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ORIGINAL RESEARCH

Prevalence, Demographic and Clinical Characteristics of Individuals with Early Onset Type 2 Diabetes in the USA: an NHANES Analysis 1999–2020

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ABSTRACT

Introduction: Early onset type 2 diabetes (T2D), diagnosed before age 40 years, is potentially more aggressive than later-onset disease and is increasing in prevalence globally. We examined the prevalence of early onset T2D in the USA and characterised this population.

Methods: Data from the longitudinal series of NHANES cross-sectional surveys conducted between 1999 and 2020 were analysed retrospectively. The prevalence of diagnosed and undiagnosed early onset T2D was estimated across this period and the demographics, clinical characteristics and frequency of comorbidities in this population were described. Findings were compared with the US later-onset T2D population during the same period.

Results: The prevalence of diagnosed and undiagnosed early onset T2D increased from 1.42% (standard error 0.19) and 0.18% (0.09), respectively, during the 1999–2000 survey cycle to 1.72% (0.24) and 0.35% (0.06), respectively, during the 2017–2020 cycle. Compared with those with later-onset disease, participants with early onset T2D had a lower mean poverty–income ratio, were more likely to be Hispanic or have no health insurance and less likely to be non-Hispanic white or have private or Medicare insurance (all $p<0.05$). Individuals with early onset T2D generally had a worse cardiometabolic profile, with higher mean glycated haemoglobin, Homeostatic Model Assessment for Insulin Resistance score, fasting insulin and glucose, body mass index and waist circumference but were less likely to have congestive heart failure, coronary heart disease, stroke, chronic kidney disease or cancer (all $p<0.05$). All comparisons remained statistically significant after adjustment for T2D duration among participants with diagnosed T2D.

Conclusions: These findings suggest that early onset T2D may disproportionately affect underserved populations with a higher likelihood of having cardiometabolic risk factors, suggesting a more aggressive disease that warrants the need for better diagnoses and treatment. Further

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research is needed to explore the potential link between cardiometabolic profile, risk of complications and longer-term cardiovascular outcomes in people with early onset T2D.

PLAIN LANGUAGE SUMMARY

The number of people affected by type 2 diabetes (T2D) before the age of 40 years (early onset T2D) is increasing globally, and these individuals may have more diabetes-related medical issues than those who develop the disease later in life. We estimated the number of people with early onset T2D in the USA and described their characteristics using data from a series of surveys conducted between 1999 and 2020. In particular, we examined their demographics (e.g. age, gender, race/ethnicity, income), important clinical characteristics that give us information about their health (e.g. insulin and glucose levels, weight, cholesterol levels, blood pressure, liver function, etc.) and coexisting medical disorders. We compared these results with people diagnosed with T2D at ≥ 40 years of age (later-onset T2D). Between 1999–2000 and 2017–2020, the number of people with diagnosed and undiagnosed early onset T2D increased in the USA from 1.42% and 0.18%, respectively, to 1.72% and 0.35%, respectively. Compared with people with later-onset T2D, people with early onset T2D had a lower poverty–income ratio (meaning they were, on average, poorer), were more likely to be Hispanic or have no health insurance, were less likely to be white or have private or Medicare insurance and had a worse clinical characteristic profile but were less likely to have coexisting disorders, regardless of how long ago they were diagnosed. Our findings suggest that early onset T2D disproportionately affects certain ethnicities and underserved populations, is associated with higher health risks and may be a more aggressive disease, warranting better diagnoses and treatment.

Keywords: Characteristics; Comorbidities; Early onset; Later-onset; National Health and Nutrition Examination Survey; Prevalence; Type 2 diabetes; USA

Key Summary Points

Why carry out this study?

Early onset type 2 diabetes, diagnosed before 40 years of age, is increasingly prevalent globally and may be a more aggressive disease than later-onset type 2 diabetes, diagnosed at ≥ 40 years of age; however, the prevalence of early onset type 2 diabetes in the USA is unknown, as is the frequency of comorbidities related to early onset disease among affected individuals.

We aimed to characterise the prevalence of undiagnosed and diagnosed early onset type 2 diabetes in the USA as well as the demographics, clinical characteristics and frequency of disease-related comorbidities in these individuals.

What was learned from the study?

Our findings indicate that the prevalence of undiagnosed early onset type 2 diabetes has increased over time in the USA; early onset disease disproportionately affects underserved populations; and people with early onset type 2 diabetes generally have a worse cardiometabolic profile than those with later-onset disease.

Early onset type 2 diabetes may be associated with higher cardiometabolic risk that should be better diagnosed and treated.

Further research is needed to explore the potential link between the cardiometabolic profile of people with early onset type 2 diabetes, the risk of complications and longer term cardiovascular outcomes.

