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Impact of Diabetes Against the Future Risk of Developing Gout

Luis A. García Rodríguez, MD[1], **Lucia Cea Soriano, BPharm**[1], and **Hyon K. Choi, MD, DrPH**[2]
[1]Spanish Centre for Pharmacoepidemiological Research (CEIFE).

[2]Section of Rheumatology and the Clinical Epidemiology Unit, Boston University School of Medicine, Boston, MA

Abstract

OBJECTIVE—Although type-2 diabetes is considered a comorbid condition of gout, the uricosuric effect of glycosuria or the impaired inflammatory response in diabetes may actually reduce the future risk of gout. We evaluated the impact of diabetes on the future risk of developing gout.

METHODS—We conducted a case-control study nested in a UK general practice database (the Health Improvement Network) by identifying all incident cases of gout (N=24,768) and randomly sampled 50,000 controls who were 20–79 years between 2000 and 2007. We examined the independent effect of type-1 and type-2 diabetes on the development of incident gout.

RESULTS—After adjusting for age, sex, body mass index, general practitioner visits, smoking, alcohol intake, ischemic heart disease, and presence of cardiovascular risk factors, the relative risk (RR) for incident gout among diabetes patients, as compared with individuals with no diabetes was 0.67 (95% CI, 0.63 to 0.71). The multivariate RRs with the duration of diabetes of 0–3, 4–9, and ≥ 10 years were 0.81 (95% CI, 0.74 to 0.90), 0.67 (95% CI, 0.61 to 0.73), and 0.52 (95% CI, 0.46 to 0.58), respectively. The inverse association was stronger with type 1 diabetes than with type 2 diabetes (multivariate RR, 0.33 vs. 0.69; P value < 0.001). The inverse association was stronger among men than women (multivariate RR [95% CI], 0.59 [0.53 to 0.64] vs. 0.90 [0.80 to 1.00]; P value for interaction <0.001).

CONCLUSIONS—Individuals with diabetes are at a lower future risk of gout independent of other risk factors. These data provide support for a substantial role of the pathophysiology associated with diabetes (e.g. the uricosuric effect of glycosuria and the impaired inflammatory response) against the risk of developing gout.

Keywords

Diabetes; gout; uric acid; insulin; metabolic syndrome

INTRODUCTION

Although diabetes is considered a comorbid condition of gout, a common and excruciatingly painful inflammatory arthritis,[1–3] pathophysiologic mechanisms associated with diabetes suggest that having diabetes may actually reduce the future risk of gout. For example, several previous studies have shown that individuals with type 2 diabetes (or blood glucose >10 mmol/L [180 mg/dL]) have substantially lower serum uric acid levels than normal individuals, likely due to the uricosuric effect of glycosuria.[4–8] Furthermore, the impaired

Corresponding Author: Hyon K. Choi, M.D., Dr.P.H., Professor of Medicine, Section of Rheumatology and the Clinical Epidemiology Unit, Boston University School of Medicine, 650 Albany Street, Suite 200, Boston, MA 02118, Tel: (617) 638-5490 Fax: (617) 638-5239, hchoius@bu.edu.

inflammatory response observed in diabetes may play a protective role against the risk of gout, which is the direct result of an intense inflammatory response to urate crystals.[9] While these data suggest that diabetes could lead to a lower future risk of gout, no study has investigated this potential influence of diabetes on the risk of gout.[5] To examine this link, we analyzed a cohort of 24,768 patients newly diagnosed with gout and 50,000 controls from The Health Improvement Network (THIN) database.

