Supplementary Materials

Improved prediction of fracture risk leveraging a genome-wide polygenic risk score

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Fig. S1. Distribution of discrepancies in minor allele frequencies of SNPs between the China Kadoorie Biobank (CKB) and the UK Biobank. The distribution was derived based on 13,848 gSOS SNPs available in CKB. Minor allele frequency discrepancy may exceed 0.5 because some SNPs had reversed minor and major alleles in these two cohorts.
Fig. S2. Distribution of standardized gSOS among 90,172 individuals of European ancestry. Individuals who experienced incident major osteoporotic fracture or incident hip fracture had significantly lower standardized gSOS than those who did not experience incident fracture. This trend was consistent in both women (t-test p-value = 4.5x10^{-33} for major osteoporotic fracture; 1.0x10^{-9} for hip fracture) and men (t-test p-value = 1.8x10^{-23} for major osteoporotic fracture; 1.7x10^{-9} for hip fracture).
**Fig. S3.** Cumulative incidence of major osteoporotic fracture in (A) the MrOS US cohort and (B) the SOF cohort, and cumulative incidence of hip fracture in (C) the MrOS US cohort and (D) the SOF cohort. Both cohorts enrolled elderly men or women aged $\geq 65$ years. Kaplan-Meier estimates were used to estimate the cumulative incidence, censored at 90 years.
Table S1: Summary of model training and selection in the UK Biobank. This table is adapted from supplementary Table S3 in Forgetta et al [1].

| GWAS\(^*\) p-value threshold | \(5 \times 10^{-3}\) | \(5 \times 10^{-4}\) | \(5 \times 10^{-5}\) | \(5 \times 10^{-6}\) | \(5 \times 10^{-7}\) | \(5 \times 10^{-8}\) |
|------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| No. of total SNPs            | 642,127        | 345,111        | 227,478        | 166,576        | 130,130        | 104,836        |
| No. of activated SNPs by LASSO | 40,864        | 21,717        | 13,793        | 10,348        | 7,999         | 6,823         |
| \(\lambda\) parameter\(^\dagger\) | 0.0032        | 0.0028        | 0.0021        | 0.0016        | 0.0015        | 0.0013        |
| Proportion of variance explained\(^\ddagger\) | 24.53%        | 24.99%        | 24.89%        | 24.75%        | 23.86%        | 23.38%        |
| Lower bound of 95% CI        | 22.54%        | 22.99%        | 22.89%        | 22.75%        | 21.88%        | 21.41%        |
| Upper bound of 95% CI        | 26.55%        | 27.02%        | 26.91%        | 26.77%        | 25.87%        | 25.38%        |

\(^*\) Genome-wide association study performed in the training dataset (N = 341,449)

\(^\dagger\) \(\lambda\) in the LASSO model optimized in the model selection dataset (N = 5,335)

\(^\ddagger\) Highest proportion of variance explained achieved in the model selection dataset with optimized \(\lambda\)
Table S2: Summary of Pearson correlation between gSOS and clinical risk factors.

| Cohort              | UK Biobank Test Dataset (N = 80,014) | MrOS US (N = 4,663) | MrOS Sweden (N = 1,880) | SOF (N = 3,615) | CKB (N = 25,034) |
|---------------------|--------------------------------------|---------------------|--------------------------|----------------|-----------------|
|                     |                                      | Malmo               | Gothenburg               |                |                 |
| Age                 | 0.01 (0.00 – 0.01)                   | 0.00 (-0.03 – 0.03) | 0.02 (-0.05 – 0.08)      | 0.02 (-0.01 – 0.06) | 0.01 (0.00 – 0.02) |
| Sex                 | 0.00 (-0.01 – 0.00)                  | NA                  | NA                       | NA             | 0.01 (0.00 – 0.02) |
| Baseline BMI        | 0.00 (0.00 – 0.01)                   | 0.02 (-0.01 – 0.05) | 0.01 (-0.05 – 0.08)      | 0.00 (-0.04 – 0.03) | -0.01 (-0.02 – 0.00) |
| Prior fracture      | -0.07 (-0.08 – 0.06)                 | -0.09 (-0.12 – 0.06) | -0.09 (-0.16 – 0.03)     | -0.09 (-0.15 – 0.02) | -0.12 (-0.15 – 0.09) |
| Smoking             | 0.00 (-0.01 – 0.01)                  | -0.04 (-0.07 – 0.01) | -0.08 (-0.14 – 0.08)     | 0.02 (-0.04 – 0.08) | 0.01 (-0.02 – 0.04) |
| Corticosteroids use | 0.00 (-0.01 – 0.01)                  | 0.01 (-0.02 – 0.04) | 0.00 (-0.07 – 0.03)      | -0.03 (-0.09 – 0.01) | 0.05 (0.02 – 0.09) |
| Rheumatoid arthritis| -0.01 (-0.01 – 0.00)                 | 0.01 (-0.01 – 0.04) | -0.03 (-0.09 – 0.04)     | 0.04 (-0.02 – 0.10) | 0.00 (-0.03 – 0.03) |
| Parental fracture   | 0.00                                 | NA                  | -0.05 (-0.09 – 0.02)     | 0.02 (-0.06 – 0.01) | -0.05 (-0.09 – 0.01) |
| At-risk drinking    | NA                                   | -0.01 (-0.04 – 0.02) | 0.01 (-0.05 – 0.08)      | -0.02 (-0.08 – 0.05) | -0.01 (-0.04 – 0.02) |
| Falls               | NA                                   | -0.01 (-0.04 – 0.02) | 0.01 (-0.06 – 0.07)      | -0.04 (-0.10 – 0.02) | 0.00 (-0.04 – 0.03) |
| Secondary osteoporosis | 0.00 (-0.01 – 0.00)              | NA                  | NA                       | NA             | NA              |

