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## Associations of age at T2D detection with hemoglobin A1c in a national inception cohort of U.S. Veterans with diabetes

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### Abstract

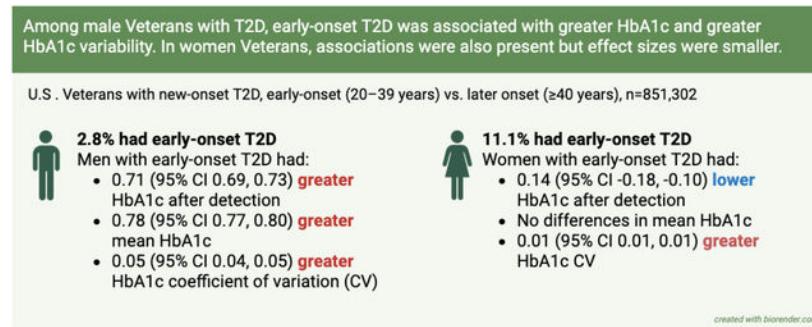
**Objective:** To investigate associations of age at type 2 diabetes (T2D) detection with HbA1c.

**Research Design and Methods:** We examined associations of early-onset T2D (age of detection 20–39 years) and age at T2D detection with HbA1c in Veterans with incident T2D (1/1/2008–12/31/2016; n=851,302).

**Results:** About 3% (n=22,649) of men and 11% (n=5,117) of women had early-onset T2D. Among men, compared to later-onset T2D, men with early-onset T2D had a 0.71 (95%CI 0.69,0.73) greater HbA1c after detection, a 0.78 (95%CI 0.77,0.80) greater mean HbA1c, and a 0.05 (95%CI 0.04,0.05) greater coefficient of variation (CV). Each 10-year decrease in age was associated with greater HbA1c after detection, mean HbA1c, and HbA1c CV ( $\beta$  0.21 (95%CI 0.21,0.21), 0.25 (95%CI 0.24,0.25), 0.02 (95%CI 0.02,0.02), respectively). In women, early-onset T2D was associated with a 0.14 (95%CI -0.18,-0.10) lower HbA1c after detection and a 0.01 greater CV (95%CI 0.01,0.01). Each ten-year decrease in age was associated with greater mean HbA1c and CV ( $\beta$  0.09 (95%CI 0.08,0.10); 0.01 (95%CI 0.01,0.01), respectively).

**Conclusion:** Among male Veterans, early-onset T2D was associated with greater HbA1c and greater HbA1c variability. Similar results were seen among women but of lesser magnitude. Longitudinal research examining sex-specific impacts of early-onset T2D on clinical course is needed.

### Graphical Abstract



## INTRODUCTION

In adolescents (ages 10–19 years) with T2D, loss of  $\beta$ -cell function and glycemic control occur early in the course of disease (1), and aggressive treatment does not delay progression (2). On the other hand, in older adults (ages  $\geq 40$  years), progression of  $\beta$ -cell loss can be delayed with treatment (3; 4). Early-onset adult type 2 diabetes (T2D that is diagnosed between ages 20 and 39 years) is increasingly prevalent (5) and is associated with poor long-term outcomes, including high rates of microvascular complications, macrovascular complications, and comorbid psychiatric disease (6). However, information about glycemic control early in the course of disease is lacking for populations with early-onset adult T2D. We hypothesized that early-onset adult T2D would be associated with measures of adverse glycemic control including greater HbA1c and greater HbA1c variability. Further, because adverse consequences of T2D are generally greater in women compared to men over time (7–9), we evaluated whether associations of early-onset T2D with HbA1c outcomes were different in women compared to men. We hypothesized that adverse patterns of HbA1c and HbA1c variability would be greater in women with early-onset T2D compared to their later onset counterparts—more so than the difference seen in men—because of hormonal differences, differences in body composition, or because women with might face delayed diagnosis and undertreatment due to gender-based disparities in care. Findings may impact recommendations for glucose monitoring and treatment in the future.

