

Decrements in health-related quality of life associated with adverse events in people with diabetes

Supplementary Material

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Supplementary Tables

Supplementary Table S1: Identifying adverse events of interest

Adverse events in trial		Hospital Episode Statistics data
Cardiovascular disease		
Myocardial infarction	✓† Evidence of cardiac necrosis and other evidence of acute MI and no other diagnosis was likely. Silent MI not included.	
Coronary revascularisation (urgent)	✓† Coronary angioplasty, stenting or coronary artery bypass grafting.	
Coronary revascularisation (non-urgent)	✓† Coronary angioplasty, stenting or coronary artery bypass grafting.	
Transient ischaemic attack	✓† Transient episode of neurological dysfunction, lasting less than 24 hours, without clear evidence of acute infarction, haemorrhage, trauma or other cause.	
Ischaemic stroke	✓† Acute symptomatic episode of focal or global neurological dysfunction as a result of infarction which lasted >24 hours, lead to death, or was associated with imaging evidence of acute infarct corresponding with clinical syndrome	
Heart failure	✓‡	✓ ICD-10 codes in primary diagnosis position: I50 Heart failure; I110, I130, I132 Hypertensive heart disease with (congestive) heart failure; I255, I420, I425, I426, I427, I428, I429, I430, I431, I432, I438 Congestive cardiomyopathy
Bleeding		
Intracranial haemorrhage	✓† Includes spontaneous intracranial bleeds or those associated with injury in the absence of major trauma	
Gastrointestinal bleed	✓†	
Other major bleed	✓† Major bleeds that required hospitalisation or transfusion, or was fatal or disabling. Excludes eye bleeds	
Cancer		

Gastrointestinal tract cancer	✓ [†]	
Non-gastrointestinal tract cancer	✓ [†] Excludes non-melanoma skin cancer	
Microvascular disease		
Amputation	✓ [‡] Lower limb amputation	✓ OPCS-4 codes: X09 Amputation of leg; X10 Amputation of foot; X11 Amputation of toe
End-stage renal disease	✓ [‡] Includes participants who had dialysis or renal transplant	✓ Algorithm & ICD-10 codes from Bush et al. (2017) ¹

[†]Events corresponding to these endpoints were sought for and adjudicated in the ASCEND study.² The date of event occurrence recorded in the study was used.

[‡]These endpoints were not sought for nor adjudicated in ASCEND. Hospital episode data was used to supplement the identification of these events. Earliest recorded date between the two sources used.

References:

1. Kathryn Bush, John Nolan, Qiuli Zhang, Will Herrington, Cathie Sudlow. Definitions of End Stage Renal Disease for UK Biobank Phase 1 Outcomes Adjudication. Published August 2017. Accessed May 7, 2021. https://biobank.ndph.ox.ac.uk/ukb/docs/alg_outcome_esrd.pdf
2. The ASCEND Study Collaborative Group. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med*. 2018;379(16):1529-1539. doi:10.1056/NEJMoa1804988

Supplementary Table S2: Definitions of candidate variables included for selection

Variables	Categories (if categorical)	Note
Diabetes type	Type 1 Type 2	
Sex	Male Female	
Smoking status	Current smoker Former/never smoker	
Race	White Indian/Pakistani/Bangladeshi African/Caribbean	
Townsend Index	Q1: <-2.42 Q2: >=-2.42, <-0.44 Q3: >=-0.44, <1.79 Q4: >= 1.79, <4.75 Q5: >= 4.75	Measure of socioeconomic status calculated using postcode at randomization. Higher value indicates greater deprivation. Stratified according to range of scores of 2011 UK population quintiles.
Hypertension	Y / N	
Diabetic retinopathy	Y / N	
Use of statin	Y / N	
Use of ACE inhibitor or ARB	Y / N	
Age (years)		At time of EQ-5D questionnaire response.
Diabetes duration (years)	<10 >=10, <15 >=15, <25 >=25	At time of EQ-5D questionnaire response.
BMI (kg/m ²)	<25 >=25, <30 >=30, <35 >=35	Based on self-reported height and weight
HbA1c (IFCC mmol/mol)	< 48 >= 48, < 64 >= 64	
HDL cholesterol (mmol/L)	< 1.0 >= 1.0, < 1.5 >= 1.5	
Non-HDL cholesterol (mmol/L)	< 2.5 >= 2.5, < 3.5 >= 3.5	
Systolic blood pressure (mmHg)	<130 >=130, <140 >=140	
Diastolic blood pressure (mmHg)	<75 >=75, <85	
Urinary albumin/creatinine ratio (mg/mmol)	< 3 >=3	
eGFR (ml/min/1.73m ²)	< 45 >= 45, < 60 >= 60, < 90	Calculated from blood cystatin C concentration using the CKD-EPI formula

	>=90	
Disease history (adverse events listed below)	No history <=1 yr > 1yr	Time since event occurrence relative to date of questionnaire response. <=1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than a year prior to EQ-5D questionnaire response.
Myocardial infarction		
Coronary revascularisation (non-urgent)		
Coronary revascularisation (urgent)		
Transient ischaemic attack		
Ischaemic stroke		
Heart failure		
GI tract cancer		
Non-GI tract cancer		
Intracranial haemorrhage		
GI bleed		
Other major bleed		Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed.
Amputation		
End-stage renal disease		

BMI, body mass index; HbA1c, glycated haemoglobin; IFCC, International Federation of Clinical Chemistry; HDL, High-density lipoprotein; eGFR, estimated glomerular filtration rate; GI, gastrointestinal.

Age, diabetes duration and disease histories were at time of EQ-5D questionnaire response. Other patient characteristics and clinical risk factors were measured at recruitment into the ASCEND study.

