Rate of Decline in Kidney Function and Age-of-Onset or Duration of Type 2 Diabetes

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Research Article

Keywords: Younger onset diabetes, Diabetes duration, End-stage kidney disease, Estimated glomerular filtration rate

Posted Date: March 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-289704/v1

Version of Record: A version of this preprint was published at Scientific Reports on July 19th, 2021. See the published version at https://doi.org/10.1038/s41598-021-94099-3.

Abstract

The association between rate of kidney function decline and age-of-onset or duration of type 2 diabetes has not been well investigated. We aimed to examine whether rates of estimated glomerular filtration rate (eGFR) decline differ by age-of-onset or duration in people with type 2 diabetes. Using the Action to Control Cardiovascular Risk in Diabetes study dataset rates of eGFR decline were calculated using a joint-longitudinal-survival model and were compared among groups defined by the age-of-onset (0–39, 40–49, 50–59, 60–69 and > 70 years) and 5-year diabetes duration intervals. Changes in renal function were evaluated using median of 6 (interquartile range: 3–10) eGFR measurements per person. eGFR decline was the slowest in those with an age-at-diagnosis of 50 – 59 years or those with duration of diabetes < 5 years. The rates of eGFR decline were significantly greater in those with an age-of-onset < 40 years or those with duration of diabetes > 20 years compared to those diagnosed at 50 – 59 or those with duration of diabetes < 5 years (-1.98 vs -1.61 ml/min/year; -1.82 vs -1.52 ml/min/year; respectively ($p < 0.001$). Those with youngest age-of-onset or longest duration of type 2 diabetes had more rapid declines in eGFR compared to those diagnosed at middle age or those with shorter duration of diabetes.

Introduction

Type 2 diabetes diagnosed at a younger age is reported to run an aggressive course and have higher rates of complications compared to older onset type 2 diabetes [1–4]. Indeed, a number of studies have shown that the risk of end-stage kidney disease (ESKD) is higher in younger-onset type 2 diabetes than in older-onset type 2 diabetes, and this excess risk is primarily attributable to attainment of a longer duration of diabetes [2,5,6]. This would suggest that for renal outcomes, younger onset type 2 diabetes is not inherently more aggressive than older onset type 2 diabetes. However, results of these studies of ESKD may be limited, as those younger at onset of diabetes will typically need to have had a greater decline in renal function to reach the ESKD endpoint, as their estimated glomerular filtration rate (eGFR) is typically higher when diabetes is diagnosed compared to their older counterparts. Thus, similar incidence of ESKD may co-exist with different rates of decline in renal function. To gain further understanding of any differences in pathophysiology between younger and older onset or those with shorter and longer duration of type 2 diabetes, analyses of changes in kidney function over time should also be examined. The aim of this study, therefore, was to examine whether rates of eGFR decline differ by age-of-onset or duration in people with type 2 diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial dataset provides a large sample size with multiple measures of eGFR over time, allowing this aim to be comprehensively explored.

Methods

Study design and participants

Detailed information about the ACCORD study is described elsewhere [7]. In brief, ACCORD was a multicentre randomised clinical trial in the US and Canada, comprising 10,251 people with type 2

diabetes, glycated haemoglobin levels of 7.5% or more, aged 40–79 with a history of cardiovascular disease (CVD) or the presence of risk factors for CVD. ACCORD recruited participants between 2003 and 2005. The passive ACCORD Follow-On (ACCORDION) study involved observation of those members of the ACCORD population who agreed to participate for long-term follow-up.

The ACCORD study was approved by the Institutional Review Boards of each study centres and adhered to the principles of the Declaration of Helsinki.
All study participants provided written informed consent forms [8]. For the current analysis, we included 9917 participants after excluding those with missing diabetes duration (n = 92), missing baseline eGFR (n = 59) or absence of any eGFR measurements after baseline (n = 183).

Demographic and clinical variables

Socio-demographics, medical history, concomitant medication use, lifestyle behaviours, health-related quality of life, measures of physical and clinical examinations incorporating kidney function were recorded with different frequency by treatment group assignment as described previously [9]. Medical history including diabetes related data are collected and documented at baseline in the form of a detailed initial medical history and reviewed and recorded at specified follow-up visits.

Serum creatinine was measured at baseline and every 4 months thereafter until the end of the trial and at least once during the post-trial period. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate eGFR [10]. Detailed information about measurement methods for laboratory parameters is available in previous reports [7,11].

