# Clinical and Metabolic Characterization of Adults With Type 2 Diabetes by Age in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) Cohort

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## OBJECTIVE

**Differences in type 2 diabetes phenotype by age are described, but it is not known whether these differences are seen in a more uniformly defined adult population at a common early stage of care. We sought to characterize age-related clinical and metabolic characteristics of adults with type 2 diabetes on metformin monotherapy, prior to treatment intensification.**

## RESEARCH DESIGN AND METHODS

**In the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE), participants were enrolled who had type 2 diabetes duration <10 years, had $HbA_{1c}$ 6.8–8.5%, and were on metformin monotherapy. Participants were randomly assigned to one of four additional glucose-lowering medications. We compared baseline clinical and metabolic characteristics across age categories (<45, 45 to <55, 55 to <65, and ≥65 years) using ANOVA and Pearson $\chi^2$ tests.**

## RESULTS

**Within the GRADE cohort ($n$ = 5,047), we observed significant differences by age, with younger adults having greater racial diversity, fewer medications for common comorbidities, lower prevalence of CVD, higher weight and BMI, and more pronounced hyperglycemia and diabetic dyslipidemia and with metabolic profile indicating lower insulin sensitivity (inverse fasting insulin [1/(fasting insulin)], HOMA of steady-state insulin sensitivity, Matsuda index) and inadequate β-cell response (oral disposition index) ($P < 0.05$ across age categories).**

## CONCLUSIONS

**Clinical and metabolic characteristics of type 2 diabetes differ by age within the GRADE cohort. Younger adults exhibit more prominent obesity-related characteristics, including higher obesity levels and lower insulin sensitivity and β-cell compensation. Given the increasing burden of type 2 diabetes and complications, particularly among younger populations, these age-related distinctions may inform risk factor management approaches and treatment priorities. Further study will determine whether age-related differences impact response to therapy.**



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**A complete list of members of the GRADE Research Group can be found in the supplementary material online.*

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Type 2 diabetes is highly heterogeneous, representing complex pathophysiology and patient-centered factors. Although type 2 diabetes is uniformly characterized by hyperglycemia due to inadequate β-cell insulin secretion, usually on a background of insulin resistance, its presentation and disease course vary considerably among individuals (1).

The heterogeneity of type 2 diabetes is increasingly appreciated, with implications of patient characteristics on disease progression and complication risk. Age has been recognized as an important variable mapping to different phenotypic presentations of type 2 diabetes (2). Studies at both ends of the age spectrum also implicate differences in phenotype presentation by age. The Restoring Insulin Secretion (RISE) studies contrast lower insulin sensitivity, greater insulin secretion, and more aggressive course of disease in youth with impaired glucose tolerance and early type 2 diabetes with those seen in adults with impaired glucose tolerance and early type 2 diabetes (3,4). At the older end of the age spectrum, diabetes is highly prevalent, affecting 29.2% of those aged ≥65 years (5). Age-related decline in pancreatic islet function, defects in insulin secretion, and a mild age-related diabetes phenotype have been described, suggesting distinct clinical and metabolic characteristics in older adults (2,6).

While there is an emerging picture of differences in characteristics and course of type 2 diabetes by age of onset, it is not known whether these differences are seen in a more uniformly defined adult population at a common early stage of care. The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) enrolled 5,047 adults with type 2 diabetes representing the initial stage of treatment intensification from metformin monotherapy to randomly assigned dual therapy (7). The objective of this analysis was to determine whether there are age-related differences in clinical and metabolic phenotype and concomitant cardiometabolic risk factors at this common initial treatment intensification stage. These differences, if seen, may have clinical implications for treatment priorities and response to given treatment.

## RESEARCH DESIGN AND METHODS

The study design for GRADE has previously been described (7,8). GRADE is a multicenter randomized controlled trial conducted at 36 centers across the U.S. (7). Clinical centers were selected through a competitive peer review in response to a funding opportunity announcement from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and selected in part to ensure broad national representation, including representation of the overall racial and ethnic diversity of people with type 2 diabetes. Sites varied in practice environment (e.g., academic, community, closed model HMOs, and Veterans Health Administration health care systems).

The full protocol can be accessed from https://grade.bsc.gwu.edu. The protocol was approved by the institutional review board at each clinical center. All participants gave written informed consent prior to any study procedures. The enrollment period was from July 2013 to August 2017. The ClinicalTrials.gov identifier is NCT01794143.

### Participants

GRADE was designed to represent patients early in the course of type 2 diabetes requiring treatment intensification following metformin monotherapy. Key randomization eligibility criteria included the following: type 2 diabetes diagnosed at age ≥30 years (or age ≥20 years for Native American/Alaskan Native patients), diabetes duration <10 years, metformin monotherapy with a minimum dose of 1,000 mg/day for a minimum of 8 weeks at final run-in, $HbA_{1c}$ 6.8–8.5% (51–69 mmol/mol), and willingness to take a second oral or injectable glucose-lowering medication as randomly assigned. Key exclusion criteria included use of diabetes medications other than metformin within the prior 6 months, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 $m^2$, history of severe liver disease or ALT >3 times upper limit of normal, major cardiovascular event within the previous year, history of pancreatitis, new diagnosis or treatment for cancer (other than nonmelanoma skin cancer) within the previous 5 years, and planned pregnancy for women of childbearing potential (7,8).