Supplementary Table S3: Characteristics of 11683 participants included in the analysis, before and after imputation of missing data

	Before imputation	After imputation
Participant characteristics at entry into the ASCEND study		
Diabetes type		
Type 1	707 (6.1%)	707 (6.1%)
Type 2	10976 (93.9%)	10976 (93.9%)
Sex		
Male	7347 (62.9%)	7347 (62.9%)
Female	4336 (37.1%)	4336 (37.1%)
Smoking status		
Current smoker	813 (7.0%)	813 (7.0%)
Former/Never smoker	10734 (91.9%)	10870 (93.0%)
Missing	136 (1.2%)	
Race		
White	11282 (96.6%)	11450 (98.0%)
Indian/Pakistani/Bangladeshi	147 (1.3%)	147 (1.3%)
African/Caribbean	86 (0.7%)	86 (0.7%)
Missing	168 (1.4%)	
Townsend Index[†]		
Q1: <-2.42 (least deprived)	5232 (44.8%)	5258 (45.0%)
Q2: >=-2.42, <-0.44	2934 (25.1%)	2934 (25.1%)
Q3: >=-0.44, < 1.79	1851 (15.8%)	1851 (15.8%)
Q4: >= 1.79, < 4.75	1237 (10.6%)	1237 (10.6%)
Q5: >= 4.75 (most deprived)	403 (3.4%)	403 (3.4%)
Missing	26 (0.2%)	
Hypertension		
Y	7173 (61.4%)	7248 (62.0%)
N	4435 (38.0%)	4435 (38.0%)
Missing	75 (0.6%)	
Diabetic retinopathy		
Y	2232 (19.1%)	2232 (19.1%)
N	9359 (80.1%)	9451 (80.9%)
Missing	92 (0.8%)	
Use of statin		
Y	8919 (76.3%)	8919 (76.3%)
N	2764 (23.7%)	2764 (23.7%)
Use of ACE Inhibitor or ARB		
Y	6818 (58.4%)	6818 (58.4%)
N	4865 (41.6%)	4865 (41.6%)
Age (years)		
Mean (SD)	62.8 (8.5)	62.3 (8.5)
<50	757 (6.5%)	757 (6.5%)
>=50, <60	3542 (30.3%)	3542 (30.3%)
>=60, <70	5024 (43%)	5024 (43%)
>=70	2360 (20.2%)	2360 (20.2%)

Diabetes duration (years)		
Mean (SD)	9.7 (9.3)	9.6 (9.2)
<5	3765 (32.2%)	3867 (33.1%)
>=5, <10	3348 (28.7%)	3680 (31.5%)
>=10, <20	2608 (22.3%)	2730 (23.4%)
>=20	1374 (11.8%)	1406 (12%)
Missing	588 (5%)	
Body-mass index (kg/m²)		
Mean (SD)	31.0 (6.4)	31.0 (6.4)
<25	1539 (13.2%)	1540 (13.2%)
>=25, <30	4224 (36.2%)	4269 (36.5%)
>=30, <35	3426 (29.3%)	3456 (29.6%)
>=35	2412 (20.6%)	2418 (20.7%)
Missing	82 (0.7%)	
HbA1c (IFCC mmol/mol)		
Mean (SD)	54.4 (12.4)	54.6 (10.9)
< 48	2532 (21.7%)	3134 (26.8%)
>= 48, < 64	3625 (31.0%)	6653 (56.9%)
>= 64	1361 (11.6%)	1896 (16.2%)
Missing	4165 (35.7%)	
HDL cholesterol (mmol/L)		
Mean (SD)	1.27 (0.35)	1.27 (0.29)
< 1.0	1630 (14.0%)	1655 (14.2%)
>= 1.0, < 1.5	4206 (36.0%)	8243 (70.6%)
>= 1.5	1672 (14.3%)	1785 (15.3%)
Missing	4175 (35.7%)	
Non-HDL cholesterol (mmol/L)		
Mean (SD)	2.88 (0.83)	2.88 (0.68)
< 2.5	2650 (22.7%)	2902 (24.8%)
>= 2.5, < 3.5	3398 (29.1%)	7247 (62.0%)
>= 3.5	1460 (12.5%)	1534 (13.1%)
Missing	4175 (35.7%)	
Systolic blood pressure (mmHg)		
Mean (SD)	135.9 (15.0)	135.8 (13.2)
<130	2622 (22.4%)	3233 (27.7%)
>=130, <140	2390 (20.5%)	4283 (36.7%)
>=140	3479 (29.8%)	4167 (35.7%)
Missing	3192 (27.3%)	
Diastolic blood pressure (mmHg)		
Mean (SD)	77.3 (9.3)	77.5 (8.2)
<75	3149 (27.0%)	3834 (32.8%)
>=75, <85	3650 (31.2%)	6004 (51.4%)
>=85	1687 (14.4%)	1845 (15.8%)
Missing	3197 (27.4%)	
Urinary albumin/creatinine ratio (mg/mmol) ‡		
< 3	6644 (56.9%)	10481 (89.7%)

≥ 3	854 (7.3%)	1202 (10.3%)
Missing	4185 (35.8%)	
eGFR (ml/min/1.73m²)[§]		
< 45	209 (1.8%)	243 (2.1%)
≥ 45 , < 60	584 (5.0%)	817 (7.0%)
≥ 60 , < 90	3081 (26.4%)	4636 (39.7%)
≥ 90	3645 (31.2%)	5987 (51.2%)
Missing	4164 (35.6%)	

Participant characteristics at EQ-5D questionnaire response

Age (years)

Mean (SD)	68.5 (8.3)	68.5 (8.3)
<60	1693 (14.5%)	1693 (14.5%)
≥ 60 , <70	4856 (41.6%)	4856 (41.6%)
≥ 70 , <80	3978 (34%)	3978 (34%)
≥ 80	1156 (9.9%)	1156 (9.9%)

Diabetes duration (years)

Mean (SD)	16.4 (9.4)	16.4 (9.6)
<10	2732 (23.4%)	2769 (23.7%)
≥ 10 , <15	3663 (31.4%)	3999 (34.2%)
≥ 15 , <25	3131 (26.8%)	3303 (28.3%)
≥ 25	1569 (13.4%)	1612 (13.8%)

Summary values are N (%) unless otherwise specified. HbA1c, glycated haemoglobin; IFCC, International Federation of Clinical Chemistry; HDL, High-density lipoprotein; eGFR, estimated glomerular filtration rate;

ACE, Angiotensin converting enzyme; ARB, Angiotensin II receptor blocker.