* Pearson correlation (95% CI)
## Table S3: Summary of incidence of osteoporotic fracture.

| Cohort                  | UK Biobank Test Dataset (N = 80,014) | MrOS US (N = 4,663) | MrOS Sweden (N = 1,880) | SOF (N = 3,615) |
|-------------------------|--------------------------------------|---------------------|-------------------------|-----------------|
| **Major osteoporotic fracture (%)** |                                      |                     |                         |                 |
| Total                   | 1,189 (1.5)                          | 560 (12.0)          | 337 (17.9)              | 707 (20.6)      |
| gSOS range              |                                      |                     |                         |                 |
| < 1%                    | 25 (3.1)                             | 11 (26.8)           | 9 (47.4)                | 9 (33.3)        |
| 1-5%                    | 79 (2.5)                             | 44 (21.6)           | 20 (26.7)               | 37 (26.6)       |
| 5-20%                   | 269 (2.2)                            | 104 (14.4)          | 61 (21.6)               | 134 (26.3)      |
| 20-40%                  | 266 (1.7)                            | 123 (13.0)          | 71 (18.8)               | 168 (24.6)      |
| 40-60%                  | 251 (1.6)                            | 111 (11.6)          | 81 (21.5)               | 136 (19.9)      |
| 60-80%                  | 176 (1.1)                            | 109 (11.7)          | 49 (13.0)               | 116 (16.9)      |
| 80-95%                  | 103 (0.9)                            | 48 (7.4)            | 40 (14.2)               | 85 (16.2)       |
| 95-99%                  | 17 (0.5)                             | 8 (4.6)             | 6 (8.0)                 | 20 (14.8)       |
| ≥ 99%                   | 3 (0.4)                              | 2 (5.6)             | 0 (0)                   | 2 (5.4)         |
| **Hip fracture (%)**    |                                      |                     |                         |                 |
| Total                   | 209 (0.3)                            | 273 (5.9)           | 129 (6.9)               | 556 (15.6)      |
| gSOS range              |                                      |                     |                         |                 |
| < 1%                    | 7 (0.9)                              | 7 (17.1)            | 3 (15.8)                | 6 (20.0)        |
| 1-5%                    | 10 (0.3)                             | 20 (9.8)            | 5 (6.7)                 | 36 (24.7)       |
| 5-20%                   | 47 (0.4)                             | 51 (7.1)            | 23 (8.2)                | 100 (18.7)      |
| 20-40%                  | 40 (0.3)                             | 55 (5.8)            | 26 (6.9)                | 128 (17.9)      |
| 40-60%                  | 42 (0.3)                             | 59 (6.2)            | 37 (9.8)                | 102 (14.4)      |
| 60-80%                  | 36 (0.2)                             | 56 (6.0)            | 18 (4.8)                | 102 (14.4)      |
| 80-95%                  | 25 (0.2)                             | 20 (3.1)            | 15 (5.3)                | 63 (11.7)       |
| 95-99%                  | 2 (0.1)                              | 4 (2.3)             | 2 (2.7)                 | 17 (12.2)       |
| ≥ 99%                   | 0 (0)                                | 1 (2.8)             | 0 (0)                   | 2 (5.1)         |
