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Association between body mass index trajectories and type 2 diabetes incidence over an 18-year follow-up in the Tehran Lipid and Glucose Study

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Body mass index (BMI) is a well-known risk factor for type 2 diabetes mellitus (T2DM). We aimed to identify BMI trajectory patterns and evaluate their association with T2DM during 18 years of follow-up. We included 6026 participants aged 20 to 65 from the prospective population-based Tehran Lipid and Glucose Study (TLGS). The BMI trajectory patterns were identified using latent growth mixture modeling (LGMM) during the measurement period. The association between the BMI trajectory patterns and future T2DM was evaluated using the Cox proportional hazard regression models. Three BMI trajectory patterns of low-increasing (38.6%), medium-increasing (47.1%), and high-increasing (14.3%) were detected. The participants in the medium-increasing and high-increasing BMI trajectory groups had HRs of 1.87 (95% CI 1.53–2.28) and 3.41(95% CI 2.71–4.29) for T2DM incidence, respectively. Within the normoglycemic subpopulation, the high-increasing BMI group had an HR of 3.82 (95% CI 2.79–5.24) compared to the low-increasing BMI group, while in the prediabetic subpopulation, the high-increasing BMI group had an HR of 2.93 (95% CI 2.04–4.19) compared to the low-increasing BMI group. Body weight varies in a relatively stable pattern in adulthood over the long-term period. Medium and high-increasing BMI trajectory patterns have a significantly increased risk for future T2DM in both normoglycemic and prediabetic individuals. Identifying BMI trajectory patterns can help healthcare providers in early prediction, risk assessment, and monitoring strategies development for the prevention of T2DM.

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disease that affects more than 450 million individuals worldwide[1,2]. With the rapidly increasing prevalence, the number of people with T2DM is projected to surpass 700 million by 2045[3]. Moreover, diabetes is associated with various morbidities, leading to a high socioeconomic burden and a 1.3-2 times higher risk of mortality[1,4–6]. In Iran, the prevalence of T2DM is approximately 15%, and T2DM is the fourth leading cause of death[7]. Although genetics is considered an important predisposing factor for T2DM development, environmental factors such as diet, physical activity, lifestyle, and exposure to air pollution also play a significant role. They can be modified to decrease the risk of developing future diabetes[8].

Among many modifiable factors, obesity is one of the main contributing factors to the development and progression of T2DM. The prominent effect of lifestyle interventions and weight loss on the risk of T2DM has been demonstrated in several studies[9–11]. Obesity is quantified using different indices, with body mass index (BMI) being the most commonly used[12]. Consequently, previous studies have investigated the association of BMI with glycemic status and onset of T2DM, unraveling the role of high BMI as an independent risk factor for T2DM[13–16]. It is still unclear how weight varies through time before the onset of the disease[17–19]. Baseline BMI or its change does not fully capture an individual's BMI trend and its effect on clinical outcomes. This can mislead clinicians about the effectiveness of weight loss attempts, as weight regain and weight variability are highly probable[20]. Previous studies fail to account for long-term changes and may misclassify individuals' risk due to short observation periods, study settings, and methodologies[21]. Understanding the trends in BMI

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over time, rather than relying on single measurements, might offer a more insightful perspective on how BMI correlates with the development of T2DM[22,23].

There is an ongoing controversy over the association of BMI trends with T2DM and limited literature exploring BMI as a dynamic risk factor. Herein, we sought to investigate how patterns of BMI change in the life course and correlate with the development of T2DM in a large cohort study with data from the Tehran Lipid and Glucose Study (TLGS). The findings of this study can shed light on how investigating BMI trajectory patterns can help healthcare providers in early diabetes prediction, enhanced risk assessment, and prevention and monitoring strategies.

Methods and materials

Study design

The current study was carried out within the TLGS framework. The TLGS is a large prospective population-based study established in 1999 to investigate the prevalence and risk factors of non-communicable diseases[24]. The examination visits were conducted at approximately three-year intervals during 18 years of follow-up, consisting of a total of six follow-up examination visits.

Among 9,566 participants aged 20–65 years included in this study, we excluded participants with baseline diabetes ($n=877$), malignancy ($n=23$), participants taking systemic glucocorticoids ($n=68$), and those with missing covariates ($n=1,126$). Moreover, individuals with fewer than three BMI measurements in the measurement period ($n=775$), those who developed diabetes within the measurement period ($n=448$), and those who experienced pregnancy within this period ($n=223$) were also excluded (Fig. 1). The study timeline of the current study was split into two distinct timeframes: a 9-year period as the BMI measurement period to identify the BMI trajectory patterns (from the first to the end of the third examination visit), and a subsequent 9-year period focused on tracking the occurrence of T2DM (from the third examination visit to the end of the study) (Fig. 2).