Only 7589 (65%) participants returned usable blood/urine sample in the study.

[†]Townsend index stratified according to range of scores of 2011 UK population quintiles.

[‡]1896 (25%) participants who had undetectable albumin levels were reclassified as having no albuminuria (urinary albumin/creatinine ratio <3).

[§]Calculated from blood cystatin C concentration using the CKD-EPI formula.

Supplementary Table S4: Number (%) of participants included in analysis with missing EQ-5D response

EQ-5D response	N (%)
Did not respond	436 (3.7%)
Returned response	11247 (96.3%)
No. of domains missing	
0	11028 (98.1%)
1	144 (1.3%)
2	30 (0.3%)
3	15 (0.1%)
4	9 (0.1%)
5	†20 (0.2%)

†Of the 20 participants who responded to the questionnaire with all 5 domains missing, 9 had VAS score.

Supplementary Table S5: EQ-5D-5L questionnaire response from 11683 participants, before and after imputation

	Before imputation	After imputation
EQ-5D utility		
Mean (SD)	0.773 (0.220)	0.771 (0.221)
Missing	655 (5.6%)	
EQ-5D VAS score		
Mean (SD)	77.3 (17.9)	77.3 (17.9)
Missing	498 (4.3%)	
Reported full health[†]		
Yes	3110 (26.6%)	3258 (27.9%)
No	7918 (67.8%)	8425 (72.1%)
Missing	655 (5.6%)	
EQ-5D dimensions		
Mobility		
1	6212 (53.2%)	6466 (55.3%)
2	2453 (21.0%)	2584 (22.1%)
3	1641 (14.0%)	1720 (14.7%)
4	836 (7.2%)	871 (7.5%)
5	39 (0.3%)	42 (0.4%)
Missing	502 (4.3%)	
Self-care		
1	9494 (81.3%)	9925 (85%)
2	970 (8.3%)	1023 (8.8%)
3	545 (4.7%)	571 (4.9%)
4	137 (1.2%)	147 (1.3%)
5	16 (0.1%)	17 (0.1%)
Missing	521 (4.5%)	
Usual activities		
1	6868 (58.8%)	7156 (61.3%)
2	2264 (19.4%)	2380 (20.4%)
3	1430 (12.2%)	1503 (12.9%)
4	492 (4.2%)	516 (4.4%)
5	119 (1.0%)	128 (1.1%)
Missing	510 (4.4%)	
Pain/Discomfort		
1	4204 (36%)	4392 (37.6%)
2	4041 (34.6%)	4214 (36.1%)
3	2053 (17.6%)	2155 (18.4%)
4	768 (6.6%)	805 (6.9%)
5	111 (1.0%)	117 (1%)
Missing	506 (4.3%)	
Anxiety/Depression		
1	7905 (67.7%)	8255 (70.7%)
2	2133 (18.3%)	2249 (19.3%)
3	923 (7.9%)	981 (8.4%)

4	144 (1.2%)	148 (1.3%)
5	47 (0.4%)	50 (0.4%)
Missing	531 (4.5%)	

Summary values are N (%) unless otherwise specified. The five levels of EQ-5D-5L are defined as follows: 1 no problem, 2 slight problems, 3 moderate problems, 4 severe problems, 5 extreme problems/unable to.

[†] Full health refers to rating 1 for all EQ-5D dimensions.

Supplementary Table S6: Mean (SD) of EQ-5D utility by number of comorbid adverse events

No. of comorbid events	N (%)	Mean (SD) of EQ-5D utility	
		van Hout tariff	DSU tariff
0	9970 (85.3%)	0.781 (0.216)	0.776 (0.216)
1	1375 (11.8%)	0.722 (0.241)	0.715 (0.243)
2	267 (2.3%)	0.683 (0.261)	0.677 (0.261)
>= 3	71 (0.6%)	0.648 (0.236)	0.638 (0.252)

The most frequent co-occurring events among ASCEND participants were myocardial infarction and urgent coronary revascularisation (N = 140), followed by stroke and TIA (N = 44). There were fewer than 20 occasions for other co-occurring events.

Supplementary Table S7: Mean (SD) of EQ-5D utility by adverse event and time since event occurrence

Time since event occurrence	No. of participants (%)	Mean (SD) of EQ-5D utility	
		van Hout tariff	DSU tariff
Myocardial infarction			
No history	11494 (98.4%)	0.77 (0.22)	0.77 (0.22)
<=1yr	34 (0.3%)	0.72 (0.26)	0.72 (0.26)
>1yr	155 (1.3%)	0.72 (0.24)	0.71 (0.25)
Coronary revascularisation (non-urgent)			
No history	11496 (98.4%)	0.77 (0.22)	0.77 (0.22)
<=1yr	28 (0.2%)	0.78 (0.21)	0.78 (0.19)
>1yr	159 (1.4%)	0.74 (0.22)	0.73 (0.23)
Coronary revascularisation (urgent)			
No history	11533 (98.7%)	0.77 (0.22)	0.77 (0.22)
<=1yr	25 (0.2%)	0.70 (0.26)	0.71 (0.25)
>1yr	125 (1.1%)	0.73 (0.25)	0.72 (0.25)
Transient ischaemic attack			
No history	11469 (98.2%)	0.77 (0.22)	0.77 (0.22)
<=1yr	38 (0.3%)	0.64 (0.28)	0.62 (0.30)
>1yr	176 (1.5%)	0.70 (0.24)	0.68 (0.25)
Ischaemic stroke			
No history	11485 (98.3%)	0.77 (0.22)	0.77 (0.22)
<=1yr	42 (0.4%)	0.72 (0.20)	0.71 (0.21)
>1yr	156 (1.3%)	0.68 (0.25)	0.67 (0.25)
Heart failure			
No history	11578 (99.1%)	0.77 (0.22)	0.77 (0.22)
<=1yr	30 (0.3%)	0.51 (0.27)	0.51 (0.27)
>1yr	75 (0.6%)	0.66 (0.24)	0.64 (0.25)
GI tract cancer			
No history	11537 (98.8%)	0.77 (0.22)	0.77 (0.22)
<=1yr	31 (0.3%)	0.73 (0.23)	0.71 (0.24)
>1yr	115 (1.0%)	0.73 (0.23)	0.72 (0.24)
Non-GI tract cancer			
No history	11022 (94.3%)	0.77 (0.22)	0.77 (0.22)
<=1yr	113 (1.0%)	0.77 (0.22)	0.76 (0.23)
>1yr	548 (4.7%)	0.74 (0.23)	0.73 (0.23)
Intracranial haemorrhage			
No history	11661 (99.8%)	0.77 (0.22)	0.77 (0.22)
<=1yr	2 (0.0%)	0.49 (0.35)	0.48 (0.41)
>1yr	20 (0.2%)	0.56 (0.39)	0.60 (0.33)
GI bleed			
No history	11580 (99.1%)	0.77 (0.22)	0.77 (0.22)
<=1yr	16 (0.1%)	0.58 (0.27)	0.58 (0.27)
>1yr	87 (0.7%)	0.64 (0.29)	0.64 (0.29)
Other major bleed			
No history	11613 (99.4%)	0.77 (0.22)	0.77 (0.22)