METHODS

Study population

The Health Improvement Network (THIN) contains computerized medical records entered by general practitioners in the UK.[10] Data on approximately 4 million patients are systematically recorded and sent anonymously to THIN. THIN collects and organizes this information in order to be used for research projects. The computerized information includes demographics, details from general practitioners' (GPs) visits, diagnoses from specialists' referrals and hospital admissions, results of laboratory tests and a free text section (information available on request). Prescriptions issued by the general practitioner are directly generated from the computer. An additional requirement for participating practices is recording of the indication for new courses of therapy. The READ classification is used to code specific diagnoses, and a drug dictionary based on data from the MULTILEX classification is used to code drugs (NHS [National Health Service] Terminology Service; http://www.connectingforhealth.nhs.uk/terminology/readcodes.2006) (Multilex Drug Data File; http://www.firstdatabank.co.uk/products/multilex/). The current study was approved by the NHS South-East Multi-Centre Research Ethics Committee.

We conducted a nested case-control study using data from the THIN database between January 2000 and December 2007. The cohort included all individuals aged 20–89 years with a registration status of permanent or died in the last THIN update. Study cohort members were required to have two or more years of enrolment with the GP, at least one GP visit and one prescription in the two years before entering the study period. Start date corresponded to the date when all these eligibility criteria were met. Individuals had to be free of gout and cancer before entering the study. Members of this cohort were followed until the date of one of the following endpoints: gout detection, 90th birthday, death, or end of study period, which ever came first. The final cohort consisted of 1,775,505 persons followed for an average of 5.2 years.

Ascertainment of Gout—We identified all individuals with a first ever diagnosis of gout recorded by a GP with an automatic search using READ codes. The date of gout onset (index date) was defined as the earliest of the date of first diagnosis of gout or first anti-gout treatment (allopurinol, colchicine, and uricosuric drugs) among individuals with a diagnosis of gout. We considered an incident case all gout patients with an index date (gout onset) occurring after the cohort entry start date (N=24,768).

To evaluate the robustness of gout ascertainment, we performed a sensitivity analysis restricting gout cases to those receiving anti-gout treatment. To this end, we used the following operational definition: we identified within 90 days after first ever diagnosis of gout (index date) any anti-gout treatment (colchicine, probenecid and uricosuric drugs) and/or a prescription of NSAIDs on the same index date. A similar case definition of gout has been shown to have a validity of 90% in the General Practice Research Database.[11,12]

Control Sampling—We selected 50,000 controls that were randomly sampled from the same cohort where gout cases were ascertained. A date encompassed within the study period was generated at random for each of the members of the cohort, if the random date for a

study member was included in his/her eligible person-time (follow-up period), we marked that person-day as an eligible control. The same exclusion criteria were applied to controls as to cases. Controls were frequency-matched to cases by age within one year, sex and calendar year (year of first ever gout diagnosis). The random date for controls was used as index date in the case-control analysis.

Exposure Assessment (Type 1 and Type 2 Diabetes)

We identified all individuals with diabetes mellitus in the computerized medical records occurring before the index date, as described elsewhere in detail.[13] The date of diabetes onset was defined as the minimum of the date of first ever recorded diagnosis of diabetes or first antidiabetic prescription. The types of diabetes have been described elsewhere in detail. [13] Briefly, if diabetes type was recorded and the GP had recorded only one specific diabetes type, it was assigned to that type of diabetes. When no diabetes type was recorded or both types were recorded in one patient, we used age at diagnosis to determine the type. For example, individuals diagnosed with both types, younger than 30 years and treated with insulin were assigned to type 1, and individuals older than 50 years treated primarily with oral anti-diabetics were assigned to type 2. For the rest of the patients, we manually reviewed each patient's electronic medical records to assign a diabetes type. There were no type 1 diabetes patients without at least one insulin Rx. For type 2 diabetes we subdivided patients according to treatment into the following groups: no pharmacological treatment prior to index date, treated only with oral antidiabetics, and treated with insulin. We calculated duration of diabetes as the time interval between the date of first diagnosis of diabetes and the index date.

Covariate Assessment

Demographics and traditional life style factors such as alcohol use, smoking and BMI, as well as comorbidities such as ischaemic heart disease (IHD), hypertension, hyperlipidemia, and renal failure, were collected from the database before the index date. The numbers of GP visits, referrals, and hospitalizations in the year prior to the index date were also ascertained.

