

Supplementary Online Content

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

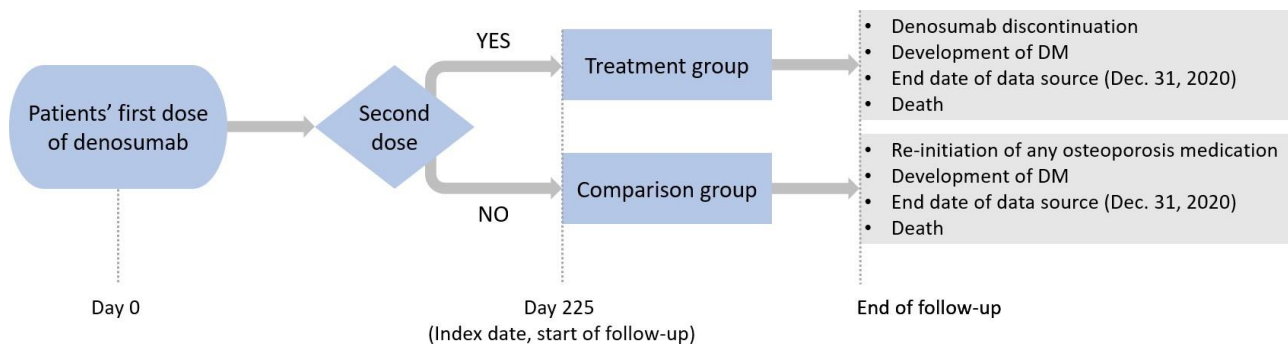
eAppendix 1. The specific datasets from the National Health Insurance Research Database(NHIRD) that we used for data analyses

The demographic data, medical claims for inpatient, outpatient, and emergency care services, and drug prescription details that we used for analyses were sourced from several datasets within Taiwan's NHIRD. These datasets include Registry for Beneficiaries, Ambulatory Care Expenditures by Visits, Inpatient Expenditures by Admissions, Expenditures for Prescriptions Dispensed at Contracted Pharmacies, Details of Ambulatory Care Orders, Details of Inpatient Orders, and Details of Prescriptions Dispensed at Contracted Pharmacies. The NHIRD covers prescription data, dispensing data, and all claims data. Mortality information was obtained by cross-referencing the NHIRD with the Taiwan National Register of Death. The NHIRD is maintained by the Health and Welfare Data Science Center, Ministry of Health and Welfare in Taiwan, and is accessible for formal research applications. For more detailed information on the NHIRD, please refer to the following references.^{1,2}

