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Latent Class Trajectory Analysis of Risk Factors Uncovers Progression to Type 2 Diabetes

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Abstract

We identified trajectories of diabetes risk factors in the Longitudinal Epidemiologic Assessment of Diabetes Risk (LEADR) cohort analyzing 8 years of electronic health records on 1.4 million patients, and investigated associations between trajectories and progression to new onset Type 2 diabetes.

Design and Methods: Analyzing LEADR data (2010-2016), we applied Latent Class Trajectory Analysis (LCTA) to classify patterns of risk factor change. There were 824,043 patients with BMIs; 955,128 patients with systolic blood pressures; 957,491 patients with diastolic blood pressures; 300,137 patients with HDLs; 267,553 patients with non-HDL cholesterol; and 297,026 patients with triglycerides. Patients had to have data for all risk factors being assessed. Association between trajectories and incidence of type 2 diabetes for 94,551 patients was assessed using negative binomial regression analysis.

Results: Compared to a static BMI trajectory, those with a sustained weight increase (25%+ from starting BMI) were at higher risk of type 2 diabetes over 4.8 years of follow-up (range 2.0 to 8.0 years) (adjusted rate ratios ranged 1.53-1.62, p-value<0.05). Patients with a BMI decrease trajectory (of ~10%), were at reduced risk of diabetes (adjusted rate ratios ranged 0.54-0.74, p-value<0.05). BP and lipid trajectories had significant associations with diabetes onset.

Conclusions: Regardless of the starting BMI, those who increased their BMI by 25% within two years and maintained the higher weight were significantly at increased risk of type 2 diabetes. Monitoring BMI change and other known risk factor trajectories, BP and lipids, are additional tools for identifying patients at risk for type 2 diabetes.

Introduction

In the United States, diabetes ranks seventh in leading causes of death, and accounts for nearly \$327 billion in total medical expenditures¹, with type 2 diabetes mellitus accounting for 90 to 95 percent of all diabetes cases^{2,3}. Various factors are associated with the risk of developing type 2 diabetes, including weight, age, race/ethnicity, blood pressure, lipid levels, physical activity, other chronic conditions, and genetics^{2,4,5}. The combined effect of these risk factors is a major public health concern, and better management of lifestyle risk factors (e.g., weight, physical activity, diet) may help in addressing the incidence of type 2 diabetes in the United States^{6,7}.

Understanding the patterns of potentially modifiable risk factors, such as BMI, blood pressure, and blood lipids, may help in better predicting health outcomes and prevention strategies⁸. Research suggests the relationship between BMI and type 2 diabetes^{9,10},

altered glucose metabolism¹¹, and insulin resistance¹², is not only due to the presence of BMI above a certain threshold, but also due to changes in BMI over time. A retrospective analysis of nationally representative data estimated 9 percent of diabetes cases could have been prevented had obese individuals decreased their BMI over the 10-year study period¹³. Further, a recent study has suggested the monitoring of change in BMI as an indicator for diabetes screening¹⁴. While recent studies have examined the overall pattern of BMI levels over time^{15,16,17}, few studies to our knowledge have explored the changing patterns of BMI and their relationship to type 2 diabetes¹⁶. In addition, few studies have examined the potential impact of blood pressure and serum lipid trajectories on risk of developing type 2 diabetes^{18,19,20,21}.

Using electronic health records (EHR) from the Longitudinal Epidemiologic Assessment of Diabetes Risk (LEADR) cohort²², we examined the trajectories of multiple risk factors for type 2 diabetes including: BMI, serum triglycerides, HDL cholesterol, non-HDL cholesterol, systolic (SBP) and diastolic blood pressure (DBP). We then investigated the associations between the trajectories and development of new onset type 2 diabetes.

Research Design and Methods

Study Population

The LEADR cohort is a dynamic database consisting of patients aged ≥ 18 years from nine participating healthcare networks across the United States who have at least four encounters with the healthcare system, each occurring at least 14 days apart, and at least 24 months between the first and last encounters (an encounter is defined as individual times when either one or more conditions, observations, procedures, drug records, or visit records occurred). To identify incident cases of type 2 diabetes, those with type 1 diabetes, type 2 diabetes, gestational diabetes, or unspecified diabetes at cohort entry or during their first 12 months in the cohort were excluded. This analysis used the first wave of the LEADR cohort, which had 1.4 million patients seen between January 1, 2010, and December 31, 2016.