Statistical analysis

We estimated the odds ratio and 95% confidence intervals for gout associated with diabetes by means of unconditional logistic regression, adjusted for the frequency-matched variables, GP visits and the following potential risk factors: BMI (five categories), alcohol use (six categories), smoking (non-smoker, current smoker, past smoker, and unknown), IHD, hypertension, hyperlipidemia and renal failure. Under our study design, the OR is an unbiased estimator of the incidence rate ratio, and we have reported OR estimates as relative risks (RRs) throughout this paper.

We performed stratified analyses by gender because previous reports suggested the inverse associations between diabetes and serum uric acid levels were significantly stronger among men than women.[5,14] We tested the significance of the interaction with a likelihood ratio test by comparing a model with the main effects of the two variables (diabetes and sex) and the interaction term with a reduced model with only the main effects. Similarly, we examined the potential interaction between diabetes and diuretic use, as the latter is a strong risk factor of hyperuricemia and gout.

RESULTS

The study included 24,768 newly diagnosed cases of gout and 50,000 controls, and their characteristics are shown in Table 1. As anticipated, gout was associated with increased GP visits, alcohol use, increased adiposity, IHD, hypertension, hyperlipidemia, and renal failure.

A previous diagnosis of diabetes was associated with a lower risk of developing gout in the future (Table 2). After adjusting for age, gender, calendar year, and GP visits, the RR for gout among individuals with diabetes was 0.85 (95% CI, 0.80 to 0.90). After adjusting for other covariates, the RR became more protective (0.67; 95% CI, 0.63 to 0.71). The inverse association was stronger with type 1 diabetes than with type 2 diabetes (multivariate RR, 0.33 vs. 0.69; P value < 0.001) (Table 2). Furthermore, the inverse association was stronger with treated type 2 diabetes than with untreated type 2 diabetes (multivariate RR, 0.61 vs. 0.91; P value < 0.001). The magnitude of association with treated type 2 diabetes did not materially differ between cases treated with insulin and with oral anti-diabetic agents (e.g multivariate RR among men, 0.52 vs 0.55). In our sensitivity analysis, restricting gout cases to those with anti-gout treatment (N=19,749), the multivariate RR was 0.69 (95% CI, 0.64 to 0.73) with overall diabetes, 0.37 (95% CI, 0.26 to 0.52) with type 1 diabetes, and 0.70 (95% CI, 0.66 to 0.75) with type 2 diabetes.

There was a graded, inverse association between the duration of diabetes and the future risk of gout (p for trend < 0.001). The multivariate RRs with the duration of all diabetes of 0–3, 4–9, and ≥ 10 years were 0.81 (95% CI, 0.74 to 0.90), 0.67 (95% CI, 0.61 to 0.73), and 0.52 (95% CI, 0.46 to 0.58), respectively. This graded association remained evident for type 2 diabetes (p for trend < 0.001), whereas the strong inverse association with type 1 diabetes was evident from the first year of the diagnosis without a substantial change with a longer duration of diabetes (p for trend = 0.84) (Table 3).

In our stratified analyses, the inverse association was significantly stronger among men than women (multivariate RR, 0.59 vs. 0.90; P value for interaction <0.001) (Table 2). Similarly, the association was stronger among individuals without diuretic use than among diuretic users (multivariate RR, 0.58; 95% CI, 0.53 to 0.64 vs. multivariate RR, 0.72; 95% CI, 0.66 to 0.79; P value for interaction, 0.009). In all subgroups we evaluated, the inverse association with type 1 diabetes remained stronger than with type 2 diabetes.