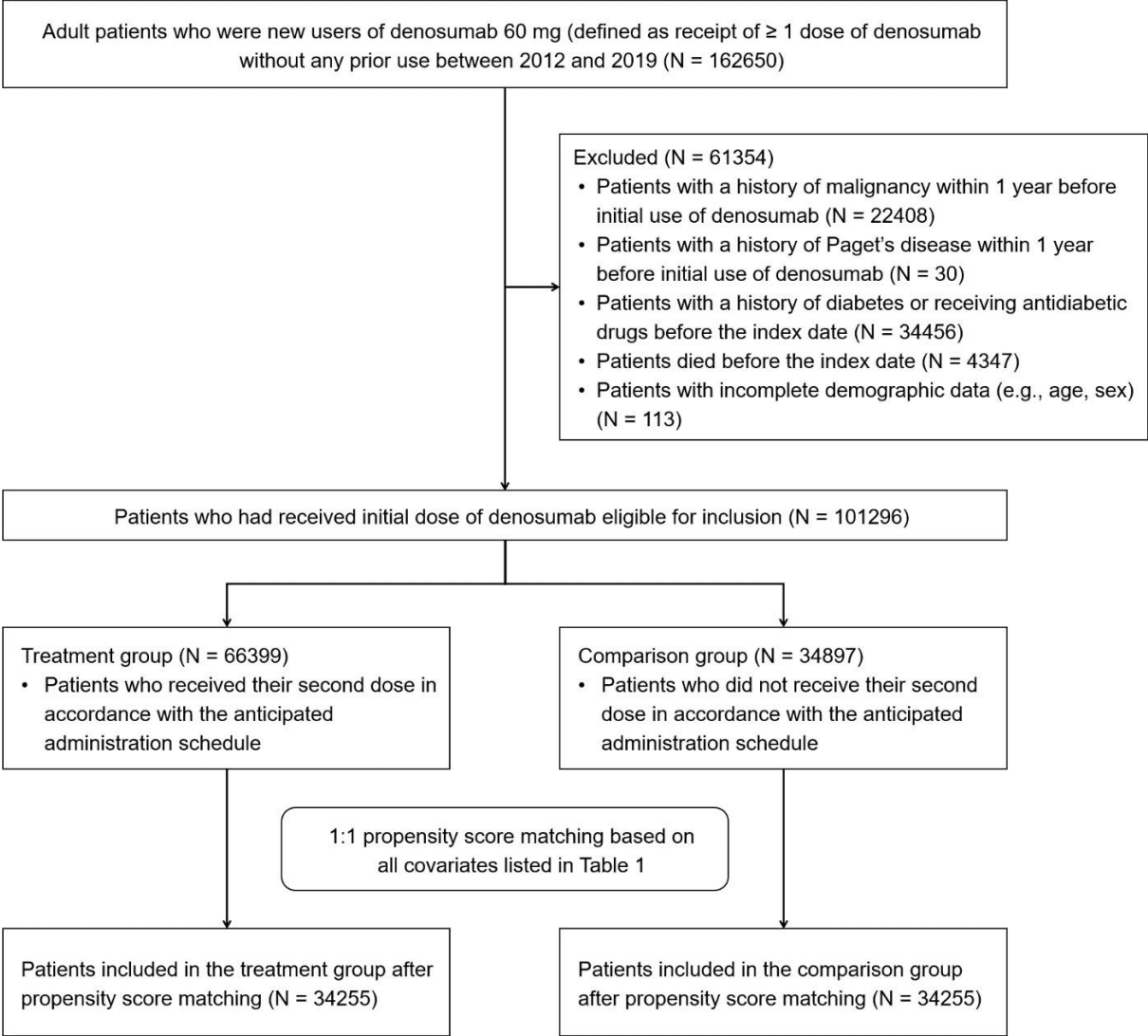
eReferences.

1. Hsieh CY, Su CC, Shao SC, et al. Taiwan's National Health Insurance Research Database: past and future. *Clin Epidemiol*. 2019;11:349-58.
2. Hsing AW, Ioannidis JP. Nationwide population science: lessons from the Taiwan National Health Insurance Research Database. *JAMA Intern Med*. 2015;175(9):1527-9.

eFigure 1. Schema of the study design



eFigure 2. Flowchart of patient selection



eTable 1. Diagnosis and drug codes for identifying baseline comorbidities, co-medications, and negative control outcomes

Comorbidities	ICD-9-CM / ICD-10-CM codes
Chronic Obstructive Pulmonary Disease	491, 492, J41, J42, J44
Systemic Lupus Erythematosus	7100, M32
Asthma	493, J45
Inflammatory bowel disease	556, K51
Multiple sclerosis	340, G35
Sarcoidosis	135, D86
Gout	274, M10
Rheumatoid arthritis	714, M05, M06
Cataract	366, H25
Congestive heart failure	428, I50
Dementia	290, F01, F03, F05
Depression	311, F32, F33
Diabetes mellitus	250, E10, E11
Dyslipidemia	E780, E781, E782, E783, E784, E785, 272
Gastrointestinal bleeding	578, K920, K921, K922
Glaucoma	365, H40, H42
Hemorrhagic stroke	430, 431, 432, I60, I61, I62
Hypertension	401, 402, 403, 404, 405, I10
Ischemic heart disease	410, 411, 412, 413, 414, I20, I21, I22, I23, I24, I25
Ischemic stroke	433, 434, I63
Lung cancer	162, C33, C34
Macular degeneration	3625, H353
Osteoarthritis	715, M15, M16, M17, M18, M19
Parkinson disease	332, G20
Peptic ulcer	531-534 or K25, K26, K27, K28
Pneumonia	J12, J13, J14, J15, J16, J17, J18, 480-486
Renal failure	584, 585, 586, N18
Schizophrenia	295, F20
Skin cancer	172, 173, C43, C44, C4A
Hip fracture	820, 820.2, 820.8, 733.14, S72.0--A, S72.1--A, S72.2--A, M80.051A, M80.052A, M80.059A, M84.451A, M84.452A,
Vertebral fracture	805.0, 805.2, 805.4, 805.8, 733.13, S12.---A, S22.0--A, S32.0--A , M48.50XA, M48.52XA, M48.53XA
Humerus fracture	812, 812.2, 812.4, 733.11, S42.2--A, S42.3--A, S42.4--A, M80.021A, M80.022A, M80.029A, M84.421A, M84.422A, M84.429A

