**Supplemental Figure S1: Overall Study Design**

361 English GP practices

Mean HbA1c in each patient calculated

 Follow-Up

N=104,617 patients aged 40-89 years on (QOF) diabetes register as of 1/1/2008 and registered for at least 1 year

N=96,630
Type 2 diabetes

N=141,768

matched controls1

Infection rates in 2010-15 compared by mean HbA1c level during 2008-09

(i) within diabetes only, with HbA1c=6-7% as reference group

(ii) using matched controls as reference group

Excluded

no matched control (n=100)

N=5,863
Type 1 diabetes

N=3,342
matched controls1

Infections during 2010-15 categorised by type and summarised as

(i) Any plus prescription

(Ii) Any as hospitalisation

(iii) Cause of death

N=4,496 Type 1
with HbA1c 2008-09

Excluded

During 2008-09: 13 practices leave CPRD (n=3,412), dies (n=6,636), de-registers (n=5,368), no HbA1c (n=2,393), control no longer eligible (n=1,496)

N=1,852 Type uncertain with HbA1c 2008-09

N=2,124
Type uncertain

N=78,964 Type 2 with HbA1c 2008-09

N=8,231

matched controls1

Re-categorised from T1

has no insulin or has other anti-DM medication in 2008-09 (n=267)

1/1/2008

1/1/2010

31/12/2015

1 – Age-sex practice matched controls were required to have no Read codes for diabetes in their record as of 1/1/2010, but could develop diabetes during follow-up

T1 code only

**Type 1
N=5,139**

Insulin
+ no ADM in 2007

Insulin only pre 2007

Insulin in 2007
+ no other ADM ever

Uncertain
N=93

T2 code only

**Type 2
N=64**

No Insulin ever

All others

**Type 2
N=93,237**

T1 & T2 codes or Non-specific only

Insulin in 2007
+ no other ADM ever
+ no gestational DM ever

**Type 1
N=724**

Uncertain
N=1,213

All others

**Type 2
N=3,329**

ADM = Anti-diabetic medicine

Insulin only pre 2007
+ no other ADM ever

Uncertain
N=47

Insulin
+ ADM in 2007

Uncertain
N=759

Any Insulin ever
+ no other ADM ever
+ gestational DM ever

Uncertain
N=12

**All T1DM (1/1/2008)
N=5,863**

**All T2DM (1/1/2008)
N=96,630**

What combination of DM OQF Read codes does the patient have by January 1st 2008?

All Uncertain (1/1/2008) N=2,124

**All T1DM (1/1/2010)
N=4,496**

**All T2DM (1/1/2010)
N=78,964**

All Uncertain (1/1/2008) N=1,852

See Figure S1 for derivation of how patients with diabetes on 1/1/2008 were followed up and re-classified by type as of 1/1/2010

**Supplemental Figure S2:** Derivation of diabetes type at beginning of study (1/1/2008)

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**Supplemental Figure S3: Distribution of mean HbA1c during 2008-9 and number of eligible measurements by DM type**
Note: Dotted lines represent mean number of HbA1c measurements per patient, with the scale represented on the secondary y-axis.



**Supplemental Figure S4:** Summary of Infection Rates during 2010-15 by mean HbA1c level during 2008-9, All diabetes (black) and matched controls (white)
Note: Infections are presented in descending frequency ordered, with different scales on each row.

