisms proposed to explain the increasing prevalence of obesity.[181] Epidemiologic evidence shows a clear link between intensive insulin therapy and weight gain in adults[182,183] and youth with type 1 diabetes,[116] possibly owing to the 'unphysiologic' metabolic effects of insulin replacement.[184] For example, exogenous insulin in type 1 diabetes immediately circulates systemically, instead of making a first pass through the portal vein, increasing the anabolic influence on muscle and adipose tissue.[185] This association of insulin therapy and weight gain has also been attributed to decreased glucosuria with tighter glucose control,[186,187] increased caloric intake to treat hypoglycemia,[188,189] increased lipogenesis and fat accumulation and decreased catabolism associated with peripheral hyperinsulinemia,[185,186] which are needed to suppress hepatic glucose production.[190] Type 1 diabetes itself may also be associated with alterations in total energy expenditure and metabolic flexibility, as well as disruption of appetitive hormone signaling, although literature is sparse.[181]

In addition, there are behavioral and psychosocial factors specific to type 1 diabetes and its daily management that may promote unhealthy weight status,[189]

including fear of hypoglycemia,[191] diabulimia,[192] or hypoglycemia-induced binging.[10] Fear of hypoglycemia has been reported as a patient-perceived barrier to physical activity among some youth;[193] several studies have demonstrated that children with type 1 diabetes engage in less physical activity than their peers.[194-196] Youth with type 1 diabetes are at an increased risk of developing disordered eating behaviors, ranging from subclinical behaviors to insulin manipulation in the form of complete omission or intentional under-dosing results for weight loss.[197,198] Finally, it has been posited that recurrent hypoglycemia and its associated intense hunger and permission to eat discouraged sugary foods may lead to over-eating, guilt, restriction, and possibly more episodes of hypoglycemia, creating a self-perpetuating cycle of disordered eating behavior resembling binge eating disorder and bulimia[130,199,200] that may interfere with weight loss and maintenance efforts.

Trends in the type 1 diabetes population parallel epidemiological shifts in the general population associated with the childhood obesity epidemic.[201] In addition, youth with type 1 diabetes share risk factors for overweight and obesity with youth who not have type 1 diabetes,[189] suggesting a role of an obesigenic environment and behavioral aspects that are not specific to diabetes management.

The clinical implications of obesity in type 1 diabetes largely center around long term cardiovascular disease risk.[10,11] Excess adiposity contributes to central obesity, dyslipidemia, elevated blood pressure, and insulin resistance, all of which increase the risk for long-term cardiovascular events.[8,11,202] Recent reviews propose that weight gain associated with insulin therapy may reduce or nullify the benefits of good metabolic control,[155] where individuals in the DCCT who received intensive insulin therapy and

gained the most weight had a significantly higher incidence of major cardiovascular disease events compared to those with minimal weight gain after 14 years of follow-up study.[149] In addition, evidence suggests that the development of other chronic complications of type 1 diabetes may be accelerated by obesity, including retinopathy and neuropathy.[203-205]

2.2.3 Current approaches to clinical management

There are a breadth of clinical strategies and recommendations for general weight loss and weight gain prevention in youth and young adults,[206] ranging from diet alone, diet and exercise, exercise alone, meal replacements, very-low-energy diets, to weight-loss medications and bariatric surgery.[207] Due to heterogeneous response to these interventions,[208] best-practices for weight management emphasize selection of weight-oriented strategies that are tailored to the individual child and family, including dietary goals, physical activity, the home environment, and other self-management behaviors.[209]

For youth with type 1 diabetes, weight management must be integrated with glycemic control, where insulin therapy remains central to medical management.[181] However, recommendations to this end often lack intentional considerations of long-term metabolic effects or energy balance, inadvertently promoting insulin intensification at the expense of weight gain or increased hypoglycemia/carbohydrate rescue. Conceivable weight management approaches for type 1 diabetes include an array of options including lifestyle recommendations as well as non-insulin adjunct therapeutics that may be applied depending on the severity of obesity and ultimate weight goals.[146,189] Currently, however, there are no clinical practice recommendation specific

for type 1 diabetes weight management informed by rigorous, randomized research studies,[181] although a pilot trial funded by the National Institutes of Health is currently underway.

2.3 Background on Precision Medicine

2.3.1 Overview of precision medicine

Precision medicine is an emerging field that aims to support personalized medicine decisions with reproducible research,[12,13] the goal of which is to match subgroups of patients to therapies based on the markers that indicate differential response.[14,15] Such research is imperative particularly when disease presentation, including clinical features and etiologic correlates, or responses to disease treatment are expressed with great heterogeneity across patients.[12,210] The idea at the core of personalized medicine, which seeks to target treatments to individual patients to account for patient heterogeneity, is not new; physicians engage in this work as part of clinical practice.[13,211] Precision medicine, which extends personalized medicine to a population level and seeks to target treatments (or preventative steps) to patients in an empirically-based, scientifically-rigorous, reproducible, and generalizable way, is novel.[12]

Since the rollout of the national Precision Medicine Initiative to personalize approaches toward improving health and treating disease,[13] this paradigm has been effectively applied in the realm of cancer,[212] asthma,[213] and neurological diseases.[214]

2.3.2 Precision medicine for population health

A precision medicine framework can be applied to improve population health via a subgroup approach, which matches patients or subgroups of patients to therapies based on the markers that indicate differential response to therapy.[15,215-217] Subgroup-based precision medicine attempts to segment the population by risk or response into a number of individual strata, to each of which differential interventions may be applied.[14] Application of interventions across population subgroups may increase efficiency and efficacy of prevention and treatment,[14,15] while also reducing costs of care.[218]

Three factors are necessary for precision medicine to improve the health of a patient population. First, there needs to be underlying disease variability with multiple relevant targets for intervention. Second, there must be multiple treatment options that have sufficiently heterogenous responses. Finally, there must be clear clinical markers to link therapies to subgroups of patients likely to exhibit a positive response.[14]

2.3.2.1 Disease phenotyping

A central interest of precision medicine for population health is the stratification of complex diseases, such as diabetes, into more homogeneous patient phenotypes, or subtypes of disease, for targeted therapies or treatment strategies.[219,220] The term phenotype describes ‘any observed quality of an organism, such as its morphology, development or behaviors’, and may include traits that are controlled by genes as well as those that reflect environmental factors.[221] Historically, phenotype was used to describe observable characteristics of a person corresponding to a specific genotype.[220] In recent years, however, the term has been adopted and expanded to describe groups of patients who share a disease diagnosis but are distinct regarding their genomic,

biochemical, or clinical data.[220] Phenotypes can consist of a single parameter (i.e. glycemia) or a group of related features to represent a more complex pathologic state (i.e. metabolic health). Related to the concept of a disease phenotype is a disease ‘endotype’; an "endotype" is proposed to be a subtype of a condition defined by a distinct pathophysiological mechanism. While disease ‘phenotype’ describes ‘clinically observable characteristics’ of a disease without direct relationship to an underlying pathophysiology, ‘endotypes’ describe subtypes of a disease defined by an intrinsically ‘distinct pathogenetic mechanism’ and are discussed heavily in the context of precision medicine for asthma.[222,223]

A challenge for precision medicine is identifying phenotypic subgroups that are meaningfully different from each and sufficient homogenous such that differentiated recommendation or therapies may be provided to each stratum that is effective, cost-effective, and minimizes the prevention of harm.[14,220]

2.3.2.2 Biomarkers

Related to the concept of a phenotype are biomarkers. Biomarkers are broadly defined as any characteristic of an individual that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[224] In a precision medicine framework, an appropriate biomarker is essential to identify patients similar to other cohorts who have historically presented or responded in a specific way.[12,225] Biomarkers can serve a prognostic role, conferring information about a patient’s long-term prognosis or disease status, a predictive role, conferring information about the likelihood that a given intervention will benefit or harm a patient, or a prescriptive role, conferring information

on which course of intervention is preferred for a patient.[12] Like phenotypes, biomarkers are not constrained to a biological basis, but defined by their reliable correlation with differential clinical outcomes or response to intervention.[15,219] The selection of markers depends directly on the way in which patient subgroups are conceptualized or the method by which the population is stratified; a challenge in the field of precision medicine is the transformation of high-dimensional and high-volume data into singular biomarkers or a subset of biomarkers that can predict outcomes and responses with accuracy and robustness.[225]

2.3.2.3 Dynamic treatment regimes

Precision medicine is most clearly operationalized as a dynamic treatment regime, a sequence of decision rules in which a patient is assigned to an intervention based on other available covariates, referred to as 'tailoring variables.'[12] An optimal dynamic treatment regime is estimated from data and maximizes the mean of a specified clinical outcome, or multiple outcomes, when applied to a patient population.[12] Precision medicine recommendations can be based on decision rules estimated from observational data or from clinical trials designed specifically to generate data for this purpose.[12 226,227]

2.3.3 Precision medicine in diabetes care

Diabetes has been described as a heterogeneous disease in which there is a need for more precise 'cataloging of risk factors, identification of pathophysiological pathways and prognostic course, selection of effective therapies, and prediction of outcomes or complications'.[228] Precision medicine in the setting of diabetes has been explored primarily in the context of type 2 diabetes, including pharmacogenetics[229,230]

and attempts to characterize more precise T2D patient populations.[231,232] A notable study by Ahlqvist *et al.* used unsupervised, data-driven approaches to stratify newly diagnosed patients with type 1 and type 2 diabetes in the Swedish All New Diabetics in Scania cohort into subgroups based on six demographic and clinical features, including glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, and homoeostatic model assessment estimates of β-cell function and insulin resistance.[232] The resulting subgroups showed differing patterns of disease progression and risk of complications including diabetic kidney disease and retinopathy,[232] providing compelling evidence regarding the importance of stratified medicine to improve unequal prognosis within the same disease classification.[233]

In type 1 diabetes, it has been suggested that future precision medicine approaches will require more precise patient characterization than past clinical phenotypes[234] that may confer information about variability in further clinical, physiological, and molecular features that vary across the patient population.[235,236] To date, efforts to capture more granular phenotypes have resulted in the conception of new subtypes of type 1 diabetes, including latent autoimmune diabetes and genetic forms which may be responsive to different treatment regimens (i.e. sulfonylureas).[228] However, the majority of research to date is represented by conceptual reviews and viewpoints.[236,237] [234,238,239] There are few examples of applied precision medicine research for the clinical care of type 1 diabetes.

2.4 Motivation for Dissertation Studies

2.4.1 Identified clinical needs and research priorities

A thorough review of the literature reveals new priorities for research in type 1 diabetes. First, recent epidemiologic evidence suggests a need for new care paradigm to optimize two outcomes, weight and glycemic control, for which treatment is inherently related and potentially antagonistic. Second, profound heterogeneity suggests that a deeper understanding of more precise disease subtypes within the complex population is imperative for a precision health system for diabetes.[240,241] Therefore, research is needed to characterize the type 1 diabetes patient population in terms of the major clinical phenotypes who can be approached as subgroups for strategies to tailored to the presentation of key clinical outcomes and the drivers thereof. It is important that an understanding of disease subtypes must be reproducible, interpretable, and actionable,[242] thereby moving the field towards established markers for subgroup-based precision medicine approaches to integrate weight management with the complexities of routine type 1 diabetes care, including both weight loss and prevention of obesity.

2.4.2 Current gaps in the evidence and rationale of approach

Several key gaps in understanding the clinically-relevant phenotypes for weight management and glycemic control in type 1 diabetes were identified. First, although epidemiological evidence suggests population-level associations between BMI and HbA1c,[2,128,243,244] the clinical evolution of type 1 diabetes to include overweight and obesity poses an opportunity to extend the type 1 diabetes etiological classification of disease into a study of the patient subgroups based on weight and glycemic control and understand the clinical utility of this classification system. Second, the majority of

published CGM data in youth and adolescent populations have come from diabetes technology clinical trials where study criteria excluded participants with elevated HbA1c levels,[245] thus, the generalizability to the larger type 1 diabetes population is severely limited[3,143] and there is a need to understand how CGM data can be used to derive clinical phenotypes integrating multiple measures of dysglycemia. Such multifaceted dysglycemia may facilitate a more robust way to study how patterns in transient blood glucose levels act as underlying drivers of weight and glycemic control over time.

2.4.3 Key research questions

There are three key research questions addressed in the following three chapters. Each chapter represents an original research manuscript that is currently under review. Chapter 3 addresses the research question: Are there subgroups of youth with type 1 diabetes who share an observed clinical phenotype based on weight status and glycemic control? Chapter 4 addresses the research question: Are these weight-glycemia phenotypic subgroups susceptible to different cardiovascular disease risk factors and diabetes complications? Finally, Chapter 3 addresses the research questions: Are there further subgroups of youth with type 1 diabetes who share a clinical phenotype based on continuous glucose monitoring measures of dysglycemia? How are dysglycemia phenotypes associated with cross-sectional and longitudinal weight and glycemic control?

CHAPTER 3. CHARACTERIZING THE WEIGHT-GLYCEMIA PHENOTYPE OF TYPE 1 DIBETES IN YOUTH AND YOUNG ADULTHOOD

Individuals with type 1 diabetes present with diverse body weight status and degrees of glycemic control, which may warrant different treatment approaches. The aim of the study was to identify subgroups sharing phenotypes based on *both* weight and glycemia and compare characteristics across subgroups. Participants with type 1 diabetes in the SEARCH Study cohort (n=1,817, 6.0-30.4 years) were seen at a follow-up visit ≥5 years after diagnosis. Hierarchical agglomerative clustering was applied to five measures summarizing the joint distribution of BMI z-score (BMIz) and hemoglobin A1c (HbA1c), estimated by reinforcement learning tree predictions from 28 covariates. Interpretation of cluster weight status and glycemic control was based on mean BMIz and HbA1c, respectively. The sample was 49.5% female and 55.5% non-Hispanic white (NHW); mean±SD age=17.6±4.5 years, diabetes duration=7.8±1.9 years, BMIz= 0.61±0.94, and HbA1c=76±21 mmol/mol (9.1±1.9%). Six weight-glycemia clusters were identified, including four normal-weight, one overweight, and one subgroup with obesity. No cluster had a mean HbA1c <58 mmol/mol (7.5%). Cluster 1 (34%) was normal-weight with the lowest HbA1c and comprised 85% NHW participants with the highest socioeconomic position, insulin pump use, dietary quality, and physical activity. Subgroups with the very poor glycemic control (i.e. ≥108 mmol/mol (≥12.0%); Cluster 4, 4.4%, and Cluster 5, 7.5%) and obesity (Cluster 6, 15.4%) had a lower proportion of NHW youth, lower socioeconomic position, and reported decreased pump use and

poorer health behaviors ($p<0.01$). The study shows that there are distinct subgroups of youth and young adults with type 1 diabetes that share weight-glycemia phenotypes. Subgroups may benefit from tailored interventions addressing differences in clinical care, health behaviors, and underlying health inequity.

3.1 Introduction

As the prevalence of obesity increases worldwide, recent data have shown that the prevalence of overweight and obesity in youth and young adults with type 1 diabetes is even higher than in the general population.[1,2] Excess adiposity increases the risk of cardiovascular disease later in life which is already elevated up to 10-fold in persons with type 1 diabetes. Therefore, there are early efforts to integrate weight management, including both weight loss and prevention of overweight and obesity, with the complexities of routine type 1 diabetes care.[146]

However, the rising numbers of youth and young adults with type 1 diabetes who are overweight or obese has also contributed to the heterogeneity in the type 1 diabetes patient population. Given that appropriate treatment algorithms may vary markedly across the broad spectrum of body weight and glycemia,[236] the type 1 diabetes patient population is a good candidate for precision medicine, which matches interventions to different subgroups of patients expected to show a positive response.[12,15] Epidemiological evidence suggests population-level associations between BMIz and HbA1c;[2,243] however, surprisingly little is known about how weight status and glycemic control are co-distributed across the population and interact to form more nuanced clinical phenotypes of type 1 diabetes. The weight-glycemia phenotype may confer information about goals for treatment and effectiveness of specific therapeutic strategies

for optimizing outcomes simultaneously, especially given that weight gain may be an unintended consequence of intensive insulin therapy in some individuals.[184]

Previous work used data-driven approaches to stratify adults with type 1 diabetes and type 2 diabetes into subgroups based on six 'raw' clinical and physiologic features.[246] Subgroups showed differences in progression of type 2 diabetes and risk for complications.[246] However, few studies have characterized heterogeneity in weight and glycemia *within* the etiologic diagnosis of type 1 diabetes. Therefore, our objective was to use data from a large, diverse cohort of youth and young adults with type 1 diabetes to identify and characterize subgroups sharing clinical phenotypes of type 1 diabetes based on weight status, measured by BMIz, and glycemic control, measured by HbA1c.

3.2 Materials and Methods

3.2.1 Study population

The SEARCH for Diabetes in Youth Study began in 2000 with an overarching objective to describe the incidence and prevalence of youth-onset diabetes in the US by age, sex, and race/ethnicity. Youth and young adults with diabetes diagnosed <20 years of age ("youth") were identified from a population-based incidence registry network at five U.S. sites (South Carolina; Cincinnati, Ohio and surrounding counties; Colorado with southwestern Native American sites; Seattle, Washington and surrounding counties; and Kaiser Permanente Health Plan, Inc., Southern California).[247] A subset of participants with newly diagnosed diabetes between 2002 and 2006 and in 2008 were recruited for a follow-up 'cohort' visit between 2012-2015 if they had attended a baseline visit, had ≥5 years of diabetes duration, and were aged ≥10 years. The subset of youth who were included the SEARCH cohort visit were not significantly different than all other

SEARCH youth diagnosed between the years of 2002 and 2008 in terms of average diabetes onset age, demographics, or clinical measures.[74]

Inclusion criteria for this report consisted of incident cases of type 1 diabetes between 2002-2006 and 2008 who attended the SEARCH cohort visit. Diabetes type for these analyses was based on an etiological classification using diabetes autoantibodies and estimated insulin sensitivity score (euglycemic clamp-validated equation including waist circumference, HbA1c and triglyceride levels) from the baseline visit.[248] Participants who were missing BMIz or HbA1c measures at the cohort visit (n=183) were excluded. The study was approved by Institutional Review Boards with jurisdiction, and the parent, adolescent or young adult, or both provided consent or assent for all participants.

3.2.2 Research visits

Trained personnel administered questionnaires; measured height, weight, and blood pressure; and obtained fasting blood samples. BMI was defined as weight (kilograms) divided by height (meters^2) and converted to a Z-score based on US growth reference data.[249] To facilitate study across youth and young adults, BMIz for individuals $\geq$20 years was estimated assuming an age of 20 years (the maximum age represented in the growth reference); this approach has been operationalized in previous SEARCH studies[74,250] and elsewhere.[251] A blood draw occurred after an 8 hour overnight fast, and medications, including short-acting insulin, were withheld the morning of the visit.

3.2.3 Laboratory measures

Blood samples were obtained under conditions of metabolic stability, defined as no episodes of diabetic ketoacidosis in the preceding month and the absence of fever

and acute infections. They were processed locally and shipped within 24 hours to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA). HbA1c was measured by a dedicated ion exchange high–performance liquid chromatography instrument (TOSOH Bioscience, San Francisco, CA).

3.2.4 Other measures

Demographic measures included sex and self-reported race and ethnicity, categorized as non-Hispanic white, non-Hispanic black, Hispanic, Asian, Native American, Pacific Islander, and other. Highest education by either parent was classified as less than high school degree, high school graduate, some college through associate degree, and bachelor's degree or more. Annual household income was classified as >$75,000, $50,000-75,000, $25,000-49,999 and <$25,000. Socioeconomic position measures included parental education and household income. Healthcare access was measured by health insurance type, classified as none, private, Medicaid, or other.

Insulin regimen was classified as pumps, long-acting with short/rapid-acting insulin injections with ≥3 injections per day, and any other form of multiple or singular daily injections. Self-reported frequency of self-monitoring of blood glucose (SMBG) was categorized as <1, 1-3, and >3 times per day. Diabetes care provider was classified as pediatric endocrinologist, adult endocrinologist, and all other healthcare providers (pediatrician, family practice doctor, nurse practitioner, etc.).

Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CESD).[252] Quality of Life was measured using the Center for Pediatric Quality of Life Inventory™ (PedsQL).[125] The CESD and PedsQL were modeled as continuous variables. Physical activity and screen time were assessed

using questionnaires. High physical activity was classified as vigorous activity 3–7 days weekly. High screen time was classified as 2 or more hours of screen-time per day. Data from a validated food frequency questionnaire (FFQ) was available for 1,643 participants. Dietary quality was assessed by adherence to the Dietary Approaches to Stop Hypertension (DASH) diet using an index score ranging from zero to 80.

3.2.5 Statistical methods

We used cluster analysis to identify and characterize subgroups sharing clinical phenotypes of T1D based on weight status and glycemic control. As opposed to unsupervised clustering analysis, where there is no outcome measure or data labels, we wished to perform a semi-supervised cluster analysis guided by the two outcomes of interest. A challenge in identifying supervised clusters is that noise in a given outcome may obscure true subgroups of clinical interest.[253] Therefore, rather than cluster individuals based on the observed values of BMIz and HbA1c at the cohort visit, we employed a novel, semi-supervised clustering technique to group individuals in SEARCH by five measures of the *joint distribution* of BMIz and HbA1c at the cohort visit: the means and variances of BMIz and HbA1c and their covariance. Although the data used for analysis are cross-sectional, we can obtain an estimate of the within-patient variance by fitting a model for the patient's deviation from their expected outcome, which is the formal definition of variance. The five values summarizing the joint distribution of BMIz and HbA1c were predicted for each individual using reinforcement Learning Trees (RLTs), a type of tree-based machine learning technique,[254] and 28 other characterizing variables that were available for each patient (*X*-variables). The 28 *X*-variables were chosen to capture a breadth of individual

characteristics available at the cohort visit including sociodemographic, clinical, anthropometric, laboratory, psychosocial and behavioral measures (see **Supplemental Table 3.1**). Any given *X*-variable was missing from at most 12% of individuals and imputed by a multiple imputation method, missForest.[255] The resulting RLT-estimated outcomes represent smoothed outcome measures, de-noised by the *X*-variables, which maintain the individual level signal with reduced noise or measurement error.[254] (Of note, the 28 *X*-variables were only used to predict measures of the joint distribution of BMIz and HbA1c for each individual and were not used directly in the cluster analysis.)

The five clustering variables (RLT-predicted means and variances of BMIz and HbA1c and their covariance) were standardized and a hierarchical clustering algorithm with Ward's D2 method and Euclidean distance was applied. The number of clusters was chosen using the NbClust package in R [256] and restricted to considering between four and nine clusters. The smallest cluster was restricted to greater than 50 people for adequate statistical power (>85%) to detect small to medium effects in cluster comparisons.[257] Clustering stability was assessed by sequentially omitting individual clusters, one at a time, and evaluating the agreement of the remaining clusters using the Adjusted Rand Index (ARI).[258] For more information on imputation methods, RLT parameters, clustering methods, stability assessments, and additional analyses, see **Section 3.6, Supplemental Material**.

Clusters were ordered by increasing weight status and then by increasing mean HbA1c. Clusters were named based on mean BMIz and HbA1c using traditional clinical cut-point for ease of interpretation. Cluster weight status was classified as underweight (mean BMIz <-1.64), normal weight (mean BMIz -1.64-<1.04), overweight (mean BMIz

1.04-<1.64), and obesity (mean BMIz ≥1.64), corresponding to <5th, 5-<85th, 85th-<95th, and ≥95th percentile for age and sex, respectively.[18] Cluster glycemic control was defined as good (mean HbA1c <58 mmol/mol (<7.5%)), moderate (mean HbA1c 58-<75 mmol/mol (7.5-<9.0%)), poor (mean HbA1c 75-<108 mmol/mol (9.0-<12.0%)), and very poor (mean HbA1c ≥108 mmol/mol (≥12.0%)).[3] This method of cluster nomenclature does not necessarily represent the weight status and glycemic control of each individual within cluster and instead was selected to facilitate cluster-level phenotypic interpretation and comparisons thereof.

The cross-sectional correlates of each cluster were summarized using descriptive statistics. Date are presented as mean±standard deviation (SD). Overall-tests of difference as well as pairwise comparisons were carried out using ANOVA, t-tests, and chi-squared tests, or Fisher's exact tests, where appropriate. We accounted for multiple comparisons in 1) overall tests of difference, and 2) post-hoc pairwise comparisons between individual clusters. Overall tests were corrected via a Bonferroni adjustment. For pairwise comparisons, we report q-values, which control for the positive False Discovery Rate[259] (pFDR) (see **Section 3.5, Supplemental Material**). p-values and q-values were evaluated at the 0.05 significance level. Data analyses were performed using the statistical analysis software package R version 3.4.1 and SAS 9.4 (SAS Institute, Cary, NC).

3.3 Results

The study included 1,817 individuals with type 1 diabetes, with a mean age of 17.6 (range 6.0-30.4 years) and a mean type 1 diabetes duration of 7.8 years (Table 3.3.1). Six weight-glycemia phenotypic clusters were identified based on measures of

the joint distribution of BMIz and HbA1c (**Figure 3.1**). Based on mean measures, Cluster 1 (n=618, 34.0%) was normal weight with moderate glycemic control (mean BMIz 0.59±0.59, mean HbA1c 61±12 mmol/mol (7.7±1.1%)). Cluster 2 (n=195, 10.7%) was also classified as normal weight with moderate glycemic control but showed a slightly lower mean BMIz and higher mean HbA1c than Cluster 1 (mean BMIz -0.68±0.66, mean HbA1c 68±10 mmol/mol (8.4±0.9%)). Cluster 3 (n=509, 28.0%) was normal weight with poor glycemic control (mean BMIz 0.56±0.62, mean HbA1c 86±12 mmol/mol (10.0±1.1%)). Cluster 4 (n=79, 4.4%%) was normal weight with very poor glycemic control (mean BMIz -1.05±0.83, mean HbA1c 113±15 mmol/mol (12.5±1.4%)). Cluster 5 (n=137, 7.5%) was overweight with very poor glycemic control (mean BMIz 1.29±0.69, mean HbA1c 109±15 mmol/mol (12.1±1.5%)). Cluster 6 (n=279, 15.4%) was those with obesity and moderate glycemic control (mean BMIz 1.74±0.42, mean HbA1c 70±11 mmol/mol (8.6±1.0%)). **Figure 3.2A** depicts the density distribution of BMIz and HbA1c within each weight-glycemia cluster.

Cluster 1 (normal weight with moderate glycemic control) was the largest cluster, comprising 34% of the sample. Based on mean BMIz and HbA1c measures closest to clinical targets, this group was selected as the referent group for individual comparisons. **Tables 3.1** and **3.2** depict the sociodemographic characteristics and the diabetes care, psychosocial, and behavioral factors according to the six weight-glycemia clusters. Participants in Cluster 1 were 46% female, 88% non-Hispanic white and were characterized by the highest measures of socioeconomic position, including 74% having parents with a bachelor's degree or more and 85% with private health insurance. This group also had the highest prevalence of insulin pump use and

frequency of SMBG, the lowest level of depressive symptoms, the highest quality of life, the highest dietary quality, and the highest levels of physical activity (overall $p<0.001$).

One cluster emerged with poor glycemic control (Cluster 3, normal weight with poor glycemic control) and two with mean HbA1c >108 mmol/mol (12.0%) (Cluster 4, normal weight with very poor glycemic control; Cluster 5, overweight with very poor glycemic control). The latter two were the smallest subgroups, comprising approximately 4% and 8% of the sample, respectively. Compared to Cluster 1, these clusters included a significantly higher proportion of non-white individuals (58% and 50%), with the highest proportion of non-Hispanic black individuals in Cluster 4 (28%) and highest prevalence of Hispanic individuals in Cluster 5 (23%) ($q<0.001$). Clusters 4 and 5 also had lower measures of socioeconomic position and significantly lower insulin pump use and less frequent SMBG (**Table 3.2;** all $q<0.001$). Approximately 38% of individuals in Cluster 4 and 41% of Cluster 5 experienced an episode of diabetic ketoacidosis in the past 6 months compared to 10% in Cluster 1. Finally, Clusters 4 and 5 were characterized by higher depressive symptoms, lower quality of life, poorer dietary quality, and greater a proportion of high screen time (all $q<0.001$).

Two clusters were classified as overweight and having obesity (Cluster 5, overweight with very poor glycemic control; Cluster 6, obesity with moderate glycemic control). Compared to Cluster 1, both subgroups contained a higher proportion of females (66% in Cluster 5 and 55% in Cluster 6) and non-white youth. Cluster 6 was also characterized by moderately lower measures of socioeconomic position compared to Cluster 1 (all $q<0.001$).

Additional post-hoc pair-wise comparisons were made between Cluster 5 and Cluster 6, the two overweight/obesity subgroups (**Supplemental Tables 3.2, 3.3,** and **3.4).** Compared to Cluster 6 (obesity with moderate glycemic control), Cluster 5 (overweight with poor glycemic control) comprised more female (q=0.028) and non-white participants (q<0.001). Individuals in Cluster 5 were older at the follow-up visit (q<0.001) and had lower socioeconomic position (q<0.001 for parental education, income, and insurance type) with no significant differences in diabetes duration (p=0.15). These participants were also less likely to use an insulin pump or report frequent SMBG (q<0.001). There was a higher prevalence of high screen time in Cluster 5 (p=0.001) with no significant differences in physical activity (q=0.34).

Table 3.3 depicts other clinical measures across the weight-glycemia clusters. Compared to Cluster 1, Clusters 3, 4, 5, and 6 showed significantly higher blood lipids levels. Cluster 5 showed higher total cholesterol, LDL cholesterol, and triglycerides compared to both the referent Cluster 1 and Cluster 6 (obesity). This group also exhibited higher mean systolic and diastolic blood pressure levels than Cluster 1 and a higher mean diastolic blood pressure compared to Cluster 6 (all q<0.001).

3.4 Discussion

In a large, diverse cohort of youth and young adults with type 1 diabetes, we found evidence of subgroups that share distinct weight-glycemia phenotypes including varying combinations across BMIz and glycemic control parameters. None of the clusters that were identified had a mean Hba1c <58 mmol/mol to be classified as good glycemic control, underscoring that youth and young adults with type 1 diabetes are not meeting the targets put forward by the American Diabetes Association and International

Society for Pediatric and Adolescent Diabetes.[260] Based on mean measures, four clusters were largely normal weight, with the remaining two clusters classified as overweight and having obesity, although there were individuals across all weight status categories who were captured in each cluster based on measures of the joint distribution. Examination of the latter two subgroups reveal that while overweight and poor glycemic control can co-occur in young people with diabetes (i.e. the weight-glycemia phenotype of Cluster 5, comprising 8% of the sample), obesity is not always associated and does not necessarily account for those with poor or very poor glycemic control (i.e. the weight-glycemia phenotype of Cluster 6, comprising 15% of the sample).

Clinical recommendations for individuals with HbA1c levels above target may differ based on weight status, especially given the complicated physiologic relationships between weight and glycemia.[181] For example, approaches for under or normal weight individuals may be centered on insulin intensification while approaches for overweight individuals could balance the glycemic benefits of insulin intensification with the potential for weight gain *via* concurrent behavioral modifications or pharmacological/surgical intervention.[84]

Given the high-risk for long-term complications, we focus our discussion on Clusters 4 and 5, the subgroups with the poorest glycemic control (HbA1c >108 mmol/mol), as well as Cluster 6, the subgroup with obesity and moderate glycemic control. Together, they account for approximately 27% of the study population.

The results corroborate previous reports that glycemic control differs by race and ethnicity among youth and young adults with type 1 diabetes[3,236] and is also associated with lower measures of socioeconomic position including parental education, income,

and health insurance type. The results also substantiate other studies showing that lower household income and parental education level associate with overweight/obesity status in type 1 diabetes[189] and are consistent with reports that youth with type 1 diabetes who are of Hispanic ethnicity and females are at the highest risk of overweight or obesity.[163] This finding is particularly concerning given recent data suggesting that the incidence of type 1 diabetes is increasing most rapidly among Hispanic youth.[39]

Weight-glycemia clusters also showed significant differences in several aspects of clinical care, psychosocial outcomes, and health behaviors that were measured concurrently with BMIz and HbA1c. In our study, the best mean glycemic control was associated with higher use of insulin pump therapy[4] and increased frequency of blood glucose monitoring.[89]

The psychosocial correlates of clusters were consistent with previous studies, including a positive relationship between mean HbA1c levels and mean depressive symptoms and a negative association between mean HbA1c levels and mean perceived quality of life measures.[261] Differences in potentially modifiable behavioral factors underscore that physically active lifestyle and decreased sedentary time are associated with lower BMI and percentage of body fat among people with type 1 diabetes.[189] Unfortunately, overall dietary quality measures were low, even among youth and young adults with the most favorable weight-glycemia phenotype, consistent with previous findings.[121]

The significant differences in clinical parameters across weight-glycemia clusters implicate potential disparity in long-term cardiovascular disease risk across these subgroups.[184] The combination of very high HbA1c and increased insulin needs of

Cluster 5, the overweight subgroup with very poor glycemic control, is suggestive of insulin resistance.[163,184] This group also exhibited the worst cardiovascular disease risk profile including elevated lipid and blood pressure levels. Laboratory measures were significantly elevated compared to Cluster 6, despite the higher mean BMIz of Cluster 6. More work is needed to understand how adiposity and hyperglycemia jointly contribute to cardiovascular disease risk profiles.

One of the most striking results is the pattern with which all other demographic, socioeconomic, clinical care, psychosocial, and behavioral factors track across the clusters derived from measures of the joint distribution of weight and glycemia. It is relevant to note that nonwhite race/ethnicity, lower socioeconomic position and healthcare access, and poorer psychosocial well-being have been shown to be associated with each other and with glycemic control elsewhere in SEARCH studies.[4,261] A maximally effective precision medicine approach to co-optimize weight and glycemia will concern itself with underlying biology as well as characteristics of individuals and resource constraints that may influence outcomes over time. Although the cross-sectional cluster analysis is not designed for causal conclusions, future research is needed to develop the specific interventional strategies to impact weight and glycemia outcomes that considers the close relationships among these economic, social, and cultural factors.

The study has several weaknesses. Despite the collective use of gap statistics and supporting graphs, selection of the number of clusters is subjective. Additional external validation studies are required to understand the generalizability of major weight-glycemia phenotypes across other observational cohort studies of T1D. In

addition, BMIz was used as a proxy for weight status, although this measure may not reflect adiposity.[262,263] and the large age range necessitated imputation of BMIz for participants over 20 years of age using z-score data for age 20 years. To assess for differential error of BMIz on participant age (i.e. youth versus young adults), we stratified the sample by age at follow-up visit (<21 years, n=1,399, ≥21 years, n=418) and independently evaluated clusters in each sample (**Supplemental Table 3.6, Supplemental Figure 3.1**). Despite significant differences in sample sizes, we found largely consistent clustering results in both strata, suggesting that the measure of BMIz did not bias the nature of the clusters across different age ranges. Finally, the current study is cross-sectional and cannot elucidate temporal associations with the weight-glycemia phenotypes nor the longitudinal clinical outcomes. Studies that test these subgroups show different rates or patterns in the emergence of type 1 diabetes complications and cardiovascular disease risk factors may help to inform clinical utility of this weight-glycemia phenotype.

The study also has several strengths. One is inherent in the analytic design; this approach to characterize a phenotype based on two outcomes allows real-life phenotypes to emerge rather than forcing a fit based on a-priori clinical cut-points for weight and glycemic control. In additional analyses, the six weight-glycemia clusters were compared to strata of the same sample defined by clinical cut-points for overweight/obesity and poor glycemic control (see **Supplemental Tables 3.6 and 3.7**). The strata corroborated main descriptive results (i.e. differences in sociodemographic characteristics across subgroups with differing levels of glycemic control), providing face validity to the weight-glycemia clusters. However, the use of a priori cut-points was

found to be less well-suited to identify subgroups sharing clinically-significant yet more nuanced weight-glycemia phenotypes who may otherwise distinguish themselves in a clustering approach, such as the subgroups with very poor glycemic control. For example, clinical cut-points collapsed all individuals in Clusters 3, 4, and 5 in the same strata of glycemic control, despite the notable differences in glycemia (refer to these subgroups in relation to the dashed line denoting poor glycemic control at HbA1c 75 of mmol/mol (9.0%) in **Figure 3.1B.)** A further strength of the study was the novel semi-supervised statistical methods used to identify a phenotype based on two clinical outcomes and their relationship to each other, using all patient information to adjust for potential measurement error and within-person heterogeneity. Additional analyses explored clusters based on the raw (i.e observed) measures of BMIz and HbA1c, denoted “Y-clusters,” for comparison (**Figure 3.2B**). The Y-clusters showed multiple nodes of density and larger within-cluster distribution of BMIz and HbA1c, suggesting higher within-cluster variability due to noise in the raw or observed outcomes that obscures underlying clustering structure in the data. The advantage of clusters driven by predicted measures of the *joint distribution* is that this method uses *X*-variables to denoise the raw outcome measures, thereby maximizing data available in the cohort study to understand the underlying variance in weight and glycemia, and their relationship as a clinical phenotype. Finally, to our knowledge, this is the first study to investigate the spectrum of the weight-glycemia phenotypes of type 1 diabetes and their broad epidemiologic correlates using the large, diverse SEARCH cohort. The study complements previous efforts to address heterogeneity in adult diabetes[246] with a focus on type 1 diabetes in a younger age range to inform earlier interventions.

3.5 Conclusions

In conclusion, we show that the heterogeneous population of youth and young adults with type 1 diabetes is comprised of identifiable subgroups with shared weight-glycemia clinical phenotypes based on measures of the joint distribution of BMIz and HbA1c. Importantly, overweight and obesity present with varying degrees of glycemic control in this population, implicating different therapeutic and clinical strategies to concurrently address weight and glycemia across subgroups. To this end, a precision medicine framework may facilitate a systems-based approach to address health inequity and deliver targeted strategies needed to optimize obesity and dysglycemia, particularly when both are poorly controlled.