| Cohort                      | UK Biobank Test Dataset (N = 80,014) | MrOS US (N = 4,663)§ | MrOS Sweden (N = 1,880)¶ | SOF (N = 3,615)¶ |
|----------------------------|-------------------------------------|----------------------|---------------------------|-------------------|
| **Major osteoporotic fracture (95% CI)** |                                     |                      |                           |                   |
| gSOS                       | 0.680 (0.673 – 0.688)               | 0.621 (0.609 – 0.633) | 0.597 (0.576 – 0.618)    | 0.629 (0.617 – 0.640) |
| Prior fracture             | 0.667 (0.660 – 0.675)               | 0.616 (0.603 – 0.628) | 0.560 (0.538 – 0.582)    | 0.629 (0.618 – 0.641) |
| Smoking                    | 0.654 (0.646 – 0.661)               | 0.591 (0.579 – 0.603) | 0.556 (0.535 – 0.577)    | 0.607 (0.596 – 0.619) |
| Corticosteroids use        | 0.651 (0.643 – 0.659)               | 0.587 (0.574 – 0.599) | 0.548 (0.526 – 0.570)    | 0.604 (0.593 – 0.616) |
| Rheumatoid arthritis       | 0.653 (0.646 – 0.661)               | 0.594 (0.582 – 0.606) | 0.548 (0.527 – 0.570)    | 0.606 (0.594 – 0.617) |
| Parental fracture          | NA                                  | 0.597 (0.585 – 0.610) | 0.550 (0.528 – 0.572)    | 0.607 (0.595 – 0.618) |
| At-risk drinking           | NA                                  | 0.603 (0.590 – 0.617) | 0.549 (0.527 – 0.570)    | 0.600 (0.588 – 0.613) |
| Falls                      | NA                                  | 0.592 (0.580 – 0.604) | 0.584 (0.562 – 0.606)    | 0.604 (0.592 – 0.615) |
| Secondary osteoporosis     | 0.653 (0.645 – 0.661)               | NA                   | NA                        | NA                |
| **Hip fracture (95% CI)**  |                                     |                      |                           |                   |
| gSOS                       | 0.739 (0.724 – 0.754)               | 0.651 (0.635 – 0.667) | 0.588 (0.559 – 0.616)    | 0.617 (0.605 – 0.630) |
| Prior fracture             | 0.732 (0.716 – 0.748)               | 0.639 (0.623 – 0.655) | 0.564 (0.534 – 0.594)    | 0.615 (0.603 – 0.627) |
| Smoking                    | 0.728 (0.712 – 0.745)               | 0.637 (0.621 – 0.653) | 0.567 (0.536 – 0.599)    | 0.597 (0.585 – 0.610) |
| Corticosteroids use        | 0.728 (0.711 – 0.744)               | 0.632 (0.606 – 0.640) | 0.572 (0.542 – 0.601)    | 0.595 (0.583 – 0.608) |
| Rheumatoid arthritis       | 0.732 (0.715 – 0.749)               | 0.629 (0.612 – 0.645) | 0.565 (0.535 – 0.595)    | 0.597 (0.585 – 0.610) |
| Parental fracture          | NA                                  | 0.631 (0.615 – 0.648) | 0.572 (0.540 – 0.603)    | 0.597 (0.585 – 0.610) |
| At-risk drinking           | NA                                  | 0.640 (0.621 – 0.659) | 0.565 (0.535 – 0.595)    | 0.598 (0.584 – 0.612) |
| Falls                      | NA                                  | 0.628 (0.612 – 0.644) | 0.580 (0.548 – 0.611)    | 0.596 (0.584 – 0.609) |
| Secondary osteoporosis     | 0.726 (0.710 – 0.742)               | NA                   | NA                        | NA                |

* Based on all individuals with available information
† Derived from logistic regression models adjusted for age and sex
‡ Derived from logistic regression models adjusted for age
Table S5: Details of net reclassification improvement of major osteoporotic fracture risk prediction using FRAX-gSOS.