DISCUSSION

In this large general practice cohort, we found that men with diabetes had a 41% lower future risk of gout. This inverse association was independent of age, BMI, smoking, alcohol intake, presence of ischemic heart disease, hyperlipidemia, hypertension, and renal failure. Furthermore, the inverse association was evident with both type 1 and type 2 diabetes, although the risk reduction associated with type 1 diabetes was substantially larger (73% vs 39% reduction). Similarly, treated type 2 diabetes, a marker for severe diabetes or high levels of glucose, showed a lower risk of gout than untreated diabetes. Type 2 diabetes showed a clear dose response relationship with the duration of diabetes, whereas type 1 diabetes revealed a reduced risk of gout from the first year of the diagnosis. Finally, the inverse association was weaker among women, as suggested by previous findings based on serum uric acid measurements.[5,14] The current study provides the first large-scale evidence for the independent protective effect of diabetes against the future risk for gout.

Individuals with diabetes are at a lower future risk of gout likely through the uricosuric effect of glycosuria, which occurs when the blood glucose level is greater than approximately 10 mmol/L (180 mg/dL).[5,6] For example, a nationally representative study showed that an HbA1c level ≥ 9% was associated with a lower serum uric acid level than an

HbA1c level < 5% by 1.1 mg/dL among men and by 0.4 mg/dL among women (P-value for interaction < 0.0001). Corresponding odds ratios for hyperuricemia as an outcome showed 0.24 (95% CI, 0.09 to 0.67) among men and 0.51 (95% CI, 0.25 to 1.03) among women.[5] Similarly, studies have shown that a history of diabetes was significantly associated with lower levels of serum uric acid [4–8] and the inverse association was significantly stronger among men than women.[5] These previous data based on serum uric acid, the causal intermediate of gout, closely agree with the current study findings based on gout, the clinical outcome.

Our findings might appear counterintuitive given the strong cross-sectional associations between hyperuricemia, gout and the metabolic syndrome,[9,15–20] which is considered a prediabetes status. However, it is important to note that this strong association exists during prediabetes status when increased serum urate levels are primarily influenced by increased insulin levels associated with insulin resistance, without the counteracting uricosuric effect of glycosuria, which becomes evident when diabetes develops. For example, a large prospective cohort study showed that, as compared with normal individuals, the prevalence of hyperuricemia was 74% higher in men with prediabetes, but was 63% lower in men with diabetes.[4] The corresponding serum uric acid level differences compared with normal individuals were 0.3 mg/dL and −0.77 mg/dL.[4] This difference became increasingly negative with increasing duration of diabetes.[4] Thus, these data suggested that individuals with prediabetes are at a higher risk of developing gout, but once they develop diabetes their risk drops to a lower level than that of non-diabetic individuals, as our data also indicate. The latter notion was further supported by the stronger protective association seen with type 1 diabetes and a longer duration of type 2 diabetes, likely due to a prolonged period of relative hypouricemia in these cases.

Furthermore, the impaired inflammatory response observed in diabetes may play a protective role against the risk of gout, which is the direct result of an intense inflammatory response to urate crystals.[9] Urate crystals are able to directly initiate, amplify, and sustain an intense inflammatory attack because of their ability to stimulate the synthesis and release of humoral and cellular inflammatory mediators.[9] Many of these inflammatory components have been found to be impaired in diabetes, including decreased microvascular responses to inflammatory mediators such as histamine and bradykinin,[21,22] reduced protein leakage and edema formation,[23–25] reduced mast cell degranulation,[26] impairment of neutrophil adhesion to the endothelium and migration to the site of inflammation,[27–30] production of reactive oxygen species and reduced release of cytokines and prostaglandin by neutrophils,[31–33] increased leukocyte apoptosis, and reduction in lymph node retention capacity.[34,35] These findings further provide potential biologic mechanisms that may underlie the inverse association observed in this study.