Outcome assessment

In this analysis, we specifically focused on the progression of CKD, and therefore evaluated the annual absolute and percentage changes in eGFR. Rates of eGFR decline were calculated and compared based on the age-of-onset of diabetes, which was classified into 5 groups: 0 – 39, 40 – 49, 50 – 59, 60 – 69 and over 70 years and 5-year duration of diabetes intervals [5,12]. ESKD during the trial period is defined as a need for dialysis or renal transplantation or decline of eGFR ≤ 15 mL/min per 1.73 m^2 in the absence of an acute reversible cause. ESKD events during the post-trial period in ACCORDION were not captured. Thus, for the post-trial period, we defined ESKD as progression to a sustained eGFR ≤ 15 mL/min per 1.73 m^2.

Statistical analyses

Rates of eGFR decline were calculated using a joint longitudinal-survival model and were compared based on the age-of-onset or duration of diabetes [13–15]. In brief, joint-longitudinal survival model is a method that takes into account potentially informative censoring when modelling longitudinal data by simultaneously modelling the longitudinal and survival outcome. Model 1 included socio-demographic factors; for model 2, baseline smoking, family history of CVD, personal CVD history, diabetes duration, body mass index, blood pressure levels, use of renin-angiotensin-aldosterone system (RAAS) blockers,

glycated haemoglobin, serum lipid levels and urine albumin/creatinine ratio (UACR) were added to model 1. The trajectories of eGFR stratified by age-of-onset of diabetes over time were visualised using duration as the time scale in the analysis. Moreover, in order to determine if hyperfiltration affected the results, rates of eGFR decline were estimated including only those with a baseline eGFR of less than 120 ml/min/1.73 m^2 in a sensitivity analysis. In a further sensitivity analysis, we restricted the analysis to the trial period in which more frequent creatinine measurements were performed. All statistical analyses were performed in Stata for Windows, version 15 (Stata corporation) and R version 3.6.0 (www.r-project.org).

We received a de-identified dataset from the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) after obtaining institutional review board approval from the human research ethics committees of the Alfred Hospital (Project No: 214/18) and Monash University (Project No: 13458), Melbourne, Australia.

Results

Tables 1 and 2 show that at baseline, the median age was 62.0 years (interquartile range (IQR): 57.6 – 67.0), the median eGFR was 89.7 mL/min/1.73m^2, and 35.0% had a prior CVD history. The median age-of-onset of diabetes was 52.2 (IQR: 46.2–58.0) and median diabetes duration was 9.0 (IQR: 5.0–15.0) which were similar for males and females. At baseline, those with an age-of-onset under 40 years or those with duration of diabetes longer than 20 years had poorer glycaemic control, higher UACR and higher prevalence of current smoking. They were more likely to be prescribed RAAS-blockers compared to other age-of-onset or diabetes duration groups (Table 1).

Table 1
Baseline characteristics of study participants according to the age-of-onset of diabetes

Characteristics	Overall	Age-of-onset of diabetes (years)				
		0 – 39	40 – 49	50 – 59	60 – 69	70+
n (%)	9917	945 (9.5)	2926 (29.5)	4264 (43)	1561 (15.8)	221 (2.2)
Baseline age (yr; median [IQR])	62.0 (57.6, 67.0)	58.0 (55.3, 62.6)	58.8 (56.1, 62.8)	61.8 (58.4, 65.7)	69.1 (66.1, 72.4)	76.2 (74.1, 78.1)
Diabetes duration (yr; median [IQR])	9.0 (5.0, 15.0)	23.0 (19.0, 30.0)	13.0 (10.0, 18.0)	7.0 (4.0, 11.0)	5.0 (3.0, 8.0)	3.0 (1.0, 5.0)
Follow-up (yr, mean [SD])	7.0 (2.7)	6.9 (3.1)	7.0 (3.1)	7.1 (3.1)	6.6 (3.0)	5.5 (2.7)
Male (n [%])	6107 (61.6)	542 (57.3)	1815 (62.0)	2633 (61.7)	983 (63.0)	136 (61.5)
Race (n [%])						
White	6191 (62.4)	504 (53.3)	1736 (59.3)	2714 (63.7)	1083 (69.4)	154 (69.7)
Black	1883 (19.0)	217 (23.0)	595 (20.3)	773 (18.1)	261 (16.7)	37 (16.7)
Hispanic	709 (7.2)	97 (10.3)	216 (7.4)	311 (7.3)	72 (4.6)	13 (5.9)
Other	1134 (11.4)	127 (13.4)	379 (13.0)	466 (10.9)	145 (9.3)	17 (7.7)
Education (n [%])						
< High school	1442 (14.5)	147 (15.5)	391 (13.4)	588 (13.8)	270 (17.3)	46 (20.8)
High school graduate	2620 (26.4)	266 (28.2)	722 (24.7)	1102 (25.8)	466 (29.8)	64 (28.9)
Some college	3257 (32.9)	312 (33.1)	1016 (34.7)	1406 (33.0)	463 (29.7)	60 (27.2)
≥College graduate	2598 (26.2)	220 (23.2)	797 (27.2)	1167 (27.4)	362 (23.2)	51 (23.1)
Current smoker (n [%])	1375 (13.9)	145 (15.3)	451 (15.4)	594 (13.9)	169 (10.8)	16 (7.2)
HbA1c (%; median [IQR])	8.1 (7.6, 8.9)	8.3 (7.8, 9.1)	8.2 (7.7, 9.0)	8.1 (7.5, 8.8)	7.9 (7.5, 8.6)	7.8 (7.3, 8.6)