Table 3.1. Sociodemographic Characteristics According to Weight-Glycemia Phenotype Clusters 1-6

Characteristics, Mean (SD) or n (%)		Weight-Glycemia Cluster						
	All N=1817	Cluster 1 n=618 (34.0%)	Cluster 2 n=195 (10.7%)	Cluster 3 n=509 (28.0%)	Cluster 4 n=79 (4.4%)	Cluster 5 n=137 (7.5%)	Cluster 6 n=279 (15.4%)	p-value†
Weight-Glycemia								
BMIz	0.61 (0.94)	0.59 (0.59)	-0.68 (0.65)**	0.56 (0.62)	-1.05 (0.83)**	1.29 (0.69)**	1.74 (0.42)**	<0.0001
HbA1c (mmol/mol)	76 (21)	61 (12)	68 (10)	86 (12)	113 (15)	109 (15)	70 (11)	<0.0001
HbA1c (%)	9.1 (1.9)	7.7 (1.1)	8.4 (0.9)**	10.0 (1.1)**	12.5 (1.4)**	12.1 (1.5)**	8.6 (1.0)**	<0.0001
Weight Status‡								<0.0001
Underweight	36 (2.0)	0 (0.0)	17 (8.7)	1 (0.2)	18 (22.8)	0 (0.0)	0 (0.0)	
Normal Weight	1152 (63.4)	467 (75.6)	177 (90.8)**	390 (76.6)	61 (77.2)**	47 (34.3)**	10 (3.6)**	
Overweight	390 (21.5)	138 (22.3)	1 (0.5)**	105 (20.6)	0 (0.0)**	42 (30.7)**	104 (37.3)**	
Obesity	239 (13.2)	13 (2.1)	0 (0.0)**	13 (20.6)	0 (0.0)**	48 (35.0)**	165 (59.1)**	
Glycemic Control§								<0.0001
Good	306 (16.8)	237 (38.4)	31 (15.9)**	2 (0.4)**	0 (0.0)**	0 (0.0)**	36 (12.9)**	
Moderate	656 (36.1)	312 (50.5)	112 (57.4)**	86 (16.9)**	0 (0.0)**	2 (1.5)**	155 (51.6)**	
Poor	704 (38.8)	69 (11.2)	52 (26.7)**	389 (76.4)**	28 (35.4)**	67 (48.9)**	99 (35.5)**	
Very Poor	151 (8.3)	0 (0.0)	0 (0.0)	32 (6.3)**	51 (64.6)**	68 (49.6)**	0 (0.0)**	

Demographic Characteristics								
Age at follow-up (years)	17.6 (4.5)	17.6 (5.0)	16.8 (4.6)*	17.3 (4.1)	19.0 (4.0)*	18.8 (3.6)**	17.7 (4.3)	0.008
Age at diagnosis (years)	9.8 (4.1)	9.8 (4.5)	9.3 (4.0)	9.5 (3.8)	11.1 (3.9)*	10.7 (3.3)*	9.7 (3.9)	0.014
Diabetes duration (months)	93.3 (22.8)	92.2 (23.0)	88.8 (23.1)*	94.1 (22.6)	95.2 (22.4)	97.3 (22.1)*	95.1 (22.9)*	0.050
Female	898 (49.4)	282 (45.6)	62 (31.8)**	286 (56.2)**	25 (31.7)*	90 (65.7)**	153 (54.8)*	<0.0001
Race/ethnicity¶								<0.0001
Non-Hispanic White	1380 (76.0)	542 (87.7)	167 (85.6)	351 (69.0)**	46 (58.2)**	69 (50.4)**	205 (73.5)**	
Non-Hispanic Black	173 (9.5)	17 (2.8)	7 (3.6)	69 (13.6)**	22 (27.9)**	32 (23.4)**	26 (9.3)**	
Hispanic	222 (12.2)	45 (7.3)	19 (9.7)	75 (14.7)**	11 (13.9)**	31 (22.6)**	41 (14.7)**	
Asian Pacific Islander	28 (1.5)	12 (1.9)	2 (1.0)	9 (1.8)**	0 (0.0)**	2 (1.5)**	3 (1.1)**	
Native American	9 (0.5)	1 (0.2)	0 (0.0)	2 (0.4)**	0 (0.0)**	3 (2.2)**	3 (1.1)**	
Other	4 (0.2)	0 (0.0)	0 (0.0)	3 (0.6)**	0 (0.0)**	0 (0.0)**	1 (0.4)**	
Socioeconomic Position								
Parental Education								<0.0001
Bachelor’s degree or more	956 (52.6)	459 (74.3)	143 (73.3)	182 (35.8)**	19 (24.0)**	33 (24.1)**	120 (43.0)**	
Some college through Assoc. degree	578 (31.8)	121 (19.6)	40 (20.5)	217 (42.6)**	32 (40.5)**	61 (44.5)**	107 (38.4)**	
High School degree	214 (11.8)	32 (5.2)	9 (4.6)	86 (16.9)**	20 (25.3)**	28 (20.4)**	39 (14.0)**	

Less than high school degree	69 (3.8)	6 (1.0)	3 (1.5)	24 (4.7)**	8 (10.1)**	15 (11.0)**	13 (4.7)**	
Household Income								<0.0001
>$75,000	682 (37.5)	320 (51.8)	98 (50.2)	138 (27.1)**	7 (7.6)**	22 (16.1)**	98 (25.1)**	
$50,000-75,000	271 (14.9)	99 (16.0)	37 (19.0)	57 (11.2)**	6 (7.6)**	22 (16.1)**	50 (17.9)**	
$25,000-49,000	297 (16.4)	71 (11.5)	26 (13.3)	110 (21.6)**	21 (26.6)**	20 (14.6)**	49 (17.6)**	
<$25,000	277 (15.2)	4 (7.4)	16 (8.2)	103 (20.2)**	25 (31.7)**	47 (34.3)**	40 (14.3)**	
Don't know/refused to answer	290 (16.0)	82 (13.3)	18 (9.2)	101 (19.8)**	21 (26.6)**	26 (19.0)**	42 (15.1)**	
Health insurance type								<0.0001
Private	1309 (72.0)	527 (85.3)	152 (78.0)*	326 (64.1)**	38 (48.1)**	64 (46.7)**	202 (72.4)**	
Medicaid/Medicare	360 (19.8)	53 (8.6)	28 (14.4)*	140 (27.5)**	33 (41.8)**	47 (34.3)**	59 (21.2)**	
None	65 (3.6)	10 (1.6)	3 (1.5)*	24 (4.7)**	5 (6.3)**	16 (11.7)**	7 (2.5)**	
Other	83 (4.6)	28 (4.5)	12 (6.2)*	19 (3.7)**	3 (3.8)**	10 (7.3)**	11 (3.9)**	

All measures are from the cohort visit, unless stated otherwise.
Abbreviations: SD – standard deviation; BMIz – body mass index z-score; HbA1c – hemoglobin A1c.
†Bonferroni-corrected p-value for overall test of difference, based on use of ANOVA, Chi-squared or Fisher's exact test as appropriate. *significant pairwise comparison Cluster 1, where q<0.05. **significant pairwise comparison to Cluster 1, where q<0.001. Pairwise comparisons controlled for the positive false discovery rate.
‡Weight status defined based on BMIz. Underweight was defined as cluster mean BMIz <-1.64 corresponding to the 5th percentile for age and sex. Normal weight was defined as cluster mean BMIz ≥-1.64 and <1.04, corresponding to ≥-the 5th and <85th percentile for age and sex. Overweight was defined as cluster mean BMIz ≥ 1.04 and <1.64, corresponding to ≥85th percentile and <95th percentile for age and sex. Obesity was defined as cluster mean BMIz ≥ 1.64 corresponding to ≥ 95th percentile for age and sex.

[§]Glycemic control was based on HbA1c and defined as good (mean HbA1c <58 mmol/mol (<7.5%)), moderate (mean HbA1c 58 - <75 mmol/mol (7.5 - <9.0%)), poor (mean HbA1c 75 - <108 mmol/mol (9.0 - <12.0%)), and very poor (mean HbA1c ≥108 mmol/mol (≥12.0%))
[¶]Self-reported race and ethnicity were collected using 2000 U.S. Census questions.

Table 3.2. Diabetes Care, Psychosocial, and Behavioral Factors According to Weight-Glycemia Clusters 1-6

Characteristics, Mean (SD) or n (%)		Weight-Glycemia Cluster						
	All N=1817	Cluster 1 n=618 (34.0%)	Cluster 2 n=195 (10.7%)	Cluster 3 n=509 (28.0%)	Cluster 4 n=79 (4.4%)	Cluster 5 n=137 (7.5%)	Cluster 6 n=279 (15.4%)	p-value†
Diabetes Care Factors								
Insulin Regimen								<0.0001
Pump	1036 (57.0)	446 (72.2)	125 (64.1)*	246 (48.3)**	22 (27.9)**	29 (21.2)**	168 (60.2)**	
Long + Short/Rapid Insulin, 3+ Times/Day	341 (18.8)	84 (13.6)	38 (19.5)*	100 (19.7)**	25 (31.7)**	44 (32.1)**	50 (17.9)**	
Long+ Other Combination‡	440 (24.2)	88 (14.2)	32 (16.4)*	163 (32.0)**	32 (40.5)**	64 (46.7)**	61 (21.9)**	
Insulin dose (daily units/Kg)	0.86 (0.38)	0.80 (0.40)	0.78 (0.31)*	0.90 (0.34)**	1.00 (0.42)**	1.01 (0.48)**	0.84 (0.32)*	<0.0001
Blood Glucose Monitoring Frequency								<0.0001
<1/day	107 (5.9)	15 (2.4)	8 (4.1)*	39 (7.7)**	9 (11.4)**	25 (18.3)**	11 (3.9)**	
2-4 x/day	501 (27.6)	90 (14.6)	46 (23.6)*	197 (38.7)**	40 (50.6)**	62 (45.3)**	66 (23.7)**	
>4x/day	1209 (66.5)	513 (83.0)	141 (72.3)*	273 (53.6)**	30 (38.0)**	50 (36.5)**	202 (72.4)**	
Acute Complications (Past 6 Mo)§								
1+ Severe Hypoglycemic Episode	130 (7.2)	56 (9.1)	10 (5.1)	28 (5.5)*	4 (5.1)	6 (4.4)	26 (9.3)	0.273
1+ Diabetic Ketoacidosis Episode	332 (18.3)	61 (9.9)	25 (12.8)	124 (24.4)**	30 (38.0)**	56 (40.9)**	36 (12.9)	<0.0001
Diabetes Care Provider								0.507
Pediatric Endocrinologist	1007 (55.4)	332 (53.7)	108 (55.4)	303 (58.5)*	40 (50.6)	67 (48.9)	157 (56.5)	

Adult Endocrinologist	344 (18.9)	136 (22.0)	31 (15.9)	82 (16.1)*	15 (19.0)	26 (19.0)	54 (19.4)	
All Other[¶]	466 (25.6)	150 (24.3)	56 (28.7)	124 (24.4)*	24 (30.4)	44 (31.1)	68 (24.4)	
Psychosocial Factors								
Depressive Symptoms (CEDS Score)[††]	10.1 (8.7)	7.8 (7.4)	8.3 (7.8)	12.1 (8.8)**	12.7 (11.0)**	15.3 (10.2)**	9.8 (8.4)**	<0.0001
Quality of Life (Peds QL Score)[‡‡]	82.3 (13.3)	85.3 (12.1)	85.4 (11.0)	79.9 (13.3)**	77.7 (16.8)**	75.9 (14.2)**	82.1 (13.1)**	<0.0001
Lifestyle Behavioral Factors								
Adherence to DASH Diet[§§]	46.5 (9.4)	48.7 (9.1)	46.7 (8.6)*	45.3 (9.5)**	44.0 (9.0)**	44.9 (8.8)**	45.2 (9.8)**	<0.0001
Total Energy Intake (kcal)	1699 (788)	1694 (760)	1623 (688)	1746 (860)	1960 (1153)*	1791 (764)*	1559 (623)*	0.010
Total Energy from Fat (%)	37.5 (6.2)	36.8 (6.0)	37.3 (6.6)	38.0 (6.3)*	37.5 (5.9)	38.0 (6.1)	38.0 (6.1)	0.188
Total Energy from Carbohydrate (%)	48.1 (8.2)	49.1 (7.8)	48.3 (8.5)	47.6 (8.6)*	48.2 (7.8)	47.0 (8.3)*	47.1 (7.9)**	0.060
Total Energy from Protein (%)	16.1 (2.6)	16.1 (2.5)	16.3 (2.5)	16.0 (2.7)	15.7 (2.4)	16.4 (2.8)	16.5 (2.5)	0.300
Physically Active[¶¶]	1063 (58.5)	429 (69.4)	118 (60.5)*	264 (51.9)**	36 (45.6)	69 (50.4)**	147 (52.7)**	<0.0001
High Screen Time[¶¶]	924 (50.9)	234 (37.9)	78 (40.0)	309 (60.7)**	57 (72.2)**	96 (70.1)**	150 (53.8)**	<0.0001

All measures are from the cohort visit.
Abbreviations: DASH – Dietary Approach to Stop Hypertension.
Missing Data: n=4 for 1+ Diabetic Ketoacidosis episodes. N=174 for DASH Score, total energy, total energy from carbohydrate, total energy from protein, and total energy from fat. Missingness not different across clusters (p>0.05)
[†]Bonferroni-corrected p-value for overall test of difference, based on use of ANOVA, Chi-squared or Fisher's exact test as appropriate. *significant pairwise comparison Cluster 1, where q<0.05. **significant pairwise comparison to Cluster 1, where q<0.001. Pairwise comparisons controlled for the positive false discovery rate.

‡Includes 2+ Times/Day OR Any Insulin Combination (Excl. Long), 3+ Times/Day OR Any Insulin(s) taken 1x/Day, or any Insulin combination (Excl. Long) 2+/Day
§Self-reported, in the past 6 months
¶Includes family practice doctor, general practice doctor, internist, nurse diabetes educator, nurse practitioner/physician's assistant, dietician/nutritionist, other, unknown, and none
††Center for Epidemiologic Studies Depression Scale, total score
‡‡Peds QL, total score
§§Dietary Approach to Stop Hypertension diet, total score
¶¶Physically active defined as exercise 3-7 days per week. High screen time defined as 2+hours of screen-time per day

Table 3.3. Clinical Characteristics According to Weight-Glycemia Phenotype Clusters 1-6

Characteristics, Mean (SD) or n (%)		Weight-Glycemia Cluster						
	All N=1817	Cluster 1 n=618 (34.0%)	Cluster 2 n=195 (10.7%)	Cluster 3 n=509 (28.0%)	Cluster 4 n=79 (4.4%)	Cluster 5 n=137 (7.5%)	Cluster 6 n=279 (15.4%)	p-value†
Lipids								
Total Cholesterol, mg/dL	169.6 (34.7)	156.2 (25.7)	154.5 (25.7)	177.0 (31.0)**	185.2 (37.6)**	207.9 (51.9)**	172.4 (29.9)**	<0.0001
HDL Cholesterol, mg/dL	55.2 (13.7)	56.5 (13.2)	57.2 (14.2)	57.0 (13.8)*	53.5 (12.6)*	50.6 (13.3)**	50.5 (12.3)**	<0.0001
LDL Cholesterol, mg/dL	96.1 (27.9)	86.6 (21.5)	83.5 (21.8)*	100.6 (26.1)**	104.9 (28.8)**	120.3 (38.4)**	103.1 (27.0)**	<0.0001
VLDL Cholesterol, mg/dL	18.2 (12.5)	13.1 (5.0)	13.8 (5.8)	19.5 (10.5)**	27.0 (16.5)**	36.5 (25.4)**	18.7 (9.4)**	<0.0001
Triglycerides, mg/dL	92.3 (70.8)	65.6 (25.0)	68.8 (29.1)	97.7 (52.4)**	141.7 (123.4)**	195.0 (152.3)**	93.5 (47.1)**	<0.0001
Blood Pressure								
Systolic Blood Pressure, mmHg	106.0 (10.9)	104.9 (10.6)	102.7 (11.2)*	105.3 (10.1)	104.4 (11.4)	111.1 (9.8)**	110.2 (11.6)**	<0.0001
Diastolic Blood Pressure, mmHg	68.5 (8.9)	66.7 (8.5)	66.0 (8.9)	55.6 (23.5)**	69.2 (9.5)*	73.1 (8.2)**	71.1 (32.9)**	<0.0001

Abbreviations: HDL– High Density Lipoproteins; LDL – Low Density Lipoproteins. VLDL – Very Low Density Lipoproteins.

†Bonferroni-corrected p-value for overall test of difference, based on use of ANOVA, Chi-squared or Fisher's exact test as appropriate. *significant pairwise comparison Cluster 1, where q<0.05. **significant pairwise comparison to Cluster 1, where q<0.001. Pairwise comparisons controlled for the positive false discovery rate.

*significant pairwise comparison Cluster 1, where q<0.05. **significant pairwise comparison to Cluster 1, where q<0.001. Controlled for the positive false discovery rate.

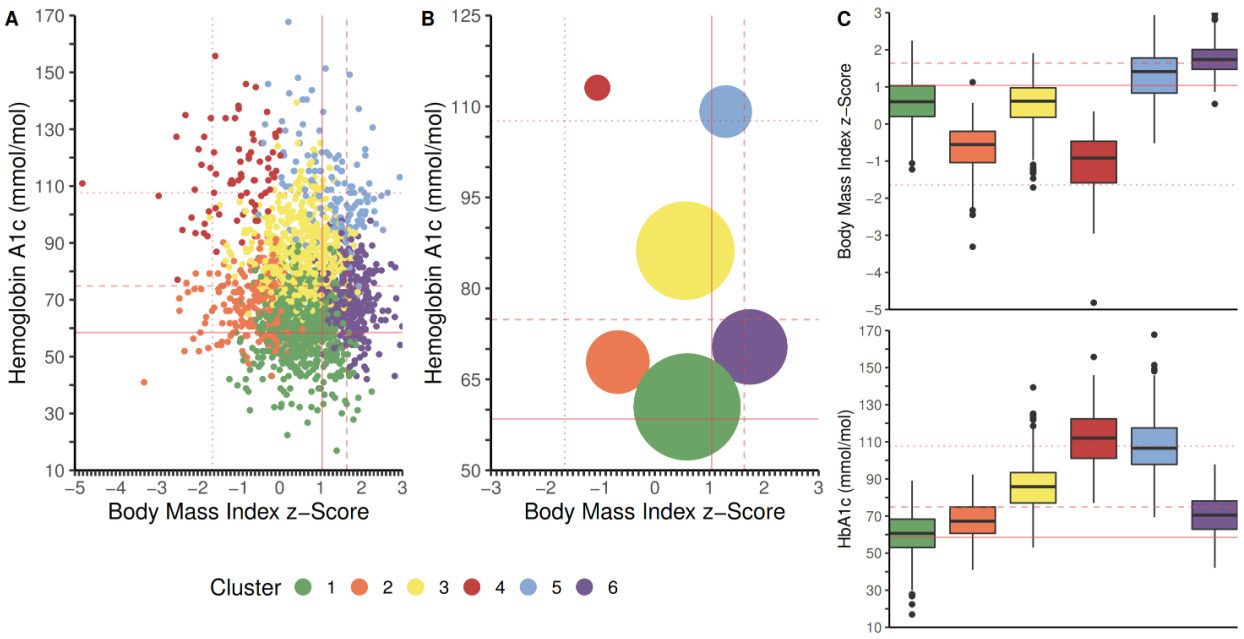


Figure 3.1. Weight-glycemia phenotypic clusters from the SEARCH for Diabetes in Youth Study. Panel A: Scatter plot by body mass index (BMIz) and hemoglobin A1c (HbA1c); each point represents an individual. Panel B: Bubble plot by BMIz and HbA1c; size of circle represents number of individuals within the cluster. Panel C: Box and Whisker plot for BMIz and HbA1c. On the X-axis, the dotted line denotes the BMIz cutoff for underweight (BMIz <-1.64, corresponding to<5th percentile for age and sex), the solid line denotes BMIz cutoff for overweight (BMIz ≥ 1.04, corresponding to ≥ 85th percentile for age and sex), and the dashed lined denotes the BMIz cutoff for obesity (BMIz ≥ 1.64, corresponding to ≥ 95th percentile for age and sex). On the Y-axis, the solid line denotes HbA1c cutoff for moderate glycemic control (HbA1c ≥ 7.5% [58 mmol/mol]), the dashed line denotes the HbA1c cutoff for poor glycemic control (HbA1c ≥ 75 mmol/mol (9.0%)), and the dotted line denotes the HbA1c cutoff for very poor glycemic control (HbA1c ≥ 108 mmol/mol (12.0%)). Clusters include: Cluster 1 (n=618, 34.0%): normal weight with moderate glycemic control (mean BMIz 0.59±0.59, mean HbA1c 61±12 mmol/mol (7.7±1.1%)); Cluster 2 (n=195, 10.7%): normal weight with moderate glycemic (mean BMIz -0.68±0.66, mean HbA1c 68±10 mmol/mol (8.4±0.9%)); Cluster 3 (n=509, 28.0%): normal weight with poor glycemic control (mean BMIz 0.56±0.62, mean HbA1c 86±12 mmol/mol (10.0±1.1%)); Cluster 4 (n=79, 4.4%%): normal weight with poor glycemic control (mean BMIz -1.05±0.83, mean HbA1c 113±15 mmol/mol (12.5±1.4%)); Cluster 5 (n=137, 7.5%): overweight with poor glycemic control (mean BMIz 1.29±0.69, mean HbA1c 109±15 mmol/mol (12.1±1.5%)); Cluster 6 (n=279, 15.4%): obesity with moderate glycemic control (mean BMIz 1.74±0.42, mean HbA1c 70±11 mmol/mol (8.6±1.0%)).

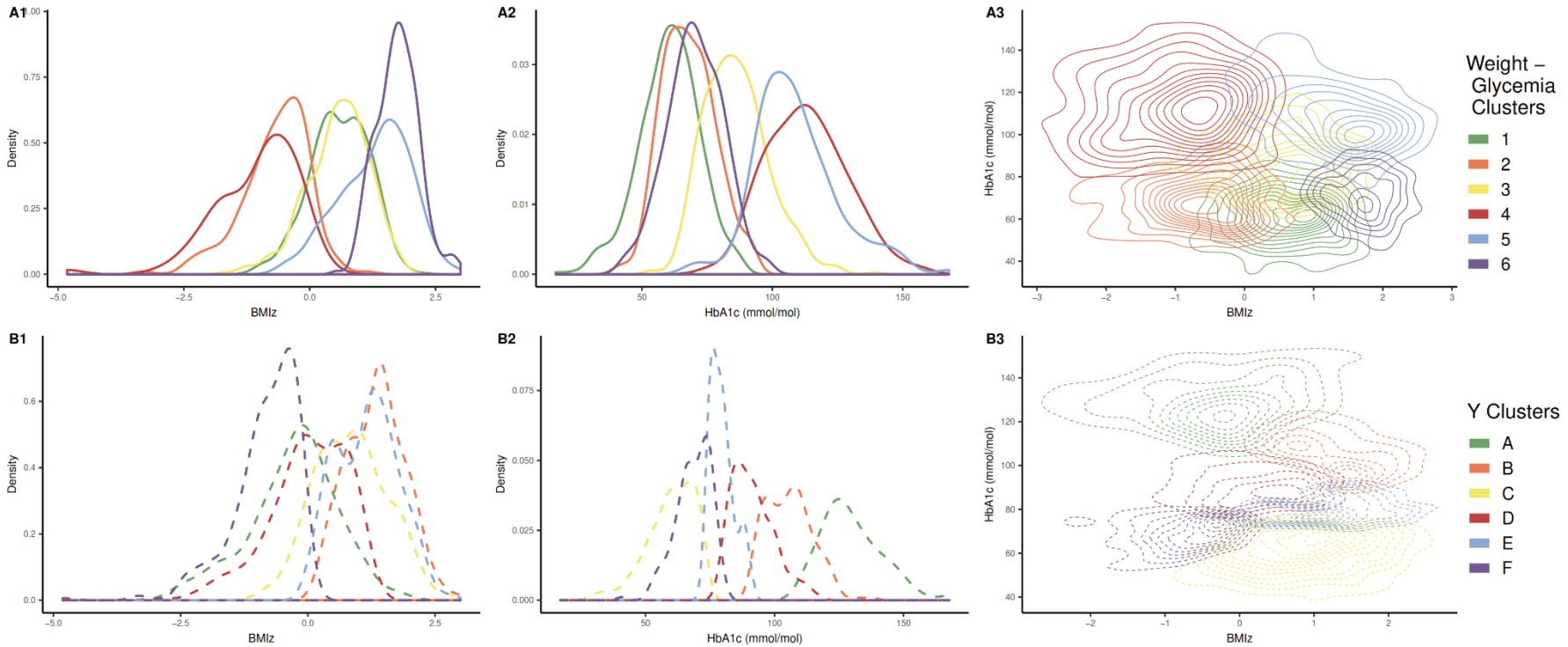


Figure 3.2. Density distribution plots of body mass index z-score (BMIz) and hemoglobin A1c (HbA1c). Panel A depicts weight-glycemia phenotypic clusters, based on predicted measures of the joint distribution of BMIz and HbA1c. A1: Density distribution of BMIz by weight-glycemia cluster. A2: Density distribution of HbA1c by weight-glycemia cluster. A3: Density distribution plot of BMIz and HbA1c by weight-glycemia cluster. Panel B depicts Y-clusters, based on raw, observed measures of BMIz and HbA1c. B1: Density distribution of BMIz by Y-cluster. B2: Density distribution of HbA1c by Y-cluster. B3: Density distribution plot of BMIz and HbA1c by Y-cluster. Ideal clustered subgroups should show distinct, unimodal density distributions. The area under each cluster's curve integrates to 1.

3.6 Supplemental Material

3.6.1 Imputation methods

The clinical outcomes of interest to guide the formation of clusters include BMIz (Y1) and HbA1c (Y2) at the cohort visit. We denote other variables including modifiable and non-modifiable characteristics as X-variables; 28 patient co-variates were chosen to capture a breadth of individual characteristics available at the follow-up visit including sociodemographic, clinical, anthropometric, laboratory, psychosocial and behavioral measures (see **Supplemental Table 3.1**).

To perform Reinforcement Learning Trees (RLT), only complete data can be used. To avoid bias due to possible missing not at random (MNAR) data (i.e. the reason X is missing is related to its missing values), missing X-variables were imputed. In short, a model for each covariate was constructed using all other covariates as predictors. Missing values were replaced with their model predicted values recursively until convergence. As opposed to basic linear models, random forest models were used to capture more complicated relationships between the predictors. This missForest algorithm[255] is described in further detail as follows:

Consider that there are p covariates, $X_1, \ldots, X_p$.

1. A Strawman imputation is performed for all variables initially: each missing value of X_1 is replaced by the median of all observed values of X_i if the variable is continuous, for i=1, . . ., p. If X_1 is categorical, it is replaced by the mode.

2. For all records where X_1 is observed, build a random forest model to predict X_1 using the remaining p-1 covariates, which are either observed or Strawman imputed.
3. Repeat step 2 for all p covariates.
4. Update all Strawman imputed values with their model predicted values from steps 2-3.
5. Repeat the model building and updating steps until desired convergence is observed.

This relatively new method imputes missing values using a random forest prediction model instead of a typical regression and has been shown to work well with highly correlated features. Simulations on this imputation algorithm was performed to show that the joint distribution of covariates is roughly preserved, using Kolmogorov-Smirnov test on the imputed missing at random (MAR) data and the original data. The performance of this imputation method was found to be comparable to that of widely used methods such as multiple imputation by chained equations.[264]

3.6.2 Reinforcement learning trees

The primary objective of the cluster analysis was to group individuals based on a precise weight-glycemia phenotype, i.e. two outcomes that exist across a continuum with variable relationships to each other. To avoid limitations of conventional supervised clustering,[265] we employed a novel, semi-supervised clustering technique to group individuals by five measures of joint distribution of BMIz and HbA1c measured at the follow-up visit: the means and variance of BMIz and HbA1c and their covariance. These measures were estimated by RLT using the X-variables described above (see

Supplemental Table 3.1). Variables that were derived from multiple primary measures were not problematic for RLT as they represented nontrivial derivations of the primary measures.

After imputation, five RLTs were constructed to predict the outcomes and model the variances of and the covariance between BMIz and HbA1c, based on the X-variables. RLT is a tree-based machine learning method that uses bootstrapping and reinforcement learning and exhibits significantly improved performance over traditional tree-based methods, such as random forests.[266] An advantage of RLT is that it assigns a variable importance (VI) value to each variable at each node, selects the variable with highest VI upon which to split, and mutes those with the smallest VI. VI allows for the identification of the factors which most differentiate between subgroups. RLT was performed using primarily default settings from the RLT package in R, Version 3.4.2., with the exception of using 500 trees for stability, and permitting linear combination splits of up to two variables.

3.6.3 Clustering methods

Instead of using the entire covariate space which could be computationally expensive, we thus lowered the dimension to 5 where we believe the following conditional joint distribution of the two outcomes (assuming multivariate normal distribution of the two outcomes) is sufficient to represent the clinical situation of patient features. We define the measure $\widehat{U}_i$ for each individual $i = 1, \dots, n$ as follows.

$$\hat{U}_i = \begin{bmatrix} \hat{U}_1 \\ \hat{U}_2 \\ \hat{U}_3 \\ \hat{U}_4 \\ \hat{U}_5 \end{bmatrix}_i = \begin{bmatrix} \widehat{E}[Y_1|X]/\sigma_1 \\ \widehat{E}[Y_2|X]/\sigma_2 \\ \sqrt{\widehat{Var}[Y_1|X]}/\sigma_1 \\ \sqrt{\widehat{Var}[Y_2|X]}/\sigma_2 \\ \widehat{Corr}_Z[Y_1, Y_2|X] \end{bmatrix}_i, \quad \text{(Eq. 3.1)}$$

where $\sigma_k = \frac{1}{n-1} \sum_{i=1}^{n} (\widehat{U}_{i,k} - \bar{\widehat{U}}_k)'$ for $k = 1, 2$, $\bar{\widehat{U}}_k$ is the average of $\widehat{U}_{i,k}$'s for all $i = 1, \dots, n$, and $\widehat{Corr}_Z$ is the Fisher's z-transformation on the correlation, which is calculated from the covariance estimate.

We standardized the means, variances, and covariance so that they are all comparable on the same unit scale; more specifically, we standardized by scaling over the standard deviation and then take Fischer's z-transformation on the correlation calculated from the covariance.

Because the values in $\widehat{U}$ were standardized to the same scale, we used Euclidean distance measure to determine the dissimilarity between individuals i and j, for $i, j = 1, \dots, n$:

$$D_{ij} = \sqrt{(\widehat{U}_i - \widehat{U}_j)' (\widehat{U}_i - \widehat{U}_j)} \qquad \text{(Eq. 3.2)}$$

This measure directly informs how far two individuals are based on their outcomes, denoised by the X-variables.

A hierarchical clustering algorithm with Ward's D2 method and Euclidean distance was applied to the standardized $\widehat{U}$. The number of clusters was chosen using the NbClust package in R,[256] which takes a vote from 30 methods for choosing number of clusters, including commonly used methods such as gap statistics and average silhouette. The algorithm was restricted to considering clusters between 4 and 9 to characterize the wide range of BMIz and HbA1c at the SEARCH cohort visit but avoid overfitting issues or obscure clinical interpretation. The smallest cluster was restricted to contain at least 50 individuals for adequate statistical power to detect differences in

characteristics between groups. Multiple members of the analysis team provided judgment using all the available information.

3.6.4 Clustering stability

To assess clustering stability, the analysis was repeated sequentially omitting individuals from the same cluster one cluster at a time and observing the distribution of remaining individuals into five clusters. In other words, all individuals from the first cluster are removed, and the analysis is repeated, clustering the remaining individuals into five clusters. Individuals from the first cluster are then brought back in while individuals from the second cluster are removed, and the analysis is repeated again, and so on. For each iteration, the Adjusted Rand Index (ARI) was reported as a measure of clustering stability.[258] ARI measures how similar two clustering methods are, correcting for chance. The mean ARI observed from these six analyses was 0.785±0.05. We interpret the limited variation and a high mean ARI as evidence that our identified clusters are sufficiently stable; the cluster assignments are not sensitive to the removal of other clusters.

3.6.5 Adjustments for multiple comparisons

For each characterizing variable, pairwise comparisons between each cluster and the referent cluster (Cluster 1) were carried out using t-tests and chi-squared or Fisher's exact tests, where appropriate. To control for the positive False Discovery Rate (pFDR)[259] associated with the pairwise comparisons, appropriate adjustments were made separately to continuous and categorical variables, with an additional Bonferroni correction to account for the two categories (continuous and categorical). q-values reported in **Supplemental Tables 3.2-3.4** can be considered as "posterior Bayesian p-

values," or the posterior probability that the null hypothesis is falsely rejected. q-values have been reported in place of p-values, because q-values control for the pFDR whereas p-values control for the Family Wise Error Rate (FWER), or the probability that at least one false rejection has been made. q-values were evaluated at the significance level of 0.05.

3.6.6 Additional analyses

3.6.6.1 Comparison to clusters based on raw, observed measures of BMIz and HbA1c

RLT estimates of the outcomes were selected to capture the joint distribution of and provide smoothed outcome measures informed by the X-variables, as each individual is expected to exhibit some level of within-patient heterogeneity; the smoothed outcomes maintain the individual level signal with reduced noise [254]. Additional analyses to test the validity of clustering methodology explored clustered subgroups based on the raw, observed outcome measures Y1 (BMIz) and Y2 (HbA1c). These clusters were denoted as "Y-Clusters" and are depicted in **Figure 3.2B.** Compared to the weight-glycemia cluster, these clusters showed multiple density nodes for BMIz and HbA1c within clusters, as well as a representation of all outliers within a single cluster (**Figure 3.2B).** Although the Y-clusters based on the raw outcome measures displayed significantly different mean measures of BMIz and HbA1c, the clusters showed a larger within-group distribution of BMIz and HbA1c measures (**Supplemental Table 3.6**). Together, this analysis suggested that noise in the raw, observed outcome variables may obscure the true subgroups of interest.[253]

3.6.6.2 Age-stratified analyses

To facilitate study across youth and young adults, BMIz for individuals ≥20 years was estimated assuming an age of 20 years (the maximum age represented in the growth reference); this approach has been operationalized in previous SEARCH studies[74,250] and elsewhere.[251] Given known challenges in the use of BMIz and in the context of the present analysis, further analyses were undertaken to assess whether the use of BMIz may bias the nature of the clusters. To check the validity of the imputed z-scores and assess for possible differential bias in the results by age (i.e. youth versus young adults), we stratified the sample by age at follow-up visit (<21 years, n=1,399, ≥21 years, n=418) and independently evaluated clusters in each sample. The number of clusters was chosen using the NbClust package in R[256] and restricted to considering between four and nine clusters. Clusters across age strata were compared for consistency in BMIz and HbA1c. We found six clusters in the Under 21 Years stratum and five clusters in the 21 Years and Older stratum (**Supplementary Table 3.6, Supplementary Figure 3.1**). No evidence of differential bias from BMIz was found; the resulting weight-glycemia phenotypes were largely consistent in the stratified samples, where Clusters 3 and 4 in the Under 21 stratum merged to form one aggregated cluster (Cluster 3) in the 21 and Older stratum. Cluster 3 and 4 merged among the ≥21-year-old strata to show one combined cluster (normal weight with poor-very poor glycemic control); this result likely reflects increases in HbA1c known to occur around 17 years of age and last through a mean of 30 years.[107]

3.6.6.3 Comparison to a priori Weight-Glycemia Classifications

An additional, exploratory study used clinical cut-points for BMIz and HbA1c to classify youth and young adults with type 1 diabetes into six weight-glycemia classes and study the proportion and correlates of each subgroup. This analysis was meant to provide context for the cluster analysis, to check the validity of clustered subgroups, and to test if clusters may be useful in gleaning additional insights into the weight-glycemia phenotype of type 1 diabetes.

The study sample from the main cluster analysis was used. Participants were excluded if they were missing a measure of BMIz (n=151) or HbA1c (n=32). A very small proportion of participants were classified as underweight (BMIz<-1.64; ~2%); these participants were excluded to prevent misclassification bias associated with combining subgroups in the analysis.

One and two cut-points were operationalized for weight status and glycemic control, respectively. Weight status was classified as normal weight (BMIz <1.04, corresponding to <85th percentile for age and sex) versus combined overweight/obesity (BMIz ≥1.04, corresponding to ≥85th percentile). Glycemic control was classified as good (HbA1c <7.5% [58 mmol/mol], moderate (HbA1c 7.5-<9.0% [58 - <75 mmol/mol], and poor (HbA1c ≥9.0% [75 mmol/mo]).[3] Crosstabulation of the cut-points yielded six weight-glycemia classes. Descriptive statistics were used to summarize and compare BMIz, HbA1c, and a subset of sociodemographic and clinical characteristics measured at the cohort visit across subgroups. All analyses used a two-sided p-value of 0.05.

The final sample included 1785 youth and young adults with type 1 diabetes (50% female, 76.1% non-Hispanic white, mean age 17.6±4.5 years, mean diabetes

duration 7.8±1.9 years.) The mean BMIz was 0.66±0.87 and the mean HbA1c was 9.1±1.8%. Shown in **Supplemental Table 3.7,** the normal weight subgroup with poor glycemic control represented 1/3 of the sample, comprising the largest weight-glycemia class (Class 1C, 30%). Only 11% of the of SEARCH sample was classified as normal weight with good glycemic control (Class 1A). By contrast, approximately 17% of the sample was classified as overweight or obese with poor glycemic control. The smallest subgroup was overweight or obese with adequate glycemic control (5.6%). The proportion of youth classified as overweight and obese was not significantly different across strata of glycemic control (p=0.60).

There were significant differences in sociodemographic and clinical characteristics across weight-glycemic classes (**Supplementary Table 3.8**). Compared to subgroup with ideal weight and glycemia (Class 1A), subgroups with poor glycemic control (1C and 2C) had lower parental education, income, and private insurance use; these subgroups reported significantly lower pump use and frequency of glucose monitoring ($p < 0.001$). The overweight/obese subgroup with poor glycemic control (Class 2C) also had the highest proportion of females (66.1% versus 44.3% in Class 1A), non-Hispanic Black youth (18.1% versus 2.5%), and Hispanic youth (16.4% versus 9.9%; all $p < 0.0001$).

These results reinforce profound heterogeneity in the clinical presentation of type 1 diabetes; all degrees of glycemic control are represented in normal weight as well as overweight/obese youth. Second, relatively few youths show appropriate weight and

glycemia. Finally, the unequal distribution of socioeconomic position and aspects of clinical care across race/ethnicity is consistent with characteristics of the weight-glycemia clusters.

Supplemental Table 3.1. 28 X-variables for Reinforcement Learning Trees. All measures are from the 5+ year follow-up visit unless specified

Sociodemographic measures	Age at diagnosis, diabetes duration, sex (baseline), race/ethnicity (baseline), parental education attainment, household income level, insurance type
Clinical measures	insulin dose, insulin regimen, frequency of blood glucose monitoring, severe hypoglycemic episodes in the last 6 months, emergency room visits in the last 6 months, hospitalizations in the last 6 months
Anthropometric and laboratory measures	waist circumference, waist to height ratio, systolic and diastolic blood pressure, total cholesterol, non-HDL cholesterol, HDL cholesterol, LDL cholesterol (calculated), triglycerides
Psychosocial and behavioral measures	depressive symptoms, quality of life score, physical activity, smoking status

Supplemental Table 3.2. q-values† for Pairwise Comparisons of Sociodemographic Characteristics According to Weight-Glycemia Phenotype Clusters 1-6

Characteristics			Weight-Glycemia Cluster			
	Cluster 1 vs. Cluster 2	Cluster 1 vs. Cluster 3	Cluster 1 vs. Cluster 4	Cluster 1 vs. Cluster 5	Cluster 1 vs. Cluster 6	Cluster 5 vs. Cluster 6
Weight-Glycemia						
BMIz	4.15E-71	0.144659	5.67E-29	1.76E-21	2.28E-148	1.41E-10
HbA1c (%)	4.88E-16	1.08E-181	3.35E-47	3.68E-75	5.43E-31	1.91E-63
Weight Status‡	7.20E-18	0.335682	1.88E-08	2.29E-39	5.89E-112	9.72E-17
Glycemic Control§	4.61E-11	6.17E-154	3.78E-62	4.28E-93	2.56E-22	9.65E-40
Age at follow-up (years)	0.024023	0.16736	0.002432	5.69E-04	0.228048	0.004529
Age at diagnosis (years)	0.070913	0.065987	0.006348	0.008597	0.269702	0.007673
Diabetes duration (months)	0.037604	0.075612	0.114815	0.009293	0.037353	0.146216
Female	6.62E-04	4.09E-04	0.016631	2.74E-05	0.008735	0.027848
Race/ethnicity¶	0.335682	1.03E-15	1.24E-12	1.20E-21	1.47E-07	2.93E-05
Parental Education	0.388102	1.30E-36	1.54E-22	1.44E-30	2.03E-18	4.09E-04
Household Income	0.249101	1.20E-21	6.11E-19	1.70E-20	1.64E-05	3.33E-06
Insurance type	0.045741	6.97E-18	1.35E-13	1.41E-23	1.90E-06	5.79E-07

Blank cells indicate variables where the overall test of difference was not statistically significant and no pairwise comparisons were performed.

†Controlled for the positive False Discovery Rate (pFDR). q-values can be considered as “posterior Bayesian p-values,” or the posterior probability that the null hypothesis is falsely rejected. q-values have been reported in place of p-values, because q-values control for the pFDR. q-values were evaluated at the significance level of 0.05.

‡Weight status defined based on body mass index z-score (BMIz). Underweight was defined as cluster mean BMIz <-1.64 corresponding to the 5th percentile for age and sex. Normal weight was defined as cluster mean BMIz ≥-1.64 and <1.04, corresponding to ≥-the 5th and <85th percentile for age and sex. Overweight was defined as cluster mean BMIz ≥ 1.04 and <1.64, corresponding to ≥85th percentile and <95th percentile for age and sex. Obesity was defined as cluster mean BMIz ≥ 1.64 corresponding to ≥ 95th percentile for age and sex.

[§]Glycemic control was based on hemoglobin A1c (HbA1c) and defined as good (mean HbA1c <58 mmol/mol (<7.5%)), moderate (mean HbA1c 58 - <75 mmol/mol (7.5 - <9.0%)), poor (mean HbA1c 75 - <108 mmol/mol (9.0 - <12.0%)), and very poor (mean HbA1c ≥108 mmol/mol (≥12.0%))
[¶]Self-reported race and ethnicity were collected using 2000 U.S. Census questions.

