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Diabetes Res Clin Pract. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Diabetes Res Clin Pract. 2020 July ; 165: 108235. doi:10.1016/j.diabres.2020.108235.

Prevalence of Microvascular and Macrovascular Disease in the Glycemia Reduction Approaches in Diabetes - A Comparative Effectiveness (GRADE) Study Cohort

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Contribution Statement:

All authors affirm that authorship is merited based on the ICMJE authorship criteria. IB, JPC, CD, JBG, HKS, MEL, KJM, RP-B, EBS, and DJW contributed to the conception and design of this manuscript. IB, JPS, CD, JBG, HKS, KJM, JP, ERS, RP-B and EZS contributed to the acquisition of data for this manuscript. IB contributed to the statistical analysis of data for this manuscript. CB, IB, RMC, JPC, CD, JBG, MSK, HKS, KJM, RP-B, ERS, EBS, EZS, and DJW contributed to the interpretation of data and results for this manuscript. CD, KJM, RP-B, and ERS contributed to the supervision and management of research for this manuscript. IB, CD, HKS, HKS, MEL, KJM, and RP-B contributed to the drafting of this manuscript. CB, IB, RMC, JPC, CD, JBG, MSK, HKS, KJM, JP, RP-B, ERS, EBS, EZS, and DJS contributed to the critical review of this manuscript. IB, KJM and RP-B are guarantors of this work, and as such, had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Clinical Trials Registration: NCT01794143

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Abstract

Aims: The Glycemia Reduction Approaches in Diabetes - A Comparative Effectiveness (GRADE) trial is a randomized clinical trial comparing glycemic effects of four diabetes medications added to metformin in type 2 diabetes (T2D). Microvascular and macrovascular diseases are secondary outcomes. We evaluated the prevalence and risk factor relationships for microvascular and macrovascular complications in the GRADE cohort at study entry.

Methods: Complication prevalence and risk factors were analyzed based on data from screening in all consenting participants meeting GRADE eligibility. Logistic regression and Z-statistics were used to assess risk factor relationships with complications.

Results: We enrolled 5047 T2D participants [mean age 57 years; 36% female; mean knownT2D duration 4 years (all<10 years); mean HbA1c 8.0% (~64mmol/mol) at screening]. Urinary albumin/creatinine ratio (ACR) ≥30 mg/gram was present in 15.9% participants; peripheral neuropathy (by Michigan Neuropathy Screening Instrument) in 21.5%; cardiovascular autonomic neuropathy by electrocardiography-derived indices in 9.7%; self-reported retinopathy in 1.0%. Myocardial infarction ascertained by self-report or electrocardiogram was present in 7.3%, and self-reported history of stroke in 2.0%.

Conclusions: In the GRADE cohort with <10 years of T2D and a mean HbA1c of 8.0%, diabetes complications were present in a substantial fraction of participants, more so than might otherwise have been expected.

Keywords

Diabetes; complications; prevalence; treatment; comparative effectiveness; pragmatic

INTRODUCTION

The morbidity and mortality associated with diabetes mellitus are driven by the associated microvascular and macrovascular complications [1–5], which contribute substantially to the cost of diabetes to health care systems [6]. While available evidence shows that glycemic control may account for ~ 50% of the risk of overall complications in patients with type 1

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and type 2 diabetes [7, 8], glycemia most directly affects the risk of microvascular complications, with a more modest association with macrovascular disease [9, 10]. Nonglycemic risk factors such as hypertension, hyperlipidemia, and obesity also contribute to the risk of complications, with different epidemiologic relationships between glycemia and microvascular versus glycemia and macrovascular complications [4, 10–14].

The Glycemia Reduction Approaches in Diabetes - A Comparative Effectiveness (GRADE) Study is a prospective clinical trial designed to compare the glycemic effects of four randomly assigned diabetes medications added to metformin as second-line therapy in individuals with Type 2 diabetes (T2D) of less than 10 years of known diabetes duration [15]. Here we report the prevalence of diabetes-related microvascular and macrovascular complications in all consenting participants meeting GRADE eligibility at the time of eligibility screening, and their associations with risk factors.

MATERIAL AND METHODS

The overall design, methods of recruitment, and characteristics of the randomized GRADE cohort have been reported previously [15, 16]. In brief, 5047 consenting participants with T2D treated with metformin only, with HbA1c between 51 and 69 mmol/mol (6.8% and 8.5%), and meeting other eligibility requirements were enrolled between 2013 and 2017 (NCT01794143) [16]. All participating sites had Institutional Review Board approval and all participants provided a written consent. Participants who met screening criteria underwent a run-in period. Those who met central lab-measured HbA1c inclusion criteria at the end of run-in and adhered to study visit attendance and study-provided metformin were randomly assigned to one of four study medications. For the current analyses, we used laboratory values measured at the time of initial eligibility screening in all consenting participants meeting GRADE eligibility, prior to study-driven modification of diabetes medications including metformin.

2.1 Laboratory methods.

Screening HbA1c values were measured in local clinical laboratories at GRADE sites; these local HbA1c values were used in the current analyses. Total glycemic exposure was calculated as the screening HbA1c value multiplied by self-reported diabetes duration. Other laboratory measurements were performed by the Central Biochemistry Laboratory (Advanced Research and Diagnostic Laboratory, Department of Laboratory Medicine and Pathology, University of Minnesota), using standardized procedures and appropriate quality control surveillance. Serum and urine creatinine were measured by an enzymatic method (Roche Diagnostics, Indianapolis, IN) traceable to Isotope Dilution Mass Spectroscopy (IDMS). Plasma glucose was measured in EDTA plasma by a hexokinase method on the Roche cobas c501 chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Insulin and C-peptide were measured in EDTA plasma on the Roche cobas e601 immunoassay analyzer using a sandwich immunoassay (Roche Diagnostics, Indianapolis, IN). eGFR was calculated using the CKD-EPI equation [17]. Urine albumin was measured on a single sample using an immunoturbidimetric method (Roche Diagnostics, Indianapolis, IN). Cholesterol was measured using a cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN). HDL-

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cholesterol was measured using the Roche HDL-Cholesterol 4th generation direct method (Roche Diagnostics, Indianapolis, IN). Triglycerides were measured using Triglyceride GB reagent (Roche Diagnostics, Indianapolis, IN). LDL was calculated using the Friedewald equation if the triglyceride concentration was <400 mg/dL (LDL-C = TC – HDL-C – triglyceride/5.0) [18].