In addition to the LEADR cohort inclusion criteria, for the trajectory analysis, patients were required to have at least two measures for each one of the above noted predefined risk factors ≥ 14 days apart; sample sizes for each high-risk factor trajectory analysis differed based on availability of clinical measurements for patients. The resulting patient sample size for risk factors were: BMI 824,043, SBP 955,128, DBP 957,491, HDL 300,137, non-HDL 267,553, and triglycerides 297,026. To meet the requirement to have all risk factor trajectories for type 2 diabetes generated, to be included in the study, the result was 94,551 LEADR patients met this criterion.

Trajectories of High-Risk Factors

Using latent class trajectory analysis (LCTA), we classified patients according to their high-risk factor patterns over time. For each selected risk factor, we examined actual change in measurements over time. Measures were grouped into 6-month windows starting from the date of first measure with a maximum of up to 10 windows, totaling 5 years of follow-up. For each risk factor, the mean risk factor value with the 6-month windows were used in the analysis, with the mid-date of the 6-month windows assigned to be the corresponding time score. When latent class trajectories differed only in level, and failed to differentiate on patterns of change, we repeated the analysis on percentage change from baseline over time. This occurred only for BMI, for which an additional LCTA was conducted on percentage change (defined as $[\text{BMI}_{\text{at observed timepoint}} - \text{BMI}_{\text{baseline}}] / \text{BMI}_{\text{baseline}}$). We also looked at age and sex differences in trajectories to identify differential patterns in risk factor dynamics.

Using the software Mplus (version 8.2)²³, we conducted latent class trajectory analysis (LCTA) with 3-, 4-, 5- and 6-classes, allowing intercept, slope and quadratic terms to vary across classes, but not within classes (i.e., individuals were grouped into latent classes with the assumption that everyone in the group followed the same trajectory). The final number of classes and the best-fit model for each trajectory were determined by comparing Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), entropy, and bootstrapped likelihood ratio test results. In addition, the resulting classes for each model were required to have at least 0.5 percent of the study sample represented. Once the classes from the best-fit model for each risk factor were established, a nominal categorical variable, i.e., class membership, was created to describe the trajectory membership of each patient for each risk factor. Each patient was assigned to the trajectory class for which they had the highest posterior probability of membership. The latent class trajectory curves were plotted using estimated sample means within each sex and/or age stratum.

Based on the observed differences in trajectory patterns for each risk factor, the final BMI and percentage change in BMI trajectories were stratified for males and females by age group, (18-44, 45-64, and 65 years and older, respectively). For blood pressure (SBP and DBP) trajectories, the analysis was only stratified by age group, as further stratification by sex did not reveal substantial differences in the trajectory patterns between males and females. For serum lipids, the trajectory patterns among sex and age groups were similar, therefore these trajectories were not stratified.

New Onset of Type 2 Diabetes

Type 2 diabetes was defined using a combination of diagnosis records, prescription drugs, and lab values. These were: 1) diagnosis of type 2 diabetes or unspecified diabetes made on two dates within 24 months (diagnosis dates ≥ 14 days apart), or 2) a prescription for metformin or glucagon-like peptide-1 (GLP1) agonists and a type 2 diabetes or unspecified diabetes diagnosis on any encounter, or 3) a prescription for an antidiabetic agent, or 4) hemoglobin A1c lab result $\geq 6.5\%$ or fasting plasma glucose ≥ 126 mg/dl, or random glucose ≥ 250 mg/dl.