Time since event occurrence	No. of participants (%)	Mean (SD) of EQ-5D utility	
		van Hout tariff	DSU tariff
<=1yr	7 (0.1%)	0.74 (0.23)	0.73 (0.25)
>1yr	63 (0.5%)	0.65 (0.28)	0.65 (0.29)
Amputation			
No history	11623 (99.5%)	0.77 (0.22)	0.77 (0.22)
<=1yr	10 (0.1%)	0.42 (0.36)	0.41 (0.34)
>1yr	50 (0.4%)	0.56 (0.25)	0.56 (0.25)
End-stage renal disease			
No history	11641 (99.6%)	0.77 (0.22)	0.77 (0.22)
<=1yr	8 (0.1%)	0.68 (0.14)	0.68 (0.15)
>1yr	34 (0.3%)	0.64 (0.28)	0.62 (0.29)

<=1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than a year prior to EQ-5D questionnaire response; GI, gastrointestinal. Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed.

Supplementary Table S8: EQ-5D utility of patients with diabetes associated with patient characteristics, clinical risk factors and adverse events

Variable	EQ-5D utility (95% CI)
(Intercept)	0.906 (0.891, 0.920)**
Sex (ref: Male)	
Female	-0.023 (-0.031, -0.015)**
Current smoker (ref: N)	
Y	-0.052 (-0.067, -0.037)**
Townsend index (ref: Q1 (least deprived))	
Q2	-0.009 (-0.019, 0)
Q3	-0.042 (-0.053, -0.03)**
Q4	-0.069 (-0.082, -0.056)**
Q5 (most deprived)	-0.074 (-0.095, -0.053)**
Age at time of questionnaire (per 10 years, centered at 70)	
Age	-0.014 (-0.02, -0.009)**
Age ²	-0.006 (-0.01, -0.002)**
BMI (ref: <25 kg/m²)	
>=25, <30	-0.033 (-0.045, -0.02)**
>=30, <35	-0.066 (-0.079, -0.053)**
>=35	-0.134 (-0.148, -0.12)**
Diabetes duration at time of questionnaire (ref: <10 years)	
>=10, <15	-0.011 (-0.021, 0)*
>=15, <25	-0.026 (-0.037, -0.015)**
>=25	-0.029 (-0.043, -0.016)**
eGFR (ref: >=90 ml/min/1.73m²)	
>=60, <90	-0.03 (-0.039, -0.02)**
>=45, <60	-0.072 (-0.089, -0.054)**
<45	-0.08 (-0.108, -0.051)**
Albuminuria (urinary albumin/creatinine ratio >=3 mg/mmol) (ref: N)	
Y	-0.018 (-0.031, -0.005)**
Disease history (ref: no event)	
Transient ischaemic attack	
Any history	-0.057 (-0.086, -0.028)**
Ischaemic stroke	
Any history	-0.062 (-0.092, -0.032)**
Heart failure	
<=1yr	-0.183 (-0.258, -0.108)**
>1yr	-0.046 (-0.094, 0.001)
Non-GI tract cancer	
Any history	-0.026 (-0.043, -0.01)**
Intracranial haemorrhage	
Any history	-0.164 (-0.251, -0.076)**
GI bleed	
Any history	-0.091 (-0.132, -0.051)**
Other major bleed	
Any history	-0.096 (-0.146, -0.047)**
Amputation	
Any history	-0.206 (-0.259, -0.152)**

** : p-value < 0.01; * : p-value < 0.05. <=1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than a year prior to EQ-5D questionnaire response; BMI, body mass index; eGFR, estimated glomerular filtration rate; GI, gastrointestinal. Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed. Number of participants experiencing each adverse event presented in brackets next to time adverse event occurrence. Intercept value gives the EQ-

5D utility for the reference individual (male, not current smoker, living in least deprived region, aged 70, BMI $<25\text{kg/m}^2$, diabetes duration <10 years, $\text{eGFR} \geq 90\text{ml/min/1.73m}^2$, no albuminuria, with no disease history).