Data collection

A standard questionnaire was used to collect information regarding education, gender, age, medical history, family history of diabetes, and physical activity in the interview by trained medical staff. A brief physical examination, including anthropometric measurements, was performed by an experienced physician. Afterward, the participants underwent a blood sampling test in the laboratory. Individuals were followed by an annual phone call assessing the latest medical condition, and any relevant data were recorded. Moreover, all the performed evaluations were repeated every three years to update the existing data. Comprehensive details regarding the study protocol, including measurements and follow-up methods were provided in previous studies[24].

BMI measurement

Weight measurement was taken while shoes were removed, and the participants wore light clothes, using a Seca 707 digital scale with 100 g accuracy by trained health care professionals. The accuracy of the scale was

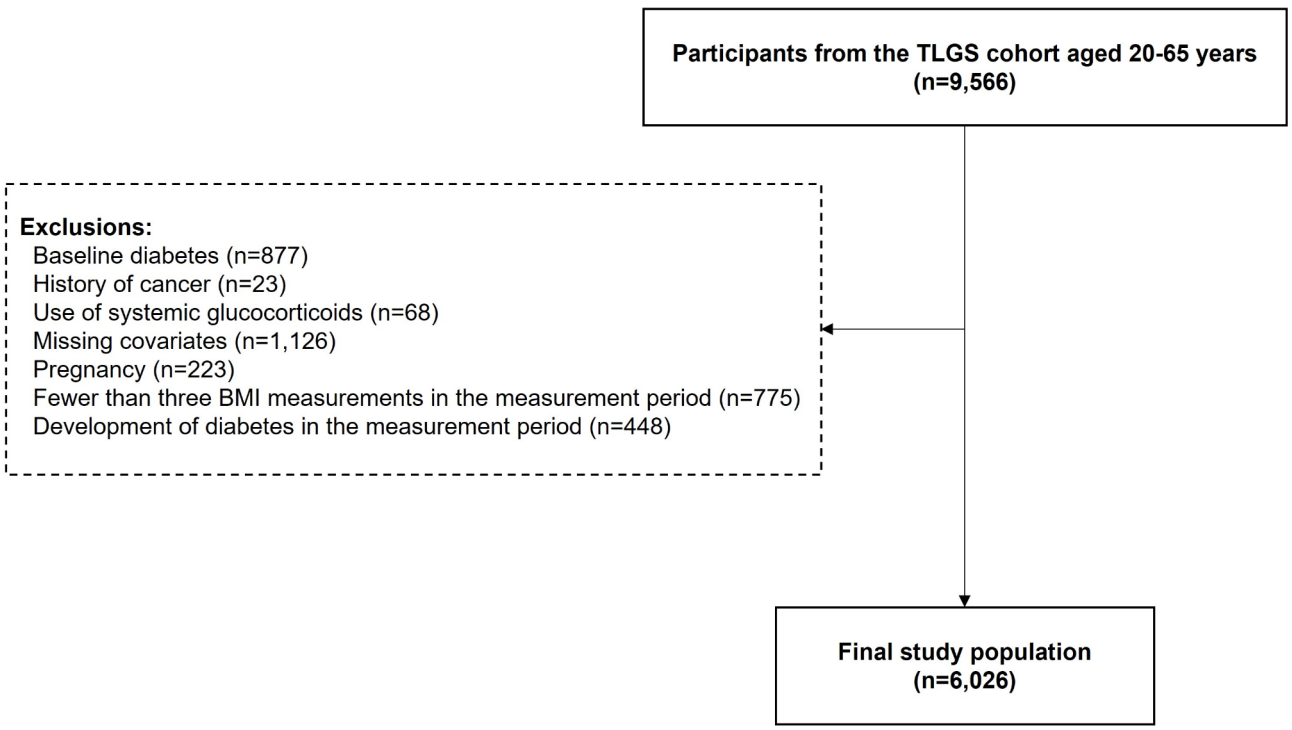

Fig. 1. Flowchart illustrating the participant selection. *TLGS* Tehran Lipid and Glucose Study.