Characteristics	Overall	Age-of-onset of diabetes (years)				
		0 – 39	40 – 49	50 – 59	60 – 69	70+
HbA1c (mmol/mol; median [IQR])	65.0 (58.5, 72.3)	67.2 (61.7, 75.9)	66.1 (60.6, 74.9)	65.0 (58.5, 72.7)	62.8 (58.5, 70.5)	61.7 (56.3, 70.5)
BMI (kg/m^2; mean [SD])	32.2 (5.4)	32.2 (5.6)	32.5 (5.5)	32.4 (5.3)	31.4 (4.9)	30.2 (4.8)
Triglycerides (mg/dl; median [IQR])	155 (106, 228)	137 (94.5, 202)	151 (102, 232)	160 (112, 236)	157 (109.5, 218.5)	148 (99, 218)
Total cholesterol (mg/dl; median [IQR])	178 (154, 207)	174 (149, 201)	177 (153, 208)	181 (157, 209)	176 (153, 203)	171 (147, 198)
Systolic BP (mmHg; mean [SD])	136.3 (17.0)	136.2 (17.1)	136.1 (16.9)	135.8 (16.8)	137.5 (18.0)	139.0 (16.5)
RAAS blockers (n [%])	6858 (69.1)	698 (73.8)	2102 (71.8)	2864 (67.2)	1039 (66.5)	154 (70.1)
CVD history (n [%])	3472 (35.0)	474 (50.1)	1113 (38.0)	1241 (29.1)	554 (35.5)	90 (40.9)
UACR (mg/g; median [IQR])	14 (7, 44)	20 (8, 86.5)	14 (7, 50)	13 (7, 37)	12 (7, 37)	17 (7, 43)
UACR categories						
A1 (normoalbuminuria)	6801 (68.6)	538 (56.9)	1949 (66.6)	3062 (71.8)	1108 (71.0)	144 (65.2)
A2 (microalbuminuria)	2468 (24.9)	297 (31.4)	743 (25.4)	991 (23.2)	371 (23.8)	66 (29.9)
A3 (macroalbuminuria)	648 (6.5)	110 (11.7)	234 (8.0)	211 (5.0)	82 (5.2)	11 (4.9)
eGFR (mL/min/1.73m^2; median [IQR])	87.2 (72.2, 96.7)	91.2 (72.7, 99.4)	91.3 (75.6, 99.1)	88.8 (73.1, 96.8)	78.6 (66.7, 90.4)	71.5 (58.6, 83.0)
eGFR categories (mL/min/1.73m^2)						
G1 (> 90)	4515 (45.5)	491 (52.0)	1549 (52.9)	2034 (47.7)	422 (27.1)	19 (8.6)
G2 (60–90)	4414 (44.5)	362 (38.3)	1149 (39.3)	1838 (43.1)	923 (59.1)	142 (64.3)
G3 (< 60)	988 (10.0)	92 (9.7)	228 (7.8)	392 (9.2)	216 (13.8)	60 (27.1)

Characteristics	Overall	Age-of-onset of diabetes (years)				
		0 – 39	40 – 49	50 – 59	60 – 69	70+

Abbreviations: IQR, interquartile range; y, year-olds; yr, year; HbA1c, glycated hemoglobin; BMI, body mass index; BP, blood pressure; RAAS blockers, renin-angiotensin-aldosterone system blockers; CVD history, cardiovascular disease history; UACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.