Supplemental Table 3.3. q-values† for Pairwise Comparisons of Diabetes Care, Psychosocial, and Behavioral Factors According to Weight-Glycemia Clusters 1-6

Characteristics	Weight-Glycemia Cluster					
	Cluster 1 vs. Cluster 2	Cluster 1 vs. Cluster 3	Cluster 1 vs. Cluster 4	Cluster 1 vs. Cluster 5	Cluster 1 vs. Cluster 6	Cluster 5 vs. Cluster 6
Diabetes Care Factors						
Insulin Regimen	0.042984	4.47E-16	3.01E-14	7.44E-28	9.96E-04	6.98E-13
Insulin dose (daily units/Kg)	0.185203	1.34E-05	1.14E-04	3.48E-06	0.043848	2.01E-04
Blood Glucose Monitoring Frequency	0.003068	5.60E-25	1.60E-18	5.09E-30	9.06E-04	1.35E-12
Use of CGM	0.335682	0.203666	0.28288	0.393682	0.036694	0.069077
Acute Complications (Past 6 Mo)‡						
Severe Hypoglycemic Episodes	--	--	--	--	--	--
Diabetic Ketoacidosis Episodes	0.159907	1.45E-10	1.51E-11	1.13E-18	0.118738	2.70E-10
Diabetes Care Provider	--	--	--	--	--	--
Psychosocial Factors						
Depressive Symptoms (CEDS Score)§	0.145573	1.83E-17	1.45E-04	1.40E-13	3.75E-04	1.67E-07
Quality of Life (Peds QL Score)¶	0.302841	5.31E-12	1.55E-04	2.79E-11	4.45E-04	2.42E-05
Lifestyle Behavioral Factors						
Adherence to DASH Diet‡‡	0.004454	3.19E-11	1.34E-05	3.60E-06	1.34E-05	0.142206
Total Energy Intake (kcal)	0.109875	0.130658	0.034153	0.090996	0.00527	0.002503
Total Energy from Fat (%)	--	--	--	--	--	--

Total Energy from Carbohydrate (%)	--	--	--	--	--	--
Total Energy from Protein (%)	--	--	--	--	--	--
Physically Active[§§]	0.016989	2.66E-09	3.22E-05	2.74E-05	1.82E-06	0.335682
High Screen Time[§§]	0.312454	5.29E-14	1.28E-08	1.51E-11	1.05E-05	0.001483
Smoking Status	0.109654	1.78E-04	2.22E-09	7.16E-04	0.420621	0.001878

Blank cells indicate variables where the overall test of difference was not statistically significant and no pairwise comparisons were performed.

[†]Controlled for the positive False Discovery Rate (pFDR). q-values can be considered as "posterior Bayesian p-values," or the posterior probability that the null hypothesis is falsely rejected. q-values have been reported in place of p-values, because q-values control for the pFDR. q-values were evaluated at the significance level of 0.05.

[‡]Self-reported, in the past 6 months

[§]Center for Epidemiologic Studies Depression Scale, total score

[¶]Peds QL, total score

[‡‡]Dietary Approach to Stop Hypertension diet, total score

[§§]Physically active defined as exercise 3-7 days per week. High screen time defined as 2+hours of screen-time per day

Supplemental Table 3.4. q-values† for Pairwise Comparisons of Clinical Characteristics According to Weight-Glycemia Phenotype Clusters 1-6

Characteristics	Weight-Glycemia Cluster					
	Cluster 1 vs. Cluster 2	Cluster 1 vs. Cluster 3	Cluster 1 vs. Cluster 4	Cluster 1 vs. Cluster 5	Cluster 1 vs. Cluster 6	Cluster 5 vs. Cluster 6
Lipids						
Total Cholesterol, mg/dL	0.164053	6.18E-31	2.58E-09	1.88E-21	6.14E-14	5.99E-12
HDL Cholesterol, mg/dL	0.205732	0.192699	0.027915	4.94E-06	1.05E-10	0.312837
LDL Cholesterol, mg/dL	0.04247	1.06E-20	4.68E-07	6.99E-18	1.27E-17	4.88E-06
VLDL Cholesterol, mg/dL	0.071374	1.45E-32	1.21E-10	1.55E-19	4.15E-18	5.13E-13
Triglycerides, mg/dL	0.075612	1.25E-32	5.12E-07	1.68E-17	2.72E-18	4.10E-12
Blood Pressure						
Systolic Blood Pressure, mmHg	0.008237	0.211486	0.243499	2.84E-10	1.98E-10	0.155705
Diastolic Blood Pressure, mmHg	0.135977	7.46E-05	0.018749	4.07E-14	5.13E-13	0.021609

Blank cells indicate variables where the overall test of difference was not statistically significant and no pairwise comparisons were performed.

†Controlled for the positive False Discovery Rate (pFDR). q-values can be considered as “posterior Bayesian p-values,” or the posterior probability that the null hypothesis is falsely rejected. q-values have been reported in place of p-values, because q-values control for the pFDR. q-values were evaluated at the significance level of 0.05.

Supplemental Table 3.5. Measures of Weight and Glycemic Control According to Y-Clusters 1-6

Characteristics, Mean (SD) or n (%)		Y Clusters						
	All N=1817	Cluster A n=60 (3.3%)	Cluster B n=166 (9.2%)	Cluster C n=806 (44.4%)	Cluster D n=316 (4.4%)	Cluster E n=301 (17.4%)	Cluster F n=168 (9.3%)	p-value†
Weight-Glycemia								
BMIz	0.61 (0.94)	-0.28 (0.86)	1.33 (0.56)	0.84 (0.72)	0.00 (0.81)	1.16 (0.60)	-0.81 (0.61)	<0.001
HbA1c (%)	9.1 (1.9)	14.0 (1.1)	11.8 (0.8)	7.6 (0.9)	10.5 (0.8)	9.4 (0.4)	8.4 (0.63)	<0.001
Weight Status‡								<0.001
Underweight	36 (2.0)	5 (8.3)	0 (0.0)	0 (0.0)	13 (4.1)	0 (0.0)	18 (10.7)	
Normal Weight	1152 (63.4)	52 (88.7)	54 (32.5)	491 (60.9)	285 (90.2)	120 (38.9)	150 (89.3)	
Overweight	390 (21.5)	2 (3.3)	63 (38.0)	189 (23.6)	18 (5.7)	118 (39.2)	0 (0.0)	
Obese	239 (13.2)	5 (8.3)	0 (0.0)	0 (0.0)	13 (4.1)	0 (0.0)	18 (10.7)	
Glycemic Control§								<0.001
Good	306 (16.8)	0 (0.0)	0 (0.0)	292 (36.2)	0 (0.0)	0 (0.0)	14 (8.3)	
Moderate	656 (36.1)	0 (0.0)	0 (0.0)	514 (63.8)	0 (0.0)	27 (9.0)	115 (68.5)	
Poor	704 (38.8)	0 (0.0)	93 (56.0)	0 (0.0)	298 (94.3)	274 (91.0)	39 (23.2)	
Very Poor	151 (8.3)	60 (100.0)	73 (44.0)	0 (0.0)	18 (5.7)	0 (0.0)	0 (0.0)	

Abbreviations: BMIz – body mass index z-score. HbA1c – Hemoglobin A1c.
Y-clusters were generated based on the raw, observed measures of outcomes Y1 (BMIz) and Y2 (HbA1c).
†Bonferroni-corrected p-value for overall test of difference, based on use of ANOVA, Chi-squared or Fisher's exact test as appropriate.
‡Weight status defined based on body mass index z-score (BMIz). Underweight was defined as cluster mean BMIz <-1.64 corresponding to the 5th percentile for age and sex. Normal weight was defined as cluster mean BMIz ≥-1.64 and <1.04, corresponding to ≥-the 5th and <85th percentile for age and sex. Overweight was defined as cluster mean BMIz ≥ 1.04 and <1.64, corresponding to ≥85th percentile and <95th percentile for age and sex. Obesity was defined as cluster mean BMIz ≥ 1.64 corresponding to ≥ 95th percentile for age and sex.
§Glycemic control was based on hemoglobin A1c (HbA1c) and defined as good (mean HbA1c <58 mmol/mol (<7.5%)), moderate (mean HbA1c 58 - <75 mmol/mol (7.5 - <9.0%)), poor (mean HbA1c 75 - <108 mmol/mol (9.0 - <12.0%)), and very poor (mean HbA1c ≥108 mmol/mol (≥12.0%))

Supplementary Table 3.6. Body Mass Index Z-Score (BMIz) And Hemoglobin A1c (HbA1c) According To Weight-Glycemia Phenotype Clusters, in the Full Sample and Stratified by Age at the Follow-Up Visit (<Vs ≥21 Years)

All participants								
	All N=1.817	**Cluster 1** n=618 (34.0%)	**Cluster 2** n=195 (10.7%)	**Cluster 3** n=509 (28.0%)	**Cluster 4** n=79 (4.4%)	**Cluster 5** n=137 (7.5%)	**Cluster 6** n=279 (15.4%)	p-value
BMIz	0.61 (0.94)	0.59 (0.59)	-0.68 (0.65)	0.56 (0.62)	-1.05 (0.83)	1.29 (0.69)	1.74 (0.42)	<0.0001
HbA1c (mmol/mol)	76 (21)	61 (12)	68 (10)	86 (12)	113 (15)	109 (15)	70 (11)	<0.0001
HbA1c (%)	9.1 (1.9)	7.7 (1.1)	8.4 (0.9)	10.0 (1.1)	12.5 (1.4)	12.1 (1.5)	8.6 (1.0)	<0.0001
Participants Under 21 Years								
	All N=1,399	**Cluster 1** n=377 (27.0)	**Cluster 2** n=104 (7.4%)	**Cluster 3** n=360 (25.7%)	**Cluster 4** n=145 (10.4%)	**Cluster 5** n=136 (9.7%)	**Cluster 6** n=277 (19.8%)	p-value
BMIz	0.60 (0.93)	0.32 (0.59)	-1.00 (0.61)	0.51 (0.5)	-0.01 (0.96)	1.71 (0.39)	1.44 (0.49)	<0.0001
HbA1c (mmol/mol)	77 (20)	62 (10)	70 (13)	83 (12)	113 (16)	89 (13)	67 (11)	
HbA1c (%)	9.2 (1.8)	7.8 (0.9)	8.6 (1.2)	9.7 (1.1)	12.5 (1.5)	10.3 (1.2)	8.3 (1.0)	<0.0001
Participants 21 Years and Older								
	All N=418	**Cluster 1** n=127 (30.4%)	**Cluster 2** n=96 (23.0%)	**Cluster 3** n=59 (6.0%)	**Cluster 4** n=70 (16.8%)	**Cluster 5** n=66 (15.8%)		p-value
BMIz	0.64 (1.00)	0.90 (0.49)	-0.22 (0.64)	-0.32 (1.12)	1.03 (0.70)	1.80 (0.46)		<0.0001
HbA1c (mmol/mol)	73 (22)	56 (13)	64 (13)	104 (16)	91 (14)	67 (13)		
HbA1c (%)	8.8 (2.0)	7.3 (1.2)	8.0 (1.2)	11.7 (1.5)	10.5 (1.3)	8.3 (1.2)		<0.0001
Abbreviations: BMIz – body mass index z-score. HbA1c – Hemoglobin A1c.								

Supplemental Table 3.7. Six Weight-Glycemia Classifications for Youth and Young Adults with Type 1 Diabetes Based on 1 Cut-Point for Weight Status and 2 Cut-Points for Glycemic Control

		Glycemia			
Class, n (overall %) Mean BMIz Mean HbA1c, mmol/mol (%) Row % Column %		A. Adequate (HbA1c <58 mmol/mol (7.5%))	B. Fair (HbA1c ≥58 mmol/mol and <75 mmol/mol (≥7.5% and <9.0%))	C. Poor (HbA1c 75 mmol/mol (≥9.0%))	Total
Weight	1. Normal weight (BMIz <1.04)	**Class 1A,** n=203 (11.4%) Mean BMIz: 0.18±0.58 Mean HbA1c: 51±7 mmol/mol (6.8±0.6%) 17.6% 67.2%	**Class 1B,** n=415 (23.3%) Mean BMIz: 0.18±0.62 Mean HbA1c: 68±4 mmol/mol (8.2±0.4%) 35.9% 64.0%	**Class 1C,** n=537 (30.1%) Mean BMIz: 0.14±0.63 Mean HbA1c: 93±16 mmol/mol (10.7±1.5%) 46.5% 64.3%	1155 (64.7%)
	2. Overweight/Obese (BMIz ≥1.04)	**Class 2A,** n=99 (5.6) Mean BMIz: 01.58±0.38 Mean HbA1c: 49±8 mmol/mol (6.6±0.7%) 15.7%) 32.8%	**Class 2B,** n=233 (13.1%) Mean BMIz: 01.56±0.41 Mean HbA1c: 66±4 mmol/mol (8.2±0.4% 37.0%) 36.0%	**Class 2C,** n=298 (16.7%) Mean BMIz: 1.57±0.39 Mean HbA1c: 91±13 mmol/mol (10.5±1.2%) 47.3% 35.7%	391 (21.9%)
	Total	302 (16.9%)	648 (36.3%)	835 (46.8%)	1785 (100%) Mean BMIz: 0.66±0.87 Mean HbA1c: 76±20 mmol/mol (9.1±1.8)

Abbreviations: BMIz – body mass index z-score. HbA1c – Hemoglobin A1c. Class Nomenclature: 1 versus 2 signifies Normal Weight versus Overweight/Obese. A, B, and C signifies good, moderate, and poor glycemic control, respectively.

Supplementary Table 3.8. Selected Characteristics According to the 4 Weight-Glycemia Classifications

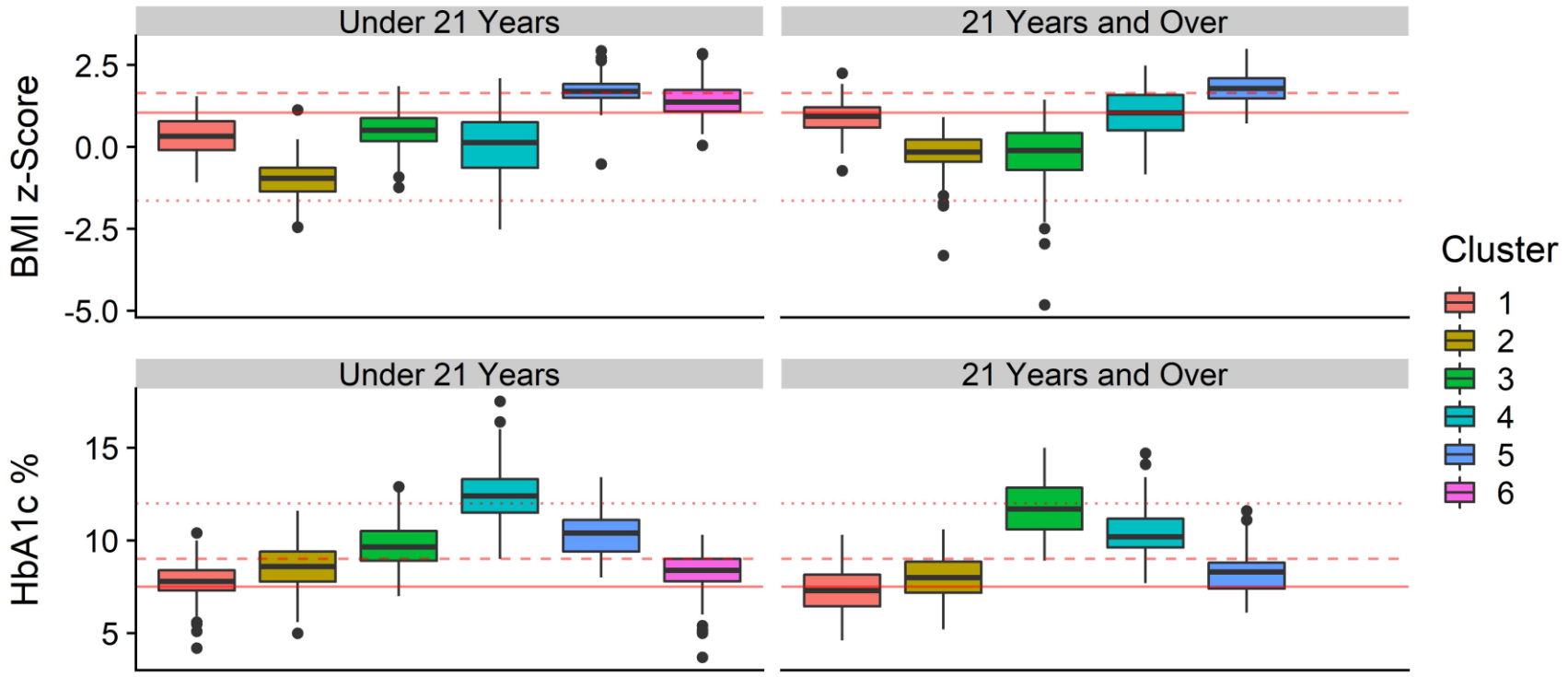
Characteristics, Mean (SD) or n (%)	Weight-Glycemia Class							
	All	Class 1A: Nw, Good glycemic control	Class 1B: Nw, Moderate glycemic control	Class 1C: Nw, Poor glycemic control	Class 2A: Ow/Ob, Good glycemic control	Class 2B: Ow/Ob, Moderate glycemic control	Class 2C: Ow/Ob, Poor glycemic control	p-value†
	N=1785	N=203	N=415	N=537	N=99	N=233	N=298	
Weight and Glycemia Measures								
BMIz	0.66 (0.87)	0.18 (0.58)	0.18 (0.62)	0.14 (0.63)	1.58 (0.38)	1.56 (0.41)	1.57 (0.39)	<0.0001
HbA1c, %	9.1 (1.8)	6.8 (0.6)	8.2 (0.4)	10.7 (1.5)	6.6 (0.7)	8.2 (0.4)	10.5 (1.2)	<0.0001
Demographic Characteristics								
Female	892 (50.0)	90 (44.3)	175 (42.2)	263 (49.0)	42 (42.4)	125 (53.7)	197 (66.1)	<0.0001
Age at Cohort Visit, years	17.6 (4.5)	18.7 (4.9)	16.2 (4.8)	17.8 (4.2)	20.5 (4.7)	17.3 (4.4)	17.7 (3.8)	<0.0001
Age at Diagnosis, years	9.8 (4.1)	11.0 (4.4)	8.5 (4.1)	9.9 (4.0)	12.1 (4.1)	9.5 (4.1)	9.8 (3.6)	<0.0001
Diabetes Duration, months	93.2 (22.8)	92.3 (23.66)	89.9 (22.5)	94.8 (23.0)	100.6 (23.1)	92.8 (21.3)	93.6 (22.8)	0.0004
Race/ethnicity								<0.0001
Non-Hispanic White	1358 (76.1)	172 (84.7)	356 (85.8)	384 (71.5)	73 (73.7)	184 (79.0)	189 (63.4)	
Non-Hispanic Black	166 (9.3)	5 (2.5)	14 (3.4)	67 (12.5)	10 (10.0)	16 (6.9)	54 (18.1)	
Hispanic	218 (12.2)	20 (9.9)	38 (9.2)	71 (13.2)	11 (11.1)	29 (12.5)	49 (16.4)	

Socioeconomic Position								
Parental Bachelor's degree or more	932 (52.0)	154 (76.6)	255 (61.9)	229 (44.0)	54 (54.6)	122 (52.6)	118 (40.4)	<0.0001
Household Income >$75,000	668 (15.3)	92 (45.5)	199 (48.0)	149 (27.9)	33 (33.3)	98 (42.4)	97 (32.8)	<0.0001
Private Health insurance	1278 (72.0)	168 (82.8)	328 (79.6)	336 (63.2)	77 (77.8)	176 (75.9)	193 (65.2)	<0.0001
Diabetes Care Factors								
Insulin pump use (versus multiple daily injections)	1009 (57.6)	137 (70.3)	279 (67.6)	243 (45.8)	55 (63.2)	142 (61.2)	153 (52.0)	<0.0001
Blood Glucose Monitoring >4x/day	1158 (66.9)	158 (80.6)	328 (80.8)	280 (53.6)	58 (65.2)	170 (74.2)	164 (56.8)	<0.0001
1+ Severe Hypoglycemia‡	130 (7.3)	18 (8.9)	27 (6.5)	30 (5.6)	12 (12.1)	26 (11.2)	17 (5.7)	0.0235
1+ Recent Diabetic Ketoacidosis Episode[c]	324 (18.2)	15 (7.4)	61 (14.7)	145 (27.2)	13 (13.1)	26 (11.2)	64 (21.5)	<0.0001

Abbreviations: Nw - normal weight. Ow/Ob – overweight and obese. SD – standard deviation; BMIz – body mass index z-score; HbA1c – hemoglobin A1c

†P-value for overall test of difference, based on use of ANOVA, Chi-squared, of Fishers Exact test as appropriate.

‡ Self-reported, in the past 6 months. DKA is an acute complication of hyperglycemia.



Supplementary Figure 3.1. Box and whisker plot for BMIz and HbA1c of the age-stratified weight-glycemia phenotypic clusters from the SEARCH for Diabetes in Youth Study. Participants were stratified by age at the cohort visit (<21 and ≥21 years, i.e. 21 years and over) and clustered based on the joint distribution of body mass index z-score (BMIz) and hemoglobin A1c (HbA1c) at the 5+ year cohort visit of the SEARCH study. For the 21 Years and Over Strata, five clusters were modeled.

CHAPTER 4. LONGITUDINAL PHENOTYPES OF ESTABLISHED TYPE 1 DIABETES IN YOUTH BASED ON WEIGHT AND GLYCEMIA AND THEIR ASSOCIATION WITH EARLY AND SUBCLINICAL COMPLICATIONS OF DIABETES

The aim of the study was to test whether longitudinal 'weight-glycemia' phenotypes increase susceptibility to early or subclinical complications of type 1 diabetes. Youth with type 1 diabetes (n=570) were clustered based on body mass index z-score (BMIz) and hemoglobin A1c (HbA1c) from a baseline visit (mean diabetes duration: 1.4±0.4 years) and 5+ year follow-up visit (mean diabetes duration: 8.2±1.9 years) using k–means clustering for longitudinal data. Logistic regression modeling tested cluster associations with seven early or subclinical complications measured at follow-up, adjusting for sex, race/ethnicity, age, and duration. Four longitudinal weight-glycemia clusters were identified: The Referent Cluster (n=195, 34.3%), The Hyperglycemia Only Cluster (n=53, 9.3%), the Adiposity Only Cluster (n=206, 36.1%), and the Adiposity and Increasing Hyperglycemia Cluster (n=115, 20.2%). After adjustment and compared to the Referent Cluster, the Hyperglycemia Only Cluster had elevated odds of dyslipidemia (odds ratio (OR) 2.22, 95% CI 1.15-4.29), retinopathy (OR 9.98, 95% CI 2.49-40.0) and diabetic kidney disease (DKD) (OR 4.16, 95% CI 1.37-12.62). The Adiposity and Increasing Hyperglycemia Cluster had elevated odds of hypertension (OR 2.18, 95% CI 1.19-4.00), dyslipidemia (OR 2.36, 95% CI 1.41-3.95), arterial stiffness (OR 2.46, 95% CI 1.09-5.53), retinopathy (OR 5.11, 95% CI 1.34-19.46), DKD (OR 3.43, 95% CI 1.29-9.11), and a 3.4 times higher odds of having two or more co-occurring complications (OR 3.4, 95% CI 1.86-6.21). The study shows that

there are distinct weight-glycemia phenotypes over the first decade of type 1 diabetes. Exposure to obesity and worsening glycemic control may increase the overall burden of co-morbid complications.

4.1 Introduction

Subclinical and clinical complications emerge early in type 1 diabetes.[74] In youth and adolescents, multiple studies have shown that the risk for these outcomes is associated with glycemic control as measured by HbA1c.[10,74,76] However, the rising prevalence of overweight and obesity is a recently emerging problem in the clinical care of type 1 diabetes.[1,2,181] Studies suggest that obesity in the setting of type 1 diabetes can contribute to adverse cardiovascular disease outcomes and microvascular complications in adults with long-standing diabetes.[149,203,204]

There are gaps in the current understanding of how excess adiposity and degrees of suboptimal glycemic control jointly contribute to the emergence of early and subclinical diabetes complications, including both macrovascular and microvascular outcomes, among youth and young adults in the first decade of having diabetes. This information is critical given shifts in the epidemiology of overweight and obesity within this patient population and the potential for intensive insulin therapy to induce weight gain,[267] which may warrant a more flexible and integrated clinical approach that considers both weight and glycemic control for identifiable patient subgroups.

While the association between weight status and glycemic control among youth and adolescents have been studied in the first few years of disease,[243,268] few studies have characterized the co-evolution of these outcomes over a longer disease duration, and particularly outside of the partial remission, or “honeymoon” period, when blood

glucose management is particularly challenging [269]. Therefore, we employed a data-driven approach to capture the major patterns of longitudinal exposure of both weight status and glycemic control. The first objective of this study was to identify the main longitudinal 'weight-glycemia' phenotypes of established type 1 diabetes, or clusters of youth and young adults with type 1 diabetes showing similar weight status and glycemic control measures collected at two time-points: a baseline>1 year after diabetes onset and a follow-up visit at a mean of eight years disease duration. The second objective was to test how the longitudinal weight-glycemia phenotypes of type 1 diabetes were associated with different subclinical and early complications, or combinations thereof, measured at the follow-up visit.

4.2 Methods

4.2.1 Participants

Individuals diagnosed with diabetes before 20 years of age were identified by the SEARCH for Diabetes in Youth study through a population-based registry network at 5 sites in the United States (South Carolina; Cincinnati, Ohio and surrounding counties; Colorado with southwestern American Indian sites; Seattle, Washington, and surrounding counties; and Kaiser Permanente Southern California membership in 7 counties). Individuals who received a new diagnosis of type 1 diabetes in 2002-2006 or 2008 were invited to complete a baseline SEARCH visit to measure risk factors for diabetes complications. In 2011-2015, participants with ≥5 years diabetes duration who had previously completed a baseline visit were invited to participate in a follow-up visit, at which diabetes risk factors and early diabetes-related complications and comorbidities were assessed. The distribution of demographic, metabolic, and

socioeconomic characteristics of participants who completed the follow-up visit were similar to that of the larger SEARCH registry population.[74] The study was approved by Institutional Review Boards with jurisdiction, and the parent, adolescent or young adult, or both provided consent or assent for all participants.

Inclusion criteria for the present analysis consisted of incident cases of type 1 diabetes between 2002-2006 and 2008 who attended the SEARCH baseline and cohort visit (n=2,869). Diabetes type was based on an etiological classification using diabetes autoantibodies and estimated insulin sensitivity score (euglycemic clamp-validated equation including waist circumference, HbA1c and triglyceride levels) measured at the baseline visit.[248] Participants were excluded if they were missing measures of BMIz or HbA1c at the baseline or cohort visit (n=1,106) or if the baseline visit occurred <12 months after type 1 diabetes diagnosis (n=1,193) to remove non-informative variability or within-person instability in baselines measure that may occur in the first year following diagnosis (**Supplemental Figure 4.1**). The latter exclusion cut-off was selected to ensure participants were not in partial remission, or the “honeymoon period”, at their baseline visit based on data showing that more than a half and a third of youth >5 years are classified as being in remission at 3 and 6 months, respectively, based on insulin needs (U/kg/dose)[270] as well as longitudinal patterns in HbA1c, insulin dose, and C-peptide levels in the first 12 months of disease.[271] Compared to individuals included in the analysis, excluded participants showed a lower mean age, HbA1c, and pump use at baseline, with no significant differences in BMIz or age at diagnosis (**Supplemental Table 4.1**). There were no significant differences in age, BMIz, or HbA1c between these groups at the follow-up visit.

4.2.2 Research visits

Trained research staff administered questionnaires, made measurements and obtained blood samples at the in-person baseline and follow-up research visits. Participants (or parents, for younger participants) self-reported date of birth, sex, race, ethnicity, highest parental education, annual household income, and type of health insurance. For reporting of race and ethnicity, U.S. census methods[272] were used which provided a series of fixed race and ethnicity categories as well as an "other" option for the self-report by parent or participant, depending on age. These were further categorized into 'non-Hispanic white' and 'minority' racial/ethnic groups, including Hispanic (regardless of race), non-Hispanic black, American Indian, Asian/Pacific Islander and other/multiple race/ethnicities. Education and income were self-reported. Highest education by either parent was classified as less than high school degree, high school graduate, some college through associate degree, and bachelor's degree or more. Annual household income was classified as >$75,000, $50,000-75,000, $25,000-49,999 and <$25,000. Date of diagnosis obtained from medical records was used to calculate age of diagnosis and diabetes duration at both visits. Body mass index (BMI) was defined as weight (kilograms) divided by height (meters^2) and converted to a Z score[249]. Weight status was classified as underweight (mean BMIz <-1.64), normal weight (mean BMIz -1.64-<1.04), overweight (mean BMIz 1.04-<1.64), and obesity (mean BMIz ≥1.64), corresponding to <5th, 5-<85th, 85th-<95th, and ≥95th percentile for age and sex, respectively.[18] A blood draw occurred after an 8 hour overnight fast, and medications, including short-acting insulin, were withheld the morning of the visit. Blood samples were obtained and analyzed for hemoglobin A1c, glucose, lipids, creatinine,

and cystatin C at the central laboratory (Northwest Lipid Metabolism and Diabetes Research, Seattle, WA).

4.2.3 Outcome measures

The main outcomes for the study included seven early or subclinical diabetes complications measured at the follow-up visit. Definitions of outcomes complications were consistent with previous SEARCH studies.[74,273,274]

For the outcome of hypertension, the mean of 3 systolic and diastolic blood pressure levels was obtained using an aneroid manometer after at least 5 minutes of rest. Hypertension defined based on 2017 AAP Clinical Practice Guidelines[275] as blood pressure ≥ 130/80 mm HG or ≥ 95th percentile for ages <13 years or the use of antihypertensive medication. The outcome of dyslipidemia was based on National Cholesterol Education Program (NCEP) guidelines[276] and included High-Density Lipoproteins (HDL) dyslipidemia (HDL <35 mg/dL) and non-HDL dyslipidemia (computed as total cholesterol − HDL-cholesterol >130 mg/dL), or use of a lipid-lowering medication. Arterial stiffness was measured with the SphgymoCor-Vx device, and defined as a carotid-femoral pulse wave velocity >90th percentile compared to control participants of the SEARCH Cardiovascular Disease (CVD) ancillary study.[277] Diabetic retinopathy was assessed with 45^{o} color digital fundus images taken with a nonmydriatic camera (Visucam Pro N, Carl Zeiss Meditech) and centered on the disc and macula of both eyes. Photos masked to all clinical characteristics were graded by the Wisconsin Ocular Epidemiology Reading Center. Diabetic retinopathy was defined as mild, moderate, or proliferative retinopathy in at least one eye.[278] Diabetic kidney disease (DKD) was defined as the presence of microalbuminuria (UACR >=30 µg/mg of

creatinine) or low glomerular filtration rate (<60 mL/min/1.73m2 as estimated by the CKD-EPI equation using serum creatinine and cystatin C).[279] Peripheral neuropathy was defined as a score >2 on the Michigan Neuropathy Screening Instrument.[280] Cardiovascular autonomic neuropathy was assessed by heart rate variability using the SphygmoCor-Vx device (AtCor Medical). Electrocardiographic R-R intervals measured in a supine position were used to estimate five heart rate variability indices: the standard deviation of the intervals, root mean square differences of successive intervals, normalized high-frequency power, normalized low-frequency power, and the low-to-high frequency ratio. Cardiovascular autonomic neuropathy was defined as abnormalities in three or more of the five indices, based on <5th or >95th percentile (as appropriate) observed in age- and sex-matched control participants of the SEARCH CVD study.[277]

4.2.4 Other measures

Participants reported insulin regimen, classified as the use of an insulin pump versus any combination of multiple daily injection (MDI). Self-reported frequency of self-monitoring of blood glucose was categorized as <1, 1-3, and >3 times per day. History of severe hypoglycemia (defined as any episode requiring the help of another person) or diabetic ketoacidosis in the past 6-months were self-reported.

4.2.5 Statistical methods

Participants were clustering using k-means clustering for joint longitudinal data applied to BMIz and HbA1c values from baseline and follow-up to derive clusters of homogenous subgroups within a larger heterogeneous population.[281,282] In this procedure, participants who are homogenous in their BMIz and HbA1c measures at both time-points are clustered together. BMIz and HbA1c measures were first

standardized and participants were clustered using the KmL3D package[283] in R using Euclidean distance. Briefly, k-means is an expectation-maximization (EM) algorithm: the center of each cluster is determined as the mean of data points within the cluster in the expectation step, then data points are reassigned to the nearest cluster center in the maximization step. These two steps are repeated until the clusters no longer change. Any number of methods can be used to provide the starting cluster assignments thereby initializing the process; the kml3d procedure alternates through different initialization methods and chooses the partition with the most stability.[283] To obtain optimal solutions, we repeated estimation 500 times, 100 times each for between four- and nine-cluster solutions, exploring this as the literature suggests there are multiple longitudinal patterns of weight and glycemia, but we do not know how many accurately represents the major phenotypes.[281] The Calinski-Harabatz criterion[284] was used to evaluate the various trajectory solutions and identify the optimal number of weight-glycemia longitudinal clusters. The Calinski Criterion is a relative metric that measures the ratio of the between-group variance relative to the within-group variance. The optimal clustering solution maximizes this ratio, representing the most compact and well-separated clusters.[281,282,284]

Clusters were named based on primary exposure to adiposity (i.e., elevated BMIz) or hyperglycemia (i.e., elevated HbA1c) at both time-points. The cluster with BMIz and HbA1c measures closest to clinical targets was selected as the referent cluster.[269] This method of cluster nomenclature does not necessarily represent the weight status and glycemic control of every individual within a cluster and instead was selected to facilitate cluster-level phenotypic interpretation and comparisons thereof.

4.2.6 Cluster characteristics and associations with outcomes

The proportion of early or subclinical diabetes complications, sociodemographic characteristics, and clinical care correlates of each cluster were summarized using descriptive statistics. Overall tests of independence across clusters were carried out using ANOVA for continuous features and chi-squared tests for categorical features. Typically, Fisher's exact tests would be used to obtain the exact hypergeometric distribution for a 2x2 contingency table with low counts. However, because our tables have four rows (for four clusters), obtaining the exact distribution is computationally intensive. Therefore, we use a chi-squared test where the distribution is approximated using the Monte Carlo method with 9,999 random samples. In each sample, the feature categories are permuted, and the test statistic is computed.[285,286] We accounted for multiple comparisons in the overall tests of difference using Bonferroni adjustment. If the overall test of difference was statistically significant, pairwise comparisons were performed for all clusters against the Referent Cluster. Additional, exploratory analyses for all possible pairwise comparisons are presented in **Section 4.6, Supplemental Material, Supplemental Table 4.5.**

Logistic regression modeling was used to test how each weight-glycemia subgroup was associated with early or subclinical diabetes complications. Each outcome was modeled independently as a binary outcome, adjusting for minimum confounders: sex, race/ethnicity (non-Hispanic white versus all others), age, and diabetes duration at follow-up. Small cell sizes prohibited extensive adjustment models. An additional model tested the association of the clusters with the probability of having two or more early or subclinical complications.

All p-values were evaluated at the 0.05 significance level. Data analyses were performed using the statistical analysis software package R version 3.4.1 and SAS 9.4 (SAS Institute, Cary, NC).

4.3 Results

The final sample included 570 youth with established type 1 diabetes, 53.5% female and 70.9% non-Hispanic white race/ethnicity, with mean age at diagnosis of 9.7±4.1 years and mean age at follow-up of 17.9±4.6 years (**Supplemental Table 4.2**). The baseline visit and follow-up visit occurred at approximately 1.4±0.4 years and 8.2±1.9 years after diabetes diagnosis, respectively.

Four longitudinal weight-glycemia clusters were identified over a mean of 8 years disease duration **(Figure 4.1, Table 4.1)**. The Referent Cluster (n=195, 34.3%) showed stable low BMIz and fair glycemic control at both timepoints. The Hyperglycemia Only Cluster (n=53, 9.3%) showed low BMIz with stable high HbA1c at both time points, where mean HbA1c was 10.8±1.9% (93±21 mmol/mol) at baseline and 11.4±1.9% (100±20 mmol/mol) at follow-up. The Adiposity Only Cluster (n=206, 36.1%) showed elevated BMIz, with only 48.5% and 36.9% of individuals being classified as normal weight at baseline and follow-up, respectively, and moderate Hba1c levels at both time points (HbA1c of 7.6±1.1% (60±12 mmol/mol) and 8.1±1.0% (65±11 mmol/mol) at baseline and follow-up, respectively. The Adiposity and Increasing Hyperglycemia Cluster (n=115, 20.2%) showed high BMIz at both time points, with only approximately 30-32% of individual being classified as normal weight across time, and with increasing HbA1c over time (mean HbA1c 8.4±1.5% (67±15 mmol/mol) and 11.2±1.4% (99±15 mmol/mol) at baseline and follow-up, respectively.) A three-dimensional, interaction plot

of the longitudinal weight-glycemia clusters was created and is depicted **Supplemental Figure 4.2.**

The longitudinal weight-glycemia clusters showed significant differences in sociodemographic characteristics and aspects of type 1 diabetes clinical care (**Table 4.2**). Compared to the Referent Cluster, The Hyperglycemia Only Cluster and the Adiposity and Increasing Hyperglycemia Cluster were comprised of a significantly lower proportion of non-Hispanic white youth and reported lower levels of parental education, household income, and use of private health insurance (all $p<0.05$). These clusters also had a lower proportion of pump users and individuals who checked glucose levels four or more times per day (all $p<0.05$). There were no significant differences in sex, age, or diabetes duration at follow-up.

The prevalence of dyslipidemia, retinopathy, and diabetic kidney disease was significantly different across clusters (all $p<0.05$; **Table 4.2**). After adjustment for sex, race/ethnicity, age, and diabetes duration at follow-up, and compared to the Referent Cluster, the Hyperglycemia Only Cluster had elevated odds of Dyslipidemia (odds ratio (OR) 2.22, 95% CI 1.15, 4.29), Retinopathy (OR 9.98, 95% CI 2.49, 40.0) and DKD (OR 4.16, 95% CI 1.37, 12.62) (**Table 4.3**). The Adiposity and Increasing Hyperglycemia Cluster had elevated odds of hypertension (OR 2.18, 95% CI 1.19, 4.00), dyslipidemia (OR 2.36, 95% CI 1.41, 3.95), arterial stiffness (OR 2.46, 95% CI 1.09, 5.53), retinopathy (OR 5.11, 95% CI 1.34, 19.46), and DKD (OR 3.43, 95% CI 1.29, 9.11). There were no significant interactions by sex or race/ethnicity.

The Hyperglycemia Only Cluster and Adiposity and Increasing Hyperglycemia Cluster reported 1.1±1.0 and 1.2±1.1 total early or subclinical diabetes complications,

compared to 0.7±0.8 in the Referent Cluster ($p < 0.0001$). In adjusted models, the Hyperglycemia Only Cluster had 2.17 times higher odds than the Reference Cluster of having two or more co-occurring early or subclinical diabetes complications (OR 2.2, 95% CI 1.01, 4.68). The Adiposity and Increasing Hyperglycemia Cluster had 3.4 times higher odds of having two or more co-occurring complications (OR 3.4, 95% CI 1.86, 6.21).

4.4 Discussion

We demonstrate here that there are subgroups of youth and young adults with established type 1 diabetes sharing longitudinal phenotypes defined by patterns in weight status and glycemic control over the early natural history of type 1 diabetes. Phenotypic clusters showed different associations with early or subclinical diabetes complications at a mean of eight years diabetes duration. We focus our discussion on the longitudinal weight-glycemia phenotypes first, and then turn to their associations with complications.

The four clusters showed clinically significant differences in mean BMIz and HbA1c measures over time, providing phenotypes which integrate information from both key clinical parameters. Only 34% of the sample was captured in the Referent Cluster, suggesting that a relatively small proportion of youth and young adults with type 1 diabetes have BMIz and HbA1c measures that meet or approach clinical targets for both weight status and glycemic control. Although the Hyperglycemia Only Cluster was the smallest cluster, comprising 9% of the sample, this subgroup distinguished itself by significant hyperglycemia at both time-points. By contrast, the Adiposity Only Cluster and the Adiposity and Increasing Hyperglycemia Cluster comprised approximately 50%

of the overall sample. Despite data showing that risk for obesity increases in people with type 1 diabetes as they age,[157] the clusters showed relatively consistent measures of elevated BMIz from childhood onward. Moreover, neither age nor disease duration were significantly different across clusters at the follow-up visit, suggesting that the weight-glycemia phenotypes do not appear to be age- or duration-driven subgroups, although this finding may also be attributed to limited variability in the study population.