**Supplemental Table S1:** ICD-10 and Read codes for Infections

|  |  |  |
| --- | --- | --- |
| Infection | ICD-10 | Read Codes |
| Bone & Joint Infections | M00, M86.0-M86.2 | N010\*, N30..-N303z, N308\*, N309\*, N30y.-N30zz |
| (Acute) Cholecystitis | K80, K80.4, K81.0, K81.9 | J640\*, J643\*, J650\*, J651z, J666. |
| Endocarditis | I01.1, I33, I33.0, I33.9, I38, I39, I39.8 | A3642, A7422, A932\*, A98y3, AB2y0, AB414, G011., G14z., G51\*, G54z., G54z3, G54z4, G54zz, Gyu5E |
| Eye Infection | H10, H10.0, H10.2, H10.3, H10.5, H16\*, H44.0  | F400\*, F4A\*, F4C0.-F4C05, F4C0z, F4C2\*, F4C33, F4D1.-F4D13, F4D1z, F4D4., F4D5. |
| Gastro-Intestinal | A00-A02.0, A02.2-A09.9 | A00..-A020., A022\*, A02y.-A0z.., A3Ay2 |
| Infective Otitis Externa | H60, H60.0-H60.4, H60.8-H60.9 | F501\*, FyuN0, FyuN1, FyuN3-FyuN7 |
| LRTI | J20-J22 | H06\*, H07\* |
| Mycoses - Candidiasis | B37\* | AB2-AB2y., AB2y1-AB2z. |
| Mycoses - Other Fungal | B35-B36.9,B38-B49 | AB…-AB1z, AB3..-ABz.. |
| Pneumonia | A48.1, J12-J18 | A3A4., H20..-H2C.., Hyu08-Hyu0H |
| Sepsis | A02.1, A20.7, A22.7, A26.7, A32.7, A40-A41.9, A48.3, O85 | A021., A023., A202., A270100, A271100, A2706, A362., A38\*, A396., A3Ay100, A3C\*, A545., A98yz12, Ayu3E00- Ayu3H00, Ayu3J00, H5y0100, K190600, L090y00, L090z00, L40..11, L293\*, L403\*, SP25400 |
| (Acute) Sinusitis  | J01\* | H01\* |
| Skin - Cellulitis | H60.1, K12.2, L03\*, N73.0-N73.2 | F4D0.11, F4D14, H1y51, H1y71, J083.- J083z00, J0851, J54..11, J540.11, K2723, K2843, K403., K403100, K403z, K404., K4040, K405., K4051, K405z, M02..- M0200, M020z-M0210, M021z00, M02z.00, M03..00, M03..13, M030\*, M031.00, M032-M034000, M034013- M03y000, M03z.00, M03z000, M03zz00, M08.., M080.00, M080.13- M086., M088.- M08y.  |
| Skin - Other | A46, A49.0, J34.0, L00-L02.9, L04-L05.9, L08.1-L08.9, L30.3, L66.3, L66.4, L73.9, N73, N73.8-N73.9 | A35.., A3B1\*, J54..00, J54..12, J540., K403000, K403111, K4041-K404z, K4050, M0...- M01z0, M0201-M0205, M0211-M0213, M021z11, M02z.11-M02z.14, M03..11, M03..12, M031.11, M034011, M034012, M03y011, M03z100, M03zz11, M04..- M061.00, M062.- M07..00, M072.- M07y100, M07yz- M07z.13, M07z0- M07z2, M080.11, M080.12, M087., M09\*, M0y\*, M0z\*, M244.00, M2440- M244111, M2443- M244z |
| Surgical Site | T79.3, T80.2, T81.4, T82.6, T82,7, T83.5, T83.6, T84.5-T84.7, T85.7, T87.4, T88.0 | SP056, SP06.00, SP06.12- SP06A11, SP077, SP078, SP132, SP162, SP25.- SP253, SP255- SP25z, SP33\* |
| Tuberculosis | A15-A19.9 | A1\*, Ayu1.00, Ayu10, Ayu11, Ayu13- Ayu16, Ayu18, Ayu19, N304\*, N305\*, N306\* |
| (Other) URTI | A37-A38, H65.0-H65.1, H66\*, J02-J06.9, J36 | A33\*, A34\*, F510.00- F5103, F5200-F520z, F526.-F528., F52z.11, H02\*, H03\*, H04\*, H05\*, H15.., Hyu01- Hyu03 |
| Urinary Tract Infection | N10-N12, N13.6, N15.1, N15.9, N30\* | K103.12, K104.-K106., K10y.-K10z., K15\*, K190\*, Kyu10, Kyu1E |