Table 2
Baseline characteristics of study participants according to the duration of diabetes

Characteristics	Overall	Duration of diabetes (years)				
		0 – 4	5 – 9	10 – 14	15 – 19	20+
n (%)	9917	2114 (21.3)	2848 (28.7)	2246 (22.7)	1311 (13.2)	1398 (14.1)
Baseline age (yr; median [IQR])	62.0 (57.6, 67.0)	60.4 (56.8, 65.3)	61.4 (57.4, 66.2)	61.9 (57.7, 66.8)	62.9 (58.5, 68.3)	64.6 (60.1, 70.1)
Age at diagnosis of diabetes (yr; median [IQR])	52.2 (46.2, 58.0)	58.1 (54.3, 62.7)	54.7 (50.8, 59.7)	50.2 (46.3, 55.3)	46.4 (42.0, 51.4)	40.1 (35.0, 45.3)
Follow-up (yr; mean [SD])	6.9 (3.1)	6.9 (3.1)	7.0 (3.1)	7.1 (3.1)	7.0 (3.0)	6.6 (3.1)
Male (n [%])	6107 (61.6)	1294 (61.2)	1772 (62.2)	1383 (61.5)	810 (61.8)	850 (60.8)
Race (n [%])						
White	6191 (62.4)	1317 (62.3)	1868 (65.6)	1399 (62.3)	797 (60.8)	810 (57.9)
Black	1883 (19.0)	257 (12.2)	297 (10.4)	251 (11.2)	166 (12.7)	163 (11.7)
Hispanic	709 (7.2)	150 (7.1)	178 (6.3)	179 (7.9)	85 (6.4)	117 (8.4)
Other	1134 (11.4)	390 (18.4)	505 (17.7)	417(18.6)	263 (20.1)	308 (22.0)
Education (n [%])						
< High school	1442 (14.5)	274 (12.9)	408 (14.3)	309 (13.8)	184 (14.1)	261 (18.7)
High school graduate	2620 (26.4)	533 (25.2)	740 (26.0)	613 (26.6)	349 (26.6)	385 (27.5)
Some college	3257 (32.9)	727 (34.4)	949 (33.3)	709 (31.6)	414 (31.7)	458 (32.8)
≥College graduate	2598 (26.2)	580 (27.5)	750 (26.4)	614 (27.3)	361 (27.6)	293 (21.0)
Current smoker (n [%])	1375 (13.9)	341 (16.1)	415 (14.6)	312 (13.9)	151 (11.5)	156 (11.1)
HbA1c (%; median [IQR])	8.1 (7.6, 8.9)	7.9 (7.4, 8.7)	8.1 (7.6, 8.9)	8.2 (7.6, 8.9)	8.1 (7.6, 8.8)	8.2 (7.7, 8.9)

Characteristics	Overall	Duration of diabetes (years)				
		0 – 4	5 – 9	10 – 14	15 – 19	20+
HbA1c (mmol/mol; median [IQR])	65.0 (58.5, 72.3)	62.8 (57.3, 71.5)	65.0 (59.5, 73.7)	66.1 (59.5, 72.6)	65.0 (59.5, 72.6)	66.1 (60.6, 73.7)
BMI (kg/m^2; mean [SD])	32.2 (5.4)	32.6 (5.4)	32.4 (5.3)	32.2 (5.3)	31.8 (5.4)	31.6 (5.5)
Triglycerides (mg/dl; median [IQR])	155 (106, 228)	166 (118, 246)	165 (114, 237)	152 (105, 229)	137 (96, 205)	133 (94, 199)
Total cholesterol (mg/dl; median [IQR])	178 (154, 207)	185 (159, 213)	179 (156, 208)	177 (154, 207)	174 (151, 202)	171 (149, 199)
Systolic BP (mmHg; mean [SD])	136.3 (17.0)	135.5 (16.2)	135.1 (16.9)	136.5 (17.4)	137.6 (17.4)	138.0 (17.4)
RAAS blockers (n [%])	6858 (69.1)	1299 (61.5)	1954 (68.6)	1592 (70.8)	976 (74.4)	1037 (74.2)
CVD history (n [%])	3472 (35.0)	690 (32.6)	898 (31.5)	764 (34.0)	496 (37.8)	624 (44.6)
UACR (mg/g; median [IQR])	14 (7, 44)	11 (6, 26)	12 (6, 34)	15 (7, 50)	17 (7, 59)	22 (9, 91)
UACR categories						
A1 (normoalbuminuria)	6801 (68.6)	1631 (77.2)	2075 (72.8)	1495 (66.6)	823 (62.8)	777 (55.6)
A2 (microalbuminuria)	2468 (24.9)	414 (19.6)	632 (22.2)	591 (26.3)	376 (28.7)	455 (32.6)
A3 (macroalbuminuria)	648 (6.5)	69 (3.2)	141 (5.0)	159 (7.1)	112 (8.5)	166 (11.8)
eGFR (mL/min/1.73m^2; median [IQR])	87.2 (72.2, 96.7)	91.2 (77.7, 99.1)	88.7 (73.5, 97.4)	86.7 (72.1, 96.7)	83.7 (69.5, 94.8)	79.6 (65.2, 93.3)
eGFR categories (mL/min/1.73m^2)						
G1 (> 90)	4515 (45.5)	1134 (53.6)	1356 (47.7)	1026 (45.7)	528 (40.3)	471 (33.7)
G2 (60–90)	4414 (44.5)	852 (40.3)	1237 (43.4)	1103 (45.1)	618 (41.1)	694 (49.6)
G3 (< 60)	988 (10.0)	128 (6.1)	255 (8.9)	207 (9.2)	165 (12.6)	233 (16.7)