INTRODUCTION

Early onset type 2 diabetes (T2D), defined as diagnosis before 40 years of age, is increasingly

prevalent globally and may be a more aggressive disease than later-onset T2D, defined as diagnosis at ≥ 40 years of age [1, 2]. Evidence suggests that early onset T2D is associated with increased insulin resistance and the accelerated loss of β-cell function compared with later-onset T2D, as well as a lack of response to anti-hyperglycaemic treatment such as metformin [2–4]. Furthermore, earlier onset of T2D leads to a longer lifetime exposure to hyperglycaemia and, consequently, a greater propensity for long-term diabetes-related complications [3]. Moreover, the accelerated deterioration of β-cell function and development of insulin resistance in early onset T2D compounds the risk for earlier development of these complications [5–9]. In addition, the impact of obesity in early onset T2D appears to be different from that in later-onset T2D in terms of higher prevalence and greater liver fat accumulation associated with obesity [10–13].

The Global Burden of Disease Study 2019 described a significant increase in the age-standardised incidence rate (per 100,000 population) of T2D in people aged 15–39 years of age across 204 countries from 117.22 in 1990 to 183.36 in 2019 [14]. However, although the prevalence of early onset T2D is increasing globally, the prevalence in the USA is unknown. Furthermore, most evidence on the propensity for and onset of long-term diabetes-related complications is derived from studies of youth-onset T2D populations; therefore, the frequency of comorbidities related to early onset disease among affected individuals is also unknown. Our objective was to characterise the US population with early onset T2D, examining the prevalence of undiagnosed and diagnosed early onset T2D and the demographics, clinical characteristics and frequency of disease-related comorbidities in these individuals.

METHODS

Data Source

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey of the US civilian, non-institutionalised population conducted by the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention [15]. Since 1999, NHANES has examined a nationally representative sample of about 5000 persons each year via interviews and physical examinations [15]. NHANES is the only US national health survey that includes health exams, laboratory tests by highly trained medical professionals and interviews about health, diet, and personal, social and economic characteristics for participants of all ages. Furthermore, NHANES uses a random, scientific process to select the people invited to participate. This process ensures that this group of people can accurately represent the health and nutritional status of everyone in the USA [15]. This study used NHANES data provided up to March 2020, including from demographic, socio-economic, dietary and health-related interview questions, as well as medical records, physiological measurements and laboratory test results. Continuous NHANES data were reported for a series of 2-year cycles from 1999 to 2016; however, data for 2017–2020 were combined in a 3.25-year cycle owing to the COVID-19 pandemic.

This was a secondary research study conducted using data from the publicly available deidentified NHANES database; therefore, neither institutional review board review nor formal participant consent to release (or publish) information was required. Ethical approval for the NHANES study was obtained from the NCHS Research Ethics Review Board (NHANES–NCHS Research Ethics Review Board Approval; https://www.cdc.gov/). No additional ethical consent was necessary for the secondary data analyses in this study. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Population

Data from the longitudinal series of NHANES cross-sectional surveys of US participants conducted between 1999 and 2020 were analysed retrospectively. Participants with early and later-onset T2D were identified, respectively, based on a diagnosis of T2D at < 40 or ≥ 40 years of age

(diagnosed T2D) or a fasting glucose ≥ 126 mg/dL or glycated haemoglobin (HbA1c) ≥ 6.5% in those aged < 40 years or ≥ 40 years without a T2D diagnosis (undiagnosed T2D). Women who self-reported pregnancy, had a positive pregnancy test or reported a diagnosis of T2D only during pregnancy were excluded.

Objectives

The primary objective of this study was to characterise the US population with early onset T2D, examining the prevalence of diagnosed and undiagnosed early onset T2D, and the demographics, clinical characteristics and frequency of comorbidities in these individuals. As an additional objective, we also compared individuals with early onset T2D with those with later-onset T2D (diagnosed and undiagnosed) with respect to prevalence, demographics, clinical characteristics and frequency of comorbidities.

Statistical Analysis

The study sample size was determined by the availability of data from NHANES between 1999 and 2020. The prevalence of diagnosed and undiagnosed early onset T2D was described during the first (1999–2000) and last (2017–2020) NHANES cycles, as well as estimated patient numbers, and analyses compared changes in prevalence over time by 10-year time intervals (with odds ratios [ORs]). Early onset T2D prevalence estimates were calculated using the SAS procedure SURVEYFREQ, based on NHANES interview sampling weights for each cycle of NHANES. Sensitivity analyses compared changes in prevalence over time by 10-year time intervals using ORs adjusted for age, gender and race/ethnicity using the SAS procedure SURVEYLOGISTIC (logistic regression). Equivalent additional analyses were undertaken to evaluate the prevalence of diagnosed and undiagnosed later-onset T2D.