\* - indicates a wild-card, so include all codes in hierarchy

**Supplemental Table S2:** Summary of mean HbA1c during 2008-9 among all diabetes patients (n=85,312)

|  |  |
| --- | --- |
| Baseline characteristic | Mean HbA1c calculated during 2008-9 |
|  | **All Patients** |  **<6%**  | **≥6 to <7%** | **≥7 to <8%** | **≥8 to <9%** | **≥9 to <10%** | **≥10 to <11%** | **≥11%** |
|  | n | mean (s.d.) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| All |  | 85,312 | 7.4 (1.4) | 8,013 (9.4) | 28,677 (33.6) | 25,848 (30.3) | 12,338 (14.5) | 5,738 (6.7) | 2,589 (3.0) | 2,109 (2.5) |
|  |  |  |  |  |  |  |  |  |  |  |
| Gender | Women | 38,043 | 7.4 (1.4) | 3,742 (9.8) | 13,325 (35.0) | 11,198 (29.4) | 5,203 (13.7) | 2,441 (6.4) | 1,139 (3.0) | 995 (2.6) |
|  | Men | 47,269 | 7.5 (1.4) | 4,271 (9.0) | 15,352 (32.5) | 14,650 (31.0) | 7,135 (15.1) | 3,297 (7.0) | 1,450 (3.1) | 1,114 (2.4) |
|  |  |  |  |  |  |  |  |  |  |  |
| Agea | 40-49 | 8,309 | 8.2 (1.7) | 570 (6.9) | 1,591 (19.2) | 2,199 (26.5) | 1,698 (20.4) | 1,083 (13.0) | 595 (7.2) | 573 (6.9) |
|  | 50-59 | 15,959 | 7.8 (1.5) | 1,161 (7.3) | 4,129 (25.9) | 4,755 (29.8) | 2,914 (18.3) | 1,513 (9.5) | 794 (5.0) | 693 (4.3) |
|  | 60-69 | 24,441 | 7.4 (1.3) | 2,127 (8.7) | 8,097 (33.1) | 7,820 (32.0) | 3,702 (15.2) | 1,565 (6.4) | 641 (2.6) | 489 (2.0) |
|  | 70-79 | 25,196  | 7.2 (1.1) | 2,611 (10.4) | 10,004 (39.7) | 7,947 (31.5) | 2,887 (11.5) | 1,118 (4.4) | 386 (1.5) | 243 (1.0) |
|  | 80-89 | 11,407  | 7.0 (1.2) | 1,544 (13.5) | 4,856 (42.6) | 3,127 (27.4) | 1,137 (10.0) | 459 (4.0) | 173 (1.5) | 111 (1.0) |
|  |  |  |  |  |  |  |  |  |  |  |
| DM Type | T1DM | 4,496  | 8.3 (1.4) | 105 (2.3) | 592 (13.2) | 1,324 (29.5) | 1,269 (28.2) | 748 (16.6) | 279 (6.2) | 179 (4.0) |
|  | T2DM | 78,964  | 7.4 (1.3) | 7,820 (9.9) | 27,811 (35.2) | 24,046 (30.5) | 10,602 (13.4) | 4,688 (5.9) | 2,170 (2.8) | 1,827 (2.3) |
|  | Unclassified | 1,852  | 8.3 (1.6) | 88 (4.8) | 274 (14.8) | 478 (25.8) | 467 (25.2) | 302 (16.3) | 140 (7.6) | 103 (5.6) |
|  |  |  |  |  |  |  |  |  |  |  |
| Duration of  | 0-5 years | 37,918  | 7.1 (1.2) | 4,832 (12.7) | 15,700 (41.4) | 10,737 (28.3) | 3,826 (10.1) | 1,546 (4.1) | 706 (1.9) | 571 (1.5) |
