Supplementary materials for

Denosumab and incidence of type 2 diabetes among adults with osteoporosis: population based cohort study

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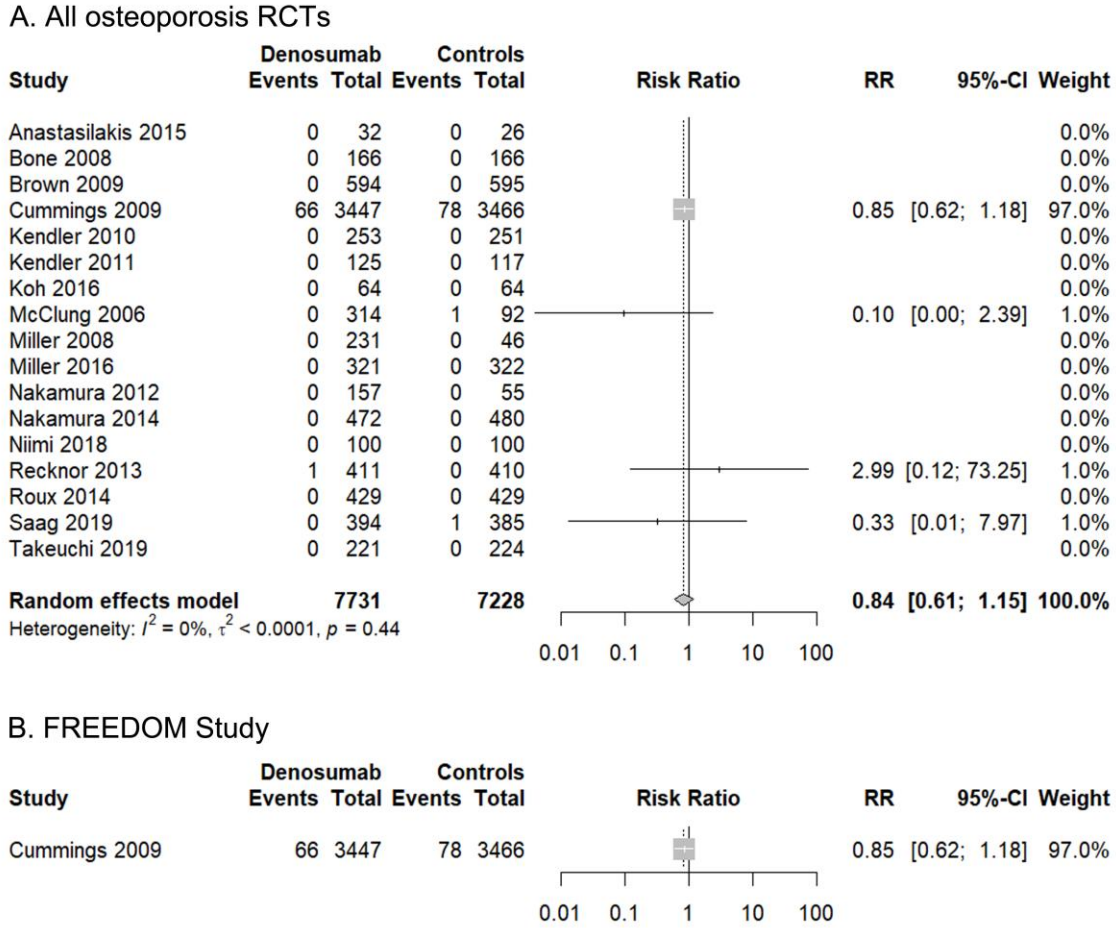
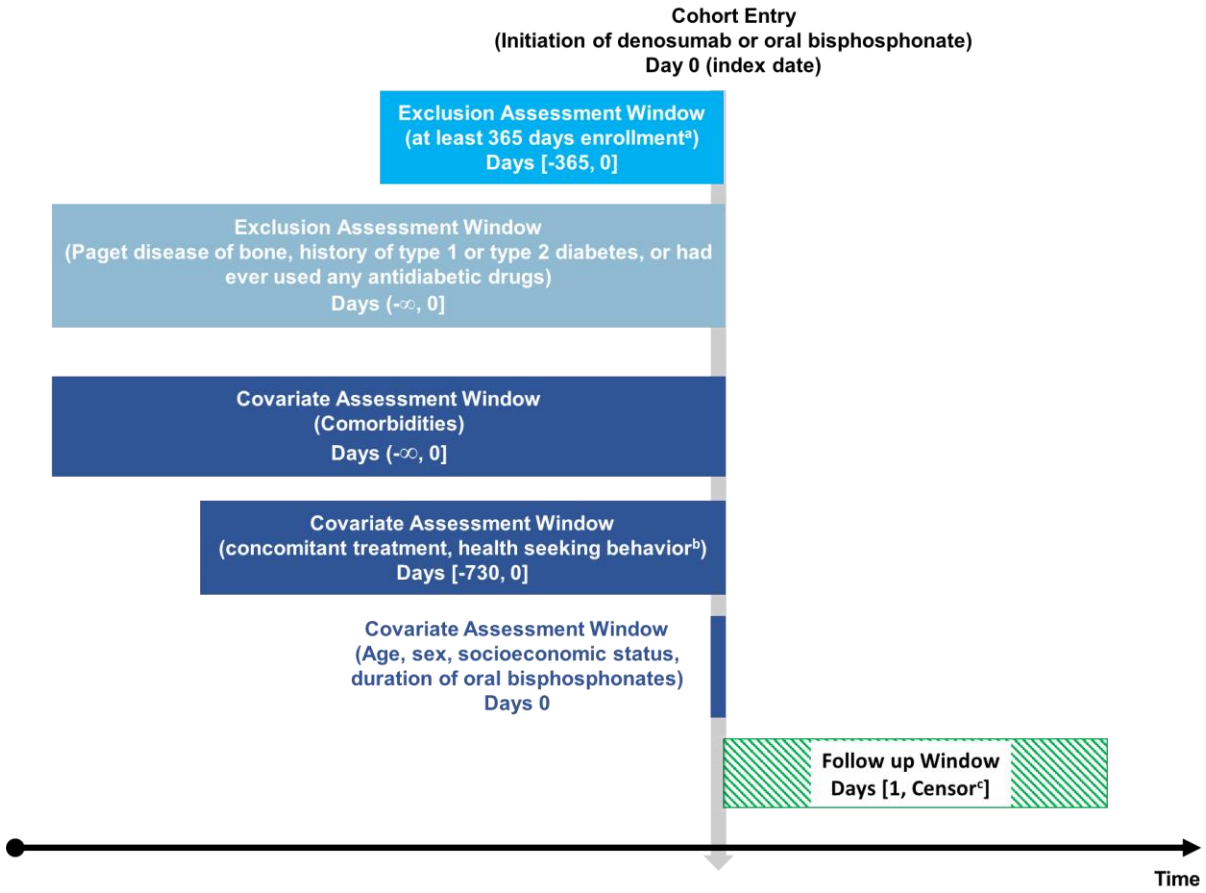