The characteristics of participants with diagnosed and undiagnosed early onset T2D (including demographics, clinical characteristics and frequency of comorbidities) were calculated using the SAS procedures SURVEYFREQ for categorical variables and SURVEYMEANS (often referred to as survey means analysis) for continuous variables. Additional across-group comparison analyses assessed the overall differences in the characteristics of participants with early versus later-onset T2D (diagnosed and undiagnosed). For categorical variables with more than two subcategories (e.g. race/ethnicity), pairwise comparisons assessed the differences between participants with early versus later-onset T2D by individual subcategory. All additional analyses were conducted using Wald chi-squared tests. Significance level for statistical tests was set at a two-sided α level of 0.05.

Sensitivity analyses adjusted for T2D duration and stratified participants with diagnosed early and later-onset T2D by years since T2D diagnosis. Post-stratification weighting provided the same distribution of T2D duration in the diagnosed early and later-onset groups for comparison. All analyses used the strata, clusters and weighting of the complex survey design of NHANES so that the analyses were generalised to the non-institutionalised population of the USA. Descriptive summary statistics were reported as mean (standard error [SE]) for continuous variables and weighted percentage (excluding number missing in denominator) for categorical variables. To maintain privacy, cell suppression was used to conceal data when data were available for fewer than 11 participants.

Missing data were handled according to the NHANES: Analytic Guidelines [16]. If ≤ 10% of data for a variable were missing from the analytic dataset, the analysis was continued without further evaluation or adjustment. If > 10% of the data for a variable were missing, it was determined whether the missing values were distributed equally across sociodemographic characteristics, and missing values were further imputed or adjusted weights were used, as necessary. No multiplicity adjustments were made for additional analyses. All statistical analyses were performed using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Role of the Funding Source

The funder of the study, Eli Lilly and Company, had a role in the study design, data collection, data analysis, data interpretation and writing of the report.

RESULTS

The NHANES data set provided information on 6665 participants diagnosed with T2D and 1942 participants with undiagnosed T2D between 1999 and 2020.

Prevalence of Early Onset T2D

The prevalence of diagnosed early onset T2D in the USA increased from 1.42% (SE 0.19) during the 2-year 1999–2000 survey cycle to 1.72% (SE 0.24) during the 3.25-year 2017–2020 cycle (Fig. 1); however, the prevalence between the two 10-year periods remained stable (OR 1.130, $p=0.1229$, not significant). The corresponding estimated number of people with diagnosed early onset T2D increased from 3.869 million in 1999–2000 to 5.560 million in the 2017–2020 cycle.

The prevalence of undiagnosed early onset T2D in the USA increased from 0.18% (SE 0.09) during the 1999–2000 survey cycle to 0.35% (SE 0.06) during the 2017–2020 cycle (Fig. 1); additionally, the prevalence increased significantly by 46% per 10-year time-period between 1999 and 2020 (OR 1.461, $p=0.0136$). This increase remained significant when adjusted for age, gender and race/ethnicity in a sensitivity analysis (adjusted OR 1.391, $p=0.0324$). The corresponding estimated number of people with undiagnosed early onset T2D increased from 0.493 million in 1999–2000 to 1.112 million in 2017–2020.

Prevalence of Later-Onset T2D

The prevalence of diagnosed later-onset T2D increased from 2.87% (SE 0.25) in 1999–2000 to 6.60% (SE 0.34) in 2017–2020 and increased significantly by 56% per 10-year time-period between 1999 and 2020 (OR 1.557, $p<0.0001$). This increase remained significant when adjusted for age, gender and race/ethnicity (adjusted OR 1.385, $p<0.0001$). The corresponding estimated number of people with diagnosed later-onset T2D increased from 7.822 million in 1999–2000 to 21.284 million in 2017–2020.

The prevalence of undiagnosed later-onset T2D increased from 1.18% (SE 0.13) in 1999–2000 to 1.73% (SE 0.14) in 2017–2020, and increased significantly by 21% per 10-year time-period between 1999 and 2020 (OR 1.208, $p=0.0005$). When adjusted for age, gender and