| Outcome: no fracture | FRAX | FRAX-gSOS | UKB | US | SWE | SOF | % reclassified |
|----------------------|------|-----------|-----|----|-----|-----|----------------|
|          | [0,20) | [20,100] |     |    |     |     |               |
| Outcome: no fracture | 77,932 | 1,299 | 1,663 | 647 | 144 | 130 | 206 | 1 4 9 11 |
| UKB | [0,20) | [20,100] |     |    |     |     |               |
| US  | 77,932 | 1,299 | 1,663 | 647 | 144 | 130 | 206 | 1 4 9 11 |
| SWE | 77,932 | 1,299 | 1,663 | 647 | 144 | 130 | 206 | 1 4 9 11 |
| SOF | 77,932 | 1,299 | 1,663 | 647 | 144 | 130 | 206 | 1 4 9 11 |

| Outcome: fracture | FRAX | FRAX-gSOS | UKB | US | SWE | SOF | % reclassified |
|-------------------|------|-----------|-----|----|-----|-----|----------------|
|                  | [0,20) | [20,100] |     |    |     |     |               |
| Outcome: fracture | 1,119 | 243 | 296 | 46 | 41 | 55 | 70 | 4 8 18 19 |
| UKB             | [0,20) | [20,100] |     |    |     |     |               |
| US              | 1,119 | 243 | 296 | 46 | 41 | 55 | 70 | 4 8 18 19 |
| SWE             | 1,119 | 243 | 296 | 46 | 41 | 55 | 70 | 4 8 18 19 |
| SOF             | 1,119 | 243 | 296 | 46 | 41 | 55 | 70 | 4 8 18 19 |

| Combined | FRAX | FRAX-gSOS | UKB | US | SWE | SOF | % reclassified |
|----------|------|-----------|-----|----|-----|-----|----------------|
|          | [0,20) | [20,100] |     |    |     |     |               |
| Combined | 79,051 | 1,542 | 2,022 | 693 | 185 | 185 | 298 | 1 4 11 13 |
| UKB          | [0,20) | [20,100] |     |    |     |     |               |
| US           | 79,051 | 1,542 | 2,022 | 693 | 185 | 185 | 298 | 1 4 11 13 |
| SWE          | 79,051 | 1,542 | 2,022 | 693 | 185 | 185 | 298 | 1 4 11 13 |
| SOF          | 79,051 | 1,542 | 2,022 | 693 | 185 | 185 | 298 | 1 4 11 13 |

* The UK Biobank Test Dataset (N = 80,014)
§ The MrOS US cohort (N = 4,663)
¶ The MrOS Sweden cohort (N = 1,880)
† The SOF cohort (N = 3,615)
Table S6: Details of net reclassification improvement of hip fracture risk prediction using FRAX-gSOS.

| Cohort  | UKB | US† | SWE‡ | SOF† | UKB | US | SWE | SOF | UKB | US | SWE | SOF |
|---------|-----|-----|------|------|-----|----|-----|-----|-----|----|-----|-----|
| **Outcome: no fracture** | | | | | | | | | | | | |
| FRAX gSOS | | | | | | | | | | | | |
| [0.3) | 75,729 | 2,170 | 125 | 976 | 1,885 | 319 | 57 | 201 | 1,885 | 319 | 57 | 201 |
| [3,100] | 510 | 319 | 162 | 240 | 1,681 | 1,576 | 1,407 | 1,587 | 23 | 17 | 10 | 13 |
| % reclassified | 75,729 | 2,170 | 125 | 976 | 1,885 | 319 | 57 | 201 | 1,885 | 319 | 57 | 201 |
| **Outcome: fracture** | | | | | | | | | | | | |
| FRAX gSOS | | | | | | | | | | | | |
| [0.3) | 154 | 79 | 5 | 87 | 20 | 25 | 3 | 31 | 11 | 24 | 38 | 26 |
| [3,100] | 5 | 7 | 6 | 39 | 30 | 162 | 115 | 399 | 14 | 4 | 5 | 9 |
| % reclassified | 154 | 79 | 5 | 87 | 20 | 25 | 3 | 31 | 11 | 24 | 38 | 26 |
| **Combined** | | | | | | | | | | | | |
| FRAX gSOS | | | | | | | | | | | | |
| [0.3) | 75,883 | 2,249 | 130 | 1,069 | 1,905 | 344 | 60 | 233 | 1,905 | 344 | 60 | 233 |
| [3,100] | 515 | 326 | 168 | 280 | 1,711 | 1,738 | 1,522 | 1,995 | 23 | 16 | 10 | 12 |
| % reclassified | 75,883 | 2,249 | 130 | 1,069 | 1,905 | 344 | 60 | 233 | 1,905 | 344 | 60 | 233 |

* The UK Biobank Test Dataset (N = 80,014)
† The MrOS US cohort (N = 4,663)
‡ The MrOS Sweden cohort (N = 1,880)
† The SOF cohort (N = 3,615)

Additional References

1. Forgetta, V., et al., *Machine Learning to Predict Osteoporotic Fracture Risk from Genotypes*. bioRxiv, 2018: p. 413716.