Journal of Diabetes and Its Complications 32 (2018) 279–290

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Age, age at diagnosis and diabetes duration are all associated with vascular complications in type 2 diabetes

Natalie Nanayakkara [a,b], Sanjeeva Ranasinha [a], Adelle Gadowski [a], Stephane Heritier [a], Jeff R. Flack [c,d,e], Natalie Wischer [f], Jencia Wong [g,h], Sophia Zoungas [a,b,i,*]

[a] School Public Health and Preventive Medicine, Monash University, Prahran, VIC, Australia
[b] Diabetes and Vascular Medicine Unit, Monash Health, Clayton, VIC, Australia
[c] Diabetes Centre, Bankstown-Lidcombe Hospital, Bankstown, NSW, Australia
[d] Faculty of Medicine, University of NSW, Sydney, NSW, Australia
[e] School of Medicine, Western Sydney University, Sydney, NSW, Australia
[f] National Association Diabetes Centres, Sydney, NSW, Australia
[g] Diabetes Centre, Royal Prince Alfred Hospital, Sydney, NSW, Australia
[h] Discipline of Medicine, The University of Sydney, Sydney, NSW, Australia
[i] The George Institute for Global Health, Camperdown, NSW, Australia

ARTICLE INFO

Article history:
Received 6 June 2017
Received in revised form 22 November 2017
Accepted 22 November 2017
Available online 7 December 2017

Keywords:
Diabetes mellitus
Type 2
Age of onset
Duration
Diabetes complications

ABSTRACT

Background: Type 2 diabetes (T2DM) is increasingly diagnosed in younger patients. The trajectory of complications in patients diagnosed at a younger or older age is not well understood. We examine the associations between age, age at diagnosis and diabetes duration and vascular complications in patients with T2DM.
Methods: A cross-sectional study of pre-specified demographic and clinical data, from 3419 adults with T2DM participating in the Australian National Diabetes Audit (2015). Factors associated with diabetes complications were analysed using logistic regression.
Results: Mean (±SD) current age was 62.9 ± 12.5 years, age at diagnosis was 49.4 ± 12.3 years and mean diabetes duration was 13.5 ± 9.4 years. Macrovascular complications were more prevalent in patients who were older at diabetes diagnosis whereas microvascular complications were more prevalent in patients who were younger at diabetes diagnosis. Age, age at diagnosis and diabetes duration were all independently associated with increased risk of macrovascular complications after adjustment for sex, smoking, BMI and microvascular complications (all $p < 0.001$). In contrast, only diabetes duration was independently associated with microvascular complications after adjustment for sex, smoking, BMI and macrovascular complications ($p < 0.001$).
Conclusions: Age, age at diagnosis, and diabetes duration were all independently associated with macrovascular complications whereas only diabetes duration was independently associated with microvascular complications.

1. Introduction

Traditionally a disease of middle and older age, type 2 diabetes (T2DM) is increasingly diagnosed in younger patients.[1,2] The care of patients with type 2 diabetes and associated complications consumes significant healthcare resources and this is likely to rise exponentially given the increasing prevalence of T2DM. The pathogenesis of long-term vascular complications of T2DM is not well characterised. Understanding the development of vascular complications in people with diabetes enables diagnosis and intervention at an earlier stage of disease resulting in better outcomes. This is particularly important for people diagnosed with diabetes at a younger age, who are likely to suffer vascular complications at an earlier stage of life and when complications result in greater disability and loss of productivity compared with older patients.

The literature contains few studies examining the relationship between age at diabetes diagnosis and long-term outcomes of patients with type 2 diabetes, and these report inconsistent findings. Some studies have suggested that younger age at diabetes diagnosis is associated with increased risk of complications[3,4] but others have not.[5] Additionally, some studies have proposed that longer diabetes duration underlies the greater risk of development of vascular complications observed in patients diagnosed at a younger age.[6]

Conflict of interest disclosure: S Zoungas reports past participation in advisory boards and/or receiving honoraria for work unrelated to this paper from AstraZeneca Pty Ltd/Bristol-Myers Squibb Australia Pty Ltd, Eli Lilly Australia, Janssen Cilag Pty Ltd, Merck Sharp & Dohme (Australia) Pty Ltd, Sanofi Aventis Pty Ltd, Novo Nordisk, Servier Laboratories Pty Ltd and Takeda Pharmaceuticals Australia Pty Ltd as well as Monash University undertaking contract work for work unrelated to this paper from Bristol-Myers Squibb Australia Pty Ltd. S Zoungas holds a NHMRC senior research fellowship. N Nanayakkara holds an Australian Post Graduate award. The remaining authors declare that they have no competing interests.
* Corresponding author at: School of Public Health and Preventive Medicine, Monash University, 43-51 Kanooka Grove, Clayton, VIC 3168, Australia.
E-mail address: sophia.zoungas@monash.edu (S. Zoungas).

https://doi.org/10.1016/j.jdiacomp.2017.11.009
1056-8727/

Significant methodological heterogeneity complicates the interpretation of such studies, with some studies adjusting the risk of vascular complications for either age at diagnosis, diabetes duration or current age, for two of three factors, or for all three. There is also considerable variation in the definitions of "younger" and "older" age at diabetes diagnosis, with some studies defining "younger" as <30 years of age, <40 years or <50 years of age. There are also some differences in the definitions, categorisation and reporting of diabetes complications.

This study aimed to (1) determine the prevalence of vascular complications and (2) to examine the associations between age, age at diagnosis and diabetes duration and vascular complications in patients with type 2 diabetes.

2. Methods

2.1. Participants

This national, cross-sectional study examined de-identified data from the 2015 Australian National Diabetes Audit (ANDA). Participants were adult patients with type 2 diabetes, presenting to one of 49 nationally accredited diabetes centres. De-identified data were sourced from a range of diabetes centres located in the community/primary care (n = 16) and secondary/tertiary care (n = 33), with patients under the care of endocrinologists, general specialists and general practitioners. Information was collected regarding all consecutive patients attending a participating diabetes centre during the one-month survey period (May or June 2015). Patients known to have type 1 diabetes, gestational diabetes and secondary diabetes were excluded. Data from previous collections (2013 and 2011) were also obtained for comparisons. The Australian National Diabetes Audit received approval from the Monash Health Human Research Ethics Committee.

2.2. Variables

Pre-specified demographic (date of birth, gender) and clinical variables (co-morbidities, date of diabetes diagnosis, diabetes complications, blood pressure, HbA1c, smoking status, medications) were extracted. Health professionals from participating centres reviewed the patients medical records including pathology results and recorded the de-identified information in a standardised data collection form. The participating centres were contacted to clarify all missing data, invalid entries and discrepancies. Ethics approval was obtained from the Monash Health Human Research Ethics Committee.

Age at diabetes diagnosis was calculated as year of diabetes diagnosis minus year of birth and categorised as <30 years, 30–49 years, 50–64 years and >65 years and also analysed as a continuous variable. Diabetes duration was calculated as year of survey minus year of diabetes diagnosis and categorised as <5 years, >5–10 years, >10–15 years and ≥15 years and analysed as a continuous variable. The main outcome variables were macrovascular complications (defined as either cardiovascular, cerebrovascular or peripheral vascular disease) and microvascular complications (defined as retinopathy, nephropathy or peripheral neuropathy). Cardiovascular disease was defined as myocardial infarction, angioplasty or coronary artery bypass graft as evidenced by medical documentation. Cerebrovascular disease was defined as cerebral stroke and transient ischemic disease due to vascular disease. Peripheral vascular disease was defined as absence of both dorsalis pedis and posterior tibial pulses (either foot). Retinopathy was defined as any degree of retinopathy on eye examination. End-stage kidney disease was defined by the requirement for dialysis therapy or having undergone kidney transplantation. Peripheral neuropathy was defined as reduced pinprick and vibration or monofilament sensation (both feet).