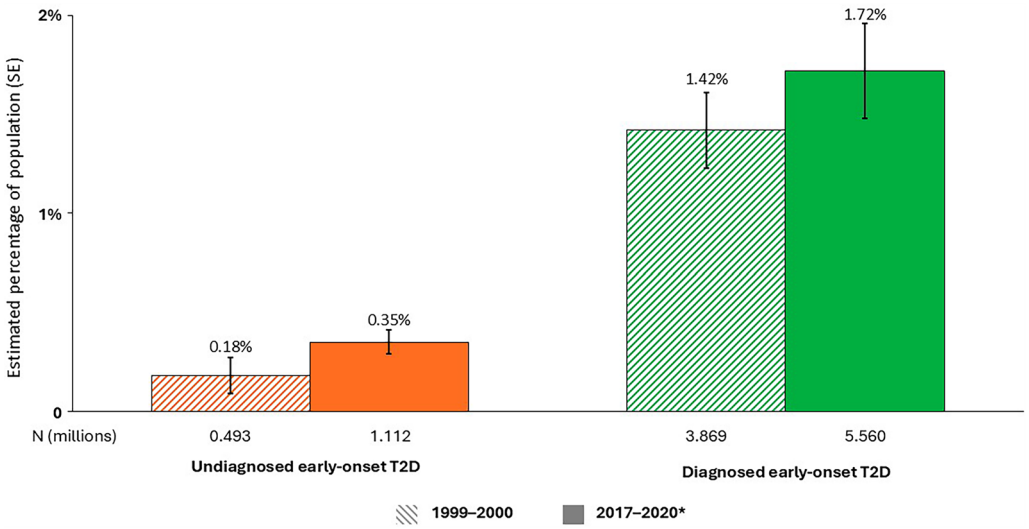

Fig. 1 Prevalence of early onset T2D in the US NHANES population (1999–2020). *NHANES data were reported for 2-year cycles from 1999 to 2016; however, data for 2017–2020 were combined owing to the COVID-19 pandemic. *NHANES* National Health and Nutrition Examination Survey, *SE* standard error, *T2D* type 2 diabetes

race/ethnicity, this increase was not significant (OR 1.055, $p=0.3054$). The corresponding estimated number of people with undiagnosed later-onset T2D increased from 3.215 million in 1999–2000 to 5.579 million in 2017–2020.

Demographics

Age, race/ethnicity, health insurance type and poverty–income ratio significantly differed between participants with early and later-onset T2D (diagnosed or undiagnosed) (Table 1). Participants with early onset T2D were on average poorer (i.e. had a lower poverty–income ratio; both $p<0.0001$), more likely to be Hispanic (both $p<0.0001$), and less likely to be non-Hispanic white (both $p<0.0001$) than those with later-onset disease (Table 1 and Supplementary Table S1). Participants with diagnosed early onset T2D were more likely to be non-Hispanic Black ($p=0.0002$; undiagnosed not significant),

Table 1 Demographic characteristics of participants with diagnosed and undiagnosed early- and later-onset T2D

Characteristic	Diagnosed T2D			Undiagnosed T2D		
	Early onset ($n=1408$)	Later onset ($n=5257$)	*p*-value	Early onset ($n=267$)	Later onset ($n=1675$)	*p*-value
Age at diagnosis, mean (SE)	28.8 (0.3)	54.9 (0.2)	< 0.0001	N/A	N/A	N/A
Current age (years), mean (SE)	47.8 (0.5)	64.1 (0.2)	< 0.0001	32.8 (0.5)	60.5 (0.4)	< 0.0001
Gender, %			0.0067			0.1792
Male	46.1	51.5		61.5	55.3	
Female	53.9	48.5		38.5	44.7	
Race/ethnicity, %			< 0.0001			< 0.0001
Non-Hispanic white	49.3	63.7		37.2	61.7	
Non-Hispanic Black	18.9	14.9		18.0	14.0	
Hispanic	23.2	12.9		30.9	16.2	
Non-Hispanic other	8.5	8.6		13.8	8.1	
Health insurance, %			< 0.0001			< 0.0001
No insurance	20.8	8.9		45.5	16.8	
Private	51.9	57.9		40.1	58.1	
Medicare	9.1	19.4		1.5	14.9	
Other public	18.1	13.8		12.9	10.2	
Poverty–income ratio, mean (SE)	2.3 (0.1)	2.7 (0.0)	< 0.0001	2.1 (0.1)	2.8 (0.1)	< 0.0001
Education, %			0.1473			0.3597
< High school	29.6	26.0		30.0	26.2	
High school diploma	25.3	26.1		28.4	25.9	
Some college or higher	45.0	47.9		41.7	47.9	
Current smoker (yes), %	21.1	15.0	< 0.0001	30.4	17.6	0.0004

N/A not applicable, *SE* standard error, *T2D* type 2 diabetes

and participants with undiagnosed T2D were more likely to be non-Hispanic other ($p=0.0167$; diagnosed not significant) than those with diagnosed or undiagnosed later-onset T2D, respectively (Supplementary Table S1).