Characteristics	Overall	Duration of diabetes (years)				
		0 – 4	5 – 9	10 – 14	15 – 19	20+

Abbreviations: IQR, interquartile range; y, year-olds; yr, year; HbA1c, glycated hemoglobin; BMI, body mass index; BP, blood pressure; RAAS blockers, renin-angiotensin-aldosterone system blockers; CVD history, cardiovascular disease history; UACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.

Changes in renal function were evaluated using 108,876 eGFR determinations over 9 years (median: 6 (IQR: 3–10) determinations per person). Tables 3 and 4 show the rates of eGFR decline according to age-of-onset or duration of diabetes. When adjusted for baseline age, sex, ethnicity and education (Model 1), those with an age-of-onset of type 2 diabetes under 40 years or those with the duration of diabetes longer than 20 years had a fastest decline in eGFR for both absolute and percentage changes compared to those diagnosed at ages 50 – 59 years or those with diabetes duration of less than 5 years (reference group). Similarly, the incidence of ESKD was significantly higher in the < 40 age-of-onset group or those with longer diabetes duration (Table S1). Those with an age-of-onset over 70 years also had an annual percentage decline in eGFR that was significantly greater than the reference group (-2.75 vs -1.99, $p < 0.001$). Results for Model 2 were similar to those for Model 1.

Table 3
Annual change in eGFR according to age-of-onset of diabetes

	N	Absolute eGFR change (mL/min/1.73 m^2 per yr)[a]	Difference in absolute eGFR change (95% CI)	Percentage eGFR change (% per yr)[a]	Difference in percentage eGFR change (95% CI)
Model 1					
0 – 39 y	945	-2.01 (2.45)	-0.38 (-0.58, -0.17)	-2.46 (2.64)	-0.47 (-0.65, -0.29)
40 – 49 y	2926	-1.78 (2.04)	-0.15 (-0.26, -0.02)	-2.13 (2.06)	-0.12 (-0.22, -0.03)
50 – 59 y	4264	-1.63 (1.88)	Reference	-1.99 (1.89)	Reference
60 – 69 y	1561	-1.68 (2.35)	-0.05 (-0.18, 0.08)	-2.21 (2.00)	-0.22 (-0.33, -0.10)
≥70 y	221	-1.89 (2.17)	-0.26 (-0.61, 0.10)	-2.75 (2.28)	-0.76 (-1.06, -0.44)
Model 2					
0 – 39 y	943	-1.98 (2.43)	-0.37 (-0.56, -0.16)	-2.35 (2.61)	-0.40 (-0.57, -0.22)
40 – 49 y	2925	-1.75 (2.06)	-0.14 (-0.25, -0.02)	-2.05 (2.25)	-0.10 (-0.18 0.01)
50 – 59 y	4261	-1.61 (1.89)	Reference	-1.95 (1.94)	Reference
60 – 69 y	1559	-1.62 (1.88)	-0.01 (-0.14, 0.13)	-2.06 (2.08)	-0.11 (-0.22, 0.01)
≥70 y	220	-1.77 (2.21)	-0.16 (-0.53, 0.20)	-2.52 (2.23)	-0.56 (-0.91, -0.21)

a: Data are mean (standard deviation).