2.2 Electrocardiograms:

Three consecutive 10-second 12-lead digitized electrocardiograms (ECGs) (GE MAC 1200 electrocardiographs) were recorded in a standardized manner with the patient resting supine. These were read centrally using an automated process at the Epidemiological Cardiology Research Center (EPICARE; Wake Forest University School of Medicine, NC) using the 2001 version of the GE Marquette 12-SL program (GE, Milwaukee, Wisconsin, USA). They were analyzed using the Minnesota criteria to ascertain prior Q-wave infarctions, and to extract indices of heart rate variability (HRV) as measures of cardiovascular autonomic neuropathy as also described below. ECG analyses were funded and implemented late in 2013, resulting in missing baseline ECGs for 214 participants.

2.3 Complication Ascertainment and Outcomes Definitions:

Nephropathy was assessed using laboratory testing, as described above, and defined as the presence of either ACR≥30 mg/gram or eGFR<60 ml/min/m^2/ 1.73 m^2, in accordance with current definitions from national guidelines [3, 19].

Retinopathy was ascertained by self-report. Participants were asked whether they had been diagnosed with diabetic eye disease or had been treated with laser therapy, eye injections, or eye surgery for diabetic eye disease.

Diabetic peripheral neuropathy (DPN) was ascertained using the Michigan Neuropathy Screening Instrument (MNSI) as priorly reported [7, 20, 21]. It includes a 15-item interviewer-administered symptom questionnaire, plus a bilateral lower extremity clinical examination assessing ankle reflexes, vibration sensation at the great toes, and abnormalities in foot appearance including amputations. DPN was defined using a composite cut-off including both the MNSI questionnaire score and the clinical examination as previously reported [20].

Cardiovascular autonomic neuropathy (CAN) was defined using indices of HRV derived from standard 12-lead ECG recordings using the recently published cut-points defining abnormally low variability based on recently published population norms from the Multi-Ethnic Study of Atherosclerosis (MESA) [22]. Two HRV indices were employed: standard deviation of normally conducted R-R intervals (SDNN) <8.2 ms, and root mean square of successive differences between normal-to-normal R-R intervals (rMSSD) <8 ms [22]. CAN was defined as the presence of abnormal values for both SDNN and rMSSD.

Myocardial infarction (MI) was ascertained by self-report (participants were asked, “Have you had a heart attack?”), and from automatically scored ECGs, as above. Stroke was ascertained by self-report (participants were asked, “Have you had a stroke?”).

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The number of evaluable subjects (denominators) for each complication varied owing to participants with missing data or technically inadequate samples.

2.4 Statistical Methods:

Discrete variables were summarized using counts and percentages, while continuous variables were summarized using means and standard deviations. The association between risk factors and outcomes was assessed separately by specific complication. Owing to small numbers, American Indian/Alaska Native, Asian, Native Hawaiian or Pacific Islander and multiple race categories (including unknown/not reported) were combined, and race was evaluated as three categories (White/African American/Other). Ethnicity was defined as Hispanic/Non-Hispanic. Odds ratios for the association between risk factors and outcomes were obtained using logistic regression models adjusted for age and sex, with additional adjustment for antihypertensive medications or lipid lowering agents for evaluation of blood pressure and lipid associations, respectively. The odds ratio (OR) for a continuous risk factor was expressed per 1 unit increment in that factor, such that the odds ratio per x units change in that risk factor is $(OR)^x$. The accompanying p value expresses whether this regression coefficient differs from zero. Statistical significance was set at $p<0.05$ without adjustment for multiple comparisons.

We were interested in providing a quantitative comparison of the strength of association of risk factors with various complications. For a quantitative risk factor (such as age), odds ratios can be made as large or small as desired by changing the units of that risk factor (e.g., per 1 day, 1 year, or per 10 years of age). In contrast, Wald Z-test values, calculated as the ratio of the estimate (log odds ratio in a logistic regression) to its standard error, are unitless, but directional such that positive Z-values correspond to direct associations, and negative Z-values corresponding to inverse associations. In addition, as any Z statistic with an absolute value of 3.89 or larger has $P<0.0001$, reporting Z values better presents information about the association under evaluation than is possible in simply reporting “$p<0.0001$”. Therefore, Z-values were used to present comparisons of the relative magnitude of risk factor associations with a given complication and were depicted using spider-plots.

RESULTS

General characteristics of the GRADE cohort have been previously presented in detail [16]. The average (mean ±SD) known diabetes duration by self-report was 4.0±2.7 years. Table 1 presents the prevalence (count (%) and denominator) of diabetes-related microvascular and macrovascular complications. For each complication, the summary statistics for selected demographic and risk factors among the cases is presented, as well at the summary statistics for the complete cohort. Micro- and macrovascular complications are assessed in relation to a more comprehensive set of demographic, laboratory and clinical measures in Supplemental Tables 1 and 2. Supplemental Table 3 presents assessment of prevalence by individual component measures of complications against the more comprehensive set of risk factors.

As shown in Table 1, the prevalence of complications ranged from 7.3% (myocardial infarction, ascertained in 4.1% by self-report and 3.2% by ECG measurement) to 21.5% (peripheral neuropathy, ascertained by the MNSI). The combined prevalence of nephropathy

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was 18%, principally based upon elevated single measures of urine albumin/creatinine ratio (15.9%) rather than reduced eGFR (2.4%) (Supplemental Table 3). Self-reported retinopathy was present in 1% of the cohort, and self-reported stroke was present in 2%.

Figure 1 presents spider plots demonstrating associations among risk factors and complications for participants. These plots provide a visual quantification of the magnitude of associations, summarizing details provided in the tables. Stronger associations are reflected by larger Z scores. Age was directly associated with prevalence of complications, with very high Z scores (Figure 1A). Female sex was associated with lower prevalence of complications, with a strong protective effect for myocardial infarction (Z= −5.9). Compared to White race, African American race was associated with a lower CAN prevalence (Z= −4.3). Those in the “Other” race category were also less likely to have CAN (Z= −2.2) but had a higher prevalence of nephropathy (Z= +2.2).