Participants with early onset T2D were more likely to have no health insurance (both $p<0.0001$) and less likely to have private (diagnosed $p=0.0061$; undiagnosed $p=0.0003$) or Medicare (both $p<0.0001$) insurance than those with later-onset disease (Supplementary Table S1). Participants with diagnosed early onset T2D were more likely to have other public insurance (diagnosed $p=0.0035$; undiagnosed not significant) than those with diagnosed later-onset T2D (Supplementary Table S1).

All significant comparisons remained statistically significant after adjustment for duration of T2D among participants with diagnosed T2D (Supplementary Table S2 and Supplementary Table S3).

There were no significant differences in level of education between participants with early onset T2D (diagnosed or undiagnosed) and corresponding participants with later-onset T2D (Table 1 and Supplementary Table 2). Participants with diagnosed early onset T2D were more likely to be female than those with diagnosed later-onset disease ($p=0.0067$) (Table 1), although this result was not statistically significant after adjustment for duration of T2D (Supplementary Table S2).

Clinical Characteristics

Participants with early onset T2D (diagnosed or undiagnosed) had higher mean HbA1c, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score, fasting insulin and glucose, body mass index (BMI) and waist circumference than corresponding participants with later-onset T2D and were more likely to have a family history of T2D (all $p<0.05$) (Table 2). Furthermore, according to BMI category, participants with early onset T2D were more likely to have obesity (defined as BMI ≥ 30 kg/m^2) than those with later-onset disease (diagnosed $p<0.0001$; undiagnosed $p=0.0008$).

Participants with diagnosed early onset T2D were more likely to be receiving no medication or insulin only (both $p<0.0001$), and less likely to be receiving an oral antidiabetic drug only ($p<0.0001$), than those with diagnosed later-onset T2D (Supplementary Table S1). Mean systolic blood pressure was lower, but mean diastolic blood pressure was higher, in participants with early onset T2D (diagnosed or undiagnosed) than in corresponding participants with later-onset T2D (all $p<0.05$) (Table 2). The proportion of participants receiving statins was lower (35.1% versus 54.5%, respectively; $p<0.0001$) and mean non-high-density lipoprotein cholesterol (non-HDL-c) was higher ($p<0.0001$) in participants with diagnosed early onset T2D than those with diagnosed later-onset disease. Mean alanine transaminase (ALT) was higher in participants with early onset T2D (diagnosed or undiagnosed; both $p<0.05$), but mean aspartate transaminase was only higher in participants with undiagnosed early onset disease than in corresponding participants with later-onset disease ($p=0.00365$).

All comparisons in participants with diagnosed T2D remained statistically significant after adjustment for duration of T2D, except fasting insulin in participants with diagnosed early versus later-onset T2D (Supplementary Table S3 and Supplementary Table S4).

Frequency of Comorbidities

Overall, there were no significant differences in general health (rated excellent to poor) between participants with early versus later-onset T2D (diagnosed or undiagnosed) (Table 3). Participants with diagnosed early onset T2D were more likely to have asthma than those with diagnosed later-onset disease ($p=0.0110$); however, participants with early onset T2D (diagnosed or undiagnosed) were less likely to have congestive heart failure (CHF), coronary heart disease (CHD), stroke, chronic kidney disease (CKD) or cancer than corresponding participants with later-onset T2D (all $p<0.05$). All significant comparisons remained statistically significant after

Table 2 Clinical characteristics of participants with diagnosed and undiagnosed early- and later-onset T2D