## METHODS

### Study setting and study population

Data used for this study came from the US Veterans Affairs Diabetes Risk (VADR) cohort, a population of Veterans free from T2D at entry to the cohort (10). The VADR is a national cohort of U.S. Veterans enrolled in the VA for primary care. Data were assembled by the New York University Grossman School of Medicine and George Mason University using data from the Corporate Data Warehouse (CDW), a data repository derived from the Veterans Health Administration (VHA) electronic medical record, from the largest integrated health care system in the United States (11). Veterans were passively enrolled into VADR if they did not have T2D as of January 1, 2008, and had at least two primary care visits at least 30 days apart within any five-year interval between January 1, 2008, and December 31, 2016. Individuals were included in the study if they did not meet any of the three following criteria for prevalent T2D before entering the cohort: 1)

2 inpatient or outpatient encounters with *International Classification of Diseases, Ninth and Tenth Revision Clinical Modification (ICD-9-CM or ICD-10-CM) codes of 250 or E08–E13, respectively*; 2) a prescription for any glucose-lowering medication other than metformin or acarbose alone; or 3) one inpatient or outpatient encounter with *ICD-9-CM or ICD-10-CM codes of 250 or E08–E13* and two instances of HbA1c  $\geq 6.5\%$ . Using these criteria, 6,082,018 Veterans were enrolled in the VADR cohort. They were then followed for the development of T2D, which was defined using the same criteria as were used to exclude prevalent diabetes cases. For this analysis, Veterans entered the cohort at the time that incident T2D was detected and were followed until they died, had an interval of  $\geq 2$  years during which they did not have any clinical encounters with the Veterans Health Administration (lost to follow-up), or the end of study follow-up (December 31, 2018). There was a median (IQR) duration of follow-up of 5.5 (2.6–9.8) person-years. The study was approved by the institutional review boards at VA Harbor Healthcare and VA Puget Sound, and the requirement for informed consent was waived for this records review study.

### Study variables

Data were collected from the VHA electronic health record. For the sex at birth variable, participants are referred to as men (male) or women (female), based on historic data practices. BMI was defined as weight in kg divided by height in meters<sup>2</sup>. For weight, height, BMI, and HbA1c, we removed biologically implausible values (weight  $< 75$  pounds or  $> 600$  pounds, height  $< 49$  inches or  $> 94$  inches, body mass index  $> 80$  kg/m<sup>2</sup> (12), and HbA1c  $> 30\%$ ). To allow comparisons with existing literature (5; 6; 13), we defined early-onset T2D as diabetes detected between age 20 and 39 years. Outcomes were HbA1c at diabetes detection, defined as the first HbA1c after criteria for T2D were met; mean HbA1c during the cohort follow-up period, defined as the average of all HbA1c values after T2D was identified; and HbA1c coefficient of variation (CV), defined as (standard deviation of mean HbA1c/mean HbA1c) \* 100 as a measure of dispersion.

### Statistical analyses

We examined distributions of covariates according to exposure status (early-onset vs. later-onset T2D and decade of age at detection) and sex at birth. We fit linear regression models assessing associations of early-onset as a binary variable or continuously measured age at detection with first HbA1c after diabetes detection, mean HbA1c after diabetes detection, and HbA1c CV after diabetes detection. We tested for the presence of significant multiplicative first-order interaction terms of sex with age at onset in models that included exposure, outcome, and adjustment variables (race, ethnicity, and BMI) along with the interaction term. We fit models stratified by sex. We conducted a sensitivity analysis restricted to individuals with  $< 30$  days between T2D detection and first HbA1c after detection and an analysis additionally adjusting for rural/urban residence and current tobacco use. We assessed for nonlinear relationships between age at T2D detection and HbA1c outcomes by fitting multivariable generalized additive models (GAM; Gaussian family, identity link function). GAM are a flexible modeling option for looking at nonlinear relationships when one is interested in characterizing and interpreting these relationships (14). The GAM models included smoothing terms for age and BMI. All analyses were

conducted in R statistical software version 4.1.2 (15). For all analyses, a two-sided p-value <0.05 was considered significant.