There were no associations between any of the assessed complications and diabetes duration, HbA1c at the time of eligibility screening, or the calculated total glycemic exposure estimate based on years since self-reported diagnosis (Figure 1B, Tables 1). Obesity measures were directly associated with nephropathy, DPN and CAN but not with stroke or myocardial infarction (Figure 1B, Table 1).

Associations of complications with blood pressure and lipids levels, and smoking are presented in Figure 1C and in Table 1. Systolic and diastolic blood pressure were directly associated with nephropathy, but not with DPN, myocardial infarction, or stroke. Diastolic blood pressure was directly associated with CAN (Table 1). In contrast, the presence of diagnosed hypertension or self-reported use of blood pressure lowering medications were strongly and directly associated with nephropathy (Z= +7.2 and +6.6, respectively), DPN (Z=+3.3 and +2.9, respectively), and myocardial infarction (Z= +6.8 and +6.9, respectively) (Supplemental Tables 1 and 2). These associations were much stronger than associations for blood pressure values as continuous measures.

These lipid and blood pressure values, and their associations with complications detailed above, were observed in the context of reasonably high prevalence of appropriately targeted medications. For example, use of Renin-Angiotensin System inhibitors [angiotensin receptor blockers (ARBs) or angiotensin converting enzyme (ACE) inhibitors] by self-report was 58%, calcium channel blockers was 14%, and statin use was 64%. Medication use was higher among the participants with prevalent diabetes complications. For example, 69% of the participants with nephropathy were on either ARBs or ACE inhibitors (20% on ARBs, 50% on ACE inhibitors, and 1% on both). Likewise, of the participants with an MI, 91% were on antihypertensive medications, and 83% were on statins. Of the participants with a stroke, 91% were on antihypertensive medications, and 79% were on statins.

Associations of complications with lipoproteins and with metabolic syndrome, defined using ATP III criteria [23], are presented in Figure 1C and in Supplemental Tables 1 and 2. LDL-cholesterol was not associated with myocardial infarction after adjustment for use of lipid lowering medications. HDL-cholesterol was inversely associated with nephropathy (Z=−3.3), DPN (Z= −4.7), CAN (Z= −2.0) and MI (Z= −3.1). Triglycerides were strongly

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associated with nephropathy (Z= +6.4), DPN (Z= +4.3) and CAN (Z= +5.8), but not with myocardial infarction or stroke. The metabolic syndrome, present in 91% of the cohort, was directly associated with nephropathy (Z= +3.6), DPN (Z= +2.4), and myocardial infarction (Z= +2.7), concordant with the underlying lipid and blood pressure relationships described above.

Table 2 presents the nephropathy-related variables according to KDIGO categories to describe our cohort using this classification system. This demonstrates that in this cohort more participants presented with elevated ACR than reduced eGFR, although more advanced proteinuria (≥300 mg/g) was present in only few cases (1.66%).

DISCUSSION

We report the prevalence of microvascular and macrovascular complications in eligible GRADE participants at the time of eligibility screening, prior to initiation of any protocol-driven changes in treatment. At screening, the GRADE cohort had an average of known diabetes duration of 4 years, HbA1c ~8.0% (~64 mmol/mol), and was obese with an average BMI of 34.3 kg/m^2. Some distinctive characteristics of this cohort are driven by the facts that the known diabetes duration and HbA1c were restricted by trial inclusion/exclusion criteria: duration <10 years and HbA1c 51–69 mmol/L (6.8% – 8.5%) at the end of run-in, as well as absence of any major CVD events within prior year or history of congestive heart failure NYHA 3 or greater. However, the GRADE cohort is similar to other contemporary US diabetes populations in terms of obesity (BMI ~34 kg/m^2), smoking (46% current or past), and treatment with blood pressure medications (69%) and lipid lowering medications (66%). [16, 19, 24]

Diabetes-associated complications were observed in our cohort, with prevalence of directly ascertained complications ranging from 7% (for myocardial infarction) to 21.5% (for diabetic peripheral neuropathy assessed with the Michigan Neuropathy Screening Instrument).

The observed rate of diabetic nephropathy in this cohort was 18.1%. This rate is principally driven by modestly elevated albumin/creatinine ratios and the systematic exclusion of participants with serum creatinine >1.4 mg/dl in women and >1.5 mg/dl in men by study design. These measurements were not confirmed using repeat testing, and therefore may overestimate the prevalence of albuminuria [25–27]. Conversely, given the high prevalence of guideline-driven blood pressure lowering medications [16], this could be an underestimate. This observed prevalence is higher than the ~6% prevalence seen in the pre-diabetic population in the Diabetes Prevention Program [27, 28] but is comparable to prevalence reported in populations with established T2D [29–33]. Expected associations with obesity, blood pressure, and lipids were observed. Only a very small subset of this population (1.66%) had evidence of more advanced albuminuria defined as ACR ≥ 300 mg/g at study entry (Table 2). GRADE selection criteria largely excluded individuals with stage 3 chronic kidney disease (G3), but the majority of those with abnormal proteinuria (A2 or greater) had eGFR exceeding 60 ml/min/1.73 m^2.

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We observed a 21.5% prevalence of DPN in GRADE ascertained using the validated MNSI, administered by trained certified personnel. The MNSI has been successfully used in large cohorts with T2D and T1D [7, 20, 21]. This prevalence is consistent with that found in other cohorts of patients with newly diagnosed T2D or prediabetes, such as the Danish arm of the Anglo-Danish-Dutch study of Intensive Treatment of Diabetes in Primary Care (ADDITION; 13% among those with screen-detected diabetes), the San Luis Valley Study (11% prediabetes, 26% diabetes), and MONICA/KORA (13% prediabetes, 28% diabetes), although there were some variations in the scoring algorithm(s) or outcome measures used to define DPN among these other cohorts[34–36]. In the GRADE cohort, age was the strongest risk factor for DPN, but other non-glycemic variables were also strongly associated including obesity, hypertension, and low HDL-cholesterol and high triglycerides. These observations are concordant with data from other contemporary cohorts with T2D or obesity [34–37].