Supplementary Table S9: EQ-5D utility of patients with diabetes associated with patient characteristics, clinical risk factors and adverse events, with (a) all adverse events included and (b) using DSU tariffs

Variable	EQ-5D utility (95% CI)	
	(a) All adverse events included	(b) DSU EQ-5D tariff
(Intercept)	0.906 (0.892, 0.92)**	0.899 (0.884, 0.913)**
Sex (ref: Male)		
Female	-0.023 (-0.032, -0.015)**	-0.018 (-0.026, -0.01)**
Current smoker (ref: N)		
Y	-0.052 (-0.067, -0.036)**	-0.055 (-0.07, -0.04)**
Townsend index (ref: Q1 (least deprived))		
Q2	-0.009 (-0.019, 0)	-0.009 (-0.019, 0)
Q3	-0.042 (-0.053, -0.031)**	-0.043 (-0.054, -0.032)**
Q4	-0.069 (-0.082, -0.056)**	-0.073 (-0.086, -0.06)**
Q5 (most deprived)	-0.074 (-0.096, -0.053)**	-0.076 (-0.098, -0.055)**
Age at time of questionnaire (per 10 years, centered at 70)		
Age	-0.014 (-0.02, -0.009)**	-0.016 (-0.021, -0.01)**
Age ²	-0.006 (-0.01, -0.002)**	-0.006 (-0.01, -0.001)*
BMI (ref: <25 kg/m²)		
>=25, <30	-0.033 (-0.045, -0.02)**	-0.031 (-0.044, -0.019)**
>=30, <35	-0.066 (-0.079, -0.053)**	-0.065 (-0.078, -0.052)**
>=35	-0.134 (-0.148, -0.12)**	-0.131 (-0.145, -0.117)**
Diabetes duration at time of questionnaire (ref: <10 years)		
>=10, <15	-0.01 (-0.021, 0)*	-0.011 (-0.022, -0.001)*
>=15, <25	-0.026 (-0.036, -0.015)**	-0.026 (-0.037, -0.015)**
>=25	-0.029 (-0.042, -0.016)**	-0.031 (-0.044, -0.018)**
eGFR (ref: >=90 ml/min/1.73m²)		
>=60, <90	-0.029 (-0.039, -0.02)**	-0.03 (-0.04, -0.021)**
>=45, <60	-0.071 (-0.089, -0.054)**	-0.073 (-0.09, -0.055)**
<45	-0.077 (-0.106, -0.048)**	-0.083 (-0.112, -0.054)**
Albuminuria (urinary albumin/creatinine ratio >=3 mg/mmol) (ref: N)		
Y	-0.017 (-0.03, -0.004)*	-0.018 (-0.031, -0.005)**
Disease history (ref: no event)		
Myocardial infarction		
Any history	-0.019 (-0.073, 0.035)	
Coronary revascularisation (non-urgent)		
Any history	-0.007 (-0.038, 0.023)	
Coronary revascularisation (urgent)		
Any history	-0.004 (-0.064, 0.057)	
Transient ischaemic attack		
Any history	-0.057 (-0.086, -0.028)**	-0.066 (-0.095, -0.037)**
Ischaemic stroke		
Any history	-0.061 (-0.091, -0.031)**	-0.061 (-0.091, -0.03)**
Heart failure		
<=1yr	-0.179 (-0.254, -0.104)**	-0.184 (-0.26, -0.109)**
>1yr	-0.043 (-0.091, 0.005)	-0.052 (-0.1, -0.004)*
GI tract cancer		
Any history	-0.015 (-0.053, 0.022)	
Non-GI tract cancer		
Any history	-0.026 (-0.042, -0.009)**	-0.028 (-0.045, -0.012)**
Intracranial haemorrhage		
Any history	-0.162 (-0.25, -0.074)**	-0.133 (-0.221, -0.045)**
GI bleed		

Variable	EQ-5D utility (95% CI)	
	(a) All adverse events included	(b) DSU EQ-5D tariff
Any history	-0.089 (-0.129, -0.048)**	-0.087 (-0.128, -0.046)**
Other major bleed		
Any history	-0.095 (-0.144, -0.045)**	-0.096 (-0.146, -0.047)**
Amputation		
Any history	-0.204 (-0.257, -0.15)**	-0.195 (-0.249, -0.141)**
End-stage renal disease		
Any history	-0.036 (-0.102, 0.029)	

** : p-value < 0.01; * : p-value < 0.05. ≤1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than a year prior to EQ-5D questionnaire response; BMI, body mass index; eGFR, estimated glomerular filtration rate; GI, gastrointestinal. Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed. Number of participants experiencing each adverse event presented in brackets next to time adverse event occurrence. Intercept values give the EQ-5D utility for the reference individual (male, not current smoker, living in least deprived region, aged 70, BMI <25kg/m², diabetes duration <10 years, eGFR ≥90ml/min/1.73m², no albuminuria, with no disease history).

Supplementary Table S10: Comparison of quality of life decrements associated with diabetes-related complications across diabetes studies

		ASCEND	ACCORD and Look AHEAD (Neuwahl et al., 2021)	ACCORD (Shao et al., 2019)	LEADER (Nauck et al., 2018)	SAVOR- TIMI 53 (Briggs et al., 2017)	ADVANCE (Hayes et al., 2016)	MEPS (Sullivan & Ghushchyan, 2016)	UKPDS (Alva et al., 2014)	TRIAD (Zhang et al., 2012)	Review (Beaudet et al., 2014)
No. of participants		11,683	15,252	8,713	3,014	16,488	11,130	20,705	3,380	7,327	
Repeated measures of QoL		N	Y	Y	Y	Y	Y	N	Y	N	
Years QoL survey conducted		2016/2017	2001 – 2012 35% (ACCORD) 14% (Look AHEAD)	2001 – 2012	2010 - 2015	2010 - 2013	2001 - 2008	2000-2011	1996 - 2007	2000/2001	
Previous CVD		0%		35%	81%	79%	32%			31%	
Instrument		EQ-5D	HUI-3	HUI-3	EQ-5D	EQ-5D	EQ-5D	EQ-5D; SF-12	EQ-5D	EQ-5D	
Model		OLS	FE	OLS FE	Mixed effects	Descriptive	FE	Median regression	FE	OLS	
Disease history (ref: no event)											
Myocardial infarction	Any history	(NS)			0.004 (NS)	-0.051	-0.026	-0.047		-0.019 (CHD other than HF)	-0.055
	<=1yr		-0.028	- 0.042 - 0.018					-0.065		
	>1yr		-0.006 (NS)	- 0.011 (NS)					0.008 (NS)		
Revascularisation	Any history	(NS)									
	<=1yr		-0.005 (NS)	- 0.038 - 0.013							
	>1yr		-0.001 (NS)	- 0.016							