2.3. Statistical analysis

All patients with type 2 diabetes were included in the analyses. Categorical variables were reported as percentages, and differences between subgroups were analysed using χ^2 test. Continuous variables were summarised as means with standard deviations (SD) or as medians with interquartile ranges (IQR). Continuous data were tested for normality to determine the appropriate method for parametric or non-parametric statistical analysis. Subgroup analyses were performed using ANOVA for normally distributed data and Mann-Whitney U/Kruskal-Wallis test for non-parametric data as appropriate. Logistic regression was used to examine the association of dichotomous outcomes (macrovascular and microvascular complications) and risk factors (current age, age at diagnosis and diabetes duration) The selection of variables was based on identifying all measured clinical variables of known or suspected prognostic importance for the outcomes of interest (and/or exhibiting $p < 0.05$ on univariate analyses). Given that age is the sum of age at diabetes diagnosis and diabetes duration, all three variables could not be analysed in the same model due to collinearity (functional dependence). In other words, any individual models could only test two variables but not all three variables. Pearson's correlation co-efficient was calculated to measure linear dependence between variables. Model 1 contained current age and duration and model 2 contained age at diabetes diagnosis and diabetes duration. Receiver operating characteristic (ROC) curves were plotted for each model and areas under the curves (AUC) calculated for comparison. The interaction effect of age and diabetes duration on the probability of macrovascular and microvascular complications was also assessed. A two-sided significance level of 0.05 was considered statistically significant.

Sensitivity analyses were conducted to 1) examine the effect of excluding participants with recent (within 12 months) diagnosis of diabetes, to allow for time for complication screening to occur and therapeutic regimens to be established and complications diagnosed and 2) examine the effect of centre type (community/primary and secondary care) or clustering by centre. Data from 2013 and 2011 were examined to investigate consistency of the effects over time. Statistical analyses were performed using Stata software version 14.2 (StataCorp, Texas, USA).

3. Results

3.1. Baseline characteristics

Data from 3419 participants were included in this study. Mean (±SD) age was 62.9 ± 12.5 years and age at diagnosis was 49.4 ± 12.3 years, with 5.6%, 44%, 39% and 11% of patients reporting age at diagnosis as <30, 30–49, 50–64 and ≥65 years, respectively. Mean (±SD) diabetes duration was 13.5 ± 9.4 years, with 18%, 19%, 20% and 43% of participants reporting durations of <5 years, 5–9 years, 10–14 years and ≥15 years, respectively. The clinical characteristics of the participants are shown, stratified by age at diabetes diagnosis (Table 1).

The mean age of the participants at time of survey increased linearly with age at diagnosis ($p < 0.001$) (Table 1). Age was positively correlated with age at diabetes diagnosis (Pearson correlation coefficient $r = 0.71$ $p < 0.001$) and diabetes duration (Pearson correlation coefficient $r = 0.38$ $p < 0.001$). Diabetes duration was inversely correlated with age at diagnosis (Pearson correlation coefficient $r = -0.26$ $p < 0.001$). Retinopathy was reported by 20.5% of patients, peripheral neuropathy by 26.7% and end stage renal failure by 5.8%. Cardiovascular disease was reported by 12.0% of patients, cerebrovascular disease by 7.1% and peripheral vascular disease by 5.8% of patients.

3.2. Macrovascular complications

Macrovascular complications were more prevalent in patients who were older at diabetes diagnosis (Table 1). In univariable models, older age, older age at diagnosis, longer diabetes duration, male sex, smoking status, eGFR, BMI and prevalent microvascular disease were all associated with an increased risk of macrovascular complications (all $p < 0.05$). In multivariable models including age or age at diagnosis and diabetes duration in 1-year increments, age, age at diagnosis and diabetes duration remained significantly associated with an increased risk of macrovascular complications

Table 1
Patient characteristics by age at diabetes diagnosis.

Characteristic	All participants	Age at diabetes diagnosis (years)				p value[a]
		<30	30–49	50–64	>65	
Participants n (%)	3419	191 (5.6)	1512 (44.2)	1346 (39.4)	370 (10.8)	
Current age (years), mean (SD)	62.9 (12.5)	43.4 (14.5)	57.4 (10.6)	67.7 (8.0)	77.4 (6.0)	<0.001
Male, n (%)	1862 (53.9)	69 (36.5)	791 (53.0)	754 (56.6)	208 (56.7)	<0.001
Age at diabetes diagnosis (SD)	49.4 (12.3)	24.3 (4.5)	41.4 (5.3)	56.2 (4.1)	70.2 (4.6)	<0.001
Diabetes duration (years), mean (SD)	13.5 (9.4)	19.2 (9.4)	16.1 (9.7)	11.5 (7.5)	7.2 (5.4)	<0.001
Initial visit n (%)	585 (17.3)	32 (17.5)	229 (15.7)	234 (17.9)	78 (21.9)	0.040
Complications						
Macrovascular complications	1096 (35.4)	41 (24.1)	435 (32.7)	448 (37.4)	137 (41.4)	<0.001
IHD (MI/CAGS)	410 (12.0)	20 (11.5)	282 (21.1)	308 (25.8)	96 (29.2)	<0.001
Stroke	248 (7.1)	8 (4.2)	96 (6.4)	103 (7.7)	28 (7.6)	0.223
PVD	233 (8.2)	0 (0.0)	26 (5.7)	129 (9.7)	254 (16.0)	<0.001
Microvascular complications	1366 (44.1)	78 (45.4)	671 (49.4)	460 (39.0)	128 (39.9)	<0.001
Retinopathy, n (%)	682 (20.5)	53 (28.7)	370 (25.8)	202 (15.7)	43 (12.2)	<0.001
Peripheral neuropathy, n (%)	916 (26.7)	49 (26.5)	429 (29.0)	324 (24.3)	94 (25.9)	0.045
End stage renal failure, n (%)	196 (5.8)	11 (6.3)	104 (7.9)	66 (5.7)	17 (5.3)	0.118
eGFR, mean (SD)	208 (6.9)	90.3 (48.9)	78.5 (35.2)	71.3 (26.6)	64.8 (25.6)	<0.001
Microalbuminuria, n (%)	248 (8.1)	16 (8.4)	262 (17.3)	273 (20.3)	69 (18.7)	0.001
Blood glucose control						
HbA1c (%), mean (SD)	8.2 (1.8)	8.7 (2.0)	8.5 (1.9)	8.0 (1.7)	7.7 (1.7)	<0.001
HbA1c (mmol/mol), mean (SD)	66.0 (19.3)	73.8 (18.3)	66.5 (20.1)	61.6 (18.2)	56.3 (15.8)	<0.001
Other major risk factors						
Systolic blood pressure (mm Hg), mean (SD)	132.8 (18.5)	130.2 (20.1)	132.0 (17.7)	133.1 (18.5)	135.0 (20.1)	0.0077
Diastolic blood pressure (mm Hg), mean (SD)	74.6 (10.6)	76.7 (11.6)	75.3 (10.4)	73.7 (10.5)	73.2 (10.8)	<0.001
Antihypertensive therapy, n (%)	2583 (75.7)	111 (59.7)	1093 (74.0)	1036 (78.7)	296 (81.32)	<0.001
Total cholesterol (mmol/l), mean (SD)	4.2 (1.2)	4.5 (1.2)	4.3 (1.2)	4.1 (1.1)	4.1 (1.1)	<0.001
LDL-cholesterol (mmol/l), mean (SD)	2.1 (1.2)	2.3 (1.0)	2.2 (1.0)	2.1 (1.5)	2.0 (0.9)	0.0897
HDL-cholesterol (mmol/l), mean	1.1 (0.4)	1.1 (0.3)	1.1 (0.3)	1.2 (0.4)	1.2 (0.3)	0.0003
Triglyceride (mmol/l), mean (SD)	2.3 (2.0)	2.4 (2.1)	2.4 (2.3)	2.1 (1.7)	2.1 (1.4)	0.0042
Lipid lowering therapy, n (%)	2534 (72.9)	104 (54.5)	1095 (72.8)	1020 (76.2)	272 (73.5)	<0.001
Current smoking, n (%)	1515 (50.9)	70 (40.9)	659 (50.8)	566 (49.7)	143 (45.3)	0.044
BMI (kg/m^2), mean (SD)	33.2 (7.5)	35.2 (8.7)	33.9 (8.0)	32.9 (6.9)	30.7 (5.9)	<0.001

