**Supplemental Table S1**, STROBE Checklist for observational studies.

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| --- | --- | --- | --- |
| **Section/Topic** | Item No | Recommendation | Reported on Page No |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | 1 |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2-3 |
| Introduction | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 6-8 |
| (*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed  *Case-control study*—For matched studies, give matching criteria and the number of controls per case |  |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-10 |
| Data sources/measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-10 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 11 |
| Study size | 10 | Explain how the study size was arrived at | 6-7, supplemental fig. 1 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 11 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 11-12 |
| (*b*) Describe any methods used to examine subgroups and interactions | 11 |
| (*c*) Explain how missing data were addressed | - |
| (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed  *Case-control study*—If applicable, explain how matching of cases and controls was addressed  *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | - |
| (*e*) Describe any sensitivity analyses | 11 |

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| --- | --- | --- | --- |
| **Section/Topic** | Item No | Recommendation | Reported on Page No |
| Results | | | |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Supplemental fig. 1 |
| (b) Give reasons for non-participation at each stage | - |
| (c) Consider use of a flow diagram | Supplemental fig. 1 |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 12 |
| (b) Indicate number of participants with missing data for each variable of interest | - |
| (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 13 |
| Outcome data | 15\* | *Cohort study*—Report numbers of outcome events or summary measures over time | 14 |
| *Case-control study—*Report numbers in each exposure category, or summary measures of exposure | - |
| *Cross-sectional study—*Report numbers of outcome events or summary measures | - |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Tab. 2 |
| (*b*) Report category boundaries when continuous variables were categorized | - |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | - |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 14 |
| Discussion | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 15 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 17-18 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 18 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 15-17 |
| Other Information | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 19 |

*\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

**Supplemental Table S2.** Identification of diabetes, exposure and covariables.

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| --- | --- | --- |
|  | **ICD-10 codes** | **ATC codes** |
| Diabetes mellitus | E10, E11, E12, E13, E14, G63.2, H28.0, H36.0, M14.2, O24, R73 | A10A, A10B |
| Alendronate |  | M05BA04 |
| Denosumab |  | M05BX04 |
| Other anti-osteoporotic treatment |  | M05BA01-3, M05BA05-8  M05BB01-3, M05BB  M05BX01-3, M05BX05-53  H05B, H05AA |
| Heavy smoking | J41-J44, J47,  Z720, F17, T652 | N07BA, N06AX12.  After age 40: R03A, R03B, R03C, R03DA, R03DB, R03DC, R03DX07 |
| Alcohol abuse | T51, G312, G621, I426, K292, K70, K852, K860, F10 | N07BB01, N07BB03, N07BB05 |
| Obesity | E66 | A08A |
| Hyperthyroidism | E05 | H03B |
| Hypothyroidism | E03 | H03A |
| Glucocorticoid use |  | H02AB |
| Pancreatitis | K86.0, K86.1, K85.0, K85.1, K85.2, K85.3, K85.8, K85.9 |  |
| Hypoglycemia | E15, E16.0-E16.2 |  |
| Insulin use |  | A10A |
| Hypertension | I10-I13, I15, R03.0 | ACE/ARB, central, calcium-channel block: C09, C02DB, C02CA, C02AB, C02AC, C08.  Thiazides: C03AA, C03AB, C03BA.  Loop-diuretics: C03CA, C03CB, C03EB.  Potassium saving: C03D.  Combinations: C03E.  Beta blokcers: C07A |
| Statin use |  | C10AA |
| Opioid use |  | N02A |
| Psychoactive/  Psycholeptic drugs |  | N05, N06 |
| Peptic ulcer | K22.1, K25-K28 |  |
| Renal impairment | I12, I13, N02-N04, N07, N11, N12, N14, N18-N19, Q60-Q61  E10.2, E11.2, N083 |  |

