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Gout and the risk of Alzheimer's disease: a population-based, BMI-matched cohort study

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Abstract

Objective—While gout is associated with cardiovascular (CV)-metabolic comorbidities and their sequelae, the antioxidant effects of uric acid may have neuroprotective benefits. We evaluated the potential impact of incident gout on the risk of developing Alzheimer's disease (AD) in a general population context.

Methods—We conducted an age-matched, sex-matched, entry-time-matched and body mass index (BMI)-matched cohort study using data from The Health Improvement Network, an electronic medical record database representative of the UK general population, from 1 January 1995 to 31 December 2013. Up to five non-gout individuals were matched to each case of incident gout by age, sex, year of enrolment and BMI. We compared incidence rates of AD between the gout and comparison cohorts, excluding individuals with prevalent gout or dementia at baseline. Multivariate hazard ratios (HRs) were calculated, while adjusting for smoking, alcohol use, physician visits, social deprivation index, comorbidities and medication use. We repeated the same analysis among patients with incident osteoarthritis (OA) as a negative control exposure.

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Results—We identified 309 new cases of AD among 59 224 patients with gout (29% female, mean age 65 years) and 1942 cases among 238 805 in the comparison cohort over a 5-year median follow up (1.0 vs 1.5 per 1000 person-years, respectively). Univariate (age-matched, sex-matched, entry-time-matched and BMI-matched) and multivariate HRs for AD among patients with gout were 0.71 (95% CI 0.62 to 0.80) and 0.76 (95% CI 0.66 to 0.87), respectively. The inverse association persisted among subgroups stratified by sex, age group (<75 and ≥75 years), social deprivation index and history of CV disease. The association between incident OA and the risk of incident AD was null.

Conclusions—These findings provide the first general population-based evidence that gout is inversely associated with the risk of developing AD, supporting the purported potential neuroprotective role of uric acid.

INTRODUCTION

Hyperuricaemia is the key causal precursor for gout, the most common inflammatory arthritis, and is associated with an increased risk of cardiovascular (CV)-renal comorbidities and their sequelae.[1–5] However, as a major natural antioxidant in the body, uric acid has been estimated to account for more than 50% of the antioxidant capacity of plasma.[6] Furthermore, the antioxidant properties of uric acid have been hypothesised to protect against the development or progression of neurodegenerative conditions such as Parkinson's disease (PD).[7–9]

With these potentially neuroprotective properties, uric acid has been hypothesised to protect against oxidative stress, a prominent contributor to dopaminergic neuron degeneration in PD,[910] which may also play an important role in the pathogenesis of Alzheimer's disease (AD).[1112] Indeed, a prospective, population-based study has found that higher serum uric acid (SUA) levels were associated with a lower risk of incident dementia over an 11 year follow-up period (HR adjusted for age, sex and CV risk factors, 0.89 (95% CI 0.80 to 0.99) per SD increase of SUA).[13] Furthermore, the same study found that higher SUA levels at baseline were associated with better cognitive function later in life, for all cognitive domains. Notably, this study investigated overall dementia, thus including both AD and vascular dementia. To our knowledge, no studies have examined the relationship between gout and the risk of AD. In this study, we evaluated the potential impact of incident gout on the risk of developing AD in a general population context.

METHODS

Data source

The Health Improvement Network (THIN) is a computerised medical record database from general practices in the UK.[14] Data on approximately 10.2 million patients from 580 general practices are systematically recorded by general practitioners (GPs) and sent anonymously to THIN. Because the National Health Service in the UK requires every individual to be registered with a GP regardless of health status, THIN is a population-based cohort representative of the UK general population. The computerised information includes demographics, details from GP visits, diagnoses from specialists' referrals and hospital

admissions, results of laboratory tests and additional systematically recorded health information including height, weight, blood pressure, smoking status and vaccinations. The Read classification is used to code specific diagnoses,[15] and a drug dictionary based on data from the Multilex classification is used to code drugs.[16] Health information is recorded onsite at each practice using a computerised system with quality control procedures to maintain high data completion rates and accuracy.

