Racial/ethnic and socioeconomic disparities in the use of newer diabetes medications in the Look AHEAD study

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Summary

Background Among patients with type 2 diabetes, minority racial/ethnic groups have a higher burden of cardiovascular disease, chronic kidney disease, and hypoglycaemia. These groups may especially benefit from newer diabetes medication classes, but high cost may limit access. We examined the association of race/ethnicity with the initiation of newer diabetes medications (GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors).

Methods We conducted a secondary analysis of the Look AHEAD (Action for Health in Diabetes) trial including participants with at least one study visit after April 28, 2005. Cox proportional hazards models were used to estimate the association between race/ethnicity and socioeconomic factors with time to initiation of any newer diabetes medication from April 2005 to February 2020. Models were adjusted for demographic and clinical characteristics.

Findings Among 4,892 participants, 63.6%, 15.7%, 12.6%, 5.2%, and 2.9% were White, Black, Hispanic, American Indian or Alaskan Native (AI/AN), or other race/ethnicity, respectively. During a median follow-up of 8.3 years, 2,180 (45.2%) participants were initiated on newer diabetes medications. Race/ethnicity was associated with newer diabetes medication initiation (p=.019). Specifically, initiation was lower among Black (HR 0.81, 95% CI 0.70 −0.94) and AI/AN participants (HR 0.51, 95% CI 0.26−0.99). Yearly family income was inversely associated with initiation of newer diabetes medications (HR 0.78, 95% CI 0.62−0.98) comparing the lowest and highest income groups. Findings were mostly driven by GLP-1 receptor agonists.

Interpretation These findings provide evidence of racial/ethnic disparities in the initiation of newer diabetes medications, independent of socioeconomic factors, which may contribute to worse health outcomes.

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Keywords: Racial disparities; Diabetes care; Newer medications; Medication initiation; Socioeconomic disparities; Diabetes outcomes

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Introduction

Racial/ethnic minorities with type 2 diabetes mellitus have worse glycaemic control and higher rates of diabetes complications and mortality.[1−3] Socioeconomic status has also been found to impact diabetes outcomes

Research in context

Evidence before this study

There is strong and consistent observational evidence for racial/ethnic disparities in health outcomes for patients with diabetes, and barriers to accessing medications for chronic conditions. Clinical practice guidelines recommend the preferential use of newer classes of diabetes medications in my clinical scenarios, especially with, or at high risk for, cardiovascular and renal complications. We therefore sought to examine whether there are differences by race/ethnicity in initiation of newer diabetes medications in the US during the period after these drugs came to market. We searched PubMed, Embase and Web of Science and found no studies reporting the association between race/ethnicity and newer diabetes medication use.

Added value of this study

In this study, we provide the first data to our knowledge examining racial/ethnic differences in the initiation of newer classes of diabetes medications. We were able to show that individuals of all minority race/ethnicities had lower initiation of newer diabetes medications compared to white individuals and initiation of newer diabetes medications was significantly lower for black and American Indian or Alaskan Native individuals. This effect was independent of socioeconomic status and clinical factors (glycemic control and intensity of diabetes therapy). While income was inversely associated with initiation of newer diabetes medications, adjustment for income and other socioeconomic factors did not substantially attenuate the effect of race/ethnicity, suggesting that there are factors beyond medication cost contributing to lower initiation in racial/ethnic minorities.

Implications of all the available evidence

Racial/ethnic disparities in the initiation of newer diabetes medications have important clinical consequences. These groups may especially benefit from the use of newer diabetes medications given their reno- and cardio-protective effects. Lack of access to newer diabetes medications could widen the existing disparities in diabetes care and contribute to the worse outcomes experienced by minority race/ethnicity groups. Further study is needed to understand if these differences are driven by systemic health systems, physician-specific or patient-specific factors. Doing so may help in the design of interventions that reduce barriers to care and improve diabetes outcomes for racial/ethnic minorities.

such that individuals with lower income or educational attainment have worse glycaemic control and higher diabetes-related mortality.[4,5] Further, among patients with diabetes, minority race/ethnicity and lower socio-economic status are associated with greater cost-limited access of diabetes medications.[6,7]

In the past 20 years, three newer classes of diabetes medications became available in the U.S.: glucagon-like peptide receptor agonists (GLP-1RAs) in 2005, dipeptidyl peptidase 4 inhibitors (DPP-4Is) in 2006, and sodium/glucose cotransporter 2 inhibitors (SGLT-2Is) in 2013.[8] Given the evidence for cardiovascular and renal benefits, GLP-1RAs and SGLT-2Is are the preferred second-line medication classes for patients with atherosclerotic cardiovascular disease, heart failure or chronic kidney disease.[8] In addition, all newer diabetes medications classes have a substantially lower risk of hypoglycaemia and weight gain compared to sulfonylureas or insulin.[8] However, these newer medications are expensive, creating concerns about equitable access[6,8,9].

Racial/ethnic minorities, and lower income and educational attainment groups, have a higher burden of chronic kidney disease, worse cardiovascular outcomes, and higher rates of severe hypoglycaemia.[2,3,10−12] Therefore, these groups may especially benefit from the use of newer diabetes medications. Lack of access to newer diabetes medications could widen the existing disparities in diabetes care.

