# Type 1 Diabetes Genetic Risk in 109,954 Veterans With Adult-Onset Diabetes: The Million Veteran Program (MVP)

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## OBJECTIVE

**To characterize high type 1 diabetes (T1D) genetic risk in a population where type 2 diabetes (T2D) predominates.**

## RESEARCH DESIGN AND METHODS

**Characteristics typically associated with T1D were assessed in 109,594 Million Veteran Program participants with adult-onset diabetes, 2011–2021, who had T1D genetic risk scores (GRS) defined as low (0 to <45%), medium (45 to <90%), high (90 to <95%), or highest (≥95%).**

## RESULTS

**T1D characteristics increased progressively with higher genetic risk ($P < 0.001$ for trend). A GRS ≥ 90% was more common with diabetes diagnoses before age 40 years, but 95% of those participants were diagnosed at age ≥40 years, and they resembled T2D in mean age (64.3 years) and BMI (32.3 kg/m$^2$). Compared with the low risk group, the highest-risk group was more likely to have diabetic ketoacidosis (low 0.9% vs. highest GRS 3.7%), hypoglycemia prompting emergency visits (3.7% vs. 5.8%), outpatient plasma glucose <50 mg/dL (7.5% vs. 13.4%), a shorter median time to start insulin (3.5 vs. 1.4 years), use of a T1D diagnostic code (16.3% vs. 28.1%), low C-peptide levels if tested (1.8% vs. 32.4%), and glutamic acid decarboxylase antibodies (6.9% vs. 45.2%), all $P < 0.001$.**

## CONCLUSIONS

**Characteristics associated with T1D were increased with higher genetic risk, and especially with the top 10% of risk. However, the age and BMI of those participants resemble people with T2D, and a substantial proportion did not have diagnostic testing or use of T1D diagnostic codes. T1D genetic screening could be used to aid identification of adult-onset T1D in settings in which T2D predominates.**

Type 1 diabetes (T1D) was historically characterized as "juvenile onset," reflecting presentation in childhood or adolescence (1). However, T1D may also present in adults, with an onset that can be more gradual than juvenile-onset T1D and fewer features typically associated with severe insulin deficiency, such as diabetic ketoacidosis (DKA) (2–4). Individuals with "adult-onset" T1D may also have age and BMI similar to individuals with type 2 diabetes (T2D) (5). As a result, it may be difficult at presentation to distinguish adult-onset T1D from T2D.

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Identification of adult-onset T1D in populations where T2D predominates is clinically important, because effective management of T1D is more likely to include use of continuous glucose monitoring and other intensive modalities (3,6). Moreover, a substantial proportion of T1D may begin in adulthood. For example, a recent UK Biobank (UKB) analysis showed that 42% of individuals with genetically defined T1D had onset at age 31–60 years. Although the UKB study was restricted to individuals of White European (EUR) ancestry and there have been few studies of multiancestry populations (7), a recent review (2) concluded that adult-onset T1D is more common than childhood-onset T1D, as shown from epidemiological data from both high-risk areas such as Northern Europe and low-risk areas such as China.

Because individuals known to have T1D generally precludes enlistment in the U.S. military, nearly all veterans with adult-onset diabetes are usually presumed to have T2D (8,9). The VA Million Veteran Program (MVP), launched in 2011, links genomic data to clinical history in the Veterans Administration's (VA's) electronic medical record (EMR) (10). We used the MVP data set to examine the distribution and characteristics associated with T1D genetic risk in a multiancestry U.S. population.

## RESEARCH DESIGN AND METHODS

### The MVP and MVP Participants

The MVP is an ongoing biobank study (10). Participants provide a blood sample and fill out demographic and lifestyle surveys, and DNA analysis and survey information are linked to their EMRs. Genotyping uses a 723,305-single nucleotide polymorphism (SNP) Affymetrix Axiom Biobank Array, with imputation to the 1000 Genomes Project phase 3 panel (11). All SNPs that are used in genotyping have an information metric for imputation quality score >0.3 and minor allele frequency >0.001 for all genotyped veterans in MVP. Supplementary Fig. 1 shows the derivation of the MVP population and the broader population of veterans receiving healthcare through the VA. As of 13 October 2018, the MVP had enrolled 702,740 participants. Of these, genomic information was available for 462,335; 111,657 (24.2%) met the criteria for diabetes based on both use of diabetes ICD codes and outpatient prescription of diabetes medications (12), and 109,594 (23.8%) had genomic data sufficient to compute a genetic risk score (GRS). They were generally representative of veterans receiving VA healthcare, although there were some differences in age at diabetes onset, use of insulin, and other metrics (Supplementary Table 1). The VA Central Institutional Review Board has characterized MVP analyses as exempt from individual project review.

### Data Extraction and GRS Construction

Clinical data were taken from the VA Informatics and Computing Infrastructure Corporate Data Warehouse from 2002 until 13 October 2018. Major race and ethnicity groups were assigned by the Harmonized Ancestry and Race/Ethnicity (HARE) algorithm combining self-reported and genetic information (13). MVP participants with EUR, Hispanic (HIS), and Asian (ASN) ancestry were evaluated with a 30-SNP GRS generated as described and validated previously in the UKB and Wellcome Trust Case Control Consortium in subjects with EUR ancestry (14). The 30-SNP GRS categorized relatively few African (AFR) ancestry participants as having high T1D genetic risk (Supplementary Table 2), and provided relatively weak prediction of glutamic acid dehydroxylase (GAD) antibodies or low C-peptide levels in receiver operating characteristic analyses (Supplementary Fig. 2). With the 30-SNP GRS, the area under the receiver operating characteristic curve (AUC) was 0.784 to predict GAD antibodies or low C-peptide levels for participants with EUR ancestry, but 0.718 to predict those characteristics for those with AFR ancestry ($P$ = 0.0045). In contrast, use of a 7-SNP AFR ancestry-specific GRS, generated as described previously, provided an AUC of 0.782 to predict those characteristics for participants with AFR ancestry (15). The AUCs using the 30-SNP GRS to predict those characteristics were 0.694 and 0.713 for HIS and ASN ancestry, respectively (not shown). Because of this difference in performance, T1D genetic risk in participants with AFR ancestry was evaluated with the AFR ancestry-specific GRS. This approach also resulted in GRS values that were similar with AFR and EUR ancestry, while use of an alternative 67-SNP GRS in the SEARCH for Diabetes in Youth study resulted in values that were much lower for individuals with AFR ancestry who were diabetes autoantibody positive, were insulin sensitive, or had low C-peptide levels, compared with those of similar individuals with EUR ancestry (16). With each GRS, T1D genetic risk was expressed as a percentile, and participants were characterized in ventile groups as GRS 0 to <45% (low), 45 to <90% (medium), 90 to <95% (high), and ≥95% (highest).