### Study Design

As previously described (7,8), GRADE is a multicenter, parallel treatment group, unmasked, randomized clinical trial. Eligibility was assessed at an initial screening visit. Eligible participants initiated a run-in period of 4–8 weeks during which the dose of metformin was titrated to 1,000 mg twice daily as tolerated, with extended-release metformin provided to those who could not tolerate immediate-release metformin. The run-in period was used to optimize background metformin monotherapy, provide diabetes education to all participants, and determine eligibility and ability to adhere to the study protocol. Final eligibility was determined at the final run-in visit, with a requirement of $HbA_{1c}$ 6.8–8.5% (51–69 mmol/mol) after ≥1,000 mg metformin daily for a minimum of 8 weeks. Eligible participants were then randomly assigned to one of four glucose-lowering medications (1:1:1:1): glimepiride (sulfonylurea), sitagliptin (dipeptidyl peptidase 4 inhibitor), liraglutide (glucagon-like peptide 1 receptor agonist), and glargine (basal insulin). Participants continued metformin therapy in addition to the randomly assigned treatment. Baseline data were analyzed for this analysis.

### Study Variables and Assessments

Baseline characteristics were assessed for participants during screening, run-in, and baseline randomization visits (see Supplementary Table 1 for schedule of study assessments). Data at or closest to baseline visit were analyzed and are presented. Information on demographic characteristics, medical history, and concomitant medications was collected by study staff. Race and ethnicity were obtained by self-report. Family history was defined as any first-degree relatives with diabetes. Atherosclerotic cardiovascular disease (ASCVD) pooled risk score (9) (https://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx) and Framingham Risk Score (10) were calculated. Study personnel were trained and certified on procedures for collection of physical measurements. Height, weight, and blood pressure were measured in duplicate, with height recorded to the nearest 0.1 cm and weight to the nearest 0.1 kg. Seated blood pressure was taken after 5 min rest and repeated after 1 min. Measurements were averaged. All laboratory tests were performed by the Central Biochemistry Laboratory (Advanced Research and Diagnostic Laboratory, Department of Laboratory Medicine and

**Table 1—Sociodemographic characteristics, medical history, concomitant medications, and comorbidities of GRADE cohort stratified by age-groups**

| | <45 years | 45 to <55 years | 55 to <65 years | ≥65 years | *P* |
|---|---|---|---|---|---|
| *N* | 623 | 1,436 | 1,778 | 1,210 | |
| Sociodemographic characteristics | | | | | |
| Female | 277 (44.5) | 580 (40.4) | 693 (39.0) | 287 (23.7) | <0.001 |
| Race | | | | | |
| White | 333 (53.5) | 891 (62.0) | 1,208 (67.9) | 953 (78.8) | <0.001 |
| Ethnicity | | | | | <0.001 |
| Hispanic | 206 (33.1) | 322 (22.4) | 277 (15.6) | 124 (10.2) | |
| Unknown | 5 (0.008) | 14 (0.010) | 11 (0.006) | 11 (0.009) | |
| Highest level of school achieved | | | | | <0.001 |
| Less than high school | 63 (10.1) | 103 (7.2) | 128 (7.2) | 70 (5.8) | |
| High school/GED | 138 (22.2) | 318 (22.1) | 318 (17.9) | 265 (21.9) | |
| Some college | 177 (28.4) | 409 (28.5) | 527 (29.7) | 350 (28.9) | |
| College | 164 (26.3) | 393 (27.4) | 494 (27.8) | 281 (23.2) | |
| Graduate school | 81 (13.0) | 213 (14.8) | 310 (17.4) | 244 (20.2) | |
| Income (USD) | | | | | <0.001 |
| <20,000 | 139 (25.5) | 254 (20.2) | 296 (18.7) | 171 (16.4) | |
| 20,000 to <35,000 | 96 (17.6) | 158 (12.6) | 225 (14.2) | 154 (14.8) | |
| 35,000 to <50,000 | 92 (16.9) | 191 (15.2) | 249 (15.7) | 213 (20.4) | |
| 50,000 to <75,000 | 88 (16.1) | 225 (17.9) | 264 (16.7) | 211 (20.2) | |
| ≥75,000 | 130 (23.9) | 429 (34.1) | 548 (34.6) | 294 (28.2) | |
| Medical history, concomitant medications, and comorbidities | | | | | |
| Diabetes duration (years) | 2.8 ± 2.3 | 3.6 ± 2.6 | 4.3 ± 2.8 | 4.8 ± 2.7 | <0.001 |
| Family history of diabetes | 613 (99.4) | 1,386 (98.7) | 1,729 (98.6) | 1,171 (98.8) | 0.508 |
| Current smoking status | | | | | <0.001 |
| Never | 394 (63.2) | 900 (62.7) | 922 (51.9) | 519 (42.9) | |
| Past | 128 (20.5) | 325 (22.6) | 593 (33.4) | 571 (47.2) | |
| Current | 101 (16.2) | 211 (14.7) | 263 (14.8) | 120 (9.9) | |
| MI history | 3 (0.5) | 31 (2.2) | 97 (5.5) | 121 (10.0) | <0.001 |
| Stroke history | 3 (0.5) | 9 (0.6) | 46 (2.6) | 39 (3.2) | <0.001 |
| History of nontraumatic amputation | 1 (0.2) | 1 (0.1) | 6 (0.3) | 6 (0.5) | 0.182 |
| Diagnosed with retinopathy | 4 (0.6) | 13 (0.9) | 19 (1.1) | 13 (1.1) | 0.783 |
| History of kidney disease | 16 (2.6) | 42 (2.9) | 41 (2.3) | 31 (2.6) | 0.750 |
| History of neuropathy | 25 (5.4) | 125 (12.0) | 207 (16.0) | 198 (22.8) | <0.001 |
| Diagnosed with hypertension | 268 (43.0) | 887 (61.8) | 1,274 (71.7) | 931 (76.9) | <0.001 |
| Diagnosed with elevated lipids | 296 (47.5) | 972 (67.7) | 1,361 (76.5) | 1,017 (84.0) | <0.001 |
| Medications | | | | | |
| Metformin dose at screening (mg/day) | 1,550.2 ± 524.1 | 1,566.9 ± 529.5 | 1,584.1 ± 522.9 | 1,586.1 ± 523.9 | 0.423 |
| Metformin dose at baseline (mg/day) | 1,964.7 ± 159.0 | 1,947.8 ± 199.4 | 1,945.7 ± 198.5 | 1,927.3 ± 236.5 | 0.002 |
| Lipid-lowering medication use | 236 (37.9) | 845 (58.8) | 1,257 (70.7) | 980 (81.0) | <0.001 |
| Statins | 228 (36.6) | 809 (56.3) | 1,221 (68.7) | 952 (78.7) | <0.001 |
| Aspirin ≥3 times/week | 97 (15.6) | 451 (31.4) | 953 (53.6) | 787 (65.0) | <0.001 |
| Antidepression medication use | 60 (9.6) | 166 (11.6) | 213 (12.0) | 174 (14.4) | 0.020 |