**Supplemental Table S3.** Identification of outcome; fractures

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| --- | --- |
|  | **ICD-10 codes** |
| **Major osteoporotic fracture** | Hip/femur, spine (vertebral), forearm/arm (unspecified), humerus |
| Hip/femur | S72.0, S72.1, S72.2, S72.3, S72.4, S72.7, S72.8, S72.9, M80.9B |
| Spine (vertebral) | S32.0, S32.1, S32.2, S32.3, S32.4, S32.5, S32.7, S32.8.  S12.0, S12.1, S12.2, S12.7, S12.8, S12.9., S22.0, S22.1  T08, T08.9, M48.4 M48.5, M80.9C |
| Forearm/arm unspecified | S52.0-S52.9, T10, DT10.9, M80.9A |
| Humerus | S42.2-S42.4, S42.7, S42.8 |
| **Any other fracture** | Any below |
| Wrist/hand | S62.0-S62.8 |
| Shoulder and upper arm | S42.0, S42.1, S42.2, S42.3, S42.4, S42.7, S42.8, S42.9. |
| Head/skull (incl. crush) | S02.0-S02.9, S07.0, S07.1, S07,8, S07.9 |
| Neck | S12.0, S12.1, S12.2, S12.7, S12.8, S12.9 |
| Thorax | S22.0, S22.1, S22.2, S22.3, S22.4, S22.5, S22.8 |
| Lower leg/ankle | S82.0-S82.9. |
| Foot | D.92.0, D.92.1, D.92.2, D.92.3, D.92.4, D.92.5, D.92.7, D.92.9. |
| Leg, unspecified | T12, DT12.9 |
| Stress/pathological | M84., M84.4, M80.x |

**Supplemental Table S4**. Charlson Comorbidity Index; scoring and ICD codes

|  |  |  |
| --- | --- | --- |
| **Comorbidity** | **Score** | **ICD-10 codes** |
| 1, Acute myocardial infarction | 1 | DI21, DI23, I24.1, I24.8, I24.9 |
| 2, Cardiac insufficiency | 1 | I50, I11.0, I13.0, I13.2 |
| 3, Cardiovascular disease | 1 | I70, I71, I72, I73, I74, I77 |
| 4, Cerebrovascular disease | 1 | I60-I69, G45, G46 |
| 5, Dementia | 1 | F00-F03, F05.1, G30 |
| 6, Chronic pulmonary disease | 1 | J40-J47, J60-J67, J68.4, J70.1, J70.3, J70.4, J82, J84, J85.0, J92, J95.3, J96.1, J98.2, J98.3 |
| 7, Connective tissue disease | 1 | M05-M09, M30-M36, D86 |
| 8, Peptic ulcer | - | - |
| 9, Mild liver disease | 1 | B18, K70.0-K70.3, K709, K71, K73, K74, K75.2-K75.4, B15.9, B16.9, K75.8-K75.9, K76.0 |
| 10, Diabetes mellitus | - | - |
| 11, Hemiplegia | 1 | G81, G82 |
| 12, Nephrological disease | - | - |
| 13, Late-diabetic complications | 2 | E10.3-DE10.8, E11.3-E11.8  G59.0, G63.2, N083, DH360 |
| 14, Solid cancers | 2 | C00-C75 |
| 15, Leukemia | 2 | DC91-DC95 |
| 16, Lymphoma | 2 | C81-C85, C88, C90, C96 |
| 17, Moderate to severe liver disease | 3 | B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, K76.7, I85 |
| 18, Metastatic cancer | 6 | C77-C80 |
| 19, AIDS | 6 | B20-B24 |