Characteristic	Diagnosed T2D			Undiagnosed T2D		
	Early onset (*n* = 1408)	Later onset (*n* = 5257)	*p*-value	Early onset (*n* = 267)	Later onset (*n* = 1675)	*p*-value
Family history of diabetes, %	81.5	68.8	< 0.0001	64.8	49.5	0.0013
Duration of diabetes, mean (SE)	19.0	9.3	< 0.0001	N/A	N/A	N/A
Type of anti-hyperglycaemic medication, %			< 0.0001			N/A[a]
No medication	21.5	14.2		95.0	79.8	
Insulin only	22.5	13.8		0.0	2.0	
OAD only	40.4	58.9		5.0	17.9	
Insulin + OAD	15.6	13.1		0.0	0.2	
HbA1c (%), mean (SE)	7.74 (0.08)	7.20 (0.03)	< 0.0001	7.34 (0.16)	6.96 (0.05)	0.02979
HOMA-IR, mean (SE)	16.2 (2.7)	9.6 (0.6)	0.01743	15.1 (2.6)	6.7 (0.4)	0.00172
Fasting insulin, mean (SE)	35.2 (5.5)	23.5 (1.4)	0.03656	38.9 (6.6)	18.8 (0.9)	0.00377
Fasting glucose, mean (SE)	184.6 (7.0)	157.1 (2.8)	0.00072	168.1 (11.3)	143.9 (2.5)	0.03992
BMI (kg/m^2), mean (SE)	34.9 (0.3)	32.3 (0.2)	< 0.0001	36.3 (0.7)	32.6 (0.3)	< 0.0001
BMI ≥ 30 kg/m^2, %	71.4	58.5	< 0.0001	74.4	60.3	0.0008
Waist circumference (cm), mean (SE)	113.2 (0.7)	110.1 (0.4)	0.00015	114.8 (1.6)	110.1 (0.6)	0.00774
SBP (mmHg), mean (SE)	127.7 (0.7)	131.5 (0.4)	< 0.0001	121.9 (1.1)	133.2 (0.7)	< 0.0001
DBP (mmHg), mean (SE)	73.2 (0.5)	68.3 (0.3)	< 0.0001	75.2 (1.0)	72.9 (0.5)	0.0387
Non-HDL-c (mg/dL), mean (SE)	149.3 (1.9)	135.1 (1.1)	< 0.0001	156.5 (3.7)	156.0 (1.7)	0.90404
Receiving a statin, %	35.1	54.5	< 0.0001	1.9	28.5	< 0.0001
ALT, mean (SE)	29.6 (1.5)	25.7 (0.4)	0.0094	46.2 (3.5)	30.8 (0.8)	< 0.0001
AST, mean (SE)	26.3 (1.0)	25.6 (0.3)	0.46807	34.7 (2.2)	28.0 (0.5)	0.00365

ALT alanine transaminase, *AST* aspartate transaminase, *BMI* body mass index, *DBP* diastolic blood pressure, *HbA1c* glycated haemoglobin, *non-HDL-c* non-high-density lipoprotein cholesterol, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *N/A* not applicable, *OAD* oral antidiabetic drug, *SBP* systolic blood pressure, *SE* standard error, *T2D* type 2 diabetes

[a]At least one characteristic category has a value of 0%; therefore, the *p*-value cannot be computed for this comparison, as the SE cannot be computed, and chi-squared is undefined in the SAS procedure SURVEYFREQ

adjustment for duration of T2D among participants with diagnosed T2D (Supplementary Table S5).

DISCUSSION

We have characterised the US population with diagnosed and undiagnosed early onset T2D (< 40 years of age at diagnosis), examining the

Table 3 Comorbidities of participants with diagnosed and undiagnosed early- and later-onset T2D

Comorbidity	Diagnosed T2D			Undiagnosed T2D		
	Early onset (*n* = 1408)	Later onset (*n* = 5257)	*p*-value	Early onset (*n* = 267)	Later onset (*n* = 1675)	*p*-value
Asthma, %	19.6	15.6	0.0110	17.5	12.8	0.1621
CHF, %	7.9	11.0	0.0101	0.9	5.5	0.0071
CHD, %	8.3	14.0	0.0001	0.5	7.1	0.0002
COPD, %	13.0	15.3	0.1535	5.7	9.7	0.1374
Stroke, %	6.8	10.3	0.0024	1.0	5.7	0.0056
CKD, %	18.3	27.6	< 0.0001	10.0	17.7	0.011
Dialysis, %	8.4	7.5	0.6541	0.0	0.0	N/A[a]
Cancer, %	7.9	19.1	< 0.0001	3.6	13.8	0.0098
General health, %			0.0569			0.5619
Excellent	2.2	2.4		6.0	6.2	
Very good	11.7	16.0		19.2	22.4	
Good	39.4	40.4		49.1	40.9	
Fair	35.7	31.7		22.5	25.4	
Poor	11.0	9.5		3.2	5.1	

CHD coronary heart disease, *CHF* congestive heart failure, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disorder, *N/A* not applicable, *SE* standard error, *T2D* type 2 diabetes

[a]At least one comorbidity category has a value of 0%; therefore, the *p*-value cannot be computed for this comparison, as the SE cannot be computed, and chi-squared is undefined in the SAS procedure SURVEYFREQ

prevalence, demographics, clinical characteristics and frequency of comorbidities in these individuals and comparing these details with those of the US population with diagnosed and undiagnosed later-onset disease using NHANES data from 1999 to 2020. These data indicate that undiagnosed early onset T2D has increased in prevalence over time in the USA, suggesting more attention is needed to screen and diagnose younger adults with T2D. Overall, individuals with early onset T2D (both diagnosed and undiagnosed) generally had a worse cardiometabolic profile including higher central obesity, diastolic blood pressure and ALT than those with later-onset T2D, which may increase the risk of future cardiovascular disease [17]. Furthermore, the NHANES data show that individuals diagnosed with early onset T2D were more likely to be untreated, or treated with insulin only, than people with later-onset disease, despite having higher HbA1c, suggesting that more attention is also needed to ensure that people diagnosed with early onset T2D receive the appropriate treatment.

