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Characteristics associated with early- vs. later-onset adult diabetes: the CARDIA study

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Abstract

Aims: Differences in risk profiles for individuals with early- (< 40 years old) vs. later-onset (≥ 40 years old) diabetes were examined.

Methods: A nested case-control study design using 30-year longitudinal data from the Coronary Artery Risk Development in Young Adults (CARDIA) study was used. Survey data (socio-demographics, family history, medical records, and lifestyle behaviors), obesity-related measures (body mass index, weight), blood pressure, and laboratory data (insulin, fasting glucose, 2-h

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Author contributions

ESC wrote the manuscript and researched data. FJP reviewed the manuscript and contributed to the discussion. FY analyzed data and wrote manuscript. DRJ counseled research design and contributed to data analysis and discussion. SD reviewed/edited the manuscript. GU reviewed/edited the manuscript. YC wrote the method section and reviewed/edited the manuscript. JMS reviewed/edited the manuscript, MPB reviewed/edited the manuscript, JR reviewed/edited the manuscript, and MSF reviewed/edited the manuscript.

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glucose, and lipids) were used to examine progression patterns of diabetes development in those with early-onset vs. later-onset diabetes.

Results: Of 605 participants, 120 were in early-onset group while 485 were in later-onset group. Early-onset group had a lower A Priori Diet Quality Score, but not statistically significant at baseline; however, the between-group difference became significant at the time that diabetes was first detected (p=.026). The physical activity intensity score consistently decreased from baseline to the development of diabetes in both the early- and later-onset groups. Early-onset group showed more dyslipidemia at baseline and at the time that diabetes was first detected, and rapid weight gain from baseline to the development of diabetes.

Conclusions: Emphases on lifestyle modification and risk-based diabetes screening in asymptomatic young adults are necessary for early detection and prevention.

Keywords

Young adults; Type 2 diabetes; risk prediction; early prevention

1. Introduction

The clinical manifestations of early-onset type 2 diabetes (T2D) developed prior 40 years of age differ distinctly from those of type 1 diabetes (T1D) and those of later-onset T2D (≥ 40 years of age) [1–3]. Compared to later-onset T2D, early-onset T2D is associated with a greater risk of cardiac structural changes, fatty liver disease, and microvascular complications, regardless of diabetes duration [4–6]. Early detection and implementation of programs designed to prevent and delay early-onset T2D are important for improving quality of life and reducing long-term health care costs [7–9].

At present, the clinical guidelines for screening early-onset T2D are based on or identical to those employed in later-onset T2D. However, differences in the glucose metabolism feedback loop (e.g., insulin sensitivity and insulin response to glucose) [10, 11], interactions between glucose and other metabolic risk factors (e.g., obesity, dyslipidemia, and elevated blood pressure) [12–14], and lifestyle habits (e.g., physical activity, dietary habits, and binge drinking) are observed between early- vs. later-onset T2D [15–17]. These heterogeneities may imply a missed opportunity to detect and treat early-onset T2D that may go undiagnosed for several years and to prevent further progression and complications [18]. Little is known regarding how the characteristics during young adulthood prior to diabetes development differ among individuals with early-versus later-onset T2D

This study examined differences in risk profiles for individuals with early- vs. later-onset adult diabetes. Specifically, we examined: 1) characteristics during the years before early-vs. later-onset diabetes and at the time of diabetes detection, 2) the age of onset for diabetes in early- vs. later-onset diabetes, and 3) the contributions of risk factors to early-onset diabetes development.

2. Subjects, Materials, and Methods

2.1. Study design:

A nested case-comparison study design was used.

2.2. Study population and sample:

The Coronary Artery Risk Development in Young Adults (CARDIA) study includes a prospective, multicenter longitudinal observational cohort designed to investigate the development and determinants of cardiovascular disease (CVD) and its associated risk factors in young adults. The initial examination included standardized measures of known CVD risk factors including sex, race, psychosocial, dietary, and exercise-related characteristics. In 1985–1986 (year 0), American young adults aged 18–30 years (n=5,115; mean age=24.9±3.7 years) were recruited in four field centers (Birmingham, AL; Chicago, IL; Minneapolis, MN; Oakland, CA). Since then, eight follow-ups (1987 [year 2], 1990 [year 5], 1992 [year 7], 1995 [year 10], 2000 [year 15], 2005 [year 20], 2010 [year 25], and 2015–2016 [year 30]) have been completed [17]. The IRB approvals from the local institutions and written informed consent from all participants were obtained in each examination. All data were collected with a standardized protocol, and blood samples were drawn and processed according to standard procedures.

2.3. Study Measures

2.3.1. Early-onset vs. later-onset diabetes definitions: While diabetes may be diagnosed with three different measures including: 8-hour fasting blood glucose (7.0mmol/L or ≥126mg/dL), 2-hour plasma glucose during 75g-oral glucose tolerance test (11.1mmol/L or ≥200mg/dL) or A1C (≥6.5% or 48mmol/mol) [19], the current investigation only used serum fasting glucose or use of antidiabetic medications to define adult diabetes since these are the measures that were available since the beginning of the CARDIA study. Serum fasting glucose was obtained at examination years 0, 7, 10, 15, 20, 25 and 30, and assayed using the hexokinase method at a central laboratory. The other two diagnostic measures were collected at limited time periods or with ancillary study sample; oral glucose tolerance test was done at years 10, 20, 25 while A1C was tested at years 20 and 25. The specific type of diabetes was not assessed in the CARDIA study. Prediabetes was defined as fasting glucose level of 5.6–6.9 mmol/L (100–125 mg/dL) without use of diabetes medications.