Model 1: adjusted for age, sex, race and education. **Model 2**: Model 1 + smoking, family history of cardiovascular disease (CVD), CVD history at baseline, diabetes duration, body mass index, blood pressure levels, use of renin-angiotensin-aldosterone system blockers, glycated haemoglobin level, serum lipid levels, and baseline urine albumin/creatinine, ratio. Baseline eGFR is not included in the covariate set, as it is already present in the joint longitudinal-survival model specification.

Abbreviations: eGFR, estimated glomerular filtration rate; y, years

Table 4
Annual change in eGFR according to the duration of diabetes

	N	Absolute eGFR change (mL/min/1.73 m^2 per yr)[a]	Difference in absolute eGFR change (95% CI)	Percentage eGFR change (% per yr)[a]	Difference in percentage eGFR change (95% CI)
Model 1					
0 – 4 y	2114	-1.55 (1.87)	Reference	-1.83 (1.81)	Reference
5 – 9 y	2848	-1.65 (1.94)	-0.10 (-0.23, 0.03)	-2.00 (1.94)	-0.17 (-0.28, -0.07)
10 – 14 y	2246	-1.80 (1.91)	-0.25 (-0.39, -0.11)	-2.20 (1.93)	-0.37 (-0.49, -0.26)
15 – 19 y	1311	-1.82 (2.18)	-0.27 (-0.44, -0.09)	-2.31 (2.35)	-0.48 (-0.62, -0.33)
≥20 y	1398	-1.90 (2.17)	-0.35 (-0.52, -0.17)	-2.53 (2.41)	-0.70 (-0.85, -0.55)
Model 2					
0 – 4 y	2110	-1.52 (1.81)	Reference	-1.82 (1.74)	Reference
5 – 9 y	2832	-1.62 (1.89)	-0.10 (-0.22, 0.04)	-1.91 (1.89)	-0.09 (-0.19, 0.01)
10 – 14 y	2236	-1.77 (1.92)	-0.25 (-0.38, -0.11)	-2.16 (1.95)	-0.34 (-0.45, -0.23)
15 – 19 y	1307	-1.76 (2.14)	-0.40 (-0.40, -0.06)	-2.21 (2.31)	-0.39 (-0.54, -0.25)
≥20 y	1393	-1.82 (2.17)	-0.30 (-0.46, -0.12)	-2.40 (2.39)	-0.58 (-0.72, -0.43)

a: Data are mean (standard deviation).

Model 1: adjusted for age, sex, race and education. **Model 2**: Model 1 + smoking, family history of cardiovascular disease (CVD), CVD history at baseline, diabetes duration, body mass index, blood pressure levels, use of renin-angiotensin-aldosterone system blockers, glycated haemoglobin level, serum lipid levels, and baseline urine albumin/creatinine, ratio. Baseline eGFR is not included in the covariate set, as it is already present in the joint longitudinal-survival model specification.

Abbreviations: eGFR, estimated glomerular filtration rate; y, years

Figure 1 shows the trajectories of eGFR stratified by age-of-onset of diabetes. Ten years after diagnosis, people with an age-of-onset of diabetes under 40 years had the highest average eGFR. However, they experience the most rapid decline in kidney function compared to those diagnosed later in life. Over a 10-year period (e.g. from 15 to 25 years duration), their average eGFR declines by 10 mL/min/1.73m^2 [95% confidence interval: 8.0-12.1] more than does the eGFR of those diagnosed at age 50–59 years.

Sensitivity analyses

Both absolute and percentage changes in eGFR were similar to the main results when we excluded those with eGFR > 120 mL/min/1.73 m^2 (Table S2). Results were similar in another sensitivity analysis restricted to the trial period, except that those with age-of-onset over 70 years had a slower annual absolute, but not percentage, decline in eGFR compared to the reference group (Table S3).

Discussion

Using data from this prospective cohort study, we showed that rates of eGFR decline are faster in the youngest age of type 2 diabetes onset group and in those with longest duration of diabetes compared to those with onset aged 50–59 years or those with duration of diabetes less than 5 years, respectively. We further showed that among those with similar but longer diabetes durations, the rate of eGFR decline is greatest in those with earliest diabetes onset.

The baseline clinical characteristics of study participants with younger onset or longer duration of type 2 diabetes in this study were similar to those reported in other studies [16,17]. The younger diabetes onset or those with longest duration group had worse glycaemic control and were more likely to smoke. These unfavourable risk factors may partly contribute to a more aggressive progression of diabetes and higher rates of complications.

