**Online-Only Supplemental Material**

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to:

**The Excess Risk of Lower Extremity Amputations in Persons with Type 1 Diabetes compared to the General Population.**

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# *Supplement Figure 1 - Patient Flow Chart*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type 1 DM** |  |  | **Controls** |  |
| Total number of Patients from NDR | 36,872 |  | Matched Controls | 184,360 |
|  |  |  | Death before study start 237 | 184,123 |
| Death before study start 4 | 36,868 |  | Their controls 20 | 184,103 |
|  |  |  | Amputation before study start38 | 184,065 |
| Amputations before study start291 | 36,577 |  | Their controls1448 | 182,617 |
| **Total** | **36,577** |  | **Total** | **182,617** |
|  |  |  |  |  |

# *ICD codes*

The following ICD-9 and ICD-10 codes were collected:

coronary heart disease: 410-414 (ICD-9), I20-I25 (ICD-10) (including acute myocardial infarction: 410, I21);

stroke (431-434, 436; I61-I64);

hospitalization for heart failure (428; I50);

atrial fibrillation (427D; I48);

valve disease (394-396, 424, 746; I05-I09, I34-I37, Q22-Q23);

foot ulcer (operation code 250G; ICD10 E10.5, E11.5, E12.5, E13.5, E14.5); and cancer (140-208; C00-C97).

For renal dialysis and transplantation, the following codes were used: V42A, V45B, V56A, V56W (ICD-9) and Z94.0, Z49, Z99.2 (ICD-10).

All events were collected from the inpatient register except for atrial fibrillation that was collected both from inpatient and outpatient register.

# *The SAS code for a time-updated Cox regression:*

PROC PHREG DATA = *data*;

 CLASS *mainvar* / REF = LAST;

 MODEL (*startyr*,*stopyr*)\**endpsplit*(0) = *mainvar* *&covars.* / RL;

RUN;

The dataset *data* is split up for each patient by consecutive time periods between *startyr*-*stopyr* given in years from start of study (first visit date in NDR). For each new value of any variable that is studied as time-updated in the model, there is a new observation for that patient starting with *startyr* and stopping with *stopyr* that is either a new updated value or the last updated timepoint ending up in an amputation event or a censoring event. *Endpsplit* is 0 for all consecutive observations unless it is the last observation, i.e. the last time period, where it is either 0 if censoring or 1 if the studied event has occurred at the end of that time interval (*stopyr*). *Mainvar* is for example time-updated HbA1c category with last category corresponding to controls. *&covars.* is a macro-variable including all adjustment variables, e.g. *ageupd sex* with time-updated age and sex in model 1.

SAS software link with an example: <http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_phreg_sect038.htm>

# *Supplement Table 1. Baseline characteristics of persons with type 1 diabetes and their controls with no prior amputation by categories of HbA1c at first inclusion in the register in 1998-2013*

|  | **HbA1c categories at baseline (NGSP % / IFCC mmol/mol)** |
| --- | --- |
|  | **Controls****n=182617** | **All Type I diabetes****n=36577** | **≤6.9%****(≤52 mmol/mol)****n=5867** | **7.0-7.8%****(53-62 mmol/mol)****n=9687** | **7.9-8.7%****(63-72 mmol/mol)****n=10414** | **8.8-9.6%****(73-82 mmol/mol)****n=6005** | **≥9.7%****(≥83 mmol/mol)****n=4367** | **Missing value****n=237** |
| **Women** | 82738 (45.3%) | 16567 (45.3%) | 2603 (44.4%) | 4286 (44.2%) | 4714 (45.3%) | 2733 (45.5%) | 2130 (48.8%) | 101 (42.6%) |
| **Age (years)** | 35.2 (14.6)n=182617 | 35.2 (14.6)n=36577 | 35.3 (15.2)n=5867 | 36.1 (14.8)n=9687 | 35.8 (14.5)n=10414 | 34.9 (14.1)n=6005 | 32.3 (13.5)n=4367 | 30.4 (14.4)n=237 |
| **Age category** |  |  |  |  |  |  |  |  |
| **18-34** | 102427 (56.1%) | 20495 (56.0%) | 3444 (58.7%) | 5200 (53.7%) | 5600 (53.8%) | 3307 (55.1%) | 2774 (63.5%) | 170 (71.7%) |
| **35-49** | 45377 (24.8%) | 9083 (24.8%) | 1161 (19.8%) | 2412 (24.9%) | 2717 (26.1%) | 1679 (28.0%) | 1074 (24.6%) | 40 (16.9%) |
| **50-64** | 27588 (15.1%) | 5533 (15.1%) | 977 (16.7%) | 1646 (17.0%) | 1676 (16.1%) | 819 (13.6%) | 397 (9.1%) | 18 (7.6%) |
| **65+**  | 7225 (4.0%) | 1466 (4.0%) | 285 (4.9%) | 429 (4.4%) | 421 (4.0%) | 200 (3.3%) | 122 (2.8%) | 9 (3.8%) |
| **Born in Sweden** | 158353 (86.7%) | 34028 (93.0%) | 5433 (92.6%) | 9065 (93.6%) | 9776 (93.9%) | 5570 (92.8%) | 3997 (91.5%) | 187 (78.9%) |
| **Education category** |  |  |  |  |  |  |  |  |
| **Low**  | 38640 (21.5%) | 8091 (22.4%) | 1069 (18.5%) | 1833 (19.2%) | 2229 (21.6%) | 1515 (25.6%) | 1357 (31.6%) | 88 (39.1%) |
| **Mid**  | 92477 (51.6%) | 19378 (53.7%) | 2916 (50.3%) | 4995 (52.2%) | 5656 (54.9%) | 3306 (55.9%) | 2398 (55.9%) | 107 (47.6%) |
| **High** | 48234 (26.9%) | 8629 (23.9%) | 1807 (31.2%) | 2738 (28.6%) | 2420 (23.5%) | 1097 (18.5%) | 537 (12.5%) | 30 (13.3%) |
| ***Variables in the National Diabetes Regiser only*** |  |  |  |  |  |  |  |  |
| **HbA1c (mmol/mol, IFCC)** |  | 66.1 (14.7)n=36340 | 46.7 (4.9)n=5867 | 57.7 (2.7)n=9687 | 67.1 (2.8)n=10414 | 76.9 (2.8)n=6005 | 94.1 (10.9)n=4367 |  |
| **HbA1c (%, NGSP)** |  | 8.20 (1.35)n=36340 | 6.42 (0.45)n=5867 | 7.43 (0.24)n=9687 | 8.29 (0.26)n=10414 | 9.18 (0.26)n=6005 | 10.8 (1.0)n=4367 |  |
| **Diabetes duration (years)** |  | 19.9 (14.7)n=36577 | 18.6 (16.2)n=5867 | 20.8 (15.0)n=9687 | 20.8 (14.3)n=10414 | 19.9 (13.7)n=6005 | 17.7 (13.1)n=4367 | 13.4 (14.5)n=237 |
| **Insulin method** |  |  |  |  |  |  |  |  |
| **Injection** |  | 27972 (80.3%) | 4693 (84.1%) | 7430 (79.4%) | 7837 (78.8%) | 4519 (79.5%) | 3352 (82.2%) | 141 (83.4%) |
| **Pump**  |  | 6841 (19.7%) | 886 (15.9%) | 1928 (20.6%) | 2108 (21.2%) | 1163 (20.5%) | 728 (17.8%) | 28 (16.6%) |
| **BMI (kg/m2)** |  | 25.9 (4.6)n=35343 | 25.2 (4.4)n=5639 | 25.7 (4.2)n=9460 | 26.2 (4.5)n=10149 | 26.5 (4.7)n=5838 | 25.8 (5.2)n=4149 | 26.0 (4.9)n=108 |
| **LDL (mmol/L)** |  | 2.63 (0.82)n=33009 | 2.52 (0.78)n=5265 | 2.57 (0.77)n=9015 | 2.62 (0.80)n=9571 | 2.70 (0.83)n=5405 | 2.83 (0.94)n=3721 | 2.71 (0.99)n=32 |
| **Systolic BP (mmHg)** |  | 126.1 (15.7)n=36121 | 124.7 (15.4)n=5786 | 125.7 (15.3)n=9618 | 126.6 (15.6)n=10324 | 127.3 (15.9)n=5965 | 126.2 (16.8)n=4287 | 123.4 (17.9)n=141 |
| **Diastolic BP (mmHg)** |  | 72.6 (9.3)n=36121 | 71.7 (9.0)n=5786 | 71.7 (9.2)n=9618 | 72.6 (9.1)n=10324 | 73.5 (9.4)n=5965 | 74.4 (9.7)n=4287 | 73.2 (10.1)n=141 |
| **Smoking** |  | 4435 (12.3%) | 468 (8.1%) | 880 (9.2%) | 1194 (11.6%) | 915 (15.4%) | 945 (22.2%) | 33 (21.6%) |
| **Blood pressure lowering medication** |  | 14171 (39.3%) | 1950 (33.9%) | 3791 (39.6%) | 4222 (41.0%) | 2535 (42.7%) | 1644 (38.4%) | 29 (15.1%) |
| **Lipid lowering medication** |  | 12978 (35.9%) | 1645 (28.5%) | 3506 (36.5%) | 3997 (38.7%) | 2397 (40.3%) | 1416 (32.9%) | 17 (8.7%) |
| **eGFR** |  | 93.5 (31.6)n=34328 | 91.0 (32.9)n=5513 | 91.2 (29.9)n=9283 | 92.8 (28.0)n=9881 | 94.9 (33.3)n=5629 | 101.5 (37.3)n=3973 | 101.9 (42.8)n=49 |
| **Albuminuria** |  |  |  |  |  |  |  |  |
| **Normoalbuminuria**  |  | 26797 (80.0%) | 4597 (85.4%) | 7582 (83.0%) | 7841 (80.9%) | 4137 (75.3%) | 2613 (69.3%) | 27 (71.1%) |
| **Microalbuminuria**  |  | 3796 (11.3%) | 366 (6.8%) | 860 (9.4%) | 1110 (11.5%) | 795 (14.5%) | 664 (17.6%) | 1 (2.6%) |
| **Macroalbuminuria**  |  | 2117 (6.3%) | 249 (4.6%) | 473 (5.2%) | 551 (5.7%) | 451 (8.2%) | 390 (10.3%) | 3 (7.9%) |
| **CKD stage 5**  |  | 794 (2.4%) | 172 (3.2%) | 215 (2.4%) | 186 (1.9%) | 108 (2.0%) | 106 (2.8%) | 7 (18.4%) |
| ***Registrations in the InPatient Register prior to baseline*** |  |  |  |  |  |  |  |  |
| **Acute Myocardial Infarction (I21)** | 835 (0.5%) | 808 (2.2%) | 99 (1.7%) | 223 (2.3%) | 232 (2.2%) | 150 (2.5%) | 102 (2.3%) | 2 (0.8%) |
| **Atrial Fibrillation (I48)** | 811 (0.4%) | 215 (0.6%) | 38 (0.6%) | 57 (0.6%) | 73 (0.7%) | 26 (0.4%) | 18 (0.4%) | 3 (1.3%) |
| **Coronary Heart Disease (I20-I25)** | 1667 (0.9%) | 1605 (4.4%) | 229 (3.9%) | 435 (4.5%) | 449 (4.3%) | 275 (4.6%) | 209 (4.8%) | 8 (3.4%) |
| **Heart Failure (I50)** | 438 (0.2%) | 491 (1.3%) | 74 (1.3%) | 124 (1.3%) | 143 (1.4%) | 83 (1.4%) | 60 (1.4%) | 7 (3.0%) |
| **Valve disease (I05-I09,I34-I36)** | 359 (0.2%) | 134 (0.4%) | 16 (0.3%) | 24 (0.2%) | 42 (0.4%) | 26 (0.4%) | 20 (0.5%) | 6 (2.5%) |
| **Stroke (I61-I64)** | 726 (0.4%) | 548 (1.5%) | 80 (1.4%) | 132 (1.4%) | 168 (1.6%) | 88 (1.5%) | 77 (1.8%) | 3 (1.3%) |
| **Cancer (C00-C97)** | 2093 (1.1%) | 515 (1.4%) | 100 (1.7%) | 143 (1.5%) | 153 (1.5%) | 69 (1.1%) | 48 (1.1%) | 2 (0.8%) |
| **Foot ulcer (circulatory complications) (E10.5,E11.5,E12.5,E13.5,E14.5)** | 17 (0.0%) | 1349 (3.7%) | 182 (3.1%) | 318 (3.3%) | 384 (3.7%) | 264 (4.4%) | 195 (4.5%) | 6 (2.5%) |
| For categorical variables n (%) is presented. For continuous variables Mean (SD) is presented. |