The examination at first diabetes detection was considered the “diabetes (DM) exam” in this analysis. To define early-onset (<40 years) versus later-onset (≥40 years old) diabetes, the age at diabetes exam was used. While diabetes onset, especially T2D onset, can precede diagnosis or detection for years because T2D is often asymptomatic, we used the term “onset” instead of “diagnosis” since diabetes was determined by single observation with a single diagnostic test in the current investigation

2.3.2. Clinical measurements and questionnaires: Participant- and interviewer-administered questionnaires were used to ascertain socio-demographics (e.g., age, sex, race, education, income level, health insurance), family history (e.g., natural family’s CVD history and their current living/death status), medical history and related information (e.g.,

participants' medical history including diabetes complications, and medication being taken), depressive symptoms (The Center for Epidemiological Studies-Depression ≥ 16), lifestyle behaviors (smoking, alcohol, marijuana use, sleep quality, physical activity, and dietary behaviors), and medication history. Venous blood was drawn and serum separation was performed, following which aliquots were stored at −70°C and shipped on dry ice to a central laboratory.

2.3.3. Physical activity (PA): PA was assessed in two ways: a binary level of physical activity (i.e., sedentary vs. active) and a continuous score, the total intensity score. To define the physical activity level, the statement 'physical activity in the past year' with a 5-point rating scale was used (1= physically inactive; 5 = physically very active). While levels 1 to 3 were classified as sedentary, levels 4 to 5 were classified as active. A PA intensity score (Exercise Units) was derived at each examination based on the frequency of participation over the previous 12 months for 13 moderate- and vigorous-intensity activities [20, 21].

2.3.4. Dietary quality score: Diet data were collected at study years 0, 7, and 20 using an interviewer-administered diet history. Diet quality was defined using a hypothesis-driven diet quality score, A Priori Diet Quality Score (APDQS) [17]. The APDQS included 46 food groups classified as beneficial (n=20), adverse (n=13), or neutral (n=13) based on their presumed effects on CVD. Each food group was ranked into quintiles and assigned positive scores for beneficial food groups (0 to 4), negative scores for food groups (4 to 0), and zero to the neutral food groups [17]. Possible score range is 0–132, with higher score indicating better diet quality. We used the baseline score and the closest score before or during the exam year the participant developed diabetes.

2.3.5. Obesity-related measures: Weight, height and waist circumference were measured at each examination by trained staff. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and classified as underweight (<18.5 kg/m^2), normal weight (18 to <25 kg/m^2), overweight (25 to <30 kg/m^2), or obese (≥30 kg/m^2).

2.3.6. Blood pressure: Resting seated blood pressure was measured with 3 times and the average of the 2^{nd} and 3^{rd} readings was used for the analysis. Elevated blood pressure was defined as average measured systolic or diastolic blood pressure (SBP/DBP) exceeding 120/80 mmHg, a report of using antihypertensive medication, or a "yes" response to a question of "Has a doctor ever told you that you have hypertension?"

2.3.7. Insulin and glucose: Fasting insulin and glucose were assayed at each examination except for years 2 and 5; we used the value at the year closest to the "diabetes (DM) exam" as the value at diabetes diagnosis or first detection. Two-hour insulin (uU/mL) was collected only at year 10, and thus we only reported the value in both groups. Two-hour plasma glucose was collected at years 10, 20, and 25. Thus, we reported the value at year 10 as diabetes exam value for the early-onset group. For the later-onset group, the value closest to the diabetes exam or the exam before was reported.

2.3.8. Lipid profiles: Total cholesterol, triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C), which were directly measured using standardized assays, were used. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation [22]. To assess the longitudinal trend of metabolic control, lipid profiles at baseline and "diabetes exam" were used. Dyslipidemia was defined as the presence of any of the following conditions: LDL-C ≥ 2.6 mmol/L(100 mg/dL), TG ≥ 1.69 mmol/L(150 mg/dL), or HDL-C< 1.04 mmol/L(40 mg/dL) in men or < 1.3 mmol/L(50 mg/dL) in women. The ratios of TG/HDL-C and LDL-C/HDL-C that predict CVD were also used [23]. While using cholesterol-lowering medication indicated dyslipidemia, no participant reported taking cholesterol-lowering medication at baseline or year 2.

2.4. Statistical Analyses

The 34 participants who had diabetes at CARDIA exam year 0 were excluded in the current study. An additional participant withdrawing consent was excluded for data analysis. Women who reported current pregnancy at an exam were excluded from the specific follow-up, but were included in the analysis when not pregnant. Based on these criteria, 605 participants were included in the final analysis.

Participant characteristics were summarized by early- and later-onset diabetes groups using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. The median and interquartile range (IQR) were used to describe continuous variables for non-normally distributed data. Years of observation before diabetes were calculated for each participant using the year of diabetes exam minus the baseline year.