## RESULTS

There were 851,302 individuals with incident T2D identified in the follow-up period of the VADR cohort. Participants who developed diabetes were  $63.7 \pm 11.9$  years old at diabetes detection. About 3% (n=27,766) had early-onset T2D. Compared with late-onset T2D, individuals with early-onset T2D were more likely to report female sex at birth, Black race, and Latinx ethnicity. BMI, mean HbA1c, HbA1c at diabetes detection, and HbA1c CV were all greater among individuals with early-onset T2D compared to later-onset T2D (Table 1). Men who developed diabetes were  $64.2 \pm 11.7$  years old at detection. 2.8% (n=22,649) had early-onset T2D. Women who developed diabetes were  $54.3 \pm 11.4$  years old at detection, and 11.1% (n=5,117) had early-onset T2D (Table 2). The median length of time between the date of diabetes onset and date of first HbA1c after detection was 80 days (0–4878, IQR 201).

Overall, early-onset T2D was associated with greater first HbA1c after detection, mean HbA1c, and HbA1c CV compared to later-onset (0.57 [95% CI 0.55, 0.58], 0.65 [95% CI 0.64, 0.66], 0.04 [95% CI 0.04, 0.04], respectively) (Table 3, Model 1). Each 10-year decrease in age was associated with a 0.20 greater first HbA1c after detection (95% CI 0.20, 0.20), a 0.24 greater mean HbA1c (95% CI 0.23, 0.24), and a 0.02 greater HbA1c CV (95% CI 0.02, 0.02) (Table 3, Model 2). In models testing for first-order interactions, all p-values for early-onset\*sex and age at onset\*sex interaction terms were significant at <0.001. In sex-stratified models, men with early-onset T2D had an adjusted 0.71 (95%CI 0.69, 0.73) greater first HbA1c after detection (raw values 7.6% vs. 6.7%); a 0.78 (95%CI 0.77, 0.80) greater mean HbA1c (raw values 7.6% vs. 6.7%), and a 0.05 (95%CI 0.04, 0.05) greater HbA1c CV (raw values 0.14 vs. 0.09), compared to men with later-onset T2D. Each 10-year decrease in age in men was associated with a 0.21 greater first HbA1c after detection (95% CI 0.21, 0.21), a 0.25 greater mean HbA1c (95% CI 0.24, 0.25), and a 0.02 greater HbA1c CV (95% CI 0.02, 0.02) (Table 3). In the analysis restricted to individuals with <30 days between T2D detection and first HbA1c after T2D detection, men with early-onset T2D had an adjusted 0.94 (95% CI 0.90, 0.97) and women with early-onset T2D had an adjusted 0.15 (95% CI 0.07, 0.24) greater first HbA1c after detection. Each 10-year decrease in age in men was associated with a 0.28 greater first HbA1c after detection (95% CI 0.28, 0.29) and in women a 0.11 greater first HbA1c after detection (95% CI 0.08, 0.13) (Supplementary Table 1). In an analysis additionally adjusting for rural/urban residence and current tobacco use, results were in general similar (Supplementary Table 2).

Results from the GAM models in men also demonstrated an inverse association of age at T2D detection with HbA1c outcomes. Inverse linear relationships were apparent between approximately age 40 and 70 years but not before or after (p for smoothing terms < 0.001) (Fig. 1). Women with early-onset T2D had an adjusted -0.14% (95%CI -0.18, -0.10) lower first HbA1c after detection (raw values 6.6% vs. 6.7%) and a greater HbA1c CV ( $\beta$  0.01 (95%CI 0.01, 0.01), respectively). Ten-year decreases in age were associated with greater mean HbA1c ( $\beta$  0.09 ( $\beta$  95%CI 0.08, 0.10) and HbA1c CV ( $\beta$  0.01 (95%CI 0.01, 0.01),

respectively but not with first HbA1c after T2D detection. An inverse linear relationship was present between age 50 and 70 years with a shallower slope than among men.