**Supplemental Table S5**. Baseline characteristics of subjects discontinuing treatment before end of follow-up.

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| --- | --- | --- | --- |
| **Subjects discontinuing, n (%)** | **All subjects**  n = 4,078 (47) | **Alendronate**  n = 3,922 (48) | **Denosumab**  n = 156 (32) |
| **No switch,** n (%) | 3,633 (42) | 3,484 (42) | 149 (30) |
| **Switch to other treatment,** n (%) | 445 (5) | 438 (5) | 7 (1) |
| **Age (years),** mean ± SD | 3,633 (42) | 3,484 (42) | 149 (30) |
| **Age category (years)**, n (%) | 445 (5) | 438 (5) | 7 (1) |
| 50-59 | 73.19 (9.53) | 75.78 (10.44) | 73.09 (9.48) |
| 60-69 |  |  |  |
| 70-79 | 413 (10) | 399 (10) | 14 (9) |
| ≥ 80 | 1,050 (26) | 1,022 (26) | 28 (18) |
| **Sex,** n (%) | 1,599 (39) | 1,541 (39) | 58 (37) |
| Female | 1,016 (25) | 960 (25) | 56 (36) |
| Male |  |  |  |
| **Type 2 diabetes**, n (%) | 2,785 (68) | 2,662 (68) | 123 (79) |
| **Diabetes duration in years,**  median (IQR) | 1,293 (32) | 1,260 (32) | 33 (21) |
| **History of any fracture**, n (%) | 4,012 (98) | 3,861 (98) | 151 (97) |
| **CCI,** mean ± SD | 5.23 (2.27-8.89) | 5.23 (2.26-8.85) | 5.51 (2.57-9.45) |
| **Peptic ulcer,** n (%) | 223 (6) | 213 (5) | 10 (6) |
| **Renal impairment,** n (%) | 361 (9) | 327 (8) | 34 (22) |
| **Income,** € in thousands,  median (IQR) | 26.01 (16.65-32.31) | 25.96 (19.61-32.22) | 26.89 (20.89-34.52) |
| **Marital status,** n (%) |  |  |  |
| Married | 2,034 (50) | 1,965 (50) | 69 (44) |
| Divorced | 634 (16) | 610 (16) | 24 (15) |
| Unmarried | 260 (6) | 249 (6) | 11 (7) |
| Widowed | 1,144 (28) | 1,092 (28) | 52 (33) |
| Unknown | 6 (0) | 6 (0) | 0 (0) |
| **Heavy Smoking,** n (%) | 1,466 (36) | 1,403 (36) | 63 (40) |
| **Alcohol abuse,** n (%) | 319 (8) | 310 (8) | 9 (6) |
| **Obesity,** n (%) | 763 (19) | 730 (19) | 33 (21) |
| **Pancreatitis,** n (%) | 149 (4) | 147 (4) | 2 (1) |
| **Hyperthyroidism,** n (%) | 131 (3) | 128 (3) | 3 (2) |
| **Hypothyroidism,** n (%) | 292 (7) | 281 (7) | 11 (1) |
| **Glucocorticoid use,** n (%) | 2,431 (60) | 2,345 (60) | 86 (55) |
| **Statin use**, n (%) | 3,103 (76) | 2,991 (76) | 112 (72) |
| **Insulin use**, n (%) | 784 (19) | 751 (19) | 33 (21) |
| **Hypoglycemia**, % ± SD | 70 (2) | 67 (2) | 3 (2) |
| **Hypertension**, n (%) | 3,692 (91) | 3,550 (91) | 142 (91) |
| **Opioid use**, n (%) | 3,137 (77) | 3,005 (77) | 132 (85) |
| **Anxiolytics**, n (%) | 3,589 (88) | 3,448 (88) | 141 (90) |
| **Initiation year**, n (%) |  |  |  |
| 2011 | 622 (15) | 602 (15) | 20 (13) |
| 2012 | 617 (15) | 597 (15) | 20 (13) |
| 2013 | 588 (14) | 558 (14) | 30 (19) |
| 2014 | 552 (14) | 526 (13) | 26 (17) |
| 2015 | 502 (12) | 489 (13) | 13 (8) |
| 2016 | 488 (12) | 464 (12) | 24 (15) |
| 2017 | 458 (11) | 444 (11) | 14 (9) |
| 2018 | 251 (6) | 242 (6) | 9 (6) |

All characteristics were evaluated in the time from 2000 until index date (exposure start). Data are presented as numbers (n, %), mean with SD or median with IQR.

**Supplemental Figure S1**, Flow-diagram of the study group selection process.