### Variables

Age and sex were obtained from the EMR and self-report. Diabetes onset was defined as the earliest date that criteria for diabetes were met (use of ICD doses and outpatient prescription of a diabetes medication), as used previously (12). Age, BMI, and level of hemoglobin A1c ($HbA_{1c}$) were reported at diabetes onset. Screening for T1D was assessed as measurement of GAD antibodies (positive ≥5.0 IU/mL) and/or C-peptide levels (low <0.50 ng/mL). DKA was defined as use of the ICD code, and hypoglycemia variables as described. Since MVP does not allow chart review in order to preserve participant confidentiality, we examined convenience samples of the records of veterans at the Atlanta, GA VA; for example, at hospitalizations where the DKA ICD code was used, 100% had glucose levels >250 mg/dL, and 94% had $HCO_3$ levels <18 mEq/L and/or β-hydroxybutyrate levels >1.0 mmol/L.

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Estimated glomerular filtration rate (eGFR) (using the Chronic Kidney Disease Epidemiology Collaboration equation) was obtained at MVP enrollment, and the level of non-HDL cholesterol was obtained from the most recent outpatient determination prior to 13 October 2018 (17). Cardiovascular disease (CVD), heart failure, hypertension, chronic obstructive pulmonary disease (COPD), coronary artery disease, chronic kidney disease, hyperlipidemia, atrial fibrillation, and peripheral vascular disease were determined by use of ICD-9 or ICD-10 codes (Supplementary Table 3). Pharmacologic therapy to reduce CVD risk, including statins and antihypertensives, was assessed from outpatient prescriptions.

### Statistical Analyses

Statistical analyses were performed using R 4.0.5. Variation across genetic risk categories was assessed using multinomial Cochrane-Armitage tests for discrete variables and ANOVA for continuous variables, with and without stratification by ancestry. Tests of association between T1D genetic risk and diabetes or CVD outcomes used linear regression for continuous variables and logistic regression for categorical variables, with the low genetic risk group as the referent and adjusting for age, sex, genetic ancestry, and BMI at diabetes onset.

Some MVP participants appeared to have been diagnosed with diabetes outside the VA, some of those participants were already being treated with glucose-lowering medications, and some were already using insulin. To avoid possible confounding because some participants met criteria for diabetes when they first appeared in the database, we conducted a sensitivity analysis of MVP participants who had no outpatient prescription of insulin for at least 3 months after they first met criteria for diabetes. The analysis was aimed to identify participants who met robust criteria for the diagnosis of diabetes at their first visit to the VA (use of diabetes ICD codes and prescription of glucose-lowering medications) but were not prescribed insulin at that visit. If such individuals had hyperglycemia and had an urgent need for insulin, 3 months should be sufficient to identify them.

### Data Availability Statement

Data will be shared upon request in a format available per VA mechanisms. After the data have been published, all requests will be reviewed, and data sets deemed appropriate for release will be provided to the requestor in electronic format. Data will be stored and maintained in an approved location as described in the VA Research Data Inventory Form kept on file in the research office. Curated risk factor levels and outcomes will be made available on the Genomic Information System for Integrative Science server and the Massachusetts Veterans Epidemiology Research and Information Center MVP Phenotyping Core through Dr. Kelly Cho and her colleagues.

## RESULTS

Table 1 shows that the MVP participants with adult-onset diabetes were predominantly male (95.3%), of EUR and AFR ancestry (67.4% and 23.1%, respectively), with follow-up of 12.0 ± 4.9 years (mean ± SD). There was a higher percentage of HIS ancestry and lower percentage of EUR ancestry individuals in the highest genetic risk levels (Supplementary Table 4). At diabetes onset, the higher T1D genetic risk groups also tended to have lower age and BMI, and higher $HbA_{1c}$ (all $P < 0.0001$ for trend). However, the groups were clinically comparable, with less than a 5% difference in these characteristics between the highest- versus the low-risk groups. The two highest-risk groups comprised 10% of participants with diabetes in MVP, and those groups had mean age and BMI at diabetes onset that were 64.3 years and 32.3 kg/m$^2$, respectively—more typical of T2D.

With higher T1D genetic risk, MVP participants were more likely to have had DKA (highest versus low genetic risk 3.7% vs. 0.9%, respectively), hypoglycemia sufficient to prompt an emergency department (ED) visit (5.8% vs. 3.7%), and an outpatient visit when a random plasma glucose level was <50 mg/dL (2.8 mmol/L, 13.5% vs. 7.5%). A history of DKA, emergency visits because of hypoglycemia, and outpatient hypoglycemia were more frequent in participants with GAD antibodies (19.7%, 37.7%, and 23.0%, respectively) or low C-peptide levels (24.8%, 48.5%, and 21.9%, respectively). The trends for T1D-associated characteristics to be more common in participants with a higher GRS were all statistically significant (Table 2)—even between the low- and medium-risk groups, where typical T1D characteristics such as DKA were infrequent. Compared with the low-risk group, and adjusting for demographics and BMI at diabetes onset, the medium-risk group had increased odds of having had DKA, an ED visit because of hypoglycemia, outpatient hypoglycemia, and earlier use of insulin, all $P < 0.0001$. In contrast, there were no differences in time to use of sulfonylureas, and differences in risk of CVD and other conditions were generally not significant after adjustment.

Supplementary Table 5 shows that, with higher T1D genetic risk the characteristics of MVP participants with diabetes who had EUR ancestry were generally similar when risk was expressed as ventiles as in Table 1, or in centile cutoffs as previously reported by Oram et al. (14). Supplementary Table 6 demonstrates that increasing T1D genetic risk in each of the ancestry subgroups also tended to be associated with more DKA, hypoglycemia, use of T1D ICD codes, and T1D diagnostic testing, although some features were less common than in EUR participants. Supplementary Table 7 shows the median time to meet different random plasma glucose criteria for hypoglycemia at an outpatient visit. For each definition, among those meeting the criteria, participants with higher T1D genetic risk experienced hypoglycemia more quickly than those with lower T1D risk.

The numbers of participants and the distributions of their T1D genetic risk by decades of age at diabetes onset are shown in Fig. 1, and characteristics are shone in Supplementary Table 3. The greatest number of participants were age 50–59 years at diabetes onset ($n$ = 46,940). More participants diagnosed before age 40 years were in the top 10% of the GRS distribution (GRS 90 to <95%, and ≥95%): age 20–29 years (20.3%), and age 30–39 years (12.0%), but 95% of participants in these two highest GRS groups were diagnosed at age ≥40 years. Those with later age of onset were less likely to have had DKA or use insulin, and had lower $HbA_{1c}$ levels at diabetes onset, but the prevalence of GAD antibodies or low C-peptide levels was similar across age groups.