## DISCUSSION

In a large national inception cohort of Veterans with T2D, average age at T2D detection was younger in women than in men, and T2D with onset between 20 and 39 years of age occurred more frequently in women. Among male Veterans with T2D, early-onset T2D was associated with greater HbA1c and greater HbA1c variability. In women, associations were of lesser magnitude. In men, an inverse linear relationship was apparent between approximately age 40 and 70 years but not before or after. In women, we observed an inverse linear relationship between age 50 and 70 years with a shallower slope than among men. To our knowledge, this study is the largest to compare HbA1c among adults with early-onset vs. later-onset T2D, the first to evaluate interactions of sex with age at detection on HbA1c outcomes, and the first to compare profiles of HbA1c variability. Whether the worse HbA1c profile we found in men with early-onset T2D contributes to sex differences in long-term outcomes such as total and CVD mortality is unknown.

The current findings are consistent with, and expand on, previous research in this area. In a nested case-comparison analysis of data from the Coronary Artery Risk Development in Young Adults Study (n=605), fasting glucose at time of diabetes detection was 162 mg/dL (SD 56) in early-onset participants (<40 years) compared to 143 mg/dL (SD 51) in the later-onset group (13) (unadjusted p-value 0.0006). In a cross-sectional analysis using data from the National Health and Nutrition Examination Survey, individuals <65 years old at diagnosis were more likely to have HbA1c >9% compared to those ≥65 years independent of sex, race/ethnicity, socio-economic factors, diabetes duration, family history, and body composition (16) (OR 3.2, 95%CI 1.5–6.7).

Studies in adults and youth with T2D suggest age at diabetes detection may affect insulin secretion and sensitivity. Data by age at detection in adult cohorts are limited. In youth compared to adults, measures of glucose and insulin differ by age independent of diabetes duration (17; 18). Modeling of OGTT data from youth in the Treatment Options for Diabetes in Youth Study suggest that loss of  $\beta$ -cell function occurs earlier than in adults with comparable diabetes duration (17). Direct comparisons between youth and adults with impaired glucose tolerance or new-onset T2D have been made in Restoring Insulin Secretion Study (RISE) participants. At the RISE baseline, youth were significantly more insulin resistant than adults independent of body size and had higher insulin secretion (18). These findings cannot be applied directly to adults with early-onset T2D, and studies with detailed phenotyping of adults <40 years with prediabetes or new-onset T2D are less common. However, in the Diabetes Prevention Program, participants aged 25–44 years had significantly higher HOMA-IR and corrected insulin response at baseline compared to older participants (e.g., control group HOMA-IR 7.1 [25–44 years], 6.2 [45–59 years], 5.5 [60–85 years],  $p<0.001$ ) despite similar values across the groups for fasting and 2-hour glucose (19). Detailed longitudinal characterization of younger adults with T2D is needed.

Reasons for these observed differences remain unclear. Developmental origins may contribute. There may be differences in prenatal development and fetal growth between adults who manifest overt dysglycemia before and after age 40 driven by secular increases in maternal overweight/obesity (20; 21) and gestational diabetes (22) in recent decades. Another possibility that must be considered is residual confounding, in particular by socioeconomic status, which may contribute to both age at diabetes detection and HbA1c; however, access to VHA care is provided without regard to income for eligible individuals, which may attenuate associations of socioeconomic status with both diabetes detection and HbA1c. To better understand the underlying physiology, future studies of early-onset T2D are needed that use more rigorous methods to classify diabetes subtype, such as, for example, by presence of autoantibodies.

HbA1c was not available for participants on the date that T2D was detected. Thus, for many individuals in the dataset the first HbA1c after detection may reflect “treated” T2D. In a sensitivity analysis restricted to individuals with <30 days between T2D detection and first HbA1c there were some differences.” In both men and women with early-onset T2D in this “treatment naïve” analysis there were modestly greater differences in first HbA1c after detection compared to those with later-onset than men with early-onset T2D in the primary analyses (i.e., HbA1c was comparatively “worse” prior to treatment in the early-onset populations). This might suggest that clinicians are acting relatively more quickly to intervene after T2D is detected in Veterans with early-onset T2D than in their counterparts with later onset diabetes. However, this is a possibility that requires further evaluation.