Modeling Development of Type 2 Diabetes

Negative binomial regression analysis was applied to investigate the relationship between risk factor trajectories and type 2 diabetes. In addition to the trajectories, the preliminary model assessed the association of the following co-variables with diabetes (yes/no) in the multivariable setting: age group (18 to 44 years, 45 to 64 years, and 65 and older), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/AI/AN/Other/Multiple races), sex, geographic region, usage of medicines for hypertension and hyperlipidemia, cardiovascular disease, depression, family history of diabetes, history of tobacco use, number of encounters, and first-recorded BMI. The health history of the study population was derived from the Observational Medical Outcomes Partnership (OMOP) vocabulary and descriptions²⁴. Number of health system encounters by the patient was transformed so the model estimate represents a 10-unit increase in number of encounters (number of encounters/10). We assessed interactions between trajectories of risk factors and age group and sex. Variables and interaction terms with a p-value of less than 0.10 were included in the final model. The negative binomial dispersion parameter was estimated by maximum likelihood, and the dispersion parameter was estimated to be <0.0001 , indicating lack of over-dispersion.

The primary independent variables used in the final negative binomial model for development of type 2 diabetes were trajectory classes of SBP, DBP, HDL, non-HDL, triglycerides, percentage change in BMI, and first recorded BMI. Other variables adjusted for in the model included age group, sex, race/ethnicity, region, first recorded BMI, number of encounters, history of tobacco use, and family history of diabetes. Depression, antihypertension medication use, and lipid lowering medication use were not included in the final model because the respective interaction p-values were greater than 0.10.

Results

Patient Characteristics

Table 1 presents a summary of the demographic and clinical characteristics of the analytic population at baseline

for the 94,551 patients who met the cohort inclusion criteria for the LCTA analysis. Of these, 10,785 patients (11.4%) were diagnosed with type 2 diabetes during a median follow-up of 4.8 years (range 2.0-8.0 years). The study population was 77.8% non-Hispanic white, 18.8% Hispanic, and 3.4% were either non-Hispanic black, Asian, American Indian/Native American, or other racial/ethnic group. Half of the patients were 45 to 64 years, with the rest about evenly split between 18 to 44 years (25.6%) and 65 and older (23.8%). In addition, 17.8% of the population had cardiovascular disease, 25.3% had depression,

Table 1: Characteristics of the LEADR Study Analytic Population at Baseline

Characteristic	N (%)
Total Population	94,551 (100)
Diabetes Onset	10,785 (11.4)
Race/Ethnicity	
Non-Hispanic White	73,520 (77.8)
Hispanic	17,818 (18.8)
Other (Non-Hispanic Black, Asian, AI/AN, Other, Multiple)	3,213 (3.4)
Age in 2010	
18-44	24,205 (25.6)
45-64	47,848 (50.6)
65 and older	22,498 (23.8)
Sex	
Male	41,074 (43.4)
Female	53,477 (56.6)
Health System Regions	
Rocky	53,827 (56.9)
South	10,436 (11.0)
West	30,288 (32.0)
Antihypertensive Medication Use	46,705 (49.4)
Lipid-Lowering Medication Use	35,729 (37.8)
Cardiovascular Disease	16,849 (17.8)
Depression	23,903 (25.3)
History of Tobacco Use	25,772 (27.3)
Family History of Diabetes	1,757 (1.9)
Characteristic	Mean (SD)
Body Mass Index, first measurement (kg/m ²)	28.5 (6.3)
Number of Encounters	38.6 (25.1)
Follow-Up (years)	4.6 (1.8)
Average Body Mass Index (kg/m ²)	28.6 (6.2)
Average Systolic BP (mm Hg)	126.3 (11.7)
Average Diastolic BP (mm Hg)	76.4 (7.1)
Average Serum Triglycerides* (mg/dL)	141.7 (82.8)
Average Serum HDL (mg/dL)	51.6 (14.7)
Average Serum Non-HDL (mg/dL)	136.5 (34.8)

*Serum triglycerides has a right-skewed distribution. The median value is 122.5.

NOTE: BP=blood pressure; N=number.

Patients included in this analysis had at least two measurements for each trajectory. variable, occurring at least 14 days apart (BMI, SBP, DBP, serum triglycerides, serum HDL, and serum non-HDL).

and 27.3% reported a history of tobacco use. Half the population were on antihypertensive medications (49.4%) and 37.8% on lipid-lowering medications. Mean BMI first recorded was 28.5 kg/m². Average number of encounters was 38.6 and the mean follow-up time was 4.6 years. Mean values for each of the risk factors are shown in Table 1.

