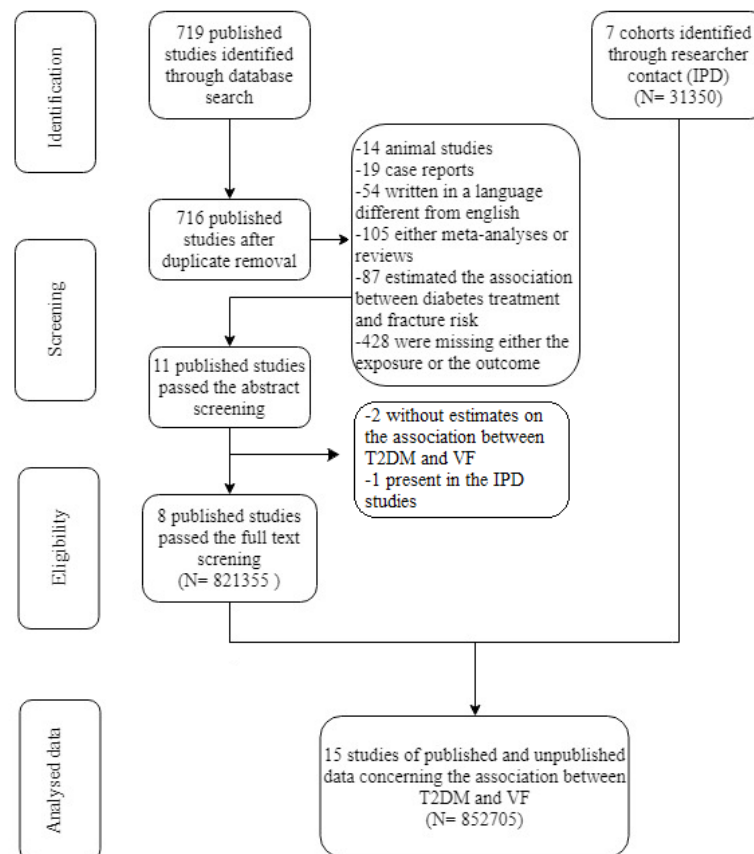


SUPPLEMENTARY DATA

Supplementary materials for: “Vertebral fractures in individuals with type 2 diabetes: more than skeletal complications alone” by Koromani F et al.

Supplementary Figure S1: Flow chart of the study population for analysis. IPD= individual participant data, T2DM= Type 2 Diabetes Mellitus, VF= Vertebral Fracture