Table 1 also shows the relationship of T1D genetic risk to "clinical suspicion" of T1D: diagnostic testing (measurement of GAD antibodies and/or C-peptide

**Table 1—Demographic and clinical characteristics of MVP veterans with diabetes by T1D genetic risk level and age at diabetes onset**

| | All | GRS low (<45%) | GRS medium (45–90%) | GRS high (90–95%) | GRS highest (>95%) | *P* value* | Total | Age 20–29 years | Age 30–39 years | Age 40–49 years | Age 50–59 years | Age 60–69 years | Age 70–79 years | Age 80+ years |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total | 109,594 | 49,320 | 49,316 | 5,479 | 5,479 | | 1,368 | 6,915 | 26,546 | 46,940 | 22,764 | 4,606 | 399 | |
| Sex | | | | | | | | | | | | | | <0.0001 |
| Male | 104,360 (95.22%) | 46,981 (95.26%) | 46,964 (95.23%) | 5,221 (95.29%) | 5,194 (94.80%) | 0.5004 | 1,098 (80.26%) | 6,045 (87.42%) | 24,517 (92.36%) | 45,355 (96.62%) | 22,365 (98.25%) | 4,537 (98.50%) | 389 (97.49%) | |
| Female | 5,234 (4.78%) | 2,339 (4.74%) | 2,352 (4.77%) | 258 (4.71%) | 285 (5.20%) | | 270 (19.74%) | 870 (12.58%) | 2,029 (7.64%) | 1,585 (3.38%) | 399 (1.75%) | 69 (1.50%) | 10 (2.51%) | |
| Category | | | | | | | | | | | | | | |
| Age, mean (SD) | 65.16 (9.83) | 65.41 (9.65) | 65.11 (9.89) | 64.44 (10.15) | 64.12 (10.54) | <0.0001 | | | | | | | | |
| 20–29 years (%) | 133 (0.12%) | 36 (0.07%) | 54 (0.11%) | 16 (0.29%) | 27 (0.49%) | <0.0001 | | | | | | | | |
| 30–39 years (%) | 1,220 (1.11%) | 459 (0.93%) | 567 (1.15%) | 86 (1.57%) | 108 (1.97%) | | | | | | | | | |
| 40–49 years (%) | 5,358 (4.89%) | 2,253 (4.57%) | 2,466 (5.00%) | 319 (5.82%) | 320 (5.84%) | | | | | | | | | |
| 50–59 years (%) | 19,498 (17.79%) | 8,561 (17.36%) | 8,871 (17.99%) | 1,010 (18.43%) | 1,056 (19.27%) | | | | | | | | | |
| 60–69 years (%) | 52,311 (47.73%) | 23,751 (48.16%) | 23,374 (47.40%) | 2,650 (48.37%) | 2,536 (46.29%) | | | | | | | | | |
| 70–79 years (%) | 22,441 (20.48%) | 10,324 (20.93%) | 10,094 (20.47%) | 990 (18.07%) | 1,033 (18.85%) | | | | | | | | | |
| 80+ years (%) | 8,577 (7.83%) | 3,905 (7.92%) | 3,869 (7.85%) | 405 (7.39%) | 398 (7.26%) | | | | | | | | | |
| HARE ancestry† | | | | | | <0.0001 | | | | | | | | <0.0001 |
| EUR | 73,872 (67.41%) | 34,337 (69.62%) | 32,440 (65.78%) | 3,538 (64.57%) | 3,557 (64.92%) | | 610 (44.59%) | 3,240 (46.85%) | 14,616 (55.06%) | 33,234 (70.80%) | 17,980 (78.98%) | 3,834 (83.24%) | 325 (81.45%) | |
| AFR | 25,274 (23.06%) | 11,376 (23.07%) | 11,372 (23.06%) | 1,263 (23.05%) | 1,263 (23.05%) | | 497 (36.33%) | 2,722 (39.36%) | 8,850 (33.34%) | 9,421 (20.07%) | 3,208 (14.09%) | 510 (11.07%) | 45 (11.28%) | |
| HISP | 9,537 (8.70%) | 3,429 (6.95%) | 4,842 (9.82%) | 630 (11.50%) | 636 (11.61%) | | 224 (16.37%) | 855 (12.36%) | 2,819 (10.62%) | 3,932 (8.38%) | 1,447 (6.36%) | 233 (5.06%) | 25 (6.27%) | |
| ASN | 911 (0.83%) | 178 (0.36%) | 662 (1.34%) | 48 (0.88%) | 23 (0.42%) | | 37 (2.70%) | 98 (1.42%) | 261 (0.98%) | 353 (0.75%) | 129 (0.57%) | 29 (0.63%) | 4 (1.00%) | |
| GRS | | | | | | | | | | | | | | <0.0001 |
| Low | | | | | | | 459 (33.55%) | 2,942 (42.55%) | 11,793 (44.42%) | 21,320 (45.42%) | 10,461 (45.95%) | 2,146 (46.59%) | 168 (42.11%) | |
| Medium | | | | | | | 631 (46.13%) | 3,154 (45.61%) | 11,974 (45.11%) | 21,040 (44.82%) | 10,263 (45.08%) | 2,044 (44.38%) | 189 (47.37%) | |
| High | | | | | | | 107 (7.82%) | 396 (5.73%) | 1,371 (5.16%) | 2,323 (4.95%) | 1,041 (4.57%) | 222 (4.82%) | 16 (4.01%) | |
| Highest | | | | | | | 171 (12.50%) | 423 (6.12%) | 1,408 (5.30%) | 2,257 (4.81%) | 999 (4.39%) | 194 (4.21%) | 26 (6.52%) | |
| Diabetes-related variables | | | | | | | | | | | | | | |
| Taking insulin | 60,454 (55.16%) | 26,750 (54.24%) | 27,110 (54.97%) | 3,156 (57.60%) | 3,438 (62.75%) | <0.0001 | 1,055 (77.12%) | 4,936 (71.38%) | 17,780 (66.98%) | 25,383 (54.08%) | 9,494 (41.71%) | 1,668 (36.21%) | 108 (27.07%) | <0.0001 |
| Taking sulfonylurea | 76,330 (69.65%) | 35,110 (71.19%) | 34,176 (69.30%) | 3,631 (66.27%) | 3,413 (62.29%) | <0.0001 | 792 (57.89%) | 5,171 (74.78%) | 20,027 (75.44%) | 32,894 (70.08%) | 14,308 (62.85%) | 2,890 (62.74%) | 212 (53.13%) | <0.0001 |
| DKA | 1,436 (1.31%) | 464 (0.94%) | 644 (1.31%) | 127 (2.32%) | 201 (3.67%) | <0.0001 | 134 (9.80%) | 267 (3.86%) | 521 (1.96%) | 409 (0.87%) | 87 (0.38%) | 18 (0.39%) | 33 (8.27%) | <0.0001 |
| Hypoglycemia diagnosis at ED | 4,410 (4.02%) | 1,836 (3.72%) | 1,989 (4.03%) | 269 (4.91%) | 316 (5.77%) | <0.0001 | 94 (6.87%) | 409 (5.91%) | 1,486 (5.60%) | 1,682 (3.58%) | 611 (2.68%) | 122 (2.65%) | 5 (1.25%) | <0.0001 |
| Outpatient glucose < 50 mg/dL | 9,118 (8.32%) | 3,718 (7.54%) | 4,134 (8.38%) | 526 (9.60%) | 737 (13.45%) | <0.0001 | 175 (12.79%) | 2,804 (40.55%) | 2,946 (11.10%) | 3,679 (7.84%) | 1,270 (5.58%) | 231 (5.02%) | 11 (2.76%) | <0.0001 |
| Years to insulin (median) | 3.22 (3.17, 3.27) | 3.50 (3.41, 3.58) | 3.23 (3.15, 3.30) | 2.45 (2.25, 2.70) | 1.40 (1.22, 1.65) | <0.0001 | 0.82 (0.47, 1.17) | 3.36 (3.13, 3.57) | 3.72 (3.61, 3.82) | 3.26 (3.18, 3.34) | 2.63 (2.46, 2.78) | 1.49 (1.19, 1.93) | 0.09 (0.03, 0.30) | <0.0001 |
| Years to insulin (mean) | 4.29 (4.30) | 4.47 (4.32) | 4.28 (4.29) | 3.91 (4.28) | 3.36 (4.14) | | 2.88 (3.82) | 4.31 (4.32) | 4.66 (4.42) | 4.23 (4.16) | 4.08 (4.43) | 3.48 (4.22) | 1.29 (2.30) | <0.0001 |