In this secondary analysis of Look AHEAD (Action for Health in Diabetes), we aimed to determine the association of race/ethnicity and socioeconomic factors with the initiation of newer classes of diabetes medications. Look AHEAD is a multicentre randomized controlled trial of an intensive lifestyle intervention for adults with type 2 diabetes that followed participants over the period when newer diabetes medication classes became available on the U.S. market. We hypothesized that participants of minority race/ethnicity would have lower initiation of newer diabetes medication.[13]

Methods

Study population

The Look AHEAD trial enrolled 5145 adults with type 2 diabetes and body mass index (BMI) ≥25 kg/m² (≥27 kg/m² if using insulin) from 16 U.S. centres with recruitment from 2001 to 2004.[14] For this study, we examined the 4892 participants with at least one follow-up visit after April 28, 2005, the date when the first newer classes of diabetes medications entered the U.S. market. Eligibility criteria for Look AHEAD included age 45−76 years, HbA1c <11% (97 mmol/mol), having a primary healthcare provider, and able to complete a maximal exercise test at baseline [14,15]. Exclusion criteria included serum creatinine >1.4 mg/dL (women) or 1.5 mg/dL (men), 4+ proteinuria, need for dialysis, or recent or exercise-limiting cardiovascular disease.[14,15]

Participants were randomized 1:1 to an intensive lifestyle intervention (ILI) or diabetes support and education (DSE), the latter being the control group. The

objective of the ILI was to reduce participants' initial body weight by 7% through sessions that encouraged increased physical activity and reduced caloric intake, self-monitoring, and, sometimes, pharmacologic weight loss interventions.[16] Diabetes care during the study was provided by participants' outside physicians. Participants in the ILI arm taking insulin, sulfonylureas, or meglitinides had additional monitoring and, when needed, temporary adjustment of diabetes medications by trial staff to prevent hypoglycaemia.[16] The DSE arm received information on nutrition and physical activity and social support delivered in group classes up to three times a year.[15] The primary outcome of Look AHEAD was time to occurrence of a combined cardiovascular outcome.[14,15] Due to futility for the primary outcome, the intervention was terminated in September 2012 with a median follow-up of 9.6 years.[15] Participants continue to be followed, and this study uses data through February 2020.

Study outcome

The primary outcome of this study is time to first use of a newer class of diabetes medication: a DPP-4I, GLP-1RA, or SGLT-2I. Medication use was determined at annual study visits using a medication inventory form completed by trained study staff with participants instructed to bring in their home medications for review. When participants did not bring their medications, staff ascertained medication changes and placed follow-up phone calls when necessary.[14,15]

Primary and secondary exposure variables

The predictors of interest in this study were race/ethnicity and socioeconomic measures. Race/ethnicity was self-reported in categories of White, Black, Hispanic, American Indian or Alaskan Native (AI/AN), Asian or Pacific Islander, and other. Asian or Pacific Islander were included in "other" for these analyses due to few participants in this group. Socioeconomic measures were assessed by standardized interviewer-administered questionnaires at study baseline. Yearly family income was analysed in five categories from less than $20,000 to greater than $80,000 or missing. Highest level of education was analysed in categories of less than high school, high school or equivalent, vocational school or some college, bachelor's degree or post-graduate degree. Employment status was analysed in categories of working full or part time, homemaker, unemployed, or missing. Health insurance was analysed in categories of individual or partner's insurance, government insurance (Medicare, Medicaid, Veterans Affairs, or Indian Health Services), other insurance, or uninsured. Source of medical care was analysed in categories of private doctor's office, hospital clinic or outpatient department, community health center, or other.

Other characteristics

Other variables added to the model include HbA1c, estimate glomerular filtration rate (eGFR, CKD-Epi equation), hypertension, BMI, and cardiovascular disease. HbA1c and eGFR were measured annually through study year four and on alternating years thereafter. Hypertension (defined as systolic blood pressure >140 mmHg or use of blood pressure lowering medications) and BMI were measured yearly using standardized protocols. History of cardiovascular disease was self-reported at baseline. Subsequent records were defined using the prespecified the Look AHEAD trial primary cardiovascular outcome: composite of myocardial infarction, stroke, or hospitalized angina ascertained through regular telephone calls to participants and adjudicated hospital records.

Statistical analysis

All continuous variables were categorized into clinically relevant groups determined a-priori. All categorical variables were analysed as nominal (non-ordered). For descriptions, see Supplemental Table 1.

Baseline characteristics were described as means or proportions and compared across categories of race/ethnicity using one-way analysis of variance for continuous variables or chi-squared tests for categorical variables. Cox proportional hazards models were used to examine the association of race/ethnicity and socioeconomic measures with the primary outcome. The time scale was calendar time from the first study visit after April 28, 2005 until the occurrence of the outcome or censoring at the date of their last study contact through February 2020. Participants with gaps due to missing study visit medication data as determined by an absent medication form were excluded from analysis for the duration of the gap and did not accrue time at risk for that period. Two multivariable models were used to assess the relationship of race/ethnicity with the primary outcome, without (Model 1) and with adjustment for socioeconomic factors (Model 2). Both models were adjusted for demographic and clinical characteristics hypothesized to have potential roles in diabetes medication selection described in "Other Characteristics" (see Supplemental Table 1), as well as Look AHEAD treatment arm and study site. A 2-sided P <0.05 was considered statistically significant. The proportional hazards assumption was checked by visual inspection of log-log hazards curves. We examined the interaction between race/ethnicity and yearly family income where we treated income as continuous. All analyses were performed using SAS software version 9.4 (Cary, NC).