Cell counts and column percentages are presented for categorical variables. Unless otherwise indicated, data are means ± SD for skewed variables for continuous variables. Pearson $\chi^2$ test and ANOVA type III *F* test *P* values appear for categorical and continuous variables, respectively. GED, General Educational Development.

Pathology, University of Minnesota) with use of standardized laboratory procedures. $HbA_{1c}$ is standardized per NGSP protocol. hs-CRP was measured in serum with a latex particle–enhanced immunoturbidimetric assay on the cobas c502 chemistry analyzer (Roche Diagnostics, Indianapolis, IN). Insulin levels are not available for the participants assigned to glargine.

A 75-g oral glucose tolerance test (OGTT) was conducted at baseline and included six time points: 0, 15, 30, 60, 90, and 120 min. Fasting and postchallenge glucose and insulin levels are reported. A surrogate measure of whole-body insulin clearance was calculated as 1,000 ($C_0/I_0$), where $C_0$ is the fasting C-peptide (nanomoles per liter) and $I_0$ is fasting insulin (picomoles per liter) (11). Measures of insulin sensitivity included inverse fasting insulin [1/(fasting insulin)] (12), HOMA (13,14), and combined glucose and insulin excursions during the OGTT (Matsuda index) (15). HOMA of steady-state insulin sensitivity (HOMA2-S) was calculated with the HOMA2 Calculator, version 2.2.3 (Diabetes Trials Unit, University of Oxford, Oxford, U.K.) (13,14). The HOMA2 calculations are an improvement of the original HOMA values, with additional factors taken into account, such as hepatic and peripheral insulin insensitivity, renal glucose losses, and proinsulin. The Matsuda index was defined as follows:

$$(10^4)/\sqrt{(I_0 \times G_0 \times I_m \times G_m)}$$

**Table 2—OGTT-based measures in GRADE cohort with stratification by age-group**

| | <45 years | 45 to <55 years | 55 to <65 years | ≥65 years | *P* |
|---|---|---|---|---|---|
| *N* | 623 | 1,436 | 1,778 | 1,210 | |
| Fasting glucose (mmol/L) | 8.7 ± 2.0 | 8.4 ± 1.7 | 8.3 ± 1.7 | 8.4 ± 1.6 | <0.001 |
| Fasting insulin (pmol/L) | 153.7 ± 106.4, 126.0 [84.0, 194.5] | 130.3 ± 85.1, 109.0 [73.0, 166.2] | 126.4 ± 88.3, 106.0 [67.0, 158.0] | 116.3 ± 78.8, 97.0 [62.0, 147.0] | <0.001 |
| Fasting C-peptide (nmol/L) | 1.4 ± 0.6 | 1.3 ± 0.5 | 1.3 ± 0.6 | 1.4 ± 0.6 | 0.126 |
| 2-h glucose (mmol/L) | 15.6 ± 3.2 | 15.8 ± 3.0 | 15.9 ± 3.0 | 16.2 ± 3.0 | <0.001 |
| 2-h C-peptide (nmol/L) | 2.9 ± 1.2 | 2.9 ± 1.1 | 3.2 ± 1.2 | 3.4 ± 1.3 | <0.001 |
| 2-h insulin (pmol/L) | 471.4 ± 357.0 | 408.5 ± 281.1 | 429.7 ± 294.5 | 432.0 ± 306.7 | 0.003 |
| Incremental OGTT $AUC_{0–120\ min}$ | | | | | |
| Glucose (mmol/L) | 5.9 ± 1.5 | 6.2 ± 1.6 | 6.2 ± 1.5 | 6.3 ± 1.6 | <0.001 |
| Glucose (mmol/L)* | 6.0 ± 4.9 | 6.2 ± 3.2 | 6.2 ± 3.0 | 6.3 ± 3.8 | 0.04 |
| C-peptide (nmol/L) | 1.0 ± 0.6 | 1.0 ± 0.5 | 1.1 ± 0.5 | 1.2 ± 0.6 | <0.001 |
| C-peptide (nmol/L)* | 1.0 ± 1.6 | 1.0 ± 1.1 | 1.1 ± 1.0 | 1.2 ± 1.3 | <0.001 |
| Insulin (pmol/L) | 243.9 ± 204.7, 176.4 [111.1, 300.2] | 214.0 ± 151.2, 174.7 [108.8, 275.4] | 229.3 ± 162.6, 189.7 [121.0, 292.7] | 238.0 ± 167.2, 188.8 [121.5, 304.0] | 0.006 |
| Insulin (pmol/L)* | 243.9 ± 525.4 | 214.0 ± 351.5 | 229.3 ± 323.8 | 238.0 ± 408.3 | <0.001 |
| OGTT-derived measures of insulin sensitivity | | | | | |
| 1/(fasting insulin) (pmol/L]) | 0.010 ± 0.010, 0.008 [0.005, 0.012] | 0.011 ± 0.008, 0.009 [0.006, 0.014] | 0.012 ± 0.014, 0.009 [0.006, 0.015] | 0.013 ± 0.010, 0.010 [0.007, 0.016] | <0.001 |
| HOMA2-S (%) | 49.2 ± 39.8, 38.5 [25.2, 57.0] | 53.7 ± 36.4, 43.9 [29.6, 65.9] | 57.6 ± 40.6, 45.8 [31.0, 71.5] | 61.1 ± 42.1, 49.8 [33.4, 76.7] | <0.001 |
| Matsuda index (1 / (μU * mg/dL$^2$)) | 2.0 ± 1.5, 1.5 [1.0, 2.3] | 2.1 ± 1.4, 1.8 [1.2, 2.7] | 2.2 ± 1.5, 1.8 [1.2, 2.7] | 2.3 ± 1.5, 1.9 [1.2, 2.8] | 0.009 |
| OGTT-derived measures of β-cell function | | | | | |
| IGI (nmol/mol) | 38.6 ± 35.4, 28.4 [16.6, 52.0] | 35.0 ± 30.2, 27.3 [16.1, 44.3] | 37.4 ± 30.9, 30.0 [17.7, 47.1] | 37.5 ± 28.8, 30.6 [17.8, 48.7] | 0.154 |
| IGI (nmol/mol)* | 33.4 ± 83.3 | 33.5 ± 55.2 | 37.5 ± 51.3 | 40.3 ± 65.3 | <0.001 |
| C-peptide index (nmol/g) | 0.7 ± 0.6 | 0.7 ± 0.5 | 0.8 ± 0.6 | 0.8 ± 0.5 | 0.002 |
| C-peptide index (nmol/g)* | 0.7 ± 1.6 | 0.7 ± 1.1 | 0.8 ± 1.0 | 0.9 ± 1.3 | <0.001 |
| Late insulin response (μU/mg) | 42.1 ± 40.8, 28.607 [15.814, 51.220] | 34.8 ± 29.3, 26.619 [15.773, 44.290] | 36.6 ± 30.5, 28.423 [16.844, 46.446] | 38.7 ± 33.0, 28.823 [17.556, 48.826] | 0.001 |
| Late insulin response (μU/mg)* | 39.5 ± 106.0 | 35.5 ± 70.8 | 39.1 ± 65.0 | 43.5 ± 81.7 | <0.001 |
| HOMA2-β (%) | 77.1 ± 46.9, 67.1 [44.0, 99.0] | 68.3 ± 36.2, 60.9 [42.1, 85.9] | 67.7 ± 34.8, 61.2 [42.0, 86.2] | 62.8 ± 32.7, 56.1 [39.6, 80.2] | <0.001 |
| Oral disposition index (mL/mg) | 1.70 ± 1.5 | 1.80 ± 1.5 | 1.90 ± 1.6 | 2.10 ± 1.5 | <0.001 |
| Oral disposition index (mL/mg)* | 1.69 ± 4.5 | 1.85 ± 3.0 | 2.10 ± 2.8 | 2.36 ± 3.5 | <0.001 |
| OGTT-derived measures | | | | | |
| Insulin clearance (μmol/pmol) | 10.740 ± 4.145 | 11.719 ± 4.071 | 12.721 ± 4.585 | 13.975 ± 4.551 | <0.001 |

Unless otherwise indicated, data are means ± SD (along with median [interquartile range] for skewed variables). ANOVA type III *F* test *P* values are reported for quantitative variables comparing across age-groups. *For select variables, supplemental means and SDs are given with adjustment for sex, race, diabetes duration, and insulin sensitivity (Matsuda index). *P* values for these adjustments are from a likelihood ratio test of least squares regression models with sex, age, race, diabetes duration, and insulin sensitivity.

where $G_0$ is fasting plasma glucose concentration (milligrams per deciliter), $I_0$ fasting plasma insulin concentration (milli-international units per liter), $G_m$ mean plasma glucose concentration during OGTT (milligrams per deciliter) from 0 to 120 min, and $I_m$ mean plasma insulin concentration during OGTT (milli-international units per liter) from 0 to 120 min (15). The Matsuda index was winsorized, at the median ± 8.9 times the distance from the median to reduce the effect of outliers.

Measures of β-cell function were also derived from the OGTT. The insulinogenic index (IGI), a measure of the early insulin response, was defined as the increment above basal insulin (or C-peptide) divided by the increment in glucose in the same interval, or $(100) \times [(I_{30} - I_0) / (G_{30} - G_0)]$, where $G_0$ and $G_{30}$ represent the fasting and 30-min plasma glucose concentration (milligrams per deciliter), respectively, and $I_0$ and $I_{30}$ the fasting and 30-min plasma insulin concentration (milliunits per liter) (16,17). We determined late-phase insulin responses post–oral glucose load by calculating the ratio of incremental insulin area under the curve (AUC) above basal levels to incremental glucose AUC above basal levels from 60 to 120 min. An oral disposition index was calculated as the product of