We also saw differences by sex at birth. Differences in the incidence and impacts of T2D by sex or gender are well established and have been thoughtfully reviewed by Huebschmann et al. (23). Briefly, sex differences in T2D incidence change across the life course, with females having comparatively higher rates of T2D than males in youth (<20 years old), no clear sex differences in younger adults (roughly 20–30 years old), and lower rates in mid-life (23). In the current cohort of Veterans with T2D, we found that age of onset between 20 and 39 years occurred more frequently in women than in men (11.1% vs. 2.8% respectively). Differences seen in our cohort may reflect changing trends in T2D incidence over time, differences in care-seeking behaviors by gender that might contribute to selection bias, and/or factors unique to our study population. It has been well demonstrated that adverse consequences of T2D on long-term outcomes such as coronary heart disease (7), vascular dementia (8) and end-stage renal disease (9) are greater in women compared with men. In the Swedish National Diabetes Registry, persons with early-onset T2D compared to later onset had a two- to four-fold greater risk of adverse outcomes including total mortality, cardiovascular mortality, heart failure, and coronary heart disease (24). Whether such differences are due to underlying biology by sex or patterns of care by gender remain unclear. Based on this prior research, we hypothesized that the impact of early-onset T2D on HbA1c and HbA1c variability would be greater in women compared to men due to gender disparities in care among younger Veterans or other factors. Interestingly, we found the opposite: Men with early-onset T2D had a substantially greater HbA1c at diabetes detection, and mean HbA1c after diabetes was detected, as well greater HbA1c variability; while in women, associations of age at detection with HbA1c were of lesser magnitude. One possible explanation that warrants careful consideration is that worsening glucose tolerance may have

more modest adverse impacts on cardiovascular risk factors in men than in women (23). If this is the case, the worse HbA1c profile we found in men with early-onset T2D may not translate into greater impacts on meaningful long-term outcomes such as total and CVD mortality. Longitudinal research examining impacts of sex differences in early-onset T2D is needed.

Our study has several strengths, including a large national sample of racially diverse U.S. adults, and the use of electronic health records to identify an inception cohort of adults with T2D. There are also some limitations: First, we were unable to adjust for early-life exposures that might contribute to early-onset diabetes (e.g., family history of T2D or maternal gestational diabetes) or for socio-economic factors. Because we relied on routine clinical laboratory testing, ICD codes, and medication use, individuals with T1D may have been mistakenly included in the study population. The proportion of such misclassification may be greater among individuals with early-onset compared to later-onset T2D; however, it is not clear whether the incidence of adult-onset T1D declines with increasing age (25). Finally, individual-level information about past gestational diabetes and pregnancy complications were not widely available. Despite these limitations, the knowledge gained here can directly impact monitoring and treatment among young adults with a diagnosis of T2D by supporting increased clinical oversight and more frequent laboratory monitoring, regardless of the true etiology of underlying diabetes.

In conclusion, age at diabetes onset was inversely associated with HbA1c outcomes in male Veterans with T2D. Associations in women were present but more modest. Early onset was common in Veterans with incident T2D, particularly female, in whom 11% had early onset. Risk factors in pregnancy and the peripartum period predict future T2D and can be used to inform care and screening (26). However, pregnancy, its complications, or peripartum care are poorly characterized in Veterans, especially those who do not utilize VA maternity care benefits (27). History of GDM and pregnancy complications should be systematically elicited, and future studies should evaluate their roles in T2D and its outcomes in women Veterans. Research examining impacts of glucose-lowering interventions by sex/gender is needed to characterize the long-term impacts of sex differences in glycemia in persons with early-onset T2D.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**ARTICLE HIGHLIGHTS**

- **Why did we undertake this study?** Information about glycemia is lacking for populations with early-onset adult T2D
- **What is the specific question(s) we wanted to answer?** Is age at diabetes detection associated with greater HbA1c and/or greater HbA1c variability in male and female Veterans with T2D?
- **What did we find?** Among male Veterans with T2D, early-onset T2D was associated with greater HbA1c and greater HbA1c variability. In women, statistically significant associations were also present, but effect sizes were of lesser magnitude.
- **What are the implications of our findings?** Longitudinal research examining the clinical course of early-onset T2D and the implications of sex differences in glycemia is needed.