Our longitudinal findings add an interesting twist to the accumulating evidence for the independent impact of both hyperuricemia and gout on the risk of type 2 diabetes.[36–38] For example, in a lifestyle intervention study of high-risk middle aged subjects with impaired glucose tolerance, baseline uric acid and its changes predicted a two-fold increase in the likelihood of developing type 2 diabetes.[36] Similarly, men with gout have been found to have a higher future risk of type 2 diabetes independent of other known risk factors.[37] Taken together with our current findings, one could conclude that while gout increases the future risk of diabetes, diabetes decreases the future risk of gout. These opposing directions of effect explain well the cross-sectional associations between the two conditions, which were surprisingly modest despite their strong associations with the metabolic syndrome. For example, a cross-sectional analysis based on the UK General Practice Research Database (GPRD) found an 11% increased prevalence of type 2 diabetes among individuals with gout,[3] and a study of male health professionals reported that the

prevalence of diabetes was 5% among men with gout and 3% among men without gout.[39] These modest, positive cross-sectional associations are likely to be the residual associations after cancelling out the opposing directions of risk posed by one condition on the future risk of the other.

Strengths and limitations of our study deserve comment. This study was performed using a large UK general practice; therefore, findings are likely to be applicable to the general population. Because the definition of gout was based on GPs' diagnoses, a certain level of misclassification of exposure is inevitable. A diagnosis of gout could have often been recorded based on the suggestive clinical presentation of gout without documentation of monosodium urate crystals. Any nondifferential misclassification of these diagnoses would have biased the study results toward the null and would not explain the strong associations and dose-response relationships observed in this study. Furthermore, when we used GPs' diagnoses of gout combined with anti-gout medication use as our case definition, our results remained similar. Finally, a potential detection bias (i.e., increased detection of gout due to clinical care associated with diabetes) would not explain the observed inverse association.

In conclusion, our findings suggest that individuals with diabetes are at a lower future risk of gout independent of other known risk factors, and the protective effect was stronger among men with type 1 diabetes or with long standing type 2 diabetes. These data provide support for a substantial role of the pathophysiology associated with diabetes (e.g. the uricosuric effect of glycosuria and the impaired inflammatory response) against the risk of developing gout.

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Table 1

Characteristics of Cases of Gout and Frequency-Matched Controls

Variable		Controls (%) N=50,000	Cases (%) N=24,768	RR (CI 95%)*
Sex	Male	36,953 (73.91)	17,946 (72.46)	–
	Female	13,047 (26.09)	6,822 (27.54)	–
Age, years	20–49	10,211 (20,42)	5,290 (21.36)	–
	50–59	10,111 (20.22)	4,873 (19.67)	–
	60–69	11,930 (23.86)	5,753 (23.23)	–
	70–79	11,896 (23.79)	5,858 (23.65)	–
	80–89	5,852 (11.70)	2,994 (12.09)	–
GP Visits, N	0–4	22,700 (45.40)	6,785 (27.39)	1 (−)
	5–9	13,201 (26.40)	6,692 (27.02)	1.69 (1.62–1.77)
	10–19	10,422 (20.84)	7,400 (29.88)	2.35 (2.25–2.46)
	≥ 20	3,677 (7.35)	3,891 (15.71)	3.42 (3.23–3.62)
Smoking	Non-Smoker	24,032 (48.06)	11,558 (46.67)	1 (−)
	Current Smoker	9,931 (19.86)	3,782 (15.27)	0.77 (0.74–0.81)
	Past Smoker	10,879 (21.76)	7,951 (32.10)	1.21 (1.16–1.26)
	Unknown	5,158 (10.32)	1,477 (5.96)	0.83 (0.78–0.89)
Alcohol, servings per week				
	Non Use	16,396 (32.79)	7,628 (30.80)	1 (−)
	1–9	13,362 (26.72)	5,960 (24.06)	1.02 (0.98–1.07)
	10–24	8,150 (16.30)	5,074 (20.49)	1.53 (1.45–1.60)
	25–42	2,152 (4.30)	2,053 (8.29)	2.37 (2.20–2.54)
	≥ 42	633 (1.27)	739 (2.98)	2.83 (2.52–3.17)
	Unknown	9,307 (18.61)	3,314 (13.38)	1.06 (1.00–1.11)
BMI	<20	1,588 (3.18)	315 (1.27)	0.61 (0.54–0.69)
	20–24.9	13,899 (27.80)	4,225 (17.06)	1 (−)
	25–29.9	16,623 (33.25)	9,169 (37.02)	1.75 (1.68–1.83)
	≥ 30	7,412 (14.82)	7,176 (28.97)	2.72 (2.59–2.86)
	Unknown	10,478 (20.96)	3,883 (15.68)	1.44 (1.37–1.52)
Ischemic Heart Disease		6,716 (13.43)	4,923 (19.88)	1.37 (1.31–1.43)
Hypertension		16,280 (32.56)	12,858 (51.91)	1.99 (1.92–2.06)
Hyperlipidemia		5,928 (11.86)	4,579 (18.49)	1.33 (1.27–1.39)
Renal Failure		467 (0.93)	947 (3.82)	2.92 (2.60–3.28)