Data management and analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) with statistical significance set at $P < 0.05$. We used t-tests and Wilcoxon rank-sum tests (for non-parametic measures) to compare differences in continuous variables for early- vs. later-onset diabetes groups. Chi-square tests were used to compare the categorical variable differences between participants with early- and later-onset diabetes. Because of sex-specific cut-offs for HDL-C, we also examined lipid profiles by sex. Multivariable logistic regression models using a backward selection method were generated to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for early-onset diabetes. To do this, we included all potential independent variables identified as risk factors in previous research when we generated each model. Also, correlations among variables were examined to add variables in the model. The final model included variables that were statistically significant risk factors for early-onset diabetes development.

3. Results

3.1. Sample Description

Of 605 participants, 120 had early-onset and 485 had later-onset adult diabetes (Table 1). The mean observation years (SD) before the DM exam were 11.2 (4.9) for the early-onset group and 24.4 (5.3) for the later-onset group. The mean age at the diabetes exam was 35.0 years in the early-onset group and 50.2 years in the later-onset group. The distribution of sex did not differ by diabetes group, but Black race predominated in both groups. More than

56% of the early-onset group and less than 34% of the later-onset group reported an annual income less than $35,000 at the diabetes exam. Compared to the early-onset group, lifetime use of marijuana in the later-onset group was higher at baseline.

The early-onset group had a nominally lower APDQS at baseline than the later-onset group. This difference became significant at the diabetes exam. A nominally higher percentage of the early-onset group reported that they were physically active at baseline and the diabetes exam. The median PA intensity score decreased from baseline to the diabetes exam in both groups.

3.2. Medical history

As Table 2 shows, the prediabetes percentage at year 0 was significantly higher in the early-onset group (13.6%) compared to the later-onset group (3.4%) ($p < .0001$). At year 0, the prevalence of anti-hypertensive medication usage was marginally higher in the early-onset group compared to later-onset group. However, a greater percentage of the later-onset group reported the use of anti-hypertensive medication at the diabetes exam. Similarly, the percentage of individuals taking aspirin, diabetes or cholesterol medications at the diabetes exam was higher among the later-onset group. There were no differences in family history of diabetes between groups.

3.3. Metabolic and Laboratory Characteristics

As Table 3 shows, the mean (SD) BMI at year 0 in the early-onset and later-onset groups was 30.4 (6.9) and 27.5 (5.7), respectively. About a half of the early-onset group (50.4%) and one-fourth of the later-onset group (27.3%) had obesity at year 0. By the time of DM exam, the majority of participants were overweight or obese while approximately 10% of early-onset and 5.8% of later-onset groups had normal weight. The mean (SD) years of overweight or obesity (BMI $\geq$ 25 kg/m^2) between baseline and the diabetes exam were 10.1 (5.2) and 21.3 (7.0) in the early- and later-onset groups, respectively (Table 3).

The mean fasting glucose at year 0 was higher in the early-onset group (4.93 ±0.71 mmol/L vs 4.70±0.48 mmol/L, p=0.0013) compared to the later-onset group. This difference was also significant at the DM exam (9.01±3.11 mmol/L vs 7.94±2.86, p=0.0006). The median fasting insulin was significantly higher in the early-onset compared to the later-onset group at baseline (year 0) but not at the DM exam.

Baseline systolic blood pressure (SBP) was modestly higher at baseline but not at the time of diabetes detection for the early-onset group compared to the later-onset group. The early-onset group had a higher mean diastolic blood pressure (DBP) at the baseline and the DM exam; however, the latter was not statistically significant.

Dyslipidemia was prevalent at the baseline as well as the DM exam. At year 0, the early-onset group showed lower HDL-C and higher TG concentrations than did the later-onset group. This pattern remained for HDL-C (lower among the early-onset group) but did not differ for TG at DM exam.

Sex differences in lipid profiles and dyslipidemia were also observed: a higher proportion of women than men experienced uncontrolled dyslipidemia at the baseline. At year 0 and the DM exam, women in the early-onset group had lower mean HDL-C than the later-onset group. In contrast, no difference between groups among men was observed in mean HDL-C at year 0. The mean HDL-C, however, had decreased for men in the early-onset group by the time of the DM exam and thus resulted in a between-group difference in mean HDL-C at the DM exam. The TG/HDL-C ratio was higher in the early-onset group than later-onset, and became more evident in men by the time of diabetes exam. For women, the median TG/HDL-C ratio was higher in the early-onset group, but the difference became decreased and statistically insignificant by the time of DM exam. Unlike TG/HDL-C ratio, LDL/HDL-C ratio showed significant differences at both year 0 and the time of the DM exam.

3.4. Estimated Odd Ratios Associated with Early-onset Diabetes

Participants with early-onset diabetes were more likely to be single and have lower education at baseline compared to participants with later-onset diabetes. Higher BMI and fasting glucose levels at baseline were also associated with early-onset development, with a 7% increase for every unit increase in BMI and a 3% increase for every unit increase in glucose (mg/dl) in the odds of early-onset diabetes development, Table 4.