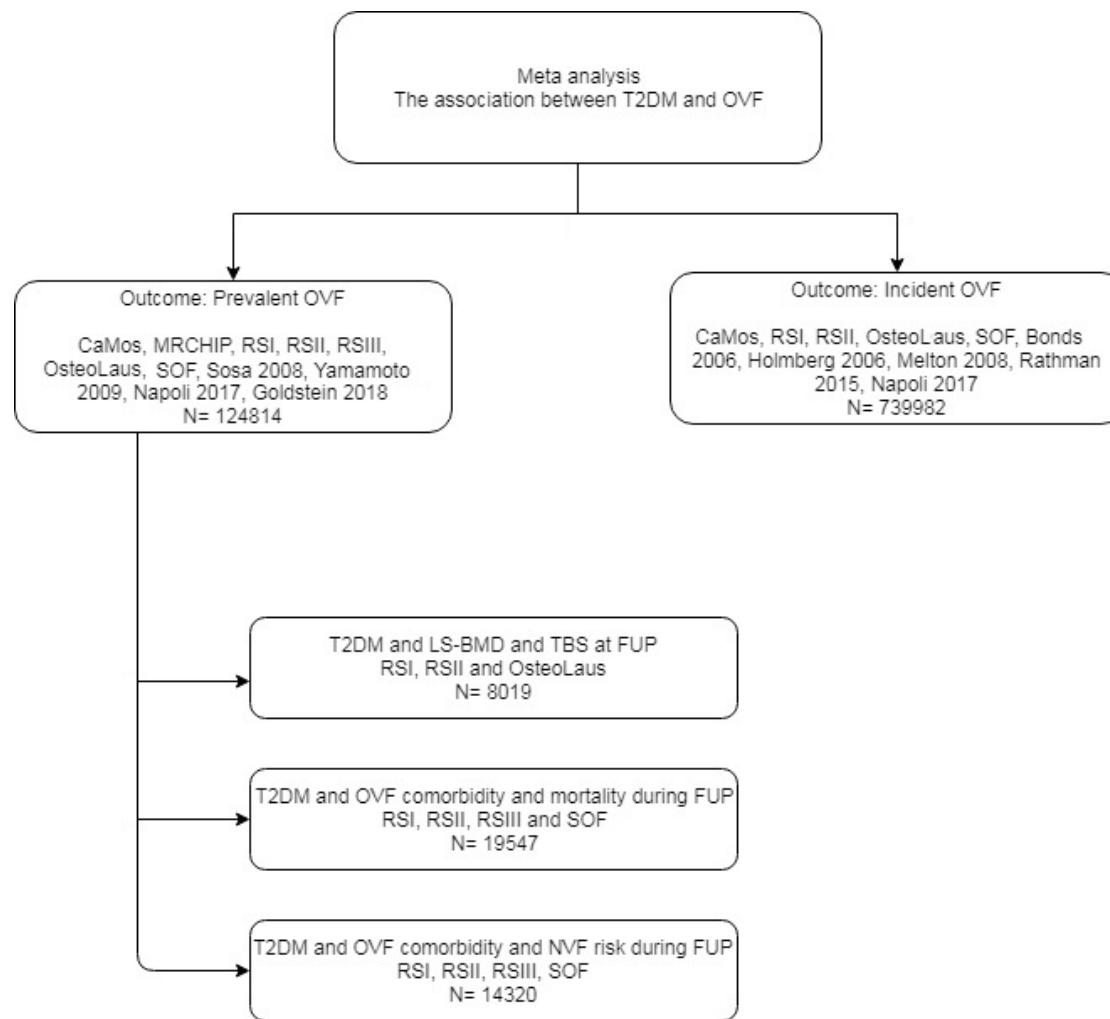
SUPPLEMENTARY DATA

Supplementary Material S2: Search strategy

Two systematic searches in PubMed were performed, using search terms and search tags for medical subject headings (MeSH), title (ti), title abstract (tiab) as follows: (("Diabetes Mellitus, type 2"[Mesh] AND "Fractures, Bone"[Mesh]) OR ("diabetes" [ti] AND "fracture" [ti])) up to February 8, 2019 and (("Diabetes Mellitus, type 2"[Mesh] AND "Fractures, Bone"[Mesh]) OR ("diabetes" [ti] AND "fracture" [ti]) OR ("fracture" [tiab] AND "diabetes" [tiab] AND "population based"[tiab])) up to February 26, 2019. The search was performed a second time as a sensitivity analysis for the first search, but also to detect more studies that could potentially be included in the meta-analysis. FK reviewed the titles and abstracts of the studies identified by both literature searches. The first triage was performed by excluding animal studies, case reports, meta-analyses, non-English abstracts. Then, for the remaining studies, the abstracts were read and classified into missing exposure (included types of diabetes other than T2DM), missing outcome (included types of fractures other than VF), and the remainder were included in the meta-analysis.