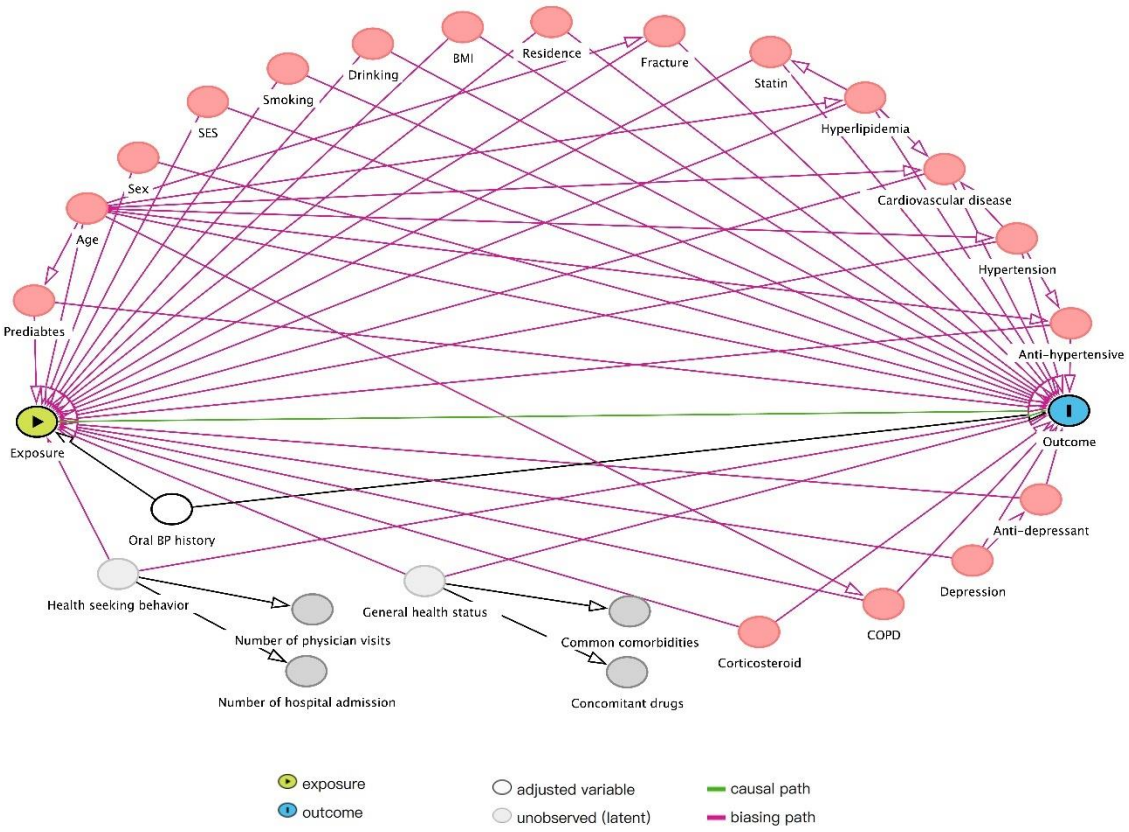
Supplemental Figure 1 Results of incident type 2 diabetes from randomized controlled trials with denosumab

The majority of randomized clinical trials (RCTs) involving denosumab have reported no cases of type 2 diabetes, with controls comprising both active comparators and placebos. FREEDOM, the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial.



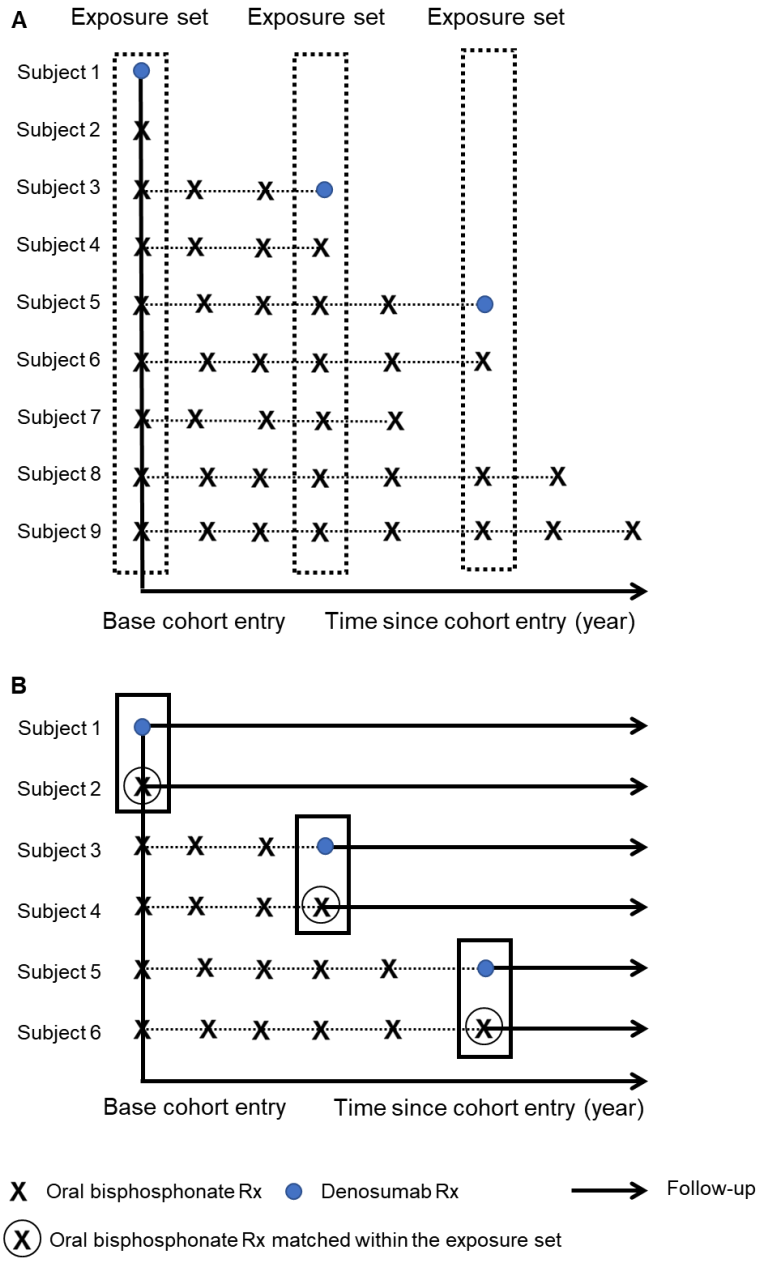
a. Patients were required to have been enrolled for at least 365 days.
b. Health seeking behavior was proxied by number of hospital admission and physician visits.
c. Earliest of: study outcome (type 2 diabetes), discontinuation of drug of interest, death, transfer out of primary care clinic, 5 years follow-up, or end of the study period (31 December 2021).