Table 5 presents the adjusted ORs for early-onset diabetes according to characteristics measured at the time diabetes was first detected (“DM exam”). Participants with early-onset diabetes were more likely to be African Americans and having health insurance. Despite modestly higher physical activity, participants with early-onset diabetes were more likely to have a worse diet quality and higher BMI at the DM exam, compared with those with later-onset diabetes. Odds of early-onset diabetes was 2.81 times higher for African Americans than Caucasians.

4. Discussion

This study demonstrated that individuals with both early-and later-onset adult diabetes have adverse metabolic profiles years in advance of diabetes. Individuals who develop early–onset diabetes had strikingly worse profiles for overall and central obesity in early adulthood compared to the later-onset group. In addition to greater adiposity earlier in life, the early-onset group had worse profiles for fasting glucose concentration, blood pressure, and lipid profiles earlier in life. Over the course of follow-up, the early-onset group had a decrease in diet quality and a steeper slope of weight gain and developed diabetes at the mean age of 35 years, which is the starting age of prediabetes and diabetes screening recently proposed by US Preventive Service Task Force [24]. Given the increasing numbers of younger cohorts, including adolescents with overweight and obesity that are being diagnosed with diabetes, prevention efforts and diabetes screening starting at younger ages are needed regardless of a specific age and are recommended by the American Diabetes Association [19].

Early detection and management of diabetes is essential [6, 19]. There are mixed research findings regarding the association between diabetes duration and complications (e.g., cardiac dysfunction later in life) because of delayed diagnosis [25–27]; a large proportion of individuals with diabetes in adulthood are unaware and undiagnosed, particularly those with

T2D [28]. In response to this concern, the current study provides key evidence about current weight status as well as accelerated weight gain and lifestyle behaviors in young adulthood as significant contributors to early-onset diabetes. This finding is consistent with previous research findings and emphasizes a pivotal role of weight gain and unhealthy lifestyle in early adulthood as well as later adulthood in regard to risk of developing diabetes [17, 29].

Accumulated research evidence identifies family history as a strong predictor of T2D [19], and our study supported the evidence: a high proportion of the participants reported a family history. We, however, were unable to distinguish a statistical difference in the family history between early- and later-onset groups (See Table 5) as all our participants developed diabetes, and we looked at the age at diagnosis, not risk factors for diabetes. Lifestyle behaviors, however, are shared within families and thus may contribute to developing early-onset diabetes [1, 15, 30]. A previous study showed that every 10% increase in the number of relatives with T2D was associated with a 1.7-year decrease in the age of onset of T2D [31]. We speculate that proactive prevention with tailored messages to target family as well as individuals would be helpful for high-risk young adults.

The prevalence of overweight and obesity in CARDIA overall was higher than contemporary national estimates. In the current study, we observed prevalence estimates of obesity at baseline nearly twice that of national estimates [32–34]. Also, rapid weight gain was observed in the early-onset group compared to the later-onset group as did high prevalence of the severe obesity (BMI≥35 kg/m^2) over 10 years. For instance, the early-onset group gained 3.74 lb per 10 years, twice the weight gain observed in the general population (1.8 – 2 lb per year) [35]. In contrast, in the later-onset group the average weight gain over 25 years was 2.19 lb per year, similar to weight gain in general population. Related to this point, individuals in the early-onset group consistently consumed a poorer quality diet than the later-onset group while they reported similar levels of physical activity (PA) compared to the later-onset group. We believe this finding should not be interpreted as PA being ineffective for health promotion, but rather that a greater level of PA is needed given the excess weight of this group.

Dyslipidemia is a common comorbidity in persons with diabetes, especially T2D [1, 12, 13, 36]. In the current study, the early-onset group showed a higher median triglyceride concentration than the later-onset group years before the diabetes exam. Additionally, a greater proportion of low HDL-C was identified in the early-onset group. In particular, women in the early-onset group showed significantly lower mean values of HDL-C at baseline as well as the diabetes exam. Poon et al. identified different long-term trajectories of metabolic risk factors between men and women, which differed by race [14]. In our current study, lower HDL-C concentration at baseline was associated with early-onset diabetes development. Whether sex-specific variables need to be tracked in order to screen for the risk of developing early-onset adult diabetes remains to be determined.

Previous research identified the ratios of TG/HDL-C and LDL-C/HDL-C as meaningful predictors of CVD, although the utility of each may differ depending on the study population [23, 37]. The TG/HDL-C ratio was higher in the early-onset group, especially in men. For women, the ratios increased over time, but were no longer significantly different

at the diabetes exam. The LDL-C/HDL-C ratio in the early-onset group was higher at both baseline and the diabetes exam, especially in women. This may suggest a sex-specific sensitivity of these measures in relation to early-onset diabetes, that could potentially be associated with increased incidence and progression of micro- and macro-vascular disease in women [36]. Further investigation is necessary in a future study.