*RR adjusted for sex, age, calendar year and GP visits

Table 2

Relative Risk of Incident Gout Associated with Diabetes

Characteristics	Controls (%) N=50,000	Cases (%) N=24,768	RR (CI 95%)*	RR (CI 95%)†
Overall				
No Diabetes	46,115 (92.23)	22,364 (90.29)	1 (−)	1 (−)
All Diabetes	3,885 (7.77)	2,404 (9.71)	0.85 (0.80–0.90)	0.67 (0.63–0.71)
Type 1 Diabetes	199 (0.40)	55 (0.22)	0.37 (0.27–0.50)	0.33 (0.24–0.46)
Type 2 Diabetes	3,686 (7.37)	2,349 (9.48)	0.88 (0.83–0.93)	0.69 (0.64–0.73)
Untreated	978 (1.96)	772 (3.12)	1.15 (1.04–1.27)	0.91 (0.82–1.01)
Treated	2,708 (5.42)	1,577 (6.37)	0.78 (0.73–0.84)	0.61 (0.56–0.65)
Men				
No Diabetes	34,018 (92.10)	16,425 (91.52)	1 (−)	1 (−)
All Diabetes	2,935 (7.94)	1,521 (8.48)	0.72 (0.68–0.78)	0.59 (0.55–0.64)
Type 1 Diabetes	166 (0.45)	36 (0.2)	0.30 (0.21–0.43)	0.27 (0.19–0.40)
Type 2 Diabetes	2,769 (7.49)	1,485 (8.27)	0.75 (0.70–0.81)	0.61 (0.27–0.66)
Untreated	728 (1.97)	519 (2.89)	1.07 (0.95–1.20)	0.86 (0.76–0.97)
Treated	2,041 (5.52)	966 (5.38)	0.64 (0.59–0.70)	0.52 (0.48–0.57)
Women				
No Diabetes	12,097 (92.72)	5,939 (87.06)	1 (−)	1 (−)
All Diabetes	950 (7.28)	883 (12.94)	1.23 (1.11–1.36)	0.90 (0.80–1.00)
Type 1 Diabetes	33 (0.25)	19 (0.28)	0.69 (0.38–1.24)	0.63 (0.34–1.16)
Type 2 Diabetes	917 (7.03)	864 (12.66)	1.25 (1.12–1.39)	0.91 (0.81–1.02)
Untreated	250 (1.92)	253 (3.71)	1.39 (1.15–1.67)	1.08 (0.89–1.31)
Treated	667 (5.11)	611 (8.96)	1.20 (1.06–1.35)	0.85 (0.75–0.97)

*RR adjusted for sex, age, calendar year and GP visits. In the stratified analyses sex was removed from the model.

†RR adjusted for sex, age, calendar year, GP visits, BMI, alcohol consumption, smoking, IHD, hypertension, hyperlipidemia and renal failure. In the stratified analyses sex was removed from the model.