BMI = Body Mass Index; HbA1c = haemoglobin A1c; IHD = ischemic heart disease.
[a] Continuous variables were summarised as means with standard deviations (SD) or as medians with interquartile ranges (IQR). Subgroup analyses were performed using ANOVA for normally distributed data and Mann-Whitney U/Kruskal-Wallis test for non-parametric data as appropriate.

(all $p < 0.001$) but BMI did not after adjustment for sex, smoking status, eGFR and prevalent microvascular disease (Table 2 and Fig. 1).

Receiver operating characteristic (ROC) curves of models predicting macrovascular complications and including either age and diabetes duration, or age at diagnosis and diabetes duration were comparable (AUC = 0.7508 for both models) indicating that both models approximated the data equally (Appendix D).

When the outcomes of coronary artery disease and cerebrovascular disease were examined separately the associations with age, age at diagnosis and diabetes duration were consistent except that diabetes duration was not associated with cerebrovascular disease after adjustment for age (Appendix C).

3.3. Microvascular complications

Microvascular complications were less prevalent in patients who were older at diabetes diagnosis, albeit in the context of a shorter disease duration (Table 1). In univariable models, older age, longer diabetes duration, male sex, past smoking, eGFR and prevalent macrovascular disease were all associated with increased risk of microvascular complications (all $p < 0.05$). In contrast, older age at diagnosis was associated with decreased risk of microvascular complications (0.99 [0.98–0.99], $p < 0.001$). In multivariable models including age and diabetes duration in 1-year increments, diabetes duration remained significantly associated with an increased risk of microvascular complications but age and age at diagnosis did not after adjustment for sex, smoking, eGFR and prevalent macrovascular disease (Table 2 and Fig. 1).

Receiver operating characteristic (ROC) curves of models predicting microvascular complications and including either age and diabetes duration, or age at diagnosis and diabetes duration were comparable (AUC = 0.7552 for both models) indicating that both models approximated the data equally (Appendix D).

When the outcomes of retinopathy, peripheral neuropathy and end stage kidney disease were examined separately, the associations with diabetes duration were consistent (Fig. 1).

3.4. Effect modification

There was no evidence of an interaction between age and diabetes duration on the odds of macrovascular disease ($p = 0.26$). In sub group analysis, for every 1 year increase in diabetes duration, the adjusted odds of macrovascular disease were similarly increased by 2% in both those aged <60 years and ≥60 years (macrovascular disease adjusted OR 1.02 [1.01–1.03], $p = 0.01$ for those aged <60 years and 1.01 [0.99–1.04], $p < 0.16$ for those aged ≥60 years.

There was evidence of an interaction between age and diabetes duration on the odds of microvascular disease ($p = 0.004$) such that the effect of longer diabetes duration was greater in younger rather than older patients. At each level of diabetes duration, the rate of increase (slope) in the probability of microvascular disease was greater for those aged <60 years than those aged ≥60 years (Fig. 2). In sub group analysis, for every 1 year increase in diabetes duration, the adjusted odds of microvascular disease were increased by 11% and 6% in those aged <60 years and those aged ≥60 years respectively (microvascular disease adjusted OR 1.11 [1.08–1.13] $p < 0.001$ for those aged <60 years and 1.06 [1.05–1.08] $p < 0.001$ for those aged ≥60 years).

3.5. Sensitivity analyses

The associations between macrovascular or microvascular complications and current age, age at diagnosis and diabetes duration, did not change in analyses excluding participants with diabetes diagnosed within 12 months (Appendix B). Furthermore, the associations were similar

Table 2
Associations between age, age at diagnosis and diabetes duration, and macrovascular and microvascular complications.

Macrovascular complications						
N = 2293	Univariable analysis		Multivariable analysis			
			Model 1[a] (age and duration)		Model 2[a] (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diabetes diagnosis (years)						
1 year increase	1.02 (1.01–1.02)	<0.001			1.03 (1.02–1.04)	<0.001
Current age (years)						
1 year increase	1.05 (1.04–1.06)	<0.001	1.03 (1.02–1.04)	<0.001		
Diabetes duration (years)						
1 year increase	1.05 (1.04–1.06)	<0.001	1.02 (1.00–1.03)	0.005	1.05 (1.03–1.06)	<0.001
Sex						
Female (ref)						
Male	2.15 (1.85–2.51)	<0.001	1.97 (1.61–2.41)	<0.001	1.97 (1.61–2.41)	<0.001
Smoking						
Never (ref)						
Past	2.00 (1.69–2.37)	<0.001	1.68 (1.36–2.07)	<0.001	1.68 (1.36–2.07)	<0.001
Current	1.42 (1.11–1.82)	0.006	2.04 (1.49–2.79)	<0.001	2.04 (1.50–2.79)	<0.001
Last measured HbA1c (%)						
Per 1% increase	0.99 (0.95–1.03)	0.564				
BMI (kg/m^2)						
Per unit increase	0.99 (0.98–1.00)	0.008	1.01 (0.99–1.02)	0.315	1.01 (0.99–1.02)	0.310
eGFR (ml/min/1.72 m^2)						
Per unit increase	0.98 (0.98–0.98)	<0.001	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	<0.001
Microvascular complications						
Nil (ref)						
Previous	3.61 (3.08–4.23)	<0.001	2.52 (2.06–3.08)	<0.001	2.52 (2.06–3.08)	<0.001
Microvascular complications						
N = 2454	Univariable analysis		Multivariable analysis			
			Model 1[b] (age and duration)		Model 2[b] (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diabetes diagnosis (years)						
1 year increase	0.99 (0.98–0.99)	<0.001			0.99 (0.99–1.00)	0.178
Current age (years)						
1 year increase	1.03 (1.02–1.04)	<0.001	0.99 (0.99–1.00)	0.172		
Diabetes Duration (years)						
1 year increase	1.08 (1.07–1.09)	<0.001	1.07 (1.06–1.09)	<0.001	1.07 (1.06–1.08)	<0.001
Sex						
Female (ref)						
Male	1.37 (1.19–1.59)	<0.001	1.28 (1.06–1.55)	0.009	1.28 (1.06–1.55)	0.009
Smoking						
Never (ref)						
Past	1.18 (1.01–1.39)	0.039	0.99 (0.81–1.21)	0.95	0.99 (0.81–1.21)	0.949
Current	0.91 (0.72–1.15)	0.428	1.12 (0.84–1.50)	0.452	1.12 (0.84–1.50)	0.451
Last measured HbA1c (%)						
Per 1% increase	1.03 (0.99–1.07)	0.197				
BMI (kg/m^2)						
Per unit increase	1.01 (0.99–1.01)	0.822				
eGFR (ml/min/1.72 m^2)						
Per unit increase	0.98 (0.98–0.98)	<0.001	0.99 (0.98–0.99)	<0.001	0.99 (0.98–0.99)	<0.001
Macrovascular complications						
Nil (ref)						
Previous	3.61 (3.08–4.23)	<0.001	2.42 (1.99–2.94)	<0.001	2.42 (1.99–2.94)	<0.001

BMI = Body Mass Index; HbA1c = haemoglobin A1c; eGFR = estimated glomerular filtration rate.
[a] Models adjusted for sex, smoking, BMI, eGFR and microvascular complications.
[b] Models adjusted for sex, smoking, eGFR and macrovascular complications.

when we adjusted the models for centre type or for the effect of clustering by centre and when data from the audits completed in 2011 (n = 3357) and 2013 (n = 2729) were analysed (data not shown).