Trajectories of High-Risk Factors

BMI

For the BMI trajectories, we first examined absolute BMI trajectories by sex and age (18 to 44 years, 45 to 64 years, and 65+ years). Five classes emerged from the initial analysis of raw BMI values, with two stable classes representing the vast majority of patients (results not shown). One class exhibited patients who were normal

to slightly overweight throughout the study period (BMI range of 22 to 27 kg/m² across stratum), and the other class represented patients who were overweight to slightly obese (BMI range of 28 to 32 kg/m² across stratum). Together, these two classes represented 85 to 90% of patients for each BMI sex and age stratum, suggesting most patients in the LEADR cohort had a static weight pattern throughout their time in the cohort. To further differentiate patterns of change in BMI, we therefore repeated the analysis on percentage change in BMI from baseline (Δ BMI), enabling identification of unique patterns of weight change regardless of a patient's starting BMI.

Each class from the Δ BMI analyses had patients with normal, overweight, or obese weights at baseline. Figure 1 A-F presents the five trajectory classes resulting from

NOTE: Trajectories during 5 years of follow-up until diagnosis of type 2 diabetes, or censoring from the study (x-axis). Mean risk-factor value and the median date of the 6-month windows were used to identify distinct trajectories of change over time. A-female age 18-44 (n=228,146), B-female age 45-64 (n=190,350), C-female age 65+ (81,350), D-male age 18-44 (n=122,662), E-male age 45-65 (n=139,125), F-male age 65+ (n=62,410). The largest proportion of the patients for each strata was assigned Δ BMI Class 1, representing static weight change.

Figure 1: Trajectory of Percentage Change in BMI (Δ BMI) by Sex and Age Group for LEADR Cohort Patients

Δ BMI for each sex and age stratum. Sample size and percentage of the population in each class are presented in Supplemental Table 1. Δ BMI Class 1 was defined by patients in all six strata who had a percentage change in BMI near zero over time (i.e., “static weight”). This class corresponds to the two large classes in the absolute BMI trajectory analysis. Patients in Δ BMI Class 2 were defined by showing an initial decrease in BMI of near 10 percent, with some strata showing a reversion to their baseline BMI over the study period (i.e., “slight weight loss”). Patients in Δ BMI Class 3 were defined by showing an initial increase in BMI nearing 10 percent, then trending back toward their baseline BMI (i.e., “slight weight gain”). Specific patterns of change over time varied across strata for defining patients in Δ BMI Class 4; in all strata for Δ BMI Class 4 the patients’ percentage change in BMI generally showed greater fluctuation compared to that of patients in Δ BMI classes 1, 2, and 3 (i.e., “fluctuating weight”). Δ BMI Class 5 was defined by patients who presented with a sharp increase in BMI from baseline of nearly 25% within 12 months and even more weight gain by the end of the follow-up period (i.e., “sustained weight increase”).

Systolic and Diastolic Blood Pressure

LCTA stratified by age, resulted in three distinct classes for SBP and DBP for each age group (Figure 2 A-F). The sample size and percentage of the population in each class is presented in Supplemental Table 2. With the exception of DBP for those ages 18-44, the blood pressures exhibited similar trajectory patterns. Class 1 represented 89.1% to 97.5% of patients in each stratum and presented relatively “static normal blood pressures.” The main difference across stratum was the baseline blood pressures for both systolic and diastolic blood pressures; the mean SBP ranged from 120 mm Hg to 130 mm Hg, and the mean DBP was approximately 75 mm Hg. Class 2 blood pressures generally presented “negative parabolic” patterns, where blood pressures initially increased, reached a point, and then decreased over time. Conversely, Class 3 presented “positive parabolic” patterns, where blood pressures decreased initially, reached a point, and then increased over time. The mean SBP readings for SBP Classes 2 and 3 remained above recommended levels throughout the study period for SBP, ranging from 127 mm Hg to 160 mm Hg; DBP values ranged from 64 mm Hg to 94 mm Hg²⁵.