Our study was not designed to disentangled contribution of adiposity versus hyperglycemia to the emergence of early or subclinical complications of diabetes, but to provide insight to their combined real-world effects on early markers for ensuing vascular outcomes. At the cluster level, we found a disparity in the relative risk for adverse outcomes across the longitudinal weight-glycemia phenotypes. Subgroups with sustained poor or worsening glycemic control showed striking rates of microvascular complications at the follow-up visit, particularly when compared to the referent subgroup. For example, 15% of the Hyperglycemia Cluster and 7% of the Adiposity and Increasing Hyperglycemia Cluster had retinopathy compared to 2% in the Referent Cluster, while the prevalence of DKD in these subgroups exceeded 15% compared to just 4.0% in the Referent Cluster. This pattern adds to existing literature showing that the emergence of microvascular complications of type 1 diabetes is related to glycemic control.[76,77] We did not find differences in the risk of peripheral or autonomic neuropathy across clusters, despite previous data showing these outcomes are associated with glycemic control and weight status.[76,77,203] The null results may reflect small cell sizes (n=35 or 7% of the sample showed peripheral neuropathy) and diminished statistical

power to detect smaller difference. It is also possible that an association may be detectable at a longer disease duration or older age.

In logistic regression modeling, the Adiposity and Increasing Hyperglycemia Cluster had a higher risk of subclinical macrovascular complications including hypertension, and hyperlipidemia and arterial stiffness, in addition to the microvascular complications seen in the Hyperglycemia Only Cluster, a worrisome finding given the elevated risk for adverse events in this population.[10] A notable finding is that this subgroup showed comparable or worse outcomes at the follow-up visit compared to the Hyperglycemia Only Cluster, the subgroup marked by sustained high HbA1c, despite having a significantly lower HbA1c at baseline. The pattern in which BMI accelerates the worsening of cardiovascular disease status, despite lower relative exposure to glycemia, is reminiscent of data from the Diabetes Control and Complications Trial showing that the incident rate of total cardiovascular disease events among individuals who received intensive insulin therapy and gained the most weight approximated the rate of those who did not receive intensive insulin therapy after 20 years of follow-up.[149] In addition, this pattern is consistent with previous SEARCH data showing that individuals with adverse metabolic risk profiles at baseline and cohort visit were ten times more likely to develop multiple complications than individuals with less adverse profiles,[274] as well as data-driven studies in large adult cohorts showing differences in end-organ damage across metabolic subtypes of type 1 diabetes.[287] Findings further resonate with the increased prevalence of these outcomes among youth with type 2 diabetes versus type 1, suggesting that obesity may contribute to the underlying pathophysiology of these outcomes.[74]

Given that dual exposure to adiposity and hyperglycemia may accelerate the development of complications, incorporation of obesity measures as part of the clinical phenotype of type 1 diabetes may provide useful prognostic information regarding long-term, adverse outcomes (particularly the macrovascular ones). Future epidemiological studies should examine the risk associated with longitudinal BMI and HbA1c, by testing individual and joint models over a longer duration, to better characterize the associations among these risk factors.

The variable patterns of BMIz and HbA1c and differential risk profiles captured from the first eight years of diabetes underscore the tremendous challenges and complexity associated with diabetes management, as well as the need for clinical practice guidelines for weight management specifically in the setting of pediatric-onset type 1 diabetes.[181,189,269] The heterogeneity across phentoypes regarding clinical presentation and outcomes, in conjunction with multiple technologic and therapeutic options available to optimize or co-optimize outcomes,[181] suggest that a stratified approach, developing treatment plans according to the unique needs of each subgroup, may be most appropriate. For example, the use of continuous glucose monitoring (CGM) systems in the adolescent population has increased and shows benefit regarding improved glycemic control in this age range.[143] Increased use of newer diabetes technology and devices may be useful in mitigating hyperglycemia as well as hypoglycemia; hypoglycemia has been implicated as a barrier to exercise and a trigger for overeating, leading to weight gain and elevated HbA1c.[189] The stratified medicine approach also holds particular promise in light of newer non-insulin adjunctive therapies,[84] i.e., pharmacological interventions that have direct impacts on both obesity

and glycemic control and thus may be most benefical in the highest-risk subgroup. To this end, more work is needed to be extend this work to a clinically-relevant platform where risk groups can be defined by easily measured criteria.

The current study should be considered in the context of its limitations. The exclusion of individials with baseline disease duration of <12 months diminished sample size and may limit generalizability, where the study population may be not representative of the full SEARCH cohort. This exclusion criteria was judged to be important to avoid other forms of bias that may result from combining two phases of the early natural history of type 1 diabetes in the baseline measures, including misclassification bias, and based on scientific evidence regarding the duration of partial remission in relevant patient populations.[270,271] The resulting phenotypes are thus representative of known challenges in glycemia that occur after the remission period[269] rather than differences in remission itself. The k-means algorithm finds clusters of equal size and thus may miss smaller subgroups. Because it is not model-based, there are no parameters to evaluate goodness-of-fit. However, the longitudinal k-means algorithm with parameters used in this analysis were shown to outperform other model based latent trajectory class analyses.[288] The selection of the final number of clusters is subjective. We used a criterion for this decision that have been shown to perform best in non-hierarchical algorithms. Only two-time points were used in the longitudinal cluster analysis, thus interim patterns in BMIz and HbA1c are not captured in these subgroups. Outcomes are prevalence measures; absolute risk difference across clusters cannot be reported. Low prevalence rates may increase the type 2 error rate for the outcomes. The hypertension outcome may be biased by misclassification of youth and young

adults taking antihypertensive medications for renal protection. Low numbers prevented the addition of additional covariates to regression models, including markers of socioeconomic position and aspects of diabetes care. The longitudinal weight-glycemia clusters and their association with outcomes was not tested in a prospective way and thus clusters are not predictive in nature. Additional exploratory analyses tested the predictive validitiy of weight-glycemia clusters derived from baseline measures only and overlapping BMIz and HbA1c at the follow-up visit with variable associations with complications; this approach was deemed to be limited by the true variability in weight and glycemia measures over the early history of type 1 diabetes and less informative regarding the joint trajectory structure inherent in the data.

There also several important strengths of this study. To our knowledge, it is the first to identify subgroups based on both weight and glycemia in established diabetes and evaluate the clinically utility for predicting long-term outcomes. The analysis takes a novel approach that integrates weight with glycemic control, a paradigm that offers a comprehensive and patient-centered approach to long-term health issues in type 1 diabetes. Clustering BMIz and HbA1c jointly produces a single grouping single nominal variable (i.e. cluster) that resumes the information contained in the both sets of variables over both time points, offering an integrated measure of exposure to adiposity and glycemia as it occurs in real life. k-means is non-parametric and there requires no prior information for clustering.[288] Capturing clinical phenotypes in youth with type 1 diabetes reflects how clinicians work to deliver individual care plans for patients and offers a platform for future research towards guidelines to comprehensively reduce the burden of co-morbid complications among young people with diabetes.

4.5 Conclusions

We found evidence of four longitudinal weight-glycemia phenotypes of established, youth-onset type 1 diabetes in first eight years after diagnosis with diabetes who experience different burdens of co-morbid early or subclinical complications. More work is needed to identify therapeutic approaches tailored to the needs and prognoses of each subgroup.

Table 4.1. Weight and Glycemia at the Baseline and Follow-Up Visit Across the Longitudinal Weight-Glycemia Phenotypes of Established Type 1 Diabetes.

		All	Referent Cluster	Hyperglycemia Only Cluster	Adiposity Only Cluster	Adiposity and Increasing Hyperglycemia Cluster	p-value
		N=570	N=195 (34.2)	N=r53 (9.3)	N=206 (36.1)	N=116 (20.4)	
Baseline	**Weight and Glycemia, mean (SD)**						
	BMIz	0.54 (1.07)	-0.36 (0.85)	-0.21 (1.02)	1.12 (0.59)**	1.36 (0.67)**	<0.0001
	HbA1c	8.1 (1.6)	7.8 (1.0)	10.8 (1.9)**	7.6 (1.1)	8.4 (1.5)**	<0.0001
	Weight Status†, n (%)						<0.0001
	Underweight	15 (2.6)	10 (5.2)	5 (9.4)	0 (0.0)**	0 (0.0)**	
	Normal Weight	364 (63.9)	183 (93.9)	46 (86.8)	100 (48.5)**	35 (30.2)**	
	Overweight	110 (19.3)	2 (1.0)	2 (3.8)	63 (30.6)**	43 (37.1)**	
	Obesity	80 (14.2)	0 (0.0)	0 (0.0)	43 (20.8)**	38 (32.8)**	
	Glycemic Control‡, n (%)						<0.0001
	Adequate	192 (33.7)	72 (36.9)	1 (1.9)**	89 (43.2)	30 (25.9)**	
	Fair	244 (42.8)	103 (52.8)	7 (13.2)**	93 (45.2)	41 (35.3)**	
	Poor	121 (21.2)	20 (10.2)	33 (62.3)**	24 (11.7)	44 (37.9)**	
	Very poor	13 (2.3)	0 (0.0)	12 (22.6)**	0 (0.0)	1 (0.9)**	
Follow-up Visit	**Weight and Glycemia, mean (SD)**						
	BMIz	0.64 (0.97)	-0.11 (0.72)	-0.27 (1.07)	1.21 (0.54)**	1.30 (0.61)**	<0.0001
	HbA1c	9.2 (1.9)	8.5 (1.2)	11.4 (1.9)**	8.1 (1.0)*	11.2 (1.4)**	<0.0001
	Weight Status†, n (%)						<0.0001
	Underweight	11 (1.9)	7 (3.6)	4 (7.6)	0 (0.0)**	0 (0.0)**	

	Normal Weight	344 (60.4)	185 (94.9)	46 (86.8)	76 (36.9)**	37 (31.9)**	
	Overweight	139 (24.4)	3 (1.5)	3 (5.7)	85 (41.3)**	48 (41.4)**	
	Obesity	76 (13.3)	0 (0.0)	0 (0.0)	45 (21.8)**	31 (26.7)**	
	Glycemic Control‡, n (%)						<0.0001
	Adequate	85 (14.9)	36 (18.5)	1 (1.9)**	48 (23.3)*	0 (0.0)**	
	Fair	213 (37.4)	90 (46.2)	4 (7.6)**	117 (56.8)*	2 (1.7)**	
	Poor	225 (39.5)	69 (35.4)	26 (49.1)**	41 (19.9)*	89 (76.7)**	
	Very poor	47 (8.3)	0 (0.0)	22 (41.5)**	0 (0.0)*	25 (21.6)**	

Abbreviations: BMIz- body mass index z-score. HbA1c- hemoglobin A1c.
Data are mean ± standard deviation[continuous], or n (%) [categorical].
Overall p-values from Chi Squared, Fisher exact tests, and ANOVA, as appropriate. Bonferroni correction was applied. Pairwise comparisons were performed for significant variables, using The Referent Cluster as the referent group. * denotes pairwise p-value <0.05. ** denotes pairwise p=value < 0.0001.
†Weight status defined based on body mass index z-score (BMIz). Underweight was defined as BMIz <-1.64 corresponding to the 5th percentile for age and sex. Normal weight was defined as BMIz ≥-1.64 and <1.04, corresponding to ≥-the 5th and <85th percentile for age and sex. Overweight was defined as BMIz ≥ 1.04 and <1.64, corresponding to ≥85th percentile and <95th percentile for age and sex. Obesity was defined as BMIz ≥ 1.64 corresponding to ≥ 95th percentile for age and sex.
‡Glycemic Control: Adequate (Hba1c <58 mmol/mol (7.5%)), fair (HbA1c ≥58 and <75 mmol/mol (≥7.5 and <9.0%)); poor (HbA1c ≥ 75 and <108 mmol/mol (≥ 9.0% and <12.0%)); very poor (HbA1c >108 mmol/mol (≥12.0%)).

Table 4.2. Early or Subclinical Diabetes Complications, Sociodemographic Characteristics, and Aspects of Type 1 Diabetes and its Clinical Care at the Follow-Up Visit Across the Longitudinal Weight-Glycemia Phenotypes of Established Type 1 Diabetes

	All	Referent Cluster	Hyperglycemia Only Cluster	Adiposity Only Cluster	Adiposity and Increasing Hyperglycemia Cluster	p-value
	N=570	N=195 (34.2)	N=53 (9.3)	N=206 (36.1)	N=116 (20.4)	
		Low BMIz and moderate HbA1c	Low BMIz, Stable High HbA1c	Stable high BMIz and moderate HbA1c	High BMIz and increasing HbA1c	
Early or Subclinical Diabetes Complications†, n (%)						
Hypertension	111 (19.5)	29 (14.9)	5 (9.6)	44 (21.4)	33 (28.5)	0.231
Dyslipidemia	180 (31.6)	46 (23.6)	23 (43.4)*	59 (28.7)	52 (44.8)**	0.003
Arterial Stiffness	54 (10.1)	15 (8.1)	3 (6.0)	18 (9.5)	18 (16.5)	1.000
Retinopathy	22 (4.0)	4 (2.1)	8 (15.1)*	2 (1.0)	8 (7.3)*	<0.0001
Diabetic kidney disease	35 (6.9)	7 (4.0)	8 (15.7)*	6 (3.3)	14 (13.5)*	0.018
Peripheral neuropathy	35 (6.2)	10 (5.2)	3 (5.7)	14 (6.9)	8 (7.0)	1.000
Cardiovascular autonomic neuropathy	63 (12.1)	24 (13.6)	9 (18.4)	21 (11.2)	9 (8.3)	1.000
Total number of early or subclinical diabetes complications, mean (SD)	0.9 (0.9)	0.7 (0.8)	1.1 (1.0)*	0.8 (0.9)	1.2 (1.1)**	<0.0001
Sociodemographic Characteristics						
Female (n)	305 (53.5)	94 (48.2)	27 (50.9)	107 (51.9)	77 (66.4)*	0.582
Non-Hispanic white (n)	404 (70.9)	161 (82.6)	27 (50.9)**	154 (74.6)*	62 (53.5)**	<0.0001
Age at visit (years)	17.9 (4.6)	18.0 (4.7)	18.9 (4.8)	17.5 (4.9)	18.0 (3.8)	1.000
Parental education of college graduate or higher	264 (46.4)	115 (59.0)	15 (28.3)**	98 (47.6)*	36 (31.0)**	<0.0001
Annual household income >$75,000	202 (35.4)	83 (42.6)	9 (17.0)*	85 (41.6)	25 (21.6)*	<0.0001

Private health insurance	391 (68.6)	144 (73.8)	26 (49.1)*	154 (74.8)	67 (57.8)*	0.003
Aspects of Type 1 Diabetes and its Clinical Care						
Diabetes duration (years)	8.2 (1.9)	8.2 (2.0)	8.2 (1.8)	8.1 (2.0)	8.3 (2.0)	1.000
Insulin dose (units/kg)	0.85 (0.43)	0.89 (0.54)	0.88 (0.48)	0.79 (0.30)	0.88 (0.39)	1.000
Insulin pump (versus MDI)	304 (53.3)	125 (64.0)	16 (30.3)**	121 (58.7)	42 (36.2)**	<0.0001
Frequency of self-monitoring of blood glucose > 4 times per day	446 (78.3)	160 (82.1)	33 (62.3)*	172 (83.5)	81 (69.8)*	0.009
Acute Complications‡						
1+ Severe Hypoglycemic Episode	43 (7.6)	12 (6.2)	5 (9.6)	19 (9.2)	7 (6.0)	1.000
1+ Diabetic Ketoacidosis Episode	109 (19.2)	28 (14.4)	14 (26.9)	34 (16.5)	33 (28.5)	0.189

Abbreviations: MDI – multiple daily injections. Kg – kilograms.
Data are mean ± standard deviation[continuous], or n (%) [categorical].
Overall p-values from from Chi Squared, Fisher exact tests, and ANOVA, as appropriate. Bonferroni correction was applied. Pairwise comparisons were performed for significant variables, using The Referent Cluster as the referent group. * denotes pairwise p-value <0.05. ** denotes pairwise p=value < 0.0001.
†Outcomes defined as follows:

Hypertension defined based on AAP Clinical Practice Guidelines, 5th Report: as of 2017: Stage 1 or 2 hypertension (blood pressure ≥ 130/80 mm HG or ≥ 95th percentile for ages <13 years) or the use of antihypertensive medication.

Dyslipidemia includes High-Density Lipoproteins (HDL) HDL and non-HDL dyslipidemia (non–HDL-cholesterol (computed as total cholesterol − HDL-cholesterol): >130 mg/dL OR HDL-cholesterol: <35 mg/dL) or use of lipid-lowering medication.

Arterial stiffness was measured with the SphgymoCor-Vx device and defined as a carotid-femoral pulse wave velocity >90th percentile compared to control participants of the SEARCH CVD study.

Diabetic Retinopathy based on digital fundus images and defined as mild, moderate, or proliferative retinopathy in at least one eye.

Diabetic kidney disease was defined as the presence of albuminuria (>30 μg/mg of creatinine) or low glomerular filtration rate (<60 mL/min/1·73m2 as estimated by the CKD-EPI equations with serum creatinine and cystatin C).

Peripheral neuropathy was defined as a score >2 on the Michigan Neuropathy Screening Instrument.

Cardiovascular autonomic neuropathy was assessed by heart rate variability using the SphygmoCor-Vx device; Cardiovascular autonomic neuropathy was defined as abnormalities in three or more of the five indices, based on <5th or >95th percentile (as appropriate) observed in age- and sex-matched control participants of the SEARCH CVD ancillary study.

‡Acute complications occurring in the previous 6 months; self-report.

Table 4.3. Odds Ratios with 95% Confidence Intervals (CI) from Multivariable Logistic Regression Models of the Association Between Longitudinal Weight-Glycemia Phenotype Clusters and Outcomes, with Adjustment for Minimum Confounder

	Model‡	Referent Cluster	Hyperglycemia Only Cluster	Adiposity Only Cluster	Adiposity and Increasing Hyperglycemia Cluster	Overall p-value
		N=195 (34.2)	N=53 (9.3)	N=206 (36.1)	N=116 (20.4)	
Early or Subclinical Diabetes Complications†						
Hypertension	Unadjusted	ref	0.61 (0.22, 1.65)	1.55 (0.92, 2.59)	2.26 (1.29, 3.98)	0.009
	Adjusted	ref	0.45 (0.16, 1.28)	1.62 (0.95, 2.77)	2.18 (1.19, 4.00)	0.006
Dyslipidemia	Unadjusted	ref	2.48 (1.32, 4.69)	1.30 (0.83, 2.03)	2.63 (1.61, 4.31)	0.003
	Adjusted	ref	2.22 (1.15, 4.29)	1.31 (0.83, 2.07)	2.36 (1.41, 3.95)	0.005
Arterial Stiffness	Unadjusted	ref	0.72 (0.20, 2.61)	1.19 (0.58, 2.44)	2.24 (1.08, 4.66)	0.092
	Adjusted	ref	0.49 (0.12, 1.90)	1.26 (0.59, 2.69)	2.46 (1.09, 5.53)	0.045
Retinopathy	Unadjusted	ref	8.40 (2.42, 29.14)	0.48 (0.09, 2.64)	3.74 (1.10, 12.73)	0.0003
	Adjusted	ref	9.98 (2.49, 40.01)	0.48 (0.08, 2.73)	5.11 (1.34, 19.46)	0.0004
Diabetic kidney disease	Unadjusted	ref	4.44 (1.53, 12.92)	0.82 (0.27, 2.48)	3.71 (1.45, 9.53)	0.0009
	Adjusted	ref	4.16 (1.37, 12.62)	0.80 (0.26, 2.44)	3.43 (1.29, 9.11)	0.003
Peripheral neuropathy	Unadjusted	ref	1.10 (0.29, 4.16)	1.36 (0.59, 3.15)	1.38 (0.53, 3.59)	0.880
	Adjusted	ref	0.99 (0.25, 3.92)	1.53 (0.65, 3.60)	1.57 (0.57, 4.35)	0.715
Cardiovascular autonomic neuropathy	Unadjusted	ref	1.43 (0.61, 3.31)	0.80 (0.43, 1.50)	0.57 (0.25, 1.28)	0.289
	Adjusted	ref	1.45 (0.60, 3.50)	0.86 (0.45, 1.63)	0.72 (0.31, 1.67)	0.552
Total Burden of Early or Subclinical Diabetes Complications						
Two or more co-occurring complications	Unadjusted	ref	2.50 (1.25, 5.00)	1.20 (0.71, 2.01)	3.00 (1.75, 5.15)	<0.0001
	Adjusted	ref	2.17 (1.01, 4.66)	1.3 (0.74, 2.26)	3.40 (1.86, 6.21)	0.0004

Abbreviations: ref – reference;

†Outcomes defined as follows:

Hypertension defined based on AAP Clinical Practice Guidelines, 5th Report: as of 2017: Stage 1 or 2 hypertension (blood pressure ≥ 130/80 mm HG or ≥ 95th percentile for ages <13 years) or the use of antihypertensive medication.

Dyslipidemia includes High-Density Lipoproteins (HDL) HDL and non-HDL dyslipidemia (non–HDL-cholesterol (computed as total cholesterol − HDL-cholesterol): >130 mg/dL OR HDL-cholesterol: <35 mg/dL) or use of lipid-lowering medication.

Arterial stiffness was measured with the SphgymoCor-Vx device and defined as a carotid-femoral pulse wave velocity >90th percentile compared to control participants of the SEARCH CVD study.

Diabetic Retinopathy based on digital fundus images and defined as mild, moderate, or proliferative retinopathy in at least one eye.

Diabetic kidney disease was defined as the presence of albuminuria (>30 μg/mg of creatinine) or low glomerular filtration rate (<60 mL/min/1·73m2 as estimated by the CKD-EPI equations with serum creatinine and cystatin C).

Peripheral neuropathy was defined as a score >2 on the Michigan Neuropathy Screening Instrument.

Cardiovascular autonomic neuropathy was assessed by heart rate variability using the SphygmoCor-Vx device;

Cardiovascular autonomic neuropathy was defined as abnormalities in three or more of the five indices, based on <5th or >95th percentile (as appropriate) observed in age- and sex-matched control participants of the SEARCH CVD ancillary study.

‡Adjusted for minimum confounders: sex, race/ethnicity (non-Hispanic white versus all others), age at follow-up, type 1 diabetes duration at follow-up

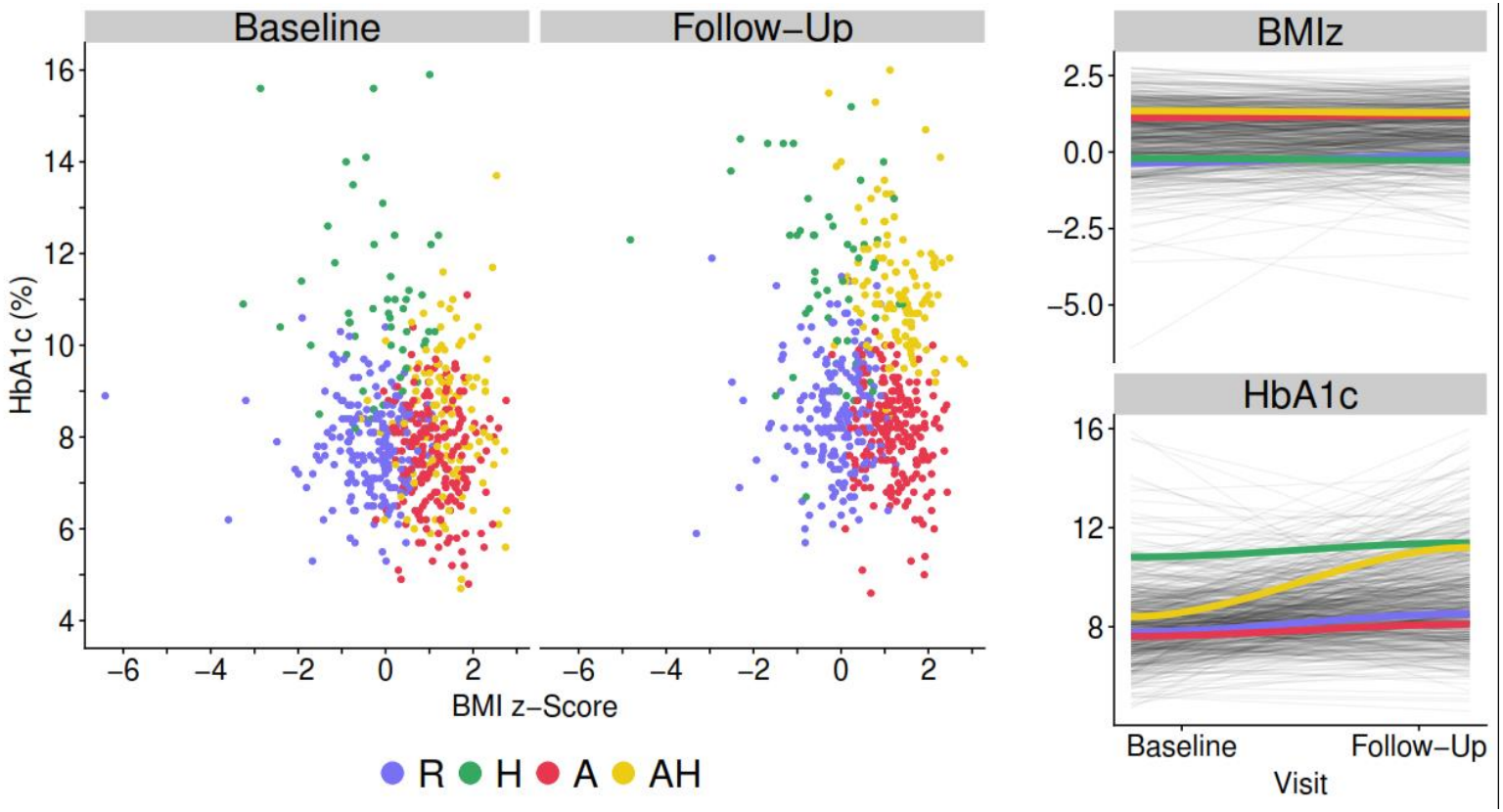


Figure 4.1. Longitudinal weight glycemia phenotypes in the SEARCH for Diabetes in Youth Study. Clusters were derived from baseline and follow-up measures of BMIz and HbA1c over a mean of 8.2 years. Clusters were named based on their main exposure, where high HbA1c is denoted by 'Hyperglycemia' (H) and elevated BMIz is denoted by 'Adiposity' (A). Four clusters were identified: the Referent Cluster (n=195, 34.2%), the Hyperglycemia Only Cluster (n=53, 9.3%), the Adiposity Only Cluster (n=206, 36.1%) , and the Adiposity and Increasing Hyperglycemia Cluster (n=116, 20.4%). Panel A: Scatter plot of BMIz and HbA1c, colored by cluster, at both time points. Panel B: Cluster trajectories of BMIz and HbA1c between baseline and follow-up visit. Abbreviations: BMIz=body mass index z-score. HbA1c=hemoglobin A1c. R= Referent Cluster. H=Hyperglycemia Only Cluster. A=Adiposity Only Cluster. AH= Adiposity and Increasing Hyperglycemia Cluster.

4.6 Supplemental Material

Supplemental Table 4.1. Selected Characteristics Between Included/Excluded Participants (with complete outcomes)

	Baseline visit < 12 months after type 1 diabetes diagnosis	Baseline visit ≥ 12 months after type 1 diabetes diagnosis	p-value[a]
	N=1,195 (67.6%)	N=570 (32.4%)	
Baseline Weight and Glycemia Measures			
BMIz	0.52 (1.03)	0.54 (1.07)	0.76
HbA1c, %	7.4 (1.3)	8.1 (1.5)	<0.01
Follow-up Weight and Glycemia Measures			
BMIz	0.60 (0.94)	0.63 (0.97)	0.45
HbA1c, %	9.1 (1.9)	9.2 (1.9)	0.25
Demographic Characteristics			
Female	575 (48.0)	304 (53.5)	0.03
Non-Hispanic White	938 (78.5)	407 (70.8)	<0.01
Age at Diagnosis, years	10.1 (3.9)	9.7 (4.1)	0.06
Diabetes Duration at Baseline Visit, Months	5.6 (3.0)	16.7 (4.9)	<0.01
Age at Baseline Visit, years	10.6 (3.9)	11.1 (4.1)	<0.01
Age at Cohort Visit, years	17.7 (4.2)	17.9 (4.6)	0.31
Baseline Socioeconomic Position			
Parental Bachelor's degree or more	624 (52.6)	244 (43.7)	<0.01
Private Health insurance	949 (80.0)	433 (76.9)	0.31
Aspects of Type 1 Diabetes and its Clinical Care			
Pump Use, n (%)	29 (4.3)	52 (15.6)	<0.01
Frequency of Blood Glucose Monitoring, mean (SD)	4.8 (0.5)	4.7 (0.6)	0.13
Abbreviations: BMIz- body mass index z-score. HbA1c- hemoglobin A1c. Data are mean ± standard deviation [continuous], or n (%) [categorical]			

Supplemental Table 4.2. Characteristics of 570 SEARCH for Diabetes in Youth Participants at their Baseline and Follow-Up Visits

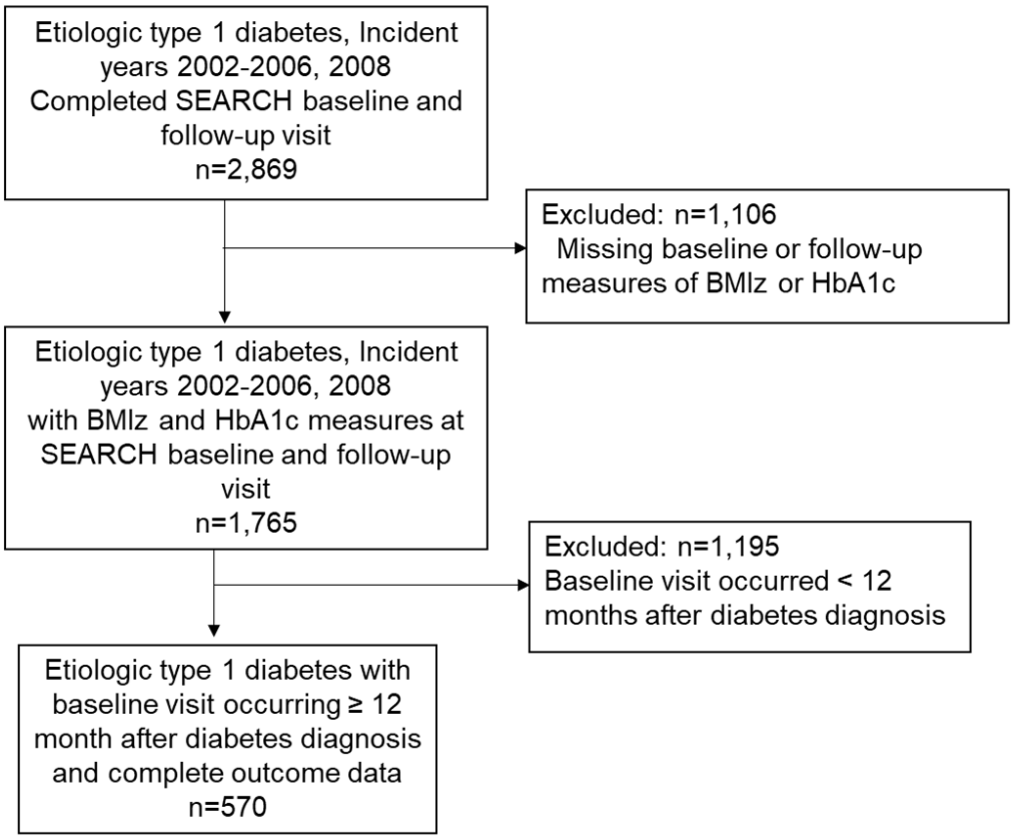
	Baseline visit		Follow up visit	
	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)
Female (n)	570	35 (53.5)	--	---
Non-Hispanic white (n)	570	404 (70.9)	--	---
Age at diagnosis (years)	570	9.7 (4.1)	--	---
Age at visit (years)	570	11.1 (4.1)	570	17.9 (4.6)
Diabetes duration (years)	570	1.4 (0.4)	570	8.2 (1.9)
Parental education (n)	561		560	
<High school graduate		27 (4.8)		27 (4.1)
High school graduate		98 (17.5)		84 (15.0)
Some college through associates		190 (33.9)		185 (33.0)
Bachelor's degree or more		246 (43.9)		264 (47.1)
Annual household income (n)	563		566	
<$25,000		94 (16.7)		103 (18.2)
$25,000 - $49,999		115 (20.4)		76 (13.4)
$50,000 - $74,999		110 (19.5)		83 (14.7)
>$75,000		198 (35.2)		202 (35.7)
DK/Refused		46 (8.2)		102 (18.0)
Health insurance (n)	564		565	
Private		433 (76.8)		291 (69.2)
Medicare/Medicaid		109 (19.3)		128 (22.7)
Other		13 (2.3)		22 (3.9)
None		9 (1.6)		24 (4.3)
Data are mean ± standard deviation [continuous], or n (%) [categorical]				

Supplemental Table 4.3. P-values for All Pairwise Comparisons

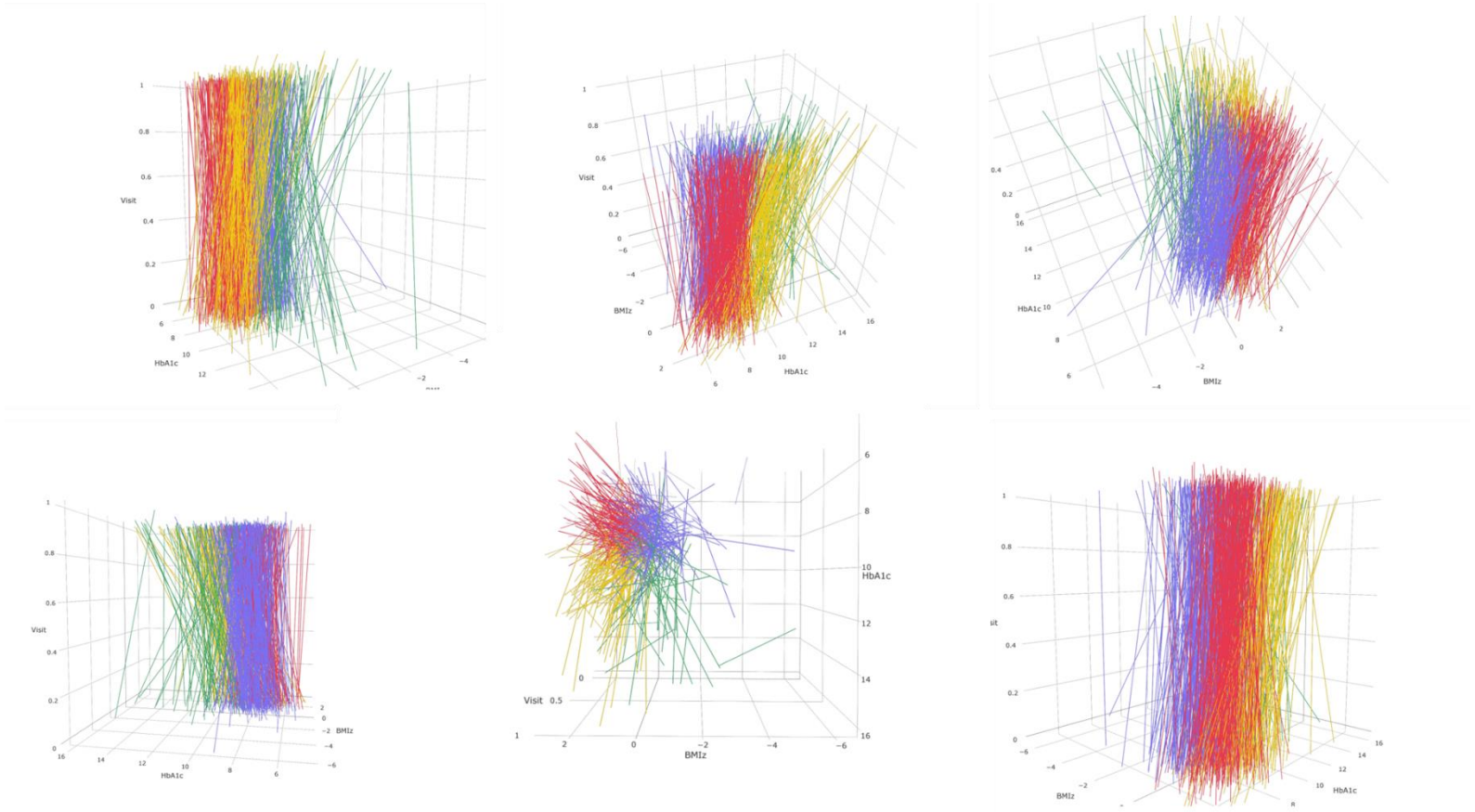
	The Hyperglycemia Only vs. the Referent Cluster	The Adiposity Only Cluster vs. the Referent Cluster	The Adiposity and Increasing Hyperglycemia Cluster vs. the Referent Cluster	The Adiposity Only Cluster vs. the Hyperglycemia Cluster	The Adiposity and Increasing Hyperglycemia Cluster vs. the Hyperglycemia Only Cluster	The Adiposity and Increasing Hyperglycemia Cluster vs. the Adiposity Only Cluster	Overall p-value
Baseline Weight and Glycemia measures							
Baseline BMIz	0.3304	<0.0001	<0.0001	<0.0001	<0.0001	0.0016	<0.0001
Baseline HbA1c	<0.0001	0.0932	0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Baseline Weight Status[†], n (%)	0.1227	<0.0001	<0.0001	<0.0001	<0.0001	0.0038	<0.0001
Baseline Glycemic Control[‡], n (%)	<0.0001	0.3059	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Follow-Weight and Glycemia measures							
Follow-up BMIz	0.3336	<0.0001	<0.0001	<0.0001	<0.0001	0.1723	<0.0001
Follow-up HbA1c	<0.0001	0.0001	<0.0001	<0.0001	0.5095	<0.0001	<0.0001
Follow-up Weight Status[†], n (%)	0.0559	<0.0001	<0.0001	<0.0001	<0.0001	0.5363	<0.0001
Follow-up Glycemic Control[‡], n (%)	<0.0001	0.0025	<0.0001	<0.0001	0.0008	<0.0001	<0.0001
Early or Subclinical Diabetes Complications[§], n (%)							
Hypertension	0.3749	0.1199	0.0052	0.0733	0.0088	0.1740	0.231
Dyslipidemia	0.0058	0.2582	0.0001	0.0472	1.0000	0.0048	0.003
Arterial Stiffness	0.7707	0.7165	0.0350	0.5795	0.0806	0.0960	1.000
Retinopathy	0.0007	0.4420	0.0323	<0.0001	0.1598	0.0045	<0.0001
Diabetic kidney disease	0.0073	0.7831	0.0082	0.0034	0.8072	0.0028	0.018
Peripheral neuropathy	1.0000	0.5311	0.6166	1.0000	1.0000	1.0000	1.000
Cardiovascular autonomic neuropathy	0.4928	0.5262	0.1871	0.2264	0.1012	0.5497	1.000

Total number of early or subclinical diabetes complications, mean (SD)	0.0078	0.2192	<0.0001	0.0429	0.5312	0.0005	<0.0001
Sociodemographic Characteristics							
Female (n)	0.7528	0.4849	0.0022	1.0000	0.0626	0.0138	0.582
Non-Hispanic white (n)	<0.0001	0.0678	<0.0001	0.0013	0.8683	0.0001	<0.0001
Age at visit (years)	0.2116	0.2896	0.9650	0.0565	0.2278	0.2840	1.000
Parental education of college graduate or higher	<0.0001	0.0275	<0.0001	0.0130	0.8569	0.0046	<0.0001
Annual household income >$75,000	0.0007	0.8397	0.0002	0.0012	0.5418	0.0004	<0.0001
Private health insurance	0.0008	0.9090	0.0039	0.0007	0.3202	0.0026	0.003
Aspects of Type 1 Diabetes and its Clinical Care							
Diabetes duration (years)	0.9898	0.3995	0.7721	0.5670	0.8190	0.3082	1.000
Insulin dose (units/kg)	0.9518	0.0347	0.8508	0.2255	0.9450	0.0622	1.000
Insulin pump (versus MDI)	<0.0001	0.3051	<0.0001	0.0003	0.4885	0.0001	<0.0001
Frequency of self-monitoring of blood glucose>4 times per day	0.0045	0.7914	0.0167	0.0020	0.3776	0.0048	0.009
Acute Complications[ll]							
1+ Severe Hypoglycemic Episode	0.3668	0.2688	1.0000	1.0000	0.5177	0.3963	1.000
1+ Diabetic Ketoacidosis Episode	0.0395	0.5834	0.0032	0.1092	1.0000	0.0148	0.189

Abbreviations: BMIz- body mass index z-score. HbA1c- hemoglobin A1c.
Overall p-values from from Chi Squared, Fisher exact tests, and ANOVA, as appropriate. Bonferroni correction was applied.
[†]Weight status defined based on body mass index z-score (BMIz). Underweight was defined as cluster mean BMIz <-1.64 corresponding to the 5th percentile for age and sex. Normal weight was defined as cluster mean BMIz ≥-1.64 and <1.04, corresponding to ≥-the 5th and <85th percentile for age and sex. Overweight was defined as cluster mean BMIz ≥ 1.04 and <1.64, corresponding to ≥85th percentile and <95th percentile for age and sex. Obesity was defined as cluster mean BMIz ≥ 1.64 corresponding to ≥ 95th percentile for age and sex.
[‡]Glycemic Control: Adequate (Hba1c <58 mmol/mol (7.5%)), fair (HbA1c ≥58 and <75 mmol/mol (≥7.5 and <9.0%)); poor (HbA1c ≥ 75 and <108 mmol/mol (≥ 9.0% and <12.0%)); very poor (HbA1c >108 mmol/mol (≥12.0%)).
[§] Outcomes defined as follows:
Hypertension defined based on AAP Clinical Practice Guidelines, 5th Report: as of 2017: Stage 1 or 2 hypertension (blood pressure ≥ 130/80 mm HG or ≥ 95th percentile for ages <13 years) or the use of antihypertensive medication.
Dyslipidemia includes High-Density Lipoproteins (HDL) HDL and non-HDL dyslipidemia (non–HDL-cholesterol (computed as total cholesterol − HDL-cholesterol): >130 mg/dL OR HDL-cholesterol: <35 mg/dL) or use of lipid-lowering medication.
Arterial stiffness was measured with the SphgymoCor-Vx device and defined as a carotid-femoral pulse wave velocity >90th percentile compared to control participants of the SEARCH CVD study.
Diabetic Retinopathy based on digital fundus images and defined as mild, moderate, or proliferative retinopathy in at least one eye.
Diabetic kidney disease was defined as the presence of albuminuria (>30 µg/mg of creatinine) or low glomerular filtration rate (<60 mL/min/1.73m2 as estimated by the CKD-EPI equations with serum creatinine and cystatin C).
Peripheral neuropathy was defined as a score >2 on the Michigan Neuropathy Screening Instrument.
Cardiovascular autonomic neuropathy was assessed by heart rate variability using the SphygmoCor-Vx device; Cardiovascular autonomic neuropathy was defined as abnormalities in three or more of the five indices, based on <5th or >95th percentile (as appropriate) observed in age- and sex-matched control participants of the SEARCH CVD ancillary study.
[‖]Acute complications occurring in the previous 6 months; self-report.