Supplemental Figure 2 Study design



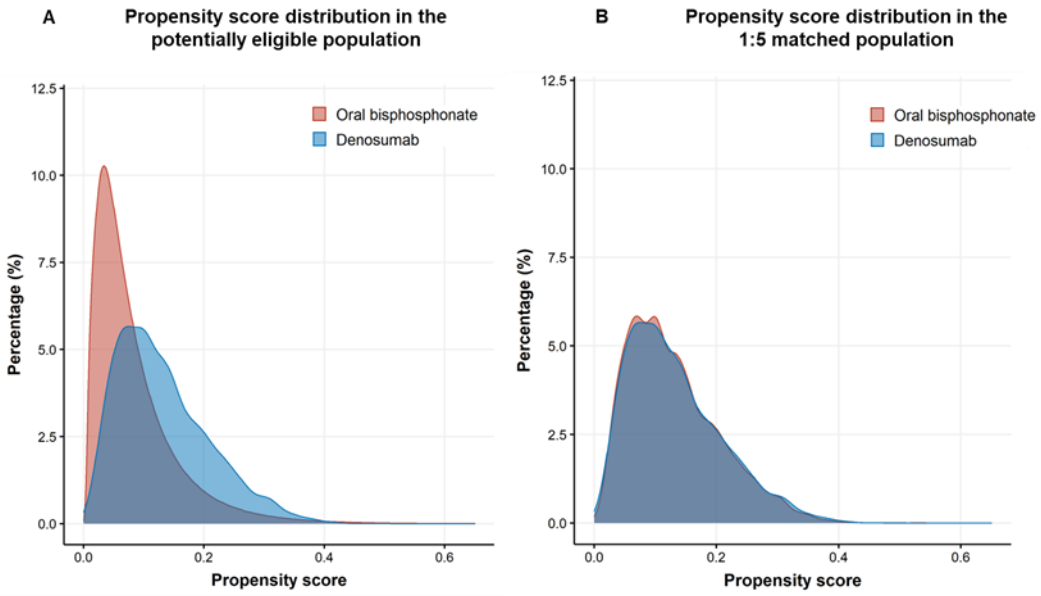
Supplemental Figure 3 Directed acyclic graph (DAG) of the study question

Illustration of the casual framework with a Directed Acyclic Graph (DAG). We considered a wide range of potential confounders. Our rationale for selecting potential confounders focused on variables associated with type 2 diabetes, which may also be associated with the drug of interest, based on current literature and subject matter expertise[1]. We included the following covariates measured at the index date: age, sex, smoking status, alcohol consumption status, body mass index (BMI), socioeconomic deprivation index (Townsend score), residence status, duration of oral bisphosphonate treatment, history of major osteoporotic fracture, comorbidities (cardiovascular disease, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease[2], depression[3], prediabetes[4]), and concomitant treatment (antihypertensive, statin, glucocorticoid, and antidepressant[5]). We considered general health status as a potential unmeasured confounder and used common comorbidities (dementia, chronic heart failure, congestive heart disease, peripheral vascular disease, other circulation diseases, venous thromboembolism, anxiety, peptic ulcer disease, renal disease, and cancer) and related concomitant drugs (non-steroidal anti-inflammatory drug, aspirin, oral anticoagulant, and proton pump inhibitor) as proxies. We also included markers of health seeking behavior, using the number of hospital admissions and visits to doctors as proxies. Oral BP history was adjusted by design. General health status and health seeking behavior were unobserved, and proxies were used. Other variables indicated with red note were adjusted in propensity score model. The DAG was plotted with DAGitty[6]. BP, bisphosphonate; SES, socioeconomic deprivation index (Townsend score); BMI, body mass index; COPD, chronic obstructive pulmonary disease.



Supplemental Figure 4 The modified new user design with time-based exposure sets

Depiction of the modified new user design with six patients. Each denosumab initiator was matched to oral bisphosphonate users within each exposure set (cluster) using propensity scores. A. The time-based exposure set was defined by a small-time interval (2 months) surrounding the timing of the denosumab prescription (depicted in the dotted box). B. Incident new user of denosumab (subject 1) was matched to incident new users of oral bisphosphonate (subject 2) who initiated treatment in the same period in their exposure set. Subjects who switched to denosumab from an oral bisphosphonate (oral bisphosphonate switchers, subjects 3 and 5) were matched to subjects who had been using oral bisphosphonates for the same duration (subjects 4 and 6) with the closet propensity score. Rx, prescriptions. This figure was adapted from previous literature [7,8].



Supplemental Figure 5 Propensity score distribution of the study groups.

This figure displays the propensity score distributions in the potentially eligible population (A) and the 1:5 matched population (B). The objective of the matching process was to identify appropriate comparators for all eligible denosumab users. Out of the 4350 denosumab users, 4301 (98.9%) were successfully matched with comparators, as indicated by the overlapping areas of propensity score distribution in the two groups.

Supplemental Method Matching procedure and sensitivity analyses

We used the following matching algorithm adapted from typical prevalent new user design[7]. (1) Form the base cohort of all users of denosumab and the comparator drugs. (2) For every new user of denosumab, identify from the base cohort every subject who had at least the same duration of exposure to the comparator drugs at the index date. (3) Perform a single Cox proportional hazards regression or conditional logistic regression analysis using all the exposure sets to derive the time-conditional propensity scores, including appropriate variables. (4) Verify for each exposure set that the time-conditional propensity score of the exposed subject lies within the range of the time-conditional propensity scores of the members of the corresponding exposure set, else eliminate the exposure set. (5) Matching process: starting chronologically with the first subject using denosumab, and comparators (matched at a variable 1:5 ratio) were selected from the exposure set with the nearest propensity score within a caliper (0.2 standard deviations of the propensity score on the logarithmic scale) (without replacement within in each exposure set, but may be reused in subsequent exposure sets). Subjects selected as comparators were eligible for subsequent exposure sets. (6) Form the matched cohorts: exclude denosumab users that failed to match with any comparators.