As previously noted, the stratum that showed a differing trajectory pattern was the youngest age group (18-44 years) for DBP. DBP Class 1 for this stratum was similar to the other strata, presenting a relatively static measurement throughout the study period (~73 mm Hg). For DBP Class 2 patients presented a slowly decreasing diastolic blood pressure, starting from ~86mm Hg and ending at ~81mm Hg. DBP Class 3 was defined by a slight

up and down pattern, but generally stayed near 85 mm Hg throughout the study period.

Lipids

HDL analysis resulted in 4 Classes being defined. (Figure 2G). The sample size and percentage of the population in each class is presented in Supplemental Table 2. For HDL Class 1, about two-thirds (67%) of the patients had HDL levels that increased slightly over time from 46.8 mg/dL to 49.5 mg/dL. This class had the lowest HDL levels of all four classes. For HDL Class 2, 19.2 percent of patients showed a slight convex-shaped trajectory over time with mean values around 68 mg/dL. Patients in HDL Class 3 (12.1%) showed a concave-shaped trajectory over time with mean values around 71 mg/dL. Lastly, in HDL Class 4, 1.9 percent of patients started with the highest concentrations (90 mg/dL), and had the most change over time.

Four LCTA classes were identified for non-HDL measures (Figure 2H). The sample size and percentage of the population in each class is presented in Supplemental Table 2. Non-HDL Class 1 represented the largest percentage of the cohort (87%) and had consistent concentrations of 130 mg/dl over the study period. The remaining 13 percent of patients, split into two classes, showed non-linear change over time and starting concentrations above recommended values²⁶.

Five LCTA classes were identified for triglyceride measures (Figure 2I). The sample size and percentage of the population in each class is presented in Supplemental Table 2. The majority of individuals in the study (83%) had consistent triglyceride concentrations across the study period. These patients were split into two classes, one with mean values around 90 mg/dL (Tri Class 1, 50%) and the other with mean values around 148 mg/dL (Tri Class 2, 33%). The remaining proportion of patients did show change over time in their triglyceride concentrations. The mean baseline concentrations in Tri Class 3 (6.6%) were 170 mg/dL, which then increased to 265 mg/dL at 30 months, then decreased to 196 mg/dL. The mean baseline concentrations in Tri Class 4 (8.6%) were 280 mg/dl, which then decreased to 187 mg/dl at 24 months, then increased to 237 mg/dl at the end of the study. Patients in Tri Class 5 (2.2%) had the highest concentrations at about 400 mg/dL throughout the study period.

Type 2 Diabetes Development

Table 2 shows the rate ratios (RR) (as exponential of the estimated coefficients) and 95% CI of all predictors of progression to diabetes based on the final negative binomial model. Given that nominally equivalent latent classes sometimes appear to meaningfully differ in their estimated mean trajectories across sex/age strata, interactions of age and sex with class were included in

all models and stratified results are presented whenever significant interactions are identified.

For trajectories of SBP measurements, compared to patients with a static trajectory pattern (SBP Class 1), classes with parabolic SBP trajectory patterns, (SBP Classes 2 and 3), were associated with higher risks of developing diabetes, (Adjusted RR [95% CI], 1.45 [1.30, 1.62] for SBP Class 2 and 1.42 [1.28, 1.56] for Class 3). Results were similar for DBP, 1.34 [1.21, 1.48] for DBP Class 2 and 1.23 [0.97, 1.55] for DBP Class 3, when compared to DBP 1. However, the difference in diabetes risk was not statistically significant (p-value=0.09) between DBP Class 3 and DBP Class 1 for DBP.

Higher levels of HDL were associated with a reduced risk of diabetes (HDL Classes 2 and 3 compared to 1), however, those in HDL Class 4 who started very high, but then decreased rapidly showed an increased risk of diabetes compared to HDL Class 1 (1.26 [1.12, 1.62]). For serum triglyceride trajectories, as levels increased, the risk of diabetes increased. Differences in diabetes risk between trajectories of non-HDL were not significant.