Supplemental Figure 4.1. Participant flow diagram



Supplemental Figure 4.2. Interactive visualization of BMIz and HbA1c at baseline and follow-up visit, colored by cluster. The X-axis represents BMIz, the Y-axis represents HbA1c, and the Z axis represents time, where 0=baseline visit and 1=follow-up visit. Four clusters were identified: The Referent Cluster (n=195, 34.2%), the Hyperglycemia Only Cluster (n=53, 9.3%), the Adiposity Only Cluster (n=206, 36.1%), and the Both Adiposity and Glycemia Cluster (n=116, 20.4%). Abbreviations: BMIz=body mass index z-score. HbA1c=hemoglobin A1c. R= Referent Cluster. H=Hyperglycemia Only Cluster. A=Adiposity Only Cluster. AH= Adiposity and Increasing Hyperglycemia Cluster. *The figure is shown here as captured still figures.*

CHAPTER 5. IDENTIFICATION OF CLINICALLY-RELEVANT DYSGLYCEMIA PHENOTYPES BASED ON CONTINUOUS GLUCOSE MONITORING DATA FROM YOUTH WITH TYPE 1 DIABETES AND ELEVATED HEMOGLOBIN A1C

The aim of the study was to identify and characterize subgroups of adolescents with type 1 diabetes and elevated hemoglobin A1c (HbA1c) who share patterns in their continuous glucose monitoring (CGM) data as 'dysglycemia phenotypes.' Data were analyzed from the Flexible Lifestyles Empowering Change randomized trial. Adolescents with type 1 diabetes (13-16 years, diabetes duration>1 year, HbA1c 64-119 mmol/mol (8.0-13.0%) wore blinded CGM at baseline for 7-days. Participants were clustered based on eight CGM metrics measuring incidence of hypoglycemia, exposure to hypoglycemia, exposure to hyperglycemia, and glycemic variability in the daytime and over night. Clusters were characterized by their baseline features and 18-month changes in HbA1c using adjusted mixed effects models. For comparison, participants were stratified by baseline HbA1c (≤/>9.0% (75 mmol/mol)). The study sample included 234 adolescents (49.8% female, age 14.8±1.1, duration 6.4±3.7 years, HbA1c 81±13 mmol/mol (9.6±1.2%). Three Dysglycemia Clusters were identified with significant differences across all CGM metrics ($p<0.001$). Dysglycemia Cluster 3 (n=40, 17.1%) showed severe hypoglycemia and glycemic variability with moderate hyperglycemia and had a lower baseline HbA1c than Clusters 1 and 2 ($p<0.001$). This cluster showed increases in HbA1c over 18-mo (p-for-interaction=0.006). No other baseline characteristics were associated with Dysglycemia Clusters. High HbA1c was associated with lower pump use, greater insulin doses, more frequent blood glucose monitoring,

lower motivation, and lower adherence to diabetes self-management (all $p<0.05$). The study shows that CGM data may be pooled, consolidated, and clustered to discover subgroups of adolescents with T1D for which glycemic control is challenged by different aspects of dysglycemia. Enhanced understanding of patient-factors including diabetes behaviors that contribute to CGM-derived dysglycemia phenotypes may reveal strategies to improve treatment.

5.1 Introduction

While HbA1c is the gold standard for measuring intermediate-term glycemic control, CGM data captures transient glucose fluctuations to various thresholds of hypoglycemia and hyperglycemia, as well as overall glycemic variability in the daytime and overnight.[6,7] These features of dysglycemia represent distinct clinical issues for individuals with type 1 diabetes which may be amenable to different self-management and medication adjustments.[6] They also confer independent risk for short and long-term complications of type 1 diabetes.[6,7,93,289] CGM data thus offers the opportunity to understand patterns of glycemia that are not represented by HbA1c and inform an individualized approach to type 1 diabetes management for decreased patient burden and better outcomes.[6]

The most effective strategy to both leverage the depth and integrate the breath of information that CGM offers remains unclear. This step is critical to inform tailored approaches to diabetes care. We focused on young individuals with type 1 diabetes and suboptimal glycemic control as it is measured by HbA1c because this population is in great need for improved clinical strategies.[5,260] Our objective was to use longitudinal CGM data from adolescents with type 1 diabetes and elevated HbA1c >8.0% (65

mmol/mol) to identify clinically-relevant subgroups sharing multifacteted patterns in hypoglycemia, hyperglycemia, and glycemic variability as distinct 'dysglycemia phenotypes'. These comprehensive dysglycemia phenotypes could be used to characterize glycemic control across the population in a more nuanced, patient-oriented manner compared to HbA1c and inform the development of future interventions.[7]

To follow best practices and maximize relevance to future research, we used a combination of CGM metrics consistent with Advanced Technologies & Treatments for Diabetes (ATTD) Congress consensus statement to standardize the reporting of CGM variables in clinical and epidemiologic research.[144] Given significant skews in the distribution of key CGM metrics across the sample that are important to clinical care, namely hypo- and hyperglycemia, it was important to identify a statistical method that would retain information from data at the extremes of the distribution. We chose a neural-network approach to clustering and grouped individuals based on their placement on a self-organzing map (SOM) constructed from eight CGM metrics selected to be maximally clinically-relevant.[290] The SOM is a machine learning technique that is robust to different distributions of data when uncovering underlying clusters.[291] We then tested for differences in the baseline sociodemographic, clinical, and pyschosocial correlates of each Dysglycemia Cluster and 18-month changes in HbA1c.

5.2 Methods

5.2.1 Study sample

Data were analyzed from the baseline visit of the Flexible Lifestyles Empowering Change randomized trial (FLEX) (ClinicalTrials.gov identifier: NCT01286350). FLEX

was a randomized clinical trial testing an adaptive, 18-month intervention including behavioral skills and problem solving for youth with type 1 diabetes, with respect to HbA1c (primary outcome), glycemic variability, cardiovascular risk factors, health-related quality of life, and cost effectiveness.[292]

5.2.2 Inclusion criteria

FLEX enrolled 258 adolescents with type 1 diabetes who were instructed to wear a blinded CGM for 7 days at baseline.[293] Participants were recruited from 05/01/2014 to 04/04/2016.[293] Eligible participants were youth ages 13-16 years with type 1 diabetes for ≥1 year, literacy in English, HbA1c 8.0-13.0% (64-119 mmol/mol), and ≥1 primary caregiver with no other serious medical conditions or pregnancy. Detailed considerations of the FLEX design and baseline participant characteristics have been described elsewhere.[293]

Participants were excluded from the present analyses if they reported a severe hypoglycemic event (an episode of hypoglycemia requiring external aid) during the study week (n=0) or if <24 hours of CGM data were missing at the baseline visit (n=24).

5.2.3 Measures

All data collection was standardized as per FLEX study protocol and are described in detail elsewhere.[293]

5.2.3.1 Continuous Glucose Monitoring

A blinded CGM [iPro®2 Professional CGM; Medtronic Diabetes, Northridge, CA; median absolute relative difference: 11.1%] was worn for a 7-day period to measure interstitial glucose levels. At the baseline visit, study participants inserted the iPro®2

CGM system with the Enlite™ sensor into abdominal subcutaneous adipose tissue. Participants were carefully instructed on the use and maintenance of the CGM and advised to calibrate the sensor before eating and before bed with an iPro2 compatible glucometer (OneTouch® Ultra® 2). The Enlite™ sensor measured interstitial glucose level every 5 minutes within the 40-400 [3-147 mmol/mol] range. On the last day of the CGM wear week, participants were reminded to send the devices back using a pre-paid box/envelope. CGM data were downloaded with CareLink iPro® System and uploaded to the coordinating center for data processing. As part of blinding, no communication from the device was available to participants.

5.2.3.2 Laboratory data

A central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA, USA) provided oversight and conducted all assays. At all timepoints, HbA1c was measured in whole blood using an automated nonporous ion exchange HPLC system (model G-7; Tosoh Bioscience).

5.2.3.3 Clinical Measures

Height was measured using a stadiometer, and weight was measured to the nearest 0.1 kg using an electronic scale. Body mass index (BMI, weight (kg) / height $(m)^2$) was calculated and then converted to an age- and sex-specific and BMI z-score (BMIz) according to the Centers for Disease Control and Prevention growth charts.

5.2.3.4 Questionnaires

Standardized questionnaires were used to collect self-reported data including race/ethnicity, highest level of parental education, duration of type 1 diabetes, insulin

delivery method (pump versus multiple daily injections (MDI)), and previous CGM use. Motivation and Intention were measured by a validated questionnaire adapted for relevance to type 1 diabetes self-management.[294,295] The *Social Problem Solving Inventory – Revised: Short (SPSI-R:S)* was used to assess adolescents' cognitive, affective, and behavioral abilities to resolve problems in everyday living.[296] Diabetes adherence over the past 3 months was measured with the *Diabetes Self-Management Profile – Self Report (DSMP-SR)*.[297] Depressive symptoms were assessed using the *Centers for Epidemiologic Study – Depression Scale (CES-D).*[298] Health-related quality of life was assessed with the *Pediatric Quality of Life Inventory™ – Generic Core Scales (PedsQL™ Generic*).[299] Fear of hypoglycemia was assessed by the *Hypoglycemia Fear Survey (HFS).*[300] Adolescent-reported diabetes-related family conflict was measured with the *Diabetes Family Conflict Scale (DFCS).*[301]

5.2.4 Statistical analysis

5.2.4.1 CGM Data Selection of Variables and Pre-processing

All CGM-variables were calculated for the 7-day wear time and were stratified by day (6:00 AM – 11:59 PM) and night (12:00 AM – 5:59 AM).[144] First, a subset of eight CGM features recommended by the Advanced Technologies & Treatments for Diabetes (ATTD) Congress consensus statement as key metrics to assess glycemic control were selected for a total of sixteen variables (see **Supplemental Material Section 5.6.1**).[144] The variables were pruned to remove highly correlated variables, biological redundancy, and degrees of freedom (**Supplemental Figure 5.1**).[302] The remaining eight CGM input metrics were selected to comprehensively characterize features of dysglycemia in the day and nighttime: area-over-curve (AOC) of hypoglycemia (level 1; 70 mg/dL [3.9

mmol/L]), incidence of hypoglycemia (level 1; 70 mg/dL [3.9 mmol/L]) lasting 15 minutes or longer, area-under-curve (AUC) of hyperglycemia range (level 2; 250 mg/dL [13.9 mmol/L]), and glycemic variability as coefficient of variation (CV) (**Supplemental Table 5.1**). As per exclusion criteria, there were no missing CGM data. All variables were left continuous and standardized to be expressed on the same scale. To facilitate clinical interpretation, clusters were also characterized by percent of time spent in hypoglycemic (<70 mg/dL [3.9 mmol/L]) and hyperglycemic (250 mg/dL [13.9 mmol/L) ranges, using the same threshold as the AOC and AUC measures, and time in range (70-180 mg/dL [3.9-10 mmol/L]).

5.2.4.2 Clustering Methods

The selection of SOM as a clustering algorithm and an in-depth methodological description are deferred to the **Supplemental Material Section 5.6.2.** Briefly, the SOM is a neural network[290] that serves as a model-based clustering method.[302,303] The *a priori* justification for selecting a neural network-based clustering approach was that it does not rely on strong assumptions about the underlying data such as the distributional assumption of multivariate normality or symmetry.[291] For measures of hypoglycemia and hyperglycemia, some individuals never experienced time below or above the threshold, resulting in severely skewed distributions resistant to transformation. Finally, SOMs have strong visualization attributes to understanding complex, multivariate relationships and improve the validity of unsupervised learning.[303]

FLEX participants were mapped based on their eight CGM measures to a 5x5 square grid SOM with a Gaussian neighborhood function using the Package 'SOMBrero' in R version 3.4.2.[304] The dimensions of the SOM were selected based on

the total sample size.[302] 1000 iterations (approximately 4.3 cycles through the full data) were run to ensure the shape of the grid stabilized. The SOM was randomly initialized and re-run 10 times on the full data to check for consistency in parameters and quality criteria (see **Supplemental Table 5.2**). The best out of 10 maps were selected based on the lowest quantization error, a measure of the average Euclidian distance between a participant's CGM measures and the codebook vector of their assigned unit (**Supplemental Material Section 5.6.3**). A hierarchical clustering algorithm was applied to the codebook vectors of the final map units using the function superclass in the SOMbrero package.[305] The NbClust package in R guided the selection of the final number of clusters, with minimum and maximum number of clusters set to one and ten, respectively.[256] Clusters from the SOM were validated for internal validity, stability, and fidelity to the original data (**Supplemental Material Section 5.6.4.**)

5.2.4.3 Baseline Characterization and Associations with Longitudinal Clinical Outcomes

The baseline correlates of each cluster were summarized using descriptive statistics. Overall-tests of difference were carried out using ANOVA and chi-squared tests or Kruskal-Wallis and Fisher's exact tests, where appropriate. Pairwise comparisons were performed via unpaired t-tests or Dunn's test. To discern the significance of Dysglycemia Clusters versus subgroups defined by HbA1c, FLEX participants were also stratified by baseline HbA1c: (≤ or >75 mmol/mol (8.0%)) and described in terms of their baseline characteristics. Significance differences across baseline HbA1c groups were tested using chi-squared tests and unpaired t-tests.

Mixed effect regression analysis was used to determine whether clusters showed differential changes in HbA1c over 18-months. A main effect was fit for visit and cluster

and a visit*cluster interaction term. Participants were treated as random effects. All models were adjusted for randomization status and site. Post-hoc comparisons by cluster were performed within each mixed model analysis and the effects were examined at each longitudinal timepoint in the FLEX study. Descriptive statistics and multilevel modeling (PROC MIXED) were conducted in SAS 9.4 (SAS Institute, Cary, NC).

5.2.4.4 Additional Statistical Considerations

SOM has been used previously to cluster small datasets, outperforming k-means on data of similar dimensions to the FLEX data.[306] P-values were evaluated at the 0.05 significance level and were not adjusted for multiple comparisons in the exploratory analysis.

5.3 Results

The final study sample included 234 adolescents with type 1 diabetes. Participants were 76.1% non-Hispanic white and 50.0% female with mean age 14.8±1.1 years and mean diabetes duration was 6.4±3.7 years (**Table 5.1**). Mean HbA1c was 9.6±1.2% (81±13 mmol/mol). Participants had blood glucose readings for a median of 160.0 hours (IQR 24.8) or approximately 6.7 days.

Figure 5.1A visualizes the 5x5 SOM grid, where individuals with similar CGM measures are assigned to proximal map units. Further visualizations are available in **Supplementary Figure 5.3**. Three clusters were identified, capturing areas of the map that were similar to each other regarding the 8 CGM metrics (**Figure 5.1B and 5.1C).** All CGM metrics showed significantly different means and medians across clusters ($p<0.001$) (**Table 5.2, Figure 5.1C**). Cluster 1 comprised 141 individuals (60.3%) and

showed severe daytime hyperglycemia with low exposure to and incidence of hypoglycemia relative to other clusters. Cluster 1 also showed the lowest glycemic variability (mean (SD) daytime and nightime CV: 35.5% (6.4%) and 35.7% (10.7%), respectively). Cluster 2 comprised 53 indiviudals (22.7%) and showed severe hyperglycemia, particularly overnight, with moderate hypoglycemia (median (IQR) daytime episodes: 4 (3)) and moderate variablity. Cluster 3 comprised 40 individuals (17.1%) and showed moderate hyperglycemia with the highest measures of hypoglycemia exposure and incidence relative to the other clusters (median (IQR) daytime episodes: 8 (5.5)). This group also showed the highest glycemic variability in the daytime and overnight (mean daytime and nightime CV: 4..1% (7.0%) and 51.7% (12.9%), respectively).

Mean baseline HbA1c was highest in Cluster 1 (9.9±1.1% (85±14 mmol/mol)) and lowest in Cluster 3 (8.7%±0.8% (72±9 mmol/mol)). In pairwise comparisons, cluster 3 showed significant differences from clusters 1 and 2 ($p<0.001$), but clusters 1 and 2 did not show significant differences from each other ($p=0.07$). No other baseline characteristics were significantly different across clusters, including BMIz. For comparison, **Table 5.1** also depicts the correlates of subgroups defined by baseline HbA1c. Compared to participants with HbA1c ≤9.0% (75 mmol/mol) at baseline, participants with a high HbA1c showed lower insulin pump use, greater insulin doses, a higher frequency of blood glucose monitoring, and lower motivation and adherence to diabetes self-management (all $p<0.05$).

HbA1c measures over 18-months were significantly different across clusters, adjusted for study site and randomization (p-for-interaction=0.006; **Figure 5.2,**

Supplemental Table 5.5). Dysglycemia Clusters 1 and 2 showed stable mean HbA1c, while Dysglycemia Cluster 3 showed significant increases over the 18-month study period (mean baseline HbA1c: 8.7% (71 mmol/mol); mean HbA1c at 18-month visit: 9.6% (81 mmol/mol). There were no signifiant differences in mean HbA1c level at the 18-month visit (p=0.71). CGM metrics at the 18-month visit for each cluster are depicted in **Supplementary Table 5.6.**

5.4 Discussion

Using 7-day blinded CGM data from 234 adolescents with type 1 diabetes and elevated HbA1c, we identified three distinct, clinically-meaningful clusters sharing phenotypes defined by different exposure to and incidence of hypoglycemia, exposure to hyperglycemia, and glycemic variability. All eight CGM metrics were significantly different across clusters and can thus considered to be relevant for the clustering definition. Subgroups showed differences in baseline and longitudinal HbA1c but were not different not with respect to other baseline characteristics. These results reinforce the concept that adolescents with type 1 diabetes and elevated HbA1c do not show homogenous patterns in CGM-measures of blood glucose dynamics; this analytic approach can help refine understanding of dysglycemia patterns to better identify interventions. Interestingly, different patterns in dysglycemia are not explained by the individual sociodemographic, clinical, or psychosocial characteristics that typically drive treatment recommendations regarding HbA1c.

To our knowledge, there is limited data available for comparison because the majority of existing CGM data collected in comparable age ranges are from adolescents with lower HbA1c levels.[143] Patterns in dysglycemia across clusters are consistent with

other CGM studies suggesting that a positive association between glycemic variability and the risk for hypoglycemia.[307]

A previous cluster analysis using 3-days of data from self-monitoring blood glucose values provided evidence for distinct glycemic profiles among a small sample of adults with type 1 diabetes.[308] Although all FLEX participants had elevated HbA1c as per inclusion criteria, we found similar evidence for the existence of subgroups typified by specific blood glucose dynamics. The striking differences in CGM measures suggest that these distinct 'phenotypes' are comprised of adolescents who struggle with different aspects of their blood glucose control. For example, individuals in Cluster 1 were typified by hyperglycemia with fewer episodes of hypoglycemia and less pronounced variability, especially overnight, while individuals in Cluster 3 experienced less hyperglycemia but a median of 8 episodes of hypoglycemia per week with severe variability in the daytime and nighttime (mean CV: 47% and 52%, respectively). Measures of variability in the latter group greatly exceeded the CV threshold of 36% that has previously been proposed to indicate 'unstable' glycemia and increased risk for hypoglycemia.[307]

In the analysis to identify potential patient-related drivers of the clusters, there were no significant differences in the sociodemographic, clinical, or psychosocial measures across Clusters. One possible reason for the lack of statistically significant correlates is the small sample size which may limit statistical power. We explored the clinical utility of a 2-cluster solution to detect differences but failed to identify significant correlates to distinguish the two subgroups (**Supplemental Material Section 5.6.6**).

Another interpretation of the data is that a broad range of demographic, clinical, or psychosocial characteristics do not drive the specific blood glucose issues that may be challenging overall glycemic control among adolescents with type 1 diabetes and elevated HbA1c. It is particularly interesting that the risk factors of poor glycemic control as it is measured by HbA1c do not appear to be risk factors for poor glycemic control as it manifests as membership in a Dysglycemia Cluster. Within the FLEX sample, participants with a high baseline HbA1c showed lower insulin pump use, greater insulin doses, a higher frequency of blood glucose monitoring, and lower motivation and adherence to diabetes self-management; none of these associations emerged as correlates of Cluster membership. Other well-studied associations of suboptimal HbA1c measures in this age range were not replicated as differences across subgroups, including nonwhite race,[3] lower measures of socioeconomic position,[309] and poorer psychosocial well-being.[309] More work is needed to understand the drivers of dysglycemia phenotypes, including significant behavioral mediators or patterns that can be addressed clinically such as omitted or ill-timed boluses regarding meal initiation.

There are several points of clinical relevance for the findings. Because the extraction of key clinical metrics from longitudinal CGM data emulates the process of patient care where these measures are used to identify specific issues,[7] this study offers proof-of-principle for how CGM data may be consolidated and used to identify the subgroups of patients within a specific population of individuals with type 1 diabetes that are be recognizable to care providers as intuitive clinical phenotypes. With increasing availability of CGM data as well as documentation of treatment regime and other outcomes in electronic health records, this work may in the future offer an emerging

platform to pool data across one or more clinics to test how CGM clusters function as predictive or prescriptive phenotypes.

Outside of the clinic, the results may be used towards the development of effective interventions for this at-risk and challenging adolescent population.[5,292] Although main analysis of the FLEX intervention did not show improvements in HbA1c at 18-months,[292] a three-way interaction term between cluster, FLEX intervention randomization assignment, and timepoint was tested in exploratory longitudinal analyses; it was not statistically significant. It is possible that approaches to diabetes management in the heterogenous adolescent population are maximally effective as a set of interventions tailored to specific issues of dysglycemia, which can then be targeted towards phenotypes that are expected to maximally benefit. For example, Cluster 3 was the only subgroup to show an increase in HbA1c over 18-months; this subgroup also had the highest hypoglycemia and variability at baseline and may represent a previously-proposed sequela of recurrent hypoglycemia and overcorrection that leads to worsened glycemic control over time.[199] Therefore, this group may benefit from specific efforts addressing frequent hypoglycemia and its overcorrection early in adolescence. By contrast, interventions focused on increasing insulin doses may be salient for Cluster 1, who spends most of the time in hyperglycemic ranges with low variability, rendering hypoglycemia counseling less immediately relevant.

A further aspect of clinical significance is the presumed differential risk for acute and chronic diabetes complications across clusters. Aside from well-established risk associated with hyperglycemia,[260] the high degree of glycemic variability noted in Clusters 2 and 3 may confer additional, independent risk for micro- and macrovascular

complications, including cardiovascular disease.[93,289] Cluster 3's pattern of hypoglycemia may contribute to the development of defective symptomatic responses, positioning these individuals at an increased risk for severe hypoglycemia.[310]

The analysis has several limitations. Self-organizing maps are difficult to validate. The SOM analysis was repeated to check for consistency, and resulting clusters were assessed for stability and validity against other clustering algorithms on the raw data. Clusters showed stability in cross-validation studies with preservation of patterns in dysglycemia (**Supplemental Table 5.3, Supplemental Figure 5.4**). The results may be affected by the selection of the CGM metrics used to train the SOM. We explored dysglycemia clustering derived from a set of 16- and 24- CGM metrics and found that the recommended number of clusters and clustering solutions were not significantly impacted by additional CGM metrics, although the projection quality of the SOM was reduced (**Supplemental Table 5.4**). In addition, the SOM clusters were compared to clusters derived directly from the data.[303] Although the assumptions of the hierarchical clustering algorithm are not met using the input data, we found similar clusters with both algorithms (**Supplemental Figure 5.5, Supplemental Figure 5.6**). Together, the results suggest that the SOM clusters demonstrate internal validity, stability, and accurately represented clustering structure present in the raw data.

Additional limitations include availability of CGM data spanning 7 days versus the 14 days recommended for optimal data analysis.[144] The small sample size may be underpowered to detect differences between clusters. The inclusion and exclusion criteria of the FLEX trial limit generalizability, particularly for adolescents with lower HbA1c levels. In the present analysis, we constrained CGM metrics to be consistent

with standardized practices of CGM reporting.[144] However, additional measures of glycemic variability such as mean amplitude of glycemic excursion (MAGE) and mean of daily differences (MODD) might help to further delineate subgroups. Future work may also explore how deep learning can be used to extract hidden layers of the CGM data and explore clusters based on those hidden layers.[311]

Despite the aforementioned limitations, here, we elucidated dysglycemia phenotypes among a sample of adolescents with type 1 diabetes and suboptimal glycemic control, a population with great need for future interventions in which CGM data has only recently become available to help.[5,292] CGM metrics were selected to be consistent with best research practices,[144] and a clustering algorithm was selected to leverage information from the tails of the distribution to understand underlying cluster structure in the data.[291] The analytic approach is distinct from but compliments ongoing work to model CGM data *via* temporal analysis regarding the shape of the curve/aspects of glycemic variability,[312,313] and it may be applied to CGM data from variable durations of wear-time. In full, the study represents a novel use of CGM data towards broadening the concept of glycemic control from HbA1c to understanding a multifaceted profile that includes glycemic excursions and overall variability. Understanding of these subgroups is crucial to pave the way for targeted interventions to optimize dysglycemia and the associated clinical outcomes in type 1 diabetes.

5.5 Conclusions

Among adolescents with type 1 diabetes and elevated HbA1c, CGM data may be pooled and analyzed to uncover subgroups displaying distinct dysglycemia phenotypes, for which glycemic control is challenged by different patterns in hypoglycemia,

hyperglycemia, and glycemic variability. More work is needed to understand the risk factors for glycemic control as it is represented from CGM data by dysglycemia phenotypes for future development of phenotype-specific interventions to improve glycemic control.

Table 5.1. Baseline Characteristics of FLEX Participants Overall and by Dysglycemia Cluster and Baseline HbA1c Subgroup

		Dysglycemia Cluster				Baseline HbA1c Subgroup		
Baseline characteristics, n (%) or mean (SD)	All (n=234)	Cluster 1 (n=141, 60.3%)	Cluster 2 (n=53, 22.7%)	Cluster 3 (n=40, 17.1%)	p-value	Baseline HbA1c ≤ 75 mmol/mol (9.0%) (n=78, 33.3%)	Baseline HbA1c>75 mmol/mol (9.0%) (n=156, 66.7%)	p-value
Sociodemographic Characteristics								
Age (years)	14.8 (1.1)	14.8 (1.1)	14.9 (1.2)	15.0 (1.2)	0.60	14.7 (1.1)	14.9 (1.1)	0.09
Female sex	117 (50.0)	68 (48.2)	30 (56.6)	19 (47.5)	0.55	42 (52.9)	75 (48.1)	0.41
Non-Hispanic White†	178 (76.1)	104 (73.8)	42 (79.3)	32 (80.0)	0.59	62 (79.5)	116 (74.4)	0.38
Parental Education					0.16			0.27
Graduate degree	43 (18.5)	22 (15.8)	10 (18.9)	11 (27.5)		17 (22.1)	26 (16.8)	
College Degree	67 (20.9)	54 (38.9)	21 (39.6)	21 (52.5)		36 (46.8)	60 (38.7)	
Some College	67 (28.9)	44 (31.7)	17 (32.1)	6 (15.0)		18 (23.4)	49 (31.6)	
High School or less	26 (11.2)	19 (13.7)	5 (9.4)	2 (5.0)		6 (7.8)	20 (12.9)	
Private Health Insurance	164 (70.1)	105 (74.5)	35 (66.0)	24 (60.0)	0.16	54 (69.2)	110 (70.5)	0.84
Single adult home	30 (13.1)	17 (12.4)	8 (15.1)	5 (12.8)	0.88	11 (14.3)	19 (12.5)	0.71
Clinical Characteristics								
Duration of diabetes (years)	6.4 (3.7)	6.5 (3.8)	6.4 (3.5)	6.3 (3.8)	0.96	5.8 (3.7)	6.7 (3.7)	0.09
HbA1c (mmol/mol)	81 (5)	85 (14)	81 (11)	72 (9)	<0.001*	68 (6)	89 (11)	<0.001*
HbA1c (%)	9.6 (1.2)	9.9 (1.3)	9.6 (1.0)**	8.7 (0.8)**	<0.001*	8.4 (0.5)	10.3 (1.0)	<0.001*
HbA1c above 9.0% [75 mmol/mol]	156 (66.7)	104 (73.8)	38 (71.7)**	14 (35.0)**	<0.001*	0 (0.0)	156 (100.0)	<0.001*
Insulin Regimen					0.64			0.02*

Multiple daily injection	68 (29.2)	38 (27.1)	18 (34.0)	12 (30.0)		15 (19.2)	53 (34.2)	
Pump	165 (70.8)	102 (72.9)	35 (66.0)	28 (70.0)		63 (80.8)	102 (65.8)	
Insulin Dose, total (units/kg)	0.98 (0.33)	1.01 (0.36)	0.92 (0.24)	0.95 (0.35)	0.23	0.91 (0.26)	1.00 (0.36)	0.03*
Average frequency of self-monitoring blood glucose, daily	2.2 (0.8)	2.1 (0.8)	2.3 (0.9)	2.1 (0.7)	0.47	1.9 (0.67)	2.3 (0.9)	0.004*
BMI z-score	0.71 (0.91)	0.70 (0.92)	0.78 (0.88)	0.71 (0.95)	0.86	0.69 (0.96)	0.73 (0.89)	0.76
Weight Status					0.94			0.87
Under- or normal weight	143 (61.1)	88 (62.4)	30 (56.6)	25 (62.5)		47 (60.3)	96 (61.5)	
Overweight	56 (23.9)	32 (22.7)	14 (26.4)	10 (25.0)		18 (23.1)	38 (24.4)	
Obese	35 (15.0)	21 (14.9)	9 (17.0)	5 (12.5)		13 (16.7)	22 (14.1)	
Psychosocial Characteristics								
Motivation‡	7.6 (1.6)	7.7 (1.4)	7.7 (1.7)	7.5 (1.8)	0.76	7.9 (1.7)	7.5 (1.5)	0.03*
Intention‡	9.1 (1.0)	9.2 (0.9)	8.9 (1.1)	8.9 (1.1)	0.22	9.1 (1.1)	9.1 (1.0)	0.96
Problem solving§	105.6 (13.0)	106.2 (12.5)	105.5 (14.3)	103.5 (13.1)	0.50	106.6 (12.7)	105.1 (13.1)	0.41
Adherence to Diabetes self-management‖	55.2 (11.6)	55.5 (11.9)	53.3 (9.7)	56.7 (12.8)	0.33	59.1 (11.0)	53.2 (11.5)	0.003*
Depression symptoms¶	9.1 (8.4)	8.6 (7.6)	9.8 (10.0)	10.1 (8.7)	0.47	9.5 (9.2)	8.9 (7.9)	0.65
Quality of life#	81.0 (12.4)	81.7 (12.0)	79 (12.7)	80.6 (13.3)	0.50	81.1 (13.8)	80.9 (11.6)	0.90
Fear of hypoglycemia††								
Maintain High BG	1.2 (0.9)	1.2 (0.9)	1.2 (0.8)	1.2 (0.8)	0.99	1.1 (0.8)	1.2 (0.9)	0.70
Helplessness/Worry	1.1 (0.6)	1.1 (0.6)	1.1 (0.7)	1.1 (0.4)	0.81	1.1 (0.6)	1.1 (0.7)	0.92

Worry about negative social consequences	1.1 (0.7)	1.1 (0.8)	1.1 (0.7)	1.1 (0.6)	0.93	1.0 (0.7)	1.41 (0.7)	0.45
Diabetes Family Conflict‡‡	1.4 (0.3)	1.4 (0.4)	1.2 (0.3)	1.4 (0.3)	0.57	1.3 (0.3)	1.4 (0.3)	0.14

Abbreviations: SD – standard deviation. CGM – continuous glucose monitoring. HbA1c – hemoglobin A1c. BMI z-score – body mass index z-score.

For dyslgycemia clusters, p-values are from Chi squared or fisher exact test for categorical variables, and ANOVA or Kruskal-Wallis Test for continuous variables. For baseline HbA1c, p-values are from unpaired t-tests. *Denotes significance test of overall difference ($p<0.05$). **Denotes significant difference in unpaired, pairwise t-tests ($p<0.05$), compared to Dysglycemia Cluster 1.

† Non-Hispanic white race/ethnicity versus non-Hispanic Black, Black, and other including Asian/Pacific Islander, Native American, or unknown.

‡ Motivation and Intention were measured by a validated questionnaire adapted for relevance to type 1 diabetes self-management.

§ The Social Problem Solving Inventory – Revised: Short (SPSI-R:S); higher score indicates higher ability to resolve problems in everyday living.

‖ Diabetes Self-Management Profile – Self Report (DSMP-SR); higher score indicates higher adherence.

¶ Centers for Epidemiologic Study – Depression Scale (CES-D); higher score indicates increased depressive symptoms.

Pediatric Quality of Life Inventory™ – Generic Core Scales; higher score indicates higher quality of life

†† Hypoglycemia Fear Survey (HFS); fear of hypoglycemia measured in three domains: behaviors used to keep blood glucose high to prevent hypoglycemia (Maintain High BG), worry about helplessness (Worry/Helplessness), and worry about social consequences associated with hypoglycemia (Worry/Social Consequences); higher scores indicate greater fear.

‡‡ Diabetes Family Conflict Scale (DFCS); higher score indicates higher conflict.

Table 5.2. Input CGM Metrics at Baseline, Overall and by Dysglycemia Cluster Measured Over 7 Days

		Dysglycemia Cluster			
CGM Metrics, mean (SD), or median (IQR)	All (n=234)	Cluster 1 (n=141, 60.3%)	Cluster 2 (n=53, 22.7%)	Cluster 3 (n=40, 17.1%)	p-value
Hypoglycemia Exposure					
AOC 3.9 mmol/L (70 mg/dL), Day†	0.15 (0.52)	0.03 (0.14)	0.39 (0.35)**	1.2 (1.1)**	<0.0001*
AOC 3.9 mmol/L (70 mg/dL), Night†	0.11 (1.31)	0.00 (0.11)	0.78 (1.47)**	3.5 (4.0)**	<0.0001*
Percent of time below 3.9 mmol/L (70 mg/dL)‡, %, Day†	1.5 (4.0)	0.5 (1.5)	3.0 (3.2)**	8.7 (5.6)**	<0.0001*
Percent of time below 3.9 mmol/L (70 mg/dL)‡, %, Night†	1.8 (8.5)	0.0 (1.4)	7.3 (7.7)**	18.9 (17.2)**	<0.0001*
Hypoglycemia Incidence					
Episodes<3.9 mmol/L (70 mg/dL) for 15+ minutes, Day†	2 (5)	1 (2)	4 (3)**	8 (5.5)**	<0.0001*
Episodes<3.9 mmol/L (70 mg/dL) for 15+ minutes, Night†	1 (2)	0 (1)	2 (2)**	3 (2.5)**	<0.0001*
Hyperglycemia Exposure					
AUC 13.9 mmol/L (250 mg/dL), Day†	26.9 (21.1)	29.9 (27.4)	29.5 (17.6)	13.7 (17.5)**	<0.0001*
AUC 13.9 mmol/L (250 mg/dL), Night†	13.0 (21.1)	13.3 (21.8)	17.4 (16.6)	4.5 (11.6)**	<0.0001*
Percent of time above 13.9 mmol/L (250 mg/dL)‡, Day†	38.1 (25.8)	43.0 (27.9)	39.5 (17.2)	24.3 (20.9)**	<0.0001*
Percent of time above 13.9 mmol/L (250 mg/dL)‡, Night†	23.8 (28.0)	29.2 (32.9)	26.7 (15.7)	12.5 (13.1)**	<0.0001*
Glycemic Variability					
Coefficient of Variation, %, Day	39.8 (7.4)	35.5 (6.4)	41.4 (8.7)**	47.1 (7.0)**	<0.0001*
Coefficient of Variation %, Night	38.8 (11.9)	32.7 (10.7)	46.6 (7.8)**	51.7 (12.9)**	<0.0001*
Time in Range[a]					
Percent of time 3.9-10 mmol/L (70-180 mg/dL)), day	32.0 (20.7)	30.4 (13.9)	31.9 (13.8)	43.7 (17.2)**	<0.0001*
Percent of time 3.9-10 mmol/L (70-180 mg/dL)), night	38.3 (26.6)	36.1 (20.9)	39.5 (20.9)	47.5 (15.9)**	0.0014*

Abbreviations: SD- standard deviation. IQR- Interquartile range. AOC – area over the curve. AUC - area under the curve.
*Denotes significance test of overall difference from ANOVA or Kruskal-Wallis test ($p<0.05$). **Denotes significant difference in unpaired, pairwise t-test or Dunn's test ($p<0.05$), compared to Dysglycemia Cluster 1.
†Data were right-skewed and are reported as median (interquartile range). P-value from Kruskal-Wallis test. There were no missing data.
‡To aid in clinical interpretation of hypoglycemia and hyperglycemia exposure, the percent of time is provided to address the same threshold as the area-over-the-curve and area-under-the-curve measures. For additional clinical context, time in range is provided but was not used as an input variable for CGM clusters.