| diabetes | 5-15 years | 35,655  | 7.6 (1.4) | 2,655 (7.5) | 10,702 (30.0) | 11,391 (32.0) | 5,740 (16.1) | 2,711 (7.6) | 1,318 (3.7) | 1,138 (3.2) |
|  | >15 years | 11,739  | 8.0 (1.4) | 526 (4.5) | 2,275 (19.4) | 3,720 (31.7) | 2,772 (23.6) | 1,481 (12.6) | 565 (4.8) | 400 (3.4) |
|  |  |  |  |  |  |  |  |  |  |  |
| Deprivation  | 1 – Least  | 16,913  | 7.3 (1.3) | 1,715 (10.1) | 5,766 (34.1) | 5,303 (31.4) | 2,444 (14.5) | 1,040 (6.2) | 393 (2.3) | 252 (1.5) |
| quintile b | 2 | 19,921  | 7.4 (1.3) | 1,846 (9.3) | 6,860 (34.4) | 6,185 (31.1) | 2,810 (14.1) | 1,281 (6.4) | 539 (2.7) | 400 (2.0) |
|  | 3 | 17,707  | 7.4 (1.4) | 1,731 (9.8) | 5,913 (33.4) | 5,447 (30.8) | 2,584 (14.6) | 1,119 (6.3) | 493 (2.8) | 420 (2.4) |
|  | 4 | 17,848  | 7.5 (1.5) | 1,545 (8.7) | 5,796 (32.5) | 5,324 (29.8) | 2,653 (14.9) | 1,271 (7.1) | 675 (3.8) | 584 (3.3) |
|  | 5 – Most | 12,871  | 7.5 (1.5) | 1,170 (9.1) | 4,323 (33.6) | 3,577 (27.8) | 1,840 (14.3) | 1,022 (7.9) | 488 (3.8) | 451 (3.5) |
|  |  |  |  |  |  |  |  |  |  |  |
| Smoking  | Never | 31,204  | 7.4 (1.4) | 2,827 (9.1) | 10,485 (33.6) | 9,624 (30.8) | 4,548 (14.6) | 2,016 (6.5) | 916 (2.9) | 788 (2.5) |
| Status | Ex | 43,148  | 7.4 (1.3) | 4,250 (9.9) | 14,855 (34.4) | 13,182 (30.6) | 6,109 (14.2) | 2,755 (6.4) | 1,165 (2.7) | 832 (1.9) |
|  | Current | 10,960  | 7.7 (1.6) | 936 (8.5) | 3,337 (30.5) | 3,042 (27.8) | 1,681 (15.3) | 967 (8.8) | 508 (4.6) | 489 (4.5) |
|  |  |  |  |  |  |  |  |  |  |  |
| BMI b | 10-20 | 1,458  | 7.2 (1.6) | 299 (20.5) | 525 (36.0) | 330 (22.6) | 156 (10.7) | 57 (3.9) | 39 (2.7) | 52 (3.6) |
|  | 20-25 | 13,551  | 7.3 (1.4) | 1,817 (13.4) | 4,976 (36.7) | 3,755 (27.7) | 1,617 (11.9) | 742 (5.5) | 318 (2.4) | 326 (2.4) |
|  | 25-30 | 30,084  | 7.4 (1.3) | 2,855 (9.5) | 10,522 (35.0) | 9,493 (31.6) | 4,087 (13.6) | 1,795 (6.0) | 766 (2.6) | 566 (1.9) |
|  | 30-40 | 33,437  | 7.5 (1.4) | 2,560 (7.7) | 10,651 (31.9) | 10,295 (30.8) | 5,320 (15.9) | 2,535 (7.6) | 1,162 (3.5) | 914 (2.7) |
|  | 40+ | 6,591  | 7.7 (1.5) | 445 (6.8) | 1,934 (29.3) | 1,938 (29.4) | 1,130 (17.1) | 599 (9.1) | 299 (4.5) | 246 (3.7) |

 a Age calculated during baseline year (2008). b Patients with missing values for deprivation (IMD) (n=52) or BMI (n=191) are not shown in those categories