TIA	Any history	-0.057 (-0.086, -0.028)							-0.070		-0.029	
	<=1yr											
	>1yr											
Stroke	Any history	IS: -0.062 (-0.092, -0.032) HS: -0.164 (-0.251, -0.076) Combined: ~ -0.082 [†]				-0.046	-0.111	-0.099	-0.060	-0.165	-0.035	-0.164
	<=1yr		-0.109	-	-							
	>1yr		-0.051	-	-							
Heart failure*	Any history					-0.055	-0.065	-0.045	-0.050	-0.101	-0.042	-0.108
	<=1yr	-0.183 (-0.258, -0.108)	-0.051	-	-							
	>1yr	-0.046 (-0.094, 0.001) (NS)	-0.041	-	-							
Amputation	Any history	-0.206 (-0.259, -0.152)						-0.122	-0.095	-0.172	-0.108	-0.280
	<=1yr		-0.092									
	>1yr		-0.150									
ESRD	Any history	(NS)		-	-			-0.049	-0.038 (nephropathy including ESRD)		-0.06	-0.164
	<=1yr		-0.039									
	>1yr		-0.015									

NS, Effect is not statistically significant at $p < 0.05$; TIA, transient ischaemic attack; IS, Ischaemic stroke; HS, haemorrhagic stroke / intracerebral haemorrhage; HF, heart failure; ESRD, end-stage renal disease; CHD, coronary heart disease. ≤ 1 yr, event occurred within one year prior to EQ-5D questionnaire response; >1 yr, event occurred more than a year prior to EQ-5D questionnaire response.

*Refers to hospitalisation for heart failure in ACCORD, Look AHEAD, LEADER, ADVANCE, SAVOR-TIMI 53 studies.

†The combined estimate of QoL decrement associated with stroke (IS + HS) was calculated assuming 80% of strokes are ischaemic strokes.

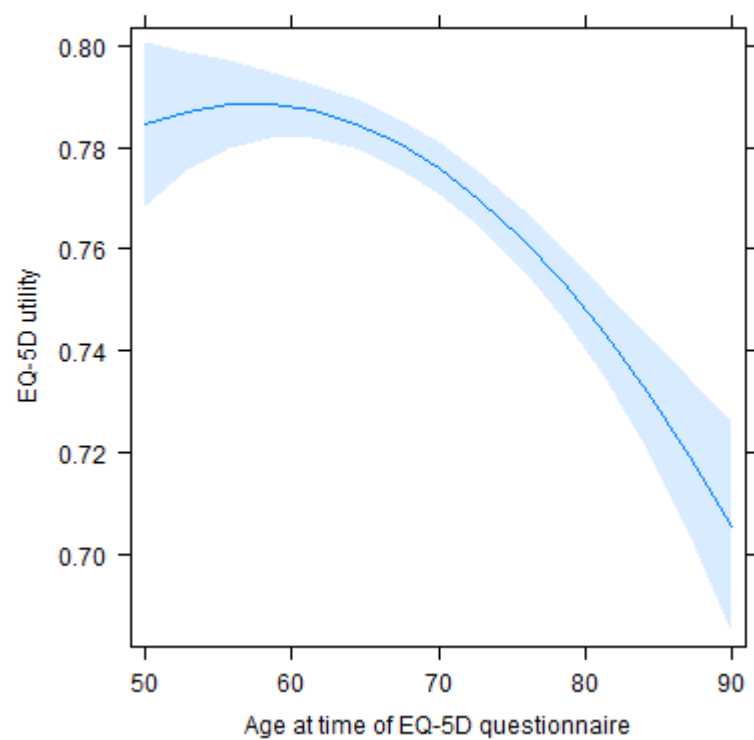
Supplementary Table S11: Comparison of quality of life decrements associated with bleeding events across studies

		ASCEND	TRANSLATE-ACS (Amin et al., 2016)	ENGAGE AF-TIMI 48 (Wang et al., 2017)
No. of participants		11683	9290	10706
Study population		Patients with diabetes without previous vascular disease, treatment arm assigned to aspirin use	Patients on dual antiplatelet therapies after percutaneous coronary intervention for acute myocardial infarction	Patients with atrial fibrillation on antiplatelet therapies
Repeated measures		N	Y	Y
Years QoL survey conducted		2016/2017	2010 – 2012	2008 – 2013
Instrument		EQ-5D	EQ-5D	EQ-5D
Model		OLS	Mixed effect	Mixed effect
Disease history (ref: no event)				
Any major bleed	Any history			
	<=1yr		BARC 2-4; at 6 months: -0.0381 BARC 3-4; at 6 months: -0.0445	
	>1yr			
Intracranial haemorrhage	Any history	-0.164 (-0.251, -0.076)		
	<=1yr			
	>1yr			
Gastrointestinal bleed	Any history	-0.091 (-0.132, -0.051)		
	<=1yr			At 3 months: -0.029
	>1yr			At 12 months: -0.010
Other major bleed	Any history	-0.096 (-0.146, -0.047)		
	<=1yr			At 3 months: -0.029
	>1yr			At 12 months: (NS)

BARC, Bleeding Academic Research Consortium's definition for bleeding types (type 2 and above are "actionable" bleeds requiring healthcare intervention). <=1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than a year prior to EQ-5D questionnaire response. Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed. In ASCEND, other major bleed also excludes eye bleeds.