CAN was ascertained based on indices of HRV derived from standard 12-lead ECG recordings using the recently published cut-points defining abnormally low variability as described [22]. Indices of HRV obtained from 10-second 12-lead ECGs recordings have been used successfully in several other large cohorts and demonstrated to be accurate predictors for mortality and cardiovascular risk [21, 36]. The CAN prevalence found in the GRADE cohort is comparable with reports from other cohorts with early T2D such as the ADDITION study, which reported prevalence of 9.0% after approximately six years follow-up and 15% after thirteen years of follow-up [34]. The risk factors most strongly associated with the presence of CAN were age, obesity, blood pressure and dyslipidemia, consistent with others [38]. The observation of lower prevalence of CAN in non-White races in the GRADE cohort adds to an inconsistent body of literature on race/ethnicity differences, with population-based studies reporting lower, matching, or higher rates of CAN and other complications in non-White race groups [39–41].

Myocardial infarction was assessed by a combination of self-report (5.1% prevalence) and automated detection of Q waves on ECG readings (3.2% prevalence), with a combined prevalence of 7.3%. Age and sex exhibited expected relationships with this outcome. Hypertension (Z= +6.8) and smoking (Z= +4.7) were also associated as expected, but among the continuous variables, only HDL cholesterol values were associated after adjustment for statin exposures with prior myocardial infarction in this cohort. The associations between blood pressure variables and myocardial infarction were modest compared with strong blood pressure effects on nephropathy, and blood pressures levels were not associated with self-reported stroke.

Notably, in our analyses, glycemia assessed by HbA1c measured in the local laboratory at the time of eligibility screening was not associated with any of the assessed complications. This is in contrast to a well-established literature demonstrating relationships between glycemia or glycemic exposure and various diabetes-related complications [7–10]. The short known duration of diagnosed diabetes, the relatively low total glycemic exposure, and the narrow range of glycemia owing to the eligibility criteria, namely HbA1c between 51 and 69 mmol/mol (6.8% and 8.5%) may have contributed to the failure to demonstrate an association of glycemia with the assessed complications. Self-reported duration of diabetes

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plus uncertainty and variability in the timing of diagnosis relative to timing of disease onset limits interpretation of this observation.

The time course of glycemia in the pre-screening window is unknown. However, the eligibility screening HbA1c best reflects the status of each patient over the period since diagnosis and prior to intervention. After, screening subjects were enrolled into a run-in period where the metformin dose was titrated upwards resulting in a decline in HbA1c. However, this screening HbA1c was measured at each clinical center local laboratory. Heterogeneity among local laboratory distributions, and random variation within laboratories could have dampened the association of the screening HbA1c with complications.

These observations allow us to focus on the relevance and impact of the non-glycemic risk factors for the assessed complications; traditional non-glycemic risk factors confer risk for diabetes-related complications in early type 2 diabetes, even in the absence of a strong relationship with glycemia. This message has been implicit in risk equations, for example the RECODe equation [42], where the contributions of risk factors other than glycemia can be quantified. These observations highlight the importance of a multifactorial approach to risk management in type 2 diabetes [43].

Strengths of this study include the objective ascertainment of nephropathy, peripheral neuropathy, and cardiovascular autonomic neuropathy. Ascertainment of prior Q-wave myocardial infarction was supplemented with self-reported events, confirming and extending the prevalence estimate. Weaknesses include the ascertainment of stroke and particularly retinopathy by self-report; prior studies have shown that self-report of retinopathy is insensitive to mild disease evident on retinal evaluations but not requiring ocular intervention [44, 45]. Other weaknesses include the fact that true diabetes duration is unknown, and the fact that these cross-sectional analyses of prevalent medical conditions and treatments are uninformative regarding temporal sequences and therefore cannot be used for inferences of causality.

In summary, in the GRADE cohort we observed rates of traditional diabetes-related complications ranging from 7–21%. These complications overall exhibited expected relationships with non-glycemic risk factors. The observed lack of association with glycemia measures is likely attributed to the constraints on diabetes duration and glycemia imposed by study enrollment criteria, but these observations highlight the relevance of non-glycemic risk factors even for complications traditionally viewed as glucose-related.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

The GRADE Study is supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health under Award Number U01DK098246. The planning of GRADE was supported by a U34 planning grant from the NIDDK (U34-DK-088043). The American Diabetes Association supported the initial planning meeting for the U34 proposal. The National Heart, Lung, and Blood

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Institute and the Centers for Disease Control and Prevention also provided funding support. The Department of Veterans Affairs provided resources and facilities. Additional support was provided by grant numbers P30 DK017047, P30 DK020541-44, P30 DK020572, P30 DK072476, P30 DK079626, P30 DK092926, U54 GM104940, UL1 TR000439, UL1 TR000445, UL1 TR001108, UL1 TR001409, UL1 TR001449, UL1 TR002243, UL1 TR002345, UL1 TR002378, UL1 TR002489, UL1 TR002489, UL1 TR002529, UL1 TR002535, UL1 TR002537, and UL1 TR002548. Educational materials have been provided by the National Diabetes Education Program. Material support in the form of donated medications and supplies has been provided by BD, Bristol-Myers Squibb, Merck, NovoNordisk, Roche Diagnostics, and Sanofi. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Dualities of Interest: RMC reports grants from National Institutes of Health, during the conduct of the study; “other” conflicts from Bristol Myers Squibb, “other” conflicts from Pfizer, outside the submitted work. CD reports grants and personal fees from Novo Nordisk, personal fees from Astra Zeneca, grants from Sanofi, grants from the Department of Defense, outside the submitted work. JBG reports grants from NIDDK, during the conduct of the study; grants and personal fees from Boehringer Ingelheim, grants from Sanofi, grants from GlaxoSmithKline, grants from Intarcia Therapeutics, grants and personal fees from AstraZeneca, personal fees from Daiichi, personal fees from NovoNordisk, grants from Merck, personal fees from PriMedCME, personal fees from Horizon CME, personal fees from Potomac Center for Medical Education, personal fees from Guthrie Clinic, personal fees from University of Kentucky, personal fees from Bioscientifica, personals fees from The Endocrine Society, outside the submitted work. MSK reports grants from Novo Nordisk, grants from Theracos, grants from Bayer, outside the submitted work. ERS reports grants and personal fees from Eli Lilly, personal fees from Sanofi, personal fees from Zucara, personal fees from MannKind, outside the submitted work. DJW reports other from NovoNordisk, outside the submitted work. RPB reports grants from National Institute of Diabetes and Digestive and Kidney Diseases, NIH (U34 DK088043 and U01 DK098246, from National Heart, Lung, and Blood Institute, from Centers for Disease Control and Prevention, and from The American Diabetes Association during the conduct of the study; grants from Astra Zeneca, personal fees from Novo Nordisk, outside the submitted work. KJM, IB, CB, JPC, HKS, MEL, JP, EZS, and EBS have nothing to disclose.