Due to the interaction of the change in BMI trajectories and age in the model, rate ratios for BMI change trajectories are shown stratified by age group. For all age groups, those with a slight weight loss trajectory (Δ BMI Class 2), had a reduced risk of diabetes compared to patients with static weight trajectory (Δ BMI Class 1) (18 to 44 years 0.74 [0.57, 0.96], 45 to 64 years 0.66 [0.55, 0.79], and 65 years and older 0.54 [0.41, 0.72]). The slight weight gain and fluctuating weight trajectories (Δ BMI Classes 3 and 4), were not statistically different from Δ BMI Class 1 in any age group. The sustained weight increase trajectory (Δ BMI Classes 5) had an increased risk of diabetes (18 to 44 years 1.63 [1.12, 2.22], 45 to 64 years 1.53 [1.23, 1.91], and 65 years and older 1.62 [1.12, 2.36]).

Baseline BMI was one of the most significant predictors of diabetes, after adjusting for all other variables in the model, with a p-value <0.0001. Each one-unit increase in BMI, yielded an increased risk of 1.05 (Table 2). Thus, an individual with a baseline BMI of 35 kg/m² has a 64 percent greater risk of diabetes compared to an individual with a baseline BMI of 25 kg/m², holding all other variables the same.

Table 2: Adjusted Rate Ratios and 95% CI from Negative Binomial Model Assessing Risk of Developing Diabetes for LEADR Cohort Patients

Predictor	Rate Ratio (95% CI)	p-value
Systolic Blood Pressure Trajectory		
Class 2 vs. 1	1.45 (1.30, 1.62)	<.0001
Class 3 vs. 1	1.42 (1.28, 1.56)	<.0001
Diastolic Blood Pressure Trajectory		
Class 2 vs. 1	1.34 (1.21, 1.48)	<.0001
Class 3 vs. 1	1.23 (0.97, 1.55)	0.09
Serum HDL Trajectory		
Class 2 vs. 1	0.69 (0.64, 0.75)	<.0001
Class 3 vs. 1	0.75 (0.68, 0.83)	<.0001
Class 4 vs. 1	1.26 (1.12, 1.43)	0.0002
Serum Non-HDL Trajectory		
Class 2 vs. 1	0.95 (0.88, 1.01)	0.10
Class 3 vs. 1	1.05 (0.91, 1.21)	0.53
Serum Triglyceride Trajectory		
Class 2 vs. 1	1.43 (1.37, 1.50)	<.0001
Class 3 vs. 1	1.92 (1.78, 2.07)	<.0001
Class 4 vs. 1	1.88 (1.76, 2.00)	<.0001
Class 5 vs. 1	2.49 (2.25, 2.76)	<.0001
Age and % BMI Change Trajectory		
Age 18 to 44 years		
BMI Class 2 vs. 1	0.74 (0.57, 0.96)	0.02
BMI Class 3 vs. 1	0.90 (0.73, 1.11)	0.33
BMI Class 4 vs. 1	1.35 (0.93, 1.96)	0.12
BMI Class 5 vs. 1	1.63 (1.12, 2.22)	0.002
Age 45 to 64 years		
BMI Class 2 vs. 1	0.66 (0.55, 0.79)	<.0001
BMI Class 3 vs. 1	1.09 (0.95, 1.26)	0.20
BMI Class 4 vs. 1	0.92 (0.70, 1.21)	0.57
BMI Class 5 vs. 1	1.53 (1.23, 1.91)	0.0002
Age 65 years and older		
BMI Class 2 vs. 1	0.54 (0.41, 0.72)	<.0001
BMI Class 3 vs. 1	0.96 (0.77, 1.20)	0.71
BMI Class 4 vs. 1	0.69 (0.45, 1.06)	0.09
BMI Class 5 vs. 1	1.62 (1.12, 2.36)	0.01
Sex		
Female vs. Male	1.07 (1.03, 1.11)	0.001
Race/Ethnicity		
Hispanic vs. Non-Hispanic White	1.10 (1.03, 1.17)	0.002
Other vs. Non-Hispanic White	1.35 (1.24, 1.46)	<.0001
Region		
Rocky vs. West	0.51 (0.48, 0.55)	<.0001
South vs. West	1.59 (1.49, 1.69)	<.0001
Baseline BMI	1.051 (1.048, 1.053)	<.0001
History of tobacco use	1.15 (1.09, 1.22)	<.0001
Family history of diabetes	1.33 (1.19, 1.49)	<.0001
Number of Encounters (10 unit change)	1.122 (1.115, 1.129)	<.0001