# *6 Supplemental Table 2. Distribution of age by gender and calendar periods*

| **Gender** | **Calendar period** | **Mean (SD)****at risk n=** |
| --- | --- | --- |
| **Men** | 1998-2001 | 39·9 (13·0) n=8350 |
| 2002-2004 | 40·5 (13·5)n=11738 |
| 2005-2007 | 41·0 (14·0)n=14386 |
| 2008-2010 | 40·8 (14·8)n=16548 |
| 2011-2013 | 41·3 (15·2)n=18245 |
| **Women** | 1998-2001 | 40·3 (13·3) n=7071 |
| 2002-2004 | 41·1 (13·8)n=9868 |
| 2005-2007 | 41·6 (14·5)n=12190 |
| 2008-2010 | 41·6 (15·2)n=14022 |
| 2011-2013 | 42·3 (15·6)n=15369 |

# *7 Supplemental Table 3. Standardized (for age and sex in first period) event rates with 95% CI per 1000 patient years for any amputation, below ankle and above ankle for diabetes patients and controls, by calendar periods.*

| **Event** | **Population** | **1998-2001** | **2002-2004** | **2005-2007** | **2008-2010** | **2011-2013** |
| --- | --- | --- | --- | --- | --- | --- |
| **All amputations** | **All diabetes patients** | 3.09 (2.56-3.62) | 3.31 (2.85-3.77) | 3.04 (2.65-3.42) | 2.50 (2.19-2.82) | 2.64 (2.31-2.98) |
|  | **diabetes patients, Men** | 3.82 (3.02-4.63) | 3.74 (3.08-4.41) | 3.79 (3.21-4.38) | 3.24 (2.75-3.74) | 3.23 (2.72-3.74) |
|  | **diabetes patients, Women** | 2.24 (1.58-2.90) | 2.80 (2.17-3.43) | 2.16 (1.68-2.64) | 1.65 (1.27-2.02) | 1.97 (1.54-2.39) |
|  | **Controls** | 0.05 (0.02-0.09) | 0.06 (0.03-0.08) | 0.05 (0.03-0.07) | 0.05 (0.03-0.07) | 0.04 (0.02-0.06) |
| **Minor amputations** | **All diabetes patients** | 1.62 (1.23-2.00) | 1.93 (1.58-2.28) | 1.87 (1.57-2.17) | 1.58 (1.32-1.83) | 1.79 (1.51-2.07) |
|  | **diabetes patients, Men** | 2.00 (1.42-2.58) | 2.29 (1.76-2.81) | 2.44 (1.97-2.91) | 2.16 (1.75-2.57) | 2.47 (2.02-2.92) |
|  | **diabetes patients, Women** | 1.16 (0.69-1.64) | 1.52 (1.05-1.98) | 1.21 (0.85-1.57) | 0.90 (0.62-1.19) | 1.00 (0.69-1.30) |
|  | **Controls** | 0.01 (-0.00-0.03) | 0.01 (0.00-0.02) | 0.01 (0.00-0.02) | 0.02 (0.01-0.03) | 0.01 (0.00-0.02) |
| **Major amputations** | **All diabetes patients** | 1.84 (1.43-2.25) | 1.92 (1.57-2.26) | 1.65 (1.37-1.93) | 1.40 (1.17-1.63) | 1.50 (1.25-1.74) |
|  | **diabetes patients, Men** | 2.29 (1.66-2.91) | 2.16 (1.65-2.66) | 1.99 (1.57-2.41) | 1.71 (1.36-2.06) | 1.66 (1.31-2.01) |
|  | **diabetes patients, Women** | 1.32 (0.81-1.83) | 1.64 (1.16-2.11) | 1.27 (0.90-1.63) | 1.04 (0.75-1.34) | 1.31 (0.97-1.65) |
|  | **Controls** | 0.05 (0.02-0.07) | 0.05 (0.02-0.07) | 0.04 (0.02-0.05) | 0.03 (0.02-0.04) | 0.03 (0.01-0.04) |

# *8 Supplemental Table 4. Adjusted HR (95% CI) for time to first amputation for T1D vs Controls by calendar period and within diabetes cohort, analysis done from model 3 and evaluated by Cox regression.*

| **Cohort** | **Calendar period/Comparison** | **HR (95% CI)****p-value** | **p-value for interaction Group\*Calendar period** |  |
| --- | --- | --- | --- | --- |
| **Any amputations** |  |
| **Type 1DM vs Controls** | **1998-2001** | 34·8 (17·5-69·3) | 0.74 |  |
|  | **2002-2004** | 30·4 (18·6-49·7) |  |  |
|  | **2005-2007** | 24·1 (15·9-36·5) |  |  |
|  | **2008-2010** | 27·1 (18·0-40·9) |  |  |
|  | **2011-2013** | 22·4 (15·6-32·0) |  |  |
| **Type 1DM cohort** | **2002-2004 vs 1998-2001** | 1·03 (0·79-1·34)p=0·83 |  |  |
|  | **2005-2007 vs 1998-2001** | 0·87 (0·66-1·14)p=0·31 |  |  |
|  | **2008-2010 vs 1998-2001** | 0·81 (0·61-1·08)p=0·15 |  |  |
|  | **2011-2013 vs 1998-2001** | 0·75 (0·56-1·01)p=0·060 |  |  |
| **Type 1DM vs Controls** | **1998-2003** | 39·1 (24·3-63·0) | 0.46 |  |
|  | **2004-2008** | 28·4 (20·5-39·3) |  |  |
|  | **2009-2013** | 28·0 (20·9-37·7) |  |  |
| **Type 1DM cohort** | **2004-2008 vs 1998-2003** | 0·87 (0·72-1·06)p=0·17 |  |  |
|  | **2009-2013 vs 1998-2003** | 0·75 (0·61-0·94)p=0·011 |  |  |
| **Minor Amputations** |  |
| **Type 1DM vs Controls** | **1998-2001** | 51.7 (16.0-167.2) | 0.65 |  |
|  | **2002-2004** | 113.4 (35.8-359.4) |  |  |
|  | **2005-2007** | 50.8 (24.7-104.5) |  |  |
|  | **2008-2010** | 71.5 (31.4-162.9) |  |  |
|  | **2011-2013** | 44.4 (24.5-80.4) |  |  |
| **Type 1DM cohort** | **2002-2004 vs 1998-2001** | 1.29 (0.89-1.87)p=0.18 |  |  |
|  | **2005-2007 vs 1998-2001** | 1.12 (0.77-1.63)p=0.56 |  |  |
|  | **2008-2010 vs 1998-2001** | 0.96 (0.65-1.42)p=0.84 |  |  |
|  | **2011-2013 vs 1998-2001** | 0.96 (0.66-1.48)p=0.96 |  |  |
| **Type 1DM vs Controls** | **1998-2003** | 67.2 (29.3-154.1) | 0.62 |  |  |  |
|  | **2004-2008** | 84.5 (43.0-165.9) |  |  |  |  |
|  | **2009-2013** | 56.1 (34.0-92.4) |  |  |  |  |
| **Type 1DM cohort** | **2004-2008 vs 1998-2003** | 0.98 (0.76-1.27)p=0.89 |  |  |
|  | **2009-2013 vs 1998-2003** | 0.88 (0.66-1.17)p=0.37 |  |  |
| **Major Amputations** |  |
| **Type 1DM vs Controls** | **1998-2001** | 26.0 (11.8-57.3) | 0.85 |  |
|  | **2002-2004** | 17.9 (10.3-31.1) |  |  |
|  | **2005-2007** | 15.4 (9.4-25.3) |  |  |
|  | **2008-2010** | 16.5 (10.4-26.5) |  |  |
|  | **2011-2013** | 16.3 (10.4-25.6) |  |  |
| **Type 1DM cohort** | **2002-2004 vs 1998-2001** | 0.83 (0.59-1.18)p=0.29 |  |  |
|  | **2005-2007 vs 1998-2001** | 0.67 (0.47-0.96)p=0.028 |  |  |
|  | **2008-2010 vs 1998-2001** | 0.66 (0.46-0.94)p=0.023 |  |  |
|  | **2011-2013 vs 1998-2001** | 0.57 (0.39-0.84)p=0.0045 |  |  |
| **Type 1DM vs Controls** | **1998-2003** | 30.6 (17.5-53.5) | 0.18 |  |  |  |
|  | **2004-2008** | 16.6 (11.5-23.9) |  |  |  |  |
|  | **2009-2013** | 21.4 (14.8-30.8) |  |  |  |  |
| **Type 1DM cohort** | **2004-2008 vs 1998-2003** | 0.72 (0.55-0.92)p=0.010 |  |  |
|  | **2009-2013 vs 1998-2003** | 0.62 (0.46-0.82)p=0.0010 |  |  |