REFERENCES

1. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D: Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care 2017, 40(1):136–154. [PubMed: 27999003]
2. Solomon SD, Chew E, Duh EJ, Sobrin L, Sun JK, VanderBeek BL, Wykoff CC, Gardner TW: Diabetic Retinopathy: A Position Statement by the American Diabetes Association. Diabetes Care 2017, 40(3):412–418. [PubMed: 28223445]
3. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD et al.: Diabetic kidney disease: A report from an ADA Consensus Conference. Diabetes Care 2014, 37(10):2864–2883. [PubMed: 25249672]
4. Brownrigg JR, Hughes CO, Burleigh D, Karthikesalingam A, Patterson BO, Holt PJ, Thompson MM, de Lusignan S, Ray KK, Hinchliffe RJ: Microvascular disease and risk of cardiovascular events among individuals with type 2 diabetes: a population-level cohort study. Lancet Diabetes Endocrinol 2016, 4(7):588–597. [PubMed: 27216886]
5. Gregg EW, Sattar N, Ali MK: The changing face of diabetes complications. Lancet Diabetes Endocrinol 2016, 4(6):537–547. [PubMed: 27156051]
6. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF: Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr 2010, 8:29. [PubMed: 20969750]
7. Pop-Busui R, Lu J, Brooks MM, Albert S, Althouse AD, Escobedo J, Green J, Palumbo P, Perkins BA, Whitehouse F et al.: Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Cohort. Diabetes Care 2013, 36(10):3208–3215. [PubMed: 23757426]
8. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN, DCCT/EDIC Research Group: Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial--revisited. Diabetes 2008, 57(4):995–1001. [PubMed: 18223010]
9. Buehler AM, Cavalcanti AB, Berwanger O, Figueiro M, Laranjeira LN, Zazula AD, Kioshi B, Bugano DG, Santucci E, Sbruzzi G et al.: Effect of tight blood glucose control versus conventional

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control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized controlled trials. Cardiovasc Ther 2013, 31(3):147–160. [PubMed: 22212499]

10. CONTROL Group, Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR et al.: Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009, 52(11):2288–2298. [PubMed: 19655124]
11. Khanam PA, Hoque S, Begum T, Habib SH, Latif ZA: Microvascular complications and their associated risk factors in type 2 diabetes mellitus. Diabetes Metab Syndr 2017, 11 Suppl 2:S577–S581. [PubMed: 28455164]
12. Bjerg L, Hulman A, Carstensen B, Charles M, Jorgensen ME, Witte DR: Development of Microvascular Complications and Effect of Concurrent Risk Factors in Type 1 Diabetes: A Multistate Model From an Observational Clinical Cohort Study. Diabetes Care 2018, 41(11):2297–2305. [PubMed: 30131399]
13. Perreault L, Pan Q, Aroda VR, Barrett-Connor E, Dabelea D, Dagogo-Jack S, Hamman RF, Kahn SE, Mather KJ, Knowler WC et al.: Exploring residual risk for diabetes and microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS). Diabet Med 2017.
14. Bebu I, Braffett BH, Orchard TJ, Lorenzi GM, Lachin JM, DCCT/EDIC Research Group: Mediation of the Effect of Glycemia on the Risk of CVD Outcomes in Type 1 Diabetes: The DCCT/EDIC Study. Diabetes Care 2019, 42(7):1284–1289. [PubMed: 30894365]
15. Nathan DM, Buse JB, Kahn SE, Krause-Steinrauf H, Larkin ME, Staten M, Wexler D, Lachin JM, GRADE Study Research Group: Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). Diabetes Care 2013, 36(8):2254–2261. [PubMed: 23690531]
16. Wexler DJ, Krause-Steinrauf H, Crandall JP, Florez HJ, Hox SH, Kuhn A, Sood A, Underkofler C, Aroda VR, Grade Research Group: Baseline Characteristics of Randomized Participants in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care 2019.
17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T et al.: A new equation to estimate glomerular filtration rate. Ann Intern Med 2009, 150(9):604–612. [PubMed: 19414839]
18. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972, 18(6):499–502. [PubMed: 4337382]
19. American Diabetes Association: 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019, 42(Suppl 1):S124–S138. [PubMed: 30559237]
20. Herman WH, Pop-Busui R, Braffett BH, Martin CL, Cleary PA, Albers JW, Feldman EL, DCCT/EDIC Research Group: Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. Diabet Med 2012, 29(7):937–944. [PubMed: 22417277]
21. Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH Jr. et al.: Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010, 376(9739):419–430. [PubMed: 20594588]
22. O'Neal WT, Chen LY, Nazarian S, Soliman EZ: Reference ranges for short-term heart rate variability measures in individuals free of cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA). J Electrocardiol 2016, 49(5):686–690. [PubMed: 27396499]
23. Grundy SM, Brewer HB Jr., Cleeman JI, Smith SC Jr., Lenfant C, National Heart Lung and Blood Institute, American Heart Association: Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Arterioscler Thromb Vasc Biol 2004, 24(2):e13–18. [PubMed: 14766739]
24. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW et al.: 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019.