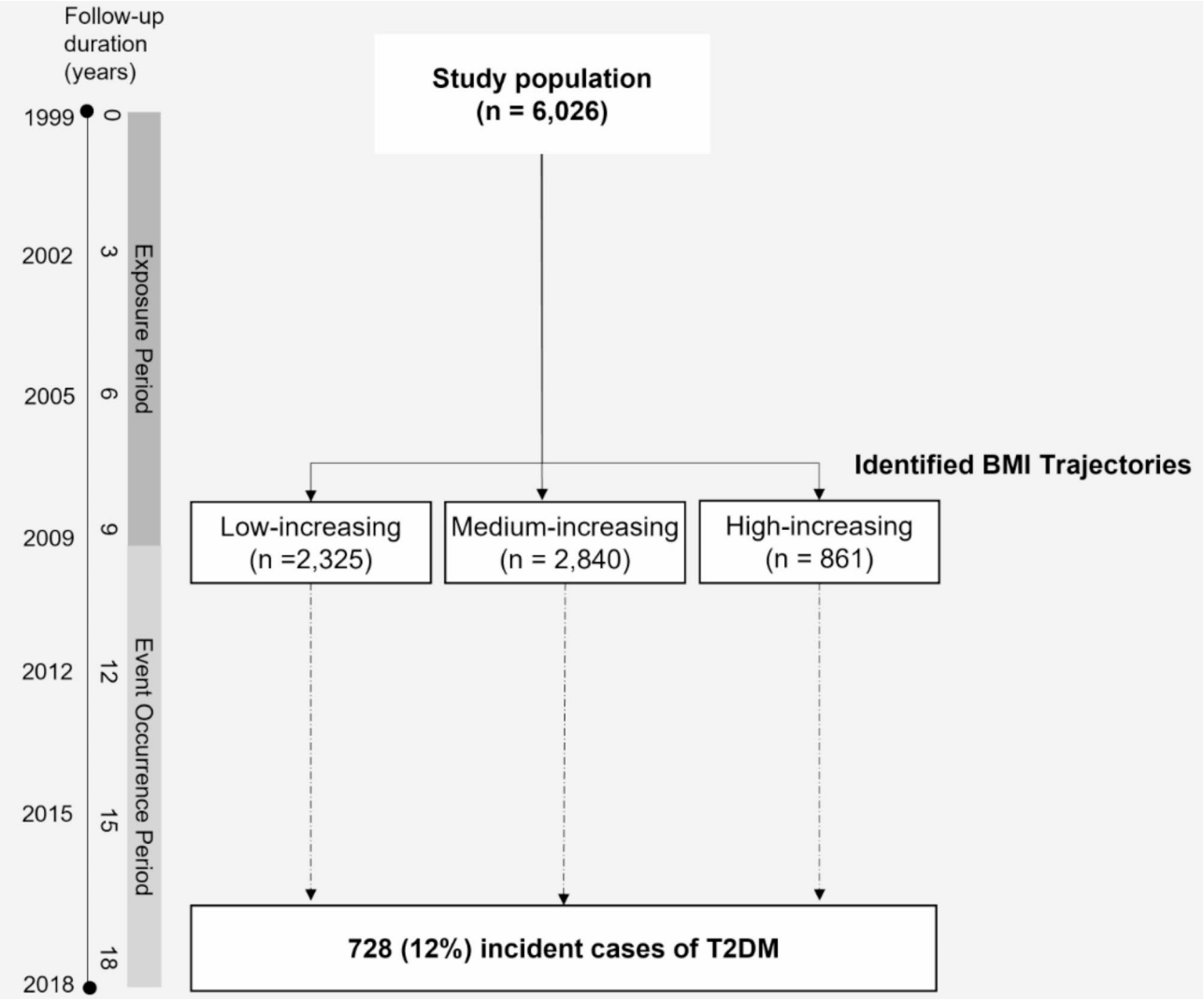

Fig. 2. Analysis flow. The study population was classified into low-increasing, medium-increasing, and high-increasing BMI trajectory patterns in the measurement period and followed for the incidence of T2DM in the event occurrence period. *BMI* body mass index; *T2DM* type 2 diabetes mellitus.

rechecked after every ten measurements. The participants' height was measured using a stadiometer with 0.5 cm accuracy while shoes were removed and shoulders were in a natural position. Body mass index was calculated by dividing the weight in kilograms by the square of height in meters (kilograms per square meter).

Biochemical measurements

A blood sample was drawn from study participants between 7:00 and 9:00 a.m. following 12 to 14 h of overnight fasting. All the samples were analyzed at the TLGS laboratory for fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C). Another blood sample was drawn 120 min after oral consumption of 82.5 g of glucose monohydrate solution, equivalent to 75 g of glucose anhydrase. The enzymatic colorimetric method with glucose oxidase was utilized to measure serum glucose levels. Every 20 tests, the assay's accuracy was evaluated using the control glucose serum, Precinorm (normal range), and Precipath (pathologic range) wherever applicable (Boehringer Mannheim, Germany; cat. no. 1446070 for Precinorm and 171778 for Precipath). The Selectra2 auto-analyzer was calibrated using a glucose standard on a daily basis. Analyzing the samples was performed once internal quality control met the required criteria.

Definitions

The education level was categorized into primary (less than 6 years), high school (6 to 12 years), and higher (more than 12 years) education. Physical activity was scored on the metabolic equivalent of the task (MET) scale based on the data from the self-reported questionnaires. Individuals with less than 600 MET minutes of physical activity per week were classified as participants with low physical activity[24]. T2DM was defined as fasting blood glucose concentration ≥ 126 mg/dL, 2-hour post-challenge plasma glucose ≥ 200 mg/dL after oral

glucose tolerance test, or taking antidiabetic medication. Prediabetes is a state of intermediate hyperglycemia. We defined prediabetes as fasting blood glucose of 110 to 125 mg/dL or 2-h post-challenge plasma glucose of 140–199 mg/dL.