**Supplemental Table S3:** IRRs additionally adjusted for co-morbidity for summary infection groups during 2010-5 by mean HbA1c level during 2008-9

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Non-DM | DM vs. non-DMa | Mean HbA1c (2008-9) in DM patientsb |
|  |  |  | **<6%** | **≥6 to <7%** | **≥7 to <8%** | **≥8 to <9%** | **≥9 to <10%** | **≥10 to <11%** | **≥11%** |
|  | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI |
| DM patients (n=85,312) vs. non-DM (n=153,341) |  |  |  |  |  |  |  |  |  |
|  Any plus prescription | **1** (reference) | **1.26** (1.25-1.28) | **1.18** (1.14-1.24) | **1.15** (1.13-1.18) | **1.23** (1.20-1.25) | **1.35** (1.31-1.39) | **1.47** (1.42-1.52) | **1.54** (1.46-1.64) | **1.69** (1.60-1.79) |
| Any as hospitalisation | **1** (reference) | **1.58** (1.53-1.64) | **1.49** (1.40-1.59) | **1.29** (1.23-1.34) | **1.44** (1.38-1.50) | **1.77** (1.67-1.87) | **2.09** (1.94-2.26) | **3.02** (2.76-3.30) | **4.09** (3.68-4.54) |
| Death from infection | **1** (reference) | **2.03** (1.76-2.34) | **1.77** (1.50-2.10) | **1.45** (1.28-1.64) | **1.69** (1.48-1.92) | **1.87**(1.56-2.24) | **1.94** (1.48-2.52) | **4.44** (3.28-6.02) | **4.64** (3.22-6.67) |
|  |  |  |  |  |  |  |  |  |  |
| DM patients only (n=85,312)  |  |  |  |  |  |  |  |  |  |
|  Any plus prescription | **\_** | **\_** | **1.02** (0.98-1.07) | **1** (reference) | **1.05** (1.02-1.07) | **1.13** (1.09-1.16) | **1.21**(1.16-1.26) | **1.25** (1.18-1.33) | **1.36** (1.29-1.44) |
| Any as hospitalisation | **\_** | **\_** | **1.16** (1.08-1.24) | **1** (reference) | **1.09** (1.03-1.14) | **1.28** (1.21-1.36) | **1.49** (1.37-1.61) | **2.09** (1.90-2.29) | **2.80** (2.52-3.10) |
| Death from infection | **\_** | **\_** | **1.24** (1.04-1.48) | **1** (reference) | **1.12** (0.98-1.30) | **1.19**(0.98-1.45) | **1.22** (0.92-1.61) | **2.74** (2.02-3.73) | **2.87** (2.02-4.10) |

 a - Poisson model conditioned on matchsets fits a term to compare DM vs. non-DM. b - Poisson model now fits HbA1c categories, with non-DM as reference category (top 3 rows) or HbA1c=6-7% as reference category (bottom 3 rows). c - Incidence Rate Ratios adjusted for age, sex, smoking, BMI, deprivation quintile and DM type as in Tables 1 and 2, and now additionally adjusted for chronic kidney disease, heart failure, hypertension, hypothyroidism, ischaemic heart disease, peripheral vascular disease, stroke & transient ischaemic attack and COPD.

**Supplemental Table S4:** Adjusted IRRs for summary infection groups during 2010-5 by updated 2-year mean HbA1c level among DM patients only, by different analysis type