When individuals experience hyperglycemia and hyperlipidemia simultaneously, glucolipotoxicity resulting in additional damage and toxic effects on β-cell function can occur [12]. If left untreated with time-dependent intervention, glucolipotoxicity would be irreversible and facilitate insulin insensitivity and non-alcoholic fatty liver disease leading to escalation of β-cell deterioration, which is a primary cause of early-onset T2D [10, 38]. Despite the higher prevalence of dyslipidemia in the early-onset group at the diabetes exam, many participants had fewer options to control dyslipidemia. First, effectiveness of statin medication was first reported in the Scandinavian Simvastatin Survival Study(4S) in 1994 [39], and the medications were not approved immediately by the Food and Drug Administration in the USA. Therefore, it was unavailable for our early-onset group that developed diabetes before 1995 (year 10 of CARDIA) [40]. Second, statin medication primarily targets LDL-C [41], and most of the dyslipidemia in the early-onset group was related to hyper-triglyceridemia or low HDL-C, which would be improved via healthy lifestyle. Our early-onset group, however, showed poorer diet quality and decreased PA over time which may resulted from the lack of knowledge of healthy lifestyle to prevent or delay T2D; the Diabetes Prevention Program began at 1996 [42, 43]. Lastly, during the early years of the CARDIA study, cholesterol treatment for CVD prevention was based on the target value of LDL-C rather than CVD risk prediction, and few CARDIA participants would have been indicated for treatment based on LDL-C alone [44]. Also, young people have low predicted 10-year risk according to the current guidelines, which limit early treatment. Since uncontrolled dyslipidemia with hyperglycemia may facilitate diabetes progression [12, 36], proactive and aggressive prevention such as personalized lifestyle intervention and continuous check-up may be needed in high-risk groups.

In the current study, a higher proportion of women experienced uncontrolled dyslipidemia, pointing to a need for further investigation in the areas related to women's health. During pregnancy, women experience "normal hyperlipidemia, especially a hyper-triglyceride condition" in order to provide an optimal supply of glucose to both the mother and the fetus [45, 46]. Therefore, subsequent research may assess among women with obesity or diabetes whether lipid profiles during pregnancy are associated with higher CHD risk later in life.

Social determinants of health may contribute to the development of early-onset adult diabetes [1, 30, 47]. The analysis showed that being African Americans, single, having lower education or having health insurance is associated with early-onset diabetes at the time of diabetes exam. However, these findings should be carefully interpreted because of the possibility of detection bias (e.g., Affordable Care Act). A meticulous investigation is necessary in the future.

Despite the strengths of this study, several limitations exist. First, while T2D probably predominated in CARDIA, some participants may have developed T1D, especially in the early-onset group [19]. Since the CARDIA study did not collect the autoimmune markers to determine T1D, it is impossible to discriminate between T1D and T2D within the CARDIA data. A future study targeting youths and young adults with diabetes need to consider this regard to obtain more accurate results. Second, not all of the characteristics included in the CARDIA study were regularly collected, and the 5-year data collection interval may have resulted in missed changes in characteristics. Additionally, diabetes diagnosis has been determined by single observation with serum fasting glucose and use of antidiabetic drugs. Currently, the American Diabetes Association (ADA) recommends a 3-year interval to screen for diabetes risk in high-risk groups, and two abnormal test results from the same sample or in two separate test samples [19]. Because of 5-year data collection interval, there is a possibility of persons classified as later-onset group may actually be the early-onset group. For this reason, a careful interpretation is necessary. Third, the minimum age at enrollment for CARDIA was 18 years and we were unable to assess characteristics before this age that would contribute to diabetes development (e.g., childhood obesity). According to the recent recommendation by the ADA, risk–based screening for T2D is appropriate for asymptomatic children after the onset of puberty or 10 years of age [19]. Since obesity, unhealthy lifestyle (e.g., physical inactivity), early-onset T2D in childhood are increasing [48], clinicians should actively adopt recent ADA's recommendations into their practice in order to early detection and prevention of T2D. Also, weight changes from childhood to young adulthood need to be tracked as potential risk factor for developing early-onset T2D. Fourth, some antidiabetic drugs may interfere with weight gain or other CVD risk factors, and the researchers identified statistic difference in antidiabetic therapy between groups at the time of diabetes exam. Therefore, meticulous interpretation is necessary to avoid any error. Lastly, we used backward selection to determine risk factors for early onset diabetes, as presented in Tables 4 & 5. As such, our model adjustments were parsimonious and our results may be subject to confounding and do not necessarily reflect causal associations. However, our findings contribute to the evidence supporting the identification of those who may benefit from risk-based screening in young adulthood.

Conclusions

Adverse profiles for traditional diabetes risk factors were observed well before the onset of diabetes for individuals who developed adult diabetes, and those who developed early-onset diabetes had substantially worse profiles during young adulthood. Obesity occurred often among the early-onset diabetes group in early adulthood before the onset of diabetes, and they experienced more rapid weight gain by the time of diabetes onset. This early-onset group had worse profiles in young adulthood for nearly every major diabetes and CVD risk factor earlier in life. These findings strongly support the recent ADA's recommendations for risk-based screening for type 2 diabetes in asymptomatic youths and young adults regardless of their young age.

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Table 1.