Note: Sample size is 94,551 patients. The largest proportion of the patients for each risk factor trajectory was assigned Class 1, generally representing a static BMI, blood pressure, or lipid value

Each of the adjusted variables had a significant relationship with diabetes. Compared to males, females

were at greater risk of developing diabetes (1.07 [1.03, 1.11]). Likewise, those with history of tobacco (1.15 [1.09, 1.22]), family history of diabetes (1.33[1.19, 1.49]), and increasing number of encounters (1.12 [1.12, 1.13]) were also at increased risk of diabetes. While there was no significant difference was found between Hispanic and Non-Hispanic White individuals, those classified as Other were significantly more likely to develop diabetes (1.35 [1.24, 1.46]). Last, the rate ratio ranged from 0.51 (0.48, 0.55) to 1.59 (1.49, 1.69), indicating the healthcare system the patient received care influenced risk of developing diabetes.

Conclusions

By applying a LCTA approach to a large EHR cohort, we identified classes with similar underlying trajectories of longitudinal percentage change in BMI, blood pressure, and lipids that may be helpful in managing a patient's type 2 diabetes risk. Trajectory groups indicating an increased risk of type 2 diabetes included 1) patients with blood pressures in hypertensive range for at least one 6-month time period, 2) patients with triglyceride levels consistently at or above 150 mg/dL throughout their time in the cohort, and 3) patients with sustained weight increase throughout their time in the cohort. In addition, slight decreases in BMI over time was associated with reduced risk. Our findings emphasize the importance of monitoring weight, blood pressure, and serum lipids over time to identify patients at risk for type 2 diabetes. Furthermore, the potential value of tracking percentage change in BMI from baseline over time for a patient may provide additional information about their risk of progression to type 2 diabetes.

Results from our trajectory analyses identified patterns of physical and clinical laboratory measures that can be used to evaluate a patient's risk for developing type 2 diabetes. Chief among risk reduction is weight control as reflected in BMI measures. For example, like previous studies, our study shows that after controlling for various risk factors, increasing BMI raises the risk for type 2 diabetes (12,16). Among the trajectories, the highest rate ratios associated with diabetes was the class associated with an initial increase in BMI of at least 25% within two years and maintenance of the increased weight (i.e., sustained weight increase). Our study also found patients with an approximate 10 percent increase in BMI during their first two years in the study, but with a gradual return to baseline weight moderated the risk of diabetes onset, after adjusting for baseline BMI. Conversely, patients with an approximate 10 percent decrease in BMI, showed a significant reduction in risk of diabetes onset, after adjusting for baseline BMI. Our results align with previous studies indicating weight management is an effective strategy for reducing the risk of type 2 diabetes^{27,28}.

We identified three distinct patterns for SBP and DBP measures overtime. For both trajectory models that crossed acceptable hypertension reading levels, our data confirmed other research findings, that hypertension is a significant risk factor for type 2 diabetes²⁹. There are few studies that have examined trajectories of blood lipid trajectories and their relationship to chronic diseases^{30,31}. Our study found that higher values of serum HDL over time were associated with reduced risk of diabetes onset, while higher values of serum non-HDL and triglycerides were associated with increased risk of disease. To recap our study's inclusion criteria, there were two strict observational data requirements for a patient to be included in the analyses in this paper. First, each patient had to meet or exceed the LEADR criterion that required a specific number of visits to one of the 9 health systems included in LEADR over the specific time period being observed. Second was the requirement for each patient to have an adequate number of clinical values recorded in their EHR to allow for the generation of multiple class trajectories for that patient over the specific time period being observed. Patients who were excluded from these analyses lacked sufficient EHR data for one or both of these data requirements, and therefore were not included in the analyses. The resulting total population of 94,565 that met these observational criteria are thereby a well-defined sample of patients from the larger LEADR cohort who had adequate health system visits and records of clinical measurements.