4. Discussion

In this study of 3419 Australian patients with T2DM, we demonstrate that after accounting for other known risk factors, age, age at diagnosis, and diabetes duration were independently associated with macrovascular complications whereas only diabetes duration was independently associated with microvascular complications. These associations remained consistent when the components of the composite outcomes were examined individually. In addition, there was evidence of effect modification such that the effect of longer diabetes duration on the risk of microvascular complications was greater in in those aged ≤60 years compared with those aged ≥60 years.

The associations between increasing age or age at diagnosis and macrovascular disease were maintained when other cardiovascular risk factors were adjusted for. The inference here is that increasing age is contributing to the increase in risk of macrovascular disease seen with older age at diagnosis. Additionally, there appears to be an interaction between age and diabetes duration, such that the increase in risk of

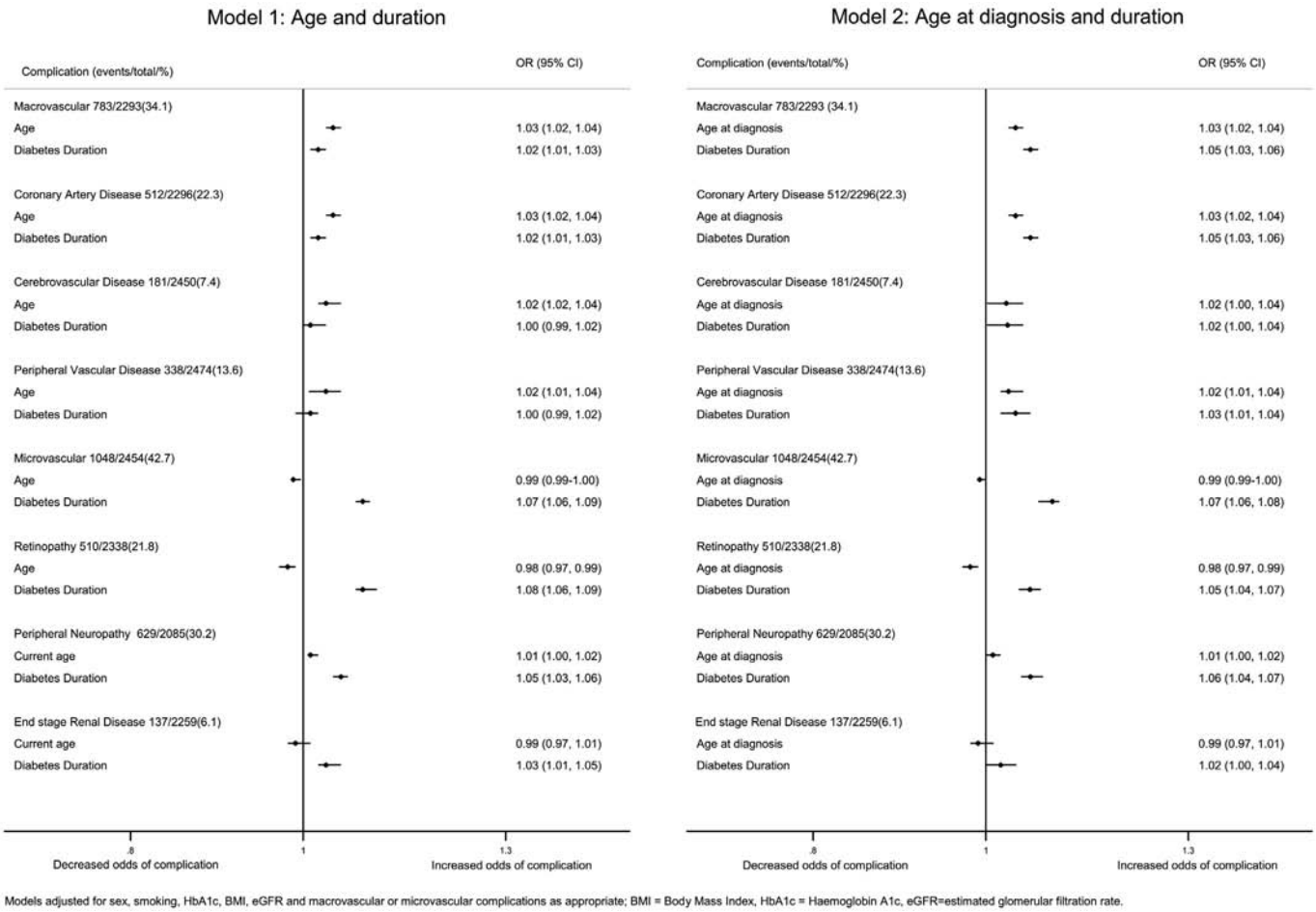


Fig. 1. The adjusted odds of macrovascular and microvascular complications by i) age and diabetes duration and ii) age at diabetes diagnosis and diabetes duration.

macrovascular and microvascular complications attributable to increased duration is greater for those diagnosed <60 years of age compared to those diagnosed ≥60 years of age.

Our findings are clinically relevant as they may inform the risk status of people diagnosed with diabetes at a younger or older age. Intensive glycaemic management during the early stages of type 2 diabetes leads to fewer diabetes complications, a concept known as metabolic memory.[7] Screening for type 2 diabetes allows the identification of these patients at an earlier stage of the disease, so that they may benefit from intensive glycaemic control and management of cardiovascular risk factors over a longer period.

Screening for macrovascular complications is especially important for older patients with diabetes who are at highest short-term absolute risk. Our results, as well as those of other studies[8] suggest that age remains one of the most important risk factors for the development of macrovascular complications. However, people diagnosed with diabetes at a younger age have a longer duration of diabetes and a longer lifetime risk of developing significant complications, thus intensive glycaemic control and optimisation of cardiovascular risk factors will be of particular importance across their lifespan.

The findings of this study are somewhat consistent with those of the UKPDS[9] and ADVANCE[8] trials but differ from those reported from studies in Chinese, Hong Kong and Pima Indian populations.[6,10,11] The UKPDS reported that age at diabetes diagnosis was not associated with an increased risk of myocardial infarct, but that older age at diabetes diagnosis was a predictor of retinopathy and neuropathy but not microalbuminuria.[9] ADVANCE[8] reported that macrovascular events were associated with age, age at diagnosis and diabetes duration but that microvascular events were only associated with diabetes duration. In contrast, the CNHSS,[10] Hong Kong Diabetes Registry[11] and Pima Indian[6] studies, concluded that patients diagnosed with diabetes at a younger age were at increased risk of cardiovascular disease even after adjustment for diabetes duration. As the studies were methodologically similar, the differences may be due to the ethnic diversity of the cohorts studied. Additionally, the CNHSS study found the impact of age to be strongest for those with BMI < 24. As the majority of patients in our study were obese we could not examine this finding. We found that patients diagnosed with type 2 diabetes at a younger age had a longer duration of diabetes and were thus at increased risk of both macrovascular and microvascular complications; this is consistent with several,[12–14] but not all studies[3,4] examining diabetic retinopathy and related eye complications. Another study comparing young onset type 2 diabetes patients with type 1 diabetes patients of similar age of onset, concluding that patients with type 2 diabetes had greater mortality, primarily driven by cardiovascular deaths despite a shorter duration of diabetes and similar glycaemic exposure.[15]

This is the first study to examine the associations between age, age at diagnosis and diabetes duration in an Australian context. The strength of this analysis includes a large dataset incorporating patients from a nationwide survey. The data are likely to be representative of patients seen in diabetes centres throughout Australia with data collected from every state and territory of the country and a stable dataset though the years. The results from the 2015 collection were consistent with analyses of data from 2013 and 2011 adding to the strength of our findings.