Statistical analysis

We identified BMI trajectory patterns using the latent class trajectory analysis model with the 'lcmm' package in R 3.0.3 software[25]. This model assigns each individual to one of several latent classes. In each latent class, repeated measures of individuals in that class were analyzed using a linear mixed-effects model. The optimal number of classes and class sizes were estimated from the data using the Bayesian information criterion, high posterior probability, mean probability of group membership, and root mean error of approximation (RMEA). In this model, BMI was the dependent variable, time was represented as age in years at each examination visit, and sex was regarded as a confounding factor. We limited the model to a maximum of five classes. To ascertain that all identified classes were clinically meaningful in terms of proportion, each class was required to consist of at least 5% of the study population. Individuals with missing data at baseline were excluded. The rate of data lost during the follow-up in the TLGS was under 5%, and the missing data were randomly distributed, so a complete case analysis was performed. The trajectory classes were identified in total, in men and women, and in the normoglycemic and prediabetic subgroups separately.

The baseline characteristics of the participants were reported according to the BMI trajectory classes. Trajectory classes were compared using a one-way analysis of variance, Kruskal Wallis H test, and chi-square tests. The association between BMI trajectory groups and T2DM incidence was examined using multivariate Cox regression models as hazard ratios (HRs) and 95% confidence intervals (CIs). Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for education, smoking, physical activity, and DM family history. Model 3 was adjusted for Model 2 and baseline BMI, anti-hypertensive drug use, lipid-lowering drug use, fasting plasma glucose, systolic blood pressure, HDL-C, TC, and TG. Statistical analyses were performed by R-3.0.3 software (StataCorp, college station, TX, USA) and STATA 14.2 (R Foundation for Statistical Computing, Vienna, Austria), and a P-value < 0.05 was considered statistically significant.

Results

Of the 6026 study participants, 2,632 (43.7%) were male and 3,394 (56.3%) were female. The mean age of participants was 38.61 ± 11.66 years, and the mean population BMI was 26.68 ± 4.34 kg/m^2. Over the follow-up period (median [IQR], 15 [11–16] years), 728 (12.08%) incident T2DM were identified, of which 394 cases (7.94%) occurred in normoglycemic participants and 334 cases (31.45%) in the prediabetic participants. Participants were classified based on the BMI trajectory patterns into low-increasing (class1) with a BMI of 22.72 ± 2.12 kg/m^2, medium-increasing (class2) with a BMI of 27.78 ± 2.13 kg/m2, and high-increasing (class3) with a BMI of 33.72 ± 2.98 kg/m^2 (Fig. 3; Table 1).

The baseline characteristics of the study population were reported based on the BMI trajectory classes in Table 1. The mean values of bassline age, BMI, waist circumference, blood pressure, FPG, and TG were higher in the high-increasing BMI trajectory group compared to the low-increasing BMI group. In addition, the proportion of women, participants with less education, and non-smokers were more significant in the high-increasing BMI trajectory pattern. There was no difference in the prevalence of the low physical activity status and family history of diabetes across the BMI trajectory classes.

The HRs for T2DM incidence were 1.87 (95%CI: 1.53–2.28) and 3.41 (95%CI: 2.71–4.29) in the medium-increasing and high-increasing BMI trajectory groups, respectively (Table 2). The high-increasing BMI trajectory class had an HR of 3.54 (95%CI: 2.56–4.89) in women and an HR of 3.20 (95%CI: 2.22–4.60) in men. We also identified the BMI trajectory patterns in the subgroups of normoglycemic and prediabetic participants. (Table 3). In the normoglycemic individuals, the high-increasing BMI trajectory group had an HR of 3.82 (95%CI 2.79–5.24), while in the prediabetic individuals, the high-increasing BMI trajectory group had an HR of 2.93 (95%CI: 2.04–4.19) compared to the low-increasing BMI group with the same glycemic status.

We repeated the analysis by considering the low-increasing normoglycemic BMI trajectory pattern as the reference group for both individuals with normoglycemic and prediabetic status (Table 4). The risk of future diabetes was higher in the participants with prediabetes, regardless of their BMI trajectory class, compared to the participants with normoglycemia. In addition, the risk of future T2DM increased incrementally upon higher BMI trajectory classes. However, the association between BMI trajectories and incident diabetes was more significant in normoglycemic subjects than in those with prediabetes (P interaction = 0.013). In normoglycemic participants, the medium- and high-increasing BMI trajectory groups had HRs of 2.25 (95%CI: 1.72–2.96) and 4.46 (95%CI: 3.29–6.05), respectively. Among the individuals with prediabetes, the low-increasing, medium-increasing, and high-increasing BMI trajectory patterns were associated with HRs of 5.86 (95%CI: 4.34–7.90), 9.21 (95%CI: 6.87–12.36) and 16.85 (95%CI: 11.47–24.76), respectively compared with the low-increasing BMI trajectory from the normoglycemic individuals.