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25. Mullis P, Kochli HP, Zuppinger K, Schwarz HP: Intermittent microalbuminuria in children with type 1 diabetes mellitus without clinical evidence of nephropathy. Eur J Pediatr 1988, 147(4):385–388. [PubMed: 3294013]
26. Mason HJ, Stevenson AJ, Williman N, Morgan M: Intra individual variability in markers of proteinuria for normal subjects and those with cadmium induced renal dysfunction: interpretation of results from untimed, random urine samples. Biomarkers 1999, 4(2):118–128. [PubMed: 23885829]
27. Diabetes Prevention Program Research Group: Changes in albumin excretion in the diabetes prevention program. Diabetes Care 2009, 32(4):720–725. [PubMed: 19131464]
28. Mather KJ, Pan Q, Knowler WC, Funahashi T, Bray GA, Arakaki R, Falkner B, Sharma K, Goldstein BJ, Diabetes Prevention Program Research Group: Treatment-Induced Changes in Plasma Adiponectin Do Not Reduce Urinary Albumin Excretion in the Diabetes Prevention Program Cohort. PLoS One 2015, 10(8):e0136853. [PubMed: 26312480]
29. Bakris G, Viberti G, Weston WM, Heise M, Porter LE, Freed MI: Rosiglitazone reduces urinary albumin excretion in type II diabetes. J Hum Hypertens 2003, 17(1):7–12. [PubMed: 12571611]
30. Cooper ME, Perkovic V, McGill JB, Groop PH, Wanner C, Rosenstock J, Hehnke U, Woerle HJ, von Eynatten M: Kidney Disease End Points in a Pooled Analysis of Individual Patient-Level Data From a Large Clinical Trials Program of the Dipeptidyl Peptidase 4 Inhibitor Linagliptin in Type 2 Diabetes. Am J Kidney Dis 2015, 66(3):441–449. [PubMed: 25960304]
31. Bakris GL, Toto RD, McCullough PA, Rocha R, Purkayastha D, Davis P, Guard Study Investigators: Effects of different ACE inhibitor combinations on albuminuria: results of the GUARD study. Kidney Int 2008, 73(11):1303–1309. [PubMed: 18354383]
32. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B et al.: Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med 2016.
33. O'Connor PJ, Ismail-Beigi F: Near-Normalization of Glucose and Microvascular Diabetes Complications: Data from ACCORD and ADVANCE. Ther Adv Endocrinol Metab 2011, 2(1):17–26. [PubMed: 23148169]
34. Andersen ST, Witte DR, Dalsgaard EM, Andersen H, Nawroth P, Fleming T, Jensen TM, Finnerup NB, Jensen TS, Lauritzen T et al.: Risk Factors for Incident Diabetic Polyneuropathy in a Cohort With Screen-Detected Type 2 Diabetes Followed for 13 Years: ADDITION-Denmark. Diabetes Care 2018, 41(5):1068–1075. [PubMed: 29487078]
35. Franklin GM, Kahn LB, Baxter J, Marshall JA, Hamman RF: Sensory neuropathy in non-insulin-dependent diabetes mellitus. The San Luis Valley Diabetes Study. Am J Epidemiol 1990, 131(4):633–643. [PubMed: 2316495]
36. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A, Kora Study Group: Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. Diabetes Care 2008, 31(3):464–469. [PubMed: 18039804]
37. Callaghan BC, Xia R, Reynolds E, Banerjee M, Rothberg AE, Burant CF, Villegas-Umana E, Pop-Busui R, Feldman EL: Association Between Metabolic Syndrome Components and Polyneuropathy in an Obese Population. JAMA Neurol 2016, 73(12):1468–1476. [PubMed: 27802497]
38. Moon SS, Choi YK, Seo HA, Jeon JH, Lee JE, Jeong JY, Lee JY, Lee DH, Park WJ, Kim JG et al.: Relationship between cardiovascular autonomic neuropathy and coronary artery calcification in patients with type 2 diabetes. Endocr J 2010, 57(5):445–454. [PubMed: 20185862]
39. Konen JC, Summerson JH, Bell RA, Curtis LG: Racial differences in symptoms and complications in adults with type 2 diabetes mellitus. Ethn Health 1999, 4(1–2):39–49. [PubMed: 10887461]
40. Winkley K, Thomas SM, Sivaprasad S, Chamley M, Stahl D, Ismail K, Amiel SA: The clinical characteristics at diagnosis of type 2 diabetes in a multi-ethnic population: the South London Diabetes cohort (SOUL-D). Diabetologia 2013, 56(6):1272–1281. [PubMed: 23494447]
41. Tahrani AA, Altaf QA, Piya MK, Barnett AH: Peripheral and Autonomic Neuropathy in South Asians and White Caucasians with Type 2 Diabetes Mellitus: Possible Explanations for Epidemiological Differences. J Diabetes Res 2017, 2017:1273789. [PubMed: 28409160]

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42. Basu S, Sussman JB, Berkowitz SA, Hayward RA, Yudkin JS: Development and validation of Risk Equations for Complications Of type 2 Diabetes (RECODe) using individual participant data from randomised trials. The Lancet Diabetes & Endocrinology 2017, 5(10):788–798. [PubMed: 28803840]

43. Gaede P, Oellgaard J, Carstensen B, Rossing P, Lund-Andersen H, Parving HH, Pedersen O: Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia 2016, 59(11):2298–2307. [PubMed: 27531506]

44. Grassi MA, Mazzulla DA, Knudtson MD, Huang WW, Lee KE, Klein BE, Nicolae DL, Klein R: Patient self-report of prior laser treatment reliably indicates presence of severe diabetic retinopathy. Am J Ophthalmol 2009, 147(3):501–504. [PubMed: 19054495]

45. Patty L, Wu C, Torres M, Azen S, Varma R, Los Angeles Latino Eye Study Group: Validity of self-reported eye disease and treatment in a population-based study: the Los Angeles Latino Eye Study. Ophthalmology 2012, 119(9):1725–1730. [PubMed: 22537615]

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Highlights

- In the GRADE cohort prevalence of diabetes-related complications at baseline ranged from 7–21%.
- These complications overall exhibited expected relationships with non-glycemic risk factors.
- Expected relationships with glycemia were not seen, likely owing to study enrollment criteria.
- These observations provide a baseline for observations of randomized treatment effects.