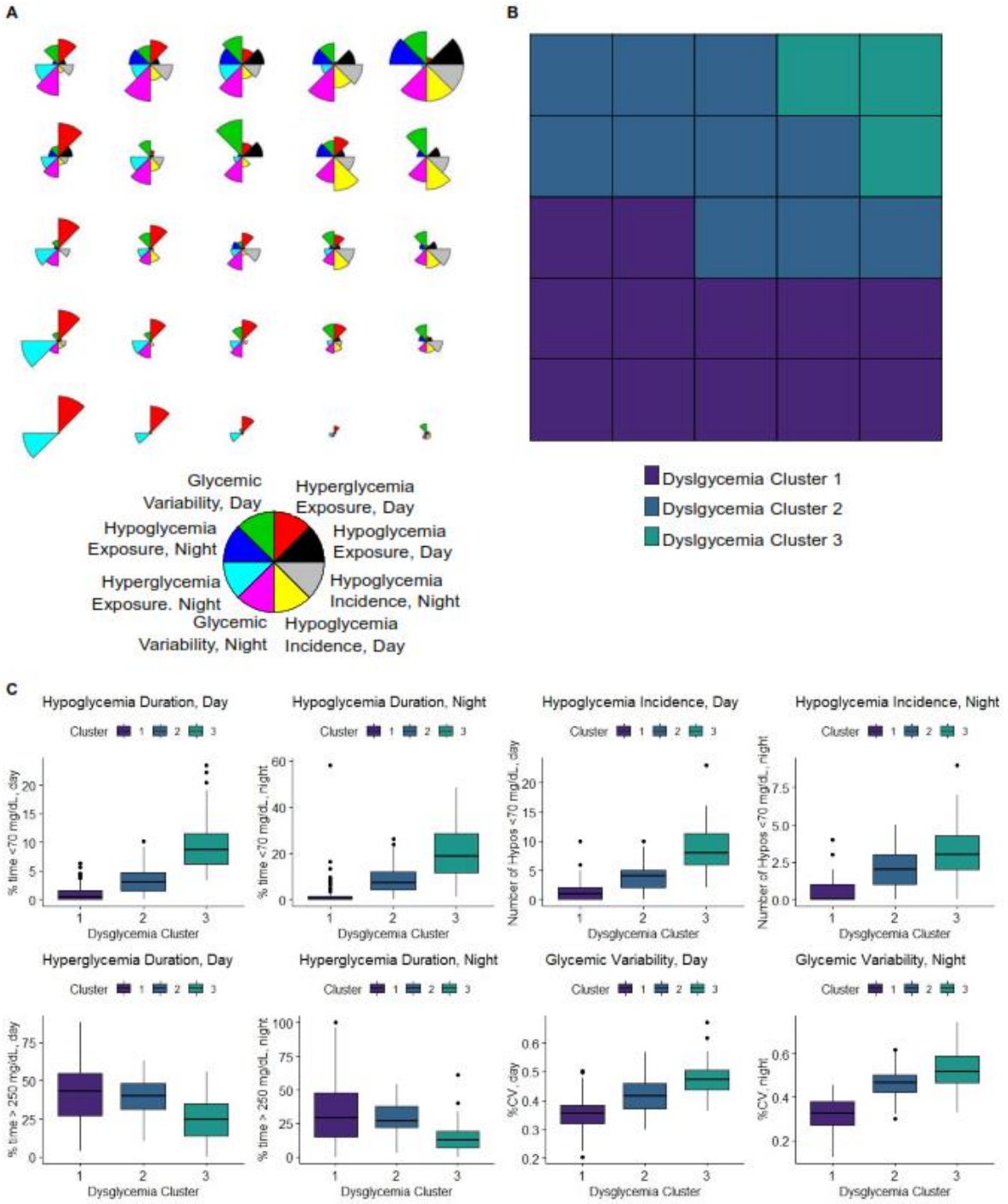


Figure 5.1. Use of a self-organizing map (SOM) trained by 7-day continuous glucose monitoring (CGM) data to identify dysglycemia clusters at baseline of the FLEX trial (n=234). The clustering is carried out using a two-level approach, where the dataset is first clustered onto the units SOM and then the units SOM is clustered. A 5x5 SOM with 25 map units and a 3-cluster solution were selected. All CGM-variables were calculated for the 7-day wear time and were stratified by day (6:00 AM – 11:59 PM) and night (12:00 AM – 5:59 AM). Panel A: Radar plots showing the integrated CGM profile

of each of the 25 units on the 5x5 SOM, as determined by the individuals assigned to that region. Each input CGM variable is represented by a different color in the radar. Input CGM variables were defined as follows: Hypoglycemia Exposure: area-over-the-curve of 70 mg/dL [3.9 mmol/L], Hypoglycemia Incidence: average number of hypoglycemic (<70 mg/dL [3.9 mmol/L]) episodes lasting 15 or more minutes, Hyperglycemia Exposure: area-under-the-curve of 250 mg/dL [13.9 mmol/L], and Glycemic Variability: % coefficient of variation. Abbreviations: CV – coefficient of variation. Panel B: The SOM colored by Dysglycemia Cluster assignments. Each unit was assigned to a Dyslgycemia Cluster. Dysglycemia Cluster assignments (Cluster 1, Cluster 2, and Cluster 3) are shown by colored boxes. Panel C: CGM measures of hypoglycemia, hyperglycemia, and glycemic variability across the 3 Dysglycemia Clusters. To aid in clinical interpretation of hypoglycemia and hyperglycemia exposure, the percent of time are depicted in place of the area-over-the-curve and area-under-the-curve measures that were used to construct the SOM. Data represents 7-days of blinded CGM wear. All $p<0.001$. Hypoglycemia Exposure is depicted as percent of time <70 mg/dL [3.9 mmol/L]. Hypoglycemia Incidence is depicted as average number of hypoglycemic (<70 mg/dL [3.9 mmol/L]) episodes lasting 15 or more minutes. Hyperglycemia Exposure is depicted as percent of time >250 mg/dL [13.9 mmol/L]. Glycemic Variability is depicted as % coefficient of variation. Abbreviations: CV – coefficient of variation.

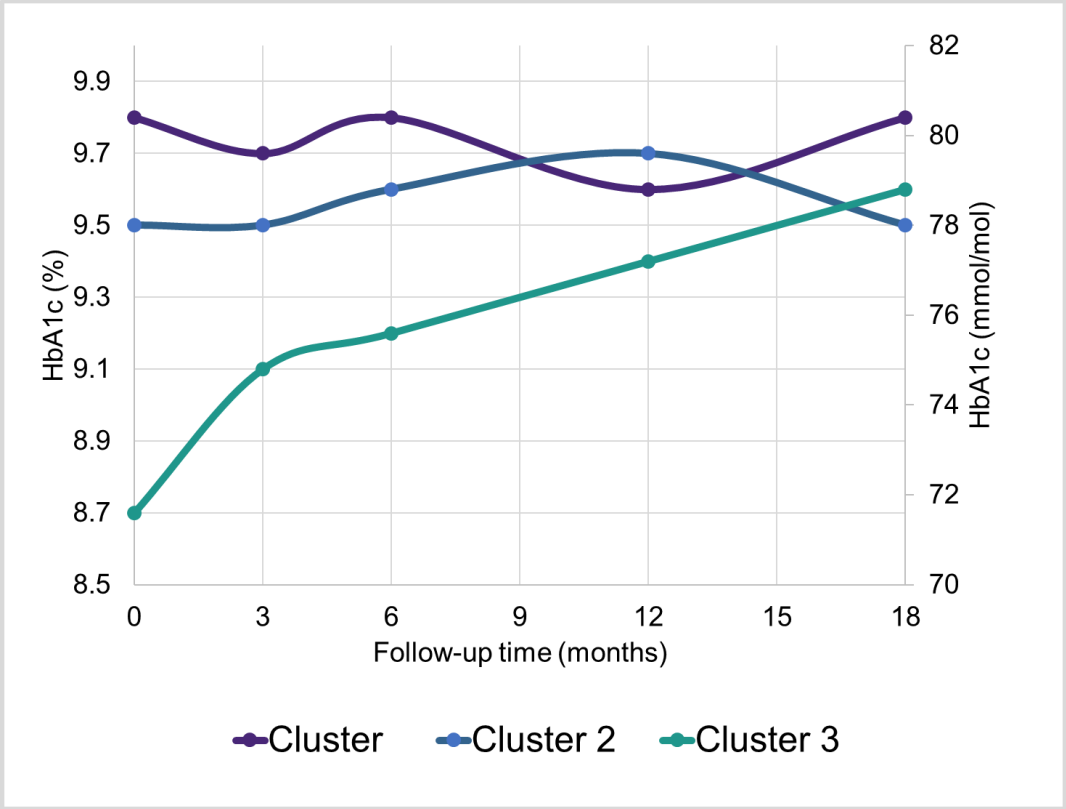


Figure 5.2. Longitudinal hemoglobin A1c (HbA1c) outcomes of FLEX participants by dysglycemia cluster, adjusted for FLEX study site and randomization assignment (p-for-interaction=0.006). The p-for-interaction represents Type 3 Test of Fixed Effects for timepoint x cluster interaction term. Missing data— Baseline: n=0; 3-month HbA1c: n= 10; 6-month HbA1c: n= 14; 12-month HbA1c: n=20; 18-month HbA1c: n=16. Abbreviations: HbA1c – hemoglobin A1c.

5.6 Supplemental Material

5.6.1 Pruning of CGM data for cluster analysis: selection of variables

All CGM-variables were calculated for the 7-day wear time and were stratified by day (6:00 AM – 11:59 PM) and night (12:00 AM – 5:59 AM).[144] These included median glucose, area-under-curve (AUC) of level 1 hyperglycemic range (10.0 mmol/L (180 mg/dL), AUC of level 2 hyperglycemic range (> 13.9 mmol/L (250 mg/dL)), area the over curve (AOC) of level 1 hypoglycemic range (<3.9 mmol/L, 70 mg/dL), AOC of level 2 hypoglycemic range (<3.0 mmol/L (54 mg/dL)), incidence of level 1 hypoglycemia lasting 15 minutes or longer over, incidence of level 2 hypoglycemia lasting 15 minutes or longer, and glycemic variability was reported as coefficient of variation (CV). Cut-points for glucose used to describe hypoglycemia were established according to recommended values,[144,314] CV represents the standard deviation corrected for the mean and was chosen as a primary measure of glycemic variability because the magnitude of glycemic variability is highly correlated with the level of the mean.[144] AOC and AUC was used in the place of duration of time for measures of hypo- and hyperglycemia as this measure integrates the severity of a high or low glucose along with the duration of the abnormality.[144] Time-in-range (i.e. percentage of time between 70 mg/dL and 180 mg/dL) was not included due to overlap in information with the selected AOC and AUC variables.

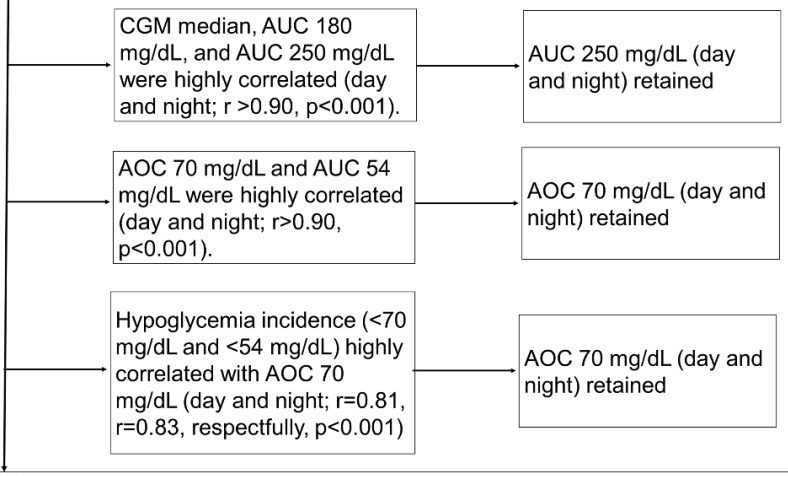
Data were then examined to remove highly correlated variables, biological redundancy, and degrees of freedom in the variables used to construct the SOM (**Supplemental Figure 5.1**).[302] First, a subset of eight CGM features recommended by the Advanced Technologies & Treatments for Diabetes (ATTD) Congress as key

metrics to assess glycemic control, reported by day and night, were selected for a total of sixteen variables.[144] Examination of correlation matrices indicated that CGM median, AUC of level 1 hyperglycemia, and AUC of level 2 hyperglycemia were highly correlated ($r>0.90$, $p<0.001$). AUC of level 2 hyperglycemia (13.9 mmol/L, 250 mg/dL) was retained to assess hyperglycemia in the day and nighttime. AOC of level 1 and level 2 hypoglycemia were highly correlated ($r>0.90$, $p<0.001$). AOC of level 1 hypoglycemia (3.9 mmol/mol, 70 mg/dL) was retained to more broadly capture hypoglycemia. Finally, the daytime incidence of level 2 hypoglycemia was correlated with both the daytime incidence of level 1 hypoglycemia ($r=0.81$, $p<0.001$) and daytime AOC level 1 hypoglycemia ($r=0.83$, $p<0.001$) and was dropped. This left eight variables in the final analysis intended comprehensively characterize features of dysglycemia including hypoglycemia, hyperglycemia, and glycemic variability. The final CGM input variables are shown in **Supplemental Figure 5.1 and Supplemental Table 5.1.**

Supplemental Table 5.1. 8 Continuous Glucose Monitoring (CGM) Metrics for SOM Analysis, Selected to Capture Glucose Exposure, Hyperglycemia, Hypoglycemia, and Glycemic Variability, in the Day and Nighttime.*

Clinical Significance	**Variable**
Hypoglycemia Exposure	Area above curve 3.9 mmol/L (70 mg/dL), day
	Area above curve 3.9 mmol/L (70 mg/dL), night
Hypoglycemia Incidence	Number of 15 min or longer periods with glucose <3.9 mmol/L (70 mg/dL)
	Number of 15 min or longer periods with glucose <3.9 mmol/L (70 mg/dL)
Hyperglycemia Exposure	Area under curve 13.9 mmol/L (250 mg/dL), day
	Area under curve 13.9 mmol/L (250 mg/dL), night
Glycemic Variability	Coefficient of variability, day
	Coefficient of variability, night
Day defined as 6:00 AM-11:59 PM. Night defined as 12:00 AM-5:59 AM.	

A: Full 16 CGM metrics selected to capture glucose exposure, hyperglycemia, hypoglycemia, and glycemic variability, in the day and nighttime	
Clinical Significance	Variable
Hypoglycemia Exposure	Area above the curve 70 mg/dL, day
	Area above the curve 70 mg/dL, night
	Area above the curve 54 mg/dL, day
	Area above the curve 54 mg/dL, night
Hypoglycemia Incidence	Number of 15 min or longer periods with glucose<70 mg/dL, day
	Number of 15 min or longer periods with glucose<70 mg/dL, night
	Number of 15 min or longer periods with glucose<54 mg/dL, day
	Number of 15 min or longer periods with glucose<54 mg/dL, night
Hyperglycemia Exposure	Area under curve 180 mg/dL, day
	Area under curve 180 mg/dL, night
	Area under curve 250 mg/dL, day
	Area under curve 250 mg/dL, night
Glycemic Variability	Coefficient of variability, day
	Coefficient of variability, night
Median glucose	Median glucose, day
	Median glucose, night
Day defined as 6:00 AM-11:59 PM. Night defined as 12:00 AM-5:59 AM.	



B: Pruned CGM metrics for SOM analysis.	
Clinical Significance	Variable
Hypoglycemia Exposure	Area above curve 70 mg/dL, day
	Area above curve 70 mg/dL, night
Hypoglycemia Incidence	Number of 15 min or longer periods with glucose<70 mg/dL, day
	Number of 15 min or longer periods with glucose<70 mg/dL, night
Hyperglycemia Exposure	Area under curve 250 mg/dL, day
	Area under curve 250 mg/dL, night
Glycemic Variability	Coefficient of variability, day
	Coefficient of variability, night
Day defined as 6:00 AM-11:59 PM. Night defined as 12:00 AM-5:59 AM.	

Supplemental Figure 5.1. Flow chart for selection of the final eight Input CGM Metrics used to train the SOM. A: Full sixteen CGM metrics selected to capture glucose exposure, hyperglycemia, hypoglycemia, and glycemic variability, in the day and nighttime. B: Pruned CGM metrics for SOM analysis. Data were pre-processed to remove highly correlated variables, biological redundancy, and degrees of freedom in the variables used to construct the SOM.

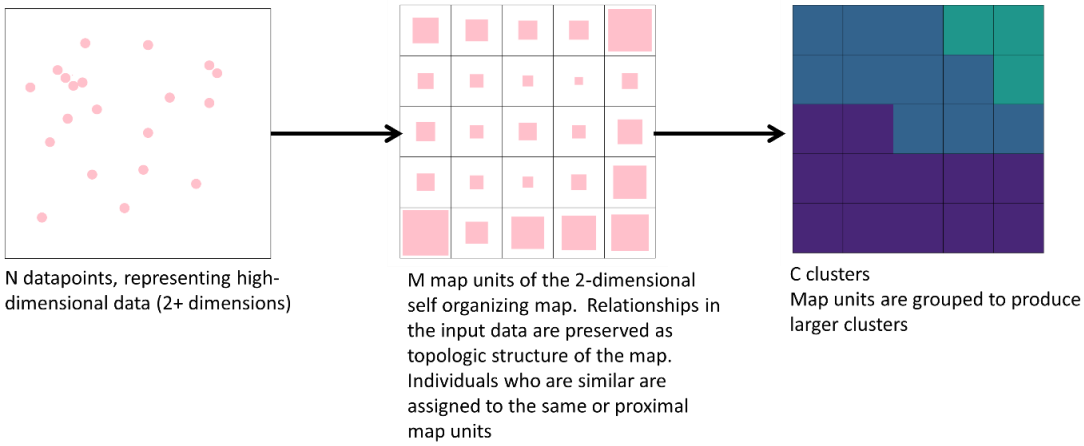
5.6.2 Selection of the clustering algorithm

5.6.2.1 Explanation of the Self-Organizing Map (SOM) algorithm

SOMs are a neural network approach that serves as a model-based static clustering method.[290,315] The SOM is particularly useful for clustering high dimensional data. SOMs may be used to identify clusters via a 2-step clustering approach. After the map units of the SOM have adapted to the topological shape of the dataset, each map unit reflects a cluster. The SOM map units can then be to identify larger clusters, with the benefit of noise reduction compared to the raw data (**Supplemental Figure 5.2**, adapted).[316]

The main function of the SOM is to map the CGM input data from an 8-dimensional space to a two-dimensional space while maintaining the original relationships as the topological structure of the map.[290,291] The size of the SOM and number of map units is pre-specified by the researcher. Each unit contains an '8-dimensional' codebook vector; each dimension corresponds to one of the eight CGM metrics available for each participant. The SOM network learns the shape of a dataset by repeatedly adjusting the codebook vectors to move its map units closer to the data points.[290] At first, each of the units are randomly positioned. Individual data points are then randomly fed into the algorithm. Each new data point funds the closest map unit, which is called the Best Matching Unit (BMU). By adjusting the codebook vectors, the BMU moves closer to the new data point. The learning rate, which measures the distance that the BMU moves with each new data point, decreases with each iteration and eventually stabilizes at a minimum value. The BMU's neighbors within a given radius move closer to the new data point as well; the value for the radius decreases

after each iteration. After the map has been trained, the map units coalesce around areas with high density of data points and thus reflect the overall topological shape of the data.[303] The SOM captures similarities between participants in the arrangement of the final map units such that individuals that are near each other in the input space (i.e. have similar CGM measures) are mapped to nearby units in the SOM, while those with dissimilar measures are mapped to more distant units.[290] Through multiple iterations, the units of the SOM will coalesce around areas with high density of data points and can be regarded as mini-clusters.[303] The SOM can serve as a clustering technique when neighboring map units are further grouped into larger clusters based on the codebook vectors.[303]



Supplemental Figure 5.2. 2-step clustering using SOM. The clustering is carried out using a two-level approach, where the dataset is first clustered using the SOM and then the SOM is clustered.

5.6.2.2 SOMs for dimension reduction and clustering of non-normally distributed or non-symmetrical data

Briefly, examination of individual variable distributions revealed that several of the raw data were not normally distributed with severe right-skew and clumping at zero, including measures of hypoglycemia and hyperglycemia for which some individuals

never experienced time below or above the threshold. The resulting data is not appropriate for clustering algorithms that invoke assumptions the normality or the symmetry of the data, including k-means and hierarchical approaches. Since the information contained in the skew was considered central to the understanding the distinct subgroups of youth who may experience different aspects of dysglycemia, categorization was not an appropriate option.

The SOM is an unsupervised, machine learning technique that is robust to different distributions of data when uncovering underlying clusters. Compared to other unsupervised machine learning methods, SOM is appropriate non-linear data reduction (unlike principle components analysis) and robust to skewed input data (unlike k-means or hierarchical clustering algorithms), with the benefit that it controls dimension reduction and grouping at the same time.[291] SOM clustering solutions have been shown to provide more accurate recovery of underlying cluster structure in the context of skewed input data.[291] The ability of the SOM to accommodate skewed input data and capture information in the tails of the distribution was considered critical to understanding the range of dysglycemia in the sample.

5.6.2.3 SOMs for visualization of data

In addition, the SOM allows for the visualization of complex multivariate relationships represented by the high-dimensional input space.[303,315] The prominent visualization capacities may be used to first examine the multivariate relationships represented in the high-dimensional input space prior to clustering.[303,315] This step helps to ensure that the resulting clusters are valid regarding each of the input metrics.[316] This was considered a key strength of the method in the context of the present analysis,

where there were data labels to guide the formation of clusters but reasonable assumptions about how the CGM metrics may be co-distributed across the study sample.

5.6.3 Selection of final map

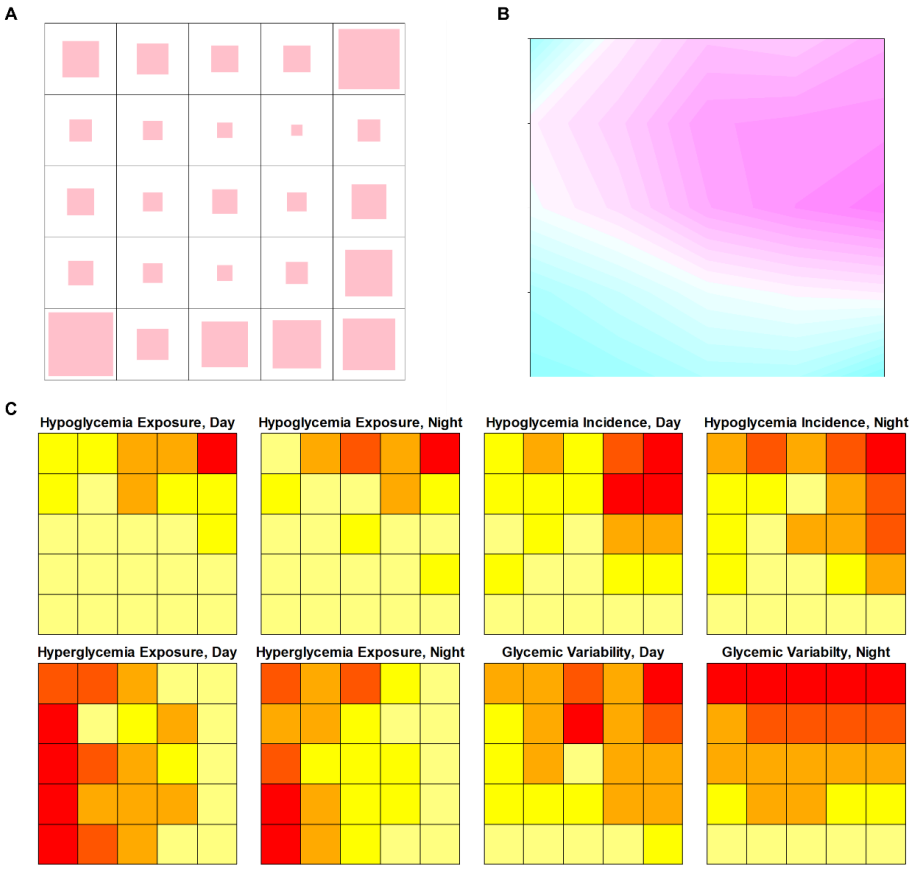
A symmetrical 5x5 square grid SOM was selected based on the sample size and checked that it was optimized to prevent empty cells, at least 5-10 observations per cell.[302] Based on observed stability of the map across testing and training partitions. The final map was run on the full dataset to maximize statistical power. The SOM was created and re-run 10 times on the full data to check for consistency in parameters (neighborhood size, topographic error, quantization error (**Supplemental Table 5.2**). For every SOM instance, we shuffled the training set, randomly initializing the map from the training set, and incrementally trained a SOM with map size of 5x5 using 1000 iterations (~4.3 times through the data). Each SOM map that was trained interpedently on the same input data, but from different random initializations. The best out of 10 maps were selected (based on the lowest quantization error, defined as the average Euclidian distance of all segments to the prototype vector of their assigned unit. The quantization error calculates the mean squared Euclidean distance between the sample vectors and their respective cluster prototypes. It is a decreasing function of the size of the map.[305] The quantization error is an unbounded positive number. The closer it is from 0, the better the projection quality. The topographic error, or vector projection, is the simplest measure of topology preservation. It calculates the ratio of sample vectors of which the second BMU is not in the direct neighborhood of the best matching unit.[305] The topographic error value varies between 0 (good projection quality) and 1 (poor

projection quality). There is a tradeoff between measures, as increasing projection quality decreases the projection properties.[305] The quantization error of the final map 4.7 and the topographic error was 0.0, suggesting that all observations have a second-best unit which is in the neighborhood of the best matching unit.

Supplemental Table 5.2. Topographic Error and Quantization Error for the Chosen Ap and Average Over 10 Trained Maps

	Topographic Error	**Quantization Error**
Chosen Map	0.004	4.117
Average (10 Maps)	0.003 ± 0.003	0.118
Quantization error is defined as the average Euclidian distance of all segments to the prototype vector of their assigned unit; decreasing values indicate higher map quality. Topographic error is a measure of topology preservation measure defined as the ratio of sample vectors for which the second-best matching unit is not in the direct neighborhood of the best matching unit.		

Supplemental Figure 5.3 depicts the final map. **Supplemental Figure 5.3A** visualizes the 5x5 SOM grid and the relative frequency of individuals assigned to resulting 25 map units. Individuals with similar CGM measures are assigned to proximal map units (**Supplemental Figure 3B**)**.** Measures of hypoglycemia exposure and incidence were highest in the upper right corner of the map, while measures of hyperglycemic exposure were greatest along the bottom left side of the map (**Supplemental Figure 5.3C)**. Daytime and overnight measures of each CGM metric showed related patterns across the map units.



Supplemental Figure 5.3. The self-organizing map (SOM) trained by 7-day continuous glucose monitoring (CGM) data from the baseline of the FLEX trial (n=234). A 5x5 SOM with 25 map units was constructed. All CGM-variables were calculated for the 7-day wear time and were stratified by day (6:00 AM – 11:59 PM) and night (12:00 AM – 5:59 AM). Panel A: Frequency map of showing the relative proportion of individuals assigned to each unit on the SOM. Each unit is represented by a colored square with a region corresponding to the relative number of data points it represents (bottom). The larger the colored square, the more datapoints are represented by that unit. Panel B: The SOM colored to represent the average distance between neighboring units, integrating distance between all eight CGM metrics. The map is colored by distance between 8 input CGM metrics at each of the 25 units. Units representing similar datapoints are separated by shorter distances and are shown in blue, while units corresponding to vastly different sets of data points are separated by larger distance and are denoted by a pink color. Panel C: Colors of eight CGM-input metrics on the SOM. The map in Figure 5.1A can be re-printed for each input variability colored according to the characteristics of the participants assigned to each of the 25 units of the map. The patients that are located on a given unit determine the color for the respective area of the SOM. The color scale indicates the mean of each variable, where high values are represented by red and low values are represented by light yellow. Each of the 8 maps is colored for a single CGM metric.

5.6.4 Validation studies

Clusters from the SOM were validated for internal validity, stability, and fidelity to the original data. Each validation study is outline below.

5.6.4.1 Internal Validation

We performed 5-fold cross-validation to assess stability of the clusters derived from the SOM. The full dataset was segmented into 5 random partitions and the effect of leaving out 1 partition of data was analyzed by retraining SOMs on the remaining 4 partitions. The Rand Index and Adjusted Rand Index was used to assess the overlap between ‘trained’ clusters, derived from the test data on the trained map, and ‘test’ clusters, derived directly from a SOM in the testing data.[317] The Adjusted Rand Index accounts for the number of clusters ranges from 0 to 1 and provides a measure of how "similar" the units within a cluster grouping are, where 1 would indicate that all of the stores in each given cluster assignment are similar, negative numbers of close to 0 suggest poor agreement and 1 is the maximum that reflects identical clustering.[318]

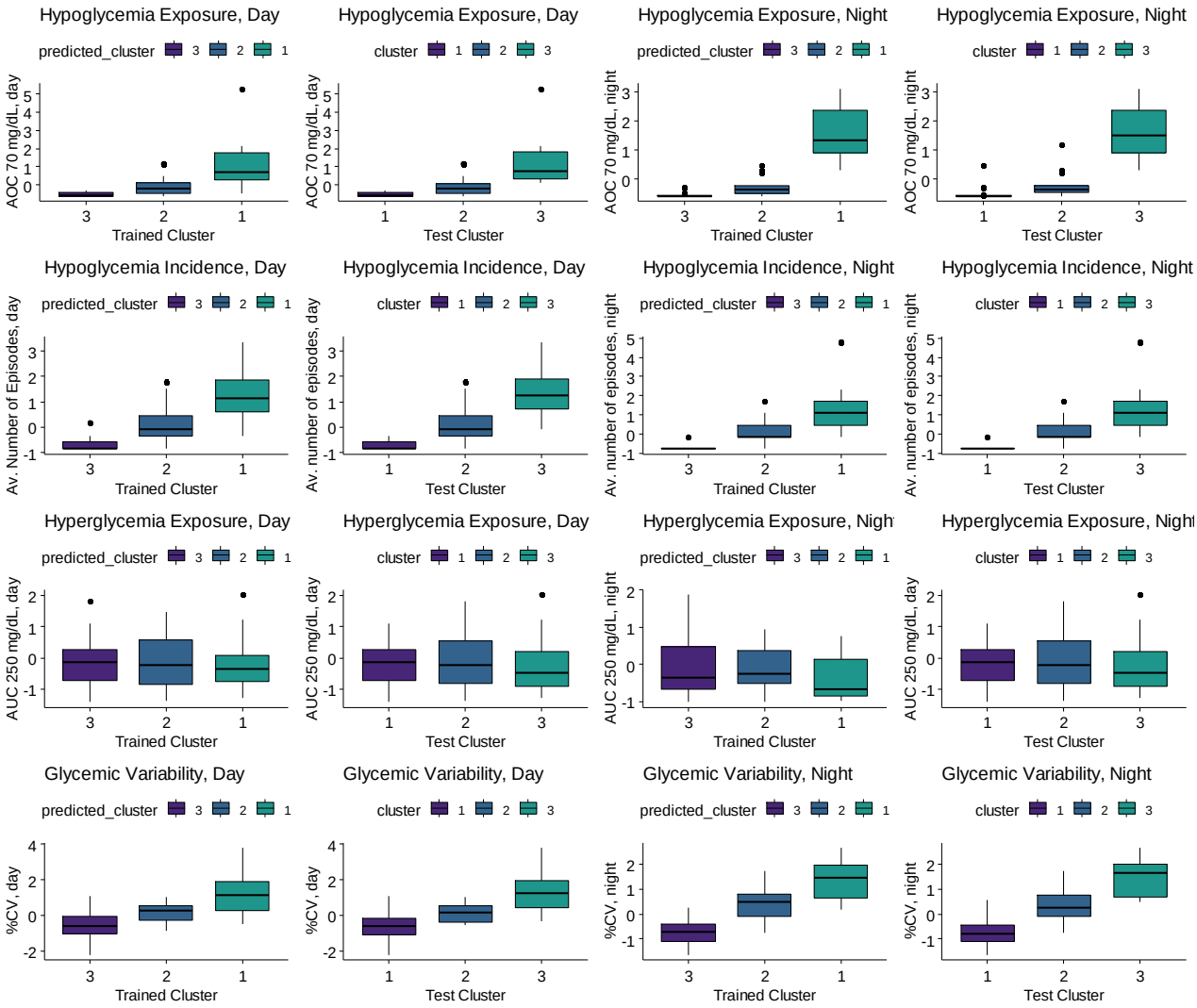
The mean Adjusted Rand Index of the 5-fold cross-validation study was 0.56 ± 0.16, suggesting acceptable stability of clusters derived from each training iteration.[258,317,319]

To further explore the stability of clusters from the SOM, the ARI calculated from a 3-6-fold cross validation, although sample size is limited for larger partitions of data. The results are shown in **Supplemental Table 5.3.** The Adjusted Rand Index was sustained as the size of the testing set decreased, suggesting stability across varying sizes of testing and training data partitions.

Supplemental Table 5.3. Cross-Validation Results from Various Data Partitions (full sample size, n=234)

Cross-Validation	n of testing set	Adjusted Rand Index, mean (SD)
3-Fold	75	0.54 (0.12)
4-Fold	63	0.59 (0.19)
5-Fold	46	0.56 (0.15)
6-Fold	41	0.54 (0.25)

The distribution of each of the eight input CGM metrics were examined across the trained and test clusters (shown in **Supplemental Figure 5.4**). This data suggested that the relative meaning of each cluster was preserved between iterations with respect to the variables used to train the SOM.



Supplemental Figure 5.4. Distribution of each of the 8 CGM metrics across trained and test clusters

5.6.4.2 Clustering Stability

Dysglycemia Clusters derived from the eight input CGM metrics were compared to Dysglycemia Clusters derived from a SOM trained with a larger amount of metrics, including input datasets of 16 and 24 total CGM metrics. All metrics were selected to be consistent with the reporting of CGM for clinical and research use.[144] The resulting

Dyslycemia Clusters from each SOM were compared for evidence of stability across a larger subset of CGM input variables (**Supplemental Table 5.4**).

The Adjusted Rand Index for each clustering solutions derived from the additional CGM metrics were approximately 0.4, suggesting sufficiently stability across larger input datasets. An examination of the distribution of the 8-input CGM variables consistent across all maps revealed nearly identical patterning of variables across Dysglycemia Clusters, suggesting that addition CGM metrics did not contribute variability to disrupt the clustering solution. In addition, the SOM trained on larger input datasets showed significantly higher quantization error, suggesting low projection quality of the resulting SOM.[320]

Supplemental Table 5.4. Clusters Derived from 8, 16, and 32 CGM Metrics

Number of CGM Metrics	Specified Number of Clusters	Adjusted Rand Index,* mean (SD)	Quantization Error,* mean (SD)
8†	3	N/A	4.46 (0.17)
16‡	3	0.43 (0.05)	9.08 (0.21)
24§	3	0.38 (0.12)	15.16 (0.22)

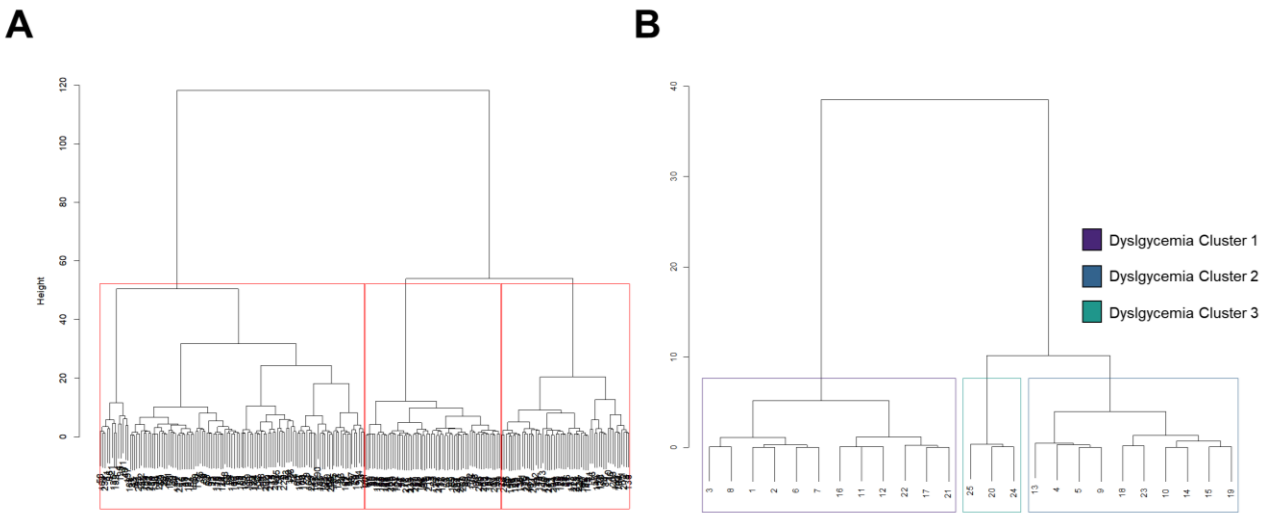
Abbreviations: CGM – continuous glucose monitoring. SD – deviation.
*represents the mean of 10 random, iterative SOM trained on the same data
†8 CGM input metrics included: Area above curve (AOC) <3.9 mmol/L (70 mg/dL), day; AOC 3.9 mmol/L (70 mg/dL), night; Number of 15 min or longer periods with glucose <3.9 mmol/L (70 mg/dL), average per day; Number of 15 min or longer periods with glucose <3.9 mmol/L (70 mg/dL), average per night; Area under curve (AUC) 13.9 mmol/L (250 mg/dL), day; AUC 13.9 mmol/L (250 mg/dL), night; Coefficient of variability, day; Coefficient of variability, night.
‡16 CGM input metrics included: AOC <3.9 mmol/L (70 mg/dL), day; AOC 3.9 mmol/L (70 mg/dL), night; AOC 3.0 mmol/L (54 mg/dL), day; AOC 3.0 mmol/L (54 mg/dL), night; Number of 15 min or longer periods with glucose <3.9 mmol/L (70 mg/dL), average per day; Number of 15 min or longer periods with glucose <3.9 mmol/L (70 mg/dL), average per night; Number of 15 min or longer periods with glucose <3.0 mmol/L (54 mg/dL), average per day; Number of 15 min or longer periods with glucose <3.0 mmol/L (54 mg/dL), average per night; AUC 10 mmol/L (180 mg/dL), day; AUC 10.0 mmol/L (180 mg/dL), night; AUC 13.9 mmol/L (250 mg/dL), day; AUC 13.9 mmol/L (250 mg/dL), night; Coefficient of variability, day; Coefficient of variability, night; Median glucose, day; Median glucose, night.

[§]24 CGM input metrics included: AOC <3.9 mmol/L (70 mg/dL), day; AOC 3.9 mmol/L (70 mg/dL), night; AOC 3.0 mmol/L (54 mg/dL), day; AOC 3.0 mmol/L (54 mg/dL), night; Number of 15 min or longer periods with glucose <3.9 mmol/L (70 mg/dL), average per day; Number of 15 min or longer periods with glucose <3.9 mmol/L (70 mg/dL), average per night; Number of 15 min or longer periods with glucose <3.0 mmol/L (54 mg/dL), average per day; Number of 15 min or longer periods with glucose <3.0 mmol/L (54 mg/dL), average per night; AUC 10 mmol/L (180 mg/dL), day; AUC 10.0 mmol/L (180 mg/dL), night; AUC 13.9 mmol/L (250 mg/dL), day; AUC 13.9 mmol/L (250 mg/dL), night; AUC 16.6 mmol/L (300 mg/dL), day; AUC 16.6 mmol/L (300 mg/dL), night; Coefficient of variability, day; Coefficient of variability, night; Standard deviation, day; Standard deviation, day; Mean rate of glucose change, day; Mean rate or glucose change, Night; Median glucose, day; Median glucose, night; Percentage of time in range 3.9-10 mmol/L (70-180 mg/dL), day; Percentage of time in range 3.9-10 mmol/L (70-180 mg/dL), night.