Study design

The study population included individuals aged ≥40 years who had at least 1 year of active enrolment with the general practice during 1 January1995–31 December 2013 (n=3 727 437). Individuals diagnosed with gout or any dementia prior to the start of follow-up were excluded. We conducted a cohort analysis of AD among adults with incident gout compared with up to five non-gout individuals matched by age, date of study entry, enrolment year and body mass index (BMI) within a calliper of ±0.5 kg/m^2 (comparison cohort) using data from THIN. We matched on BMI, as obesity is a strong risk factor for gout[17] and has been consistently associated with dementia.[18,19] Participants entered the cohort when all inclusion criteria were met or on the matched date for subjects in the comparison cohort (index date), and were followed until they developed AD, died, left the THIN database or the follow-up ended, whichever came first.

Gout case ascertainment

Gout was defined by diagnostic code using the Read classification.[20] Through a computer search using Read codes, we identified all patients with a first-ever diagnosis of gout recorded by a GP (n=59 224). This date of gout diagnosis was the index date. To evaluate the robustness of gout case ascertainment, we performed a sensitivity analysis where we restricted gout cases to those with a gout diagnosis plus those receiving gout treatment (colchicine or urate-lowering drugs (ie, allopurinol, febuxostat or probenecid)) (n=31 799). A similar case definition of gout has been shown to have a validity of 90% in the General Practice Research Database (GPRD),[21,22] in which 60% of patients overlap with THIN.

AD ascertainment

Our primary outcome was the first recorded diagnosis of AD (see online supplementary table S1 for the list of AD diagnostic codes). The dementia codes were shown to have a positive predictive value of 83% in a validation study based on the UK GPRD.[23] The incidence rates (IRs) of AD per 1000 person-years in our cohort according to age categories <75 years and 75–90 years were 0.6 and 4.0 cases among men and 1.2 and 4.8 cases among women, respectively. These rates were comparable with previous estimates from the GPRD database[24] and other population-based studies.[25]

Assessment of covariates

All comorbidities, lifestyle factors, social–economic deprivation index (SDI), use of CV drugs and healthcare use (ie, GP visits) were collected prior to the index date. Specifically, comorbidities included a history of ischaemic heart disease, stroke, hypertension, hyperlipidaemia and diabetes mellitus. Lifestyle factors such as BMI, smoking status and

alcohol consumption were recorded to the nearest possible measurement prior to the index date. The SDI was measured by the Townsend Deprivation Index Score, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).[2627] Use of CV drugs (ie, aspirin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers, diuretics and non-steroidal anti-inflammatory drugs (NSAIDs)) and the number of visits to a GP were ascertained within 1 year prior to the index date.

A comparison analysis of osteoarthritis as a negative control exposure

As there has been no purported association between osteoarthritis (OA) and AD, we used the same approach to analyse the risk of incident AD among patients with incident OA (n=206 664) as compared with 828 018 age-matched, sex-matched, entry-time-matched and BMI-matched individuals without OA.

Statistical analyses

We compared the baseline characteristics between gout and comparison cohorts. We identified incident cases of AD during the follow-up and calculated the eligible person-time and IRs. We then estimated the cumulative incidence of AD in each cohort, accounting for the competing risk of death.[28] Cox proportional hazard regression models were used to calculate HRs after accounting for matched clusters (age, sex, entry-time and BMI). Our intermediate multivariate model was adjusted for lifestyle factors (smoking and alcohol consumption), and GP visits, whereas our full multivariate model adjusted additionally for comorbidities and CV medication use. In all multivariate models, we additionally adjusted for BMI as a continuous variable to eliminate residual confounding. Stepwise adjustments for adding each covariate into the model were also presented to display the impact of each covariate adjustment. In addition, we conducted further subgroup analyses by sex, age group (<75 years vs 75–90 years), social deprivation index (≤2: low depravity vs >2: high depravity) and comorbidity (ie, hypertension, hyperlipidaemia and CV disease). We tested the significance of heterogeneity with a likelihood ratio test by comparing a model with the main effects, the stratifying variable and the interaction terms to a reduced model with only the main effects. For all analyses, missing values for covariates (ie, smoking and alcohol use) were imputed by a sequential regression method based on a set of covariates as predictors (IVEware for SAS, V.9.2; SAS Institute, Cary, North Carolina, USA). To minimise random error, we imputed five datasets and then combined estimates from these datasets.[2930]

RESULTS

The study cohort included 59 224 patients with gout and 238 805 matched non-gout individuals. The mean age at baseline was 65 years and approximately 71% of the population was men. Baseline characteristics of the cohorts are shown in table 1. Patients with gout tended to consume more alcohol, visit their GP more often and have more CV-metabolic comorbidities and more frequent use of CV medicines.