# *9 Supplement Table 5. All models - Hazard ratios for all amputations and 95% confidence intervals for Type 1DM versus the reference group, time-updated mean HbA1c categories, albuminuria categories and eGFR categories examined by Cox regression*

|  | **Hazard ratio (95% CI)****p-value** |
| --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** |
| **Amputation**  | **All** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** |
|  |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **Group All Type I diabetes with no prior amputation** | 53.6 (44.3 - 64.8)<.0001 | 39.3 (32.1 - 48.1)<.0001 | 51.7 (42.7 - 62.5)<.0001 | 67.9 (55.5 - 83.2)<.0001 | 89.3 (70.7 - 112.9)<.0001 | 31.5 (25.6 - 38.8)<.0001 | 38.0 (31.1 - 46.3)<.0001 | 45.7 (37.0 - 56.6)<.0001 | 55.1 (43.1 - 70.5)<.0001 |
|  |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **<=52 mmol/mol (<=6.9%)** | 19.5 (14.4 - 26.6)<.0001 | 13.0 (9.5 - 17.9)<.0001 | 17.8 (13.0 - 24.2)<.0001 | 24.2 (17.7 - 33.1)<.0001 | 33.0 (23.6 - 45.9)<.0001 | 11.8 (8.5 - 16.3)<.0001 | 14.8 (10.8 - 20.2)<.0001 | 18.5 (13.4 - 25.5)<.0001 | 23.2 (16.4 - 32.6)<.0001 |
| **53-62 mmol/mol (7.0-7.8%)** | 32.8 (26.2 - 41.1)<.0001 | 21.8 (17.1 - 27.7)<.0001 | 29.7 (23.7 - 37.3)<.0001 | 40.5 (32.1 - 51.1)<.0001 | 55.1 (42.6 - 71.3)<.0001 | 18.6 (14.6 - 23.7)<.0001 | 23.3 (18.5 - 29.4)<.0001 | 29.2 (22.9 - 37.1)<.0001 | 36.5 (28.0 - 47.8)<.0001 |
| **63-72 mmol/mol (7.9-8.7%)** | 50.0 (40.5 - 61.9)<.0001 | 34.0 (27.1 - 42.6)<.0001 | 46.3 (37.4 - 57.3)<.0001 | 63.1 (50.6 - 78.7)<.0001 | 86.0 (67.1 - 110.1)<.0001 | 28.1 (22.3 - 35.4)<.0001 | 35.2 (28.3 - 43.8)<.0001 | 44.1 (35.1 - 55.5)<.0001 | 55.3 (42.6 - 71.6)<.0001 |
| **73-82 mmol/mol (8.8-9.6%)** | 92.8 (74.5 - 115.7)<.0001 | 64.2 (50.9 - 80.8)<.0001 | 87.4 (70.2 - 108.9)<.0001 | 119.1 (94.8 - 149.7)<.0001 | 162.3 (125.7 - 209.5)<.0001 | 49.1 (38.8 - 62.1)<.0001 | 61.5 (49.0 - 77.1)<.0001 | 77.0 (60.7 - 97.7)<.0001 | 96.5 (73.8 - 126.1)<.0001 |
| **>=83 mmol/mol (>=9.7%)** | 232.4 (185.2 - 291.6)<.0001 | 161.5 (127.5 - 204.4)<.0001 | 220.0 (175.8 - 275.4)<.0001 | 299.8 (237.4 - 378.5)<.0001 | 408.5 (315.1 - 529.6)<.0001 | 116.9 (91.8 - 148.9)<.0001 | 146.5 (116.0 - 185.0)<.0001 | 183.5 (143.6 - 234.5)<.0001 | 229.9 (174.6 - 302.6)<.0001 |
|  |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **Normoalbuminuria** | 27.0 (21.8 - 33.4)<.0001 | 23.1 (18.5 - 29.0)<.0001 | 27.0 (21.8 - 33.5)<.0001 | 31.5 (25.1 - 39.6)<.0001 | 36.7 (28.2 - 47.8)<.0001 | 20.6 (16.4 - 25.9)<.0001 | 23.1 (18.5 - 28.7)<.0001 | 25.8 (20.4 - 32.7)<.0001 | 28.9 (22.0 - 37.9)<.0001 |
| **Microalbuminuria** | 72.5 (57.8 - 91.0)<.0001 | 59.8 (46.8 - 76.5)<.0001 | 69.8 (55.5 - 87.8)<.0001 | 81.4 (64.3 - 103.1)<.0001 | 95.0 (72.9 - 123.8)<.0001 | 48.0 (37.4 - 61.7)<.0001 | 53.7 (42.4 - 68.0)<.0001 | 60.1 (47.0 - 76.8)<.0001 | 67.2 (51.0 - 88.6)<.0001 |
| **Macroalbuminuria** | 148.5 (118.7 - 185.7)<.0001 | 122.7 (96.4 - 156.2)<.0001 | 143.2 (114.3 - 179.3)<.0001 | 167.0 (132.3 - 210.7)<.0001 | 194.8 (149.9 - 253.1)<.0001 | 89.2 (69.5 - 114.5)<.0001 | 99.8 (78.9 - 126.3)<.0001 | 111.6 (87.4 - 142.6)<.0001 | 124.9 (94.8 - 164.5)<.0001 |
| **CKD stage 5** | 505.1 (397.6 - 641.6)<.0001 | 411.4 (318.0 - 532.3)<.0001 | 479.9 (377.4 - 610.3)<.0001 | 559.9 (438.0 - 715.6)<.0001 | 653.0 (497.7 - 856.9)<.0001 | 273.7 (209.6 - 357.3)<.0001 | 306.1 (237.7 - 394.2)<.0001 | 342.4 (263.7 - 444.5)<.0001 | 383.0 (286.7 - 511.7)<.0001 |
|  |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **CKD stage 1 (eGFR >=90)** | 27.3 (21.4 - 34.8)<.0001 | 24.2 (18.8 - 31.0)<.0001 | 27.9 (21.9 - 35.5)<.0001 | 32.2 (24.9 - 41.7)<.0001 | 37.3 (27.8 - 49.9)<.0001 | 21.6 (16.8 - 27.7)<.0001 | 24.1 (18.8 - 30.8)<.0001 | 26.8 (20.6 - 34.9)<.0001 | 29.9 (22.2 - 40.4)<.0001 |
| **CKD stage 2 (eGFR 60-89)** | 37.6 (30.3 - 46.7)<.0001 | 32.3 (25.7 - 40.7)<.0001 | 37.4 (30.1 - 46.4)<.0001 | 43.2 (34.3 - 54.4)<.0001 | 49.9 (38.3 - 65.0)<.0001 | 29.9 (22.2 - 40.4)<.0001 | 31.3 (25.0 - 39.1)<.0001 | 34.9 (27.5 - 44.2)<.0001 | 38.9 (29.6 - 51.2)<.0001 |
| **CKD stage 3 (eGFR 30-59)** | 87.2 (69.3 - 109.8)<.0001 | 72.0 (56.0 - 92.7)<.0001 | 83.2 (65.9 - 105.1)<.0001 | 96.2 (75.7 - 122.1)<.0001 | 111.1 (85.1 - 145.1)<.0001 | 53.5 (41.3 - 69.4)<.0001 | 59.7 (46.8 - 76.2)<.0001 | 66.6 (51.9 - 85.6)<.0001 | 74.3 (56.2 - 98.2)<.0001 |
| **CKD stage 4 (eGFR 15-29)** | 152.3 (109.5 - 211.7)<.0001 | 126.3 (89.5 - 178.1)<.0001 | 145.9 (104.8 - 203.2)<.0001 | 168.6 (120.6 - 235.8)<.0001 | 194.8 (136.5 - 278.1)<.0001 | 84.5 (59.4 - 120.1)<.0001 | 94.3 (67.0 - 132.6)<.0001 | 105.1 (74.3 - 148.8)<.0001 | 117.3 (81.0 - 169.7)<.0001 |
| **CKD stage 5 (eGFR <15, dialysis or transplantation)** | 496.3 (390.6 - 630.5)<.0001 | 411.9 (318.4 - 532.7)<.0001 | 475.9 (374.3 - 605.1)<.0001 | 549.9 (429.9 - 703.4)<.0001 | 635.4 (483.1 - 835.6)<.0001 | 267.9 (204.9 - 350.1)<.0001 | 298.8 (231.8 - 385.1)<.0001 | 333.3 (256.3 - 433.2)<.0001 | 371.7 (277.6 - 497.7)<.0001 |
| Model 1: Adjusted for time-updated age and sex.Model 2: Adjusted for time-updated age, sex and time-updated diabetes duration centered at 30, 40, 50 and 60 years.Model 3: Adjusted for time-updated age, sex, born in Sweden, maximum education level, baseline comorbidities and time-updated diabetes duration centered at 30, 40, 50 and 60 years. |

# *10 Supplement Table 6. All models Adjusted hazard ratios for all Amputation and 95% confidence intervals for time-updated mean HbA1c categories and Normoalbuminuria versus the reference group examined by Cox regression*