Discussion

This large-scale prospective longitudinal study investigated the time-serial changes of BMI and its association with the development of T2DM among the Iranian population during adulthood over 18 years of follow-up. We identified three distinct trajectories of low-increasing, medium-increasing, and high-increasing BMI by applying growth mixture modeling. Compared with the low-increasing BMI trajectory pattern, participants with medium-increasing and high-increasing BMI trajectory patterns had a 1.87-fold and 3.41-fold increased risk of developing T2DM. This association was significant in both sexes regardless of glycemic status. Within normoglycemic adults, those with high-increasing BMI trajectory patterns had a higher risk of T2DM compared

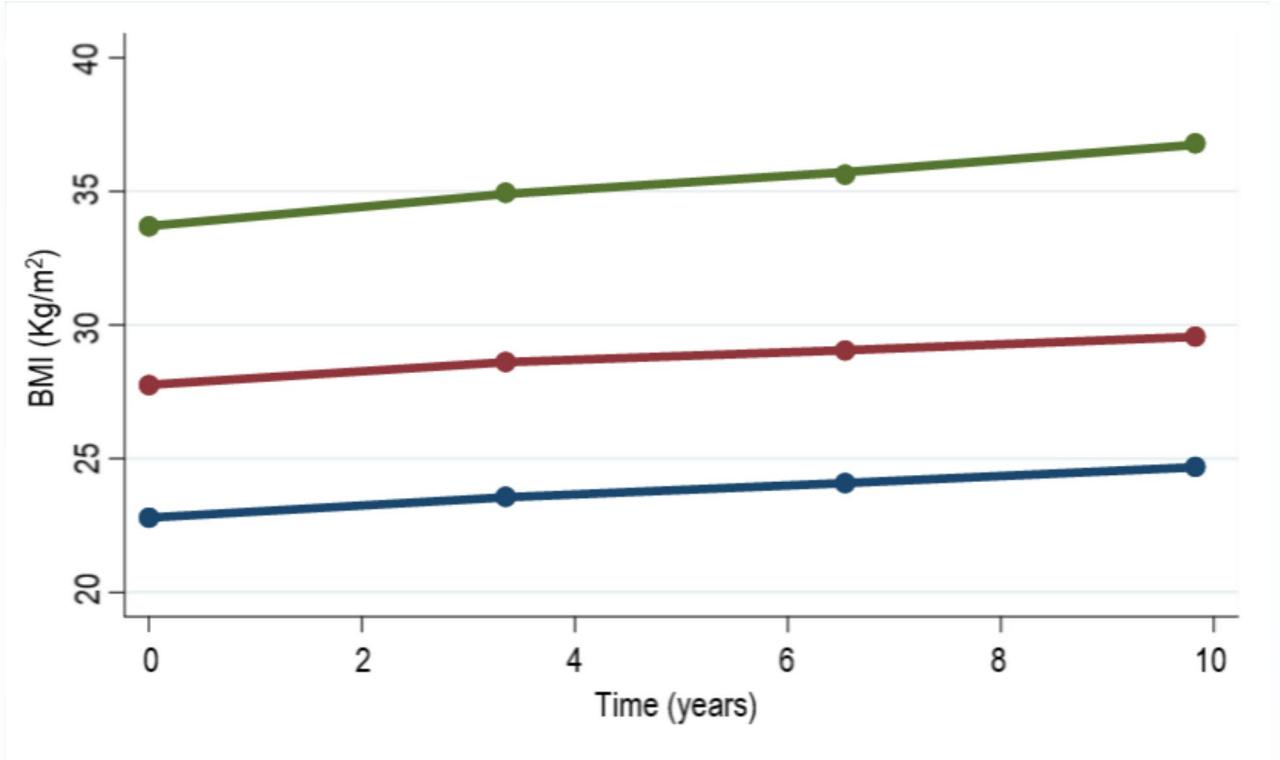

Fig. 3. Body mass index trajectory patterns detected during the measurement period. The study population was classified into low-increasing (blue line, class 1), medium-increasing (red line, class 2), and high-increasing (green line, class 3) BMI groups. *BMI* body mass index.

with the risk in prediabetic adults with the same BMI trajectory patterns. Prediabetic individuals with higher BMI trajectory patterns had about a 17-fold increase in the risk of T2DM compared with normoglycemic individuals within the lower BMI trajectory group.

Although BMI trajectories showed an increasing trend over time in low-increasing, medium-increasing, and high-increasing BMI categories, no substantial changes were observed in the BMI categories of individuals over long-term follow-up. This finding shows that although BMI has an increasing trend over time, the BMI category remains almost stable during adulthood. In line with our findings, the study by Zheng et al. on 39,321 participants in China[23], the five distinct BMI trajectory patterns identified remained stable. Also, the National Health and Nutrition Examination Survey (NHANES) in the United States revealed that stable non-obese and stable obese individuals constituted 77–83% of the general adult population in 2000s[26]. These findings show that despite the high prevalence of weight control attempts[20], overweight and obese individuals tend to have high BMI over a decade of follow-up. Metabolic adaptation, non-adherence to weight maintenance programs[21,27,28], and genetic determinants associated with obesity traits[29] are some probable explanations.