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | DM Typec | Updated 2-year average mean HbA1c in DM patientsb | Attributable risk fractions |
|  | **Type 1** | **Type 2** |  **<6%** | **≥6 to <7%** | **≥7 to <8%** | **≥8 to <9%** | **≥9 to <10%** | **≥10 to <11%** | **≥11%** |  |
|  | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **ARd**  |
| Any plus prescription | **1** (refer-ence) | **1.02** (0.98-1.07) | **1.04** (1.01-1.07) | **1** (refer-ence) | **1.04** (1.02-1.06) | **1.14** (1.11-1.16) | **1.19** (1.16-1.23) | **1.28** (1.23-1.33) | **1.26** (1.20-1.31) | **6.1** |
| Any as hospitalisation | **1** (refer-ence) | **1.49** (1.35-1.65) | **1.29** (1.20-1.38) | **1** (refer-ence) | **1.02** (0.97-1.07) | **1.30** (1.22-1.37) | **1.58** (1.47-1.70) | **2.07** (1.89-2.26) | **2.53** (2.29-2.80) | **14.4** |
| Death from infection | **1** (refer-ence) | **1.86** (1.37-2.53) | **1.51** (1.25-1.83) | **1** (refer-ence) | **1.10** (0.94-1.29) | **1.40** (1.15-1.69) | **1.50** (1.16-1.93) | **2.24** (1.63-3.10) | **2.72** (1.90-3.89) | **17.2** |

Note - Reference category in Poisson models are patients with DM and HbA1c between 6 to 7%.
a- IRR from GEE Poisson model adjusted for age in year, sex, smoking, BMI, deprivation quintile and type of diabetes. b – Re-calculated every January 1st based on all HbA1c measurements in previous 2 years. Patients no longer registered or without measurements not included in later years. Analysis based on 372,850 patient x year observations. c – Type uncertain also fitted in model (estimates not shown). d - Attributable risk fractions for infections for a baseline scenario of HbA1c=6-7% among all patients with diabetes.

**Supplemental Table S5:** Bradford Hill Criteria([1](#_ENREF_1)) for hyperglycaemia and infection risk

|  |  |
| --- | --- |
| Strength | Strong associations were observed, up to 3 times higher risk for patients with the most elevated levels of HbA1c compared with optimal control for both T1 and T2DM |
| Consistency | Almost all infection categories considered show an increased risk with higher HbA1c, as did our summary measures of infection (any episode requiring a prescription, any requiring hospitalisation, and infection-related mortality). Several other recent database studies have demonstrated similar, though more limited, findings([2](#_ENREF_2), [3](#_ENREF_3)).  |
| Specificity | The association with HbA1c is not specific to one infection or even limited to infections, but this would not be expected based on our understanding of the potential mechanisms. Lack of specificity should not therefore be regarded as an argument against the relationship being causal. |
| Temporality | In our cohort design, with frequent measurements of HbA1c, we are confident that the chronic hyperglycaemia arose before the infection episode. We were able to eliminate reverse causality by removing measurements of HbA1c close to or at the time on the infection episode.  |
| Biological gradient | Very strong dose response relationships observed between HbA1c and infection risk, particularly for more serious infections. A rise in infection risk was seen across increasing categories of HbA1c. This remained after adjusting for type, duration, and key comorbidities.  |
| Plausibility & Coherence | Plausible mechanisms are varied, but focus on relative immune function impairment in DM patients([4](#_ENREF_4), [5](#_ENREF_5)). Laboratory evidence has seen adverse effects of glycaemia on macrophage function and T cell complement. Laboratory studies have also shown that metformin reduces the intracellular growth of *Mycobacterium tuberculosis*([6](#_ENREF_6)) and may limit Staphylococcus aureus growth([7](#_ENREF_7)). |
| Experiment | Very limited evidence exists. One trial (DCCT) demonstrated lower risks of some infections in the more intensively managed group ([8](#_ENREF_8)), but there remains a major gap in the knowledge base. |
| Analogy | Randomised evidence supports an effect of glycaemia on microvascular([9](#_ENREF_9)), and to some extent macrovascular outcomes([10-13](#_ENREF_10)). Moreover microvascular disease is undoubtedly one of the mechanisms linking HbA1c to infection via neuropathies and amputations([14](#_ENREF_14)) ([15](#_ENREF_15)). Macrovascular disease may also be important([16](#_ENREF_16)). |

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