|  | **Hazard ratio (95% CI)****p-value** |
| --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** |
| **Amputation** | **All** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** |
| **Time updated mean HbA1c categories and Albuminuria** |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **<=52 mmol/mol (<=6.9%) – Normoalbuminuria** | 9.3 (5.7 - 15.1)<.0001 | 7.1 (4.3 - 11.6)<.0001 | 9.0 (5.6 - 14.7)<.0001 | 11.5 (7.1 - 18.8)<.0001 | 14.7 (8.9 - 24.4)<.0001 | 6.2 (3.7 - 10.4)<.0001 | 7.5 (4.5 - 12.4)<.0001 | 9.0 (5.3 - 15.0)<.0001 | 10.8 (6.3 - 18.3)<.0001 |
| **53-62 mmol/mol (7.0-7.8%) – Normoalbuminuria** | 19.0 (14.2 - 25.5)<.0001 | 14.3 (10.6 - 19.4)<.0001 | 18.3 (13.7 - 24.5)<.0001 | 23.4 (17.3 - 31.5)<.0001 | 29.8 (21.6 - 41.3)<.0001 | 13.0 (9.6 - 17.7)<.0001 | 15.7 (11.7 - 21.1)<.0001 | 18.8 (13.9 - 25.5)<.0001 | 22.6 (16.2 - 31.5)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) – Normoalbuminuria** | 28.7 (22.0 - 37.5)<.0001 | 22.0 (16.6 - 29.0)<.0001 | 28.1 (21.5 - 36.7)<.0001 | 35.9 (27.2 - 47.3)<.0001 | 45.8 (33.7 - 62.2)<.0001 | 19.7 (14.9 - 26.1)<.0001 | 23.7 (18.0 - 31.1)<.0001 | 28.4 (21.4 - 37.7)<.0001 | 34.1 (24.9 - 46.7)<.0001 |
| **73-82 mmol/mol (8.8-9.6%) – Normoalbuminuria** | 40.2 (28.8 - 56.2)<.0001 | 31.3 (22.2 - 44.0)<.0001 | 39.9 (28.6 - 55.8)<.0001 | 51.0 (36.2 - 71.9)<.0001 | 65.2 (45.2 - 94.1)<.0001 | 26.4 (18.7 - 37.3)<.0001 | 31.8 (22.7 - 44.5)<.0001 | 38.1 (26.9 - 54.0)<.0001 | 45.8 (31.5 - 66.5)<.0001 |
| **>=83 mmol/mol (>=9.7%) – Normoalbuminuria** | 160.7 (116.1 - 222.3)<.0001 | 129.3 (93.2 - 179.5)<.0001 | 165.4 (119.8 - 228.2)<.0001 | 211.1 (151.2 - 294.8)<.0001 | 269.7 (188.0 - 386.9)<.0001 | 106.7 (76.5 - 148.8)<.0001 | 128.1 (92.3 - 178.0)<.0001 | 153.9 (109.4 - 216.5)<.0001 | 184.8 (127.6 - 267.5)<.0001 |
| **<=52 mmol/mol (<=6.9%) - Not Normoalbuminuria** | 58.2 (39.1 - 86.5)<.0001 | 40.0 (26.4 - 60.5)<.0001 | 51.1 (34.2 - 76.3)<.0001 | 65.3 (43.7 - 97.5)<.0001 | 83.4 (55.1 - 126.3)<.0001 | 32.6 (21.5 - 49.4)<.0001 | 39.2 (26.1 - 58.7)<.0001 | 47.0 (31.3 - 70.6)<.0001 | 56.5 (37.0 - 86.2)<.0001 |
| **53-62 mmol/mol (7.0-7.8%)- Not Normoalbuminuria** | 71.5 (54.7 - 93.4)<.0001 | 49.5 (37.0 - 66.1)<.0001 | 63.2 (48.2 - 82.9)<.0001 | 80.8 (61.4 - 106.1)<.0001 | 103.1 (76.9 - 138.4)<.0001 | 38.7 (28.8 - 52.0)<.0001 | 46.5 (35.2 - 61.5)<.0001 | 55.8 (42.1 - 74.1)<.0001 | 67.0 (49.4 - 91.1)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) - Not Normoalbuminuria** | 106.6 (84.2 - 134.9)<.0001 | 77.4 (60.0 - 99.8)<.0001 | 98.9 (78.0 - 125.5)<.0001 | 126.4 (99.0 - 161.3)<.0001 | 161.4 (123.1 - 211.8)<.0001 | 60.2 (46.5 - 78.1)<.0001 | 72.3 (56.6 - 92.4)<.0001 | 86.8 (67.4 - 111.9)<.0001 | 104.3 (78.6 - 138.4)<.0001 |
| **73-82 mmol/mol (8.8-9.6% ) - Not Normoalbuminuria** | 173.7 (136.6 - 220.9)<.0001 | 129.0 (99.9 - 166.5)<.0001 | 164.8 (129.5 - 209.7)<.0001 | 210.6 (164.1 - 270.2)<.0001 | 268.9 (203.7 - 355.1)<.0001 | 96.6 (74.4 - 125.4)<.0001 | 116.0 (90.4 - 148.8)<.0001 | 139.3 (107.4 - 180.7)<.0001 | 167.2 (125.0 - 223.7)<.0001 |
| **>=83 mmol/mol (>=9.7%) - Not Normoalbuminuria** | 385.0 (299.8 - 494.3)<.0001 | 292.3 (225.3 - 379.3)<.0001 | 373.5 (291.4 - 478.8)<.0001 | 477.3 (368.7 - 617.8)<.0001 | 609.6 (457.2 - 812.6)<.0001 | 207.3 (158.5 - 271.2)<.0001 | 249.0 (192.3 - 322.4)<.0001 | 299.0 (228.3 - 391.6)<.0001 | 359.0 (265.8 - 485.0)<.0001 |
| Model 1: Adjusted for time-updated age and sex.Model 2: Adjusted for time-updated age, sex and time-updated diabetes duration centered at 30, 40, 50 and 60 years.Model 3: Adjusted for time-updated age, sex, born in Sweden, maximum education level, baseline comorbidities and time-updated diabetes duration centered at 30, 40, 50 and 60 years. |

# *Supplement Table 7*. *All models Adjusted hazard ratio of all amputations for persons with type 1DM versus controls and 95% confidence intervals for time-updated mean HbA1c categories and coexisting normoalbuminuria and eGFR>60 ml/min.*

|  | **Hazard ratio (95% CI)****p-value** |
| --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** |
| **Amputation** | **All** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** |
| **Time updated mean HbA1c categories and eGFR** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **<=52 mmol/mol (<=6.9%) - eGFR>=60** | 11.1 (7.1 - 17.2)<.0001 | 8.9 (5.7 - 13.8)<.0001 | 11.0 (7.1 - 17.0)<.0001 | 13.6 (8.7 - 21.2)<.0001 | 16.8 (10.6 - 26.7)<.0001 | 7.8 (4.9 - 12.4)<.0001 | 9.1 (5.8 - 14.5)<.0001 | 10.8 (6.8 - 17.1)<.0001 | 12.7 (7.8 - 20.6)<.0001 |
| **53-62 mmol/mol (7.0-7.8%) - eGFR>=60** | 19.4 (14.7 - 25.6)<.0001 | 15.3 (11.4 - 20.4)<.0001 | 18.9 (14.3 - 25.0)<.0001 | 23.4 (17.5 - 31.2)<.0001 | 29.0 (21.1 - 39.7)<.0001 | 13.5 (10.1 - 18.1)<.0001 | 15.9 (12.0 - 21.1)<.0001 | 18.7 (13.9 - 25.1)<.0001 | 22.0 (15.9 - 30.4)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) - eGFR>=60** | 33.8 (26.4 - 43.2)<.0001 | 27.0 (20.9 - 34.9)<.0001 | 33.4 (26.1 - 42.7)<.0001 | 41.4 (32.0 - 53.5)<.0001 | 51.2 (38.4 - 68.4)<.0001 | 24.1 (18.6 - 31.2)<.0001 | 28.3 (22.1 - 36.3)<.0001 | 33.4 (25.7 - 43.3)<.0001 | 39.2 (29.2 - 52.7)<.0001 |
| **73-82 mmol/mol (8.8-9.6%) - eGFR>=60** | 53.5 (40.7 - 70.5)<.0001 | 43.4 (32.7 - 57.6)<.0001 | 53.7 (40.8 - 70.7)<.0001 | 66.5 (50.0 - 88.5)<.0001 | 82.4 (60.1 - 113.0)<.0001 | 36.4 (27.3 - 48.5)<.0001 | 42.8 (32.4 - 56.6)<.0001 | 50.4 (37.7 - 67.5)<.0001 | 59.3 (42.9 - 82.0)<.0001 |
| **>=83 mmol/mol (>=9.7%) - eGFR>=60** | 170.5 (128.5 - 226.3)<.0001 | 142.9 (107.4 - 190.2)<.0001 | 177.0 (133.7 - 234.2)<.0001 | 219.0 (163.1 - 294.2)<.0001 | 271.3 (195.7 - 376.2)<.0001 | 117.6 (87.9 - 157.3)<.0001 | 138.4 (104.0 - 184.3)<.0001 | 162.9 (120.5 - 220.3)<.0001 | 191.6 (137.1 - 267.8)<.0001 |
| **<=52 mmol/mol (<=6.9%) - eGFR<60** | 56.1 (36.6 - 86.0)<.0001 | 40.3 (25.9 - 62.9)<.0001 | 49.9 (32.4 - 76.8)<.0001 | 61.8 (40.1 - 95.1)<.0001 | 76.5 (49.1 - 119.4)<.0001 | 32.7 (20.9 - 51.1)<.0001 | 38.5 (24.9 - 59.5)<.0001 | 45.3 (29.3 - 70.1)<.0001 | 53.3 (33.9 - 83.7)<.0001 |
| **53-62 mmol/mol (7.0-7.8%) - eGFR<60** | 78.0 (58.6 - 103.8)<.0001 | 56.8 (41.7 - 77.3)<.0001 | 70.3 (52.6 - 94.0)<.0001 | 87.0 (65.0 - 116.5)<.0001 | 107.8 (78.9 - 147.3)<.0001 | 43.4 (31.8 - 59.4)<.0001 | 51.1 (38.0 - 68.8)<.0001 | 60.2 (44.6 - 81.3)<.0001 | 70.8 (51.3 - 97.7)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) - eGFR<60** | 123.6 (95.8 - 159.6)<.0001 | 92.5 (70.2 - 121.9)<.0001 | 114.6 (88.5 - 148.5)<.0001 | 141.8 (109.0 - 184.6)<.0001 | 175.7 (131.7 - 234.4)<.0001 | 67.2 (50.6 - 89.2)<.0001 | 79.1 (60.5 - 103.4)<.0001 | 93.1 (70.7 - 122.5)<.0001 | 109.5 (81.0 - 148.0)<.0001 |
| **73-82 mmol/mol (8.8-9.6%) - eGFR<60** | 220.9 (169.4 - 288.1)<.0001 | 167.5 (126.3 - 222.2)<.0001 | 207.5 (158.8 - 271.1)<.0001 | 256.8 (195.4 - 337.4)<.0001 | 318.1 (236.0 - 428.7)<.0001 | 117.2 (87.5 - 157.0)<.0001 | 137.9 (104.4 - 182.3)<.0001 | 162.3 (122.0 - 216.0)<.0001 | 190.9 (139.8 - 260.9)<.0001 |
| **>=83 mmol/mol (>=9.7%) - eGFR<60** | 462.1 (350.2 - 609.8)<.0001 | 355.4 (265.6 - 475.6)<.0001 | 440.1 (333.4 - 581.0)<.0001 | 544.7 (409.9 - 723.8)<.0001 | 674.8 (495.1 - 919.7)<.0001 | 248.5 (184.1 - 335.5)<.0001 | 292.5 (219.3 - 390.1)<.0001 | 344.3 (256.2 - 462.9)<.0001 | 405.0 (293.4 - 559.1)<.0001 |
| Model 1: Adjusted for time-updated age and sex.Model 2: Adjusted for time-updated age, sex and time-updated diabetes duration centered at 30, 40, 50 and 60 years.Model 3: Adjusted for time-updated age, sex, born in Sweden, maximum education level, baseline comorbidities and time-updated diabetes duration centered at 30, 40, 50 and 60 years. |