Subgroup and sensitivity analysis

We conducted exploratory subgroup analyses using the fully adjusted model (Model 2). We assessed for multiplicative interactions of our primary association,

Characteristic*	Overall (n = 4892)	White (n = 3111)	Black (n = 766)	Hispanic (n = 614)	AI/AN (n = 255)	Other (n = 146)	p-value†
Intensive Lifestyle Intervention Arm (%)	2461 (50.3)	1561 (50.2)	384 (50.1)	309 (50.3)	129 (50.6)	78 (53.4)	0.96
Age, mean (SD), years	58.7 (6.8)	59.5 (6.8)	58.0 (6.7)	57.4 (6.3)	55.3 (7.2)	58.4 (6.9)	<0.001
Age category (%)							<0.001
45−54 years	1185 (24.2)	651 (20.9)	196 (25.6)	173 (28.2)	127 (49.8)	38 (26.0)	
55−64 years	2700 (55.2)	1723 (55.4)	438 (57.2)	362 (59.0)	96 (37.7)	81 (55.5)	
65−76 years	1007 (20.6)	737 (23.7)	132 (17.2)	79 (12.9)	32 (12.6)	27 (18.5)	
Female (%)	2927 (59.8)	1607 (51.7)	583 (76.1)	445 (72.5)	201 (78.8)	91 (62.3)	<0.001
Yearly family income (%)							<0.001
> $80,000	1302 (26.6)	1048 (33.7)	126 (16.5)	67 (10.9)	82 (32.2)	11 (7.5)	
$60,000−80,000	725 (14.8)	500 (16.1)	114 (14.9)	64 (10.4)	61 (23.9)	27 (18.5)	
$40,000−60,000	910 (18.6)	584 (18.8)	143 (18.7)	108 (17.6)	49 (19.2)	26 (17.8)	
$20,000−40,000	932 (19.1)	484 (15.6)	177 (23.1)	183 (29.8)	21 (8.2)	26 (17.8)	
<$20,000	538 (11.0)	161 (5.2)	107 (14.0)	177 (28.8)	18 (7.1)	43 (29.5)	
Missing	485 (9.9)	334 (10.7)	99 (12.9)	15 (2.4)	24 (9.4)	13 (8.9)	
Highest level of education (%)							<0.001
Post Graduate degree	937 (19.6)	722 (23.8)	125 (16.6)	45 (7.4)	8 (3.3)	37 (26.6)	
Bachelor's degree	1069 (22.4)	798 (26.3)	149 (19.7)	66 (10.9)	16 (6.6)	40 (28.8)	
Vocational / some college	1816 (38.0)	1088 (35.8)	343 (45.4)	208 (34.4)	122 (50.2)	55 (39.6)	
High School or equivalent	648 (13.6)	389 (12.8)	103 (13.6)	100 (16.5)	51 (21.0)	5 (3.6)	
Less than high school	310 (6.5)	41 (1.4)	35 (4.6)	186 (30.7)	46 (18.9)	2 (1.4)	
Employment status (%)							<0.001
Working full or part time	3128 (63.9)	2059 (66.2)	473 (61.8)	346 (56.4)	150 (58.8)	100 (68.5)	
Homemaker	837 (17.1)	469 (15.1)	116 (15.1)	174 (28.3)	53 (20.8)	25 (17.1)	
Unemployed	381 (7.8)	240 (7.7)	72 (9.4)	36 (5.9)	24 (9.4)	9 (6.2)	
Missing	546 (11.2)	343 (11.0)	105 (13.7)	58 (9.5)	28 (11.0)	12 (8.2)	
Type of health insurance (%)							<0.001
Private insurance	3808 (78.0)	2665 (85.8)	587 (76.9)	329 (53.6)	111 (43.5)	116 (79.5)	
Government	616 (12.6)	324 (10.4)	114 (14.9)	66 (10.8)	102 (40.0)	10 (6.9)	
Other insurance	88 (1.8)	47 (1.5)	13 (1.7)	19 (3.1)	3 (1.2)	6 (4.1)	
Uninsured	371 (7.6)	69 (2.2)	49 (6.4)	200 (32.6)	39 (15.3)	14 (9.6)	
Source of medical care (%)							<0.001
Private doctor's office	3619 (74.2)	2622 (84.4)	533 (69.9)	319 (52.0)	39 (15.5)	106 (72.6)	
Hospital clinic or outpatient department	613 (12.6)	237 (7.6)	119 (15.6)	88 (14.3)	149 (59.1)	20 (13.7)	
Community health center	357 (7.3)	75 (2.4)	48 (6.3)	169 (27.5)	54 (21.4)	11 (7.5)	
Other	291 (6.0)	171 (5.5)	63 (8.3)	38 (6.2)	10 (4.0)	9 (6.2)	
HbA1c, mean (SD),%	7.3 (1.2)	7.2 (1.1)	7.5 (1.3)	7.5 (1.3)	7.5 (1.3)	7.2 (1.1)	<0.001
HbA1c category (%)							<0.001
< 6.0% / 42 mmol/mol	365 (7.5)	265 (8.5)	39 (5.1)	36 (5.9)	17 (6.7)	8 (5.5)	
6.0−6.4% / 42−46 mmol/mol	865 (17.7)	565 (18.2)	126 (16.5)	100 (16.3)	43 (16.9)	31 (21.2)	
6.5−6.9% / 48−52 mmol/mol	1018 (20.8)	697 (22.4)	140 (18.3)	108 (17.6)	45 (17.7)	28 (19.2)	
7.0−7.9% / 53−63 mmol/mol	1511 (30.9)	963 (31.0)	238 (31.1)	189 (30.8)	73 (28.6)	48 (32.9)	
8.0−8.9% / 64−74 mmol/mol	742 (15.2)	422 (13.6)	143 (18.7)	111 (18.1)	44 (17.3)	22 (15.1)	
≥ 9.0% / 75 mmol/mol	391 (8.0)	199 (6.4)	80 (10.4)	70 (11.4)	33 (12.9)	9 (6.2)	
eGFR, mean (SD), mL/min/1.73m^2	89.7 (16.0)	87.1 (15.0)	95.5 (18.2)	94.3 (14.0)	93.6 (16.9)	87.0 (16.8)	<0.001
eGFR category (%)							<0.001
≥ 90	2742 (56.2)	1567 (50.5)	480 (63.2)	448 (73.1)	171 (67.1)	76 (52.1)	
60−90	1898 (38.9)	1364 (43.9)	254 (33.4)	147 (24.0)	71 (27.8)	62 (42.5)	
< 60	239 (4.9)	174 (5.6)	26 (3.4)	18 (2.9)	13 (5.1)	8 (5.5)	
BMI, mean (SD), kg/m^2	35.9 (5.9)	36.0 (5.9)	36.6 (6.0)	35.3 (5.7)	35.8 (6.3)	34.7 (5.8)	<0.001
BMI categories (%)							0.001
25−29	732 (15.0)	455 (14.6)	96 (12.5)	106 (17.3)	40 (15.8)	35 (24.0)	
30−34	1723 (35.3)	1101 (35.4)	247 (32.3)	239 (39.0)	90 (35.6)	46 (31.5)	
35−39	1336 (27.3)	852 (27.4)	227 (29.6)	153 (25.0)	62 (24.5)	42 (28.8)	