Unadjusted comparison of socio-demographics and lifestyle habits in participants with early- vs. later- onset diabetes (N=605)

	Early-onset DM (n=120)		Later- onset DM (n=485)		P-value for baseline comparison	P-value for DM exam comparison
	Baseline (Year 0)	DM first detection	Baseline (Year 0)	DM first detection		
Mean age (SD), years	23.74(3.71)	34.95(3.44)	25.80(3.47)	50.16(5.39)	<0.001 *	<0.0001 *
Mean years (SD) of observation before DM	N/A	11.24(4.87)	N/A	24.37(5.29)		<0.0001 *
Gender					0.6698	0.6698
Male, n (%)	61(50.83)	61(50.83)	236(48.66)	236(48.66)		
Female, n (%)	59(49.17)	59(49.17)	249(51.34)	249(51.34)		
Race					0.6860	0.6860
Black, n (%)	82(68.33)	82(68.33)	322(66.39)	322(66.39)		
White, n (%)	38(31.67)	38(31.67)	163(33.61)	163(33.61)		
Marital Status					0.1433	0.1206
Single, n (%)	93(77.50)	69(57.50)	342(70.81)	239(49.59)		
Non-single or being married, n (%)	27(22.50)	51(42.50)	141(29.19)	243(50.41)		
Employment						0.1016
Full time or part time		85(75.89)		270(67.84)		
Other		27(24.11)		128(32.16)		
Education					0.1214	0.3484
High school (HS) or less	82(77.36)	62(53.45)	307(69.77)	221(48.57)		
More than HS	24(22.64)	54(46.55)	133(30.23)	234(51.43)		
Income level <$35000	N/A	60(56.07)	N/A	157(33.19)		<0.0001 *
No health insurance	N/A	16(14.41)	N/A	67(13.87)		0.8818
n (%) of perceived financial difficulty	17(14.17)	10(8.85)	68(14.02)	71(14.73)	0.9671	0.1009
n (%) of ever use of marijuana in lifetime	72(60.50)	71(59.66)	338(69.98)	303(64.19)	0.0470	0.3595
n (%) of alcohol use	96(80.00)	76(63.33)	402(83.06)	337(71.40)	0.4305	0.0859
n (%) of tobacco use	46(39.32)	47(39.17)	231(47.73)	212(44.63)	0.2154	0.4404
Lifestyle factors						
n (%) of physically active	44(36.67)	26(21.85)	153(31.61)	69(16.71)	0.2903	0.1969
Median (IQR) of total intensity score,	313(489.5)	191(324)	324(391)	174(271)	0.8678	0.1160

	Early-onset DM (n=120)		Later- onset DM (n=485)		P-value for baseline comparison	P-value for DM exam comparison
	Baseline (Year 0)	DM first detection	Baseline (Year 0)	DM first detection		
Mean (SD) of diet (APDQS) score	58.15(11.85)	63.53(11.43)	60.11(12.05)	66.35(11.66)	0.1146	0.0262 *
n (%) of poor sleep quality reported		20(17.86)		85(17.89)		0.9925

† Total Intensity Score was reported using median with interquartile range (IQR) since data were non-normally distributed.

* p-value<0.05 was considered as statistically significant.

Table 2.

Unadjusted comparison of medical and family history in participants with early- vs. later- onset diabetes (N=605)

	Early-onset DM (n=120)		Later- onset DM (n=485)		P-value for baseline comparison	P-value for DM exam comparison
	Baseline (Year 0)	DM first detection	Baseline (Year 0)	DM first detection		
n(%) of having pDM at Baseline	16(13.56)		16(3.38)		<0.0001*	
n (%) of persons with pDM prior to DM	N/A	52 (43.33)	N/A	338(69.69)	N/A	<0.0001*
*Mean(SD) of exam showing pDM	N/A	0.50(0.62)	N/A	1.26 (1.14)	N/A	<0.0001*
Mean number of visits attended	N/A	4.70(1.20)	N/A	6.97(1.69)	N/A	<0.0001*
Mean (SD) BMI of persons with pDM in a follow-up and developed DM later	29.85(6.66)	36.49(9.23)	27.85(5.87)	35.92(8.19)	0.0269*	0.6468
Mean (SD) BMI of persons without pDM during the follow-ups, but developed DM	30.78(7.11)	35.51(7.76)	26.73(5.35)	35.35(7.64)	<0.0001*	0.8835
n (%) of family DM history						
. Paternal side	64(53.33)	66(55.00)	269(55.46)	276(56.91)	0.6744	0.7069
. Maternal side	75(62.50)	82(68.33)	291(60.00)	320(65.98)	0.6160	0.6249
. Sibling	42(35.00)	67(55.83)	161(33.20)	282(58.14)	0.7078	0.6464
. Female history (mother +sister)	81(67.50)	94(78.33)	315(64.95)	365(75.26)	0.5987	0.4808
. Male history (father+ brother)	70(58.33)	80(66.67)	296(61.03)	348(71.75)	0.5884	0.2729
n (%) of medication taking history						
Anti-diabetic medication	N/A	50 (41.32)	N/A	279 (58.00)	N/A	0.0011*
Anti-hypertensive med	9(7.50)	30(25.00)	18(3.73)	274(56.85)	0.0737	<0.0001*
Heart med	1(0.84)	2(1.85)	9(1.86)	11(2.48)	0.4342	0.7006
≠Cholesterol med	N/A	5(4.24)	N/A	164(34.38)	N/A	<0.0001*
n (%) of mental disorder	11(9.24)	6(5.00)	45(9.41)	63(13.18)	0.9545	0.0122*
n (%) of depressive symptoms (CES-D≥ 16)	N/A	30(26.79)	N/A	113(24.25)	N/A	0.5764
n (%) of co-morbidity						
heart problem	3(2.56)	12(10.43)	26(5.51)	66(14.63)	0.1876	0.2435
stroke	0 (0.0)	1(0.90)	0 (0.0)	12(2.5)	-	0.3006
gestational diabetes	N/A	9(27.27)	N/A	22(17.60)	N/A	0.2133
kidney problem	7(5.93)	6(5.17)	32(6.61)	39(8.57)	0.7881	0.2252