# *Supplement Table 8. All models - Hazard ratios for minor amputations and 95% confidence intervals for people with type 1DM versus controls, time-updated mean HbA1c categories, albuminuria categories and eGFR categories examined by Cox regression*

|  | **Hazard ratio (95% CI)****p-value** |
| --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** |
| **Amputation below ankle** | **All** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** |
| **Overall, n events=689, data used = 100.0%** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **Group All Type I diabetes with no prior amputation** | 112.3 (79.2 - 159.4)<.0001 | 90.3 (63.2 - 129.2)<.0001 | 114.2 (80.5 - 162.2)<.0001 | 144.3 (99.9 - 208.3)<.0001 | 182.4 (121.7 - 273.4)<.0001 | 75.7 (52.6 - 109.0)<.0001 | 86.3 (60.2 - 123.8)<.0001 | 98.4 (67.3 - 143.9)<.0001 | 112.3 (73.7 - 171.0)<.0001 |
| **Time updated mean HbA1c categories, n events=686, data used = 99.9%** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **<=52 mmol/mol (<=6.9%)** | 39.1 (24.3 - 62.9)<.0001 | 29.5 (18.2 - 47.9)<.0001 | 38.2 (23.7 - 61.5)<.0001 | 49.4 (30.4 - 80.4)<.0001 | 64.0 (38.4 - 106.8)<.0001 | 27.3 (16.7 - 44.7)<.0001 | 32.0 (19.7 - 52.0)<.0001 | 37.4 (22.8 - 61.5)<.0001 | 43.7 (25.9 - 74.0)<.0001 |
| **53-62 mmol/mol (7.0-7.8%)** | 67.7 (46.1 - 99.2)<.0001 | 50.4 (34.0 - 74.9)<.0001 | 65.3 (44.5 - 95.8)<.0001 | 84.5 (56.9 - 125.4)<.0001 | 109.3 (71.5 - 167.3)<.0001 | 45.0 (30.2 - 67.2)<.0001 | 52.7 (35.6 - 77.9)<.0001 | 61.6 (41.1 - 92.4)<.0001 | 72.0 (46.5 - 111.7)<.0001 |
| **63-72 mmol/mol (7.9-8.7%)** | 100.6 (69.5 - 145.8)<.0001 | 76.2 (52.0 - 111.5)<.0001 | 98.6 (68.0 - 142.8)<.0001 | 127.6 (87.0 - 187.1)<.0001 | 165.1 (108.9 - 250.3)<.0001 | 65.6 (44.6 - 96.7)<.0001 | 76.8 (52.5 - 112.2)<.0001 | 89.8 (60.5 - 133.2)<.0001 | 105.0 (68.3 - 161.5)<.0001 |
| **73-82 mmol/mol (8.8-9.6%)** | 197.5 (135.6 - 287.5)<.0001 | 150.9 (102.7 - 221.6)<.0001 | 195.3 (134.2 - 284.1)<.0001 | 252.7 (171.5 - 372.6)<.0001 | 327.1 (214.6 - 498.4)<.0001 | 123.4 (83.4 - 182.6)<.0001 | 144.4 (98.3 - 212.1)<.0001 | 168.9 (113.1 - 252.0)<.0001 | 197.5 (127.6 - 305.6)<.0001 |
| **>=83 mmol/mol (>=9.7%)** | 504.1 (344.4 - 738.0)<.0001 | 386.7 (262.4 - 569.9)<.0001 | 500.4 (342.6 - 730.9)<.0001 | 647.6 (437.7 - 958.3)<.0001 | 838.1 (548.0 - 1281.9)<.0001 | 299.7 (201.5 - 445.6)<.0001 | 350.5 (237.2 - 517.8)<.0001 | 409.9 (273.0 - 615.4)<.0001 | 479.4 (308.0 - 746.3)<.0001 |
| **Time updated albuminuria categories, n events=589, data used = 98.6%** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **Normoalbuminuria** | 57.7 (39.8 - 83.6)<.0001 | 53.3 (36.5 - 77.7)<.0001 | 58.9 (40.6 - 85.4)<.0001 | 65.3 (44.1 - 96.6)<.0001 | 72.2 (46.7 - 111.7)<.0001 | 48.6 (33.1 - 71.4)<.0001 | 50.4 (34.5 - 73.7)<.0001 | 52.4 (35.1 - 78.2)<.0001 | 54.3 (34.8 - 85.0)<.0001 |
| **Microalbuminuria** | 170.5 (116.5 - 249.5)<.0001 | 153.8 (103.7 - 228.1)<.0001 | 170.1 (116.1 - 249.1)<.0001 | 188.4 (126.8 - 280.0)<.0001 | 208.6 (135.2 - 321.9)<.0001 | 130.6 (87.5 - 195.1)<.0001 | 135.5 (91.7 - 200.2)<.0001 | 140.6 (93.6 - 211.2)<.0001 | 145.9 (93.3 - 228.1)<.0001 |
| **Macroalbuminuria** | 301.9 (206.2 - 442.2)<.0001 | 271.6 (183.0 - 403.2)<.0001 | 300.4 (205.0 - 440.1)<.0001 | 332.8 (224.1 - 494.3)<.0001 | 368.4 (239.0 - 567.9)<.0001 | 209.2 (139.4 - 314.1)<.0001 | 217.0 (146.2 - 322.0)<.0001 | 225.2 (149.5 - 339.4)<.0001 | 233.7 (149.2 - 366.2)<.0001 |
| **CKD stage 5** | 974.7 (655.5 - 1449.2)<.0001 | 868.5 (575.3 - 1311.0)<.0001 | 960.5 (645.8 - 1428.5)<.0001 | 1064.3 (707.9 - 1600.0)<.0001 | 1178.0 (757.2 - 1832.5)<.0001 | 623.7 (408.4 - 952.6)<.0001 | 646.8 (428.6 - 975.9)<.0001 | 671.5 (439.1 - 1026.8)<.0001 | 696.7 (439.2 - 1105.2)<.0001 |
| **Time updated eGFR categories, n events=571, data used = 99.0%** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **CKD stage 1 (eGFR >=90)** | 53.0 (35.6 - 78.8)<.0001 | 50.1 (33.5 - 74.8)<.0001 | 54.6 (36.7 - 81.3)<.0001 | 59.6 (39.1 - 90.8)<.0001 | 65.0 (40.8 - 103.6)<.0001 | 45.9 (30.6 - 69.0)<.0001 | 47.2 (31.5 - 70.7)<.0001 | 48.5 (31.6 - 74.5)<.0001 | 49.8 (31.0 - 80.2)<.0001 |
| **CKD stage 2 (eGFR 60-89)** | 89.6 (61.8 - 129.8)<.0001 | 83.7 (57.3 - 122.3)<.0001 | 91.3 (62.9 - 132.6)<.0001 | 99.6 (67.2 - 147.7)<.0001 | 108.6 (70.1 - 168.4)<.0001 | 75.3 (51.2 - 110.8)<.0001 | 77.3 (52.9 - 113.2)<.0001 | 79.5 (53.1 - 118.9)<.0001 | 81.7 (52.1 - 128.0)<.0001 |
| **CKD stage 3 (eGFR 30-59)** | 221.6 (150.6 - 326.2)<.0001 | 202.8 (135.8 - 302.9)<.0001 | 221.2 (150.0 - 326.2)<.0001 | 241.3 (161.4 - 360.8)<.0001 | 263.1 (169.4 - 408.7)<.0001 | 160.5 (106.4 - 242.1)<.0001 | 164.9 (110.6 - 245.9)<.0001 | 169.5 (111.9 - 256.7)<.0001 | 174.2 (110.6 - 274.5)<.0001 |
| **CKD stage 4 (eGFR 15-29)** | 287.0 (171.5 - 480.5)<.0001 | 262.8 (155.4 - 444.5)<.0001 | 286.7 (171.2 - 480.3)<.0001 | 312.8 (184.7 - 529.5)<.0001 | 341.1 (195.6 - 594.9)<.0001 | 190.8 (111.7 - 325.9)<.0001 | 196.0 (115.7 - 332.2)<.0001 | 201.5 (117.4 - 345.7)<.0001 | 207.2 (117.0 - 366.8)<.0001 |
| **CKD stage 5 (eGFR <15, dialysis or transplantation)** | 958.2 (644.4 - 1424.9)<.0001 | 874.6 (580.3 - 1318.3)<.0001 | 953.9 (641.2 - 1418.9)<.0001 | 1040.4 (690.5 - 1567.7)<.0001 | 1134.7 (726.0 - 1773.4)<.0001 | 623.1 (408.2 - 950.9)<.0001 | 640.1 (424.0 - 966.4)<.0001 | 658.0 (429.3 - 1008.5)<.0001 | 676.2 (424.5 - 1077.1)<.0001 |
| Model 1: Adjusted for time-updated age and sex.Model 2: Adjusted for time-updated age, sex and time-updated diabetes duration centered at 30, 40, 50 and 60 years.Model 3: Adjusted for time-updated age, sex, born in Sweden, maximum education level, baseline comorbidities and time-updated diabetes duration centered at 30, 40, 50 and 60 years. |

# *Supplement Table 9. All models - Hazard ratios for major amputations and 95% confidence intervals for people with Type 1DM versus controls, time-updated mean HbA1c categories, albuminuria categories and eGFR categories examined by Cox regression*