SUPPLEMENTARY DATA

Supplementary Figure S3: Studies included in the meta-analysis and in the exploratory analysis



SUPPLEMENTARY DATA

Supplementary Table S4: Characteristics of the studies included in the meta-analysis. Study year refers to year of recruitment of participants for unpublished studies and to year when the study was published for the published studies. NA= Not available, NR=Not reported, VF=vertebral fracture,

| Study (Year) | Country | Sample size | Number (%women) | Prevalent type 2 diabetes | Prevalent VF | Incident VF | Mean age at baseline (years) | BMI (kg/m ²) | Mean Follow up (years) | Ascertainment of type 2 diabetes | Ascertainment of VF | Model (estimates reported) | Study Design |
|--------------------------|---------|-------------|-----------------|---------------------------|--------------|-------------|------------------------------|--------------------------|------------------------|---|--|--|--------------------|
| Published studies | | | | | | | | | | | | | |
| Bonds 2006(1) | USA | 93405 | 93405 (100.0) | 5285 (5.6) | NA | 1438 (1.5) | 63.5 (7.4) | NR | 7 | An affirmative answer to the question asked at baseline: did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant? or the reported use of a medication to treat diabetes at baseline. | Self-reported | Age, ethnicity, weight, height, time-dependent history of falls, previous fracture, history of osteoporosis, trouble seeing at baseline, alcohol and tobacco use, calcium and vitamin d intake, exercise, bisphosphonates, oestrogen, steroid, insulin. SERm, thyroid hormone use (HR) | Prospective study |
| Holmberg 2006(2) | Sweden | 33346 | 10902 (32.7) | 381 (1.1) | NA | 294 (0.8) | 45.6 (6.8) | 24.5 (3.3) | 17 | General practitioner records | General practitioner records with radiographic confirmation | Age, BMI, resting pulse, serum triglycerides, serum cholesterol, serum creatinine, smoking, poor self-rated health (Relative Risk) | Prospective cohort |
| Melton 2008(3) | USA | 1964 | 972 (49.4) | 1964 (100.0) | NA | 329 (16.7) | 61.7 (14.0) | NR | 12 | Two consecutive fasting plasma glucose levels ≥ 7.8 mmol/dl [140 mg/dl] or | Radiologist's report on presence of compressed or collapsed vertebra | Year, Age and sex standardized incidence rates (Standardized Incidence ratio) | Retrospective |

SUPPLEMENTARY DATA

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|------------------|-------|------|-------------|------------|------------|-----------|------------|------------|-----|--|---|--|--------------------------|
| | | | | | | | | | | both 1- and 2-h levels \geq 11.1 mmol/dl [200 mg/dl] during a standard oral glucose tolerance test as recorded in contemporary medical records | | | |
| Sosa 2008(4) | Spain | 208 | 208 (100.0) | 111 (53.3) | 10 (4.8) | NA | 70.8 (5.4) | 33.3 (4.4) | NA | General practitioner records | Lateral radiographs from T4 to L4 were read and scored based on quantitative morphometry assisted by Morpho-Express device and graded based on Genant' grading system (either grade 1, 2 or 3) | (OR) | Cross-sectional study |
| Yamamoto 2009(5) | Japan | 996 | 759 (76.2) | 298 (29.9) | 270 (27.1) | NA | 66.2 (8.5) | 22.4 (3.2) | NA | Clinically diagnosed Diabetes | Lateral radiographs from T4 to L4 were read and scored by technicians based on quantitative morphometry assisted by SpineAnalyzer and graded based on Genant' grading system (either grade 1, 2 or 3) | Age, sex, BMI, BMD (OR) | Cross-sectional |
| Napoli 2017(6) | USA | 5554 | NA | 875 (15.7) | 420 (7.5) | 184 (3.3) | 73.6 (5.9) | NR | 4.6 | Self-report, use of diabetes medication, or fasting plasma | Lateral radiographs from T4 to L4 were read and | Age, race, clinic site, BMI, aBMD (OR) | Prospective cohort study |