We performed a series of post-hoc sensitivity analyses to test the robustness of the study findings. Firstly, to provide a more objective evaluation of the study endpoint, we defined type 2 diabetes using laboratory tests only, including fasting blood sugar ≥7.0 mmol/L, random glucose level ≥11.1 mmol/L, glucose tolerance test result ≥11.1 mmol/L, or HbA1c level ≥6.5%[4]. Secondly, to account for potential glucose benefits and carry-over effects of bisphosphonates, we performed a stratified analysis by prior bisphosphonate exposure and restricted the analysis only to those treated with bisphosphonate less than 12 months. Thirdly, to improve the comparability between the study groups, we repeated the primary analysis excluding those with preexisting peptic ulcer or renal diseases. Fourthly, to examine the long-term effect, we extended the follow-up to 10 years. Fifthly, to account for potential medication adherence bias, we restricted the study populations to those with a medication possession ratio (MPR) ≥0.8, calculated by cumulative defined daily doses (DDD) divided by the treatment duration[9]. Sixthly, to examine the potential impact of different definitions of drug discontinuation, we repeated the analysis using an alternative definition of a gap over 360 days between successive prescriptions. Seventhly, to account for potential indication bias, we repeated the analysis using monotherapy of alendronate as the comparator. Eighthly, instead of the as-treated approach, we performed an analysis using an observational analog intention-to-treat approach, allowing patients to switch between treatment groups during the follow-up. Ninthly, to examine the potential impact of incomplete data, we repeated the primary analysis using multiple imputations for variables with missing values (i.e., BMI 6%, alcohol consumption status 9%, smoking status 2%, and socioeconomic deprivation index 13.6%). We imputed 5 data sets, calculated the effect estimates for each imputed dataset, and averaged estimates and their CIs obtained from each imputed data set using Rubin's rules[10,11]. Tenthly, to examine the effect of denosumab in those treated with bisphosphonates, we performed an analysis with a pure switcher design. Eleventhly, to examine the possible carry-over effect of bisphosphonates, we further examined the difference in incidence rate between the two treatment groups at 1 to 5 years follow-up. Twelfthly, we performed an additional sensitivity analysis using more proxies of general health by including osteoarthritis, rheumatoid arthritis, gout, liver diseases,

asthma, pneumonia, history of major surgeries, history of injuries, and sleep disorders, all measured at index date. Lastly, to further account for potentially unbalanced censoring between groups, we used inverse probability weighting in sensitivity analysis 5. For inverse probability weighting, we used the same sets of covariates listed in Supplemental Figure 3; baseline covariates were measured at the index date, while time-varying covariates were updated monthly; age, sex, smoking status, alcohol drinking, BMI, and Townsend score were treated as fixed covariates and were not updated monthly.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R-4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). In SAS, we used PROC SQL and DATA steps to prepare the data. For the matching process, we used the R-package "dplyr (1.0.7)" and for fitting the propensity score model and proportional hazard regression, we used the R-package "survival (3.2-13)". We used a robust variance estimator for log-hazard ratio when using matching with replacement[12].

Supplemental Table 1 Specification and emulation of a target trial comparing switching to denosumab or continuing an oral bisphosphonate on the risk of type 2 diabetes using observational data

Protocol component	Target pragmatic trial specification (a hypothetical RCT that is ideal for answering this question)	Target trial emulation (using observational data to best approximate the RCT comparison)
Eligibility criteria	Age ≥45, between 2011 and 2021; Patients using oral bisphosphonates or not yet receiving any anti-osteoporosis treatment; At least 1 year of up-to-standard data in a THIN primary care practice;	Same as the target trial;
Treatment strategies	(1) Denosumab treatment: initiating or switching to denosumab; (2) Oral bisphosphonate treatment: initiating or continuing with an oral bisphosphonate; In the above strategies, patients are not allowed to switch to any other anti-osteoporosis drug (i.e., intravenous bisphosphonate, estrogens, selective estrogen receptor modulators, teriparatide, or a combination of these medications); patients are also not allowed to discontinue the initially assigned medication;	Same as for the target trial;
Treatment assignment	Eligible individuals are randomly assigned to one of the two "treatment strategies" stratified by duration of oral bisphosphonate (months) and are aware of the strategy to which they have been assigned;	We classify patients according to the strategy that they received at time zero and emulate randomization by propensity score matching; time zero is defined as the switch date or date of incident use for denosumab users and their matched oral bisphosphonate controls.
Outcomes	Incident type 2 diabetes;	Same as for the target trial;
Follow-up	Starts at the time of assignment to a strategy and ends at the earliest of diagnosis of type 2 diabetes, death, 5 years after time zero or administrative end of follow-up;	Starts at the switch date or date of incident use for denosumab users and their matched oral bisphosphonate controls;
Casual contrasts	Per-protocol effect;	Observational analog of the per-protocol effect;
Statistical analysis	Intention-to-treat analysis; Per-protocol analysis;	Observational analog of the per-protocol analysis;

Supplemental Table 2 Baseline characteristics of the study population before matching

Characteristics	Oral bisphosphonates (n=207481)	Denosumab (n=4350)	Standardized difference
Period of cohort entry, N (%)			
2005 and before	24162 (11.6)	0 (0.0)	
2006-2010	57655 (27.8)	0 (0.0)	
2011-2015	81982 (39.5)	2101 (48.3)	
2016-2021	43682 (21.1)	2249 (51.7)	
Age at cohort entry, mean (SD)	71.7 (11.9)	69.3 (10.6)	0.22
Women, N (%)	167847 (80.9)	4102 (94.3)	0.42
Residential care, N (%)	14259 (6.9)	202 (4.6)	0.10
Townsend deprivation index score, mean (SD)	2.3 (1.6)	2.2 (1.5)	0.05
Body mass index category, N (%)			0.32
Normal	72450 (34.9)	1784 (41.0)	
Obese	31276 (15.1)	453 (10.4)	
Overweight	59546 (28.7)	1116 (25.7)	
Underweight	21421 (10.3)	750 (17.2)	
Unknown	22788 (11.0)	247 (5.7)	
Smoking status, N (%)			0.16
Current	25688 (12.4)	421 (9.7)	
Former	59985 (28.9)	1180 (27.1)	
Never	113977 (54.9)	2663 (61.2)	
Unknown	7831 (3.8)	86 (2.0)	
Alcohol consumption status, N (%)			0.18
Current	125932 (60.7)	2575 (59.2)	
Former	6553 (3.2)	162 (3.7)	
Never	47829 (23.1)	1241 (28.5)	
Unknown	27167 (13.1)	372 (8.6)	
History of major osteoporotic fracture*, N (%)	62323 (30.0)	2210 (50.8)	0.43
Comorbidity before cohort entry, N (%)			
Hypertension	95797 (46.2)	2172 (49.9)	0.08
Hypercholesterolemia	29864 (14.4)	679 (15.6)	0.03
Chronic obstructive pulmonary disease	39105 (18.8)	894 (20.6)	0.04
Dementia	10309 (5.0)	221 (5.1)	0.005
Cerebrovascular disease	15770 (7.6)	371 (8.5)	0.03
Congestive heart disease	7770 (3.7)	219 (5.0)	0.06
Myocardial infarction	9399 (4.5)	185 (4.3)	0.01
Chronic heart failure	8741 (4.2)	248 (5.7)	0.07
Peripheral vascular disease	7144 (3.4)	153 (3.5)	0.004