***Continued on p. 5***

**Table 1—Continued**

| | All | GRS low (<45%) | GRS medium (45–90%) | GRS high (90–95%) | GRS highest (>95%) | *P* value* | Total | Age 20–29 years | Age 30–39 years | Age 40–49 years | Age 50–59 years | Age 60–69 years | Age 70–79 years | Age 80+ years |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Years to sulfonylurea (median) | 0.51 (0.49, 0.53) | 0.52 (0.50, 0.56) | 0.50 (0.47, 0.53) | 0.55 (0.45, 0.67) | 0.44 (0.35, 0.53) | 0.2400 | 1.06 (0.81, 1.38) | 0.69 (0.59, 0.80) | 0.45 (0.41, 0.50) | 0.56 (0.53, 0.60) | 0.44 (0.39, 0.50) | 0.26 (0.19, 0.34) | 0.13 (0.02, 0.32) | 0.0017 |
| eGFR at enrollment (mean) § | 73.12 (26.17) | 72.88 (25.74) | 73.19 (26.68) | 74.21 (25.68) | 73.62 (25.80) | 0.0019 | 97.94 (48.49) | 86.34 (29.02) | 77.98 (27.44) | 72.19 (24.31) | 66.68 (22.44) | 59.88 (21.13) | 57.75 (18.71) | <0.0001 |
| A1c at diabetes onset (mean) § | 7.74 (2.22) | 7.70 (2.05) | 7.75 (2.09) | 7.84 (2.11) | 8.00 (4.09) | <0.0001 | 8.57 (2.68) | 8.24 (2.57) | 7.81 (2.35) | 7.40 (2.32) | 7.18 (1.65) | 7.08 (1.39) | 7.10 (1.27) | <0.0001 |
| BMI at diabetes onset (mean)§ | 33.00 (6.23) | 33.17 (6.16) | 33.00 (6.26) | 32.67 (6.39) | 31.95 (6.34) | <0.0001 | 33.18 (7.24) | 34.62 (6.99) | 33.91 (6.72) | 33.08 (6.10) | 32.07 (5.53) | 30.14 (4.79) | 28.62 (4.77) | <0.0001 |
| Age at diabetes onset, years (mean) | 53.48 (9.62) | 53.76 (9.43) | 53.44 (9.65) | 52.70 (9.98) | 52.13 (10.50) | <0.0001 | 25.41 (3.19) | 35.83 (2.67) | 45.41 (2.77) | 54.54 (2.82) | 63.32 (2.72) | 72.98 (2.58) | 82.33 (2.66) | <0.0001 |
| Years of follow-up (mean) | 11.99 (4.88) | 11.96 (4.86) | 11.98 (4.88) | 12.00 (4.93) | 12.31 (5.06) | <0.0001 | 12.12 (5.09) | 13.10 (5.09) | 13.52 (4.85) | 11.77 (4.42) | 10.71 (5.18) | 10.41 (4.85) | 6.83 (3.52) | <0.0001 |
| T1D diagnostic | | | | | | | | | | | | | | |
| T1D ICD code any use | 19,402 (17.70%) | 8,028 (16.28%) | 8,657 (17.55%) | 1,178 (21.50%) | 1,539 (28.09%) | <0.0001 | 605 (44.23%) | 1,948 (28.17%) | 6,496 (24.47%) | 7,696 (16.40%) | 2,313 (10.16%) | 320 (6.95%) | 14 (3.51%) | <0.0001 |
| T1D ICD code at least 50% | 1,587 (1.45%) | 280 (0.57%) | 691 (1.40%) | 195 (3.56%) | 421 (7.68%) | <0.0001 | 268 (19.59%) | 296 (4.28%) | 438 (1.65%) | 408 (0.87%) | 156 (0.69%) | 19 (0.41%) | 2 (0.50%) | <0.0001 |
| GAD tested | 2,632 (2.40%) | 902 (1.83%) | 1,177 (2.39%) | 201 (3.67%) | 352 (6.42%) | <0.0001 | 328 (23.98%) | 511 (7.39%) | 839 (3.16%) | 749 (1.60%) | 182 (0.80%) | 19 (0.41%) | 2 (0.50%) | <0.0001 |
| Percent positive if GAD tested | 517 (19.64%) | 62 (6.87%) | 233 (19.80%) | 63 (31.34%) | 159 (45.17%) | <0.0001 | 80 (24.39%) | 101 (19.77%) | 164 (19.55%) | 126 (16.82%) | 38 (20.88%) | 8 (42.11%) | 0 (0.00%) | <0.0001 |
| C-peptide tested | 6,253 (5.71%) | 2,486 (5.04%) | 2,781 (5.64%) | 409 (7.46%) | 577 (10.53%) | <0.0001 | 383 (28.00%) | 905 (13.09%) | 2,153 (8.11%) | 2,187 (4.66%) | 550 (2.42%) | 69 (1.50%) | 3 (0.75%) | <0.0001 |
| Percent low C-peptide if tested | 548 (8.76%) | 44 (1.77%) | 237 (8.52%) | 80 (19.56%) | 187 (32.41%) | <0.0001 | 71 (18.54%) | 117 (12.93%) | 171 (7.94%) | 139 (6.36%) | 44 (8.00%) | 6 (8.70%) | 0 (0.00%) | <0.0001 |
| Cardiorenal status | | | | | | | | | | | | | | |
| Non-HDL cholesterol (mean) | 150.94 (41.96) | 150.69 (42.15) | 151.15 (41.92) | 152.14 (42.52) | 150.06 (40.01) | 0.0187 | 179.04 (57.01) | 167.24 (48.59) | 154.92 (44.01) | 148.52 (40.41) | 145.86 (38.04) | 145.06 (36.32) | 147.91 (40.43) | <0.0001 |
| Heart failure | 32,185 (29.37%) | 14,727 (29.86%) | 14,402 (29.20%) | 1,517 (27.69%) | 1,539 (28.09%) | 0.0004 | 144 (10.53%) | 1,386 (20.04%) | 7,653 (28.83%) | 14,164 (30.17%) | 6,986 (30.69%) | 1,707 (37.06%) | 128 (32.08%) | <0.0001 |
| Hypertension | 105,794 (96.53%) | 47,675 (96.66%) | 47,647 (96.62%) | 5,234 (95.53%) | 5,238 (95.60%) | <0.0001 | 1,094 (79.97%) | 6,407 (92.65%) | 25,666 (96.68%) | 45,751 (97.47%) | 22,014 (96.71%) | 4,438 (96.35%) | 372 (93.23%) | <0.0001 |
| Chronic obstructive pulmonary disease | 47,635 (43.46%) | 21,685 (43.97%) | 21,306 (43.20%) | 2,322 (42.38%) | 2,322 (42.38%) | 0.0085 | 386 (28.22%) | 2,704 (39.10%) | 12,304 (46.35%) | 20,919 (44.57%) | 9,348 (41.06%) | 1,822 (39.56%) | 127 (31.83%) | <0.0001 |
| Coronary artery disease | 59,240 (54.05%) | 27,030 (54.81%) | 26,463 (53.66%) | 2,894 (52.82%) | 2,853 (52.07%) | 0.0626 | 268 (19.59%) | 2,645 (38.25%) | 13,577 (51.15%) | 26,369 (56.18%) | 13,193 (57.96%) | 2,923 (63.46%) | 239 (59.90%) | <0.0001 |
| Chronic kidney disease | 44,392 (40.51%) | 20,128 (40.81%) | 19,864 (40.28%) | 2,150 (39.24%) | 2,250 (41.07%) | 0.1466 | 321 (23.46%) | 2,145 (31.02%) | 10,584 (39.87%) | 19,297 (41.11%) | 9,542 (41.92%) | 2,294 (49.80%) | 185 (46.37%) | <0.0001 |
| Hyper-lipidemia | 104,851 (95.67%) | 47,189 (95.68%) | 47,203 (95.72%) | 5,240 (95.64%) | 5,219 (95.25%) | 0.4661 | 1,207 (88.23%) | 6,583 (95.20%) | 25,513 (96.11%) | 45,159 (96.21%) | 21,716 (95.40%) | 4,284 (93.01%) | 339 (84.96%) | <0.0001 |
| Atrial fibrillation | 23,406 (21.36%) | 10,796 (21.89%) | 10,464 (21.22%) | 1,125 (20.53%) | 1,021 (18.63%) | <0.0001 | 62 (4.53%) | 613 (8.86%) | 4,332 (16.32%) | 10,380 (22.11%) | 6,251 (27.46%) | 1,636 (35.52%) | 126 (31.58%) | <0.0001 |