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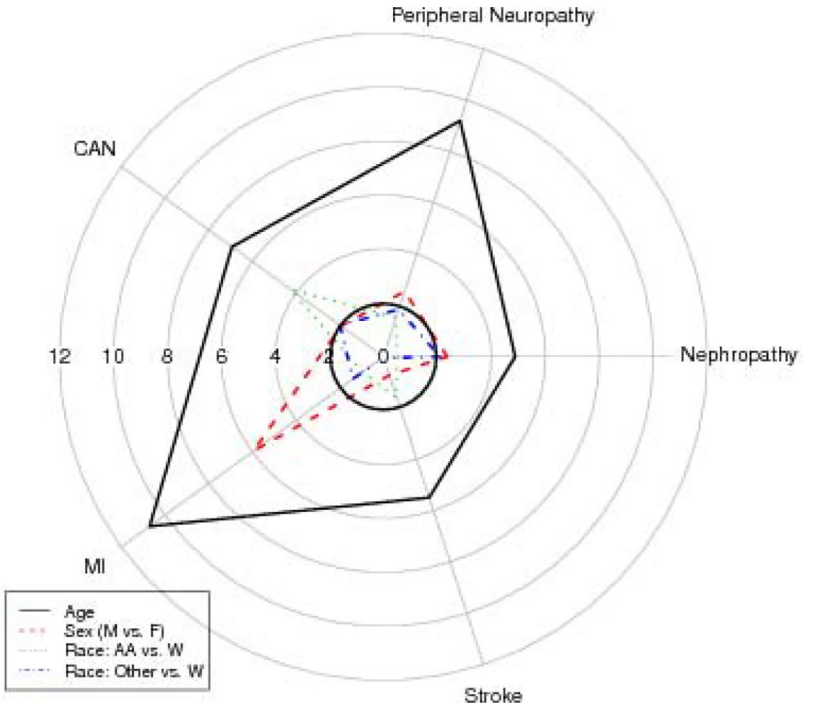

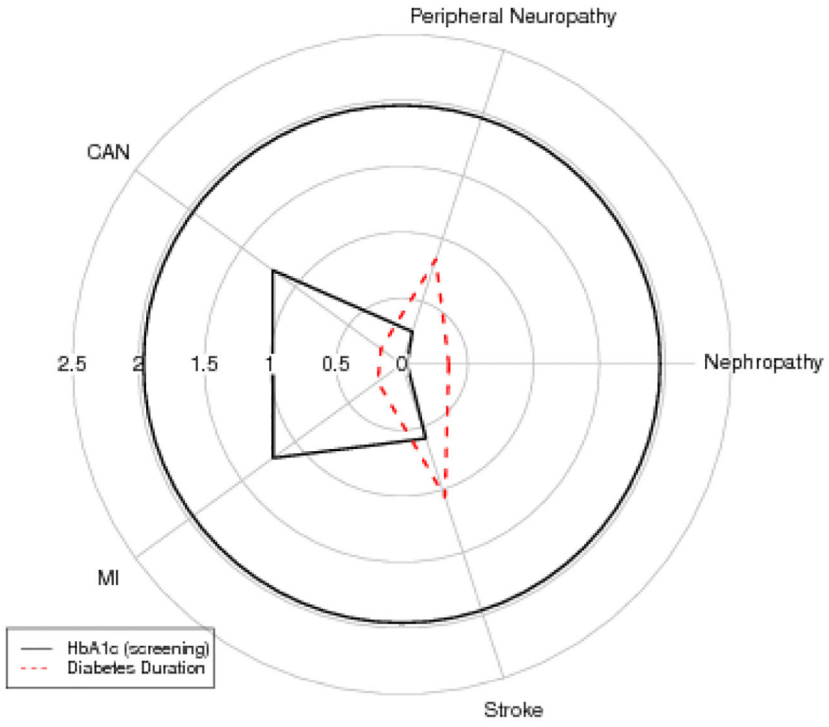

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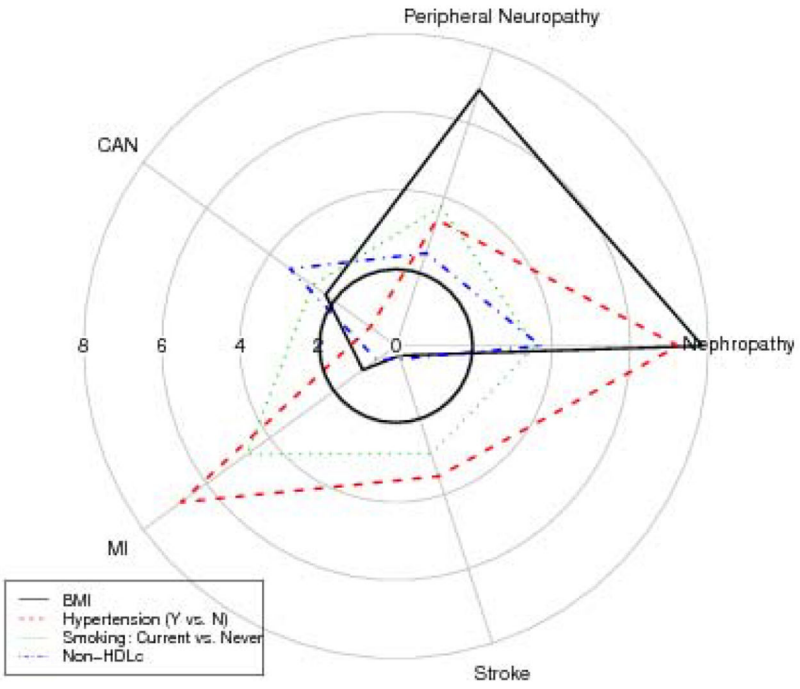

Figure 1.

Spider plots presenting absolute Z-scores relating risk factors (lines within the plots) with complications (on the rays), allowing assessment of relative strengths of risk factor associations across the various complications. The grey circles describe z-scale values; z-values larger than 1.96 in absolute value (outside the black circle) are considered nominally significant. Panel A, associations of age, sex and race with individual micro- and macrovascular complications in logistic regression models. The model evaluating age was adjusted for sex, and vice versa; the model evaluating race was adjusted for sex and race. Panel B, associations of HbA1c and known diabetes duration with individual micro- and macrovascular complications in logistic regression models adjusted for age and sex. Panel C, associations of body mass index (BMI), smoking, hypertension and non-HDL cholesterol (non-HDLc) with individual micro- and macrovascular complications in logistic regression models adjusted for age and sex. Absolute Z values are presented as the measure of strength of association. The Z-score for non-HDLc was obtained from logistic regression models adjusted for lipid-lowering agents. This presentation compares strengths of association; magnitude and directionality of these relationships are found in Table 1 and Supplemental Tables 1 and 2. Note that the scales in the three panels are different.