Other circulation diseases	68059 (32.8)	1801 (41.4)	0.18
Venous thromboembolism	10734 (5.2)	299 (6.9)	0.07
Anxiety	31134 (15.0)	803 (18.5)	0.09
Depression	29118 (14.0)	701 (16.1)	0.06
Peptic ulcer disease	8382 (4.0)	274 (6.3)	0.10
Renal disease	33651 (16.2)	949 (21.8)	0.14
Cancer	32011 (15.4)	705 (16.2)	0.02
Drugs used in 2 years before cohort entry, N (%)			
Nonsteroidal anti-inflammatory drug	98322 (47.4)	2393 (55.0)	0.15
Antihypertensive	110552 (53.3)	2526 (58.1)	0.10
Statin	67397 (32.5)	1430 (32.9)	0.008
Aspirin	47275 (22.8)	803 (18.5)	0.11
Oral anticoagulant	13905 (6.7)	336 (7.7)	0.04
Glucocorticoid	66052 (31.8)	1198 (27.5)	0.09
Benzodiazepine	28764 (13.9)	716 (16.5)	0.07
Proton pump inhibitor	88789 (42.8)	2358 (54.2)	0.23
SSRI†	3789 (1.8)	100 (2.3)	0.03
Healthcare utilization in 2 years before cohort entry			
Number of hospital admissions, mean (SD)	1.59 (2.94)	2.16 (3.56)	0.18
Number of doctor visits, N (%)			0.53
0-1	66397 (32.0)	642 (14.8)	
2-4	56333 (27.2)	918 (21.1)	
5-8	40742 (19.6)	1053 (24.2)	
9 and more	44009 (21.2)	1737 (39.9)	

Notes: * Include fractures at the hip, vertebral, wrist, humerus, pelvis, and rib. †SSRI, selective serotonin reuptake inhibitor.

Supplemental Table 3 Baseline characteristics comparison between the incident and prevalent new users of denosumab

Characteristics	Incident new users (n=961)	Prevalent new users (n=3340)	Standardized difference
Period of cohort entry, N (%)			0.17
2011-2013	168 (17.5)	638 (19.1)	
2014-2016	409 (42.6)	1411 (42.2)	
2017-2019	253 (26.3)	1002 (30.0)	
2020-2021	131 (13.6)	289 (8.7)	
Age at cohort entry, mean (SD)	77.2 (10.9)	75.3 (9.5)	0.19
Women, N (%)	864 (89.9)	3191 (95.5)	0.22
Residential care, N (%)	108 (11.2)	92 (2.8)	0.34
Townsend deprivation index score, mean (SD)	2.2 (1.5)	2.2 (1.5)	0.04
Body mass index category, N (%)			0.46
Normal	344 (35.8)	1422 (42.6)	
Obese	102 (10.6)	348 (10.4)	
Overweight	207 (21.5)	902 (27.0)	
Underweight	157 (16.3)	572 (17.1)	
Unknown	151 (15.7)	96 (2.9)	
Smoking status, N (%)			0.40
Current	97 (10.1)	323 (9.7)	
Former	255 (26.5)	914 (27.4)	
Never	532 (55.4)	2094 (62.7)	
Unknown	77 (8.0)	9 (0.3)	
Alcohol drinking status, N (%)			0.44
Current	495 (51.5)	2056 (61.6)	
Former	30 (3.1)	131 (3.9)	
Never	247 (25.7)	972 (29.1)	
Unknown	189 (19.7)	181 (5.4)	
Bisphosphonate treatment length (years, mean (SD))	0.00 (0.00)	7.21 (4.65)	-
History of major osteoporotic fracture*, N (%)	479 (49.8)	1690 (50.6)	0.02
Comorbidity before cohort entry, N (%)			
Hypertension	497 (51.7)	1650 (49.4)	0.05
Hypercholesterolemia	137 (14.3)	533 (16.0)	0.05
Chronic obstructive pulmonary disease	172 (17.9)	715 (21.4)	0.09
Dementia	99 (10.3)	120 (3.6)	0.27
Cerebrovascular disease	95 (9.9)	274 (8.2)	0.06
Congestive heart disease	70 (7.3)	147 (4.4)	0.12

Myocardial infarction	52 (5.4)	130 (3.9)	0.07
Chronic heart failure	79 (8.2)	167 (5.0)	0.13
Peripheral vascular disease	45 (4.7)	107 (3.2)	0.08
Other circulation diseases	341 (35.5)	1439 (43.1)	0.16
Venous thromboembolism	76 (7.9)	221 (6.6)	0.05
Anxiety	157 (16.3)	638 (19.1)	0.07
Depression	145 (15.1)	549 (16.4)	0.04
Peptic ulcer disease	76 (7.9)	192 (5.7)	0.09
Renal disease	247 (25.7)	689 (20.6)	0.12
Cancer	159 (16.5)	535 (16.0)	0.01
Drugs in 2 years before cohort entry, N (%)			
Nonsteroidal anti-inflammatory drug	504 (52.4)	1857 (55.6)	0.06
Antihypertensive	577 (60.0)	1920 (57.5)	0.05
Statin	302 (31.4)	1115 (33.4)	0.04
Aspirin	170 (17.7)	627 (18.8)	0.03
Oral anticoagulant	91 (9.5)	242 (7.2)	0.08
Glucocorticoid	186 (19.4)	1002 (30.0)	0.25
Benzodiazepine	148 (15.4)	556 (16.6)	0.03
Proton pump inhibitor	497 (51.7)	1825 (54.6)	0.06
SSRI†	21 (2.2)	79 (2.4)	0.01
Healthcare utilization in 2 years before cohort entry			
Number of hospital admissions, mean (SD)	2.09 (3.29)	2.15 (3.57)	0.02
Number of doctor visits, N (%)			0.35
0-1	236 (24.6)	403 (12.1)	
2-4	210 (21.9)	704 (21.1)	
5-8	205 (21.3)	837 (25.1)	
9 and more	310 (32.3)	1396 (41.8)	

Notes: *Major osteoporotic fractures include fractures at the hip, vertebral, wrist, humerus, pelvis, and rib. †SSRI, selective serotonin reuptake inhibitor.

Supplemental Table 4 Average treatment effect (ATE) and average treatment effect in those treated (ATT) in a subpopulation of incident new users

Exposure	Number of patients, n	Number of events, n	Person-years	Incident rate* (95% CI)	HR (95% CI)
ATT: propensity score matching†					
Oral bisphosphonate	4,802	89	10,345	8.6 (6.9 to 10.6)	Reference
Denosumab	961	6	2,036	3.0 (1.1 to 6.4)	0.35 (0.15 to 0.79)
ATE: inverse probability weighting ‡					
Oral bisphosphonate	125,537	3,164	290,122	10.9 (10.5 to 11.3)	Reference
Denosumab	958	8	2,085	3.8 (1.7 to 7.6)	0.34 (0.11 to 1.01)

Notes: * Per 1,000 person-years; † the same results of sensitivity analysis 1 from **Table 4**; ‡ stabilized inverse probability weights were used[13].