With respect to demographics, we found that individuals with early onset T2D (at < 40 years of age) had a lower mean poverty–income ratio, were less likely to be non-Hispanic white and were more likely to be Hispanic than those with later-onset T2D. These results are broadly aligned with those of another recent NHANES analysis [18], a National Health Interview Survey analysis [19], and prior published literature [20]. For example, McGavock et al. [20] reported that 32–59% of young people with T2D across six cohort studies were living in socioeconomically

disadvantaged households. Another analysis of NHANES data for the period from 2001 to 2018 showed that the prevalence of early onset T2D (diagnosed at < 50.5 years of age) was higher among non-Hispanic Black and Hispanic people than among non-Hispanic white people [18]. In fact, both non-Hispanic Black ethnicity and Hispanic ethnicity were highly predictive of early onset T2D. In the current study, proportions of participants with undiagnosed and diagnosed early onset T2D who were Hispanic or non-Hispanic Black were higher than the respective proportions of participants with later-onset disease. Furthermore, a recent analysis of National Health Interview Survey data between 2016 and 2022 found that minority groups and socially disadvantaged individuals had a higher incidence of diagnosed young-adult-onset T2D (diagnosed at 18–44 years of age) compared with their counterparts [19]. Combined, these data highlight that young adults who are Hispanic or non-Hispanic Black, and those from underserved backgrounds, may be relatively at high risk of developing T2D, and support the need for further studies to better understand the biological and/or environmental causes of incident T2D in these populations.

Notably, individuals with early onset T2D (both diagnosed and undiagnosed) included in our analysis generally had a worse cardiometabolic profile than those with later-onset T2D and were more likely to have central obesity despite their younger age. Participants with early onset T2D had higher mean HbA1c, HOMA-IR, fasting insulin and glucose, BMI and waist circumference than participants with later-onset disease. These findings remained consistent after adjusting for duration of diagnosed disease. Furthermore, non-HDL-c was higher in participants with diagnosed early onset T2D than in those with diagnosed later-onset disease, and statins were underused among those with early onset disease. Interestingly, diastolic blood pressure was higher in early onset versus later-onset T2D, although the clinical relevance of this finding remains to be understood. However, systolic blood pressure was lower in early versus later-onset disease, regardless of whether individuals were diagnosed or undiagnosed, a result likely driven by the biologically younger age of the early onset T2D group.

These results are consistent with a study by Wang et al. [21] that compared clinical characteristics between people with early and later-onset T2D and found that people with early onset had worse glycaemic status than those with later-onset during the T2D course, and glycaemic status was worse at the onset of T2D. In Wang et al.'s study [21], renal function measurements (estimated glomerular filtration rate, serum creatine and microalbumin creatinine ratio) were better among people with early onset in the course of T2D, while blood lipid measurements (low-density lipoprotein cholesterol, triglycerides and total cholesterol) were worse among people with early versus later-onset T2D. Similarly, a post hoc analysis of the SURPASS-1 to -3 clinical trials of tirzepatide showed that participants with early onset T2D (< 40 years of age) had worse glycaemic control, higher mean body weight and BMI and a similarly unfavourable lipid profile (i.e. elevated triglycerides and low HDL-cholesterol) at baseline versus participants with later-onset T2D [22].

In addition, research has shown that young people with T2D can have up to threefold higher amounts of liver fat compared with BMI-matched individuals without T2D and compared with people who developed T2D in mid or later life [13]. Similarly, we observed higher ALT liver enzymes in adults with early versus later-onset T2D in this study, regardless of whether individuals were diagnosed (16% higher) or undiagnosed (50% higher), though we did not have liver imaging data to correlate with this finding [23]. It is recognised that obesity, insulin resistance and metabolic dysfunction-associated steatotic liver disease tend to co-exist in the paediatric population [24]. Therefore, the rising prevalence of metabolic dysfunction-associated steatotic liver disease is of clinical concern because it is associated with cardiovascular, metabolic and renal comorbidities both in adults and in children [25–27].