5.6.4.3 Fidelity to the Original Data

The SOM approach to clustering is only valid if the clusters found using the SOM are similar to those of the original data.[321] Therefore, the SOM clusters were compared to clusters derived directly from the data to ensure that the SOM clusters accurately represented clustering structure present in the raw data.[303]

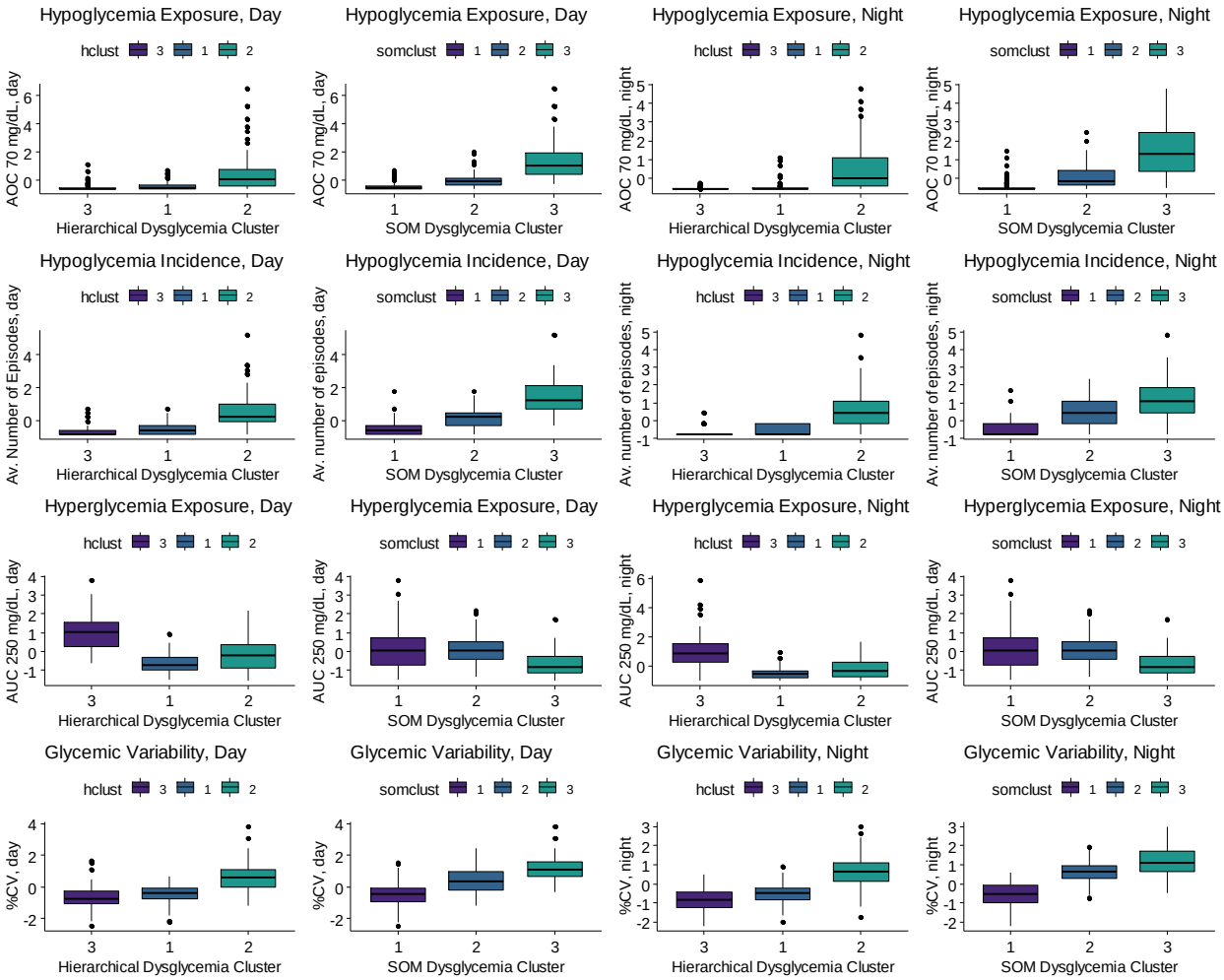
A hierarchical clustering algorithm was applied to the 8 CGM metrics as raw variables in the full dataset. All CGM Metrics were standardized to be unit-free. A hierarchical clustering algorithm with Ward's D2 method and a Euclidean distance was used. The number of clusters was selected to be 3 to facilitate comparison with the SOM clusters. Three clusters were produced, with n of 117, 60, and 57, respectively. The dendrograms for both clustering solutions are visualized in **Supplemental Figure 5.5.**



Supplemental Figure 5.5. Dendrograms produced by agglomerative hierarchical clustering algorithms, using the raw data (panel A) and the SOM (panel B). Three clusters were specified for both algorithms.

Hierarchical clustering solution was compared to the SOM clustering solution, using the full dataset. The mean ARI for 10 iterations of the SOM was 0.3±0.1.In addition, the distribution of each input CGM metric was visually inspected, using the final SOM presented in the main results (**Supplemental Figure 5.6**).

Although the assumptions of hierarchical clustering algorithm are not met using the input data, we found similar clusters with both algorithms. Together, the results suggest that the SOM clusters are consistent with clusters derived from the original data. This result is consistent with previous studies showing clustering results using SOM as an intermediate step is comparable with the results obtained directly from the data.[303]



Supplemental Figure 5.6. Distribution of 8 CGM metrics across clustering solution from self-organizing map (somclust) and hierarchical clustering algorithm (hclust)

5.6.5 Further characterization of longitudinal outcomes

5.6.5.1 Characterization of 18-mo changes in HbA1c

Mixed effect regression analysis was used to determine whether clusters showed differential changes in HbA1c over 18-months. A main effect was fit for visit and cluster and a visit*cluster interaction term. Participants were treated as random effects. All models were adjusted for randomization status and site. Post-hoc comparisons by cluster were performed within each mixed model analysis and the effects were

examined at each longitudinal timepoint in the FLEX study. These data are visualized in **Figure 5.2.**

Supplemental Table 5.5. Longitudinal Hemoglobin A1c (HbA1c) Outcomes of FLEX Participants by Dysglycemia Cluster, Adjusted for FLEX Study Site and Randomization Assignment

	Dysglycemia Cluster 1 (n=141, 60.3%)	Dysglycemia Cluster 2 (n=53, 22.7%)	Dysglycemia Cluster 3 (n=40, 17.1%)	p-for-interaction *
Mean HbA1c (SE)	Minimal hypoglycemia, low variability, severe hyperglycemia	Moderate hypoglycemia, severe variability and hyperglycemia	Severe hypoglycemia and glycemic variability, moderate hyperglycemia	0.006
Baseline, % and mmol/mol	9.8 (0.9)	9.5 (1.0)	8.7 (0.5)	
	84 (10)	80 (11)	71 (6)	
3-month, % and mmol/mol	9.7 (0.9)	9.6 (1.0)	9.1(0.5)	
	82 (10)	81 (11)	75 (6)	
6-month, % and mmol/mol	9.8 (0.9)	9.6 (1.0)	9.2 (0.5)	
	83 (10)	81 (11)	77 (6)	
12-month, % and mmol/mol	9.6 (0.9)	9.7 (1.0)	9.4 (0.5)	
	82 (10)	83 (11)	80 (6)	
18-month, % and mmol/mol	9.8 (0.5)	9.5 (0.6)	9.6 (0.3)	
	84 (6)	80 (7)	81 (3)	

Abbreviations: HbA1c- hemoglobin A1c. SE – standard error.
All estimates are adjusted for FLEX study site and randomization assignment. Missing data— Baseline: n=0; 3-month HbA1c: n= 10; 6-month HbA1c: n= 14; 12-month HbA1c: n=20; 18-month HbA1c: n=16.
*p-for-interaction represents Type 3 Test of Fixed Effects for timepoint*cluster interaction term

5.6.5.2 Characterization of CGM Metrics at the 18-month timepoint

The 8 CGM metrics that were used at baseline to train the SOM, were characterized at the 18-month time point (**Supplemental Table 5.6).** All measures were derived from 7-day blinded CGM wear, using an identical protocol to the baseline visit. At the 18-month study visit, Dysglycemia Clusters retained significant differences in hypoglycemia exposure, hypoglycemia incidence, and daytime glycemic variability. There were no longer significant differences in hyperglycemia or overnight glycemic variability. Dysglycemia Cluster 3 showed higher measures of hyperglycemia exposure at the 18-month visit, consistent with the concurrent increase in HbA1c over the study period.

Supplemental Table 5.6. Key CGM Metrics at the FLEX 18-Month Timepoint Measured from 7-Days of Blinded CGM Wear, Overall and by Dysglycemia Cluster

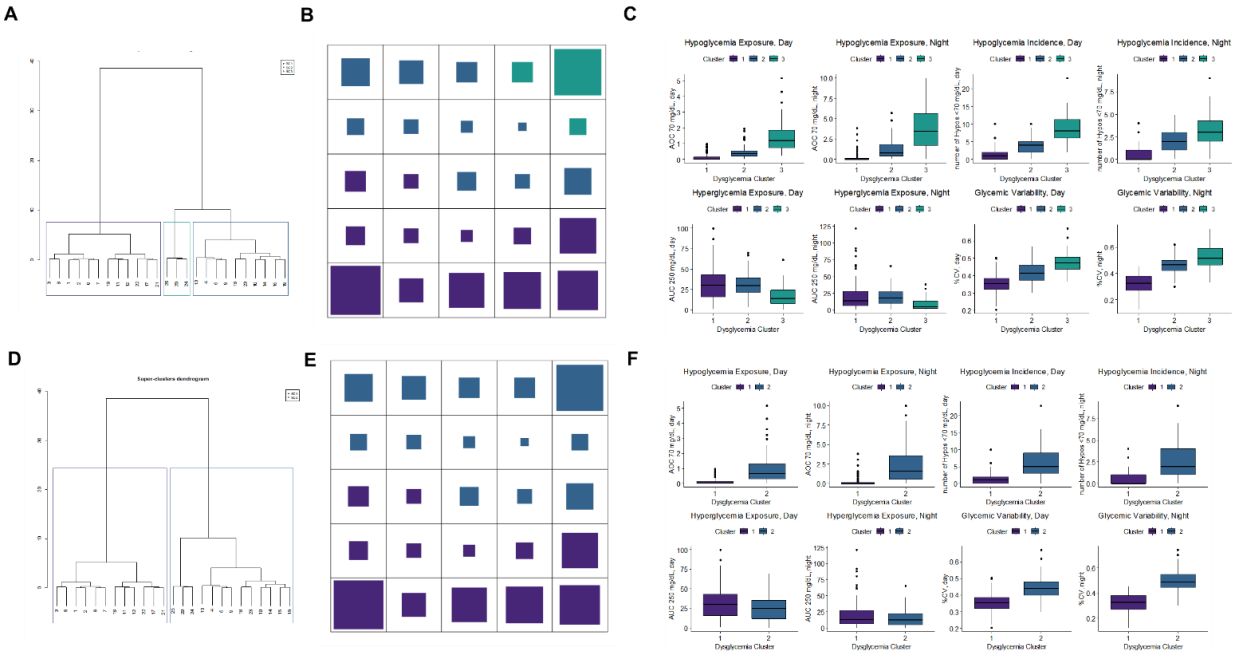
		Dysglycemia Clusters			
CGM Metrics, mean (SD), or median (IQR)	All (n=200)	Cluster 1 (n=111, 60.3 %)	Cluster 2 (n=39, 21.2%)	Cluster 3 (n=34, 18.5%)	p-value
Hypoglycemia Exposure					
AOC 3.9 mmol/L (70 mg/dL), Day†	0.07 (0.38)	0.04 (0.17)	0.06 (0.59)	0.19 (0.7)**	0.005*
AOC 3.9 mmol/L (70 mg/dL), Night†	0.02 (1.09)	0 (0.55)	0.02 (0.79)**	1.1 (3.2)**	0.002*
Hypoglycemia Incidence					
Episodes<3.9 mmol/L (70 mg/dL) for 15+ minutes, Day†	1 (3)	1 (3)	1 (3)	3 (1)*	0.008*
Episodes<3.9 mmol/L (70 mg/dL) for 15+ minutes, Night†	0 (2)	0 (2)	0 (1)	1 (3)	0.019*
Hyperglycemia Exposure					
AUC 13.9 mmol/L (250 mg/dL), Day†	32.4 (32.3)	31.6 (33.0)	33.5 (37.5)	35.5 (28.9)	0.751
AUC 13.9 mmol/L (250 mg/dL), Night†	20.3 (27.6)	19.1 (27.1)	20.9 (36.1)	14.6 (29.9)	0.613

Glycemic Variability					
Coefficient of Variation, %, Day	37.7 (7.9)	36.8 (7.2)	39.0 (8.9)	40.6 (9.2)**	0.041*
Coefficient of Variation %, Night	36.9 (1.5)	36.3 (12.8)	38.0 (13.6)	40.5 (17.0)	0.282
Abbreviations: SD- standard deviation. IQR- Interquartile range. AOC – area over the curve. AUC - area under the curve. *Denotes significance test of overall difference from ANOVA or Kruskal-Wallis test ($p<0.05$). **Denotes significant difference in unpaired, pairwise t-test or Dunn's test ($p<0.05$), compared to Dysglycemia Cluster 1. †Data were right-skewed and are reported as median (interquartile range). P-value from Kruskal-Wallis test. There were no missing data.					

5.6.6 Characterization of the 2-Clustering Solution

The results from a clustering solution that considers 2 Dysglycemia clusters was explored. **Supplemental Figure 5.7** compares the dendrograms and visualizes the cluster assignments on the SOM for both the 2- and 3- cluster solutions. Dysglycemia Clusters 1 and 2 were combined to give the new Dysglycemia Cluster 2.

Main tables were re-run to compare the CGM features and baseline characteristics of the 2-clustering solution (**Supplemental Tables 5.7- 5.9**). No significant differences were detected across clusters regarding sociodemographic, clinical, or psychosocial characteristics.



Supplemental Figure 5.7. Comparison of 2-cluster versus 3-cluster solution for the self-organizing Map (SOM) trained by 7-day continuous glucose monitoring (CGM) data to identify dysglycemia clusters at baseline of the FLEX trial (n=234). A: 3-Clustering Solution: Dendrogram from hierarchical clustering algorithm performed on the SOM. 3 clusters were selected. Final Dysglycemia Cluster assignments (Cluster 1, Cluster 2, and Cluster 3) are shown by colored boxes. B: The SOM colored by 3 Dysglycemia Cluster assignments. Clusters are also shown across a frequency map, in which each map unit is represented by a colored square with a region corresponding to the relative number of data points it represents. The larger the colored square, the more datapoints are represented by that map unit. C: Distribution of each input CGM variable across 3 Dysglycemia Clusters. All p<0.001. D: 2-Clustering Solution: Dendrogram from hierarchical clustering algorithm performed on the SOM. 2 clusters were selected. Final Dysglycemia Cluster assignments (Cluster 1 and Cluster 2) are shown by colored boxes. E: The SOM colored by 2 Dysglycemia Cluster assignments. Clusters are also shown across a frequency map, in which each map unit is represented by a colored square with a region corresponding to the relative number of data points it represents. The larger the colored square, the more datapoints are represented by that map unit. F. Distribution of each input CGM variable across 2 Dysglycemia Clusters. All p<0.001.

Supplemental Table 5.7. Baseline Characteristics of FLEX Participants Overall and by Dysglycemia Cluster from a 2-Cluster Solution

		Dysglycemia Cluster		
Baseline characteristics, n (%) or mean (SD)	All (n=234)	Cluster 1 (n=141, 60.3%)	Cluster 2 (n=93, 39.7%)	p-value
Sociodemographic Characteristics				
Age (years)	14.8 (1.1)	14.8 (1.1)	14.9 (1.2)	0.39
Female sex	117 (50.0)	68 (48.2)	49 (52.7)	0.50
Non-Hispanic White†	178 (76.1)	104 (73.8)	74 (79.6)	0.31
Parental Education				0.20*
Graduate degree	43 (18.5)	22 (15.8)	21 (22.6)	
College Degree	67 (20.9)	54 (38.9)	23 (24.7)	
Some College	67 (28.9)	44 (31.7)	23 (24.7)	
High School or less	26 (11.2)	19 (13.7)	7 (7.5)	
Private Health Insurance	164 (70.1)	105 (74.5)	59 (63.4)	0.07
Single adult home	30 (13.1)	17 (12.4)	13 (14.1)	0.70*
Clinical Characteristics				
Duration of diabetes (years)	6.4 (3.7)	6.5 (3.8)	6.3 (3.6)	0.76
HbA1c (mmol/mol)	81 (13)	85 (14)	77 (11)	
HbA1c (%)	9.6 (1.2)	9.9 (1.3)	9.2 (1.0)	<0.001
HbA1c above 9.0% [75 mmol/mol]	156 (66.7)	104 (73.8)	52 (55.9)	<0.001
Insulin Regimen				0.40
Multiple daily injection	68 (29.2)	38 (27.1)	30 (32.6)	
Pump	165 (70.8)	102 (72.9)	63 (67.7)	
Insulin Dose, total (units/kg)	0.98 (0.33)	1.01 (0.36)	0.93 (0.30)	0.10
Average frequency of self-monitoring blood glucose, daily	2.2 (0.8)	2.1 (0.8)	2.2 (0.8)	0.38
BMI z-score	0.71 (0.91)	0.70 (0.92)	0.75 (0.91)	0.69
Weight Status				0.85
Under- or normal weight	143 (61.1)	88 (62.4)	55 (59.1)	
Overweight	56 (23.9)	32 (22.7)	24 (25.8)	
Obese	35 (15.0)	21 (14.9)	14 (15.1)	
Psychosocial Characteristics				
Motivation‡	7.6 (1.6)	7.7 (1.4)	7.6 (1.7)	0.72
Intention‡	9.1 (1.0)	9.2 (0.9)	8.9 (1.1)	0.09
Problem solving§	105.6 (13.0)	106.2 (12.5)	104.6 (13.7)	0.36
Adherence to Diabetes self-management‖	55.2 (11.6)	55.5 (11.9)	54.7 (11.2)	0.63
Depression symptoms¶	9.1 (8.4)	8.6 (7.6)	79.9 (12.9)	0.23
Quality of life#	81.0 (12.4)	81.7 (12.0)	79.9 (12.9)	0.28
Fear of hypoglycemia††				
Maintain High BG	1.2 (0.9)	1.2 (0.9)	1.2 (0.8)	0.94

Helplessness/Worry	1.1 (0.6)	1.1 (0.6)	1.1 (0.6)	0.67
Worry about negative social consequences	1.1 (0.7)	1.1 (0.8)	1.3 (0.3)	0.79
Diabetes Family Conflict‡‡	1.4 (0.3)	1.4 (0.4)	1.3 (0.3)	0.43

Abbreviations: SD – standard deviation. CGM – continuous glucose monitoring. HbA1c – hemoglobin A1c. BMI z-score – body mass index z-score.
P values are from Chi squared or fisher exact test for categorical variables, and t-tests or Kruskal-Wallis Test for continuous variables. *Denotes p value from Fisher's exact test. **Denotes significant difference in unpaired, pairwise t-test ($p<0.05$), compared to Dysglycemia Cluster 1.
Missing data— insulin dose: n=4; parental education: n=2; motivation: n=3; intention: n=3; problem solving: n=1; diabetes adherence: n=1; quality of life: n=2; fear of hypoglycemia: n=2; diabetes family conflict: n=1.
† Non-Hispanic white race/ethnicity versus non-Hispanic Black, Black, and other including Asian/Pacific Islander, Native American, or unknown.
‡ Motivation and Intention were measured by a validated questionnaire adapted for relevance to type 1 diabetes self-management.
§ The Social Problem Solving Inventory – Revised: Short (SPSI-R:S); higher score indicates higher ability to resolve problems in everyday living.
‖ Diabetes Self-Management Profile – Self Report (DSMP-SR); higher score indicates higher adherence.
¶ Centers for Epidemiologic Study – Depression Scale (CES-D); higher score indicates increased depressive symptoms.
# Pediatric Quality of Life Inventory™ – Generic Core Scales; higher score indicates higher quality of life
†† Hypoglycemia Fear Survey (HFS); fear of hypoglycemia measured in three domains: behaviors used to keep blood glucose high to prevent hypoglycemia (Maintain High BG), worry about helplessness (Worry/Helplessness), and worry about social consequences associated with hypoglycemia (Worry/Social Consequences); higher scores indicate greater fear.
‡‡ Diabetes Family Conflict Scale (DFCS); higher score indicates higher conflict.

Supplemental Table 5.8. Input CGM Metrics at Baseline Measured from 7-Days of Blinded CGM Wear, Overall and by Dysglycemia Cluster from a 2-Cluster Solution

		Dysglycemia Cluster		
CGM Metrics, mean (SD), or median (IQR)	All (n=234)	Cluster 1 (n=141, 60.3%)	Cluster 2 (n=93, 39.7%)	p-value
Hypoglycemia Exposure				
AOC 70 mg/dL [3.9 mmol/L], Day*	0.15 (0.52)	0.03 (0.14)	0.65 (1.0)	<0.001
AOC 70 mg/dL [3.9 mmol/L], Night*	0.11 (1.31)	0.00 (0.11)	1.65 (3.01)	<0.001
Hypoglycemia Incidence				
Episodes <70 mg/dL [3.9 mmol/L] for 15+ minutes†, Day*	2 (5)	1 (2)	5 (6)	<0.001
Episodes <70 mg/dL [3.9 mmol/L] for 15+ minutes†, Night*	1 (2)	0 (1)	2 (3)	<0.001
Hyperglycemia Exposure				
AUC 250 mg/dL [13.9 mmol/L], Day*	26.9 (21.1)	29.9 (27.4)	24.8 (23.1)	0.018
AUC 250 mg/dL [13.9 mmol/L], Night*	13.0 (21.1)	13.3 (21.8)	12.2 (18.0)	0.131
Glycemic Variability				
Coefficient of Variation, %, Day	39.8 (7.4)	35.5 (6.4)	44.0 (7.9)	<0.001
Coefficient of Variation %, Night	38.8 (11.9)	32.7 (10.7)	48.6 (10.2)	<0.001

Abbreviations: SD- standard deviation. IQR- Interquartile range. AOC – area over the curve. AUC- area under the curve.
*Data were right-skewed and are reported as median (interquartile range). P-value from Kruskal-Wallis test. There were no missing data.
†Average number of hypoglycemic (<70 mg/dL) episodes lasting 15 or more minutes per 24-hr period

Supplemental Table 5.9. Longitudinal Hemoglobin A1c (HbA1c) Outcomes of FLEX Participants by Dysglycemia Cluster from a 2-Cluster Solution, Adjusted for FLEX Study Site and Randomization Assignment

Mean HbA1c (SE), mmol/mol and %	Dysglycemia Cluster 1 (n=141, 60.3%)	Dysglycemia Cluster 2 (n=93, 39.7%)	p-for-interaction
Baseline	84 (10)	77 (3)	0.002
	9.8 (0.9)	9.2 (0.3)	
3-month	82 (10)	79 (3)	
	9.7 (0.9)	9.4 (0.3)	
6-month	83 (10)	79 (3)	
	9.8 (0.9)	9.4 (0.3)	
12-month	82 (10)	81 (3)	
	9.6 (0.9)	9.6 (0.3)	
18-month	84 (6)	80 (3)	
	9.8 (0.5)	9.5 (0.2)	

Abbreviations: HbA1c- hemoglobin A1c. SE – standard error.
All estimates are adjusted for FLEX study site and randomization assignment. Missing data— Baseline: n=0; 3-month HbA1c: n= 10; 6-month HbA1c: n= 14; 12-month HbA1c: n=20; 18-month HbA1c: n=16.
*p-for-interaction represents Type 3 Test of Fixed Effects for timepoint x cluster interaction term

CHAPTER 6: EVALUATION AND SYNTHESIS

This chapter provides an overview of the dissertation including its limitations and strengths, proposed future studies, a discussion of the several aspects of broad significance with the theoretical implications, and closing remarks.

6.1 Overview of the Dissertation

Three dissertation studies presented the novel application of statistical methods to identify distinct clinical phenotypes of type 1 diabetes. Chapter 3 and Chapter 4 demonstrated that within the SEARCH population of youth and young adults with type 1 diabetes, there are distinct subgroups sharing a phenotype defined by their weight status and glycemic control; subgroups show different susceptibility to early and subclinical complications of diabetes including hypertension, hyperlipidemia, retinopathy, and nephropathy within the first decade of having diabetes. Chapter 5 demonstrated that continuous glucose monitoring data may be used to identify subgroups of adolescents with type 1 diabetes based on minute-to-minute aspects of dysglycemia that represent discrete clinical issues, including hypoglycemia and glycemic variability; subgroups showed differences in longitudinal patterns of HbA1c. Together, the studies provide proof-of-principle for the existence of subgroups which can be used to inform a precision medicine approach to optimize weight management concurrent with glycemic control in a population at an exceedingly high risk for cardiovascular disease.

6.2 Limitations of Dissertation

A discussion of the limitations for each study can be found in their respective chapters (see **Sections 3.4, 4.4**, and **5.4**). However, there are several overarching limitations to the dissertation that warrant discussion, including restrictions of the data and methodologic considerations.

The study designs and their respective study populations limit the inferences that may be made. For example, the data posed challenges with regards to the ages of the participants. Analyses in SEARCH bridged youth and young adults, raising issues with combining participants of different developmental stages and providing challenges for the selection of measures of weight status (i.e. BMIz versus BMI). Due to the inclusion criteria of the FLEX trial, participants represented a very restricted age range (13-16 years old), which may introduce a form of selection bias and limits generalizability. In addition, pieces of potentially informative data were not available. For example, tanner stage data may have lent insights into developmental-specific changes in adiposity over puberty in **Chapters 3**, while interim measures of BMIz or HbA1c may have revealed non-linear longitudinal trajectories in those outcomes in **Chapter 4**. Granular insulin dosing data, such as the frequency of boluses and timing of boluses relating to major meals, may have provided a diabetes-specific behavioral correlate to better understand the different patterns of dysglycemia in **Chapter 5.**

The family of methods employed in these studies, cluster analysis, is an exploratory technique; none of the studies represent deterministic analyses.[322] Further, there are highly subjective aspects of cluster analysis where researcher decisions may bias the results, including the specification of the distance matrix or the selection of the final number of clusters.[323] Because clusters reflect the datasets on which they are

derived, the generalizability of results is limited by the inclusion and exclusion criteria specified for the analysis. Finally, establishing cluster nomenclature is challenging and often represents a trade-off between interpretability and accurate labeling of all individuals within that subgroup.

In all studies, the statistical precision was limited by sample size, particularly with regards to adjusted modeling (i.e. logistic regression modeling in **Chapter 4** and mixed effect regression analysis in **Chapter 5**). The small sample size also prevented adjustment for numerous additional covariates, which may result in biased effect estimates due to residual confounding.

An additional, significant limitation of the dissertation relates to the analytic approach and concerns the interpretation of the resulting phenotypes. The objective of the dissertation was to use machine learning approaches to identify patient phenotypes of type 1 diabetes based on key, pre-specified clinical feature and evaluate the utility of data-driven phenotypes to predict different clinical outcomes. Therefore, all analyses are descriptive in nature; by design, the resulting clusters represent prognostic subgroups and cannot be used to properly infer response to a given intervention nor selection of an optimal intervention.[324] An ideal phenotypic system should capture heterogeneity in individualized treatment or intervention approaches in addition to heterogeneity in prognosis to identify candidates for individualized treatment.[241]

Finally, these studies were not designed nor powered to study underweight in the setting of type 1 diabetes, although this phenotype may be related to the DSM V-recognized diagnosis of ‘diabulimia’[192] or other disordered eating behaviors that are prevalent in this population.[197,198] Sensitivity analyses revealed that the proportion of

youth and young adults with type 1 diabetes who are classified as underweight was very small, comprising less than 2% of the study samples.

6.3 Strengths of Dissertation

Despite the limitations, there are also several overarching strengths of the dissertation. First, the studies integrate two distinct datasets and leverage the strengths of each to derive patient subgroups. For example, the SEARCH study represents the largest population-based studies of childhood diabetes in the United States.[325] This nationally-representative cohort is thus ideal for an epidemiologic approach to characterize the significant weight-glycemia phenotypes across the population. Although CGM data is readily becoming more available, the 7-day CGM wear-time outlined in the FLEX protocol yielded a highly novel dataset due to the high mean HbA1c of the study sample at baseline, providing an opportunity to characterize dysglycemia among youth with elevated HbA1c. Despite differences in sample size and availability of measures, both datasets provided the unique opportunity to evaluate the real-life utility of the computationally derived phenotypes for predicting longer term clinical outcomes, including the emergence of early/subclinical diabetes complications after approximately eight years of diabetes in **Chapter 4** and 18-month changes in HbA1c in **Chapter 5**. In addition, the entire dissertation focused on youth and young adults, a highly relevant age range for future interventions towards weight management and glycemic control given data showing puberty is a challenging time for both glycemic control and body weight and may set the stage for subsequent morbidity and mortality.[107]

The three studies address specific gaps in the scientific literature. Measures of weight and glycemic control have not been integrated previously to describe the weight-glycemia phenotypes of type 1 diabetes. This approach is timely given epidemiologic data showing suboptimal glycemic control[3-5] and adverse changes in body weight[1,2] among youth and young adults with type 1 diabetes. In addition, the framework is flexible and may be easily adapted in the future to accommodate greater heterogeneity in weight, ranging from underweight to obesity, and glycemic control. The use of CGM data to derive dysglycemia phenotypes is opportune given an increase in CGM uptake among adolescents with type 1 diabetes[143] and the increasing availability of these data for research purposes.[144] To this end, the unsupervised approach to CGM data analysis may facilitate its application to a broad range of CGM datasets for future work.

These studies also address a larger gap in the field of diabetes research. Despite the establishment that a precision health system of care for diabetes needs more precise disease subtypes[240,241] that can be used to accurately predict clinical outcomes,[324] work in this area has remained largely theoretical. Results from **Chapters 3-5** represent early steps towards a precision medicine framework for type 1 diabetes and offer pragmatic examples of “precision” diabetes care, an otherwise largely vague notion.

Finally, although the statistical methods are innovative, the concept of patient phenotyping reflects how clinicians work to intuitively deliver individual care plans for patients. This approach is specifically consistent with medical standards of care for patients with diabetes, which acknowledge the profound inter-individual differences and suggest individualized care according to clinical needs, attitudes and preferences,

expected treatment effects, disease duration and comorbidities or complications, resources and support system, and lifestyle.[80,85]

6.4 Proposed Future Studies

The following section describes studies that could be undertaken in the future to address limitations of the dissertation studies and build on novel findings, including epidemiologic and statistical analyses of existing data and new data collection for prescriptive discovery.

6.4.1 Related epidemiologic and statistical analyses

Existing data could be used to further understand and validate the findings from this research in several additional studies outlined below.

6.4.1.1. Studies related to the weight-glycemia phenotypes of type 1 diabetes

There are several studies that could be undertaken to explore and improve upon results presented in **Chapters 3** and **4** (i.e., the weight-glycemia phenotypes of type 1 diabetes). Phenotypic subgroups warrant external validation studies in different cohorts of youth and young adults with type 1 diabetes. For example, it would be interesting to study these subgroups in other US datasets, such as the clinic-based T1D Exchange Registry,[326] as well as international datasets, such as the Prospective Diabetes Follow-up (DPV) registry in Germany and Austria.[327] This platform may also be expanded to study weight-glycemia phenotypes of long-standing diabetes in adults and their association with hard clinical outcomes[328] versus the surrogate outcomes available in the early natural history, such as cardiovascular disease events and death. The 14+ years of follow-up available on DCCT participants enrolled in the Epidemiology of

Diabetes Interventions and Complications (EDIC) cohort study could be used for this purpose,[329] although substantial changes in the clinical care of type 1 diabetes may decrease the relevance of this dataset looking forward.

Because BMI is limited in its ability to describe differences in fat mass,[262,263] particularly among males,[330,63] these phenotypes could likely be improved by the use more precise measures of body composition that compartmentalize adiposity versus lean mass. For example, future work could use validated predictive equations to estimate body fat percentage[331] and derive 'adiposity-glycemia' clusters using the predicted variable. (Of note, we have previously used these equations to study longitudinal patterns of adiposity among youth and young adults with type 1 diabetes in the SEARCH study.[165]) Ideally, clustering could be based on direct measures of body composition, such as those collected from dual energy X-ray absorptiometry.

6.4.1.2. Studies relating to the dysglycemia phenotypes of type 1 diabetes

The results described in **Chapter 5** (i.e. the dysglycemia phenotypes of type 1 diabetes) also warrant additional studies. As with the weight-glycemia subgroups, the dysglycemia phenotypic subgroups warrant external validation in other large CGM datasets to understand their durability and the influence of other patient factors (i.e. age, diabetes duration) on the major phenotypes. Data from 14 or more days of CGM data would be ideal to understand the accuracy of data-driven subgroups using 7 versus 14 days of data, as the latter was suggested as a minimum requirement by the ATTD Consensus statement.[144] In addition, CGM data in the setting of a large clinical trial for different antihyperglycemic therapies or diabetes technology could be analyzed with these methods to reveal nuanced patterns of response that may be missed with HbA1c.

Additional data on dietary intake could be used to study specific postprandial response related to the timing, frequency, and composition of meals. Finally, the dysglycemia phenotypes may be improved with deep learning to extract hidden layers of the CGM data. [311] Hidden layers may yield more homogenous or predictive clusters compared to those derived from the clinical measures outlined in the ATTD consensus statement.

6.4.2 Prescriptive discovery and clinical trials

A clinically-actionable understanding of disease subtypes involves a classification system which not only predicts outcomes but one which also confers information about targeted therapies that are appropriate for each subtype.[324] Although the studies presented here are descriptive in nature, this dissertation give premise for larger and intentionally-designed trials to move from understanding observational phenotypes to devising their therapeutic approaches.

6.4.2.1 Possible trial designs and their limitations

There are conceivable several ways to design a clinical trial to study differential response across a set of baseline phenotypes previously demonstrated by observational studies (i.e. the weight-glycemia phenotypes or the dysglycemia phenotypes).

One option is to run a fixed intervention for all study participants, and in the analysis phase, test for a phenotype*intervention interaction for predicting the primary outcome. If the interaction is significant, one could subsequently examine differences in intervention response between subgroups to determine which phenotypes may also serve as markers for specific response patterns. This analysis could be conducted in any randomized trial testing a single intervention delivered consistently across arms.

Several studies that used computationally-generated clusters to predict response to trials have shown significant results,[332-334] although this work requires large, sometimes pooled data from multiple intervention studies to lend adequate statistical power and sufficient generalizability.[332,334] It is also possible to test the efficacy of phenotype-specific interventions by *a-priori* designing and assigning phenotype-specific interventions to the subgroups expected to benefit with a comparison of outcomes against a less-tailored standard of care.

Although the trials above would address differential response (either through analytic approach or design), the scientific conclusions may be flawed for several reasons. First, their conception and execution are directly based on phenotypes established from observational data, which may suffer from selection bias, residual confounding, and lack of randomization. Second, and most importantly, these designs skip the step of prescriptive discovery; they do not explicitly test what the optimal intervention is for a given subgroup given a range of possible options. Therefore, a better use of the observational studies is for the generation of a discovery hypotheses which can be tested *via* estimation of a dynamic treatment regime for this population.[12] As discussed in **Chapter 2**, a dynamic treatment regime formalizes precision medicine as a sequence of decision rules that are used to assign a patient to an intervention or series of interventions based on their unique covariates, which are denoted as “tailoring variables” in the context of treatment estimation.[12]

There exist clinical trial designs that are constructed to generate maximally-informative and scientific valid data for this purpose; these trials are referred to as Sequential Multiple Assignment Randomized Trial (SMART) designs.[12] SMART designs

have been described extensively elsewhere.[226] Briefly, after baseline data collection and initial randomization, the SMART embeds multiple decision points over the course of a longitudinal trial. At each decision point, new patient data are collected and intervention assignments may be re-randomized based on patient response with respect to a set of *a-priori* established rules for re-randomization. The primary outcome or outcomes are often observed after the last decision point. The SMART design allows for several important analyses upon completion: 1) the comparison of outcomes with different interventions assignments; 2) comparison of outcomes under different *sequences* of interventions, and 3) the estimation of an optimal dynamic treatment regime for the population under study, from which responders and non-responders to each intervention can be inferred and characterized.[12,226]

Although an optimal dynamic treatment can be estimated from the observational data, an advantage of SMART designs is that they address limitations of observational data described above including lack of randomization and unmeasured confounders.[12] In addition, compared to traditional single-stage randomized trials, SMARTs can be used to characterize delayed effects (i.e. intervention effects which show a long-term effect only when followed by a second intervention or lasting side-effects which inhibit future intervention) and diagnostic effects (i.e. an intervention which may not be effective towards the primary outcome but reveals patient data to optimize the selection of subsequent interventions).[12,226]

6.4.2.2 SMART trial design for prescriptive discovery

A SMART is proposed as an avenue of significant future work for the dissertation studies. There are three main stages of proposed future studies, including formative

work, an Exploratory SMART, and a Confirmatory Trial, depicted in **Figure 6.1** and described in detail below. The three stages are designed to be executed in sequential order, with reiteration of previous steps as necessary.

Briefly, formative work would build towards an Exploratory SMART, designed to test multiple, diverse interventions (i.e. pharmaceutical, technological, and behavioral approaches) to co-optimize weight management and glycemic control across a range of clinical needs. Participants would be recruited with a need to improve body weight, HbA1c, or both, to lend variability in the sample. Interventions will be selected based on analysis of patient data, their perceived benefit and acceptability to clinicians and patients, and the strength of the evidence base. Q-learning, a reinforcement learning method that is used for sequential decision-making,[335] would be used to estimate an adaptive intervention strategy to co-optimate weight and glycemia over the course of the trial.[335] Findings from the Exploratory SMART may be explored through further iterations of formative work and, eventually, a confirmatory phase 3-type randomized trial or hybrid confirmatory SMART design.

In the context of the dissertation studies, the significant advantages of the SMART design include:

1) The ability to assess major patterns of response and non-response to multiple interventions with multiple outcomes. There exists a very large range of clinical approaches for both diabetes management[80,86] as well as weight control,[16,206,207,336] with evidence of highly variable response.[208] In addition, composite outcomes can be intentionally constructed to represent the co-

optimization of BMIz and HbA1c, accounting for their co-evolution and situations in which one outcome may need to be prioritized.

2) The ability to account for and reveal possible positive and negative synergies between sequentially assigned interventions,[226] which may be critical given the potentially antagonistic relationship between weight and glycemic control outcomes.[267]
3) A design that recapitulates real-life clinical practice, where individuals have the chance to be re-randomized if an intervention is not successful rather than continue an ineffective intervention or drop out.[12,226]

Although analyses in Chapters 3-5 focused on youth and young adults with type 1 diabetes, the proposed studies are outlined in an adult cohort. The reason for this is twofold; first, physiologic features (i.e. insulin sensitivity, hormone regulation) are highly dynamic in puberty and health behaviors (i.e. activity levels) are irregular and evolve significantly in adolescence, resulting in decision rules that may be uninterpretable or limited in generalizability. Studies in an adult cohort may lend a more stable study sample from which Candidate Interventions can be rigorously characterized and refined before moving forward to address the challenges of the youth and adolescent cohort.