While there is good evidence showing that younger onset type 2 diabetes confers an increased risk of ESKD [2,4], a finding we confirmed here, these studies do not report on rates of eGFR decline by age-of-onset or duration of diabetes. Thus, this may not represent differences in pathophysiology of chronic kidney disease (CKD) progression between younger and older onset type 2 diabetes or how pathophysiology changes with increasing diabetes duration. Clearly, individuals who develop diabetes at a younger age will need to have had a greater decline in renal function to reach ESKD, because their initial eGFR is typically higher when diabetes is diagnosed [2,16,18]. Examination of the rate of decline in eGFR therefore provides important additional insights into the impact of younger onset or longer duration of type 2 diabetes. Our current analyses of changes in eGFR over time demonstrated that both the mean absolute and percentage annual declines in eGFR in people with younger onset type 2 diabetes appears to be greater than those diagnosed in middle age, and that the annual eGFR decline increases with increasing duration of diabetes. These findings suggest that the pathophysiological mechanisms of CKD progression in younger onset diabetes may be different to older onset diabetes.

There are several possible explanations for our findings. One possible explanation for rapid decline in eGFR in people with younger onset type 2 diabetes, is the hyperfiltration and its subsequent normalisation in this group, which may lead to greater decline in eGFR [8,19]. However, this explanation is unlikely, because differences in eGFR decline persisted after excluding those with possible hyperfiltration in our sensitivity analysis. It is possible that obesity-related mechanisms, including increased levels of fatty acids and inflammatory markers, may contribute to greater decline in kidney function in those who develop diabetes at younger age [20,21]. Furthermore, genetic predisposition and other unknown factors associated with a younger onset of type 2 diabetes may play a role in the more rapid decline in kidney function in this group [22,23].

Although people with an age-of-onset over 70 years seemed to have a greater decline in eGFR compared to the reference group in the primary analysis, when we restricted the analysis to the ACCORD trial period, this was no longer statistically significant. It is not clear why this only affected the oldest age-of-onset group. It is possible that the intensive therapy in the in-trial period was relaxed more quickly at the end of ACCORD in this group than in younger participants. Thus, eGFR started to fall more rapidly in the ACCORDION phase.

The strengths of this study are the large sample size, long follow-up and frequent serum creatinine sampling. However, our data should be interpreted carefully in the context of the following limitations. Ascertaining the exact age-of-onset in type 2 diabetes is difficult, because many people remain asymptomatic or undiagnosed for many years. In addition, we were unable to completely account for differences in duration of diabetes between age-of-onset groups. This is because age-of-onset and duration of diabetes are highly correlated, and because of the limited overlap of durations in the younger age-of-onset groups with the older age-of-onset. Moreover, what we found mainly applies to people aged over 50 years old, and cannot necessarily be extrapolated to the earlier years of diabetes in those with younger onset type 2 diabetes. Lastly, the generalizability of our findings may be limited to some extent, because the population was drawn from a clinical trial that recruited those with poor glycemic control and prior CVD or CVD risk factors. However, we believe that this cohort represents a diverse group of people with type 2 diabetes and our findings add significantly to the understanding of potential differences in progression of CKD for those with a younger onset of type 2 diabetes.

Conclusion

Our current study suggests that people with younger age-of-onset or longer duration of type 2 diabetes may have a more rapid decline in eGFR compared to those diagnosed in middle age or those with shorter duration of diabetes. These findings contribute to the body of evidence suggesting that early and careful monitoring of kidney function is warranted in those with younger onset type 2 diabetes as they are at the highest long-term risk for kidney complications. Interventions which halt or slow the decline of eGFR are needed in this group.

Declarations

Acknowledgments

The authors thank the investigators, staff, and participants of the ACCORD study for their contributions and for giving us access to this rich and valuable dataset. The ACCORD study was conducted by the ACCORD study investigators and supported the National Heart, Lung, and Blood Institute (NHLBI); by other components of the National Institutes of Health, including the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Eye Institute; by the Centers for Disease Control and Prevention; and by General Clinical Research Centers.

Conflict of interest statement

None declared.

Authors' contributions

OB, DJM, JIM and JES designed the study. OB and AS performed data analysis and interpreted the results. OB wrote the manuscript. DJM, AS and JES supervised the application of the joint longitudinal-survival model and reviewed and edited the manuscript. OB, DJM and JES are the 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.

Funding

OB is supported by a Monash University Postgraduate Research Scholarship and a Baker Bright Sparks Scholarship. J.I.M is supported by an Australian Government Research Training Program (RTP) Scholarship and Monash Graduate Excellence Scholarship. JES is supported by a National Health and Medical Research Council Investigator Grant and DJM by a National Health and Medical Research Council Senior Research Fellowship. This work is partially supported by the Victorian Government's OIS Program.