(continued)

Table 1 (*Continued*)

Characteristic*	Overall (n = 4892)	White (n = 3111)	Black (n = 766)	Hispanic (n = 614)	AI/AN (n = 255)	Other (n = 146)	p-value†
≥ 40	1097 (22.4)	702 (22.6)	196 (25.6)	115 (18.8)	61 (24.1)	23 (15.8)	
Diabetes duration, mean (SD), years	6.8 (6.6)	6.6 (6.3)	6.6 (6.5)	7.2 (6.9)	8.6 (8.5)	7.5 (7.1)	<0.001
Diabetes duration, categories (%)							0.037
0−4	2210 (45.5)	1411 (45.6)	361 (47.3)	278 (45.6)	97 (39.8)	63 (44.1)	
5−9	1345 (27.9)	896 (29.0)	205 (26.8)	151 (24.8)	63 (25.8)	39 (27.3)	
≥ 10	1289 (26.6)	785 (25.4)	198 (25.9)	181 (29.7)	84 (34.4)	41 (28.7)	
Cardiovascular disease (%)	667 (13.6)	485 (15.6)	74 (9.7)	56 (9.1)	25 (9.8)	27 (18.5)	<0.001
Hypertension (%)	4073 (83.3)	2595 (83.4)	676 (88.3)	486 (79.2)	195 (76.5)	121 (82.9)	<0.001
Insulin use (%)	741 (15.2)	422 (13.6)	140 (18.3)	108 (17.6)	49 (19.2)	22 (15.1)	0.001
Metformin use (%)	2965 (60.6)	1904 (61.2)	445 (58.1)	372 (60.6)	161 (63.1)	83 (56.9)	0.401
Sulfonylurea use (%)	2210 (45.2)	1364 (43.8)	350 (45.7)	310 (50.5)	122 (47.8)	64 (43.8)	0.038
Thiazolidinedione use (%)	1271 (26.0)	873 (28.1)	207 (27.0)	116 (18.9)	39 (15.3)	36 (24.7)	<0.001
No. of diabetes medications (%)							<0.001
0	647 (13.4)	447 (14.5)	82 (10.8)	62 (10.2)	34 (13.6)	22 (15.3)	
1	1912 (39.5)	1171 (38.0)	309 (40.7)	277 (45.6)	103 (41.0)	52 (36.1)	
2	1601 (33.1)	995 (32.3)	284 (37.4)	191 (31.4)	83 (33.1)	48 (33.3)	
≥ 3	684 (14.1)	469 (15.2)	84 (11.1)	78 (12.8)	31 (12.4)	22 (15.3)	
Diabetes Treatment Intensity (%)							<0.001
No medications	721 (14.7)	489 (15.7)	94 (12.3)	72 (11.7)	39 (15.3)	27 (18.5)	
1 non-insulin medication	1669 (34.1)	1054 (33.9)	251 (32.8)	233 (38.0)	86 (33.7)	45 (30.8)	
2 non-insulin medications	1358 (27.8)	856 (27.5)	227 (29.6)	167 (27.2)	68 (26.7)	40 (27.4)	
3+ non-insulin medications	403 (8.2)	290 (9.3)	54 (7.1)	34 (5.5)	13 (5.1)	12 (8.2)	
Insulin (with or without other meds)	741 (15.2)	422 (13.6)	140 (18.3)	108 (17.6)	49 (19.2)	22 (15.1)	