The majority of patients in this study received diabetes care at tertiary or specialised diabetes centres, and may have more severe disease compared with community-treated patients. While this is a limitation, our findings are in line with previously published large population based

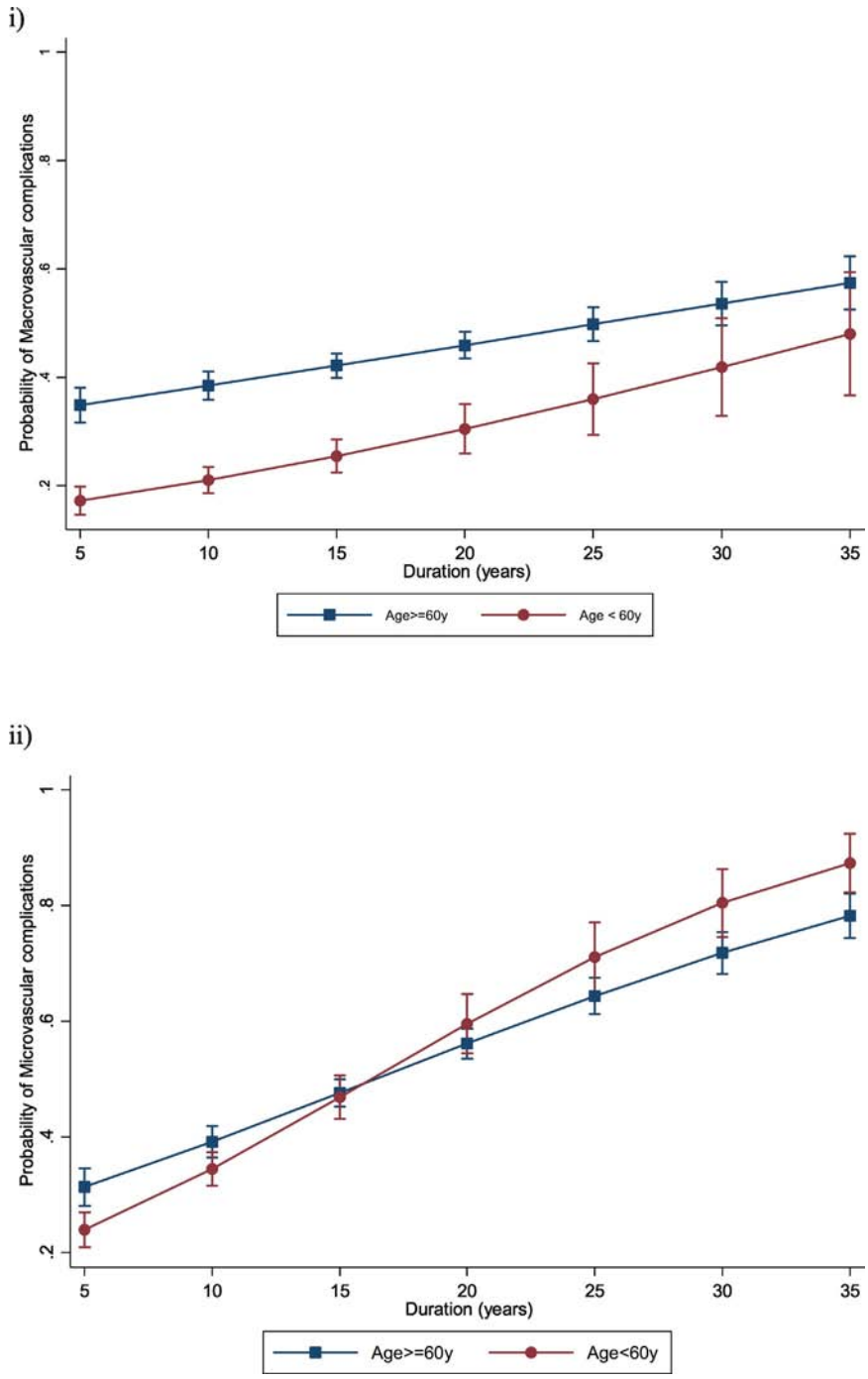


Fig. 2. The interaction effect between age and diabetes duration on the probability of i) macrovascular ($p = 0.55$) and ii) microvascular complications ($p = 0.001$).

epidemiological studies.[3,8] Another limitation was the reliance on self-report or medical records for the age at diagnosis, diabetes duration and vascular complications. Recall may be less accurate for complications occurring a long time ago, we were unable to independently confirm diagnoses. Nevertheless, previous studies suggest the validity of self-reported diabetes information.[16,17] We did not determine the timing of reported complications, so it is possible that some complications occurred prior to the diagnosis of diabetes. This is more likely to be the case for macrovascular complications, given that microvascular complications are relatively more specific for diabetes. Our study population was of limited ethnic diversity (mainly Caucasian), therefore we were unable to explore the possibility that the effect of age of diagnosis and duration of diabetes may differ across ethnic groups.[10,18,19]

5. Conclusions

In summary, in patients with type 2 diabetes, after adjustment for confounders, age or age at diagnosis and diabetes duration were independently associated with macrovascular complications but only diabetes duration was independently associated with microvascular complications. Such data emphasise the importance of intensive management for all patients with type 2 diabetes, particularly those who have longer duration of diabetes.

Acknowledgements

We would like to thank the participating patients and diabetes centres for their time and generous contribution to this work.

Authors' contributions

NN: study design, literature review, statistical analysis, critical discussion, synthesis and revision of the manuscript, SR: statistical analysis, interpretation of the data, critical discussion and revision of the manuscript revision of the manuscript, AG: critical discussion, synthesis and revision of the manuscript, SH: statistical analysis oversight, revision of the manuscript, JRF: study conception and design, critical revision of the manuscript, JW: critical revision of the manuscript NW: study conception and design, revision of the manuscript, SZ: study conception and design, analysis design, critical revision of the manuscript, supervision of graduate students on the project. All authors had contribution to study conception or design, data acquisition, analysis or interpretation, drafting and final approval of the manuscript. The authors NN, SR, SH and SZ had full access to the data and take responsibility for the integrity of the data and accuracy of the analysis. All authors have read and approved the final manuscript.

Funding

The Commonwealth Department of Health and Ageing funds the Australian National Diabetes Audit activity. This research has received no specific grant from any other funding agency in the public, commercial or not-for profit sectors.