|  | **Hazard ratio (95% CI)****p-value** |
| --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** |
| **Amputation above ankle** | **All** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** |
| **Overall, n events=725, data used = 100.0%** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **Group All Type I diabetes with no prior amputation** | 42.6 (34.0 - 53.2)<.0001 | 27.8 (21.7 - 35.6)<.0001 | 38.4 (30.6 - 48.1)<.0001 | 53.1 (41.9 - 67.2)<.0001 | 73.3 (55.8 - 96.3)<.0001 | 21.4 (16.6 - 27.5)<.0001 | 27.3 (21.5 - 34.5)<.0001 | 34.8 (27.1 - 44.7)<.0001 | 44.4 (33.2 - 59.4)<.0001 |
| **Time updated mean HbA1c categories, n events=716, data used = 99.9%** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **<=52 mmol/mol (<=6.9%)** | 15.6 (10.6 - 22.9)<.0001 | 9.0 (6.0 - 13.5)<.0001 | 13.0 (8.8 - 19.1)<.0001 | 18.6 (12.6 - 27.5)<.0001 | 26.7 (17.7 - 40.3)<.0001 | 8.1 (5.3 - 12.2)<.0001 | 10.8 (7.3 - 16.0)<.0001 | 14.4 (9.7 - 21.5)<.0001 | 19.3 (12.6 - 29.4)<.0001 |
| **53-62 mmol/mol (7.0-7.8%)** | 28.0 (21.4 - 36.6)<.0001 | 16.3 (12.1 - 21.9)<.0001 | 23.4 (17.8 - 30.7)<.0001 | 33.6 (25.5 - 44.3)<.0001 | 48.2 (35.6 - 65.4)<.0001 | 13.2 (9.8 - 17.8)<.0001 | 17.6 (13.3 - 23.3)<.0001 | 23.5 (17.7 - 31.4)<.0001 | 31.5 (22.8 - 43.3)<.0001 |
| **63-72 mmol/mol (7.9-8.7%)** | 39.3 (30.5 - 50.8)<.0001 | 23.6 (17.9 - 31.2)<.0001 | 33.9 (26.2 - 43.8)<.0001 | 48.6 (37.4 - 63.2)<.0001 | 69.8 (52.0 - 93.8)<.0001 | 18.6 (14.0 - 24.8)<.0001 | 24.9 (19.1 - 32.5)<.0001 | 33.3 (25.3 - 43.8)<.0001 | 44.5 (32.6 - 60.7)<.0001 |
| **73-82 mmol/mol (8.8-9.6%)** | 69.8 (53.3 - 91.3)<.0001 | 42.8 (32.1 - 57.2)<.0001 | 61.5 (46.9 - 80.4)<.0001 | 88.2 (66.9 - 116.3)<.0001 | 126.6 (93.0 - 172.5)<.0001 | 30.6 (22.8 - 41.1)<.0001 | 40.9 (30.9 - 54.0)<.0001 | 54.6 (40.9 - 73.0)<.0001 | 73.0 (52.7 - 101.2)<.0001 |
| **>=83 mmol/mol (>=9.7%)** | 190.1 (144.3 - 250.5)<.0001 | 117.0 (87.3 - 156.8)<.0001 | 167.9 (127.8 - 220.6)<.0001 | 241.0 (182.1 - 318.8)<.0001 | 346.0 (253.4 - 472.5)<.0001 | 78.4 (58.1 - 105.9)<.0001 | 104.8 (78.8 - 139.4)<.0001 | 140.0 (104.0 - 188.5)<.0001 | 187.1 (134.1 - 261.1)<.0001 |
| **Time updated albuminuria categories, n events=608, data used = 98.6%** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **Normoalbuminuria** | 20.6 (15.9 - 26.7)<.0001 | 15.7 (11.8 - 20.8)<.0001 | 19.6 (15.1 - 25.4)<.0001 | 24.4 (18.6 - 32.0)<.0001 | 30.5 (22.3 - 41.6)<.0001 | 13.6 (10.2 - 18.1)<.0001 | 16.5 (12.6 - 21.6)<.0001 | 20.1 (15.2 - 26.6)<.0001 | 24.4 (17.6 - 33.7)<.0001 |
| **Microalbuminuria** | 48.1 (36.2 - 63.8)<.0001 | 34.7 (25.3 - 47.6)<.0001 | 43.3 (32.4 - 57.8)<.0001 | 54.0 (40.4 - 72.2)<.0001 | 67.4 (48.8 - 93.1)<.0001 | 26.2 (19.0 - 36.2)<.0001 | 31.8 (23.6 - 42.9)<.0001 | 38.7 (28.5 - 52.4)<.0001 | 47.0 (33.5 - 65.9)<.0001 |
| **Macroalbuminuria** | 118.5 (90.6 - 155.1)<.0001 | 86.1 (63.8 - 116.4)<.0001 | 107.5 (81.8 - 141.2)<.0001 | 134.0 (101.7 - 176.7)<.0001 | 167.3 (122.6 - 228.3)<.0001 | 59.3 (43.4 - 80.9)<.0001 | 72.0 (54.1 - 95.9)<.0001 | 87.6 (65.3 - 117.4)<.0001 | 106.4 (76.5 - 148.0)<.0001 |
| **CKD stage 5** | 427.5 (321.4 - 568.5)<.0001 | 305.7 (222.7 - 419.6)<.0001 | 381.4 (285.9 - 508.8)<.0001 | 475.6 (356.0 - 635.3)<.0001 | 593.8 (430.9 - 818.4)<.0001 | 194.1 (139.8 - 269.5)<.0001 | 235.9 (173.9 - 320.0)<.0001 | 286.7 (210.1 - 391.4)<.0001 | 348.5 (246.7 - 492.3)<.0001 |
| **Time updated eGFR categories, n events=580, data used = 99.0%** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **CKD stage 1 (eGFR >=90)** | 22.8 (16.8 - 30.8)<.0001 | 17.8 (13.0 - 24.4)<.0001 | 22.2 (16.5 - 30.0)<.0001 | 27.8 (20.3 - 38.0)<.0001 | 34.8 (24.4 - 49.6)<.0001 | 15.4 (11.2 - 21.2)<.0001 | 19.0 (14.0 - 25.7)<.0001 | 23.3 (16.9 - 32.1)<.0001 | 28.6 (19.9 - 41.1)<.0001 |
| **CKD stage 2 (eGFR 60-89)** | 26.9 (20.6 - 35.0)<.0001 | 20.0 (14.9 - 26.9)<.0001 | 25.1 (19.2 - 32.8)<.0001 | 31.3 (23.8 - 41.3)<.0001 | 39.2 (28.6 - 53.8)<.0001 | 16.7 (12.4 - 22.6)<.0001 | 20.6 (15.6 - 27.1)<.0001 | 25.2 (19.0 - 33.6)<.0001 | 31.0 (22.4 - 43.0)<.0001 |
| **CKD stage 3 (eGFR 30-59)** | 55.0 (41.5 - 72.9)<.0001 | 38.4 (27.8 - 53.2)<.0001 | 48.1 (35.9 - 64.4)<.0001 | 60.1 (45.0 - 80.4)<.0001 | 75.2 (54.6 - 103.5)<.0001 | 26.7 (19.1 - 37.3)<.0001 | 32.8 (24.1 - 44.5)<.0001 | 40.2 (29.6 - 54.7)<.0001 | 49.5 (35.3 - 69.3)<.0001 |
| **CKD stage 4 (eGFR 15-29)** | 122.0 (81.7 - 182.3)<.0001 | 86.1 (56.1 - 132.3)<.0001 | 107.7 (71.8 - 161.7)<.0001 | 134.7 (89.7 - 202.1)<.0001 | 168.5 (109.8 - 258.7)<.0001 | 55.0 (35.5 - 85.4)<.0001 | 67.6 (44.5 - 102.8)<.0001 | 83.1 (54.5 - 126.6)<.0001 | 102.1 (65.3 - 159.6)<.0001 |
| **CKD stage 5 (eGFR <15, dialysis or transplantation)** | 421.5 (316.9 - 560.6)<.0001 | 300.3 (218.4 - 412.9)<.0001 | 375.6 (281.5 - 501.1)<.0001 | 469.5 (351.4 - 627.2)<.0001 | 587.5 (425.8 - 810.6)<.0001 | 185.3 (132.9 - 258.5)<.0001 | 227.7 (167.5 - 309.6)<.0001 | 279.6 (204.6 - 382.2)<.0001 | 343.7 (242.9 - 486.3)<.0001 |
| Model 1: Adjusted for time-updated age and sex.Model 2: Adjusted for time-updated age, sex and time-updated diabetes duration centered at 30, 40, 50 and 60 years.Model 3: Adjusted for time-updated age, sex, born in Sweden, maximum education level, baseline comorbidities and time-updated diabetes duration centered at 30, 40, 50 and 60 years. |

# *Supplement Table 10. Adjusted hazard ratios for minor amputation and 95% confidence intervals for time-updated mean HbA1c categories and Normoalbuminuria versus controls examined by Cox regression*

|  | **Hazard ratio (95% CI)****p-value** |
| --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** |
| **Amputation below ankle** | **All** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** |
| **Time updated mean HbA1c categories and Albuminuria** |  |  |  |  |  |  |  |  |  |
|  | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **<=52 mmol/mol (<=6.9%) – Normoalbuminuria** | 15.4 (7.4 - 32.1)<.0001 | 13.0 (6.2 - 27.3)<.0001 | 15.6 (7.5 - 32.7)<.0001 | 18.9 (8.9 - 39.8)<.0001 | 22.7 (10.5 - 49.0)<.0001 | 11.3 (5.2 - 24.6)<.0001 | 12.5 (5.8 - 27.2)<.0001 | 13.9 (6.3 - 30.5)<.0001 | 15.4 (6.8 - 34.6)<.0001 |
| **53-62 mmol/mol (7.0-7.8%) – Normoalbuminuria** | 45.4 (29.3 - 70.3)<.0001 | 37.8 (24.2 - 59.1)<.0001 | 45.6 (29.4 - 70.6)<.0001 | 54.9 (35.0 - 86.2)<.0001 | 66.2 (40.7 - 107.6)<.0001 | 34.9 (22.2 - 54.9)<.0001 | 38.7 (24.8 - 60.4)<.0001 | 43.0 (27.1 - 68.1)<.0001 | 47.6 (29.0 - 78.3)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) – Normoalbuminuria** | 63.6 (41.8 - 96.8)<.0001 | 53.5 (34.9 - 82.2)<.0001 | 64.5 (42.4 - 98.2)<.0001 | 77.8 (50.3 - 120.3)<.0001 | 93.8 (58.4 - 150.5)<.0001 | 49.6 (32.2 - 76.5)<.0001 | 55.0 (35.9 - 84.2)<.0001 | 61.0 (39.2 - 95.1)<.0001 | 67.7 (41.7 - 109.7)<.0001 |
| **73-82 mmol/mol (8.8-9.6%) – Normoalbuminuria** | 82.2 (50.1 - 135.0)<.0001 | 69.8 (42.3 - 115.2)<.0001 | 84.1 (51.3 - 138.1)<.0001 | 101.4 (60.9 - 168.8)<.0001 | 122.3 (71.1 - 210.3)<.0001 | 61.8 (37.2 - 102.6)<.0001 | 68.5 (41.5 - 113.1)<.0001 | 76.0 (45.3 - 127.5)<.0001 | 84.3 (48.6 - 146.3)<.0001 |
| **>=83 mmol/mol (>=9.7%) – Normoalbuminuria** | 290.3 (177.0 - 476.2)<.0001 | 251.3 (152.9 - 413.2)<.0001 | 303.0 (185.0 - 496.2)<.0001 | 365.3 (219.4 - 608.0)<.0001 | 440.3 (255.5 - 759.1)<.0001 | 221.8 (134.0 - 367.0)<.0001 | 245.8 (149.0 - 405.3)<.0001 | 272.8 (162.5 - 457.8)<.0001 | 302.4 (173.8 - 526.3)<.0001 |
| **<=52 mmol/mol (<=6.9%) - Not Normoalbuminuria** | 130.5 (74.1 - 229.8)<.0001 | 102.3 (57.2 - 183.0)<.0001 | 123.4 (69.9 - 217.8)<.0001 | 148.8 (83.9 - 263.9)<.0001 | 179.3 (98.9 - 325.2)<.0001 | 87.9 (48.9 - 157.9)<.0001 | 97.4 (54.8 - 173.0)<.0001 | 108.1 (60.4 - 193.4)<.0001 | 119.9 (65.4 - 219.7)<.0001 |
| **53-62 mmol/mol (7.0-7.8%)- Not Normoalbuminuria** | 139.4 (90.5 - 214.6)<.0001 | 109.4 (69.7 - 171.7)<.0001 | 131.9 (85.4 - 203.7)<.0001 | 159.0 (102.3 - 247.2)<.0001 | 191.7 (119.8 - 306.7)<.0001 | 91.7 (58.0 - 144.9)<.0001 | 101.6 (65.2 - 158.2)<.0001 | 112.7 (71.7 - 177.2)<.0001 | 125.0 (77.1 - 202.7)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) - Not Normoalbuminuria** | 209.3 (141.0 - 310.7)<.0001 | 169.3 (112.3 - 255.2)<.0001 | 204.1 (137.3 - 303.5)<.0001 | 246.1 (163.7 - 370.0)<.0001 | 296.7 (190.6 - 461.9)<.0001 | 139.2 (91.5 - 211.5)<.0001 | 154.2 (102.7 - 231.5)<.0001 | 171.1 (112.5 - 260.4)<.0001 | 189.8 (120.2 - 299.5)<.0001 |
| **73-82 mmol/mol (8.8-9.6% ) - Not Normoalbuminuria** | 379.6 (256.2 - 562.3)<.0001 | 310.9 (207.2 - 466.4)<.0001 | 374.8 (252.9 - 555.4)<.0001 | 451.8 (300.9 - 678.4)<.0001 | 544.7 (349.8 - 848.0)<.0001 | 252.0 (166.4 - 381.5)<.0001 | 279.2 (186.4 - 418.2)<.0001 | 309.9 (203.8 - 471.4)<.0001 | 343.6 (217.4 - 543.1)<.0001 |
| **>=83 mmol/mol (>=9.7%) - Not Normoalbuminuria** | 862.2 (578.2 - 1285.8)<.0001 | 715.3 (475.3 - 1076.6)<.0001 | 862.4 (579.1 - 1284.2)<.0001 | 1039.7 (688.1 - 1570.8)<.0001 | 1253.4 (799.3 - 1965.4)<.0001 | 547.9 (359.9 - 834.1)<.0001 | 607.1 (402.6 - 915.6)<.0001 | 673.8 (439.6 - 1032.8)<.0001 | 747.1 (468.9 - 1190.4)<.0001 |
| Model 1: Adjusted for time-updated age and sex.Model 2: Adjusted for time-updated age, sex and time-updated diabetes duration centered at 30, 40, 50 and 60 years.Model 3: Adjusted for time-updated age, sex, born in Sweden, maximum education level, baseline comorbidities and time-updated diabetes duration centered at 30, 40, 50 and 60 years. |