SUPPLEMENTARY DATA

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|--|-------------|--------|---------------|---------------|------------|--------------|-------------|--------------|-----|--|--|--|---|--|
| | | | | | | | | | | | glucose \geq 126 mg/dL | scored based on quantitative morphometry using the semi-quantitative method of Genant for grading. Prevalent VF was defined as SQ \geq grade 2 | | |
| Rathman 2015(7) | Germany | 598208 | 294917 (49.0) | 299104 (50.0) | NA | 85245 (14.2) | 66.1 (12.2) | 50250 (8.4)* | 3 | General practitioner records | General practitioner records based on ICD-10 (S32, T08) | cases and controls matched for sex, age, type of health insurance, and index date (HR) | Retrospective matched case control study | |
| Goldshtein 2018(8) | Israel | 87224 | 74044 (84.8) | 15378 (17.6) | 6939 (7.9) | NR | 70.4 (10.8) | NR | NR | Extracted from Health Maintenance Registry connected to GP records | Extracted from Health Maintenance Registry connected to GP records | Age and sex standardized fracture rates (Standardized Rate ratio) | Retrospective study | |
| Cohorts with individual participant data | | | | | | | | | | | | | | |
| CaMos (1995) | Canada | 5083 | 3634 (71.5) | 345 (6.8) | 407 (8.0) | 87 (2.6) | 65.5 (8.8) | 26.7 (4.0) | 5 | General practitioner records | Lateral radiographs from T4 to L4 were read and scored based on quantitative morphometry using the semi-quantitative method of Genant for grading. Prevalent VF was defined as SQ \geq grade 2 | Age, sex, BMI, corticosteroid use, anti-osteoporotic treatment, aBMD (OR) | Prospective | |
| MRCHIP 2009 | UK | 5419 | 5419 (100.0) | 230 (4.5) | 747 (14.5) | NA | 79.5 (3.9) | 26.8 (4.6) | NA | General practitioner records | Lateral radiographs were read and scored based on the McCloskey-Kanis method of defining VF | Age, sex, BMI, corticosteroid use, anti-osteoporotic treatment, aBMD (OR) | Prospective, randomized, placebo-controlled trial | |
| OsteoLaus | Switzerland | 1475 | 1475 | 60 (4.1) | 55 (3.7) | 30 (2.3) | 64.5 | 25.9 | 2.6 | Fasting blood | Semi- | Age, sex, BMI, | Prospective | |

SUPPLEMENTARY DATA

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|------------|-------------|------|-------------|------------|-----------|-----------|-------------|------------|-----|--|---|---|--------------------|
| 2009 | | | (100.0) | | | | (7.6) | (4.5) | | glucose ≥ 7.0 mmol/L, or the use of blood glucose lowering medication | quantitative approach of Genant (defined as at least one fracture of grade 2 or 3), on lateral DXA images from T4 to L4 | corticosteroid use, anti-osteoporotic treatment, aBMD (OR) | cohort |
| RSI 1989 | Netherlands | 5392 | 3125 (57.9) | 372 (6.9) | 342 (6.3) | 111 (3.2) | 67.9 (8.0) | 26.3 (3.7) | 2.5 | Fasting blood glucose ≥ 7.0 mmol/L, a non-fasting blood glucose ≥ 11.1 mmol/L (when fasting samples were unavailable), or the use of blood glucose lowering medication | Quantitative morphometry assisted by SpineAnalyzer and graded based on Genant' grading system on lateral radiographs from T4 to L4 (defined as at least one fracture of grade 2 or 3) | Age, sex, BMI, corticosteroid use, anti-osteoporotic treatment, aBMD (OR) | Prospective cohort |
| RSII 2000 | Netherlands | 2139 | 1180 (55.1) | 269 (12.6) | 134 (6.3) | 48 (4.1) | 64.55 (7.7) | 27.2 (3.9) | 2.5 | Fasting blood glucose ≥ 7.0 mmol/L, a non-fasting blood glucose ≥ 11.1 mmol/L (when fasting samples were unavailable), or the use of blood glucose lowering medication | Quantitative morphometry assisted by SpineAnalyzer and graded based on Genant' grading system on lateral radiographs from T4 to L4 (defined as at least one fracture of grade 2 or 3) | Age, sex, BMI, corticosteroid use, anti-osteoporotic treatment, aBMD (OR) | Prospective cohort |
| RSIII 2006 | Netherlands | 2742 | 1563 (57.0) | 229 (8.4) | 209 (7.6) | NA | 56.6 (6.6) | 27.6 (4.5) | NA | Fasting blood glucose ≥ 7.0 mmol/L, a non- | Quantitative morphometry assisted by | Age, sex, BMI, corticosteroid use, anti- | Prospective cohort |