We are aware that differential missing/attrition is common in EHR data, and as a result, bias can often be introduced into analysis if the estimates, including trajectory group size and membership, are not well delineated initially. Missing data can affect group sizes change over time, which in turn has important implications for using the model parameter estimates to make population-level projections. We recognize that in future analysis, applying an extension of group-based trajectory modeling that would have the ability to address missing data, non-random attrition, or truncation of data due to specific events, such as death, is warranted. Additionally, building on the analytic relationships discovered in this study, further investigation is necessary into the interplay of risk factors for type 2 diabetes, to better fully understand the effect of various combinations of trajectories on progression to disease. For example, future research could investigate how the risks associated with the trajectories are different among those with prediabetes.

Despite this study's limitations, our analyses indicate having trend data for risk factors adds an additional perspective that takes advantage of analyzing longitudinal data that provides insights to assessing risk for disease moving well beyond the contribution of a single BMI measurement.

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Conflict of Interest

All authors approved the manuscript before submission and declared no financial disclosures or conflicts of interest.

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SUPPLEMENTAL MATERIAL

Table S1: Number and Percentage of LEADR Cohort Patients in Each Trajectory Class* of Percentage Change in BMI by Sex and Age Group

Trajectory Classes	Total (N=824,043)											
	Female (N=499,846)						Male (N=324,197)					
	Age 18-44		Age 45-64		Age 65+		Age 18-44		Age 45-64		Age 65+	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	228,146	100	190,350	100	81,350	100	122,662	100	139,125	100	62,410	100
1	190,850	83.7	165,951	87.2	67,732	83.3	104,564	85.2	122,020	87.7	53,509	85.7
2	10,668	4.7	9,269	4.9	5,464	6.7	4,856	4.0	6,656	4.8	3,561	5.7
3	19,173	8.4	10,357	5.4	6,060	7.4	9,773	8.0	7,311	5.3	3,830	6.1
4	2,704	1.2	2,128	1.1	1,639	2.0	1,231	1.0	1,527	1.1	800	1.3
5	4,751	2.1	2645	1.4	455	0.6	2,238	1.8	1,611	1.2	710	1.1

* The study follow-up period is 5 years. BMI calculated as kg/m².

Table S2: Number and Percentage of LEADR Cohort Patients in Each Trajectory Class of Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), High-density Lipoprotein (HDL), non-HDL, and Triglyceride Class*

Trajectory Classes	Systolic Blood Pressure (N=955,128)						Diastolic Blood Pressure (N=957,491)						HDL (N=300,137)		Non-HDL (N=267,553)		Triglyceride (N=297,026)	
	Age 18-44		Age 45-64		Age 65+		Age 18-44		Age 45-64		Age 65+		All Ages		All Ages		All Ages	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	421,327	100.0	364,216	100.0	169,582	100.0	422,348	100.0	365,230	100.0	169,913	100.0	300,137	100.0	267,553	100.0	297,026	100.0
1	375,559	89.1	325,677	89.4	148,942	87.8	361,896	85.7	354,452	97.0	165,695	97.5	200,637	66.8	233,605	87.3	147,291	49.6
2	21,942	5.2	19,677	5.4	9,527	5.6	5,793	13.7	4,582	1.3	1,810	1.1	5,761	19.2	2,996	11.2	9,812	33.0
3	23,826	5.7	18,865	5.2	11,113	6.6	2,518	0.6	6,196	1.7	2,408	1.4	3,632	12.1	3,988	1.5	19,685	6.6
4	-	-	-	-	-	-	-	-	-	-	-	-	5,563	1.9	-	-	25,431	8.6
5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6,495	2.2

* Study period is 5 years. Blood pressures measured mm Hg, lipids measured mg/dL.