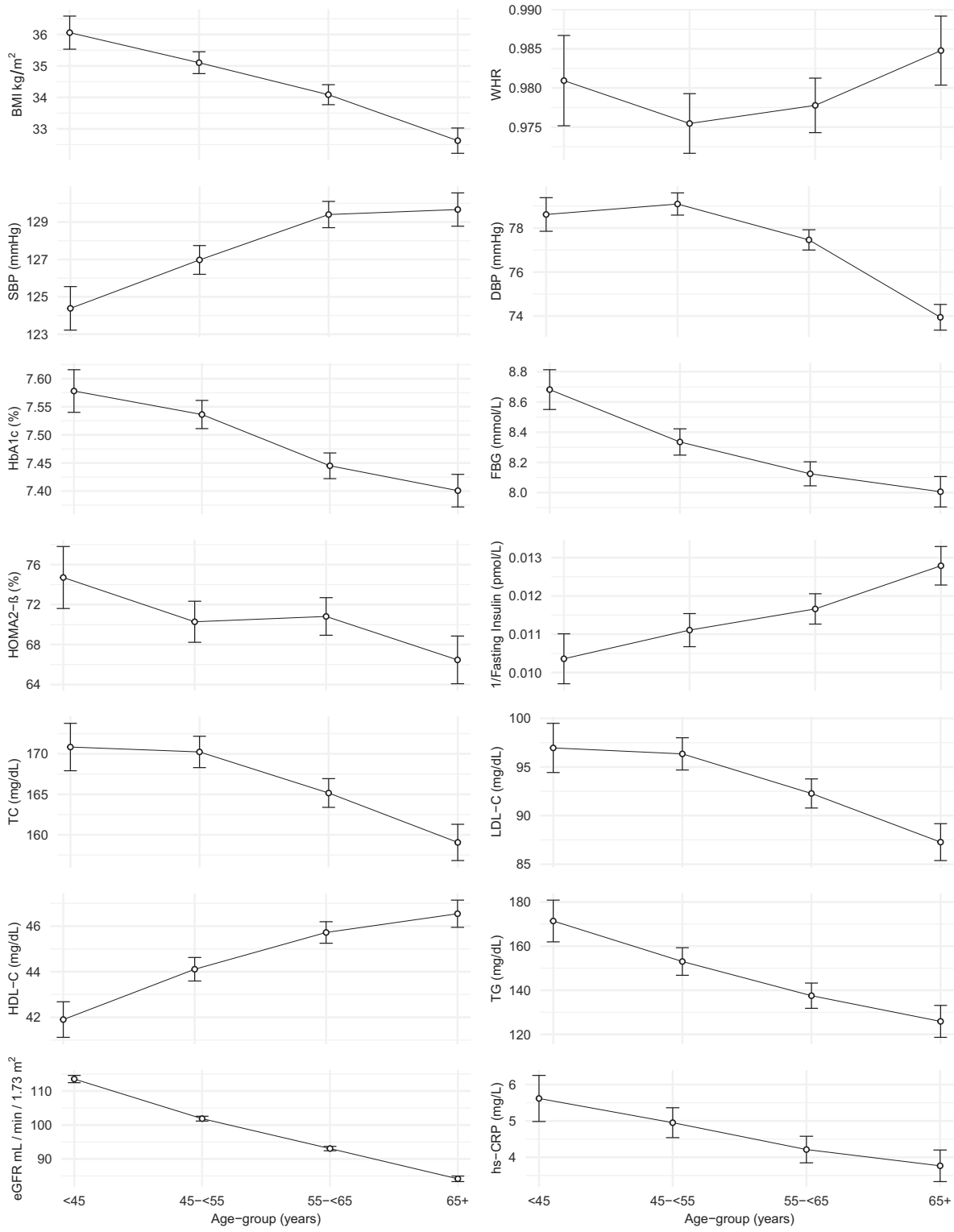


**Figure 1**—Cross-sectional trends by age-groups (<45, 45 to <55, 55 to <65, and ≥65 years). The graph shows adjusted least squares means with 95% CI bars and suggests baseline measures that tend to be consistently higher or lower across the ordinal age- groups. Spearman rank correlation coefficient was used to test for trends between age category and baseline measurements ($P < 0.001$ for all variables except for fasting blood glucose, $P = 0.01$). DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WHR, waist-to-hip ratio.