SUPPLEMENTARY DATA

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|----------|-----|--------|---------------|---------------|-------------|--------------|-------------|-------------|-----|--|--|--|--------------------|
| | | | | | | | | | | fasting blood glucose ≥ 11.1 mmol/L (when fasting samples were unavailable), or the use of blood glucose lowering medication | SpineAnalyzer and graded based on Genant' grading system on lateral radiographs from T4 to L4 (defined as at least one fracture of grade 2 or 3) | osteoporotic treatment , aBMD (OR) | |
| SOF 1986 | USA | 9550 | 9550 (100.0) | 677 (7.1) | 1910 (20.0) | 317 (27.8) | 71.6 (5.2) | 26.4 (4.4) | 3.5 | Was defined by means of interview and cases were subjects who answered "yes" to the question "Has a doctor ever told you that you had diabetes?" | Lateral radiographs were read and scored based on Black' method that calculates four ratios in the vertebral body. Prevalent fractures were defined as any ratio 3 SD's below the normal mean or (ratio-mean)/SD ≤ -3 | Age, sex, BMI, corticosteroid use, anti-osteoporotic treatment , aBMD (OR) | Prospective cohort |
| Total | | 852705 | 500091 (58.6) | 325280 (38.1) | 11173 (8.9) | 88083 (11.6) | 65.5 (11.0) | 25.56 (3.7) | | | | | |

SUPPLEMENTARY DATA

Supplementary Table S5: Baseline characteristics of the cohorts with individual participant data, shown by participating cohort. Continuous variables are shown as mean (SD) and categorical variables as numbers (percentage).

| | Overall | CaMos | MRCCHIP | Osteolaus | RSI | RSII | RSIII | SOF |
|-----------------------------------|---------------|--------------|--------------|--------------|--------------|--------------|-------------|--------------|
| n | 31530 (100.0) | 5083 (16.1) | 5149 (16.3) | 1475 (4.7) | 5392 (17.1) | 2139 (6.8) | 2742 (8.7) | 9550 (30.3) |
| Age years | 69.2 (9.1) | 65.5 (8.8) | 79.5 (3.9) | 64.5 (7.6) | 67.9 (8.0) | 64.5 (7.7) | 56.6 (6.6) | 71.6 (5.2) |
| Sex (% women) | 25676 (81.4) | 3634 (71.5) | 5149 (100.0) | 1475 (100.0) | 3125 (58.0) | 1180 (55.2) | 1563 (57.0) | 9550 (100.0) |
| Height cm | 162.4 (9.03) | 163.30 (8.9) | 155.9 (6.1) | 161.2 (6.7) | 167.2 (9.24) | 168.3 (9.17) | 170.4 (9.5) | 159.3 (5.9) |
| Weight kg | 70.4 (13.51) | 71.4 (13.5) | 65.1 (12.0) | 67.3 (12.1) | 73.7 (11.7) | 77.2 (13.3) | 80.4 (15.7) | 67.1 (11.9) |
| BMI kg/m ² | 26.6 (4.3) | 26.7 (4.0) | 26.8 (4.6) | 25.9 (4.5) | 26.3 (3.7) | 27.2 (3.9) | 27.6 (4.5) | 26.4 (4.4) |
| BMI category | | | | | | | | |
| normal weight | 1129 (35.8) | 1695 (33.3) | 1811 (35.2) | 640 (43.4) | 1942 (36.0) | 09 (28.5) | 766 (27.9) | 3832 (40.1) |
| underweight | 363 (1.2) | 64 (1.3) | 93 (1.8) | 31 (2.1) | 48 (0.9) | 14 (0.7) | 14 (0.5) | 99 (1.0) |
| overweight | 13479 (42.7) | 2238 (44.0) | 2069 (40.2) | 531 (36.0) | 2588 (48.0) | 1049 (49.0) | 297 (47.3) | 3707 (38.8) |
| obese | 6393 (20.3) | 1086 (21.4) | 1176 (22.8) | 273 (18.5) | 814 (15.1) | 467 (21.8) | 665 (24.3) | 1912 (20.0) |
| FN-BMD T-Score (continuous) | -1.32 (1.1) | -1.11 (1.1) | -1.69 (1.0) | -0.97 (1.0) | -1.27 (1.0) | -0.92 (1.1) | -0.65 (1.0) | -1.60 (1.0) |
| FN-BMD T-Score categories | | | | | | | | |
| Normal | 11277 (35.8) | 2215 (43.6) | 1154 (22.4) | 702 (47.6) | 2048 (38.0) | 1138 (53.2) | 1689 (61.6) | 2374 (24.9) |
| Osteopenia | 6053 (50.9) | 99 (47.2) | 2920 (56.7) | 707 (47.9) | 2712 (50.3) | 856 (40.0) | 986 (36.0) | 5439 (57.0) |
| Osteoporosi | 4200 (13.3) | 469 (9.2) | 1075 (20.9) | 66 (4.5) | 632 (11.7) | 145 (6.8) | 67 (2.4) | 1737 (18.2) |
| Corticosteroid use (yes) | 1379 (4.4) | 82 (1.6) | 168 (3.3) | 51 (3.5) | 94 (1.7) | 18 (0.8) | 19 (0.7) | 947 (9.9) |
| Anti-osteoporotic treatment (yes) | 2847 (9.0) | 1100 (21.6) | 0 | 114 (7.7) | 718 (13.3) | 22 (1.0) | 40 (1.5) | 853 (8.9) |
| With T2DM | 2182 (6.9) | 345 (6.8) | 230 (4.5) | 60 (4.1) | 372 (6.9) | 269 (12.6) | 229 (8.4) | 677 (7.1) |
| With prevalent VF | 3804 (12.1) | 407 (8.0) | 747 (14.5) | 55 (3.7) | 342 (6.3) | 134 (6.3) | 209 (7.6) | 1910 (20.0) |