Appendix A. Location of participating diabetes centres

State/territory	Participating centres
Australian Capital Territory	1
New South Wales	13
Northern Territory	1
Queensland	9
South Australia	1
Tasmania	3
Victoria	20
Western Australia	1

Appendix B. Effect of excluding patients with <12 months diabetes duration on the associations between age, age at diagnosis and diabetes duration, and macrovascular and microvascular complications

Macrovascular complications						
N = 2071	Univariable analysis		Multivariable model 1[a] (age and duration)		Multivariable model 2[a] (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diabetes diagnosis (years)						
1 year increase	1.02 (1.01–1.02)	<0.001			1.03 (1.02–1.04)	<0.001
Current age (years)						
1 year increase	1.04 (1.04–1.05)	<0.001	1.03 (1.02–1.04)	<0.001		
Diabetes duration (years)						
1 year increase	1.05 (1.04–1.05)	<0.001	1.02 (1.00–1.03)	0.008	1.04 (1.03–1.06)	<0.001
Sex						
Female (ref)						
Male	2.10 (1.79–2.46)	<0.001	1.93 (1.57–2.37)	<0.001	1.93 (1.57–2.37)	<0.001
Smoking						
Never (ref)						
Past	1.98 (1.66–2.36)	<0.001	1.66 (1.34–2.06)	<0.001	1.66 (1.34–2.06)	<0.001
Current	1.48 (1.14–1.93)	0.004	2.02 (1.45–2.81)	<0.001	2.02 (1.45–2.81)	<0.001
Last measured HbA1c (%)						
Per 1% increase	0.99 (0.94–1.03)	0.422				
BMI (kg/m^2)						
Per unit increase	0.99 (0.98–1.00)	0.036	1.01 (0.99–1.02)	0.296	1.01 (0.99–1.02)	0.291
eGFR (ml/min/1.72 m^2)						
Per unit increase	0.98 (0.98–0.99)	<0.001	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	<0.001
Microvascular complications						
Nil (ref)						
Previous	3.33 (2.82–3.92)	<0.001	2.40 (1.95–2.95)	<0.001	2.40 (1.95–2.95)	<0.001
Microvascular complications						
N = 2367	Univariable Analysis		Multivariable model 1[b] (age and duration)		Multivariable model 2[b] (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diabetes diagnosis (years)						
1 year increase	0.99 (0.98–0.99)	<0.001			0.99 (0.98–1.00)	0.045
Current age (years)						
1 year increase	1.02 (1.02–1.03)	<0.001	0.99 (0.98–1.00)	0.041		
Diabetes duration (years)						
1 year increase	1.08 (1.07–1.09)	<0.001	1.07 (1.06–1.09)	<0.001	1.06 (1.05–1.07)	<0.001
Sex						
Female (ref)						
Male	1.40 (1.21–1.63)	<0.001	1.38 (1.15–1.65)	0.001	1.38 (1.15–1.65)	0.001

(continued on next page)

(continued)

Microvascular complications						
N = 2367	Univariable Analysis		Multivariable model 1[b] (age and duration)		Multivariable model 2[b] (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Smoking						
Never (ref)						
Past	1.15 (0.97–1.36)	0.107				
Current	0.99 (0.77–1.28)	0.941				
Last measured HbA1c (%)						
Per 1% increase	1.00 (0.96–1.05)	0.934				
BMI (kg/m^2)						
Per unit increase	1.01 (0.99–1.02)	0.317				
eGFR (ml/min/1.72 m^2)						
Per unit increase	0.98 (0.98–0.99)	<0.001	0.99 (0.98–0.99)	<0.001	0.99 (0.98–0.99)	<0.001
Macrovascular complications						
Nil (ref)						
Previous	3.33 (2.82–3.92)	<0.001	2.35 (1.94–2.85)	<0.001	2.35 (1.94–2.85)	<0.001

BMI = Body Mass Index; HbA1c = haemoglobin A1c; eGFR = estimated glomerular filtration rate.
[a] Models adjusted for sex, smoking, BMI, eGFR and microvascular complications.
[b] Models adjusted for sex, smoking, eGFR and macrovascular complications.

Appendix C. Associations between age, age at diagnosis and diabetes duration, and coronary artery disease, cerebrovascular disease, peripheral vascular disease, retinopathy, peripheral neuropathy and end-stage kidney disease

Coronary artery disease						
N = 2296	Univariable analysis		Multivariable model 1 (age and duration)		Multivariable model 2 (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diagnosis (years)						
1 year increase	1.02 (1.01–1.03)	<0.001			1.03 (1.02–1.04)	<0.001
Current age (years)						
1 year increase	1.04 (1.04–1.05)	<0.001	1.03 (1.02–1.04)	<0.001		
Diabetes duration (years)						
1 year increase	1.04 (1.03–1.05)	<0.001	1.02 (1.01–1.03)	0.004	1.05 (1.03–1.06)	<0.001
Sex						
Female (ref)						
Male	2.38 (1.99–2.84)	<0.001	2.12 (1.69–2.66)	<0.001	2.12 (1.69–2.66)	<0.001
Smoking						
Never (ref)						
Past	2.24 (1.85–2.72)	<0.001	1.80 (1.43–2.26)	<0.001	1.80 (1.43–2.26)	<0.001
Current	1.25 (0.93–1.69)	0.134	1.61 (1.13–2.29)	0.008	1.61 (1.13–2.30)	0.008
Last measured HbA1c (%)						
Per 1% increase	0.97 (0.92–1.01)	0.151				
eGFR (ml/min/1.72 m^2)						
Per unit increase	0.98 (0.98–0.99)	<0.001	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	<0.001
BMI (kg/m^2)						
Per unit increase	0.99 (0.97–1.00)	0.042	1.01 (0.99–1.02)	0.493	1.01 (0.99–1.02)	0.487
Microvascular complications						
Nil (ref)						
Previous	2.08 (1.75–2.48)	<0.001	1.29 (1.03–1.61)	0.027	1.29 (1.03–1.61)	0.027

All models adjusted for sex, smoking, eGFR, BMI and microvascular complications; BMI = Body Mass Index; HbA1c = Haemoglobin A1c.

Cerebrovascular disease						
N = 2450	Univariable analysis		Multivariable model 1 (age and duration)		Multivariable model 2 (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diagnosis (years)						
1 year increase	1.02 (1.01–1.03)	0.037			1.02 (1.00–1.04)	0.012
Current age (years)						
1 year increase	1.04 (1.02–1.05)	<0.001	1.02 (1.00–1.04)	0.014		
Diabetes duration (years)						
1 year increase	1.03 (1.02–1.05)	<0.001	1.00 (0.99–1.02)	0.715	1.02 (1.00–1.04)	0.028
Sex						
Female (ref)						
Male	1.52 (1.11–2.08)	0.008	1.45 (1.04–2.01)	0.028	1.45 (1.04–2.01)	0.028
Smoking						
Never (ref)						
Past	1.43 (1.06–1.93)	0.020	1.18 (0.83–1.66)	0.357	1.18 (0.83–1.66)	0.357
Current	1.51 (1.00–2.28)	0.053	1.94 (1.19–3.14)	0.007	1.94 (1.20–3.15)	0.007

(continued)

Cerebrovascular disease

N = 2450	Univariable analysis		Multivariable model 1 (age and duration)		Multivariable model 2 (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Last measured HbA1c (%)						
Per 1% increase	0.99 (0.91–1.06)	0.698				
BMI (kg/m^2)						
Per unit increase	1.00 (0.98–1.02)	0.758				
eGFR (ml/min/1.72 m^2)						
Per unit increase	0.98 (0.98–0.99)	<0.001	0.98 (0.98–0.99)	<0.001	0.98 (0.98–0.99)	<0.001
Microvascular complications						
Nil (ref)						
Previous	2.28 (1.72–3.02)	<0.001	1.66 (1.18–2.33)	0.004	1.66 (1.18–2.33)	0.004

All models adjusted for sex, smoking, eGFR and microvascular complications; BMI = Body Mass Index; HbA1c = haemoglobin A1c.