***Continued on p. 6***

**Table 1—Continued**

| | All | GRS low (<45%) | GRS medium (45–90%) | GRS high (90–95%) | GRS highest (>95%) | *P* value* | Total | Age 20–29 years | Age 30–39 years | Age 40–49 years | Age 50–59 years | Age 60–69 years | Age 70–79 years | Age 80+ years |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Peripheral vascular disease | 44,909 (40.98%) | 20,475 (41.51%) | 20,038 (40.63%) | 2,195 (40.06%) | 2,201 (40.17%) | 0.0085 | 238 (17.40%) | 2,008 (29.04%) | 10,529 (39.66%) | 19,977 (42.56%) | 9,872 (43.37%) | 2,112 (45.85%) | 157 (39.35%) | <0.0001 |
| Taking statins | 102,048 (93.11%) | 45,947 (93.16%) | 45,941 (93.16%) | 5,113 (93.32%) | 5,047 (92.12%) | 0.0268 | 1,085 (79.31%) | 6,344 (91.74%) | 24,907 (93.83%) | 44,232 (94.23%) | 21,018 (92.33%) | 4,106 (89.14%) | 310 (77.69%) | <0.0001 |
| Taking antihypertensives | 105,411 (96.18%) | 47,511 (96.33%) | 47,394 (96.1%) | 5,282 (96.4%) | 5,224 (95.35%) | 0.0018 | 1,159 (84.72%) | 6,445 (93.2%) | 25,628 (96.54%) | 45,594 (97.13%) | 21,784 (95.69%) | 4,384 (95.18%) | 366 (91.73%) | <0.0001 |

*P values determined to assess trend using ANOVA for continuous variables and multinomial Cochrane-Armitage tests for categorical variables. †Race/ethnicity determined using HARE algorithm. §GAD antibody level ≥5.0 IU/mL or C-peptide levels <0.50 ng/mL were indicative of T1D.

levels) and use of T1D ICD codes. Diagnostic testing increased with higher genetic risk ($P < 0.0001$ for trend for both GAD antibodies and C-peptide levels), but was infrequent, even in the highest genetic risk group (5.9% were tested for GAD antibodies and 9.3% for C-peptide). Among those tested, the frequency of abnormal test results increased progressively across genetic risk levels for both GAD antibodies (low genetic risk 8.3% vs. highest 43.2%) and low C-peptide levels (7.3% vs. 45.2%). Use of T1D diagnostic codes was also infrequent: only 7.7% in the highest-risk group had over 50% use (a criterion for EMR-based identification of T1D), and less than 30% in the highest-risk group had any use (18).

Fig. 2 and Supplementary Table 8 show that higher T1D genetic risk in MVP participants was associated with earlier outpatient use of insulin. Those without diagnostic testing had the longest delay of insulin initiation after diabetes onset (mean 4.4 ± 4.3 years for no testing for GAD antibodies and 4.4 ± 4.3 years for measurement of C-peptide levels). Those tested but negative had earlier initiation of insulin (mean 2.3 ± 3.4 and 3.3 ± 3.9 years, respectively), while those with GAD antibodies or low C-peptide levels had the earliest use of insulin (1.1 ± 2.2 and 0.7 ± 1.7 years, respectively). However, within each group, higher T1D genetic risk tended to be associated with earlier initiation of insulin. This relationship was statistically significant among those with normal C-peptide levels or no measurement of C-peptide (both $P < 0.0001$), but not among those with low C-peptide levels, although the sample size was small. Findings were similar with testing for GAD antibodies, and in sensitivity analyses that excluded AFR ancestry or were restricted to AFR ancestry (Supplementary Table 9).