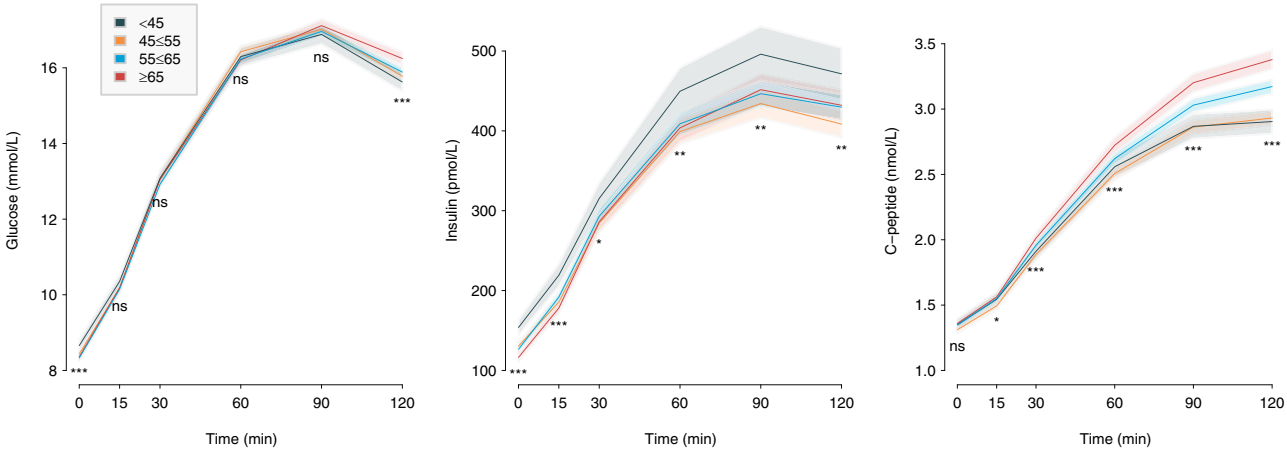


**Figure 2**—Plasma glucose, insulin, and C-peptide concentrations during the participants' OGTT, compared across the various age-groups. Dark blue, age <45 years; orange, age 45 to <55 years; light blue, 55 to <65 years; and red, ≥65 years. The symbols indicate statistical significance from ANOVA with comparison of the means between the groups: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Not significant (ns): $P \geq 0.05$. The glucose values are different in the age-groups at time 0 and time 120 min ($P < 0.001$). Insulin values are different at all time points for the age-groups. C-peptide is also different in the age-groups for all time points, except for at time 0.

the IGI and insulin sensitivity index, or IGI / $I_0$, providing an integrated measure of β-cell function with adjustment for insulin sensitivity (18,19). Similar to HOMA2-S, HOMA2 of β-cell function (HOMA2-β) was calculated with a licensed algorithm from Oxford University. HOMA2-β estimates reported here were based on insulin values, which are well correlated with HOMA2-β estimates based on glucose and C-peptide levels. This variable is a winsorized measure at cutoffs of 3.5 and 285.359 in order to limit extreme values (20).

### Statistical Analysis

Age subgroups were prespecified prior to analysis in line with the intention of GRADE investigators to enroll ∼20% older adults and to be able to capture both younger and older adult phenotypes in type 2 diabetes. Prior to analysis, the following age-groups were delineated to capture younger, middle-age, and older adult phenotypes and to ensure adequate distribution within the age-groups: age <45, 45 to <55, 55 to <65, and ≥65 years. Quantitative variables were summarized across age-groups as means, medians, SDs, and interquartile ranges, and qualitative variables were summarized as cell counts and column percentages. Comparisons between age-groups were made with use of $\chi^2$ test of independence and ANOVA type III $F$ test $P$ values for qualitative and quantitative variables, respectively (Tables 1 and 2 and Supplementary Table 2). In Fig. 1, comparisons across age-groups on select variables (BMI, waist-to-hip ratio, diastolic and systolic blood pressure, $HbA_{1c}$ at baseline, total cholesterol, triglycerides, HDL, LDL, eGFR, serum creatinine, fasting glucose, fasting insulin, HOMA2-β, insulin sensitivity, hs-CRP) included use of least squares (marginal) means and SDs with adjustment for sex, White race, and duration of diabetes. The $P$ values in the Fig. 1 legend are from Spearman correlation test for trend between age category and the baseline measurements. Comparisons of insulin, C-peptide, and glucose OGTT values across age-groups included use of one-way ANOVA for each OGTT time point in Fig. 2. IGI, C-peptide index, late insulin response, disposition index, and the incremental glucose, C-peptide, and insulin AUC measures adjusted means, SDs and $P$ values are given in Table 2. The $P$ values are from a likelihood ratio test of a least squares regression model of the β-cell function markers with adjustment for insulin sensitivity (with Matsuda index) to account for the inverse relationship between them and basic adjustment for variables sex, age, race, and diabetes duration.

## RESULTS

### Sociodemographic Characteristics by Age-group

With increasing age, the participants in the GRADE cohort had greater male prevalence ($P < 0.001$) and were less racially and ethnically diverse (Table 1 and Fig. 1). There was greater representation of Hispanic populations at younger ages, with 33.1% of the <45 years age-group being Hispanic in contrast to only 10.2% of the ≥65 years age-group ($P < 0.001$ across age subgroups). More years of education were achieved across increasing age subgroups ($P < 0.001$). Household income also differed by age-groups ($P < 0.001$) and was generally higher with increasing age (Table 1).

### Medical History, Concomitant Medications, and Comorbidities Across Age-groups

While all participants met the <10 years' duration of diabetes eligibility criteria, relatively longer duration of diabetes was seen with increasing age ($P < 0.001$). Family history of diabetes did not differ by age-groups ($P = 0.51$). Smoking history differed by age-groups ($P < 0.001$), as illustrated by the higher number of current smokers seen (16.2%) in the <45 years age-group relative to older ages (9.9% in the age ≥65 years age-group). History of diabetes complications differed by age, with reported history of heart attack, stroke, neuropathy, and diagnosis of hypertension and elevated lipids being more prevalent among those in the older age-groups ($P < 0.001$ across age-groups for all), with no difference in reported history of retinopathy or kidney disease, although patients with CKD stage 4 and

higher were excluded. In addition, among younger individuals there was lower prevalence of diagnosed hypertension and diagnosed hyperlipidemia. In line with the lower prevalence of diagnosis of these metabolic comorbidities, for younger age-groups there was a lower percentage of individuals taking common medications for comorbidities in type 2 diabetes (blood pressure medications, lipid-lowering medications/statins, and aspirin; $P <$ 0.001 across age-groups).