Supplementary Figures

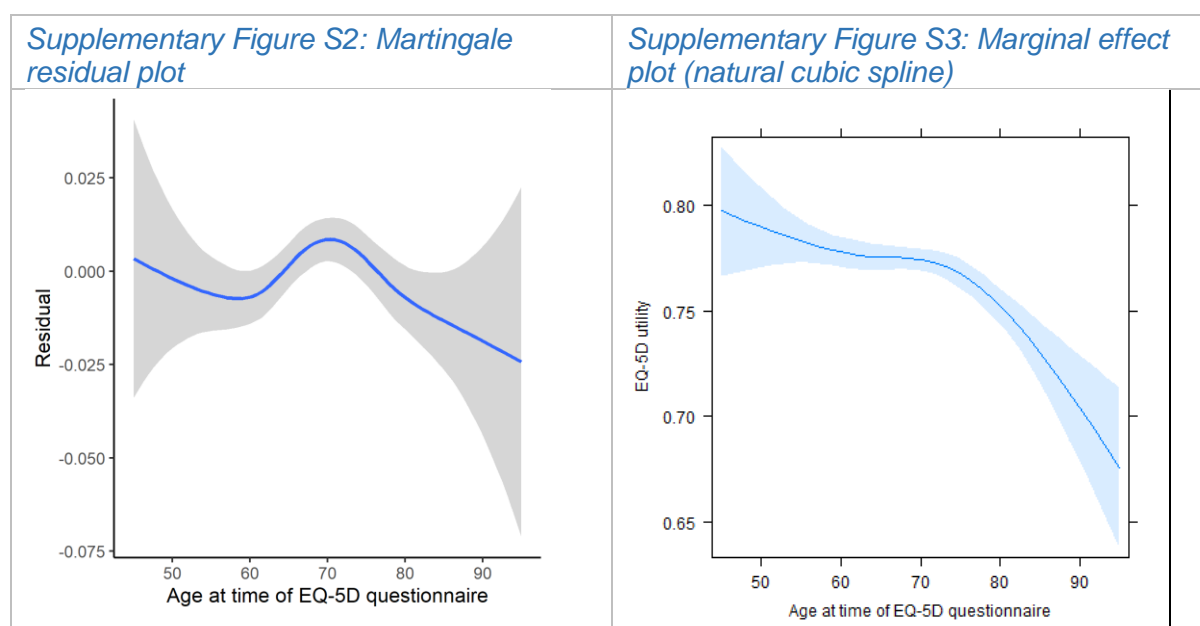
Supplementary Figure S1: Marginal effect of age on EQ-5D utility



Supplementary Section 1: Further details on statistical methods

Non-linearity of age

In the model including all covariates, the martingale residual plot of age suggested that there might be a non-linear relationship between age and health utility (Supplementary Figure S2). A natural cubic spline was fitted to explore the shape of the relationship. The shape of the spline fitted suggested that the polynomial form with degree 2 or a linear spline with a knot at 70 might be appropriate functional forms for age (Supplementary Figure S3), both of which are easy to compute. The marginal effect of the polynomial form of age seems to match that of the natural cubic spline most closely (Supplementary Table S11). In terms of performance metric (Supplementary Table S12), all three models performed similarly. Hence the polynomial form was selected.



Supplementary Table S12: Marginal effects of age on EQ-5D utility

Form of age	Marginal effect of age relative to 70 years old						
	55	60	65	70	75	80	85
Linear	0.020	0.013	0.007	0.000	-0.007	-0.013	-0.020
Natural cubic spline	0.008	0.003	0.001	0.000	-0.007	-0.022	-0.044
Polynomial degree 2	0.010	0.009	0.006	0.000	-0.009	-0.021	-0.036
Linear spline, knot at 70	0.001	0.000	0.000	0.000	-0.016	-0.031	-0.047

Supplementary Table S13: Predictive performance of models using different forms of age

Form of age	MSE	RMSE	MAPE	MPE	R ²
Linear	0.04353	0.20864	0.15311	2.04×10^{-14}	0.11083
Natural cubic spline	0.04349	0.20853	0.15310	1.84×10^{-14}	0.11175
Polynomial degree 2	0.04350	0.20858	0.15309	2.10×10^{-14}	0.11137
Linear spline, knot at 70	0.04348	0.20851	0.15305	2.09×10^{-14}	0.11194

MSE: mean squared error; RMSE: root mean squared error; MAPE: mean absolute prediction error; MPE: mean prediction error; R²: Efron's R², square of the correlation between the predicted and observed values

Model selection

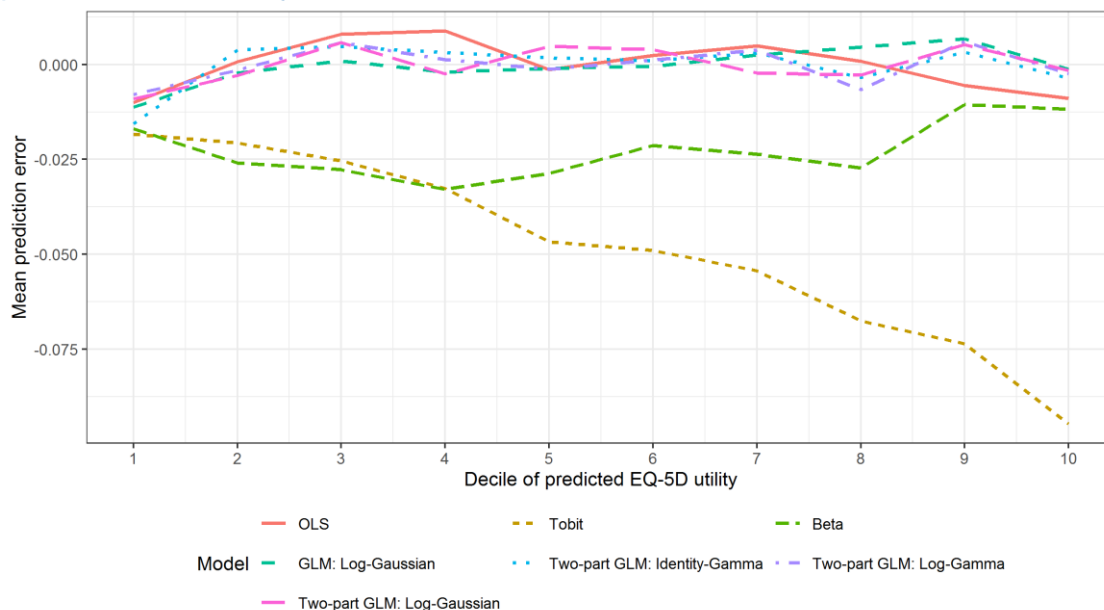
Given the features of EQ-5D utility data, the candidate models considered were ordinary least squares regression (OLS), Tobit model, beta regression model, generalised linear models (GLMs), and two-part models (logistic equation for first part, GLMs for second part). The predictive performance of each model is presented in Supplementary Table S13. With the exception of the Tobit and beta regression models, all other models performed similarly. The Tobit and beta regressions models had significantly greater negative bias reflected in the mean prediction error (MPE). In particular with the Tobit model, there is increasing bias at increasing utility values (Supplementary Figure S4). The Copas test, performed with 3-fold cross validation repeated 1000 times, was used to assess out-of-sample performance of the model.¹ Results from the Copas test (Supplementary Table S14) suggest that the two-part model with identity-gamma specification might perform slightly better than the OLS. The marginal EQ-5D decrement associated with adverse events estimated by the OLS and the two-part model with identity-gamma specification is similar (Supplementary Table S15). The OLS was chosen for parsimony. One downside of using the OLS for modelling EQ-5D utility is the possibility of predictions exceeding 1. However, the coefficients of the OLS guarantees almost no predictions above 1.