To avoid possible confounding because some MVP participants met criteria for diabetes when they first appeared in the database, we conducted a sensitivity analysis of 49,384 participants who had no outpatient prescription of insulin for at least 3 months after they first met criteria for diabetes (Supplementary Table 10). Such participants tended to be older than those with earlier use of insulin (mean 54.1 ± 9.6 years vs. 53.4 ± 9.6 years, respectively), and had shorter follow-up (mean 9.1 ± 3.2 years vs. 12.6 ± 5.0 years, respectively). The patterns with differences in T1D genetic risk remained similar to those in Table 1: participants with higher genetic risk tended to be younger, to be less obese, and to have higher $HbA_{1c}$ levels at the time of diagnosis, more DKA and hypoglycemia, more T1D diagnostic testing and use of T1D ICD codes, and earlier use of insulin, despite age and BMI at onset that resembled typical T2D.

## CONCLUSIONS

Our analysis of U.S. military veterans who were MVP participants—a population usually presumed to have T2D, since a history of typical, juvenile-onset T1D generally precludes enlistment—demonstrates that higher T1D genetic risk is associated with a progressively higher prevalence of T1D-related characteristics (8,9). Despite having an average age greater than 50 years and BMI above 30 kg/m$^2$ when diabetes was first identified in the EMR—resembling T2D—those with higher T1D genetic risk had an increased likelihood of having had DKA, hypoglycemia prompting ED visits or found incidentally at outpatient visits, GAD antibodies, and low C-peptide levels. Although at least 10% of participants with diabetes in the MVP (GRS 90–95% and >95% categories) appear to have increased risk of having such features, T1D may often be clinically unsuspected, because less than 15% of this group had diagnostic testing with measurement of GAD antibodies or C-peptide levels, and less than one-third had any use of a T1D ICD code.

There is increasing recognition that T1D may present after childhood and adolescence (2); in a recent study, over 40% of individuals of EUR ancestry with high T1D genetic risk had onset of T1D after age 30 years (4). Differences in design and population make it difficult to compare such observations with our finding that, among MVP participants with diabetes, more than 95% of those with high or the highest genetic risk of TID were diagnosed with diabetes at age ≥40 years, but the results seem consistent with previous literature. Presentation of T1D at a greater age tends to be associated with higher C-peptide levels when diabetes is first diagnosed and a slower fall in C-peptide levels over time (19,20). These characteristics could make it difficult to recognize adult-onset T1D in

**Table 2—Association between GRS risk level and diabetes outcomes compared with lowest GRS**

| | Medium versus low | | High versus low | | Highest versus low | |
|---|---|---|---|---|---|---|
| | Adj OR* | 95% CI | Adj OR* | 95% CI | Adj OR* | 95% CI |
| Diabetes-related factors | | | | | | |
| Taking insulin | 1.03 | 1.01, 1.06 $P = 0.0192$ | 1.13 | 1.07, 1.20 $P < 0.0001$ | 1.42 | 1.34, 1.51 $P < 0.0001$ |
| DKA | 1.35 | 1.20, 1.53 $P < 0.0001$ | 2.23 | 1.82, 2.73 $P < 0.0001$ | 3.28 | 2.76, 3.90 $P < 0.0001$ |
| Hypoglycemia diagnosis at ED | 1.08 | 1.02, 1.16 $P = 0.0162$ | 1.33 | 1.16, 1.52 $P < 0.0001$ | 1.56 | 1.38, 1.77 $P < 0.0001$ |
| Outpatient glucose <50 mg/dL | 1.13 | 1.08, 1.19 $P < 0.0001$ | 1.29 | 1.17, 1.42 $P < 0.0001$ | 1.91 | 1.76, 2.09 $P < 0.0001$ |
| Years to insulin† | 0.84 | 0.78, 0.90 $P < 0.0001$ | 0.62 | 0.53, 0.73 $P < 0.0001$ | 0.36 | 0.31, 0.42 $P < 0.0001$ |
| Years to sulfonylurea† | 1.00 | 0.95, 1.05 $P = 0.9995$ | 1.03 | 0.93, 1.15 $P = 0.5670$ | 0.91 | 0.82, 1.02 $P = 0.1158$ |
| eGFR at enrollment† | 1.05 | 0.76, 1.46 $P = 0.7540$ | 1.57 | 0.75, 3.26 $P = 0.2294$ | 0.58 | 0.28, 1.20 $P = 0.1397$ |
| A1c at onset† | 1.03 | 1.00, 1.07 $P = 0.0224$ | 1.09 | 1.02, 1.16 $P = 0.0129$ | 1.28 | 1.20, 1.37 $P < 0.0001$ |
| BMI at onset† | 0.91 | 0.84, 0.99 $P = 0.0198$ | 0.62 | 0.52, 0.74 $P < 0.0001$ | 0.30 | 0.26, 0.36 $P < 0.0001$ |
| Cardiorenal status | | | | | | |
| Total cholesterol—HDL | 1.09 | 0.65, 1.84 $P = 0.7510$ | 1.79 | 0.55, 5.74 $P = 0.3311$ | 0.17 | 0.05, 0.56 $P = 0.0033$ |
| Heart failure | 0.99 | 0.97, 1.02 $P = 0.6423$ | 0.95 | 0.89, 1.01 $P = 0.1302$ | 1.01 | 0.94, 1.07 $P = 0.8721$ |
| Hypertension | 1.04 | 0.97, 1.12 $P = 0.2752$ | 0.86 | 0.74, 1.00 $P = 0.0452$ | 1.00 | 0.86, 1.16 $P = 0.9776$ |
| Chronic obstructive pulmonary disease | 0.99 | 0.97, 1.02 $P = 0.4637$ | 0.97 | 0.92, 1.03 $P = 0.3428$ | 0.99 | 0.93, 1.05 $P = 0.7287$ |
| Coronary artery disease | 0.98 | 0.95, 1.00 $P = 0.0859$ | 0.95 | 0.92, 1.04 $P = 0.4934$ | 1.00 | 0.91, 1.03 $P = 0.3182$ |
| Chronic kidney disease | 0.99 | 0.96, 1.01 $P = 0.3888$ | 0.98 | 0.92, 1.04 $P = 0.5250$ | 1.08 | 1.02, 1.15 $P = 0.0093$ |
| Hyperlipidemia | 1.03 | 0.97, 1.10 $P = 0.3852$ | 1.09 | 0.94, 1.26 $P = 0.2462$ | 1.00 | 0.87, 1.15 $P = 0.9859$ |
| Atrial fibrillation | 1.00 | 0.97, 1.03 $P = 0.8734$ | 1.00 | 0.93, 1.08 $P = 0.8971$ | 0.91 | 0.84, 0.98 $P = 0.0090$ |
| Peripheral vascular disease | 0.99 | 0.96, 1.01 $P = 0.2829$ | 0.99 | 0.93, 1.05 $P = 0.6833$ | 1.01 | 0.95, 1.07 $P = 0.8194$ |
| Taking statins | 1.03 | 0.97, 1.08 $P = 0.3303$ | 1.12 | 0.99, 1.26 $P = 0.0687$ | 0.93 | 0.83, 1.03 $P = 0.1794$ |
| Taking antihypertensives | 0.98 | 0.92, 1.05 $P = 0.5816$ | 1.16 | 0.99, 1.35 $P = 0.0747$ | 1.00 | 0.96, 1.16 $P = 0.9979$ |