Table 3

Relative Risk of Gout by Duration of Diabetes

	Controls (%) N=50,000	Cases (%) N=24,768	RR (CI 95%)*	RR (CI 95%)†
Overall				
All Diabetes				
0–3 years	1,065 (2.13)	828 (3.34)	1.02 (0.93–1.13)	0.81 (0.74–0.90)
4–9 years	1,667 (3.33)	1,021 (4.12)	0.86 (0.79–0.93)	0.67 (0.61–0.73)
≥10 years	1,153 (2.31)	555 (2.24)	0.67 (0.60–0.74)	0.52 (0.46–0.58)
Type 1 Diabetes				
0–3 years	13 (0.03)	3 (0.01)	0.34 (0.09–1.25)	0.36 (0.10–1.34)
4–9 years	41 (0.08)	9 (0.04)	0.26 (0.13–0.55)	0.26 (0.12–0.55)
≥10 years	145 (0.29)	43 (0.17)	0.40 (0.28–0.57)	0.35 (0.24–0.51)
Type 2 Diabetes				
0–3 years	1,052 (2.10)	825 (3.33)	1.03 (0.94–1.14)	0.82 (0.74–0.91)
4–9 years	1,626 (3.25)	1,012 (4.09)	0.87 (0.80–0.95)	0.68 (0.62–0.75)
10 and more years	1,008 (2.02)	512 (2.07)	0.71 (0.63–0.79)	0.54 (0.48–0.61)
Men				
All Diabetes				
0–3 years	784 (2.12)	499 (2.78)	0.85 (0.76–0.96)	0.70 (0.62–0.79)
4–9 years	1,262 (3.42)	668 (3.72)	0.75 (0.68–0.83)	0.61 (0.55–0.68)
≥10 years	889 (2.41)	354 (1.97)	0.57 (0.50–0.64)	0.46 (0.40–0.53)
Type 1 Diabetes				
0–3 years	12 (0.03)	2 (0.01)	0.28 (0.06–1.30)	0.27 (0.06–1.28)
4–9 years	34 (0.09)	5 (0.03)	0.18 (0.07–0.47)	0.18 (0.07–0.47)
≥10 years	120 (0.32)	29 (0.16)	0.34 (0.22–0.51)	0.30 (0.19–0.47)
Type 2 Diabetes				
0–3 years	772 (2.09)	497 (2.77)	0.86 (0.76–0.97)	0.71 (0.62–0.80)
4–9 years	1,228 (3.32)	663 (3.69)	0.77 (0.69–0.85)	0.62 (0.56–0.70)
≥10 years	769 (2.08)	325 (1.81)	0.60 (0.52–0.69)	0.48 (0.42–0.56)
Women				
All Diabetes				
0–3 years	281 (2.15)	329 (4.82)	1.48 (1.25–1.76)	1.13 (0.94–1.35)
4–9 years	405 (3.10)	353 (5.17)	1.19 (1.02–1.38)	0.86 (0.73–1.02)
≥10 years	264 (2.02)	201 (2.95)	1.01 (0.83–1.23)	0.71 (0.57–0.87)
Type 1 Diabetes				
0–3 years	1 (0.01)	1 (0.01)	0.70 (0.04–11.28)	1.10 (0.07–17.98)
4–9 years	7 (0.05)	4 (0.06)	0.62 (0.17–2.21)	0.70 (0.19–2.61)

	Controls (%) N=50,000	Cases (%) N=24,768	RR (CI 95%)*	RR (CI 95%)†
≥10 years	25 (0.19)	14 (0.21)	0.71 (0.36–1.40)	0.58 (0.28–1.20)
Type 2 Diabetes				
0–3 years	280 (2.15)	328 (4.81)	1.49 (1.26–1.76)	1.13 (0.94–1.35)
4–9 years	398 (3.05)	349 (5.12)	1.20 (1.02–1.40)	0.87 (0.73–1.02)
≥10 years	239 (1.83)	187 (2.74)	1.04 (0.85–1.28)	0.72 (0.58–0.89)

*RR adjusted for sex, age, calendar year and GP visits.

†RR adjusted for sex, age, calendar year, GP visits, BMI, alcohol consumption, smoking, IHD, hypertension, hyperlipidemia and renal failure

IHD: ischaemic heart disease