	Early-onset DM (n=120)		Later- onset DM (n=485)		P-value for baseline comparison	P-value for DM exam comparison
	Baseline (Year 0)	DM first detection	Baseline (Year 0)	DM first detection		
liver diseases	0 (0.0)	3(2.50)	4(0.83)	30(6.25)	0.3197	0.1070
cancer	4(3.42)	6(5.00)	14(2.91)	32(6.65)	0.7729	0.5057
HIV	N/A	0(0)	N/A	7(1.48)	N/A	0.4273
Anti-platelet (i.e., Aspirin) medication	N/A	6(5.41)	N/A	153(31.74)	N/A	<0.0001 *

* P-value<0.05 was considered as statistically significant.

** if a participant did not participate in an exam, it counts as missing.

† pDM indicates prediabetes, if a participant did not participate in an exam, it counts as missing.

‡ No one reported taking a cholesterol-lowering medication before year 5.

Table 3.

Unadjusted comparison of metabolic and laboratory characteristics in participants with early- vs. later- onset diabetes (N=605)

	Early-onset DM (n=120)		Later- onset DM (n=485)		P-value for baseline comparison	P-value for the DM exam comparison
	Year 0	DM first detection	Year 0	DM first detection		
Weight	196.80(48.85)	234.66(57.88)	175.93(39.01)	229.30(54.29)	<0.0001*	0.3887
Waist circumference (cm) (mean ±SD)	90.88(16.31)	103.23(16.89)	85.00(12.59)	102.18(14.89)	0.0004*	0.5269
BMI (mean ±SD)	30.38(6.91)	35.94(8.40)	27.51(5.73)	35.75(8.02)	<0.0001*	0.8186
Obesity					<0.0001*	0.2174
Underweight, n (%)	2(1.68)	0	6(1.24)	1(0.21)		
Normal, n (%)	24(20.17)	12(10.00)	179(36.98)	28(5.79)		
Overweight, n (%)	33(27.73)	15(12.50)	167(34.50)	86(17.77)		
Obese, n (%)	60(50.42)	91(77.50)	132(27.27)	369(76.24)		
Obese ≥class II, n (%)	21(17.65)	65(54.17)	54(11.16)	242(50.00)	0.0546	0.4138
Mean year (SD) of BMI≥25	N/A	10.08(5.19)	N/A	21.29(6.96)	N/A	<0.0001*
Fasting glucose (mmol/L), mean (SD)	4.93(0.71)	9.01(3.11)	4.70(0.48)	7.94(2.86)	0.0013*	0.0006*
Median (IQR) of fasting Insulin, pmol/L	62.84(38.57)	105.74(106.92)	52.16(26.06)	102.50(93.72)	<0.0001*	0.4955
Classification of pDM					0.0221*	0.2272
5.6–6.1 mmol/L n (%)	8(50.00)		14(87.50)	41(40.59)		
6.1–6.9 mmol/L n (%)	8(50.00)		2(12.50)	60(59.41)		
Mean (SD) of 2h plasma glucose (mmol/L)	N/A	10.89(5.77)	N/A	11.92(4.89)	N/A	0.2621
Median (IQR) of 2h Insulin, pmol/L	N/A	465.23(525.94)	N/A	366.00(444.00)**	N/A	0.2198
Mean (SD) of SBP (mmHg)	116.21(11.86)	118.93(14.10)	113.50(11.88)	123.98(17.60)	0.0253*	0.0010*
Mean (SD) of DBP (mmHg)	72.86(10.93)	78.03(12.38)	70.77(9.30)	78.44(11.26)	0.0557	0.7248
Mean (SD) of Total Cholesterol (mmol/L)	4.73(0.89)	4.95(1.11)	4.72(0.93)	4.86(1.10)	0.8722	0.4121
Mean (SD) of HDL-C (mmol/L)	1.17(0.29)	1.07(0.32)	1.28(0.34)	1.24(0.38)	0.0014*	<0.0001*
Mean (SD) of HDL-C (mmol/L) (male)	1.13(0.32)	0.98(0.26)	1.19(0.30)	1.15(0.32)	0.1338	0.0001*
Mean (SD) of HDL-C (mmol/L) (female)	1.21(0.27)	1.16(0.35)	1.36(0.35)	1.34(0.40)	0.0005*	0.0040*
Mean (SD) of LDL-C (mmol/L)	3.03(0.83)	2.99(0.95)	2.99(0.86)	2.84(0.95)	0.6959	0.1277