The cumulative incidence of AD according to the study cohort is depicted in figure 1; the incidence rates and HRs for the risk of AD are shown in table 2. Compared with individuals

without gout, the age-matched, sex-matched, entry-time-matched and BMI-matched HR of AD among patients with gout was 0.71 (95% CI 0.62 to 0.80). After adjusting for all covariates, the multivariate HR was 0.76 (95% CI 0.66 to 0.87). Stepwise regressions suggested that only diuretic use accounted for a difference between these HRs (table 2).

The inverse association persisted among subgroups by sex, age group (<75 and ≥75 years), social deprivation index and history of CV disease (table 3). The protective effect of gout on AD was similar among those with and without CV disease (ie, ischaemic heart disease or stroke) (HRs, 0.65 (95% CI 0.45 to 0.92) vs 0.78 (95% CI 0.65 to 0.93)) (p for heterogeneity, 0.12) (table 3).

In our sensitivity analysis, restricting gout cases to those receiving anti-gout treatment (n=31 799) showed that both the main and subgroup results persisted (see online supplementary table S2). Furthermore, in our comparison analysis of OA as a negative control exposure, we found no association between OA and the risk of incident AD (age-matched, sex-matched, entry-time-matched and BMI-matched HR=1.05 (95% CI 0.98 to 1.10) and multivariate HR=1.02 (95% CI 0.97 to 1.08)).

DISCUSSION

In this large general practice cohort representative of the UK population, we found a 24% lower risk of AD among individuals with a history of gout, after adjustment for age, sex, BMI, socioeconomic status, lifestyle factors, prior CV-metabolic conditions and use of CV drugs. The inverse association was evident among subgroups stratified by sex, age group, social deprivation index and history of CV disease. In contrast, we found no such association with OA. These findings provide the first general population-based evidence that gout is inversely associated with the risk of developing AD, thus supporting the purported potential neuroprotective role of uric acid.

The potential biological mechanisms behind the observed inverse association are speculative. Uric acid has previously been shown to have antioxidative properties;[31] specifically, it is an effective scavenger of peroxynitrite and hydroxyl radicals (thus reducing oxidative stress)[32] and it has metal chelator properties in vitro.[3133] Thus, the possible neuroprotective effects of uric acid may be due to suppression of oxyradical accumulation and preservation of mitochondrial function,[34] thus inhibiting the cytotoxic activity of lactoperoxidase[35] and repairing free-radical-induced DNA damage.[36] In animal models of PD, uric acid has shown neuroprotective effects against oxidative stress-induced dopaminergic neuron death,[37–39] and similar neuroprotective effects have been observed in animal models of other neurological conditions, such as multiple sclerosis and spinal cord injury.[40]

Our study expands on a prospective analysis based on the Rotterdam study that showed an inverse association between prior SUA levels (ie, the causal precursor of gout) and the risk of any dementia.[13] As both vascular dementia and Alzheimer dementia were included in the Rotterdam study, the neuroprotective effect of uric acid may have been masked by the hyperuricaemia-associated increased CV risk (eg, myocardial infarction and ischaemic

stroke).[37–39] The current study investigated the specific risk of AD as an endpoint and found a consistently inverse association with the risk of AD. Further, considering AD (as opposed to vascular dementia) would be more likely to be diagnosed among individuals without CV risk factors or comorbidities, our subgroup analyses according to CV risk factors suggest that the inverse relation persists among individuals regardless of known CV comorbidities. Overall, these findings support the proposed hypothesis that supplementary use of the metabolic precursor to uric acid, like inosine or hypoxanthine, could prevent and attenuate the progression of AD.[41]