Supplementary Table S14: Predictive performance of candidate models

Model	MSE	RMSE	MAPE	MPE	R ²
OLS	0.04354	0.20866	0.15318	2.15 x 10 ⁻¹⁴	0.11063
Tobit	0.04643	0.21548	0.15524	-0.04827	0.10983
Beta	0.04446	0.21084	0.15170	-0.02266	0.10234
GLM: Log-Gaussian	0.04388	0.20947	0.15363	-0.00034	0.10377
Two-part GLM: Identity-Gamma	0.04370	0.20905	0.15317	-0.00021	0.10740
Two-part GLM: Log-Gamma	0.04368	0.20900	0.15320	-0.00015	0.10778
Two-part GLM: Log-Gaussian	0.04368	0.20900	0.15324	-0.00012	0.10781

MSE: mean squared error; RMSE: root mean squared error; MAPE: mean absolute prediction error; MPE: mean prediction error; R²: Efron's R², square of the correlation between the predicted and observed values.

Supplementary Figure S4: Mean prediction error of candidate models in each decile of predicted EQ-5D utility value



Supplementary Table S15: Results from Copas test

Model	Mean (SD) of %			
	1- α	1- δ	1- γ	% reject
OLS	0 (0)	3.4 (6)	3.4 (6)	18
Tobit	23.8 (0.5)	26.3 (4.5)	3.2 (6)	100
Beta	3 (2.1)	5.9 (6.4)	2.9 (6.6)	27
GLM: Log-Gaussian	-1.5 (0.4)	2.8 (6.5)	4.3 (6.4)	16
Two-part GLM: Identity-Gamma	-3.2 (0.7)	-0.6 (6.2)	2.5 (6.1)	11
Two-part GLM: Log-Gamma	-1.6 (0.7)	1.1 (6.2)	2.7 (6.2)	12
Two-part GLM: Log-Gaussian	-2.6 (0.5)	0.4 (6.4)	2.9 (6.2)	12

α : in-sample calibration - captures effect of mis-specification; 1- α : in-sample shrinkage;
 δ : out-of-sample calibration - captures both effect of mis-specification and overfitting; 1- δ :
out-of-sample shrinkage;
1 - γ : combines in-sample and out-of-sample shrinkage - captures effect of overfitting;
% rejected: Percentage of iterations in which Wald test, with null hypothesis that the slope
coefficient relating predicted utility to observed utility is 1, is rejected at 5% significance
threshold.

Supplementary Table S16: Decrements in EQ-5D utility associated with adverse events estimated by the OLS and the two-part GLM

Disease history (ref: no event)	Decrements in EQ-5D utility (95% CI)	
	OLS	Two-part GLM: Identity-Gamma*
Transient ischaemic attack		
Any history	-0.057 (-0.086, -0.028)	-0.062 (-0.105, -0.024)
Ischaemic stroke		
Any history	-0.062 (-0.092, -0.032)	-0.065 (-0.132, -0.057)
Heart failure		
<=1yr	-0.183 (-0.258, -0.108)	-0.195 (-0.137, 0.01)
>1yr	-0.046 (-0.094, 0.001)	-0.078 (-0.202, -0.095)
Non-GI tract cancer		
Any history	-0.026 (-0.043, -0.01)	-0.029 (-0.047, 0.002)
Intracranial haemorrhage		
Any history	-0.164 (-0.251, -0.076)	-0.117 (-0.157, 0.06)
GI bleed		
Any history	-0.091 (-0.132, -0.051)	-0.094 (-0.114, -0.011)
Other major bleed		
Any history	-0.096 (-0.146, -0.047)	-0.123 (-0.156, -0.054)
Amputation		
Any history	-0.206 (-0.259, -0.152)	-0.181 (-0.201, -0.126)

<=1yr, event occurred within one year prior to EQ-5D questionnaire response; >1yr, event occurred more than a year prior to EQ-5D questionnaire response; GI, gastrointestinal. Other major bleed refers to bleeding events that are not intracranial haemorrhage or GI bleed. Number of participants experiencing each adverse event presented in brackets next to time adverse event occurrence.

*Average marginal effect for two-part model estimated using 1000 bootstrap.²

References

1. Bilger M, Manning WG. Measuring overfitting in nonlinear models: a new method and an application to health expenditures. *Health Econ.* 2015;24(1):75-85. doi:10.1002/hec.3003

2. Li Z, Mahendra G. Using “Recycled Predictions” for Computing Marginal Effects. In: *SAS Global Forum 2010.* ; 2010.