	Early-onset DM (n=120)		Later- onset DM (n=485)		P-value for baseline comparison	P-value for the DM exam comparison
	Year 0	DM first detection	Year 0	DM first detection		
Median (IQR) of Triglyceride (TG) (mmol/L)	0.87(0.67)	1.34(1.35)	0.76(0.58)	1.34(0.95)	0.0218*	0.4480
n (%) of LDL-C≥2.6 mmol/L						
Male	37 (66.07)	29(55.77)	154(65.81)	130(57.78)	0.9707	0.7918
Female	45 (76.27)	41(70.69)	160(64.26)	139(59.15)	0.0786	0.1059
n (%) of HDL-C						
Male (<1.04 mmol/L)	22(37.93)	39(65.00)	71(30.08)	91(38.56)	0.2496	0.0002*
Female (<1.3 mmol/L)	39(66.10)	44(74.58)	117(46.99)	126(51.22)	0.0083*	0.0012*
n (%) of Triglyceride ≥1.69 mmol/L						
Male	17 (29.31)	31(51.67)	32(13.56)	101(42.80)	0.0039*	0.2171
Female	1(1.69)	15(25.42)	13(5.22)	84(34.15)	0.2424	0.1988
Dyslipidemia yes	102 (85.00)	109 (90.83)	371(76.49)	438(90.31)	0.0434*	0.8614
Dyslipidemia yes- male	47(77.05)	54(88.52)	175(74.15)	214(90.68)	0.6425	0.6135
Dyslipidemia yes- female	55(93.22)	55(93.22)	196(78.71)	224(89.96)	0.0099*	0.4407
TG/HDL-C ratio, median (IQR)						
Male	1.99(4.05)	4.36(5.18)	1.62(1.80)	3.03(3.43)	0.0669	0.0015*
Female	1.60(1.00)	2.38(1.93)	1.30(1.17)	2.39(2.43)	0.0127*	0.9731
LDL/HDL-C ratio, mean (SD)						
Male	2.74(1.17)	2.96(1.17)	2.73(1.13)	2.53(0.99)	0.9384	0.0068*
Female	2.73(0.98)	2.79(1.13)	2.32(0.95)	2.31(1.02)	0.0034*	0.0022*
Microalbuminuria (Yes. %)	N/A	1(1.35)	N/A	12(2.55)	N/A	1.000
A/C ratio, mean (SD)	N/A	17.22(31.06)	N/A	29.75(99.77)	N/A	0.5104

※The clinical measurements were converted to SI unit as following: glucose mg/DL x 0.056=mmol/L, cholesterol mg/DL x 0.026=mmol/L, Triglyceride mg/DL x 0.011=mmol/L and insulin μU/ML x 6=pmol/L

*P-value<0.05 was considered as statistically significant.

**pDM indicates prediabetes.

***2h insulin in the later-onset group was the value at year 10 since the CARDIA only collected 2h insulin at year 10.

†Trig, trig-HDL ratio, insulin and insulin-2h were reported using median with IQR since data were non-normally distributed.

‡The percentage calculation was using all non-missing value.

Table 4.

Adjusted odd ratios and 95% confidence intervals for early-onset vs later-onset diabetes using baseline (year 0) data, reduced model (N=605)

Predictors		Odds ratio	95% CI
Marital status			
	Not single	0.556	0.309–0.998
	Single	Ref	
Education			
High school or less		1.942	1.081–3.488
More than high school		Ref	
BMI (per 1 kg/m^2)		1.071	1.030–1.114
Fasting glucose (per 1 mg/dL)		1.032	1.005–1.059

Backward selection method using $P < 0.05$ was used to make the model selection. The initial model included race, gender, education, employment and marriage status, difficulty for paying basics, family income, insurance, drink and smoking status, any history of heart attack, diabetes, high blood pressure (HBP), overweight, stroke in male or female family members, participant's own HBP and high cholesterol history, heart disease, kidney disease, mental health and clinical measurements (HDL-C, LDL-C, triglycerides(trig), trig/HDL-C, LDL-C/HDL-C, DBP, SBP, BMI creatine, insulin, trig/HDL-C, LDL-C/HDL-C) and duration of overweight/obese, physical activity intensity score and diet score.

Table 5.

Adjusted odd ratios and 95% confidence intervals of risk factors for early- vs late-onset diabetes using the data at the exam when diabetes was first detected, reduced model (N=605)

Predictors		Odds ratio	95% CI
Race			
	African-Americans	2.811	1.060–7.458
	Caucasians	Ref	
Insurance			
	No	0.249	0.073–0.845
	Yes	Ref	
Diet (per 1 unit APDQS)		0.952	0.918–0.988
BMI (per 1 kg/m^2)		1.124	1.063–1.189
Physical activity (per 1 unit EU)		1.003	1.001–1.004
Overweight or obese duration (BMI ≥25) from baseline to T2D exam (year)		0.686	0.620–0.760

Backward selection method using $P < 0.05$ was used to make the model selection. The initial model included race, gender, education, employment and marriage status, difficulty for paying basics, family income, insurance, drink and smoking status, any history of heart attack, diabetes, high blood pressure (HBP), overweight, stroke in male or female family members, participant's own HBP and high cholesterol history, heart disease, kidney disease, depression, mental health and if the participant had prediabetes, clinical measurements (HDL-C, LDL-C, triglycerides (trig), DBP, SBP, BMI creatine, insulin, trig/HDL-C, LDL-C/HDL-C) and duration of overweight/obese, physical activity intensity score and diet score.