Table 1: Baseline characteristics overall and by race/ethnicity.
* N (% of column) or mean (SD)† Tested using chi-squared tests for categorical variables or one-way analysis of variance (ANOVA) for continuous variablesAI/AN, American Indian or Alaskan Native.

performing stratified analyses when merited, by factors in clinical guidelines that may affect the selection of diabetes medications including: age (<65 years, ≥65 years), gender, diabetes duration (<10 years, ≥10 years), and the presence of cardiovascular disease and chronic kidney disease.[8] We conducted four sensitivity analyses using the fully adjusted model: 1) examining initiation of each newer diabetes medication class individually; 2) stratifying by intervention arm; 3) adjusting for whether participants brought their home medications to the study visit for review; and 4) modeling death as a competing risk using the Fine and Gray approach.[17]

Role of the funding source

Results

Participant characteristics

The baseline (April 2005) characteristics of the 4892 included participants are shown in Table 1. The mean age was 58.7 years, 59.8% of participants were female, and 63.6%, 15.7%, 12.6%, 5.2%, and 2.9% of participants were White, Black, Hispanic, AI/AN, or other race/ethnicity, respectively. White participants were more likely to be male and had an older average age than minority race/ethnicity participants. There were differences by race/ethnicity in clinical characteristics with White participants having lower HbA1c, more thiazolidinedione use, and lower insulin use compared to minority participants. White participants were also more likely to have a history of cardiovascular disease and lower eGFR compared to Black, Hispanic, and AI/AN participants. White participants had greater yearly family income, higher levels of education, and were more likely to have health insurance compared to Black and Hispanic participants. Hispanic participants were substantially more likely to be uninsured than White participants (32.6% vs. 2.2%). The majority of participants brought medications to the visit for review (Supplemental Table 5).

Association of race/ethnicity and initiation of newer diabetes medications

The median follow-up time for participants was 8.3 years with a total of 41,318 person-years at risk

Characteristics	Unadjusted results		Model 1*		Model 2*	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Race/ethnicity		<0.001		<0.001		0.019
White	Reference		Reference		Reference	
Black	0.82 (0.73−0.92)		0.73 (0.64−0.84)		0.81 (0.70−0.94)	
Hispanic	0.77 (0.68−0.88)		0.82 (0.68−0.99)		0.88 (0.72−1.07)	
American Indian or Alaskan Native	0.33 (0.25−0.44)		0.53 (0.29−0.98)		0.51 (0.26−0.99)	
Other	0.79 (0.61−1.02)		0.89 (0.68−1.17)		0.93 (0.70−1.24)	
Yearly family income		<0.001				0.008
> $80,000	Reference				Reference	
$60,000−80,000	0.99 (0.87−1.13)				0.96 (0.83−1.10)	
$40,000−60,000	0.87 (0.77−0.99)				0.86 (0.75−0.98)	
$20,000−40,000	0.73 (0.64−0.84)				0.77 (0.65−0.90)	
<$20,000	0.61 (0.49−0.75)				0.78 (0.62−0.98)	
Missing	0.76 (0.64−0.90)				0.77 (0.64−0.93)	
Highest level of education		0.960				0.48
Masters, doctorate or professional degree	Reference				Reference	
BA or some graduate school	0.97 (0.86−1.10)				0.96 (0.83−1.09)	
Vocational, some college, associate degree	0.98 (0.87−1.11)				0.92 (0.81−1.05)	
High school diploma or equivalent	0.96 (0.82−1.13)				0.86 (0.72−1.02)	
Less than high school	0.92 (0.72−1.17)				0.85 (0.63−1.15)	
Employment status		0.022				0.37
Working full, part time, or student	Reference				Reference	
Homemaker	0.97 (0.86−1.10)				1.11 (0.97−1.28)	
Unemployed	0.84 (0.71−1.01)				0.99 (0.81−1.21)	
Missing	0.81 (0.70−0.95)				0.94 (0.79−1.12)	
Type of health insurance		0.003				0.32
Private insurance	Reference				Reference	
Government insurance	0.84 (0.72−0.99)				0.96 (0.79−1.15)	
Other insurance	1.34 (0.99−1.82)				1.05 (0.75−1.47)	
Uninsured	0.76 (0.60−0.96)				0.78 (0.59−1.03)	
Source of medical care		<0.001				<0.001
Private doctor's office	Reference				Reference	
Hospital clinic or outpatient department	0.67 (0.58−0.78)	<0.001			0.78 (0.66−0.93)	
Community health center	0.65 (0.52−0.82)	<0.001			0.78 (0.60−1.01)	
Other	0.56 (0.46−0.69)	<0.001			0.66 (0.53−0.83)	