Supplemental Table 5 Sensitivity analysis with an alternative definition of type 2 diabetes by laboratory tests only

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
An alternative definition of type 2 diabetes with blood glucose level or HbA1c					
Oral bisphosphonate	21,038	235	41,939	5.6 (4.9 to 6.4)	Reference
Denosumab	4,301	40	10,668	3.8 (2.7 to 5.1)	0.66 (0.48 to 0.93)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. Definition of type 2 diabetes: fasting blood sugar ≥7.0 mmol/L, random glucose level ≥11.1 mmol/L, glucose tolerance test result ≥11.1 mmol/L, or glycated hemoglobin A1c level ≥6.5%. CI, confidence interval; HR, hazard ratio.

Supplemental Table 6 Subgroup analyses stratified by prior bisphosphonate exposure

Exposure	Number of patients, n	Number of events, n	Person-years	Incident rate* (95% CI)	HR (95% CI)	P for interaction
Subgroup analysis 1: stratified by prior bisphosphonate length						
Prior bisphosphonate length of less than 36 months						
Oral bisphosphonate	8,799	161	18,501	8.7 (7.4 to 10.2)	Reference	
Denosumab	1,759	23	4,053	5.7 (3.6 to 8.5)	0.66 (0.43 to 1.02)	0.85
Prior bisphosphonate length of over 36 months						
Oral bisphosphonate	12,239	186	23,400	8.0 (6.9 to 9.2)	Reference	
Denosumab	2,542	37	6,564	5.6 (4.0 to 7.8)	0.69 (0.49 to 0.96)	NA
Subgroup analysis 2: stratified by prior cumulative defined daily dose (DDD) of bisphosphonate						
Prior cumulative DDD of bisphosphonate of less than 36 months						
Oral bisphosphonate	10,156	193	20,887	9.2 (8.0 to 10.6)	Reference	
Denosumab	2,692	39	6,402	6.1 (4.3 to 8.3)	0.66 (0.47 to 0.93)	0.99
Prior cumulative DDD of bisphosphonate of over 36 months						
Oral bisphosphonate	10,882	154	21,014	7.3 (6.2 to 8.6)	Reference	
Denosumab	1,609	21	4,215	5.0 (3.1 to 7.6)	0.65 (0.41 to 1.01)	NA

Notes: * Per 1,000 person-years, † additionally adjusted for age, sex, and propensity score. P for interaction was reported for the interaction term in the additionally adjusted models. CI, confidence interval; HR, hazard ratio; NA, not applicable.

Supplemental Table 7 Sensitivity analysis by excluding patients with preexisting peptic ulcer diseases or renal diseases

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
Excluding patients with peptic ulcer diseases or renal diseases					
Oral bisphosphonate	15,182	227	31,087	7.3 (6.4 to 8.3)	Reference
Denosumab	3,048	42	7,648	5.5 (4.0 to 7.4)	0.75 (0.54 to 1.03)
Excluding patients with peptic ulcer disease					
Oral bisphosphonate	19,218	313	38,320	8.2 (7.3 to 9.1)	Reference
Denosumab	3,869	50	9,561	5.2 (3.9 to 6.9)	0.63 (0.47 to 0.86)
Excluding patients with renal diseases					
Oral bisphosphonate	16,544	247	33,843	7.3 (6.4 to 8.3)	Reference
Denosumab	3,365	48	8,438	5.7 (4.2 to 7.5)	0.77 (0.57 to 1.05)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. CI, confidence interval; HR, hazard ratio.

Supplemental Table 8 Sensitivity analysis restricting the patient only to those switched within 12 months of oral bisphosphonates

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
The primary outcome: defined by the type 2 diabetes diagnostic codes					
Oral bisphosphonate	6,060	117	12,901	9.1 (7.5 to 10.9)	Reference
Denosumab	1,213	10	2,641	3.8 (1.8 to 7.0)	0.42 (0.22 to 0.81)
The secondary outcome: an alternative definition of type 2 diabetes with diagnostic codes, antidiabetic medication, and lab results.					
Oral bisphosphonate	6,060	158	12,858	12.3 (10.4 to 14.4)	Reference
Denosumab	1,213	17	2,640	6.4 (3.8 to 10.3)	0.53 (0.32 to 0.88)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. CI, confidence interval; HR, hazard ratio

Supplemental Table 9 Sensitivity analysis by extending the follow-up length to 10 years

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
The primary outcome: defined by the type 2 diabetes diagnostic codes					
Oral bisphosphonate	21,038	395	44,340	8.9 (8.1 to 9.8)	Reference
Denosumab	4,301	65	11,353	5.7 (4.4 to 7.3)	0.63 (0.49 to 0.82)
The secondary outcome: an alternative definition of type 2 diabetes with diagnostic codes, antidiabetic medication, and lab results.					
Oral bisphosphonate	21,038	548	44,258	12.1 (11.4 to 13.5)	Reference
Denosumab	4,301	97	11,331	8.6 (7.0 to 10.4)	0.68 (0.55 to 0.84)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. CI, confidence interval; HR, hazard ratio.

Supplemental Table 10 Sensitivity analysis only includes those with a medication possession ratio (MPR) ≥0.8

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
The primary outcome: defined by the type 2 diabetes diagnostic codes					
Oral bisphosphonate	19,501	306	37,919	8.1 (7.2 to 9.0)	Reference
Denosumab	4,051	54	9,890	5.5 (4.1 to 7.1)	0.67 (0.51 to 0.90)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. The MPR was calculated by cumulative defined daily doses (DDD) for each drug divided by the treatment duration. Analysis was performed only on subjects with high MPR (≥0.8). CI, confidence interval; HR, hazard ratio.

Supplemental Table 11 Sensitivity analysis using drug discontinuation defined by a gap over 360 days between successive prescriptions

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
The primary outcome: defined by the type 2 diabetes diagnostic codes					
Oral bisphosphonate	21,038	347	51,104	6.8 (6.1 to 7.5)	Reference
Denosumab	4,301	60	12,422	4.8 (3.7 to 6.2)	0.71 (0.54 to 0.93)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. CI, confidence interval; HR, hazard ratio.