Disclaimer

This study does not necessarily reflect the opinions or reviews of the ACCORD study investigators or NHLBI.

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Figures

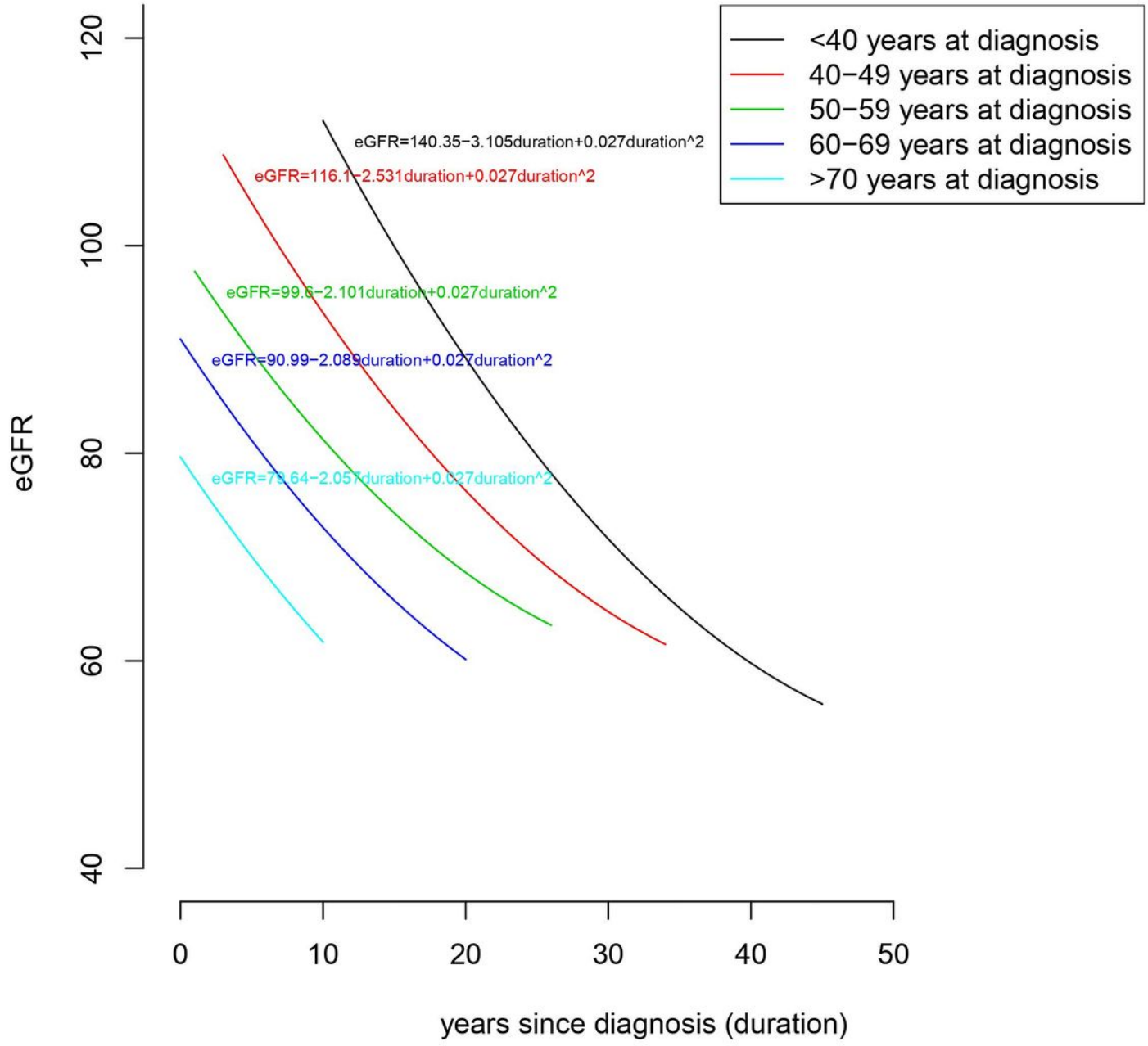

Figure 1

Estimated trajectories of log-transformed estimated glomerular filtration rate (eGFR) levels according to diabetes duration based on Model 1, stratified by age-of-onset of diabetes.

Supplementary Files

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- Supplementarymaterial.docx