Our study has several strengths and limitations. First, our study was based on a large electronic medical record (EMR) database representative of the general population; therefore, our findings are likely to be more generalisable. Because the definitions of gout and AD were based on doctors' diagnoses, a certain level of misclassification is inevitable. A diagnosis of gout could often have been recorded based on the suggestive clinical presentation of gout without documentation of monosodium urate crystals. However, any non-differential misclassification of these diagnoses would have biased the study results towards the null and would not likely explain the significant associations observed in this study. Furthermore, when we used doctors' diagnoses of gout combined with anti-gout drug use (which has previously shown a validity of 90%)[2122] as our case definition, our results tended to be even stronger. While the aforementioned Rotterdam study data[13] suggest that high SUA levels (as opposed to anti-gout medication use) are likely to explain the observed inverse association, these issues deserve further investigation. Finally, our negative control exposure analysis using OA supports that the observed inverse association is unlikely to be related to common features of arthritis such as chronic pain, NSAID use or methodological artefact, and rather is specific to gout, which is caused by hyperuricaemia.

In conclusion, our findings provide the first population-based evidence for the potential protective effect of gout on the risk of AD and support the purported neuroprotective role of uric acid. If confirmed by future studies, a therapeutic investigation that has been employed to prevent progression of PD may be warranted for this relatively common and devastating condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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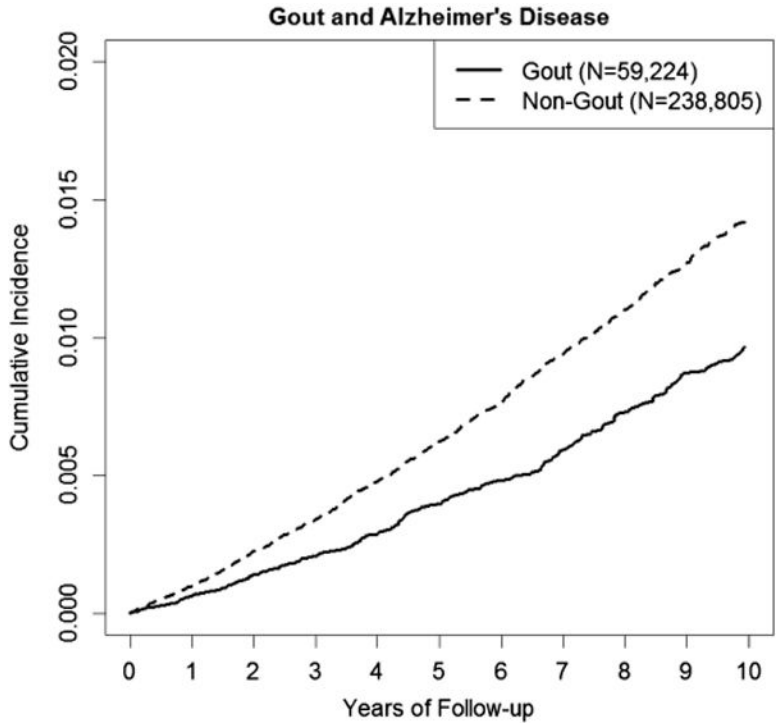

Figure 1.
Cumulative incidence of Alzheimer's disease according to the presence of gout.