Wrist fracture	813.4, 813.5, 733.12, S52.5--A, S52.5--B, S52.5--C, S52.6--A, S52.6--B, S52.6--C, M80.031A, M80.032A, M80.039A, M84.431A, M84.432A, M84.433A, M84.434A, M84.439A
Co-medications	Anatomical Therapeutic Chemical (ATC) codes
Alpha blocker	C02CA
Anti-acids	A02B
Anti-arrhythmic	C01B
Anti-dementia	N06D
Anti-depressant (excluding trazodone 'N06AX05')	N06A, N06C
Anti-gout	M04
Anti-histamine	R06
Anti-Parkinson	N04
Anti-platelet	B01AC
Anti-psychotics (excluding quetiapine 'N05AH04')	N05A
Anti-thrombotic	B01AA
Benzodiazepines	N05B, N05C
Beta blocker	C07
Bronchodilators	R03
Calcitonin	H05BA
Calcium channel blockers	C08
Diuretic	C03
Hormone replacement therapy	G03C, G03D, G03F
Hypoglycemic agents	A10
Lipid lowering agents	C10
Non-steroidal anti-inflammatory drugs	M01A
Propulsive agents	A03FA
Quetiapine	N05AH04
Raloxifene	G03XC01
Renin-angiotensin system - acting agents	C09
Oral or intravenous bisphosphonate	M05BA, M05BB
Teriparatide	H05AA02
Thiazide	C03A

eTable 2. Baseline characteristics of the denosumab treatment and comparison groups in the original population without propensity score matching

	Treatment group (N = 66399)	Comparison group (N = 34897)	Standardized difference
Age, mean years (<i>SD</i>)	76.0 (9.7)	77.8 (9.9)	-0.18
Sex, n (%)			-0.09
Male	8628 (13.0)	5605 (16.1)	
Female	57771 (87.0)	29292 (83.9)	
Year of index date, n (%)			0.06
2012 - 2014	8324 (12.5)	4229 (12.1)	
2015 - 2017	21906 (33.0)	12434 (35.6)	
2018 - 2020	36169 (54.5)	18234 (52.3)	
Income (NTD), n (%)			0.12
≥ 25000	20623 (31.1)	8977 (25.7)	
15000–24999	29557 (44.5)	17457 (50.0)	
≤ 14999	16219 (24.4)	8463 (24.3)	
Urban level of residence, n (%)			0.44
1 (most urban)	13128 (19.8)	6032 (17.3)	
2	11031 (16.6)	5594 (16.0)	
3	5031 (7.6)	2615 (7.5)	
4	1863 (2.8)	1195 (3.4)	
5	34041 (51.3)	18450 (52.9)	
6	1098 (1.7)	820 (2.4)	
7 (least urban)	207 (0.3)	191 (0.6)	
Location of residence in Taiwan, n (%)			0.16
Northern	25456 (38.3)	12189 (34.9)	
Central	11270 (17.0)	6196 (17.8)	
Southern	24046 (36.2)	13489 (38.7)	
Eastern	5239 (7.9)	2807 (8.0)	
Offshore islands	388 (0.6)	216 (0.6)	
Healthcare utilization, mean (<i>SD</i>)			
Emergency room visits	0.79 (1.6)	1.08 (2.1)	-0.16
Outpatient visits	43.02 (24.7)	40.16 (25.1)	0.11
Hospitalizations	0.57 (0.9)	0.8 (1.3)	-0.20
Fracture history, n (%)			
Hip fracture	9069 (13.7)	5198 (14.9)	-0.04
Vertebral fracture	34462 (51.9)	17751 (50.9)	0.02
Wrist or humerus fracture	2936 (4.4)	1729 (5.0)	-0.03
Comorbidities, n (%)			
Asthma	9182 (13.8)	4997 (14.3)	-0.01
Cataract	14515 (21.9)	6548 (18.8)	0.08
Congestive heart failure	4333 (6.5)	3058 (8.8)	-0.08
COPD	10836 (16.3)	6331 (18.1)	-0.05
Dementia	6404 (9.6)	4443 (12.7)	-0.10
Depression	2886 (4.4)	1615 (4.6)	-0.01
Dyslipidemia	18100 (27.3)	8310 (23.8)	0.08
Gastrointestinal bleeding	2470 (3.7)	1625 (4.7)	-0.05
Glaucoma	4117 (6.2)	1858 (5.3)	0.04
Gout	6705 (10.1)	4164 (11.9)	-0.06