Table 2: **Unadjusted and adjusted hazard ratios for initiation of any newer class of diabetes medication by race/ethnicity and socioeconomic factors.**

* Cox proportional hazards models adjusted for race/ethnicity, socioeconomic factors, study site, intervention arm, age, gender, HbA1c, diabetes duration, diabetes treatment intensity, eGFR, BMI, and history of cardiovascular disease.

accrued. Overall, 2211 participants (45.2%) initiated a newer diabetes medication during follow-up. This included 48.0% of White, 44.2% of Black, 41.4% of Hispanic, 21.6% of AI/AN, and 41.6% of other race/ethnicity participants, respectively. The results of the Cox proportional hazards models for the association of race/ethnicity and socioeconomic factors with initiation of a newer diabetes medication are shown in Tables 2 and 3, and fully-adjusted time-to-event curves by race/ethnicity are shown in Fig. 1. In the fully adjusted analysis, race/ethnicity was significantly associated with initiation of newer diabetes medications (*p*=.019) with all minority race/ethnicities having a lower hazard ratio (HR) for initiation compared to Whites. This association was strongest among Black (HR 0.81, 95% CI 0.70−0.94) and AI/AN participants (0.51, 95% CI 0.26−0.99); the CI for other race/ethnicities crossed the null. The association of race/ethnicity and initiation of newer diabetes medication was slightly attenuated after adjustment for socioeconomic factors but was significant in both models. Notably, without adjustment for socioeconomic factors, Hispanic participants had a CI that did not cross the null (HR 0.82, 95% CI 0.68−0.99). There was no significant interaction between race/ethnicity and yearly family income (*p*= .30).

Medication class	Overall (*N* = 4892)	White (*N* = 3111)	Black (*N* = 766)	Hispanic (*N* = 614)	AI/AN* (*N* = 255)	Other (*N* = 146)
First newer diabetes medication class used						
GLP-1 receptor agonist (%)	976 (20.0)	724 (23.3)	120 (15.7)	97 (15.8)	13 (5.1)	22 (15.1)
DPP-4 inhibitor (%)	1154 (23.6)	712 (22.9)	206 (26.9)	157 (25.6)	42 (16.5)	37 (25.3)
SGLT-2 inhibitor (%)	81 (1.7)	56 (1.8)	12 (1.6)	12 (2.0)	0 (0.0)	1 (1.2)
Any use of diabetes medication class during the study period						
GLP-1 receptor agonist (%)	1215 (24.8)	886 (28.5)	152 (19.8)	131 (21.3)	15 (5.9)	31 (21.2)
DPP-4 inhibitor (%)	1384 (28.3)	878 (28.2)	239 (31.2)	181 (29.5)	44 (17.3)	42 (28.8)
SGLT-2 inhibitor (%)	309 (6.3)	219 (7.0)	36 (4.7)	40 (6.5)	3 (1.2)	11 (7.5)

Table 3: Use of newer diabetes medication classes during the study period, overall and by race/ethnicity.
 * AI/AN, American Indian or Alaskan Native.
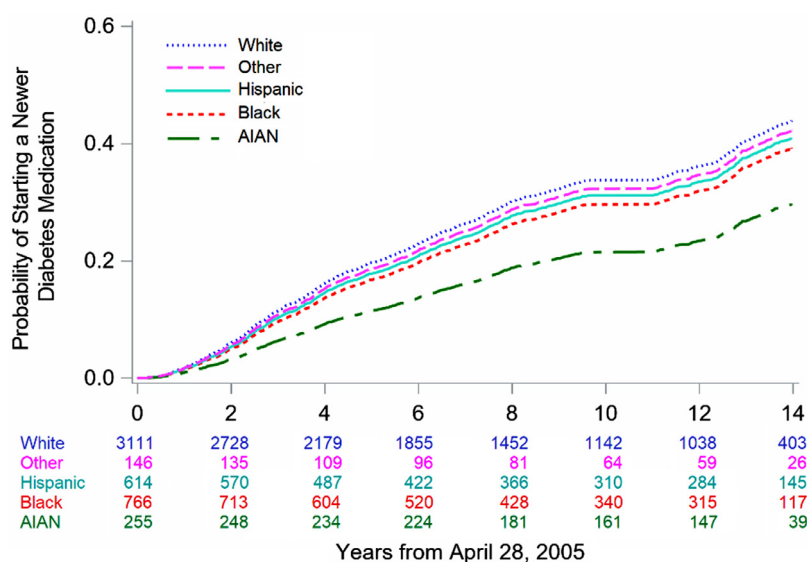
Fig. 1. Adjusted time-to-event curve for initiation of any newer class of diabetes medication by race/ethnicity.