Table 1

Baseline characteristics according to the presence of gout

Variables	Gout (n=59 224)	No gout (n=238 805)
Age, years	65.3±12.2	65.3±12.1
Sex		
Male	41 950 (70.8%)	169 749 (71.1%)
Female	17 274 (29.2%)	69 056 (28.9%)
BMI (kg/m^2)		
Mean±SD	28.5±4.6	28.2±4.2
<18.5	214 (0.4%)	600 (0.3%)
18.5–24.9	12 476 (21.1%)	51 898 (21.7%)
25.0–29.9	27 235 (46.0%)	115 671 (48.4%)
≥30.0	19 299 (32.6%)	70 636 (29.6%)
Socioeconomic deprivation index score	2.6±1.3	2.6±1.3
GP visits	5.0±3.9	4.2±3.5
Smoking		
Current	7784 (13.1%)	38 808 (16.3%)
None/past	50 690 (85.6%)	196 566 (82.3%)
Unknown	750 (1.3%)	3431 (1.4%)
Alcohol		
Current	47 526 (80.2%)	182 960 (76.6%)
None/past	8800 (14.9%)	41 788 (17.5%)
Unknown	2898 (4.9%)	14 057 (5.9%)
Hypertension	33 337 (56.3%)	101 435 (42.5%)
Hyperlipidaemia	23 966 (40.5%)	80 280 (33.6%)
Stroke	4976 (8.4%)	15 782 (6.6%)
Ischaemic heart disease	12 673 (21.4%)	38 386 (16.1%)
Diabetes	7341 (12.4%)	31 531 (13.2%)
Angiotensin-converting enzyme inhibitor (ACEI)	19 210 (32.4%)	53 459 (22.4%)
Aspirin	16 400 (27.7%)	57 133 (23.9%)
Angiotensin II receptor blockers (ARBs)	6861 (11.6%)	18 411 (7.7%)
Beta-blockers	17 957 (30.3%)	47 212 (19.8%)
Calcium channel blockers (CCBs)	13 347 (22.5%)	47 447 (19.9%)
Diuretics	26 606 (44.9%)	59 256 (24.8%)
NSAIDs	20 530 (34.7%)	49 826 (20.9%)

Data are represented as mean±SD or number (percentage).

Hyperlipidaemia: defined as a diagnosis of hyperlipidaemia or use of antihyperlipidaemics.

Socioeconomic Deprivation Index score was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

BMI, body mass index; GP, general practitioner; NSAID, non-steroidal anti-inflammatory drug.

Table 2

Incidence rates and HRs for Alzheimer's disease according to the presence of gout

	Gout (n=59 224)	No gout (n=238 805)
Cases, n	309	1942
Follow-up time, person-years	299 799	1 258 059
Mean follow-up, years	5.1	5.3
Incidence rate (cases per 1000 person-years)	1.0 (0.9 to 1.2)	1.5 (1.4 to 1.6)
Age-matched, sex-matched, entry-time-matched, BMI-matched HR (95% CI)	0.71 (0.62 to 0.80)	1.0 (reference)
+Continuous BMI-adjusted HR (95% CI)	0.71 (0.62 to 0.80)	1.0 (reference)
+Diuretics-adjusted HR (95% CI)	0.76 (0.68 to 0.87)	1.0 (reference)
+Other CV drugs (95% CI)	0.76 (0.67 to 0.87)	1.0 (reference)
+CV comorbidities (95% CI)	0.76 (0.67 to 0.88)	1.0 (reference)
+GPs visits, smoking, alcohol and SDI (95% CI)	0.76 (0.66 to 0.87)	1.0 (reference)

BMI, body mass index; CV, cardiovascular; GP, general practitioner; SDI, social–economic deprivation index.

Table 3

Incidence rates and HRs for associations between gout and Alzheimer's disease according to subgroups