# *Supplement Table 11. Adjusted hazard ratios for Minor amputation and 95% confidence intervals for time-updated mean HbA1c categories and eGFR<60/>=60 categories versus controls examined by Cox regression*

|  | **Hazard ratio (95% CI)****p-value** |
| --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** |
| **Amputation below ankle** | **All** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** |
| **Time updated mean HbA1c categories and eGFR, n events=570, data used = 98.9%** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **<=52 mmol/mol (<=6.9%) - eGFR>=60** | 19.0 (9.8 - 36.8)<.0001 | 16.7 (8.6 - 32.6)<.0001 | 19.5 (10.1 - 37.9)<.0001 | 22.8 (11.7 - 44.7)<.0001 | 26.6 (13.2 - 53.6)<.0001 | 14.7 (7.4 - 29.4)<.0001 | 16.0 (8.0 - 31.8)<.0001 | 17.3 (8.6 - 34.9)<.0001 | 18.8 (9.1 - 38.9)<.0001 |
| **53-62 mmol/mol (7.0-7.8%) - eGFR>=60** | 43.5 (28.3 - 66.9)<.0001 | 37.7 (24.3 - 58.4)<.0001 | 44.0 (28.6 - 67.6)<.0001 | 51.3 (32.9 - 80.1)<.0001 | 59.9 (37.0 - 97.0)<.0001 | 34.7 (22.2 - 54.1)<.0001 | 37.6 (24.3 - 58.3)<.0001 | 40.9 (26.0 - 64.3)<.0001 | 44.4 (27.2 - 72.5)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) - eGFR>=60** | 69.3 (46.4 - 103.5)<.0001 | 60.4 (40.1 - 91.1)<.0001 | 70.5 (47.2 - 105.4)<.0001 | 82.3 (54.1 - 125.2)<.0001 | 96.1 (60.7 - 152.1)<.0001 | 55.7 (36.7 - 84.4)<.0001 | 60.5 (40.2 - 90.9)<.0001 | 65.6 (42.8 - 100.5)<.0001 | 71.2 (44.6 - 113.8)<.0001 |
| **73-82 mmol/mol (8.8-9.6%) - eGFR>=60** | 125.2 (82.2 - 190.6)<.0001 | 110.0 (71.8 - 168.5)<.0001 | 128.3 (84.3 - 195.3)<.0001 | 149.8 (96.7 - 232.0)<.0001 | 174.8 (108.5 - 281.7)<.0001 | 98.1 (63.6 - 151.3)<.0001 | 106.5 (69.5 - 163.2)<.0001 | 115.6 (74.0 - 180.5)<.0001 | 125.5 (77.2 - 204.1)<.0001 |
| **>=83 mmol/mol (>=9.7%) - eGFR>=60** | 377.1 (245.5 - 579.2)<.0001 | 337.1 (218.9 - 519.1)<.0001 | 393.4 (256.4 - 603.6)<.0001 | 459.2 (293.4 - 718.7)<.0001 | 536.0 (328.8 - 873.8)<.0001 | 297.7 (191.8 - 462.2)<.0001 | 323.2 (209.0 - 499.8)<.0001 | 350.8 (222.3 - 553.6)<.0001 | 380.9 (231.5 - 626.6)<.0001 |
| **<=52 mmol/mol (<=6.9%) - eGFR<60** | 128.5 (69.6 - 237.4)<.0001 | 105.1 (56.0 - 197.1)<.0001 | 122.7 (66.2 - 227.2)<.0001 | 143.2 (77.0 - 266.4)<.0001 | 167.1 (88.0 - 317.4)<.0001 | 91.1 (48.4 - 171.6)<.0001 | 98.9 (53.1 - 184.2)<.0001 | 107.4 (57.3 - 201.1)<.0001 | 116.6 (60.8 - 223.4)<.0001 |
| **53-62 mmol/mol (7.0-7.8%) - eGFR<60** | 175.5 (112.2 - 274.5)<.0001 | 144.6 (90.7 - 230.5)<.0001 | 168.8 (107.6 - 264.9)<.0001 | 197.0 (124.6 - 311.4)<.0001 | 230.0 (141.3 - 374.2)<.0001 | 117.3 (73.0 - 188.5)<.0001 | 127.3 (80.4 - 201.6)<.0001 | 138.2 (86.5 - 220.8)<.0001 | 150.0 (91.1 - 247.1)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) - eGFR<60** | 270.3 (178.5 - 409.3)<.0001 | 226.4 (147.1 - 348.5)<.0001 | 264.3 (174.1 - 401.1)<.0001 | 308.5 (201.1 - 473.0)<.0001 | 360.0 (227.1 - 570.7)<.0001 | 178.2 (114.6 - 276.9)<.0001 | 193.4 (126.0 - 296.8)<.0001 | 209.9 (135.2 - 326.0)<.0001 | 227.9 (141.7 - 366.5)<.0001 |
| **73-82 mmol/mol (8.8-9.6%) - eGFR<60** | 460.9 (301.4 - 704.6)<.0001 | 387.9 (250.1 - 601.7)<.0001 | 452.8 (295.8 - 693.1)<.0001 | 528.5 (341.5 - 817.8)<.0001 | 616.9 (385.6 - 986.8)<.0001 | 299.9 (191.0 - 471.0)<.0001 | 325.6 (209.9 - 505.0)<.0001 | 353.4 (225.2 - 554.7)<.0001 | 383.7 (236.2 - 623.3)<.0001 |
| **>=83 mmol/mol (>=9.7%) - eGFR<60** | 1057.9 (690.5 - 1620.7)<.0001 | 898.2 (579.2 - 1392.9)<.0001 | 1048.3 (684.2 - 1606.4)<.0001 | 1223.6 (789.0 - 1897.6)<.0001 | 1428.2 (890.0 - 2291.8)<.0001 | 693.3 (442.0 - 1087.5)<.0001 | 752.6 (485.0 - 1167.8)<.0001 | 816.9 (519.4 - 1284.8)<.0001 | 886.9 (544.1 - 1445.5)<.0001 |
| Model 1: Adjusted for time-updated age and sex.Model 2: Adjusted for time-updated age, sex and time-updated diabetes duration centered at 30, 40, 50 and 60 years.Model 3: Adjusted for time-updated age, sex, born in Sweden, maximum education level, baseline comorbidities and time-updated diabetes duration centered at 30, 40, 50 and 60 years. |

# *Supplement Table 12. Adjusted hazard ratios for Major amputation and 95% confidence intervals for time-updated mean HbA1c categories and Normoalbuminuria versus controls examined by Cox regression*