Association of socioeconomic factors and use of newer diabetes medications

In the fully adjusted analysis, yearly family income had a graded inverse relationship with initiation of newer diabetes medications (p=.008) with a HR of 0.78 (95% CI 0.62−0.98) comparing the lowest to highest income categories (Table 2). Source of medical care was also significantly associated with initiation of newer diabetes medications (p<.001) with participants who received care in hospital-based practices or other settings being significantly less likely to initiate newer medications, compared to receiving care in private offices. Educational achievement, employment status, and type of health insurance were not significantly associated with the outcome.

Use of newer diabetes medications by medication class

Table 3 shows the frequency of use of each newer diabetes medication class, including the frequency of each medication class being the first newer diabetes medication initiated, and the frequency of use at any time during the study period. DPP-4Is were the most frequently used newer diabetes medication class, both as the first class initiated (23.6%) and any use during the study period (28.3%). These were followed closely by GLP-1Ras (20.0% first use, 24.8% any use). SGLT-2Is were used relatively infrequently (1.7% first use, 6.3% any use).

Subgroup analyses

There were no significant interactions between race/ethnicity and the primary outcome by age, gender, diabetes duration, or the presence of cardiovascular disease or chronic kidney disease (Supplemental Fig. 1).

Sensitivity analysis

The association of race/ethnicity and socioeconomic factors with initiation of GLP-1Ras only was consistent

with the primary analysis (Supplemental Table 2). Race/ethnicity and socioeconomic factors were not significantly associated with initiation of SGLT-2Is or DPP-4Is. Finding in each intervention arm were consistent with the primary analysis of both arms combined (Supplemental Table 3). There were no substantive differences from the primary analysis after adjustment for whether participants brought their home medications for review (Supplemental Tables 4 and 5) or accounting for competing risk of mortality (Supplemental Table 6).

Discussion

In this study among adults with type 2 diabetes in the Look AHEAD trial, we examined racial/ethnic differences in the initiation of newer diabetes medications from their entry onto the U.S. market in April 2005 until February 2020. We found that individuals of all minority race/ethnicities had lower initiation of newer diabetes medications compared to White participants, with initiation of newer diabetes medications being significantly lower for Black and AI/AN participants. This finding was mostly driven by GLP-1RAs. Among the socioeconomic factors examined, lower yearly family income and receiving medical care at a hospital clinic or outpatient department were significantly associated with lower initiation of newer diabetes medications. Adjustment for socioeconomic factors minimally attenuated the association of race/ethnicity with initiation of newer diabetes medications. These findings suggest that minorities with diabetes may experience barriers to initiating newer diabetes medications. Given that newer diabetes medications are especially beneficial for patients with cardiovascular disease and chronic kidney disease, and racial/ethnic minorities are disproportionately affected by these conditions, differences in the initiation of newer diabetes medications may be an important contributing factor to racial/ethnic disparities in diabetes outcomes.

This is the first study to our knowledge to examine racial/ethnic differences in the initiation of newer classes of diabetes medications. Prior studies examining racial/ethnic disparities in diabetes care have focused on medication underuse and found that Black and Hispanic groups reported greater cost and income-related medication underuse.[6,18] In this study, we adjusted for the participants' glycaemic control and intensity of diabetes therapy so that our findings reflect differences in the classes of diabetes medications initiated, independent of the aggressiveness of diabetes treatment. Our findings show that Black and AI/AN individuals had a 19% and 49% lower risk of initiating newer diabetes medications, respectively. This finding suggests that individuals of minority race/ethnicity are less likely to initiate newer diabetes medication classes than their White counterparts of similar socioeconomic status and diabetes management.

Racial/ethnic disparities in the initiation of newer diabetes medications have important clinical consequences. There is evidence from clinical trials that GLP-1Ras and SGLT-2Is have beneficial effects on cardiovascular and renal outcomes compared to other classes of diabetes medications.[19,20] As racial/ethnic minorities with diabetes have a higher burden of chronic kidney disease and worse cardiovascular outcomes,[2,3] they may have a greater indication for initiation of GLP-1Ras and SGLT-2Is, which is incongruous with our findings. There is also evidence that all newer diabetes medication classes, compared to sulfonylureas or insulin, have lower risk for hypoglycaemia,[21] which occurs more often among racial/ethnic minorities.[12,22] Therefore, reduced access to newer diabetes medications in minority race/ethnic groups who may benefit most could contribute to diabetes health disparities.

Reasons for the racial/ethnic differences in initiation of newer diabetes medications may include differences in insurance coverage, provider treatment patterns, and patient preference. In this study we were not able to distinguish between these potential causes. However, adjustment for multiple socioeconomic factors only minimally attenuated the racial/ethnic differences observed, and prior studies have found that racial and ethnic disparities in diabetes management occur even among individuals with similar income and healthcare access.[23] This suggests that there may be other factors beyond medication access that are contributing to differences in initiation of newer diabetes medications which require further study. For example, patient attitudes about treatment, which differ by race/ethnicity, may contribute to medication underuse.[24]

We examined socioeconomic factors because they are tightly linked to race/ethnicity and may mediate observed differences.[6] We found that participants with lower yearly family income had lower initiation of newer diabetes medications. This finding is likely explained by the higher cost of these newer diabetes medication with monthly national average drug acquisition costs of $175-$456, $284-$499, and $706-$930 for DPP-4Is, SGLT-2Is and GLP-1Ras, respectively.[8] Notably, we found that there was significantly lower initiation of newer diabetes medications for participants earning a yearly family income of less than $60,000, which is similar to the median yearly household income in the U.S. during the study period of $63,179 in 2018.[25] This suggests a substantial portion of U.S. patients with type 2 diabetes could be experiencing lower access to newer diabetes medications.