Peripheral vascular disease

N = 2474	Univariable analysis		Multivariable model 1 (age and duration)		Multivariable model 2 (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diagnosis (years)						
1 year increase	1.01 (1.00–1.02)	0.037			1.02 (1.01–1.04)	<0.001
Current age (years)						
1 year increase	1.04 (1.03–1.05)	<0.001	1.02 (1.01–1.04)	<0.001		
Diabetes duration (years)						
1 year increase	1.05 (1.03–1.06)	<0.001	1.00 (0.99–1.02)	0.648	1.03 (1.01–1.04)	0.001
Sex						
Female (ref)						
Male	2.02 (1.58–2.59)	<0.001	1.77 (1.35–2.31)	<0.001	1.77 (1.35–2.31)	<0.001
Smoking						
Never (ref)						
Past	1.73 (1.37–2.19)	<0.001	1.54 (1.17–2.03)	0.002	1.54 (1.17–2.03)	0.002
Current	1.46 (1.05–2.04)	0.026	2.16 (1.46–3.21)	<0.001	2.16 (1.46–3.21)	<0.001
Last measured HbA1c (%)						
Per 1% increase	1.02 (0.96–1.09)	0.450				
BMI (kg/m^2)						
Per unit increase	0.99 (0.98–1.01)	0.507				
eGFR (ml/min/1.72 m^2)						
Per unit increase	0.98 (0.98–0.99)	<0.001	0.99 (0.99–1.00)	<0.001	0.99 (0.99–1.00)	<0.001
Microvascular complications						
Nil (ref)						
Previous	8.20 (6.24–10.79)	<0.001	6.64 (4.85–9.10)	<0.001	6.64 (4.85–9.10)	<0.001

All models adjusted for sex, smoking, eGFR and microvascular complications; BMI = Body Mass Index; HbA1c = haemoglobin A1c.

Retinopathy

N = 2338	Univariable analysis		Multivariable analysis (current age and duration)		Multivariable analysis (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diagnosis (years)						
1 year increase	0.97 (0.96–0.98)	<0.001			0.98 (0.97–0.99)	<0.001
Current age (years)						
1 year increase	1.01 (1.01–1.02)	<0.001	0.98 (0.97–0.99)	<0.001		
Diabetes duration (years)						
1 year increase	1.08 (1.07–1.09)	<0.001	1.08 (1.06–1.09)	<0.001	1.05 (1.04–1.07)	<0.001
Sex						
Female (ref)						
Male	1.25 (1.05–1.48)	0.011	1.42 (1.14–1.76)	0.002	1.42 (1.14–1.76)	0.002
Smoking						
Never (ref)						
Past	0.96 (0.79–1.17)	0.678				
Current	0.76 (0.56–1.01)	0.062				
Last measured HbA1c (%)						
Per 1% increase	1.06 (1.01–1.11)	0.016	1.07 (1.00–1.13)	0.035	1.07 (1.00–1.13)	0.034
BMI (kg/m^2)						
Per unit increase	0.99 (0.98–1.01)	0.268				
eGFR (ml/min/1.72 m^2)						
Per unit increase	0.99 (0.98–0.99)	<0.001	0.99 (0.98–0.99)	<0.001	0.99 (0.98–0.99)	<0.001
Macrovascular complications						
Nil (ref)						
Previous	2.02 (1.69–2.42)	<0.001	1.39 (1.12–1.74)	0.004	1.39 (1.12–1.74)	0.004

All models adjusted for sex, HbA1c, eGFR and macrovascular complications; BMI = Body Mass Index; HbA1c = haemoglobin A1c.

Peripheral neuropathy

N = 2085	Univariable analysis		Multivariable analysis (current age and duration)		Multivariable analysis (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diagnosis (years)						
1 year increase	0.99 (0.99–1.00)	0.049			1.01 (1.00–1.02)	0.085
Current age (years)						
1 year increase	1.03 (1.02–1.04)	<0.001	1.01 (1.00–1.02)	0.080		
Diabetes duration (years)						
1 year increase	1.06 (1.05–1.07)	<0.001	1.05 (1.03–1.06)	<0.001	1.06 (1.04–1.07)	<0.001
Sex						
Female (ref)						
Male	1.33 (1.14–1.55)	<0.001	1.22 (0.98–1.51)	0.072	1.22 (0.98–1.51)	0.072
Smoking						
Never (ref)						
Past	1.18 (0.98–1.41)	0.084				
Current	1.05 (0.80–1.38)	0.713				
Last measured HbA1c (%)						
Per 1% increase	1.08 (1.03–1.13)	0.001	1.06 (1.00–1.12)	0.054	1.06 (1.00–1.12)	0.054
BMI (kg/m^2)						
Per unit increase	1.02 (1.01–1.03)	<0.001	1.04 (1.02–1.05)	<0.001	1.04 (1.02–1.05)	<0.001
eGFR (ml/min/1.72 m^2)						
Per unit increase	0.99 (0.98–0.99)	<0.001	0.99 (0.99–1.00)	<0.001	0.99 (0.99–1.00)	<0.001
Macrovascular complications						
Nil (ref)						
Previous	3.28 (2.78–3.86)	<0.001	2.57 (2.08–3.19)	<0.001	2.57 (2.08–3.19)	<0.001

All models adjusted for sex, HbA1c, BMI eGFR and macrovascular complications; BMI = Body Mass Index; HbA1c = haemoglobin A1c.

End stage renal disease

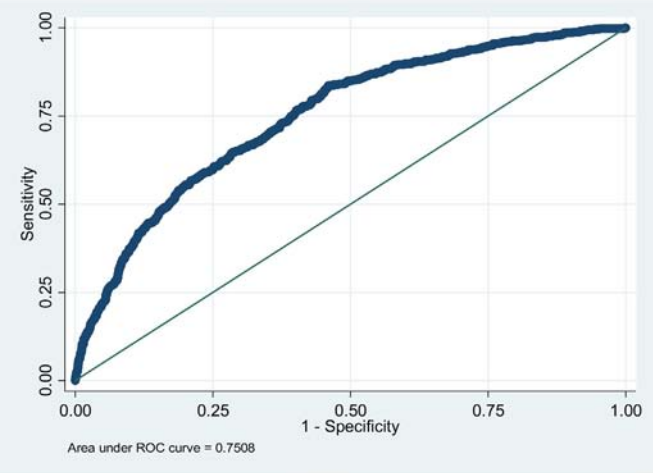
N = 2259	Univariable analysis		Multivariable analysis (current age and duration)		Multivariable analysis (age at diagnosis and duration)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diagnosis (years)						
1 year increase	0.99 (0.98–1.00)	0.021			0.99 (0.97–1.01)	0.193
Current age (years)						
1 year increase	1.02 (1.01–1.03)	0.001	0.99 (0.97–1.01)	0.187		
Diabetes duration (years)						
1 year increase	1.05 (1.04–1.07)	<0.001	1.03 (1.01–1.05)	0.001	1.02 (1.00–1.04)	0.039
Sex						
Female (ref)						
Male	1.05 (0.79–1.39)	0.756				
Smoking						
Never (ref)						
Past	1.09 (0.80–1.50)	0.580	1.00 (0.68–1.48)	0.992	1.00 (0.68–1.48)	0.993
Current	0.52 (0.28–0.96)	0.035	0.62 (0.32–1.23)	0.171	0.62 (0.32–1.23)	0.172
Last measured HbA1c (%)						
Per 1% increase	0.86 (0.78–0.94)	0.001	0.86 (0.77–0.97)	0.011	0.86 (0.77–0.97)	0.011
BMI (kg/m^2)						
Per unit increase	0.96 (0.94–0.98)	0.001	0.95 (0.93–0.98)	0.001	0.95 (0.93–0.98)	0.001
Macrovascular complications						
Nil (ref)						
Previous	3.27 (2.43–4.39)	<0.001	2.93 (2.01–4.28)	<0.001	2.93 (2.01–4.28)	<0.001

All models adjusted for sex, smoking, HbA1c, BMI and macrovascular complications; BMI = Body Mass Index; HbA1c = haemoglobin A1c.