Supplemental Table 12 Sensitivity analysis using alendronate as the comparator (switching to denosumab vs. continuing alendronate)

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
The primary outcome: defined by the type 2 diabetes diagnostic codes					
Oral bisphosphonate	13,819	194	27,142	7.2 (6.2 to 8.2)	Reference
Denosumab	2,825	31	6,654	4.7 (3.2 to 6.6)	0.65 (0.45 to 0.96)
The secondary outcome: an alternative definition of type 2 diabetes with diagnostic codes, antidiabetic medication, and lab results.					
Oral bisphosphonate	13,819	269	27,072	9.9 (8.8 to 11.2)	Reference
Denosumab	2,825	43	6,650	6.5 (4.7 to 8.7)	0.65 (0.47 to 0.90)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. CI, confidence interval; HR, hazard ratio.

Supplemental Table 13 Sensitivity analysis using an observational analogous intention to treat approach

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
The primary outcome: defined by the type 2 diabetes diagnostic codes					
Oral bisphosphonate	21,038	347	80,982	4.3 (3.9 to 4.8)	Reference
Denosumab	4,301	60	16,369	3.7 (2.8 to 4.7)	0.85 (0.65 to 1.12)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. Patients were followed until the occurrence of the study outcome, death, transfer out of primary care clinic, 5 years follow-up, or end of the study period (December 31, 2021), whichever occurred first. Patients were allowed to switch between treatment groups; in continuous bisphosphonate users, 896 patients switched to denosumab, while in those who switched to denosumab from oral bisphosphonate, 103 patients switched back to oral bisphosphonates during 5 years follow-up. CI, confidence interval; HR, hazard ratio.

Supplemental Table 14 Sensitivity analysis with multiple imputations for incomplete data

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
The primary outcome: defined by the type 2 diabetes diagnostic codes					
Oral bisphosphonate	21,085	337	42,184	8.0 (7.0 to 8.9)	Reference
Denosumab	4,300	60	10,614	5.7 (4.0 to 7.3)	0.70 (0.53 to 0.90)
The secondary outcome: an alternative definition of type 2 diabetes with diagnostic codes, antidiabetic medication, and lab results.					
Oral bisphosphonate	21,085	451	42,110	10.7 (9.5 to 11.9)	Reference
Denosumab	4,300	90	10,596	8.5 (6.5 to 10.4)	0.79 (0.62 to 0.97)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. We repeated the primary analysis using multiple imputations for variables with missing values (i.e., body mass index 6%, alcohol consumption status 9%, smoking status 2%, and socioeconomic deprivation index 13.6%). We imputed 5 data sets, calculated the effect estimates for each imputed dataset, and averaged estimates and their confidence intervals obtained from each imputed data set using Rubin's rules. CI, confidence interval; HR, hazard ratio.

Supplemental Table 15 Sensitivity analysis with more proxies of general health status

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
The primary outcome: defined by the type 2 diabetes diagnostic codes					
Oral bisphosphonate	21,004	340	41,757	8.1 (7.3 to 9.1)	Reference
Denosumab	4,293	60	10,598	5.7 (4.3 to 7.3)	0.69 (0.53 to 0.91)
The secondary outcome: an alternative definition of type 2 diabetes with diagnostic codes, antidiabetic medication, and lab results.					
Oral bisphosphonate	21,0004	463	41,685	11.1 (10.1 to 12.2)	Reference
Denosumab	4,293	90	10,579	8.5 (6.8 to 10.5)	0.76 (0.61 to 0.95)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. We performed an additional sensitivity analysis using more proxies of general health by including osteoarthritis, rheumatoid arthritis, gout, liver diseases, asthma, pneumonia, major surgeries history, injury histories, and sleep disorders all measured at index date. CI, confidence interval; HR, hazard ratio.

Supplemental Table 16 Sensitivity analysis of using inverse probability weighting to address potentially unbalanced censoring between groups

Exposure	Number of patients, n	Number of events, n	Person-years	Incident rate* (95% CI)	HR (95% CI)
Sensitivity analysis 5 from Table 4: nearest neighbor matching within specified caliper widths without replacement					
Oral bisphosphonate	20,262	340	40,866	8.3 (7.5 to 9.3)	Reference
Denosumab	4,210	59	10,428	5.7 (4.3 to 7.3)	0.68 (0.52 to 0.89)
Additional inverse probability censoring weighting for sensitivity analysis 5 †					
Oral bisphosphonate	20,262	341	41,799	8.2 (7.3 to 9.1)	Reference
Denosumab	4,210	58	10,490	5.5 (4.2 to 7.2)	0.68 (0.52 to 0.90)

Notes: * Per 1,000 person-years. † As we estimated the protocol effects, we additionally used inverse probability weighting to deal with potentially unbalanced censoring between groups. For inverse probability weighting, we used the same sets of covariates listed in Supplemental Figure 3; baseline covariates were measured at the index date, while time-varying covariates were updated monthly; age, sex, smoking status, alcohol drinking, BMI, and Townsend score were treated as fixed covariates and were not updated monthly. HR, hazard ratio; CI, confidence interval.

Supplemental Table 17 Sensitivity analysis with pure switcher design, exclusively including participants treated with bisphosphonates

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
A pure switcher design					
Oral bisphosphonate	16,236	258	31,555	8.2 (7.2 to 9.2)	Reference
Denosumab	3,340	54	8,581	6.3 (4.7 to 8.2)	0.76 (0.57 to 1.01)
A pure switcher design in the subgroup of patients with prediabetes					
Oral bisphosphonate	3,852	153	7,113	21.5 (18.2 to 25.2)	Reference
Denosumab	705	22	1,691	13.0 (8.2 to 19.7)	0.60 (0.39 to 0.94)
A pure switcher design in the subgroup of patients with body mass index over 30 ‡					
Oral bisphosphonate	1,684	81	3,522	23.0 (18.3 to 28.6)	Reference
Denosumab	348	17	949	17.9 (10.4 to 28.7)	0.78 (0.46 to 1.30)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. ‡ Patients with missing values for body mass index were excluded from the analysis. CI, confidence interval; HR, hazard ratio.

Supplemental Table 18 Incidence rate of type 2 diabetes at 1 to 5 years follow-up

Exposure	Number of patients, n*	Number of events, n	Person-years	Incident rate† (95% CI)	HR (95% CI)
Incidence rate at 1 year follow-up					
Oral bisphosphonate	21,038	131	17,576	7.5 (6.2 to 8.8)	Reference
Denosumab	4,301	20	4,272	4.7 (2.9 to 7.2)	0.64 (0.40 to 1.03)
Incidence rate at 2 years follow-up					
Oral bisphosphonate	21,038	216	28,618	7.6 (6.6 to 8.6)	Reference
Denosumab	4,301	32	7,024	4.6 (3.1 to 6.4)	0.61 (0.42 to 0.88)
Incidence rate at 3 years follow-up					
Oral bisphosphonate	21,038	276	35,420	7.8 (6.9 to 8.8)	Reference
Denosumab	4,301	43	8,816	4.9 (3.5 to 6.6)	0.63 (0.46 to 0.86)
Incidence rate at 4 years follow-up					
Oral bisphosphonate	21,038	317	39,539	8.0 (7.2 to 9.0)	Reference
Denosumab	4,301	43	9,944	5.1 (3.8 to 6.7)	0.64 (0.48 to 0.86)
Incidence rate at 5 years follow-up					
Oral bisphosphonate	21,038	347	41,900	8.3 (7.4 to 9.2)	Reference
Denosumab	4,301	60	10,617	5.7 (4.3 to 7.3)	0.68 (0.52 to 0.89)

Notes: * Recipients of denosumab users were matched up to 5 oral bisphosphonate recipients with propensity scores. † Per 1,000 person-years. CI, confidence interval; HR, hazard ratio.