In the current study, those within the medium-increasing and high-increasing BMI trajectories were 1.8 and 3.4 times more likely to develop diabetes than those within the low-increasing BMI trajectory group. This finding was consistent in men and women. In the study by Zheng et al., participants in the high BMI trajectory had a 4.6 times greater risk for the development of T2DM during a 3.84-year follow-up[21]; however, the study was limited by most participants being men, which is an important limitation in studies using trajectory clustering analysis. Moreover, the measurement and follow-up periods in their study were insufficient to reflect long-term BMI changes throughout adulthood and assess the outcome of diabetes. In contrast, the current study had a pool of participants with a balanced distribution of men and women. We measured long-term time-serial changes in BMI to accurately reflect the long-term trends and variations in the BMI of the population, and followed the participants for a decade; subsequently, assessing the cumulative risk for diabetes. In another study by Lv et al. on 3776 participants aged > 50 years at baseline, three distinct trajectory patterns of low-increasing, medium-increasing, and high-increasing were detected based on the participants' previously recorded BMI. The high-increasing BMI trajectory group had a 1.5-fold increased risk for diabetes during a mean follow-up of 11.35 years; however, their results were not statistically significant in the sex subgroups, and the recorded BMI and diabetes diagnosis were self-reported[30]. The current study, on a representative sample of the general population, revealed that men and women in both medium-increasing and high-increasing BMI trajectories were more likely to develop diabetes in the long term.

The association between BMI trajectory patterns and incident diabetes was also evaluated separately in the subgroups of normoglycemic and prediabetic individuals; this had not been studied before. Among the prediabetic subgroup, medium-increasing and high-increasing BMI trajectory groups had a 1.6-fold and 2.9-

	Total	BMI trajectory classes*			*P* value
		Class 1	Class 2	Class 3	
Number of participants	6026	2325	2840	861	–
Age (years)	38.61 ± 11.66	36.12 ± 12.01	39.72 ± 11.18	41.72 ± 10.95	< 0.001
Male, n (%)	2632 (43.68)	1200 (51.61)	1235 (43.49)	197 (22.88)	< 0.001
Body mass index (kg/m^2)	26.68 ± 4.34	22.72 ± 2.12	27.78 ± 2.13	33.72 ± 2.98	< 0.001
Waist circumference (cm)	87.22 ± 11.37	78.46 ± 7.90	90.18 ± 8.27	101.10 ± 8.99	< 0.001
Education, n (%)					< 0.001
Illiterate/primary school (< 6 yrs)	3746 (62.16)	1367 (58.80)	1805 (63.56)	574 (66.67)	
High school (6–12 years)	1375 (22.82)	508 (21.85)	648 (22.82)	219 (25.44)	
Higher education (≥ 12 years)	905 (15.02)	450 (19.35)	387 (13.63)	68 (7.90)	
Smokers, n (%)	821 (13.62)	389 (16.73)	367 (12.92)	65 (7.55)	< 0.001
Low physical activity, n (%)	4771 (79.17)	1858 (79.91)	2228 (78.45)	685 (79.56)	0.41
DM family history, n (%)	482 (9.43)	169 (8.65)	243 (10.03)	70 (9.56)	0.51
SBP (mmHg)	115.22 ± 15.86	111.25 ± 14.38	116.71 ± 16.02	121.04 ± 16.51	< 0.001
DBP (mmHg)	76.51 ± 10.24	73.27 ± 9.56	77.70 ± 9.98	81.32 ± 10.15	< 0.001
FBS (mg/dL)	88.74 ± 8.88	87.35 ± 8.79	89.35 ± 8.72	90.49 ± 9.15	< 0.001
Triglyceride (mg/dL)	159.28 ± 100.37	132.31 ± 85.86	173.08 ± 104.69	186.56 ± 105.54	< 0.001
Total cholesterol (mg/dL)	202.32 ± 43.68	190.91 ± 41.85	207.51 ± 42.63	216.02 ± 44.80	< 0.001
HDL-C (mg/dL)	41.86 ± 10.72	43.26 ± 10.90	40.71 ± 10.41	41.83 ± 10.77	< 0.001
Anti-hypertensive drug use, n (%)	193 (3.20)	38 (1.64)	107 (3.77)	48 (5.59)	< 0.001
Lipid-lowering drug use, n (%)	81 (1.34)	17 (0.73)	46 (1.62)	18 (2.09)	0.003

Table 1. Baseline characteristics of the study population according to BMI trajectory classes. *DM* diabetes, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBS* fasting blood sugar, *HDL-C* high-density lipoprotein cholesterol. *The population was classified into three trajectory classes using latent growth mixture modeling, including trajectories of low-increasing (class 1), medium-increasing (class 2), and high-increasing (class 3) body mass index. The categorical and continuous variables were reported as count (percentage) and mean ± SD, respectively.