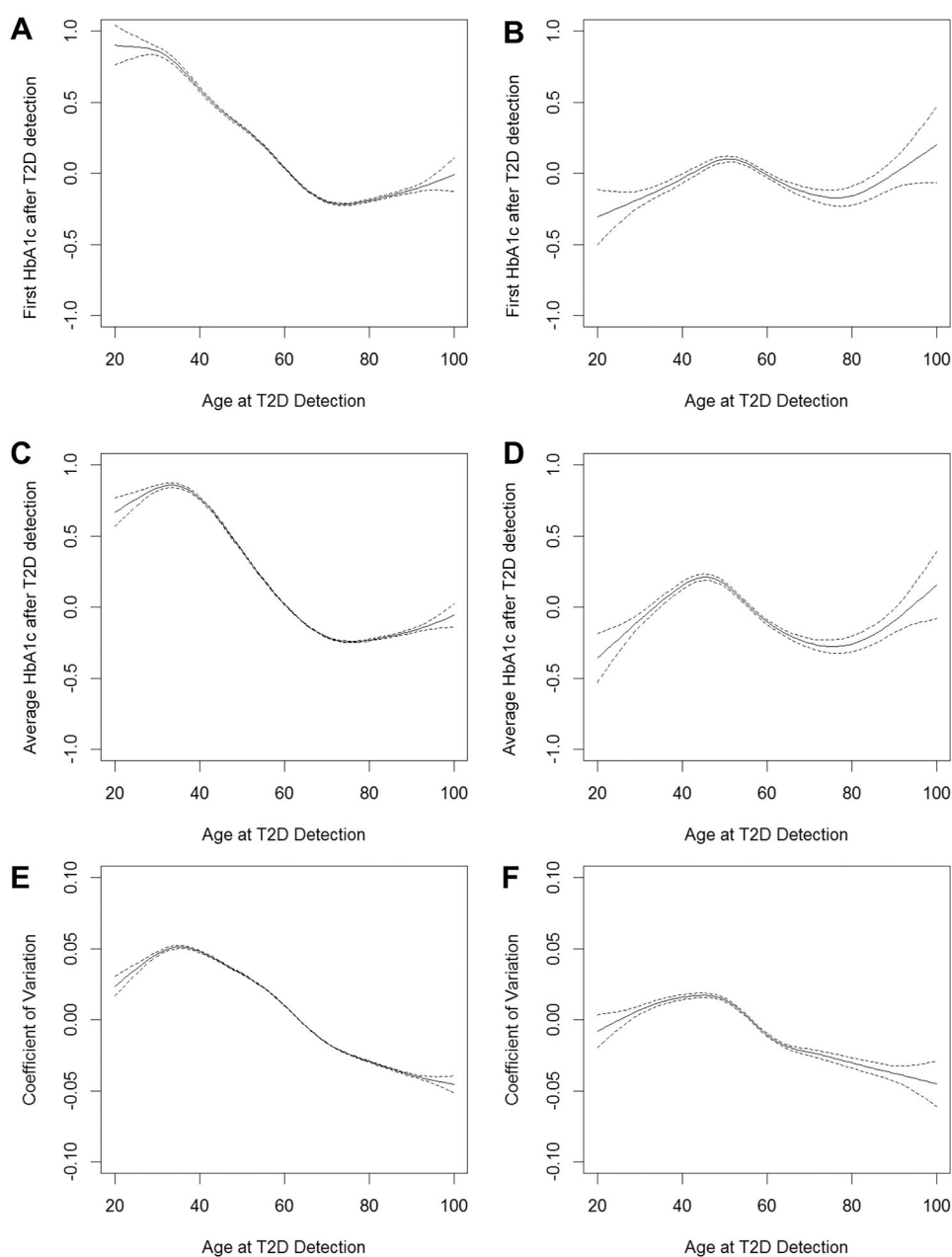


**Figure 1.** Output from sex-stratified generalized additive models adjusted for BMI, Black race, and Latinx ethnicity in men (A, C, E) and women (B, D, F).