Access to newer diabetes medications may be influenced by insurance formulary coverage and out of pocket costs. We found no significant differences by major categories of health insurance providers. However, we lacked detailed insurance data on formulary coverage, and few participants were uninsured, limiting our ability to examine these associations. Previous

studies have found that cost sharing, formulary restrictions and Medicaid expansion are associated with utilization of newer diabetes medications.[7] The relationship between insurance coverage and access to newer diabetes medications requires further study.

We also found that significant differences in initiation of newer diabetes medications by participants' primary source of medical care such that those receiving care from hospital-affiliated clinics or community health centres had lower initiation compared to those receiving care from a private doctor's office. This could be due to differences in diabetes medication prescribing patterns of the participants' primary care physicians or access to endocrinologists at different types of practices.[26] There may be differences in practice characteristics such as regional variation in treatment preferences that were not accounted for. Further, it was not until 2019 that ADA standard of care guidelines for type 2 diabetes recommended the use of newer diabetes medications for patients with pre-existing cardiovascular and renal disease, likely resulting in increased practice variation prior to this time;[8] however, our study found no significant interactions among these subgroups. Also, limited inclusion of racial/ethnic minorities in cardiovascular outcomes trials could lead to clinician concerns about initiating new medications in minorities.[27] Overall, these findings suggest that there may be practice-level variation in initiating newer diabetes medications that should be examined further.

Findings in this study were largely driven by lower initiation of GLP-1Ras among racial/ethnic minorities. Race/ethnicity was not associated with initiation of DPP4-Is or SLGT2-I's, although the latter were used infrequently during the study period. The null findings for DPP4-Is suggest that access to this class may be fundamentally different than GLP-1Ras. Previous analysis has shown that the diffusion of GLP-1 RA use after approval was slower than DPP4-Is and more concentrated in a few high prescribing practices.[28] The different mode of administration and clinical profile of the DPP4-Is and GLP-1Ras may be contributing to this.[19,20,28]

The strengths of this study include a large, well characterized population with good representation of racial and ethnic minorities from multiple study sites across the U.S. Participants were followed for a median of 8.3 years with little loss to follow-up. The study also ascertained medication use, socioeconomic and clinical data using standardized assessments by trained staff.

Limitations include the possibility of unmeasured confounding as detailed information on participants' health insurance plans were not available. Therefore, associations between specific health insurance plans and race/ethnicity could not be accounted for. As such, differences observed may reflect differences in eligibility for health insurance with different formularies and benefits. Further, only 7.6% of participants were uninsured and so it was not possible to examine the effect of insurance status on low-income groups specifically. This study did adjust for study site, but there may be regional variations in prescribing patterns not accounted for, notably AI/AN participants who were concentrated in three Southwest centres and predominantly received care from the Indian Health Service. Medication data was also ascertained annually which raises the possibility that newer medications were initiated and discontinued within that period. Non-pharmacologic diabetes treatment during the trial may also have differed by race/ethnicity; in Look AHEAD White participants responded most favourably to the study intervention.[29] Since this study examined participants enrolled in a clinical trial with primary care at baseline, there may be differences in diabetes care relative to the general population. However, trends in diabetes medication use among participants were similar to trends in the US population over the same timeframe.[30]

Conclusions

In summary, this study provides evidence of racial/ethnic and socioeconomic disparities in the initiation of newer diabetes medication among adults with overweight/obesity and type 2 diabetes. The association between race/ethnicity and initiation of newer diabetes medications persisted after accounting for differences in socioeconomic factors. These findings warrant attention as disparities in access to newer diabetes medications may exacerbate existing racial/ethnic disparities in diabetes care. Further research to understand the drivers of this disparity are needed to inform interventions that increase equitable access to diabetes treatment.

Data sharing statement

All deidentified participant data and the data dictionary through the end of the intervention period are currently available as public use datasets through the NIDDK. Look Ahead A-C and Look Ahead E data which are included in this manuscript are still in preparation for release with no set date. Data will be made available to anyone requesting the data for any purpose and without investigator support.

CRediT authorship contribution statement

Ahmed Elhussein: Data curation, Formal analysis, Conceptualization, Methodology, Validation, Writing — review & editing, Writing — original draft. **Andrea Anderson:** Formal analysis, Methodology, Validation, Writing — review & editing, Visualization. **Michael P Bancks:** Methodology, Validation, Writing — review & editing. **Mace Coday:** Methodology, Validation, Writing — review & editing. **William C Knowler:** Methodology, Validation, Writing — review & editing. **Anne Peters:** Methodology, Validation, Writing — review & editing.

Articles

Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lana.2021.100111.

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