|  | **Hazard ratio (95% CI)****p-value** |
| --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** |
| **Amputation above ankle** | **All** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** |
| **Time updated mean HbA1c categories and Albuminuria** |  |  |  |  |  |  |  |  |  |
|  | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **<=52 mmol/mol (<=6.9%) – Normoalbuminuria** | 9.3 (5.3 - 16.3)<.0001 | 6.1 (3.4 - 10.9)<.0001 | 8.3 (4.7 - 14.6)<.0001 | 11.3 (6.4 - 20.0)<.0001 | 15.4 (8.6 - 27.7)<.0001 | 5.6 (3.1 - 10.2)<.0001 | 7.3 (4.1 - 13.2)<.0001 | 9.5 (5.3 - 17.2)<.0001 | 12.4 (6.7 - 22.8)<.0001 |
| **53-62 mmol/mol (7.0-7.8%) – Normoalbuminuria** | 15.3 (10.7 - 22.0)<.0001 | 10.1 (6.9 - 14.8)<.0001 | 13.7 (9.5 - 19.7)<.0001 | 18.7 (12.9 - 27.0)<.0001 | 25.4 (17.1 - 37.8)<.0001 | 8.9 (6.0 - 13.1)<.0001 | 11.6 (8.0 - 16.7)<.0001 | 15.0 (10.3 - 21.9)<.0001 | 19.5 (13.0 - 29.3)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) – Normoalbuminuria** | 19.0 (13.4 - 27.0)<.0001 | 12.8 (8.9 - 18.6)<.0001 | 17.5 (12.3 - 24.9)<.0001 | 23.8 (16.6 - 34.1)<.0001 | 32.4 (21.9 - 48.0)<.0001 | 11.1 (7.7 - 16.2)<.0001 | 14.5 (10.1 - 20.7)<.0001 | 18.8 (13.0 - 27.1)<.0001 | 24.4 (16.3 - 36.5)<.0001 |
| **73-82 mmol/mol (8.8-9.6%) – Normoalbuminuria** | 32.0 (20.8 - 49.0)<.0001 | 22.0 (14.2 - 34.2)<.0001 | 30.0 (19.6 - 46.0)<.0001 | 40.9 (26.5 - 63.1)<.0001 | 55.6 (35.1 - 88.3)<.0001 | 17.6 (11.3 - 27.4)<.0001 | 22.9 (14.9 - 35.2)<.0001 | 29.7 (19.1 - 46.1)<.0001 | 38.6 (24.1 - 61.7)<.0001 |
| **>=83 mmol/mol (>=9.7%) – Normoalbuminuria** | 131.2 (86.6 - 198.8)<.0001 | 94.5 (62.0 - 144.2)<.0001 | 128.7 (85.3 - 194.2)<.0001 | 175.2 (114.9 - 267.3)<.0001 | 238.6 (151.6 - 375.4)<.0001 | 71.7 (46.6 - 110.3)<.0001 | 93.2 (61.1 - 142.1)<.0001 | 121.0 (78.3 - 186.9)<.0001 | 157.2 (98.5 - 251.1)<.0001 |
| **<=52 mmol/mol (<=6.9%) - Not Normoalbuminuria** | 37.6 (22.1 - 64.2)<.0001 | 22.0 (12.6 - 38.6)<.0001 | 30.0 (17.5 - 51.5)<.0001 | 40.8 (23.8 - 69.9)<.0001 | 55.6 (32.0 - 96.5)<.0001 | 17.1 (9.7 - 30.1)<.0001 | 22.2 (12.9 - 38.4)<.0001 | 28.9 (16.7 - 49.8)<.0001 | 37.5 (21.4 - 65.8)<.0001 |
| **53-62 mmol/mol (7.0-7.8%)- Not Normoalbuminuria** | 59.5 (43.1 - 82.1)<.0001 | 35.4 (24.7 - 50.7)<.0001 | 48.2 (34.6 - 67.1)<.0001 | 65.6 (47.3 - 91.1)<.0001 | 89.3 (62.9 - 126.9)<.0001 | 25.9 (18.0 - 37.4)<.0001 | 33.7 (23.9 - 47.4)<.0001 | 43.7 (31.1 - 61.5)<.0001 | 56.8 (39.3 - 82.2)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) - Not Normoalbuminuria** | 88.4 (66.7 - 117.1)<.0001 | 56.0 (40.9 - 76.7)<.0001 | 76.3 (57.3 - 101.6)<.0001 | 103.9 (77.8 - 138.8)<.0001 | 141.4 (102.5 - 195.3)<.0001 | 41.2 (29.9 - 56.8)<.0001 | 53.5 (39.7 - 72.0)<.0001 | 69.5 (51.3 - 94.1)<.0001 | 90.3 (64.3 - 126.7)<.0001 |
| **73-82 mmol/mol (8.8-9.6% ) - Not Normoalbuminuria** | 119.0 (87.9 - 161.2)<.0001 | 77.9 (56.1 - 108.1)<.0001 | 106.1 (78.2 - 143.9)<.0001 | 144.4 (105.8 - 197.1)<.0001 | 196.6 (139.3 - 277.5)<.0001 | 55.0 (39.4 - 76.9)<.0001 | 71.5 (52.1 - 98.1)<.0001 | 92.8 (67.0 - 128.6)<.0001 | 120.7 (84.0 - 173.3)<.0001 |
| **>=83 mmol/mol (>=9.7%) - Not Normoalbuminuria** | 312.4 (229.7 - 424.9)<.0001 | 210.7 (152.1 - 291.8)<.0001 | 286.9 (211.3 - 389.4)<.0001 | 390.6 (285.3 - 534.7)<.0001 | 531.8 (375.0 - 754.0)<.0001 | 139.2 (99.4 - 195.0)<.0001 | 180.9 (131.4 - 248.9)<.0001 | 234.8 (168.7 - 326.7)<.0001 | 305.2 (211.4 - 440.7)<.0001 |
| Model 1: Adjusted for time-updated age and sex.Model 2: Adjusted for time-updated age, sex and time-updated diabetes duration centered at 30, 40, 50 and 60 years.Model 3: Adjusted for time-updated age, sex, born in Sweden, maximum education level, baseline comorbidities and time-updated diabetes duration centered at 30, 40, 50 and 60 years. |

# *Supplement Table 13. Adjusted hazard ratios for Major amputation and 95% confidence intervals for time-updated mean HbA1c categories and eGFR<60/>=60 categories versus the reference group examined by Cox regression*

|  | **Hazard ratio (95% CI)****p-value** |
| --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** |
| **Amputation above ankle** | **All** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** | **Diabetes duration 30 years** | **Diabetes duration 40 years** | **Diabetes duration 50 years** | **Diabetes duration 60 years** |
| **Time updated mean HbA1c categories and eGFR, n events=578, data used = 98.9%** |  |  |  |  |  |  |  |  |  |
| **Controls (reference)** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **<=52 mmol/mol (<=6.9%) - eGFR>=60** | 10.7 (6.4 - 18.0)<.0001 | 7.5 (4.4 - 12.8)<.0001 | 9.9 (5.9 - 16.7)<.0001 | 13.1 (7.7 - 22.1)<.0001 | 17.3 (10.0 - 29.9)<.0001 | 6.8 (3.9 - 11.7)<.0001 | 8.6 (5.0 - 14.8)<.0001 | 11.0 (6.4 - 19.0)<.0001 | 14.1 (8.0 - 24.8)<.0001 |
| **53-62 mmol/mol (7.0-7.8%) - eGFR>=60** | 17.5 (12.5 - 24.5)<.0001 | 12.1 (8.5 - 17.4)<.0001 | 16.0 (11.4 - 22.4)<.0001 | 21.2 (15.0 - 29.8)<.0001 | 27.9 (19.2 - 40.7)<.0001 | 10.3 (7.1 - 14.8)<.0001 | 13.1 (9.3 - 18.5)<.0001 | 16.8 (11.8 - 23.9)<.0001 | 21.4 (14.5 - 31.5)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) - eGFR>=60** | 26.1 (19.2 - 35.4)<.0001 | 18.5 (13.4 - 25.6)<.0001 | 24.4 (18.0 - 33.1)<.0001 | 32.2 (23.5 - 44.1)<.0001 | 42.5 (29.9 - 60.5)<.0001 | 16.0 (11.5 - 22.2)<.0001 | 20.4 (15.0 - 27.9)<.0001 | 26.1 (18.9 - 36.0)<.0001 | 33.3 (23.2 - 47.8)<.0001 |
| **73-82 mmol/mol (8.8-9.6%) - eGFR>=60** | 34.0 (23.4 - 49.3)<.0001 | 24.6 (16.7 - 36.3)<.0001 | 32.5 (22.4 - 47.2)<.0001 | 42.9 (29.3 - 62.9)<.0001 | 56.7 (37.5 - 85.9)<.0001 | 19.4 (13.1 - 28.7)<.0001 | 24.8 (17.0 - 36.2)<.0001 | 31.7 (21.5 - 46.7)<.0001 | 40.4 (26.5 - 61.8)<.0001 |
| **>=83 mmol/mol (>=9.7%) - eGFR>=60** | 115.9 (79.2 - 169.7)<.0001 | 88.2 (59.9 - 129.8)<.0001 | 116.4 (79.9 - 169.7)<.0001 | 153.7 (104.0 - 227.2)<.0001 | 202.9 (132.4 - 311.0)<.0001 | 67.3 (45.3 - 99.8)<.0001 | 85.9 (58.4 - 126.3)<.0001 | 109.6 (73.4 - 163.8)<.0001 | 140.0 (90.2 - 217.2)<.0001 |
| **<=52 mmol/mol (<=6.9%) - eGFR<60** | 35.8 (20.3 - 63.1)<.0001 | 21.9 (12.1 - 39.8)<.0001 | 29.0 (16.3 - 51.5)<.0001 | 38.3 (21.6 - 67.7)<.0001 | 50.5 (28.2 - 90.6)<.0001 | 17.2 (9.4 - 31.2)<.0001 | 21.9 (12.3 - 39.1)<.0001 | 28.0 (15.7 - 49.8)<.0001 | 35.7 (19.7 - 64.6)<.0001 |
| **53-62 mmol/mol (7.0-7.8%) - eGFR<60** | 54.9 (38.6 - 78.3)<.0001 | 34.4 (23.2 - 50.9)<.0001 | 45.4 (31.6 - 65.4)<.0001 | 60.0 (41.8 - 86.0)<.0001 | 79.2 (54.0 - 116.1)<.0001 | 24.6 (16.5 - 36.7)<.0001 | 31.4 (21.6 - 45.7)<.0001 | 40.1 (27.6 - 58.3)<.0001 | 51.2 (34.5 - 76.2)<.0001 |
| **63-72 mmol/mol (7.9-8.7%) - eGFR<60** | 90.0 (65.9 - 122.9)<.0001 | 58.8 (41.6 - 83.1)<.0001 | 77.6 (56.4 - 106.8)<.0001 | 102.5 (74.4 - 141.1)<.0001 | 135.3 (95.5 - 191.7)<.0001 | 39.4 (27.6 - 56.4)<.0001 | 50.4 (36.1 - 70.2)<.0001 | 64.3 (45.9 - 90.0)<.0001 | 82.1 (56.8 - 118.5)<.0001 |
| **73-82 mmol/mol (8.8-9.6%) - eGFR<60** | 158.8 (114.4 - 220.5)<.0001 | 105.4 (73.7 - 150.7)<.0001 | 139.2 (99.8 - 194.1)<.0001 | 183.7 (131.4 - 256.9)<.0001 | 242.6 (168.5 - 349.3)<.0001 | 69.0 (47.7 - 99.9)<.0001 | 88.1 (62.3 - 124.8)<.0001 | 112.5 (79.1 - 160.0)<.0001 | 143.6 (97.9 - 210.7)<.0001 |
| **>=83 mmol/mol (>=9.7%) - eGFR<60** | 381.8 (273.1 - 533.7)<.0001 | 257.6 (179.6 - 369.5)<.0001 | 340.1 (242.7 - 476.6)<.0001 | 448.9 (319.2 - 631.3)<.0001 | 592.8 (409.2 - 858.8)<.0001 | 166.2 (114.5 - 241.4)<.0001 | 212.3 (149.3 - 301.9)<.0001 | 271.0 (189.4 - 387.6)<.0001 | 346.0 (234.3 - 510.8)<.0001 |
| Model 1: Adjusted for time-updated age and sex.Model 2: Adjusted for time-updated age, sex and time-updated diabetes duration centered at 30, 40, 50 and 60 years.Model 3: Adjusted for time-updated age, sex, born in Sweden, maximum education level, baseline comorbidities and time-updated diabetes duration centered at 30, 40, 50 and 60 years. |