BMI trajectory classes*	Events	IR (95% CI)**	HR (95% CI)			
			Unadjusted	Model 1	Model 2	Model 3
Men (*n* = 2632)						
Class 1 (*n* = 1200)	83	4.9 (4.0–6.1)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Class 2 (*n* = 1235)	185	10.8 (9.4–12.5)	2.28 (1.76–2.95)	2.28 (1.76–2.95)	2.29 (1.77–2.97)	1.89 (1.45–2.47)
Class 3 (*n* = 197)	48	18.2 (13.7–24.1)	4.01 (2.81–5.72)	4.09 (2.87–5.84)	4.15 (2.91–5.93)	3.20 (2.22–4.60)
Women (*n* = 3394)						
Class 1 (*n* = 1125)	54	3.4 (2.6–4.4)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Class 2 (*n* = 1605)	193	8.5 (7.4–9.8)	2.57 (1.90–3.47)	2.18 (1.61–2.97)	2.20 (1.62–2.99)	1.85 (1.36–2.51)
Class 3 (*n* = 664)	165	18.3 (15.7–21.3)	5.97 (4.39–8.12)	4.72 (3.44–6.48)	4.72 (3.44–6.48)	3.54 (2.56–4.89)
Total (*n* = 6026)						
Class 1 (*n* = 2325)	137	4.2 (3.5–4.9)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Class 2 (*n* = 2840)	378	9.5 (8.6–10.5)	2.33 (1.92–2.84)	2.21 (1.82–2.70)	2.22 (1.82–2.70)	1.87 (1.53–2.28)
Class 3 (*n* = 861)	213	18.3 (16.0–20.9)	4.78 (3.85–5.92)	4.50 (3.60–5.62)	4.48 (3.58–5.60)	3.41 (2.71–4.29)

Table 2. Cox proportional hazard ratios (HRs) of the identified BMI trajectory patterns for incidence of type 2 diabetes mellitus in total and according to sex. Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, education, smoking, physical activity, DM family history. Model 3: Adjusted for age, sex, education, smoking, DM family history, physical activity, baseline BMI, anti-hypertensive drug use, lipid-lowering drug use, fasting plasma glucose, systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, triglyceride. *The population was classified into three trajectory classes using latent growth mixture modeling, including trajectories of low-increasing (class 1), medium-increasing (class 2), and high-increasing (class 3) body mass index. *HR* hazard ratios, **IR* Incidence rate per 1000 person-years, *CI* confidence interval.

BMI trajectory classes*	Events	IR (95% CI)**	HR (95% CI)			
			Unadjusted	Model 1	Model 2	Model 3
Normoglycemic subjects at baseline ($n=4964$)						
Class 1 ($n=1970$)	71	2.6 (2.0–3.2)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Class 2 ($n=2317$)	207	6.3 (5.5–7.2)	2.51 (1.92–3.29)	2.43 (1.85–3.18)	2.44 (1.86–3.20)	2.00 (1.52–2.63)
Class 3 ($n=677$)	116	12.4 (10.4–14.9)	5.20 (3.87–6.98)	5.12 (3.78–6.96)	5.16 (3.80–7.02)	3.82 (2.79–5.24)
Prediabetic subjects at baseline ($n=1062$)						
Class 1 ($n=503$)	122	17.6 (14.7–21.0)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Class 2 ($n=464$)	160	26.4 (22.6–30.8)	1.62 (1.28–2.06)	1.65 (1.29–2.10)	1.64 (1.28–2.08)	1.62 (1.26–2.07)
Class 3 ($n=95$)	52	43.4 (33.1–57.0)	2.90 (2.10–4.02)	2.97 (2.09–4.21)	2.94 (2.07–4.17)	2.93 (2.04–4.19)

Table 3. Cox proportional hazard ratios (HRs) of the identified BMI trajectory patterns for incidence type 2 diabetes mellitus in normoglycemic and prediabetic individuals. Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, education, smoking, physical activity, DM family history. Model 3: Adjusted for age, sex, education, smoking, DM family history, physical activity, baseline BMI, anti-hypertensive drug use, lipid-lowering drug use, fasting plasma glucose, systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, triglyceride. *The population was classified into three trajectory classes using latent growth mixture modeling, including trajectories of low-increasing (class 1), medium-increasing (class 2), and high-increasing (class 3) body mass index. *HR* hazard ratios, ***IR* incidence rate per 1000 person-years, *CI* confidence interval.

BMI trajectory classes*	Unadjusted	Model 1	Model 2	Model 3
Normoglycemic class 1 ($n=1970$)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Normoglycemic class 2 ($n=2317$)	2.50 (1.91–3.27)	2.40 (1.83–3.15)	2.41 (1.84–3.16)	2.25 (1.72–2.96)
Normoglycemic class 3 ($n=677$)	5.15 (3.84–6.93)	4.98 (3.69–6.73)	4.97 (3.67–6.72)	4.46 (3.29–6.05)
Prediabetic class 1 ($n=503$)	7.35 (5.49–9.85)	6.29 (4.67–8.47)	6.30 (4.68–8.48)	5.86 (4.34–7.90)
Prediabetic class 2 ($n=464$)	12.06 (9.12–15.95)	10.68 (8.03–14.21)	10.63 (7.98–14.15)	9.21 (6.87–12.36)
Prediabetic class 3 ($n=95$)	21.94 (15.33–31.39)	20.16 (13.90-29.23)	19.80 (13.65–28.73)	16.85 (11.47–24.76)