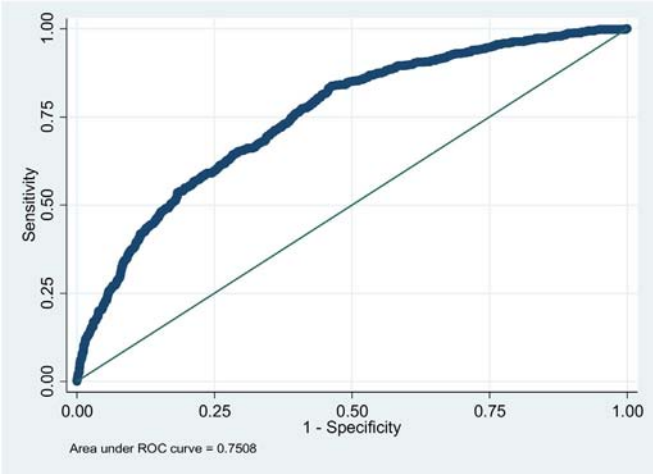
Appendix D. Receiver operator curves examining the effect of age and diabetes duration or age at diabetes diagnosis and duration on the risks of i) macrovascular and ii) microvascular complications

i) Macrovascular complications (models inclusive of sex, smoking, BMI, eGFR and microvascular disease)

Age and duration

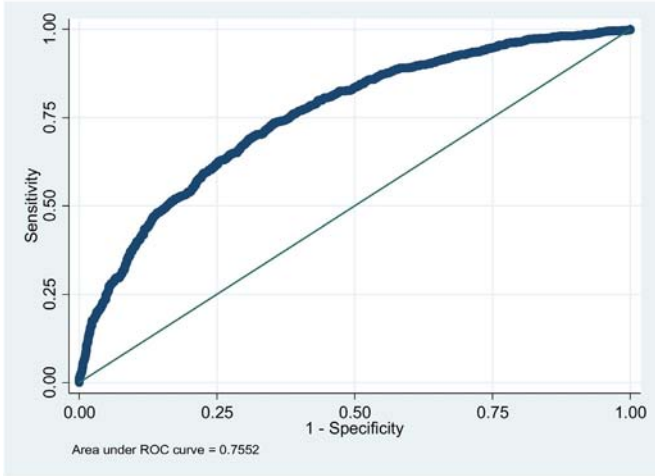


Age at diabetes diagnosis and duration

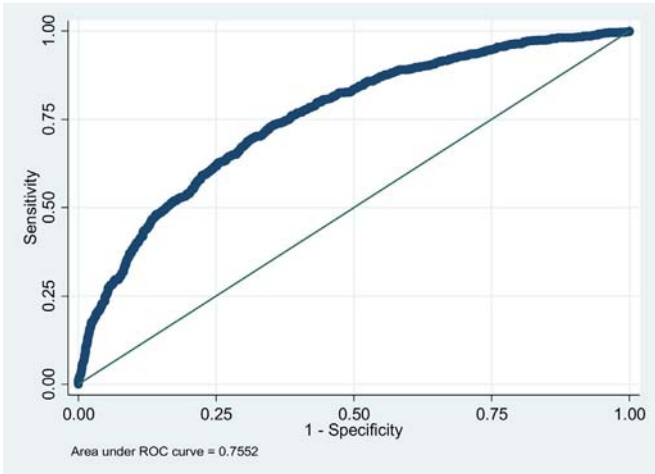


ii) Microvascular complications (models inclusive of sex, smoking, eGFR and macrovascular disease)

Age and duration



Age at diabetes diagnosis and duration



References

1. Rahelic D. 7th edition of IDF Diabetes Atlas—call for immediate action. *Lijec Vjesn.* 2016;138(1–2):57-8.
2. Song SH, Hardisty CA. Early-onset Type 2 diabetes mellitus: an increasing phenomenon of elevated cardiovascular risk. *Expert Rev Cardiovasc Ther.* 2008;6(3):315-22.
3. Hillier TA, Pedula KL. Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth. *Diabetes Care.* 2003;26(11):2999-3005.
4. Luk AO, Lau ES, So WY, Ma RC, Kong AP, Ozaki R, et al. Prospective study on the incidences of cardiovascular-renal complications in Chinese patients with young-onset type 1 and type 2 diabetes. *Diabetes Care.* 2014;37(1):149-57.
5. Mohan V, Vijayaprabha R, Rema M. Vascular complications in long-term south Indian NIDDM of over 25 years' duration. *Diabetes Res Clin Pract.* 1996;31(1–3):133-40.
6. Pavkov ME, Bennet PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. *JAMA.* 2006;296(4):421-6.
7. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008;359(15):1577-89.
8. Zoungas S, Woodward M, Li Q, Cooper ME, Hamet P, Harrap S, et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia.* 2014;57(12):2465-74.
9. Davis TM, Stratton IM, Fox CJ, Holman RR, Turner RC. U.K. Prospective Diabetes Study 22. Effect of age at diagnosis on diabetic tissue damage during the first 6 years of NIDDM. *Diabetes Care.* 1997;20(9):1435-41.
10. Huo X, Gao L, Guo L, Xu W, Wang W, Zhi X, et al. Risk of non-fatal cardiovascular diseases in early-onset versus late-onset type 2 diabetes in China: a cross-sectional study. *Lancet Diabetes Endocrinol.* 2016;4(2):115-24.
11. Chan JCN, Lau ESH, Luk AOY, Cheung KKT, Kong APS, Yu LWL, et al. Premature mortality and comorbidities in young-onset diabetes: a 7-year prospective analysis. *Am J Med.* 2014;127(7):616-24.
12. Kawasaki S, Misawa H, Tamura Y, Kondo Y, Satoh S, Hasegawa O, et al. Relationship between coronary artery disease and retinopathy in patients with type 2 diabetes mellitus. *Intern Med.* 2013;52(22):2483-7.
13. Wong J, Molyneaux L, Constantino M, Twigg SM, Yue DK. Timing is everything: age of onset influences long-term retinopathy risk in type 2 diabetes, independent of traditional risk factors. *Diabetes Care.* 2008;31(10):1985-90.
14. Cai X, Han X, Zhang S, Luo Y, Chen Y, Ji L. Age at diagnosis and C-peptide level are associated with diabetic retinopathy in Chinese. *PLoS One.* 2014;9(3):e91174.
15. Constantino MI, Molyneaux L, Limacher-Gisler F, Al-Saeed A, Luo C, Wu T, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes Care.* 2013;36(12):3863-9.
16. Kahn LB, Marshall JA, Baxter J, Shetterly SM, Hamman RF. Accuracy of reported family history of diabetes mellitus. Results from San Luis Valley Diabetes Study. *Diabetes Care.* 1990;13(7):796-8.
17. Barr EL, Tonkin AM, Welborn TA, Shaw JE. Validity of self-reported cardiovascular disease events in comparison to medical record adjudication and a statewide hospital morbidity database: the AusDiab study. *Intern Med J.* 2009;39(1):49-53.
18. Kenealy T, Elley C, Robinson E, Bramley D, Drury P, Kerse N, et al. An association between ethnicity and cardiovascular outcomes for people with Type 2 diabetes in New Zealand. *Diabet Med.* 2008;25(11):1302-8.
19. Haffner SM, Mitchell BD, Moss SE, Stern MP, Hazuda HP, Patterson J, et al. Is there an ethnic difference in the effect of risk factors for diabetic retinopathy? *Ann Epidemiol.* 1993;3(1):2-8.