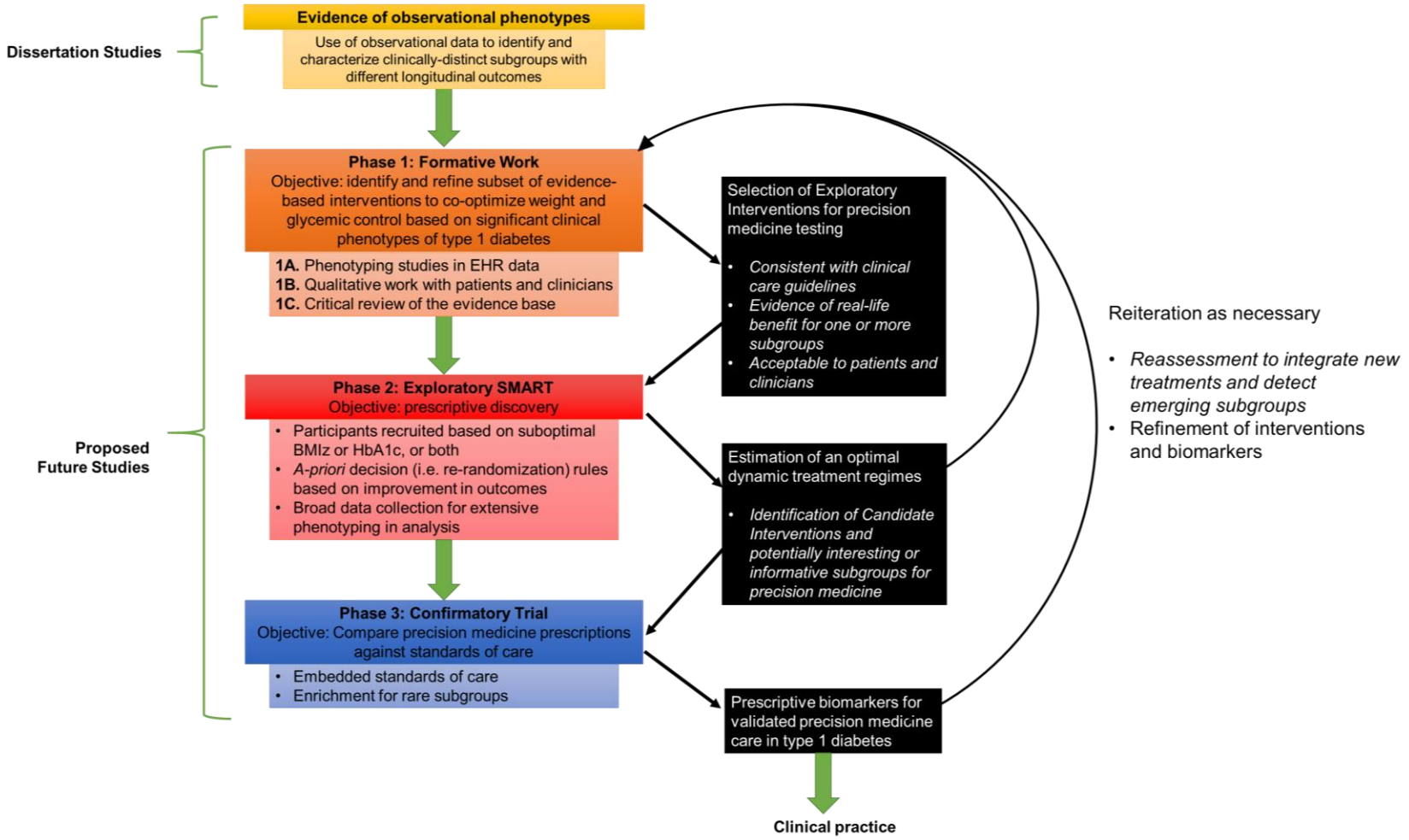


Figure 6.1. Overview of proposed future studies, informed by dissertation studies. Abbreviations: SMART – sequential multiple assignment randomized trial. EHR – electronic health record.

Stage 1: Formative Work

The goal of formative work would be to narrow in on a subset of evidence-based 'Exploratory Interventions' to co-optimize weight and glycemic control. This stage would use a combined approach of patient data analysis, qualitative studies with patients and care providers, and a rigorous review of the scientific and medical literature.

The selection of Exploratory Interventions from a broad range of available, feasible interventions would be guided by age-appropriate current standards of care for type 1 diabetes[80 337] and obesity[338 339] management with an emphasis to avoid any intervention with significant risk for adverse effects. The selection and comparison of different clinical approaches is highly consistent with the current American Diabetes Association Standards of Care, which, as outlined in **Chapter 2**, acknowledge the profound inter-individual differences that exist between patients and suggest individualized care for each patient, considering patient factors and preferences in the selection of clinical goals, glycemic targets, and therapeutic approach.[80,85]

Stage 1A: Phenotyping studies in Electronic Health Record (EHR) Data

Data in electronic health records (EHR) is being increasingly leveraged for secondary uses ranging from biomedical studies to comparative effectiveness.[340] This form of 'big data' offers tremendous potential towards the identification of hypothesized patient phenotypes (i.e. subgroups characterized in Chapters 3-5) or latent, previously uncharacterized patient phenotypes in 'real' patient data across large inpatient and outpatient hospital networks.

First, the clustering analyses described in **Chapters 3** and **4** could be replicated using relevant and available measures in EHR from individuals with type 1 diabetes,

pulled from one or more large health systems. The resulting subgroups could be studied with attention to their basic demographic characteristics, co-morbidities and other diagnosis codes, and treatment regime as it is represented by pharmaceutical prescriptions recorded elsewhere in the medical charts.

In addition, data-driven phenotyping methods can be used to read various data elements and discover underlying clinically meaningful latent patient states or phenotypes from EHR data.[341] To this end, there are emerging techniques for the large-scale discovery of computational models of disease, including subtypes or phenotypes, from this data. The literature contains multiple examples of analytic tasks that can be applied to entire EHR patient populations, including predicting disease progression, comparing effectiveness of treatments, and studying disease interactions.[342-347] For example, a recent study demonstrated the ability to identify temporal phenotypes within a population from EHR by identifying differences in the evolution of clinical states or care flow over time.[348] A different study provided a model for EHR-based phenotyping from heterogeneous patient record data (notes, laboratory tests, medications, and diagnosis codes), modeling disease subtypes in an unsupervised fashion; this model could be applied to EHR data from individuals with type 1 diabetes to identify novel computational phenotypes. Phenotypes derived from EHR could be compared to those derived from other datasets, such as observational cohort data or existing trial data, and characterized according to demographic characteristics, other health outcomes, and clinical care as outlined above.

Stage 1B: Qualitative work with patients

Parallel focus group studies with 1) individuals with type 1 diabetes and 2) endocrinologists and certified diabetes educators be used to collect data to further refined an understanding of major phenotypic subgroups and potential interventions, including their patient-perceived and clinician-perceived advantages and barriers and the main reasons why a given intervention is initiated, continued, or discontinued in real life. Qualitative methods would allow individuals with type 1 diabetes and their care providers to express views and experiences in their own words,[349] lending depth to develop a more complete understanding of the potential interventions. Patients would be queried regarding their perception of their weight and glycemic control, barriers to both, and tools and clinical strategies that they would perceive to be helpful. Specific questions may address potential interventions. Care providers would be asked to discuss their perception of major subgroups within their own patient populations that drive systematically different treatment recommendations in addition to the interventions. Discussions would be guided by a standardized set of questions, audio-taped, transcribed, and analyzed thematically using inductive qualitative methods, following a protocol previously operationalized at UNC to study barriers to weight management among youth with type 1 diabetes as pilot work for these dissertation studies.[193]

Stage 1C: Critical review of the evidence base

Exploratory Interventions identified in Stages 1A and 1C would be subject to thorough review of the relevant literature for evidence of benefit without major adverse

risk, including clinical trials, standards of care or other clinical consensus guidelines, and epidemiologic reports.

Stage 2: Exploratory SMART

Once the Exploratory Interventions have been identified, the Exploratory SMART design can execute ‘pure discovery’ science to inform the precision medicine prescription of the interventions.

When designing a SMART, there is flexibility regarding the time between randomization, the outcomes used to assess response and the *a-priori* rules used to re-randomize participants, the sequence of interventions that are possible, and the set of interventions available at each decision point. It has been suggested that these decisions should be designed to most closely mimic decisions that would be considered in clinical practice.[12,226]

Based on the actions identified to be effective as Exploratory Interventions in Phase 1, individuals with type 1 diabetes and suboptimal weight status or glycemic control (or both) will be randomized among interventions to test for precision medicine rules to guide optimal interventions for weight and glycemia. The Exploratory SMART will be adaptive to individual responses to interventions at each decision point through a set of *a priori* decision rules; rules will govern sequential randomizations based on towards optimizing weight and glycemic control, as well as patient satisfaction. The goal of the Exploratory SMART is to identify an optimal dynamic treatment rule for the data, from which the maximally-effective interventions can be identified as Candidate Interventions. Patient subgroups for whom specific Candidate Interventions are beneficial may also be revealed. All results would be tested in a follow-up, Confirmatory

Trial (see Stage 3). Based on findings from Stage 1, the Exploratory SMART may include some of the following design elements:

- *Recruitment of individuals with type 1 diabetes and a need to for improvement in weight status, glycemic control, or both.* Adults (>18 years of age, with possible further age restriction such as 30-60 years) with a diagnosis of type 1 diabetes and at least 1-year duration of diabetes could be recruited from EHR based on demonstrated suboptimal weight (BMI ≥25; i.e. overweight or obese) or glycemic control (HbA1c ≥8.0%). This recruitment approach would increase the variability in baseline weight and glycemic control and a range of individual-specific goals for interventions to inform decision rules surrounding the Exploratory Interventions (i.e. which Exploratory Intervention is most beneficial towards weight management and glycemic control individually or together). Exclusion criteria could include other characteristics including diagnosed eating disorder, celiac disease, or other serious conditions that render study participation inappropriate. Sample size calculations for the SMART design are not standard sample size calculations.[350] There are few established methods for calculation of sample size for the estimation of an optimal dynamic treatment regime; sample sizes can be calculated based on data from a pilot [351] or by the use of simulation studies to select the smallest sample size the an acceptable estimated outcome.[352] The latter approach may be used in the setting of the Exploratory SMART. As a pilot study to inform the Confirmatory Trial (see Stage 3), the exploratory pilot does not need to be fully powered to compare all intervention sequence analyses.

- *Treatment outcomes that integrate weight status with glycemic control and represent individual needs.* Instead of universal weight loss or HbA1c reduction, weight and glycemic control outcomes could be designed to reflect clinical priorities for each individual (i.e. personalized co-optimization). For example, the weight outcome could vary based on previous BMIz: weight loss could be prioritized for individuals with a previous BMIz measure categorized as overweight or obese, while weight maintenance could be prioritized for individuals with a previous BMIz measure categorized as normal weight. Similarly, HbA1c reduction could be prioritized for individuals with previous HbA1c ≥8.0%, while HbA1c maintenance could be prioritized for those with previous HbA1c <8.0%. The main treatment outcome could be represented by a composite outcome of the priorities defined above for BMIz *and* HbA1c given a participant's current weight and glyemia, requiring the use of SMART analysis methods for balancing competing outcomes.[353]
- *Exploratory Interventions that represent a mix of cutting-edge and established, major treatment regimens for type 1 diabetes with potential benefit for weight management, spanning from technologic interventions and therapeutic interventions to behavioral approaches.* An impactful trial design could simultaneously test novel clinical care paradigms including hybrid closed-loop insulin delivery systems,[170,354,355] adjuvant non-insulin therapeutics such as the addition of a sodium–glucose cotransporter-2 (SGLT-2) inhibitor drug,[84] and behavioral interventions such as structured eating throughout the day.[356-358] Of interest, the adaptive aspects of the SMART may reveal interesting positive and

negative synergies over time between sequentially assigned interventions; it is possibly that these synergies may be maximized by integrating a breadth of approaches as Exploratory Interventions rather than a series of closely related treatments. Final selection of the Exploratory Interventions would be informed by extensive formative work in Stage 1 to represent evidence-based, clinically- and patient-accepted treatment regimens with demonstrated and/or hypothesized benefit towards glycemic control and weight status in all or subgroups of participants.

- *Longitudinal trial with built-in decision points for re-randomization when intervention assignments do not show efficacy or acceptability.* The Exploratory SMART could last 12-months to allow adequate time for change in weight and glycemic control outcomes. Following the first randomization at baseline, participants could be re-randomized at one of 2 visits occurring at 4- and 8-months post-randomization based on *a priori decision rules.* The decision criteria for re-randomization could integrate clinical and patient-centered outcomes, including weight status (BMIz; weight loss or weight gain prevention, depending on current BMIz), glycemic control (HbA1c; reduction in HbA1c or maintenance of good control, depending on current HbA1c, without increase or unacceptably high CGM-derived measures of the incidence and duration of level 1 and 2 hypoglycemia), and patient satisfaction (questionnaire data; maintenance above unacceptably low patient satisfaction).
- *Extensive data collection for deep phenotyping.* Extensive baseline data collection to capture multiple levels of patient information, including demographic

characteristics, social determinants of health, health status and other clinical information, psychosocial and behavioral measures, and genomic data could facilitate enriched understanding of responders and non-responders to candidate interventions.

- *Statistical analyses to estimated tailored interventions and treatment strategies.* Data from the SMART can be analyzed with typical intent-to-treat analyses to compare initial intervention assignments regarding the means in primary outcome at trial end, with or without adjusting for confounders. In addition, precise interventions to optimize BMIz and HbA1c over the trial duration according to outcomes defined above (i.e. maximize weight loss or HbA1c reduction as needed) could be estimated using Q-learning with linear models.[227,359,360] Q-learning is a reinforcement learning technique involving a sequence of recursive regressions to model the relationship between the intervention and outcome, conditional on the patient covariates, and to ultimately select an intervention to optimize expected outcome(s) given the patient covariates.[335] The recursively estimated Q-functions are used to generate a decision rule, which is used to infer Candidate Interventions and the patient or subgroup characteristics to guide their optimal delivery regarding the estimated treatment effects. With the longitudinal design and multiple opportunities for possible re-randomization the decision rule may also confer information about the order effects of the interventions for the co-optimization of BMIz and HbA1c.

Stage 3: Confirmatory Trial

The Exploratory SMART may yield information on Candidate Interventions and the specific subgroups estimated to benefit most that ultimately inform a confirmation hypothesis. Based on the novelty and nature, results can be explored through further iterations of Stage 1 if necessary. The Candidate Interventions could then be tested in a confirmatory phase-3 type randomized trial or confirmatory hybrid SMART design that is designed to compare the precision medicine interventions against standard of care and characterize other aspects of care that are necessary, including potential adverse reactions. The objective of this stage is implementation and confirmation of precision medicine interventions. There are several special design considerations for the Confirmatory Trial.

- *Comparison to Standard of Care:* The Confirmatory trial design can be built to embed an intervention that closely resembles current standards of medical care. If the trial is adequately powered, this design will offer a head-to-head comparison of precision medicine treatments versus standards of care for a given subgroup.
- *Enrichment for rare subgroups:* Upon completion of the Exploratory SMART, the optimal treatment rule may reveal subgroups for whom a precision delivery of a Candidate Intervention makes a large (positive) difference. If those interesting and potentially-informative subgroups are rare, (i.e. occur at a lower frequency or comprise a small proportion of the overall patient population), it may be necessary to enrich for the phenotype in the Confirmatory Trial. Subgroups could represent biological subtypes of diabetes (i.e. monogenic forms) or clinical

phenotypes (i.e. small clusters discovered in Chapters 3-5). Oversampling can be accomplished with pre-designated quotas for a block design framework and recruitment using a specific biomarker or multiple biomarkers[361] for the subgroup of interest. Of note, an enrichment design is feasible only in a population in which oversampling is possible. In the case of type 1 diabetes, rare subgroups may be recruited from larger EHR networks or collaborating clinical sites.

Reassessment over time

Precision medicine is a state of continually reassessing and relearning to ensure that optimal dynamic treatment regimens are representative of the patient population and available interventions.[12] Throughout the confirmatory study (and in future studies), efforts would be focused on improving subgroup classification, which may include combining subgroups, dividing subgroups, or monitoring subgroups over time to assess for newly-emerged subgroups with changing technology and society. In addition, longitudinal studies of the same study population could be used to study how individual change over time how patterns in change impact the overall stability of precision medicine subgroups.

Finally, further studies could be developed to extend work to other age ranges such as youth and adolescents with type 1 diabetes as well as older adults.

6.4.2.3. Significance of prescriptive phenotypes

One of the most important results would be whether patterns of response to the Candidate Interventions are driven by complex or high dimensional features versus single biomarkers. While the former may be interesting for hypothesis-generation, the latter would be equally important and ideal for clinical utility, scalability, and

implementation. The relationship of the proposed SMART to the dissertation studies is that it is a reasonable hypothesis that observational phenotypes from **Chapters 3-5** may integrate and sort themselves as prescriptive phenotypes towards specific interventions in the SMARTs. (For example, subgroups with excessive hypoglycemia may benefit substantially from the predictive insulin-suspension systems or hybrid closed loop pumsp,[362] while subgroups with high BMI and HbA1c concurrently may benefit from SGLT-2 inhibitors.[363,364]) In addition, the SMARTs may generate novel, hypothesis-generating biomarkers for low acceptability or adverse effects of the interventions, for example relating to diabetes technology in youth[365-367] or non-insulin adjuvants[368] in the hypothetical interventions described above.

However, the SMART trial may also reveal non-biomedical ontologies of type 1 diabetes. Ontologies are systematic representations of knowledge that can be used to integrate and analyze large amounts of heterogeneous data, allowing precise classification of a patient.[220] If the SMART design is built to be pragmatic trial (i.e. designed to test the effectiveness of the intervention in a broad routine clinical practice[369]), it is possible that the major prescriptive phenotypes could be based in other patient-factors including other social determinants of health that affect obesity and diabetes care such as socioeconomic disparity in housing, education, and access to care.[216-218] To this end, integrating broad sources of patient data capturing economic status, resources and access to clinical care, and social support with the scientific data from the trial outcomes has the potential to create a precision health system that better matches interventions to specific subgroups that are rendered vulnerable to health

disparity, thereby working towards health equity in addition to tailoring based purely on clinical needs and underlying mechanisms of disease.[220]

Finally, public health resources and clinical practice alike ultimately rely on algorithms that operationalize different actions based on established boundaries or cut-points that balance the scientific evidence with an appropriate distribution of resources. The responder and non-responder subgroups to Candidate Interventions would also be an important step towards the development of a “precision continuum,” or a scalable, clinically-functional version of the optimal dynamic treatment regimen; these subgroups may provide biomarkers and cut-points using existing patient data sources like EHR for algorithms to be scaled in public health and clinical practice. To this end, additional major challenges in the future will be how to 1) integrate formats and structures from different sources of patient data to make them compatible[220] and 2) use the data elements in relation to a relevant decision rule to make discrete decisions for an individual in such a way that is cost-effective across the population.

6.5 Significance and Implications

6.5.1 Multiple approaches for heterogeneity in observational data

Observational studies allow for the study of human health over long periods of times, across entire populations, and with respect to multiple variables associated with human diseases.[370] Although these studies contain an implicit degree of uncertainty owing to ‘the incompleteness of models and the imperfections of data’[370], observational data and its analysis remain at the forefront of public health planning and policies to minimize epidemics in infectious diseases and decrease morbidity and mortality in no-communicable disease.[370] The analytic methods selected for the dissertation studies

demonstrate how the fundamental approach to heterogeneity in observational data can, and should, vary to reflect the goals of the paradigm they inform.

The discipline of epidemiology is central to observational data analysis.[371] Epidemiology is a quantitative science focused on identifying the population-level distribution of diseases, factors underlying their source and cause, and methods for their control.[371] It is also a method of causal reasoning based on developing and testing hypotheses pertaining to disease determinants and significant outcomes of morbidity and mortality.[371] By informing preventative programs and interventions, epidemiology has prevented innumerable cases of disease and saved millions of lives.[370]

A traditional epidemiologic analysis might focus on how an exposure-outcome relationship manifests across the population; the outcome could represent risk for adverse outcome or treatment response. Heterogeneity is largely determined by the researcher to be meaningful or not meaningful with the use of tools such as directed acyclic diagrams (DAG) prior to analysis,[371] which are used to clarify the causal relationship between exposure and outcomes, including the relevant confounders, mediators, and moderators of the association. Adjusting for confounders attempts to move towards causality by removing heterogeneity in an effect that may be due to other factors with a variable co-distribution with the outcome of interest. On the other hand, effect modification attempts to characterize meaningful or actionable heterogeneity in the form of stratified analyses; effect modifiers are specified *a-priori.*

Although the epidemiologic approach to the analysis observational data is extremely powerful for its goals, there are also limitations. First, models to describe population-level associations combine large groups of people by necessity, which may

underemphasize within-group heterogeneity and mask important subgroups within. The process of adjusting for other confounders to produce adjusted estimates of effect further diminishes the signal from heterogeneity in other individual-level characteristics. Additionally, effect modifiers have to be specified *a-priori,* relying on some knowledge base that the researcher may or may not have.

In contrast to epidemiology, where heterogeneity is treated as a challenge for the researcher to measure, categorize, and handle in analysis, a precision medicine approach directly leverages heterogeneity as an actionable aspect of intervention work to inform optimal treatment recommendations for an individual.[12] This paradigm, which focuses on treatment selection as a function of patient factors, gives an opportunity to use combine non-outcome data elements from observational data in a more flexible way than exposure, confounder, moderator, or mediator, accommodating the use of more data towards the understanding of heterogeneity in presentation and therapeutic response. The resulting output may better match what clinicians do intuitively by capturing distinct subtypes that lack causal interpretation but may better reveal variability that may be clinically-significant or meaningful regarding treatment recommendations. It also may yield an enhanced understanding the co-distribution of classical confounders or mediators across subgroups. For example, the study presented in **Chapter 5** characterized heterogeneity in terms of clinical presentation but found other significant differences in the distribution of patient factors across the subgroups; these associations are important for understanding subgroups of type 1 diabetes and may be masked in adjusted models. Finally, heterogeneity can also be

represented in the estimation of optimal treatment rules for different populations, from which distinct biomarkers can be ascertained for implementation of precision medicine.

Of note, the larger idea of inter-individual variability transcends its representation in observational data; it is pervasive throughout public health and clinical care under slightly different, although it is operationalized and labeled differently. The ways in which heterogeneity is conceptualized and quantitatively handled carries implications for the policies and care guidelines that it informs. This is depicted in **Figure 6.2,** which is not meant to be an exhaustive list but instead a reinforcement of the possibilities, significance, and implications for heterogeneity in observational data.

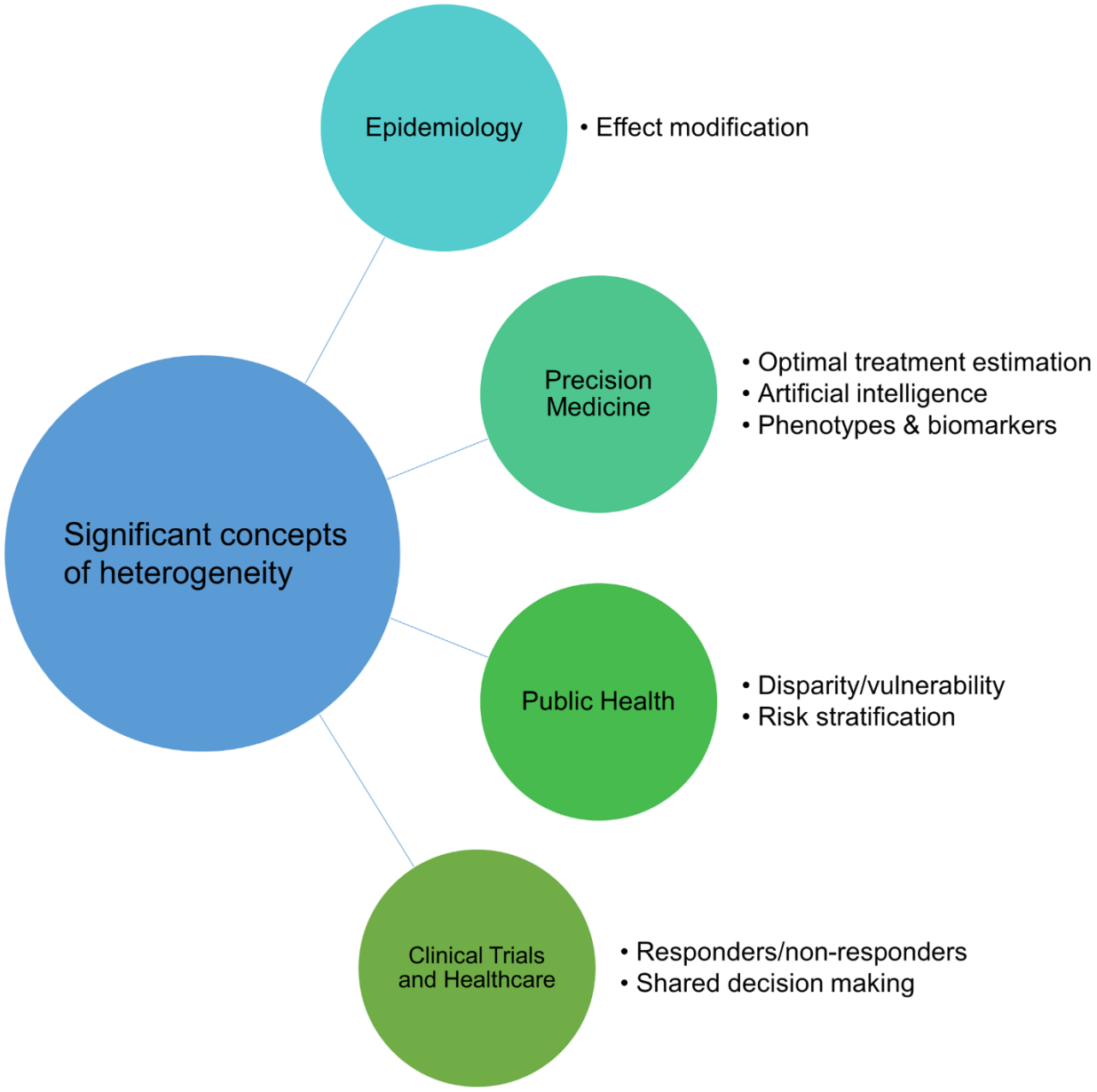


Figure 6.2. Heterogeneity in observational data represented across different fields of science and applied in health practice

6.5.2 Causality and clinical utility

The results presented in **Chapters 3-5** also point towards a distinction between analyses that are causal and analyses that are clinically-useful. Although definitions of causality vary within the discipline of epidemiology,[372] causation typically describes

exposure-outcome relationships that show temporality, positivity, exchangeability, and consistency.[373] Outcomes may be described in terms of sufficient causes, necessary causes, and component causes.[374] Whereas a model to explain a given population-level, causal association of an exposure is an incredibly powerful tool towards large policy or health recommendations, it does not necessarily provide information about multifactorial determinants of a health outcome and their interactions, especially in chronic disease.[375] In particular, salient patient features that act as important aspects of the problem representation used in clinical practice, such as demographic information and co-morbidities, are typically some of the first covariates to be adjusted in epidemiologic modeling; the resulting effect estimate is interpreted as if variation from those features has been neutralized when, in reality, information about the patient and the clinical syndrome are central to diagnostic reasoning and further decision making.

Rather, clinical medicine is rich with concepts and language that implicates stratification for more precise prognosis, prediction, and prescriptions. A precision medicine analysis designed to explore population stratification in a rigorous and reproducible may lack the qualifications for causal inference but it can place the patient in the context of his or her larger patient population,[12,15,215,218] yielding the data to answer three significant questions that are highly clinically-relevant upon new diagnosis or updated health state. First, a question of phenotype: Who else looks like the patient? Second, a question of prognosis: What happens to that subgroup? Finally, and most importantly, a question of optimal treatment: Which treatments have historically and reproducibly been helpful or harmful?

In all, the results from a study that lacks causality itself may retain clinical significance *via* accessibility to the clinical audience charged the task of estimating patient prognoses and optimal treatments day in and day out. Evaluation of such studies *in conjunction* with other available data may inform an understanding of not only the causal or probabilistic determinants of disease, but also the significant, holistic patterns of disease and their treatment. In the future, knowledge gain may be specifically maximized by study designs developed with expert input from biostatistics as well as causal epidemiology to ensure sufficient data collection to enable precision medicine analyses and address explicitly causal questions within the same study sample.

6.5.3 Value of intuitive versus novel subgroups for precision medicine

Recall from the **Chapter 2** that although precision medicine is an emerging field of research, the idea at its core is not new; physicians routinely target treatments to individual patients to account for patient heterogeneity as an implicit part of clinical practice.[13,211] The increase in precision medicine is novel in that it provides data to extend personalized medicine to a population level for the targeting of treatments to subgroups of patients in an empirically-based, scientifically-rigorous, reproducible, and generalizable way.[12]

This type of phenotyping work, in some cases, may shift the expectation and perceived value of an analysis output from novel to intuitive subgroup identification. For example, this dissertation focused on clinical phenotypes of type 1 diabetes, or subgroups within the larger population defined by a diabetes diagnosis who sharing a subset of significant clinical features. In this setting, an appropriate goal may be to

generate computation phenotypes that are biologically plausible but also recognizable and familiar as tangible subgroups to the clinical audience who cares for this population. The innovation of the program of research is thus less contingent on the discovery of new disease subtypes and instead reflects the novel use of data to reproducibly identify phenotypic subgroups that clinicians intuitively know exist (and possibly approach differently for aspects of care). This type of analysis also facilitates the characterization of such subgroups to support anecdotal evidence or clinical intuition with new data, including different outcomes and major treatment recommendations.

However, the expectations of an analysis may change based on the data elements used for phenotype generation. When using novel or unseen biological markers, such as genomic or proteomic data, the objective of an analysis may be more centered on the identification of novel disease subtypes or latent phenotypes which have not previously been characterized and are not distinguishable by other, more accessible clinical data.

Together, the intended nature of computationally-derived phenotypic subgroups and their anticipated reception among the scientific or clinical community is largely dependent on the goals of the analysis and data elements used. Importantly, the broader precision medicine framework both accommodates and needs studies that fall along this spectrum. To reform and advance healthcare in the future, the field of research may benefit from an enrichment of methods to identify both intuitive *and* novel subgroups from varied sources of data, as both flavors of disease ontology may represent actional phenotypes in different clinical and community settings.

6.5.4 The false antagonism of 'data-driven versus a-priori' as analytic approaches

Completion of the dissertation studies, including engagement in the literature and participation in conversations along the way, has revealed several specific aspects of research that may be perceived as in opposition or fundamentally incompatible. For example, as machine learning methods grow in scope and use, the conversation of how these methods fit within traditional epidemiology or biostatistics has generated a sense of tension between 'data-driven' and '*a-priori*' analyses. For the ease of discussion below, data-driven is a label to encompass exploratory or discovery analyses meant to understand characteristics or structure of high-dimensional data, while *a-priori* refers to the family of analyses designed to test the validity of one or more pre-specified hypotheses given available data.

This sense of antagonism is misguided for several reasons. First, it fails to recognize the spectrum that is encompassed by the term 'machine learning.'[376] Rather than exclusive aspects, Beam *et al.* recently described a continuum between fully human-guided and fully machine-guided data analysis, along which there is an evolving trade-off between human specification of a predictive algorithm's properties versus learning those properties from data.[376]

Second, this antagonism operationalizes an oversimplified form of a research hypothesis, one which only describes the testable type which is used to generate and evaluate a p-value for statistical significance. The issue of hypothesis testing is part of a larger conversation[377,378] in the scientific community surrounding flawed research and publication practices which drive and promote false positive results[379,380] (also known as 'P-hacking' or 'p-hacked' results'[381,382]). In that context, it is undeniably important that the upfront and intentional statement or registration of hypotheses, adherence to pre-

specified study protocol, adjustment for multiple comparisons, and encouragement of replication from multiple research groups is part of best practices to increase the rigor and reproducible of observational findings.[377]

However, not all discrepant scientific results reflect foul play, as there are instances in which a perceived lack of reproducibility may be driven by important heterogeneity in an effect of interest across one or more other aspects. For this occasion, and others, science is also advanced by discovery-oriented research in which the design and execution of a study is guided by a broader discovery hypothesis. Although the discovery hypothesis does not have an associated p-value to confirm statistical significance, this is where the line between the *a-priori* and data-driven becomes more blurred in real life; all data-driven analyses need a hypothesis to make sense. Moreover, hypotheses in these settings must be similarly researched and clearly-defined to produce a strong scientific study. For example, an extensive amount of time and research went into the construction the clustering framework for studies presented in **Chapters 3-5**, including defining a phenotype that would be maximally useful for precision heath care and selecting the variables and methods to best capture that phenotype from the data.

This brings forward the last and final misinformed aspect of the perceived distinction between data-driven and *a-priori* analyses, which is the implication that a maximum amount of data is used at once in the former but not the latter approach. In a recent perspective article, Haendel *et al.* recently wrote, ‘data without interpretation are facts without understanding.’ The authors then go on to point out that methods of inference towards understanding patient phenotypes of disease ontologies, such as

statistical analyses or machine learning, require categorizing subjects according to covariates, features, or both.[220] Just like traditional epidemiology or biostatistics, data-driven analyses such as clustering require a strong conceptual framework from which available measures can be designated as clustering versus characterizing variables, based on the both clinical context and the research question. Put otherwise, the use of machine learning methods also does not alleviate the researcher of the need to check the distribution pattern of the data and critically evaluate the results; in fact, just the opposite can occur.

6.6 Closing Remarks

A body of epidemiologic data reveals a need to improve clinical outcomes in type 1 diabetes, particularly among youth and young adults. This dissertation offers evidence that this heterogenous, complex patient population could be approached in a subgroup-based manner to address the unique goals and needs of phenotypic subgroups, based on novel approach that integrates weight with glycemic control. These studies represent an important first step towards a paradigm that offers a comprehensive and patient-centered approach to cardiovascular health in type 1 diabetes. The science integrates tenants of public health and clinical medicine with innovations in biostatistics, representing one of the earliest efforts to apply precision health towards a population who is very likely to benefit from new approaches to optimize multiple clinical outcomes for the best possible long-term health outcomes.

Looking forward, any program of research to inform a patient-oriented and pragmatic approach to medicine should incorporate individual-level physiological, clinical, and behavioral factors as well as a consideration of the larger structural

determinants of health. In diabetes care, however, it is likely that directly leveraging *heterogeneity* across these factors will transform outcomes on a population level. Central to this task is the integration and translation of major concepts from of epidemiology, precision medicine, public heath, and clinical medicine to address inter-individual differences both analytically and in practice. In the future, these studies and conversations could build a precision health system for diabetes care in the form of a collaborative pipeline, one that is designed to bridge the translation of new, cutting-edge device, drug, and nutrition research to its equitable and patient-oriented application to improve health across the entire population.

CHAPTER 7. THE EMERGENCE OF PRECISION PUBLIC HEALTH

The following essay was co-authored with Michael T. Lawson, a doctoral student in the UNC Department of Biostatistics. It is included here based on its relevance to the overall dissertation.

As personalized and precision medicine research have expanded across medical research, an international conversation has unfolded regarding its public health implications. Skeptics of precision medicine have pointed to several aspects of the precision medicine paradigm presumed to limit its applicability to public health. This section offers an alternative perspective: the goals of public health and precision medicine dovetail in precision public health, a broader category within which precision medicine lies.[12] As in precision medicine, the goal of precision public health is to discover treatment rules which leverage heterogeneity to improve clinical outcomes in a reproducible, generalizable, and adaptable way, while the scope is expanded to encompass the clinical outcomes of the whole population.[12]

Recent publications offer a variety of public health-based challenges to precision medicine, which we summarize here. First, it has been noted that precision medicine has dealt with the treatment of disease at the expense of prevention, which is equally if not more crucial to public health.[215,383] Second, precision medicine can lack rigor and reproducibility, opting for data mining techniques rather than tests of explicit hypotheses and relying on convenience samples.[384-386] Third, there may be an inherent tradeoff between precision medicine and evidence-based medicine—the two paradigms

inversely prioritize individualized versus generalizable knowledge when determining best clinical practice.[387] Fourth, due to precision medicine's emphasis on specimens relevant to the mechanism of disease, its purview may be limited to diseases with simple pathogenesis.[218,383] Fifth, any precision medicine scheme enacted in practice will require large-scale collection of genomic and other sensitive biological data, which raises a host of legal and ethical issues.[383] Sixth, and perhaps most damningly, precision medicine neglects the social determinants of health in favor of genomic and biological data, when the social determinants of health provide a stronger, sweeping gradient across which health outcomes are distributed.[384,388]

The picture these criticisms paint is grim. Should precision medicine unfold as outlined, using genomic markers with little direct utility towards effective treatment of disease in individual patients and ignoring the rest of human health, it would provide minimal gains to public health, if any, while diverting resources away from research and programs that could do more.

However, this course is far from the only one precision medicine is equipped to take, and farther still from the course it ought to take. Consider instead an approach that segments the population into subgroups, which in turn receive targeted interventions rather than a "one-size-fits-all" policy.[15,215-217] This is precisely the precision health paradigm, and it offers a middle ground between the population- and individual-centric: this approach relies on population data to measure outcomes in all subgroups, but it capitalizes on new data sources and modern statistical methods to tailor interventions.[12,15,215,218] In this paradigm, the goals of public health and the precision

medicine framework are synergistic rather than antagonistic,[216] allowing disease prevention to advance alongside treatment.[217]

Although of central importance to the precision public health paradigm,[15] the question of how to stratify the population into subgroups has received little attention thus far. To this end, we propose three key criteria for subgroup determination.

First, subgroups must be determined reproducibly. The reproducibility crisis in modern biomedical sciences has highlighted the importance of research that emphasizes scientific consistency at every stage, from study design to data management to the selection of analysis method.[12,361] This concern extends to the political sphere as well—failures in reproducibility threaten a breach of the public confidence and buy-in that are critical for any public health approach to succeed.[389]

Second, subgroups should be determined using socially responsible data. Precision public health cohorts ought to be large, inclusive, and diverse.[215] Machine learning methods provide avenues to utilize data-rich datasets and explore trends across the population, but they rely on the existence of such datasets.[389] This issue is not unique to the precision public health paradigm but falling short of inclusivity will undercut precision public health's vast potential to characterize health disparities.

Third, subgroup stratification should rely on biomarkers that inform the efficacy of intervention, rather than biomarkers that may be artifacts of broader social or economic health inequity.[390,391] As described in Chapter 2.3.2.2, biomarkers can serve a prognostic role, forecasting a patient's long-term prognosis or disease status, a predictive role, illuminating the likelihood that a given intervention will benefit or harm a patient, or a prescriptive role, providing information on which course of intervention is

preferred for a patient.[12] Prognostic biomarkers may define heterogeneous subgroups of patients within diseases, but they have limited public health utility.[1] Stratifying the population on prognostic markers that are distributed unequally across race or socioeconomic status but do not clarify treatment decisions may increase health disparities, or at the least invite fatalistic misinterpretations. Predictive and prescriptive biomarkers, on the other hand, provide directly actionable health information[12] that inform intervention implementation in addition to risk stratification.[217] This usefulness only grows when the concept of biomarker is enlarged to include data beyond a patient's –omics, such as information representing the social determinants of health well-determined by epidemiological studies, when biomarkers inform the logistics associated with determining optimal delivery of care, and when considering complex diseases, in which the environment may play a large role in reinforcing the beneficial effects of therapeutic or preventative intervention.[389]

With these criteria met, precision public health can respond to each criticism raised previously. Precision public health does not focus on treatment of disease at the exclusion of all else—the fact that much of precision medicine research to date pertains to treatment may be a symptom of the natural evolution of the field; early investigators have focused on treatment whereas the paradigm lends itself equally well to prevention. Additionally, precision population screening and prevention interventions may result in substantial cost-of-care savings. For instance, the Diabetes Prevention Program (DPP), a multisite clinical trial randomizing a multiethnic population at high risk of type 2 diabetes between different preventative treatments, demonstrated unique metabolic signatures of diabetes risk both prior to and during preventative interventions.[392] A

precision public health platform offers the best chance to capitalize on findings like these. Regarding concerns about lack of rigor and reproducibility, the answer is not to shy away from new methods and study designs, but to embrace those that offer scientifically principled solutions.[393] Moreover, obtaining results that are consistent and reliable across cohorts is a challenge common to all of medical science, not one that haunts precision medicine alone. The priorities of evidence-based medicine and precision medicine cooperate in precision public health, which accounts for the needs of the population by tailoring decisions to subgroups within. As with any health data that uses sophisticated and sensitive data sources, precision public health research should rely on the legal and technical best practices that govern data management and security,[361] which may well be simplified by future advances in computation and encryption. Finally, by incorporating the social determinants of health, a stratified approach to complex diseases offers a platform to study both biologically and non-biologically based etiology, as well as one equipped to explore real-life phenotypes and differential response patterns.

Despite the consensus that improvements in access to certain basic needs including preventative medicine are necessary and must be applied across an entire population for true public health impact, a way to operationalize that consensus eludes us. Precision public health provides one possible avenue forward. A society that truly cares about the health outcomes of its entire population should be willing to allocate resources to those who need them, and can benefit from them, the most. Stratifying a diverse, complex population based on socially responsible, scientifically rigorous predictive or prescriptive biomarkers may help guide the efficient use of resources to

help those at highest risk.[216-218] In this light, precision medicine appears not inimical, but complementary, to the tenets of public health. Used in conjunction with modern biostatistics, evidence-based clinical practice, and best practices of preventative medicine, the precision medicine paradigm provides a powerful tool to account for the fact that the biggest chronic diseases worldwide are tied to barriers stemming from racial, socioeconomic, and other forms of health disparity. This task is far from trivial. It will require close collaboration across science, mathematics, and policy, and innovation within all of them. But, in the end, that will likely prove to be a strength, not a weakness, of the paradigm: precision public health offers an inclusive, interdisciplinary space where the cutting edge of science intersects with the urgency to correct the most challenging health disparities in society today.

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