Supplemental Table 19 Diagnostic codes list of type 2 diabetes

Diagnostic code	Code type	Description
C100112	Read	Non-insulin dependent diabetes mellitus
C103y00	Read	Other specified diabetes mellitus with coma
C109.00	Read	Non-insulin dependent diabetes mellitus
C109000	Read	Non-insulin-dependent diabetes mellitus with renal comps
C109011	Read	Type II diabetes mellitus with renal complications
C109012	Read	Type 2 diabetes mellitus with renal complications
C109100	Read	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109.11	Read	NIDDM - Non-insulin dependent diabetes mellitus
C109111	Read	Type II diabetes mellitus with ophthalmic complications
C109112	Read	Type 2 diabetes mellitus with ophthalmic complications
C109.12	Read	Type 2 diabetes mellitus
C109.13	Read	Type II diabetes mellitus
C109200	Read	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Read	Type II diabetes mellitus with neurological complications
C109212	Read	Type 2 diabetes mellitus with neurological complications
C109300	Read	Non-insulin-dependent diabetes mellitus with multiple comps
C109312	Read	Type 2 diabetes mellitus with multiple complications
C109400	Read	Non-insulin dependent diabetes mellitus with ulcer
C109411	Read	Type II diabetes mellitus with ulcer
C109412	Read	Type 2 diabetes mellitus with ulcer
C109500	Read	Non-insulin dependent diabetes mellitus with gangrene
C109511	Read	Type II diabetes mellitus with gangrene
C109512	Read	Type 2 diabetes mellitus with gangrene
C109600	Read	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Read	Type II diabetes mellitus with retinopathy
C109612	Read	Type 2 diabetes mellitus with retinopathy
C109700	Read	Non-insulin dependent diabetes mellitus - poor control
C109711	Read	Type II diabetes mellitus - poor control
C109712	Read	Type 2 diabetes mellitus - poor control
C109900	Read	Non-insulin-dependent diabetes mellitus without complication
C109911	Read	Type II diabetes mellitus without complication
C109912	Read	Type 2 diabetes mellitus without complication
C109A00	Read	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Read	Type II diabetes mellitus with mononeuropathy
C109B00	Read	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Read	Type II diabetes mellitus with polyneuropathy
C109B12	Read	Type 2 diabetes mellitus with polyneuropathy

C109C00	Read	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Read	Type II diabetes mellitus with nephropathy
C109C12	Read	Type 2 diabetes mellitus with nephropathy
C109D00	Read	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11	Read	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Read	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Read	Non-insulin depend diabetes mellitus with diabetic cataract
C109E11	Read	Type II diabetes mellitus with diabetic cataract
C109E12	Read	Type 2 diabetes mellitus with diabetic cataract
C109F11	Read	Type II diabetes mellitus with peripheral angiopathy
C109F12	Read	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Read	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Read	Type II diabetes mellitus with arthropathy
C109G12	Read	Type 2 diabetes mellitus with arthropathy
C109H11	Read	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Read	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Read	Insulin treated Type 2 diabetes mellitus
C109J11	Read	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Read	Insulin treated Type II diabetes mellitus
C109K00	Read	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10F.00	Read	Type 2 diabetes mellitus
C10F000	Read	Type 2 diabetes mellitus with renal complications
C10F011	Read	Type II diabetes mellitus with renal complications
C10F100	Read	Type 2 diabetes mellitus with ophthalmic complications
C10F.11	Read	Type II diabetes mellitus
C10F111	Read	Type II diabetes mellitus with ophthalmic complications
C10F200	Read	Type 2 diabetes mellitus with neurological complications
C10F211	Read	Type II diabetes mellitus with neurological complications
C10F300	Read	Type 2 diabetes mellitus with multiple complications
C10F311	Read	Type II diabetes mellitus with multiple complications
C10F400	Read	Type 2 diabetes mellitus with ulcer
C10F411	Read	Type II diabetes mellitus with ulcer
C10F500	Read	Type 2 diabetes mellitus with gangrene
C10F511	Read	Type II diabetes mellitus with gangrene
C10F600	Read	Type 2 diabetes mellitus with retinopathy
C10F611	Read	Type II diabetes mellitus with retinopathy
C10F700	Read	Type 2 diabetes mellitus - poor control
C10F711	Read	Type II diabetes mellitus - poor control
C10F900	Read	Type 2 diabetes mellitus without complication
C10F911	Read	Type II diabetes mellitus without complication
C10FA00	Read	Type 2 diabetes mellitus with mononeuropathy

C10FA11	Read	Type II diabetes mellitus with mononeuropathy
C10FB00	Read	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Read	Type II diabetes mellitus with polyneuropathy
C10FC00	Read	Type 2 diabetes mellitus with nephropathy
C10FC11	Read	Type II diabetes mellitus with nephropathy
C10FD00	Read	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Read	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Read	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Read	Type II diabetes mellitus with diabetic cataract
C10FF00	Read	Type 2 diabetes mellitus with peripheral angiopathy
C10FF11	Read	Type II diabetes mellitus with peripheral angiopathy
C10FG11	Read	Type II diabetes mellitus with arthropathy
C10FH00	Read	Type 2 diabetes mellitus with neuropathic arthropathy
C10FH11	Read	Type II diabetes mellitus with neuropathic arthropathy
C10FJ00	Read	Insulin treated Type 2 diabetes mellitus
C10FJ11	Read	Insulin treated Type II diabetes mellitus
C10FK00	Read	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FK11	Read	Hyperosmolar non-ketotic state in type II diabetes mellitus
C10FL00	Read	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Read	Type II diabetes mellitus with persistent proteinuria
C10FM00	Read	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11	Read	Type II diabetes mellitus with persistent microalbuminuria
C10FN00	Read	Type 2 diabetes mellitus with ketoacidosis
C10FN11	Read	Type II diabetes mellitus with ketoacidosis
C10FP00	Read	Type 2 diabetes mellitus with ketoacidotic coma
C10FQ00	Read	Type 2 diabetes mellitus with exudative maculopathy
C10FR00	Read	Type 2 diabetes mellitus with gastroparesis

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