### Physical Assessments by Age-group

Weight and BMI differed by age-groups, with younger age-groups having higher body weight and BMI (mean ± SD weight in kilograms: age <45 years 104.2 ± 26.1, 45 to <55 years 102.1 ± 23.5, 55 to <65 years 99.7 ± 21.6, ≥65 years 95.6 ± 18.8; $P <$ 0.001 across age-groups). Mean BMI ranged from 36.2 ± 8.0 kg/m$^2$ in the <45 years age-group to 32.5 ± 5.5 kg/m$^2$ in the ≥65 years age-group ($P <$ 0.001 across age-groups). Waist-to-hip ratio increased ($P <$ 0.001), while hip circumference decreased ($P <$ 0.001), with increasing age. Systolic blood pressure was lower in younger age-groups, while diastolic blood pressure was lower in older age-groups ($P <$ 0.001 across age-groups), with younger individuals more likely to be at a blood pressure goal of <140/90 mmHg ($P <$ 0.05 across age-groups) (Fig. 1 and Supplementary Table 2).

### Clinical Laboratory and Risk Score Assessments

Increasing age was associated with lower $HbA_{1c}$ (%) within the GRADE cohort ($P <$ 0.001 across age-groups). A pattern of diabetic dyslipidemia (higher total cholesterol, higher triglycerides, lower HDL cholesterol) was seen in younger individuals ($P <$ 0.001 across age-groups for total cholesterol, triglycerides, HDL, LDL), with younger individuals less likely to be at LDL <100 mg/dL ($P <$ 0.001 across age-groups). Younger individuals also had higher hs-CRP ($P <$ 0.001). eGFR was lower and serum creatinine was higher with increasing age ($P <$ 0.001 across age-groups). ASCVD pooled cohort risk score and Framingham Risk Score were higher in older age-groups ($P <$ 0.001 across age-groups) (Fig. 1 and Supplementary Table 2).

### OGTT-Based Measures

Age groups were similar in glucose concentration at all time points except at 0 and 120 min, with lower fasting glucose though higher 120-min postchallenge glucose seen with increasing age ($P <$ 0.001 across age-groups). Insulin concentrations differed at all time points across age-groups (Fig. 2). 2-h postchallenge insulin levels were different across age-groups ($P$ = 0.003) and highest in those age <45 years. C-peptide showed differences at all time points except time 0 min, with older age-groups showing higher levels of C-peptide. Incremental AUC of glucose and C-peptide were also higher with increasing age ($P <$ 0.001 across age-groups). Insulin clearance increased with increasing age ($P <$ 0.001). HOMA2-S ($P <$ 0.001) and Matsuda index ($P$ = 0.009) were higher with increasing age. 1/(fasting insulin), as a measure of insulin sensitivity, was higher with increasing age ($P <$ 0.001 across age-groups), while HOMA2-β, as a measure of insulin secretion, and the late insulin response were lower with increasing age ($P <$ 0.001 across age-groups). The IGI did not differ across age-groups, though C-peptide index did ($P$ = 0.002) (Table 2 and Fig. 2). Oral disposition index, which provides a measure of β-cell function with adjustment for insulin sensitivity, was higher with increasing age ($P <$ 0.001 across age-groups).

## CONCLUSIONS

Within the uniform stage of initial treatment intensification of type 2 diabetes from metformin monotherapy to dual therapy captured by GRADE, there were remarkable differences in phenotypic characteristics by age. In general, younger age in adults with type 2 diabetes was associated with more prominent obesity-related characteristics, including higher BMI, lipid profile characterized by diabetic dyslipidemia (higher total cholesterol, LDL cholesterol, and triglycerides and lower HDL cholesterol), and higher serum hs-CRP. Conversely, older individuals meeting the same glycemic criteria were characterized by lower BMI and higher prevalence of cardiovascular complications and statin treatment. In addition, younger individuals were less likely to have diagnosis and treatment for hypertension and hyperlipidemia, despite, or contributing to, the higher levels of dyslipidemia.

The metabolic characterization by age in the GRADE cohort is consistent with clinical characteristics. In general, younger age within this adult cohort at the initial treatment intensification stage had lower measures of insulin sensitivity, higher insulin levels, hyperinsulinemic responses following glucose challenge, and higher HOMA2-β though with lower oral disposition index, which overall suggests perhaps more abnormal β-cell compensation once insulin sensitivity is accounted for. This is also consistent with a more obesity-driven phenotype in younger individuals with type 2 diabetes.

Much of our understanding of impact of age on phenotypic characteristics in type 2 diabetes is derived from dedicated studies at either end of the age spectrum. The RISE studies, for example, included careful assessment and contrasting of metabolic manifestations of impaired glucose tolerance or recent type 2 diabetes in youth compared with adults as well as response to treatment with metformin or insulin glargine. Notably, there were no differences in body weight, BMI, or triglycerides in the youth compared with adults in RISE, whereas in our age subgroups there was a clear difference in BMI and lipid profiles by age. This may reflect different populations of recruitment, as the mean age in the RISE adult population (~53 to 55 years) was more similar to the younger subgroups described here in GRADE. In RISE, youth had more profound insulin resistance, hyperinsulinemia, β-cell hyperresponsiveness, and lower insulin clearance, with more aggressive deterioration of β-cell function over time, compared with the RISE adult population (3,4,21). Consistent with our characterization of the younger subgroups in GRADE, lower whole-body insulin clearance has been reported to parallel the reduced insulin sensitivity seen in obese adolescents, with reduced hepatic insulin clearance in obese youth thought to contribute to the decline in β-cell function over time (22). The lower insulin clearance seen here in the younger subgroups of GRADE might portend a

potentially more aggressive deterioration of β-cell function. Whether there is greater deterioration with younger age in GRADE is not yet known. Analysis of the changes in metabolic profile in response to different treatment groups will be of significant interest in GRADE.