Gout status	N	Cases	Follow-up time (person-years)	Mean follow-up (years)	Incidence rate (cases per 1000 person-years)	Age, sex, entry-time, and BMI-matched HR (95% CI)*	+ GPs visits, continuous BMI, smoking, and alcohol adjusted HR (95% CI)	+ comorbidity and CVD drug adjusted HR* (95% CI)
Total								
Yes	59 224	309	299 799.1	5.1	1.0 (0.9 to 1.2)	0.71 (0.62 to 0.80)	0.70 (0.62 to 0.80)	0.76 (0.66 to 0.87)
No	238 805	1942	1 258 058.9	5.3	1.5 (1.4 to 1.6)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Female								
Yes	17 274	122	83 951.9	4.9	1.5 (1.2 to 1.7)	0.65 (0.53 to 0.80)	0.68 (0.55 to 0.83)	0.72 (0.58 to 0.90)
No	69 056	856	355 988.2	5.2	2.4 (2.2 to 2.6)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Male								
Yes	41 950	187	215 847.3	5.1	0.9 (0.7 to 1.0)	0.75 (0.63 to 0.88)	0.73 (0.61 to 0.87)	0.80 (0.67 to 0.95)
No	169 749	1086	902 070.8	5.3	1.2 (1.1 to 1.3)	1.0 (reference)	1.0 (reference)	1.0 (reference)
<75 years								
Yes	44 407	141	244 754.2	5.5	0.6 (0.5 to 0.7)	0.77 (0.63 to 0.94)	0.77 (0.63 to 0.93)	0.79 (0.65 to 0.97)
No	180 066	850	1 025 029.2	5.7	0.8 (0.8 to 0.9)	1.0 (reference)	1.0 (reference)	1.0 (reference)
75–90 years								
Yes	14 817	168	55 045.0	3.7	3.1 (2.6 to 3.6)	0.66 (0.55 to 0.78)	0.66 (0.55 to 0.78)	0.72 (0.60 to 0.87)
No	58 739	1092	233 029.7	4.0	4.7 (4.4 to 5.0)	1.0 (reference)	1.0 (reference)	1.0 (reference)
High socioeconomic depravity (SDI>2)								
Yes	23 277	121	117 926.0	5.1	1.0 (0.9 to 1.2)	0.64 (0.50 to 0.83)	0.69 (0.54 to 0.87)	0.71 (0.55 to 0.92)
No	92 583	810	489 553.6	5.3	1.7 (1.5 to 1.8)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Low socioeconomic depravity (SDI≤2)								
Yes	35 947	188	181 873.2	5.1	1.0 (0.9 to 1.2)	0.75 (0.62 to 0.90)	0.72 (0.57 to 0.91)	0.78 (0.61 to 0.99)
No	146 222	1132	768 505.3	5.3	1.5 (1.4 to 1.6)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Hypertension								
Yes	33 337	192	159 670.2	4.8	1.2 (1.0 to 1.4)	0.73 (0.60 to 0.88)	0.73 (0.60 to 0.88)	0.74 (0.61 to 0.91)
No	101 435	927	487 592.5	4.8	1.9 (1.8 to 2.0)	1.0 (reference)	1.0 (reference)	1.0 (reference)
No hypertension								
Yes	25 887	117	140 128.9	5.4	0.8 (0.7 to 1.0)	0.76 (0.59 to 0.98)	0.75 (0.58 to 0.97)	0.78 (0.60 to 1.01)

Gout status	N	Cases	Follow-up time (person-years)	Mean follow-up (years)	Incidence rate (cases per 1000 person-years)	Age, sex, entry-time, and BMI-matched HR (95% CI)*	+ GPs visits, continuous BMI, smoking, and alcohol adjusted HR (95% CI)	+ comorbidity and CVD drug adjusted HR* (95% CI)
No	137 370	1015	770 466.5	5.6	1.3 (1.2 to 1.4)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Hyperlipidaemia								
Yes	23 966	121	101 617.9	4.2	1.2 (1.0 to 1.4)	0.66 (0.51 to 0.86)	0.65 (0.50 to 0.84)	0.69 (0.52 to 0.91)
No	80 280	623	345 379.8	4.3	1.8 (1.7 to 2.0)	1.0 (reference)	1.0 (reference)	1.0 (reference)
No hyperlipidaemia								
Yes	35 258	188	198 181.3	5.6	0.9 (0.8 to 1.1)	0.70 (0.58 to 0.84)	0.70 (0.58 to 0.84)	0.75 (0.62 to 0.91)
No	158 525	1319	912 679.1	5.8	1.4 (1.4 to 1.5)	1.0 (reference)	1.0 (reference)	1.0 (reference)
CVD								
Yes	15 691	87	70 580.6	4.5	1.2 (1.0 to 1.5)	0.56 (0.40 to 0.78)	0.54 (0.39 to 0.75)	0.65 (0.45 to 0.92)
No	49 189	508	236 346.2	4.8	2.1 (2.0 to 2.3)	1.0 (reference)	1.0 (reference)	1.0 (reference)
No CVD								
Yes	43 533	222	229 218.5	5.3	1.0 (0.8 to 1.1)	0.74 (0.63 to 0.88)	0.74 (0.63 to 0.88)	0.78 (0.65 to 0.93)
No	189 616	1434	1 021 712.8	5.4	1.4 (1.3 to 1.5)	1.0 (reference)	1.0 (reference)	1.0 (reference)

*Adjusted for the covariates in table 1, except for the subgroup variables.

BMI, body mass index; CVD, cardiovascular disease; GP, general practitioner; SDI, social–economic deprivation index.