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Table 1 –

Microvascular and Macrovascular Complications in GRADE: Prevalence in association with selected risk factors

	Full Study Cohort	NePhroPathy		PeriPheral Neuropathy		Cardiovascular Autonomic Neuropathy		Myocardial Infarction		Stroke	
Count (%) [Denominator]	**5047**	**897 (18.1%) [4947]**		**1083 (21.5%) [5023]**		**452 (9.7%) [4629]**		**368 (7.3%) [4994]**		**103 (2.0%) [5047]**	
	Mean (SD) or %	**Mean (SD) or %**	**OR p**	**Mean (SD) or %**	**OR p**	**Mean (SD) or %**	**OR p**	**Mean (SD) or %**	**OR p**	**Mean (SD) or %**	**OR p**
Age (year)	56.7 (10)	58.3 (10.4)	**1.02** <0.0001	59.3 (9.4)	**1.03** <0.0001	59.7 (8.9)	**1.04** <0.0001	62.6 (7.8)	**1.04** <0.0001	62.2 (8)	**1.06** 0.0001
Sex (Females, %)[1]	36	32	**0.83** 0.018	31	**0.83** 0.01	31	0.81 0.053	18	**0.43** <0.0001	29	0.85 0.47
Race African-American[2]	20	18	0.95 0.61	17	0.87 0.13	15	0.51 <0.0001	14	0.86 0.34	23	1.49 0.11
Race Other[2]	14	16	**1.25** 0.04	11	0.82 0.07	10	**0.72** 0.048	9	0.76 0.16	11	1.02 0.95
BMI (kg/m^2)	34.3 (6.8)	35.6 (7.5)	**1.04** <0.0001	35.1 (6.9)	**1.04** <0.0001	34.4 (7)	**1.02** 0.026	33.7 (6)	1.01 0.29	33.4 (5.8)	1.00 0.80
HbA1C screening (%)	8.0 (1.0)	8.0 (1.0)	1.00 0.97	8.0 (1.0)	1.01 0.80	7.9 (0.9)	0.94 0.23	7.8 (0.9)	0.93 0.22	7.8 (0.9)	0.94 0.55
HbA1C screening (mmol/mol)	64 (11)	64 (11)	1.00 0.97	64 (11)	1.00 0.80	63 (10)	0.99 0.23	62 (10)	0.99 0.22	62 (10)	0.99 0.55
Known Diabetes Duration (years)	4 (2.7)	4.1 (2.8)	1.01 0.72	4.3 (2.8)	1.01 0.40	4.3 (2.8)	1.00 0.84	4.4 (2.8)	1.00 0.82	4.7 (3)	1.04 0.29
Systolic BP (mm Hg)	128.3 (14.7)	131.7 (16.2)	**1.02** <0.0001	129.3 (14.6)	1.00 0.38	129.9 (15.7)	1.00 0.28	130.1 (16.3)	1.00 0.69	131.7 (15.6)	1.01 0.17
Diastolic BP (mm Hg)[4]	77.3 (9.9)	78.4 (10.9)	**1.02** 0.0001	77 (10)	1.00 0.60	77.8 (10.5)	**1.01** 0.019	76.8 (10.7)	1.00 0.46	77.2 (10.6)	1.01 0.36
LDLc mmol/L)	2.35 (0.81)	2.34 (0.83)	1.00 0.37	2.33 (0.79)	1.00 0.55	2.30 (0.77)	1.00 0.97	2.12 (0.79)	1.00 0.33	2.27 (0.86)	1.00 0.21
HDLc (mmol/L)	1.12 (0.31)	1.09 (0.29)	**0.99** 0.0008	1.08 (0.29)	**0.98** <0.0001	1.09 (0.30)	**0.99** 0.042	1.06 (0.28)	**0.52** 0.002	1.14 (0.35)	1.22 0.55
(log) Triglycerides (mmol/L)	4.9 (0.6)	5.0 (0.6)	**1.51** <0.0001	4.9 (0.6)	**1.30** <0.0001	5.0 (0.6)	**1.65** <0.0001	4.9 (0.5)	1.08 0.43	4.8 (0.5)	0.88 0.46
Smoking never[3] (%)	54	50	**0.68** 0.0004	46	**0.67** 0.0002	50	**0.68** 0.008	36	**0.46** <0.0001	42	**0.45** 0.0037
Smoking past[3] (%)	33	34	**0.69** 0.001	40	0.90 0.36	35	**0.67** 0.01	46	**0.69** 0.02	37	**0.49** 0.01

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Population values for risk factors, prevalences of diabetes-related complications, and associations among risk factors and complications evaluated as odds ratios. The denominator reflects the number of participants with evaluable data for each complication. Odds ratio analyses were adjusted for age and sex, except that the model for Age was adjusted only for Sex, while the model for Sex was adjusted only for Age.

[1]Sex: reference group=Males;

[2]Race: reference group=White;

[3]Smoking: reference group=Current smoker.

Analyses of blood pressure variables were performed with adjustment for antihypertensive medication use, and similarly analyses of lipid variables were performed with adjustment for lipid-lowering medication use. OR=odds ratio. The model for Age was adjusted only for Sex. The model for Sex was adjusted only for Age. The OR denotes the odds ratio per 1 unit change in a given risk factor, such that the odds ratio per *x* units change in that risk factor is (OR)^x. Odds ratios for terms with significant associations are highlighted in bold. More complete results (i.e., additional risk factors) are presented in Supplemental Table 1, with 95% confidence intervals and Wald z-values for the odds ratios reported in Supplemental Table 2.

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Table 2.

Estimated Glomerular Filtration Rate (eGFR) vs. Albumin:Creatinine Ratio (ACR cross-classification with number (%) of participants within each cell. Percent is expressed relative to the total number of participants.

	ACR (mg/g)				
eGFR (ml/min/1.73m^2)	**A1 (<30)**	**A2 (30–299)**	**A3 (≥300)**	**Missing**	**All**
G1 (≥90)	2719 (53.87)	456 (9.04)	41 (0.81)	52 (1.03)	3268 (64.75)
G2 (60–89)	1331 (26.37)	238 (4.72)	40 (0.79)	47 (0.93)	1656 (32.81)
G3a (45–59)	94 (1.86)	22 (0.44)	2 (0.04)	2 (0.04)	120 (2.38)
G3b (30–44)	1 (0.02)	0 (0.00)	1 (0.02)	0 (0.00)	2 (0.04)
Missing	1(0.02)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.02)
All	4146 (82.15)	716 (14.19)	84 (1.66)	101 (2.00)	5047 (100.00)