**Table 1.**

Characteristics of U.S. Veterans Affairs Diabetes Risk (VADR) National Cohort participants who developed T2D during follow-up, overall and stratified by time of diabetes detection

|                                    | Overall<br>n = 851,302 | Early vs. later onset     |                            | Decade of diabetes detection |                           |                           |                            |                            |                          |  |
|------------------------------------|------------------------|---------------------------|----------------------------|------------------------------|---------------------------|---------------------------|----------------------------|----------------------------|--------------------------|--|
|                                    |                        | Early-onset<br>n = 27,766 | Later onset<br>n = 823,536 | <30 years<br>n = 3,887       | 30–39 years<br>n = 23,879 | 40–49 years<br>n = 76,955 | 50–59 years<br>n = 184,826 | 60–69 years<br>n = 330,917 | >69 years<br>n = 230,838 |  |
|                                    |                        | At enrollment             |                            |                              |                           |                           |                            |                            |                          |  |
| Age at enrollment, years           | 60.2 ± 11.9            | 31.3 ± 4.1                | 61.1 ± 9.3                 | 26.8 ± 1.9                   | 35.5 ± 2.9                | 45.3 ± 2.8                | 55.1 ± 2.9                 | 63.6 ± 2.7                 | 80.0 ± 5.3               |  |
| Female sex                         | 46154 (5.4)            | 5117 (18.4)               | 41037 (5.0)                | 819 (21.1)                   | 4298 (18.0)               | 9686 (12.6)               | 18055 (9.8)                | 10231 (3.1)                | 3065 (1.3)               |  |
| Black race                         | 164061 (19.3)          | 7519 (27.1)               | 156542 (19.0)              | 894 (23.0)                   | 6625 (27.7)               | 25045 (32.5)              | 56514 (30.6)               | 53734 (16.2)               | 21249 (9.2)              |  |
| Latinx ethnicity                   | 49784 (5.9)            | 4009 (14.4)               | 45775 (5.6)                | 668 (17.2)                   | 3341 (14.0)               | 6536 (8.5)                | 12112 (6.6)                | 16575 (5.0)                | 10552 (4.6)              |  |
| Urban residence                    | 383,519 (45.1)         | 12,490 (45.0)             | 371,029 (45.1)             | 4,442 (87.5)                 | 16,425 (68.8)             | 50,880 (66.1)             | 108,876 (58.9)             | 128,985 (40.0)             | 73,911 (32.0)            |  |
| Current smoker                     | 124,596 (14.6)         | 3,541 (12.8)              | 121,055 (14.7)             | 1,340 (34.5)                 | 5,162 (21.6)              | 18,187 (23.6)             | 46,946 (25.4)              | 41,829 (12.6)              | 11,132 (0.5)             |  |
| Body mass index, kg/m <sup>2</sup> | 32.2 ± 6.5             | 35.7 ± 7.2                | 32.1 ± 6.4                 | 33.8 ± 7.6                   | 36.0 ± 7.1                | 35.5 ± 6.9                | 33.5 ± 6.9                 | 32.1 ± 6.2                 | 29.9 ± 5.4               |  |
| Systolic blood pressure, mmHg      | 132.8 ± 21.4           | 130.0 ± 18.3              | 132.9 ± 21.5               | 128.8 ± 17.9                 | 131.3 ± 18.7              | 132.6 ± 20.2              | 132.8 ± 21.2               | 132.9 ± 21.8               | 133.2 ± 22.5             |  |
| Diastolic blood pressure, mmHg     | 75.8 ± 12.5            | 81.2 ± 12.7               | 75.6 ± 12.5                | 80.5 ± 12.8                  | 81.8 ± 12.4               | 80.5 ± 12.4               | 77.4 ± 12.3                | 74.4 ± 11.8                | 70.8 ± 12.2              |  |
| Total cholesterol, mg/dL           | 168.5 ± 44.5           | 189.4 ± 54.1              | 167.9 ± 44.0               | 190.6 ± 54.1                 | 188.1 ± 51.4              | 181.4 ± 48.7              | 171.5 ± 45.2               | 162.9 ± 41.1               | 157.3 ± 37.5             |  |
| Triglycerides, mg/dL               | 174.7 ± 156.3          | 251.8 ± 342.6             | 172.4 ± 146.9              | 250.0 ± 356.6                | 239.2 ± 293.0             | 205.5 ± 214.1             | 179.5 ± 152.2              | 163.5 ± 114.2              | 139.8 ± 85.4             |  |
| At or after T2D detection          |                        |                           |                            |                              |                           |                           |                            |                            |                          |  |
| Age at T2D detection, years        | 63.7 ± 11.9            | 34.7 ± 3.9                | 64.7 ± 10.8                | 27.7 ± 1.9                   | 35.9 ± 2.8                | 45.9 ± 2.8                | 55.6 ± 2.9                 | 64.9 ± 2.8                 | 77.9 ± 5.9               |  |
| # of HbA1c measurements            | 24.6 ± 17.7            | 26.1 ± 18.6               | 24.6 ± 17.7                | 23.0 ± 18.2                  | 26.6 ± 18.6               | 30.4 ± 19.2               | 29.4 ± 18.9                | 26.4 ± 17.4                | 16.3 ± 13.0              |  |
| First HbA1c after T2D detection    | 6.8 ± 1.5              | 7.4 ± 2.3                 | 6.7 ± 1.5                  | 7.4 ± 2.6                    | 7.4 ± 2.2                 | 7.2 ± 1.9                 | 7.0 ± 1.8                  | 6.7 ± 1.4                  | 6.5 ± 1.0                |  |
| Mean HbA1c                         | 6.7 ± 1.1              | 7.5 ± 1.7                 | 6.7 ± 1.1                  | 7.4 ± 2.0                    | 7.5 ± 1.7                 | 7.3 ± 1.4                 | 6.9 ± 1.2                  | 6.6 ± 1.0                  | 6.5 ± 0.8                |  |
| Coefficient of variation of HbA1c  | 0.09 ± 0.08            | 0.13 ± 0.09               | 0.09 ± 0.07                | 0.12 ± 0.10                  | 0.14 ± 0.09               | 0.13 ± 0.09               | 0.11 ± 0.08                | 0.08 ± 0.07                | 0.06 ± 0.05              |  |