Given the biologically younger mean ages of participants with early versus later-onset T2D, it is perhaps unsurprising that individuals with early onset T2D (diagnosed and undiagnosed) were less likely to have relevant comorbidities,

such as CHF, CHD, stroke, CKD or cancer in this analysis. Similarly, Wang et al. [21] found that the proportion of patients with cardiovascular disease, CKD, hypertension and hyperlipidaemia was higher in people with later-onset T2D than in those with early onset during the entire course of T2D. However, given that individuals with early onset T2D appear to have a worse cardiometabolic profile and will generally live with T2D for longer than individuals with later-onset disease, it might be expected that individuals with early onset T2D will develop relevant comorbidities at a younger age and be more likely to develop these comorbidities during their lifetimes. In fact, over a median follow-up period of 5.63 years in a retrospective analysis of the Swedish National Diabetes Registry, patients with T2D diagnosed at ≤ 40 years of age had the highest excess risk for most adverse outcomes relative to controls from the general population, with adjusted hazard ratios (95% confidence intervals [CIs]) of 2.05 (95% CI: 1.81–2.33) for total mortality, 2.72 (95% CI: 2.13–3.48) for cardiovascular-related mortality, 1.95 (95% CI: 1.68–2.25) for non-cardiovascular mortality, 4.77 (95% CI: 3.86–5.89) for heart failure and 4.33 (95% CI: 3.82–4.91) for CHD [28]. Similarly, another study concluded that early onset T2D was associated with a higher risk of cardiovascular and all-cause mortality compared with later-onset T2D based on weighted multivariate Cox regression analyses of data from NHANES 1999–2018 [29]. The discrepancies between these findings and those of the current study are likely a result of varying data types (e.g. longitudinal versus non-longitudinal data) or the application of different additional statistical estimation methodologies.

Furthermore, a retrospective cohort study compared age- and sex-matched people with T2D onset at 18 to < 40, 40 to < 60 and 60–90 years of age in the Taiwan National Health and Insurance Research Database from 2000 to 2012 [30]. That study found that people with T2D onset before 40 years and between 40 and 60 years of age were associated with excess risks of death, macrovascular and microvascular complications and leg amputation compared with people with disease onset after 60 years of age. However, Huang et al. [31] determined, via a propensity score-matched cohort analysis, that individuals with onset of diabetes at age ≤ 40 years had a higher risk of microvascular complications, but not macrovascular complications, compared with those with later-onset disease. These studies support the need for further research of long-term outcomes in individuals with early onset T2D.

Collectively, data on early onset T2D have clinically important implications for clinical decision-making and guideline-directed care given the evidence that age at T2D diagnosis may be prognostically important for survival and cardiovascular risks [27]. Furthermore, the increasing prevalence of early onset disease predicts larger populations of adults with early onset T2D worldwide in the future, particularly among certain ethnicities. However, aspects of early onset T2D remain incompletely understood, and further research on better identification of early onset T2D, related complications, long-term outcomes and, ultimately, measures to prevent early onset T2D is needed.

Strengths and Limitations

NHANES provides a large representative sample of the non-institutionalised US population, and the data included in this study spanned multiple 2-year cycles of continuous NHANES, combined to increase the robustness of our estimates. Furthermore, the inclusion of data on individuals with undiagnosed T2D, in addition to those with a T2D diagnosis, allowed for a more comprehensive understanding of the epidemic burden of T2D in the USA.

However, NHANES provides cross-sectional data and includes non-institutionalised civilians who participated in the survey. Furthermore, this study is limited by self-reported data, with potential for recall bias, given that the data for each cycle were collected over a 2- or 3-year period. It should also be noted that cause–effect inferences cannot be made on the basis of a cross-sectional survey; for example, risk factors related to the incidence of comorbidities could be evaluated.

CONCLUSIONS

Our findings indicate that the prevalence of undiagnosed early onset T2D has increased over time in the USA. Early onset T2D disproportionately affects certain ethnicities, such as Hispanic people and non-Hispanic Black people, as well as underserved populations. Individuals with early onset T2D generally have a worse cardiometabolic profile than those with later-onset disease, including higher HbA1c, BMI, waist circumference, non-HDL-c and ALT, even after adjustment for duration of diabetes, suggesting that early onset T2D may be a more aggressive disease with higher cardiometabolic risk that should be better diagnosed and treated.

Further research is needed to explore the potential link between the cardiometabolic profile of people with early onset T2D, the risk of complications and longer term cardiovascular outcomes.

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Data Availability. The datasets generated during and/or analysed during the current study are available in the NHANES repository, NHANES Questionnaires, Datasets, and Related Documentation (cdc.gov).

Declarations

Conflict of Interest. Clare J. Lee, Brandon K. Bergman, Ray Gou and Kristina S. Boye are full-time employees and minor stockholders of Eli Lilly and Company. Suzanne Williamson works as a consultant for Eli Lilly and Company.

Ethical Approval. This was a secondary research study conducted using data from the publicly available deidentified NHANES database; therefore, neither institutional review board review nor formal participant consent to release (or publish) information was required. Ethical approval for the NHANES study was obtained from the NCHS Research Ethics Review Board (NHANES–NCHS Research Ethics Review Board Approval; https://www.cdc.gov/). No additional ethical consent was necessary for the secondary data analyses in this study. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

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