Hemorrhagic stroke	930 (1.4)	713 (2.0)	-0.05
Hypertension	33426 (50.3)	18770 (53.8)	-0.07
Inflammatory bowel disease	182 (0.3)	82 (0.2)	0.01
Ischemic heart disease	11219 (16.9)	6563 (18.8)	-0.05
Ischemic stroke	3526 (5.3)	2343 (6.7)	-0.06
Macular degeneration	3689 (5.6)	1774 (5.1)	0.02
Multiple sclerosis	47 (0.1)	16 (0.1)	0.01
Osteoarthritis	32533 (49.0)	17349 (49.7)	-0.01
Parkinson disease	3035 (4.6)	1854 (5.3)	-0.03
Peptic ulcer	15444 (23.3)	8637 (24.8)	-0.03
Pneumonia	4952 (7.5)	3644 (10.4)	-0.10
Renal failure	5976 (9.0)	3794 (10.9)	-0.06
Rheumatoid arthritis	3941 (5.9)	1964 (5.6)	0.01
Sarcoidosis	18 (0.0)	11 (0.0)	-0.00
Schizophrenia	225 (0.3)	163 (0.5)	-0.02
Systemic Lupus Erythematosus	836 (1.3)	338 (1.0)	0.03
Previous osteoporosis medication, n (%)			
Oral or intravenous bisphosphonate	17045 (25.7)	8464 (24.3)	0.03
Teriparatide	2695 (4.1)	1595 (4.6)	-0.03
Calcitonin	1903 (2.9)	1155 (3.3)	-0.03
Raloxifene	5777 (8.7)	2860 (8.2)	0.02
Baseline medications, n (%)			
Alpha blocker	1870 (2.8)	1113 (3.2)	-0.02
Anti-acids	36075 (54.3)	20332 (58.3)	-0.08
Anti-arrhythmic	5474 (8.2)	3194 (9.2)	-0.03
Anti-dementia	5275 (7.9)	2975 (8.5)	-0.02
Anti-depressant	12429 (18.7)	7183 (20.6)	-0.05
Anti-gout	5222 (7.9)	3465 (9.9)	-0.07
Anti-histamine	44149 (66.5)	23426 (67.1)	-0.01
Anti-Parkinson	4934 (7.4)	2958 (8.5)	-0.04
Anti-platelet	19019 (28.6)	11246 (32.2)	-0.08
Anti-psychotics	10185 (15.3)	6388 (18.3)	-0.08
Anti-thrombotic	1243 (1.9)	685 (2.0)	-0.01
Benzodiazepines	41667 (62.8)	22976 (65.8)	-0.06
Beta blocker	20392 (30.7)	11151 (32.0)	-0.03
Bronchodilators	27798 (41.9)	15348 (44.0)	-0.04
Calcium channel blockers	26829 (40.4)	15710 (45.0)	-0.09
Diuretic	14671 (22.1)	9767 (28.0)	-0.14
Hormone replacement therapy	1839 (2.8)	737 (2.1)	0.04
Lipid lowering agents	17072 (25.7)	8009 (23.0)	0.06
NSAID	58744 (88.5)	31512 (90.3)	-0.06
Propulsive agents	29791 (44.9)	17040 (48.8)	-0.08
Quetiapine	4269 (6.4)	3265 (9.4)	-0.11
RAS-acting agents	25542 (38.5)	14454 (41.4)	-0.06

COPD: Chronic Obstructive Pulmonary Disease; IQR: interquartile range; NTD: New Taiwan Dollar; NSAID: non-steroidal anti-inflammatory drugs; RAS: renin-angiotensin system; SD: standard deviation.