Supplementary Table S6: The association between T2DM and prevalent VF across tertiles of age at baseline, BMI categories in the overall

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population and stratified by sex

| | Overall (n, OR 95% CI) | | Men (n, OR 95% CI) | | Women (n, OR 95% CI) | |
|-------------------------------|---------------------------|-------------------|-----------------------|-------------------|-------------------------|-------------------|
| Without stratification | | | | | | |
| | 31530 | 0.85 (0.73-0.99) | 5854 | 0.87 (0.61- 1.21) | 25676 | 0.84 (0.71- 0.98) |
| Stratified by age tertiles | | | | | | |
| Age 45.5 to 66.0 at baseline | 10472 | 0.88 (0.60- 1.26) | 3571 | 0.94 (0.55- 1.51) | 6899 | 0.90 (0.5- 1.50) |
| Age 66.0 to 74.0 at baseline | 10737 | 0.91 (0.72- 1.14) | 1414 | 1.31 (0.69- 2.35) | 9324 | 0.86 (0.66- 1.09) |
| Age 74.0 or older at baseline | 10321 | 0.76 (0.60- 0.95) | 869 | 0.51 (0.22-1.07) | 9453 | 0.79 (0.62- 1.00) |
| Stratified by BMI categories | | | | | | |
| Underweight | 363 | 3.38 (0.78- 1.33) | 34 | NA | 329 | 7.77 (1.53- 43.8) |
| Normal weight | 11295 | 0.90 (0.67- 1.20) | 1789 | 0.93 (0.42- 1.82) | 9506 | 0.90 (0.64- 1.23) |
| Overweight | 13479 | 0.88 (0.70- 1.10) | 3100 | 0.94 (0.57- 1.48) | 10379 | 0.86 (0.66- 1.10) |
| Obese | 6393 | 0.72 (0.54- 0.94) | 931 | 0.77 (0.36- 1.51) | 5462 | 0.71 (0.52- 0.95) |