*Odds ratio adjusted (Adj OR) for sex, age, HARE ancestry, and BMI at enrollment. †Tested association of continuous variables with genetic risk using linear regression.

settings where T2D predominates, because relative preservation of insulin secretion might make features typical of severe insulin deficiency less frequent early in the natural history of disease. However, we found that T1D genetic risk was associated with a significantly increased frequency of both DKA and hypoglycemia even in the medium-risk group compared with the low-risk group (Table 2), suggesting broad clinical relevance.

Our findings of earlier use of insulin with higher T1D genetic risk even in MVP participants who were not tested for GAD or C-peptide, or tested and not found to have antibodies or low C-peptide levels (Fig. 2 and Supplementary Table 7), differ from those of Grubb et al. (21), who reported that increased T1D genetic risk in EUR individuals with onset of diabetes after age 35 years was associated with earlier use of insulin only in individuals with GAD antibodies. Because our GRS was the same as that used in the Grubb study, except for participants with AFR ancestry, and sensitivity analyses yielded similar results when participants with AFR ancestry were excluded, it is possible that the discrepancy could be due to testing for GAD antibodies in all participants in the Grubb study, in contrast to measurement prompted by clinical circumstances in MVP.

Our findings indicate that, in T2D predominant populations, the 10% with the highest genetic risk of T1D are at increased risk of having clinical features consistent with T1D. However, prototypical T1D characteristics, such as DKA or hypoglycemia prompting ED visits, are likely to be infrequent (Table 1). More often, their endogenous insulin deficiency may be suggested by hypoglycemia at routine outpatient visits (Table 1 and Supplementary Table 7), and by a relatively early need for insulin (Fig. 2). Patients with such features could be screened for T1D by testing for GAD antibodies or C-peptide levels, and assessment of genetic risk may also be useful.

The clinical importance of recognition of adult-onset T1D is not simply education and earlier initiation of insulin than in typical T2D (3), but earlier use of continuous glucose monitoring. Use of this technology in veterans is associated with improvement in $HbA_{1c}$ levels and reduced hospitalizations (22), has been shown in randomized trials to improve glycemic control (6), and, in Australia, the technology is provided free to people with T1D who are less than 21 years of age (23), and subsidized for people with T1D who are older (24). The need for appropriate management has been shown in the U.K., where $HbA_{1c}$ levels in study participants with unrecognized adult-onset T1D were worse than those in participants with juvenile-onset T1D—despite generally better preservation of β-cell function (3). Moreover, our findings likely apply to most patient populations with adult-onset diabetes, not only to veterans.

The strengths of our study include a large sample size, inclusion of MVP participants across the U.S., and ancestral diversity, which is greater than in most other biobanks. Our study also had limitations. First, generalizability could be limited because participants are predominantly male, although the genetic etiology of T1D is thought to be autosomal (25). Second, although a GRS provides strong predictive potential for many diseases, we were unable to assess differences in environmental exposure and other factors that could influence genetic expression (26). Third, HIS and some other ancestries had relatively small sample sizes. Fourth, although solicitation to participate in the MVP is VA wide, our analysis found both similarities and differences between the MVP and

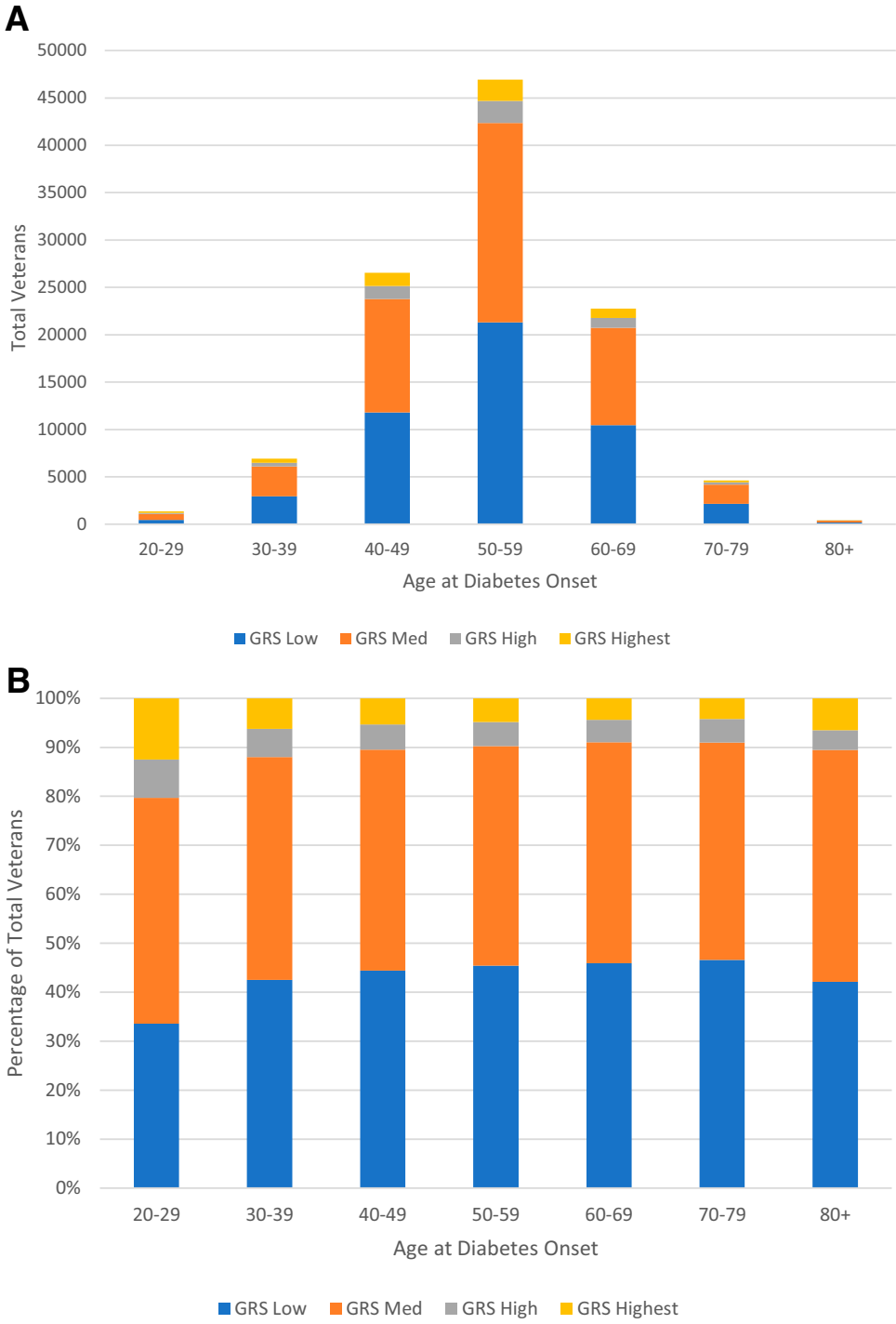


**Figure 1**—Distributions of T1D genetic risk in groups with different ages (in years) at onset of diabetes (*A*) numbers of MVP participants within each age category and (*B*) as a percentage of participants within each age category.