Table 4. Cox proportional hazard ratios (HRs) of the identified BMI trajectory patterns for incidence type 2 diabetes mellitus in normoglycemic and prediabetic individuals considering the normoglycemic low-increasing BMI trajectory group as reference. Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, education, smoking, physical activity, DM family history. Model 3: Adjusted for age, sex, education, smoking, DM family history, physical activity, baseline BMI, anti-hypertensive drug use, lipid-lowering drug use, fasting plasma glucose, systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, triglyceride. *The population was classified into three trajectory classes using latent growth mixture modeling, including trajectories of low-increasing (class 1), medium-increasing (class 2), and high-increasing (class 3) body mass index. *HR* hazard ratios, *IR* Incidence rate per 1000 person-years, *CI* confidence interval.

fold increased risk for future diabetes compared to the low-increasing prediabetic trajectory class. Among the normoglycemic subgroup, individuals in the medium-increasing and high-increasing BMI trajectory groups had a 2-fold and 3.8-fold risk for diabetes compared to the low BMI trajectory group (Table 3). Although all BMI trajectory classes in the prediabetic subgroup had a higher risk of future T2DM compared to the reference group (low- increasing BMI trajectory classes in the normoglycemic subgroup) (Table 4), in subgroup analysis within normoglycemic subjects higher BMI trajectory patterns were more strongly associated with incidence of T2DM (Table 3). Our research shows that people with BMI levels above the normal range, even those with normal blood sugar levels, should be checked regularly and manage their weight to prevent type 2 diabetes in future.

Clinical application

Those with a medium-increasing BMI trajectory pattern (increase from 27.8 kg/m^2 to 29.6 kg/m^2 at follow-up) carry a moderate risk of developing T2DM (1.8-fold increased risk compared to the low-increasing pattern) and they may benefit from lifestyle modifications, such as weight management through a balanced diet and regular exercise to improve insulin sensitivity and monitoring of blood glucose and blood pressure. Regular health check-ups and screenings should be maintained to catch any potential issues early in this group. Those with a high-increasing BMI trajectory pattern (increase from 33.7 kg/m^2 at baseline to 36.8 kg/m^2 at follow-up) are at a significantly higher risk of developing T2DM (3.4-fold increased risk compared to the low-increasing pattern) and they benefit from more intensive interventions, such as aggressive weight loss through a comprehensive weight management program, increased physical activity to improve insulin sensitivity and glucose metabolism and monitoring of blood glucose and blood pressure, with adjustments to medication as needed. In this group, regular health check-ups and screenings should be maintained to monitor the patient's progress and address

any potential issues promptly and they might also be considered for T2DM prevention medications, such as metformin under medical guidance.

The current study has several strengths. This population-based cohort study was conducted on a representative sample of Tehranian residents over 18 years of follow-up. Moreover, applying growth mixture modeling trajectory analysis helped us to categorize the population into unobserved subgroups that share similar patterns while also accounting for variations among individuals in the same subgroups. The models were adjusted stepwise for potential confounders, including age, sex, education level, family history of diabetes, physical activity, obesity, fasting plasma glucose, systolic blood pressure, HDL-C, TC, TG, anti-hypertensive drug use, and lipid-lowering drug use. In addition, the trajectory patterns for BMI were also separately identified in the subgroup of men and women and normoglycemic and prediabetic subjects. However, the study was conducted in a specific population (Tehran Lipid and Glucose Study), which may limit the generalizability of the findings to other populations. Additionally, we did not have sufficient data for HbA1c and defined prediabetes and diabetes based on FPG and 2-hour post-challenge glucose test. The method used to identify BMI patterns over the examination visits may have missed a small number of participants (less than 5%) who may have shown improving or aggravating patterns in BMI because of lifestyle changes, leading to misclassification of these individuals.

We conclude that the weight conditions in adult individuals, as indicated by BMI, exhibit a relatively stable pattern over 18 years. Adults with higher trajectory patterns over a long time are at increased risk of T2DM despite having normoglycemic status. This emphasizes the significance of the need for intervention for individuals with BMI above the normal range before the onset of prediabetes to prevent T2DM development. This finding emphasizes the importance of early assessment and intervention in individuals with elevated BMI, as well as the potential for using BMI trajectory patterns to predict and prevent the development of T2DM.

Data availability

Datasets generated during and analyzed during the current study are not publicly available due to institutional policies but are available from the corresponding author on reasonable request.

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Author contributions
Authors' contribution: All authors contributed to writing the manuscript. NH: designing, conceptualization, and writing the manuscript; LM: conceptualization, designing, methodology, and editing the manuscript; HA: project administration and editing the final draft; AA: designing, and editing the manuscript; SM: data analysis; FA: project supervision and editing the final draft; SPM: writing and editing the manuscript. All authors reviewed the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The current study was conducted according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Research Review Committee of the Endocrine Research Center of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.MSP.REC.1402.607). All participants in the study provided informed written consent.

Additional information
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