A mild age-related diabetes phenotype has been described by Ahlqvist et al. (2) in the cluster analysis of the Swedish All New Diabetics in Scania (ANDIS) cohort, based on variables of GAD antibodies, age at diagnosis, BMI, $HbA_{1c}$, and HOMA2 estimates of β-cell function and insulin resistance. Mild age-related diabetes was characterized by modest metabolic derangements and less risk of complications than seen in severe insulin-resistant diabetes, while another cluster was characterized by insulin resistance and high BMI, and yet another labeled as mild obesity–related diabetes, speaking to the heterogeneity seen in type 2 diabetes. Mild age-related diabetes was characterized by a lower HOMA2-β than that seen in severe insulin resistance diabetes. Reduced insulin response to hyperglycemic challenge and insulin secretory defects, with levels of insulin sensitivity controlled for, have been described, and β-cell sensitivity to incretin hormones has been postulated to be decreased with increased age, contributing to glucose intolerance and post-challenge hyperglycemia seen in the older population (6).

It is important to note, however, that interpreting OGTT measures is complex and one needs to consider a multitude of factors, including β-cell function, glucose stimulus, insulin clearance, and insulin sensitivity. The oral disposition index calculated here suggests that overall β-cell compensation, which represents an assessment of insulin secretion in relation to the prevailing sensitivity (18,19), may be even lower in the younger age-groups, despite the first-glance appearance of higher measures of β-cell function (such as with HOMA2-β). In another analysis of the GRADE cohort, the oral disposition index was directly associated with age and inversely with BMI, $HbA_{1c}$, and triglycerides/HDL cholesterol, consistent with the age-related phenotype we have described here (23). An understanding of primary etiologic contributors within different age-groups may allow better tailoring of therapy and help with addressing progression of underlying disease.

There are several strengths to the current analysis. The GRADE cohort represents a diverse population recruited among 36 centers across the U.S., with 35% representing non-White populations, 19.8% African American or Black, and 18.4% Hispanic (7). Sociodemographic characteristics were broadly represented (7). Detailed clinical and metabolic variables were systematically collected across all sites. Further, this analysis uniquely provides a detailed clinical and metabolic characterization of type 2 diabetes by age-group during a common treatment stage in adults with type 2 diabetes, representing a juncture of treatment decision-making. By intention, with study eligibility and design of the clinical trial, adults enrolled in GRADE had type 2 diabetes of $<$10 years' duration and were at a point of requiring further treatment intensification beyond metformin monotherapy. The findings allow one to consider age and age at diabetes diagnosis both as important clinical factors and physiologic indicators that may influence care goals, even at this earlier stage of therapy.

An important limitation to note is that the GRADE cohort represents participants willing to enroll in the prospective randomized GRADE clinical trial across the U.S., who met the inclusion criteria of metformin monotherapy and the predefined $HbA_{1c}$ range. Our results are therefore reflective of a population that is able and willing to participate in this long-term clinical trial within this stage of therapy and may not be generalizable, for example, to people with diabetes who may have had much poorer control. In addition, the analyses presented are a cross-sectional evaluation of the cohort. Longitudinal follow-up of the cohort and impact of the randomly assigned treatment will provide valuable information on the impact of age within this treatment stage on efficacy of assigned therapy. Finally, it is possible that some of the clinical and metabolic differences by age may be in part attributable to differences in other patient characteristics or comorbidities.

Our findings are potentially of importance for the care of relatively younger adults diagnosed with type 2 diabetes. Earlier onset of type 2 diabetes, in both youth and adulthood, is increasingly prevalent and is associated with obesity, minority ethnicity, and lower socioeconomic status, as we also describe here. Further, early-onset type 2 diabetes is associated with increased risk of developing microvascular and macrovascular complications, as well as premature mortality, suggesting the need for more aggressive risk factor management. Yet, as our analysis highlights, even within a common treatment stage of type 2 diabetes, and despite the higher levels of obesity and dyslipidemia, younger adults are less likely to be diagnosed and treated for their metabolic risk factors (24). This may be related to traditional viewpoints that complications are primarily seen with increasing age, yet it is important to recognize that early-onset type 2 diabetes is associated with both a more aggressive course of diabetes and overall higher risk of complications. Furthermore, current risk scores (e.g., ASCVD pooled risk score [9] and Framingham Risk Score [10]) are largely driven by age, as seen here, and thus may underestimate the metabolic burden and risk in a younger population with type 2 diabetes. Finally, epidemiologic trends suggest that the younger demographics of adults with type 2 diabetes (age 18–44 years, 45–64 years) may largely be contributing to the recent resurgence and increase in diabetes complications in the U.S. (25). Placing our findings in this context, there is a need for greater awareness of the high risks of complications in individuals with early-onset type 2 diabetes and need for greater attention to risk reduction approaches in this high-risk population.

In summary, age is an important clinical factor to consider in patients with type 2 diabetes, even within a uniformly defined window of treatment stage, as represented by the GRADE cohort. Among adults with type 2 diabetes requiring intensification from metformin monotherapy to dual therapy, age was associated with distinct clinical and metabolic characteristics, with younger age associated with more obesity and diabetic dyslipidemia and lower insulin sensitivity and β-cell compensation, along with less diagnosis and treatment of hypertension and dyslipidemia, and older age with greater prevalence of cardiovascular disease. Given the changing demographics of

diabetes, these findings highlight the need for more aggressive management of risk factors, including lipid, blood pressure, and management of obesity, particularly in younger populations. Further study will inform whether these distinct age-related clinical characteristics seen during the initial treatment intensification stage impact response to treatment and thus guide choice of therapy.

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