the broader VA population (Supplementary Table 3). Fifth, the main T1D GRS we used has been extensively characterized, but was developed in a EUR population (21); although we used a separate GRS for participants with AFR ancestry, our analysis may not apply to other ancestries. Sixth, because assessment of GAD antibodies and C-peptide levels was infrequent and not systematic, patterns found in our study might have been biased because of selection based on clinical presentation and circumstances. Seventh, we evaluated outpatient prescription of diabetes medications to avoid possible misidentification based on need for insulin to manage hyperglycemia in the hospital, but we appreciate that, once insulin is initiated, there may be no attempt to withdraw it. Similarly, we defined diabetes onset according to the use of diagnosis codes and prescription of medications, but some MVP participants may have had preexisting diabetes upon entry into the EMR. Our findings are supported by the observation of similar patterns in the subset who had no

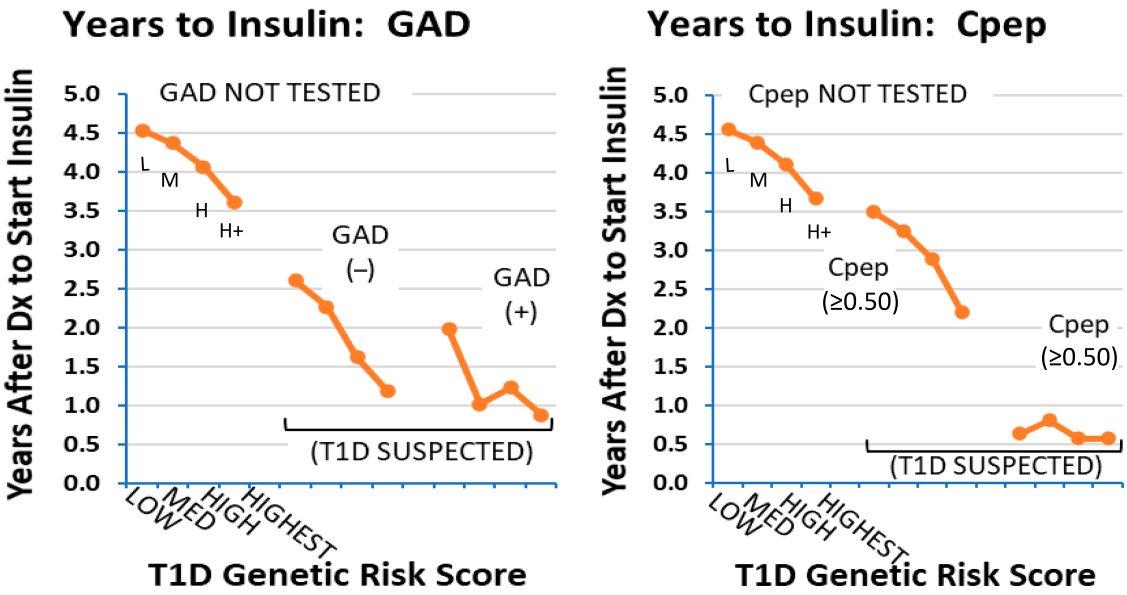


**Figure 2**—Mean years to starting insulin by GAD antibody and C-peptide testing status and genetic risk level. L, M, H, and H+ correspond to low, medium, high, and highest genetic risk score levels. T1D Suspected corresponds to those veterans who have been tested for GAD or C-peptide (Cpep). GAD antibody level ≥5.0 IU/mL or C-peptide levels <0.50 ng/mL were indicative of T1D. Time values per testing and genetic risk categories are included in Supplementary Table 8.

prescription of insulin for 3 months after they met diagnostic criteria. In addition, setting GAD antibody and/or C-peptide level cutoffs lower would increase sensitivity but lower specificity, and conversely, but it would be beyond the scope of this article to include accounting for the potential use of higher or lower cutoffs. Also, it should be recognized that use of insulin is associated with increased risk of hypoglycemia even when T1D is unlikely (e.g., in individuals with a low T1D genetic risk such as those with GRS 0–45th percentile [not shown]). Finally, while it would also be of interest to compare T1D genetic risk with GAD antibodies and/or C-peptide levels as predictors of hypoglycemia, DKA, and insulin use, direct comparisons were not possible, because the GRS was performed in all MVP participants but measurements of GAD antibodies and C-peptide levels were not; the MVP data set is administrative, reflecting what tests clinicians ordered, not a registry or a prospective study.

In conclusion, a substantial proportion of the participants with diabetes in MVP who have a high genetic risk of T1D may have clinical T1D despite its preclusion to enlistment. However, among those with the top 10% of genetic risk of T1D, less than 15% were tested for GAD antibodies or C-peptide levels, and less than 30% had any use of T1D diagnostic codes. Because adult-onset T1D may be unrecognized in settings where T2D predominates, additional screening may be needed to guide identification and facilitate appropriate management. As the integration of genetic data into healthcare evolves, our study suggests that there may be a role for using a T1D GRS to help identify individuals at higher risk for T1D who could benefit from additional diagnostic testing.

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**Duality of Interest**. Within the past several years, L.S.P. has served on Scientific Advisory Boards for Boehringer Ingelheim and Janssen, and has or had research support from Merck, Pfizer, Eli Lilly, Novo Nordisk, Sanofi, PhaseBio, Roche, Abbvie, Vascular Pharmaceuticals, Janssen, Glaxo SmithKline, and the Cystic Fibrosis Foundation, and is also a cofounder, officer, board

member, and stockholder of a company, Diasyst, Inc., which markets software aimed to help improve diabetes management. R.A.O. had a UK Medical Research Council Confidence in Concept grant to work with Randox to develop a T1D GRS biochip, and has received research funding from Randox. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** Study design was conceived by P.K.Y., S.L.J., S.R., M.K.R., and L.S.P. Genomic data collection and organization were performed by the MVP. Clinical data construction and organization were performed by B.R.C. Analyses were performed by P.K.Y. and L.S.P. All authors contributed to interpretation of results and writing of the manuscript, in addition to critical revision of the final draft. P.K.Y. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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