eTable 3. Detailed results of the analyses stratified by age, sex, and comorbidities

	Event no.	Person-years	Incidence rate ^a	HR (95% CI) ^b
Age < 65 years				
Treatment group	148	6125.5	24.2	1.02 (0.83-1.27)
Comparison group	201	8928.3	22.5	1 (ref.)
Age ≥ 65 years				
Treatment group	1868	50059.1	37.3	0.8 (0.75-0.85)
Comparison group	3019	64956.7	46.5	1 (ref.)
Males				
Treatment group	317	7509.1	42.2	0.85 (0.73-0.97)
Comparison group	524	10456.8	50.1	1 (ref.)
Females				
Treatment group	1699	48675.6	34.9	0.81 (0.76-0.86)
Comparison group	2696	63428.2	42.5	1 (ref.)
Dyslipidemia				
Treatment group	531	13643.6	38.9	0.82 (0.73-0.91)
Comparison group	816	17450.7	46.8	1 (ref.)
No dyslipidemia				
Treatment group	1485	42541.0	34.9	0.81 (0.76-0.87)
Comparison group	2404	56434.3	42.6	1 (ref.)
Hypertension				
Treatment group	1280	30260.1	42.3	0.79 (0.74-0.85)
Comparison group	2103	40003.3	52.6	1 (ref.)
No hypertension				
Treatment group	736	25924.5	28.4	0.86 (0.78-0.94)
Comparison group	1117	33881.7	33.0	1 (ref.)
Ischemic heart disease				
Treatment group	496	10393.0	47.7	0.82 (0.73-0.92)
Comparison group	753	13054.7	57.7	1 (ref.)
No ischemic heart disease				
Treatment group	1520	45791.6	33.2	0.81 (0.76-0.86)
Comparison group	2467	60830.2	40.6	1 (ref.)
Renal failure				
Treatment group	368	5139.6	71.6	0.85 (0.74-0.97)
Comparison group	546	6695.2	81.6	1 (ref.)
No renal failure				
Treatment group	1648	51045.0	32.3	0.81 (0.76-0.86)
Comparison group	2674	67189.7	39.8	1 (ref.)

CI: confidence interval; HR: hazard ratio; no.: number; ref.: reference.

^aPer 1000 person-years.

^bHR was calculated by Cox proportional hazards model in the propensity score-matched population

eTable 4. Results of the negative control outcome analyses

	N	Event no.	Person-years	Incidence rate ^a	HR (95% CI) ^b
Diagnosis of asthma					
Treatment group	40353	1716	64461.8	26.6	0.95 (0.89-1.01)
Comparison group	40353	2373	87398.7	27.2	1 (ref.)
Diagnosis of lung cancer					
Treatment group	47035	326	77275.7	4.2	1.05 (0.90-1.21)
Comparison group	47035	418	106038.1	3.9	1 (ref.)
Diagnosis of skin cancer					
Treatment group	47123	145	77435.3	1.9	1.04 (0.84-1.30)
Comparison group	47123	187	106332.9	1.8	1 (ref.)
Antidepressant use					
Treatment group	36759	3865	56393.6	68.5	0.98 (0.94-1.02)
Comparison group	36759	5009	74842.4	66.9	1 (ref.)
Thiazide use					
Treatment group	44767	1513	71883.4	21.0	0.97 (0.91-1.04)
Comparison group	44767	2043	97518.0	20.9	1 (ref.)

DM: diabetes mellitus; CI: confidence interval; HR: hazard ratio; no.: number; ref: reference.

^a Per 1000 person-years.

^b HR was calculated by the Cox proportional hazards model in the propensity score-matched population

eTable 5. Reasons for end of follow-up or censoring in the treatment and comparison groups in the primary analysis

	Overall (N = 68,510)	Treatment group (N = 34,255)	Comparison group (N = 34,255)
Reasons, N (%)			
Development of study outcome	5236 (7.6)	2016 (5.9)	3220 (9.4)
Anti-osteoporosis drug initiation	6624 (9.7)	NA	6624 (19.3)
Denosumab treatment cessation	17706 (25.8)	17706 (51.7)	NA
Death	5514 (8.0)	1680 (4.9)	3834 (11.2)
Data source end date	33430 (48.8)	12853 (37.5)	20577 (60.1)

NA: not applicable