Estimates are odds ratios and respective 95% CI

NA- not available due to very low numbers in that analysis

Adjusted for age, (sex), BMI, corticosteroid use, anti-osteoporotic treatment, FN-BMD, cohort

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Supplementary Table S7: The association between type 2 diabetes and FN-BMD measured at baseline and with LS-BMD and TBS measured at follow up.

| FN-BMD at baseline | | LS-BMD at follow up | | LS-TBS at follow up | |
|--|------------------------|------------------------|-------------------------|---------------------------|---------------------------|
| Men N= 5554 | Women N= 23019 | Men N= 2782 | Women N= 5037 | Men N= 2782 | Women N= 5037 |
| Model 1: Adjusted for age + study + corticosteroid use + anti-osteoporotic treatment | | | | | |
| 0.029 (0.018 to 0.041) | 0.046 (0.039 to 0.053) | 0.040 (0.013 to 0.066) | 0.065 (0.039 to 0.091) | -0.039 (-0.055 to -0.023) | -0.046 (-0.060 to -0.032) |
| Model 2: Model 1+ BMI | | | | | |
| 0.013 (0.01 to 0.025) | 0.022 (0.015 to 0.029) | 0.016 (-0.10 to 0.043) | 0.020 (-0.004 to 0.045) | -0.019 (-0.035 to -0.004) | -0.041 (-0.048 to -0.033) |

Estimates are unstandardized beta and respective 95% CI from linear regression models

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Supplementary Table S8: Sensitivity analysis performed in the meta-analysis to estimate the association between type 2 diabetes and *incident* VF

*In the stratification for sex the study from Rathmann(7) is excluded because they have reported point estimates for both sexes together

| Stratification for sensitivity analysis | N | OR (95% CI) | Heterogeneity |
|--|----------|--------------------|----------------------|
| Overall | 739982 | 1.66 (1.04-2.31) | 95.3, p<0.01 |
| Sex* | | | |
| Men | 27970 | 1.25 (0.85-1.84) | 0%, p=0.9 |
| Women | 111840 | 1.22 (0.83-1.79) | 40.5%, p=0.12 |
| Previously published | | | |
| Published | 731020 | 2.02 (1.22-3.36) | 97.7%, p<0.01 |
| Unpublished | 8962 | 0.95 (0.64;1.41) | 0%, p=0.4 |
| Definition of VF | | | |
| Morphometry | 13059 | 1.09 (0.80-1.46) | 0%, p=0.6 |
| Clinical | 726923 | 2.18 (1.25-3.82) | 98%, p<0.01 |
| Study design | | | |
| Prospective | 139810 | 1.25 (1.04-1.50) | 1%, p=0.4 |
| Retrospective | 600172 | 2.76 (1.23-6.18) | 99%, p<0.01 |
| Excluding each study | | | |
| Bonds 2006(1) | 646577 | 1.57 (1.01-2.44) | 96%, p<0.01 |
| Rathmann 2015(7) | 141774 | 1.57 (1.03-2.40) | 91%, p<0.01 |
| Holmberg 2006(2) | 706636 | 1.50 (0.98-2.30) | 96%, p<0.01 |
| Napoli 2017(6) | 735885 | 1.57 (1.03-2.41) | 96%, p<0.01 |
| Melton 2008(3) | 738018 | 1.35 (1.26-1.45) | 1%, p=0.4 |
| CaMos | 736649 | 1.66 (1.09-2.52) | 96%, p<0.01 |
| OsteoLaus | 738681 | 1.51 (1.00-2.28) | 96%, p<0.01 |
| RS II | 738825 | 1.63 (1.07-2.47) | 96%, p<0.01 |
| RS I | 737953 | 1.61 (1.06-2.43) | 96%, p<0.01 |
| SOF | 738840 | 1.63 (1.07-2.48) | 96%, p<0.01 |

SUPPLEMENTARY DATA

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