Data are presented as mean ± SD for continuous variables and n (%) for categorical variables.

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**Table 3.** Associations of timing of diabetes detection with HbA1c outcomes among all participants who developed T2D and among men and women who developed T2D in the U.S. Veterans Affairs Diabetes Risk (VADR) National Cohort, n=851,302

|                                                                     | Overall |            | Men     |            | Women   |              | Interaction model             |
|---------------------------------------------------------------------|---------|------------|---------|------------|---------|--------------|-------------------------------|
|                                                                     | $\beta$ | 95% CI     | $\beta$ | 95% CI     | $\beta$ | 95% CI       | p for age x sex interaction * |
| Model 1: Early (20–39 years) vs. later (≥40 years) at T2D detection |         |            |         |            |         |              |                               |
| First HbA1c after T2D detection                                     | 0.57    | 0.55, 0.58 | 0.71    | 0.69, 0.73 | -0.14   | -0.18, -0.10 | <0.001                        |
| Mean HbA1c after T2D detection                                      | 0.65    | 0.64, 0.66 | 0.78    | 0.77, 0.80 | 0.00    | -0.03, 0.04  | <0.001                        |
| A1c coefficient of variation                                        | 0.04    | 0.04, 0.04 | 0.05    | 0.04, 0.05 | 0.01    | 0.01, 0.01   | <0.001                        |
| Model 2: Younger age at T2D detection, per decade                   |         |            |         |            |         |              |                               |
| First HbA1c after T2D detection                                     | 0.20    | 0.20, 0.20 | 0.21    | 0.21, 0.21 | 0.01    | 0.00, 0.02   | <0.001                        |
| Mean HbA1c after T2D detection                                      | 0.24    | 0.23, 0.24 | 0.25    | 0.24, 0.25 | 0.09    | 0.08, 0.10   | <0.001                        |
| A1c coefficient of variation                                        | 0.02    | 0.02, 0.02 | 0.02    | 0.02, 0.02 | 0.01    | 0.01, 0.01   | <0.001                        |

Abbreviations: BMI, body mass index; CI, confidence interval; T2D, type 2 diabetes  
Models adjusted for Black race, Latinx ethnicity, and BMI  
\* p for interaction taken from models including first-order interaction terms (age\*sex at birth) among all participants