# Supplementary Appendix

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

Supplement to: Bischoff-Ferrari HA, Willett WC, Oray EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 2012;367:40-9. DOI: 10.1056/NEJMoa1109617.

Appendix: 11-09617

June 11th 2012-06-11

**A Pooled Analysis to Define Vitamin D Dose Requirements for Fracture Prevention**

**Table of Contents Appendix:**

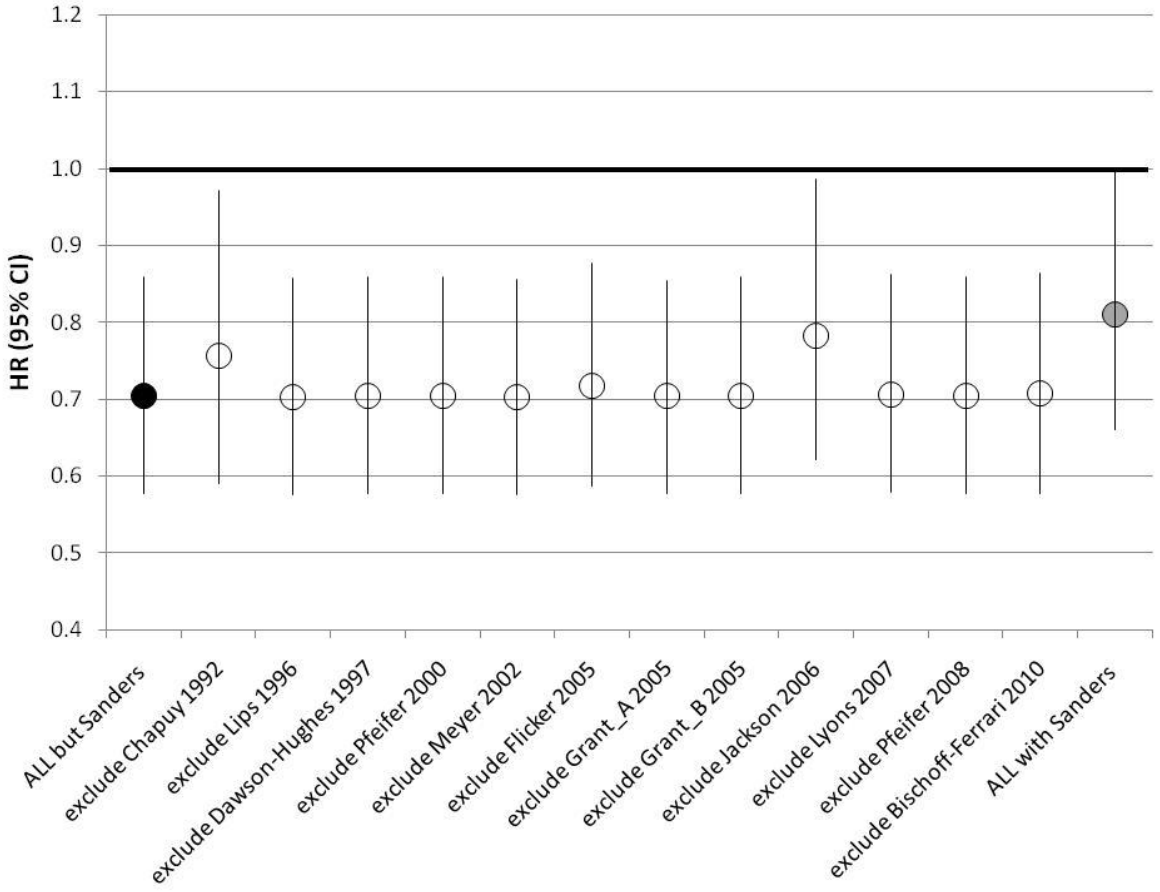
**Appendix 1:** Treatment dose, adherence-adjusted dose, and actual intake of vitamin D and calcium in treated subjects and controls by trial

| | Vitamin D | | | Calcium | | |
|---|---|---|---|---|---|---|
| | | Mean | | | Mean | |
| Study (n treatment group) | Treated dose | Adherence-adjusted treatment dose | Actual dose | Treated dose | Adherence-adjusted treatment dose | Actual dose |
| **Chapuy 1992**[10] | | | | | | |
| Treatment (n = 1634) | 800 | 800 | 800 | 1200 | 1200 | 1200 |
| Controls (n = 1636) | 0 | 0 | 0 | 0 | 0 | 0 |
| **Lips 1996**[14] | | | | | | |
| Treatment (n = 1291) | 400 | 340 | 340 | 0 | 0 | 0 |
| Controls (n = 1287) | 0 | 0 | 0 | 0 | 0 | 0 |
| **Dawson-Hughes 1997**[12] | | | | | | |
| Treatment (n = 187) | 700 | 618 | 618 | 500 | 441 | 441 |
| Controls (n = 202) | 0 | 0 | 0 | 0 | 0 | 0 |
| **Pfeifer 2000**[18] | | | | | | |
| Treatment (n = 74) | 800 | 760 | 760 | 1200 | 1140 | 1140 |
| Controls (n = 74) | 0 | 0 | 0 | 1200 | 1140 | 1140 |
| **Meyer 2002**[15] | | | | | | |
| Treatment (n = 560) | 400 | 380 | 528 | 0 | 0 | 0 |
| Controls (n = 565) | 0 | 0 | 159 | 0 | 0 | 0 |
| **Flicker 2005**[20] | | | | | | |
| Treatment (n = 304) | 1067 | 844 | 844 | 600 | 476 | 476 |
| Controls (n = 297) | 0 | 0 | 0 | 600 | 466 | 466 |
| **Grant A**[16] | | | | | | |
| Treatment (n = 1335) | 800 | 608 | 613 | 0 | 0 | 2 |
| Controls (n = 1321) | 0 | 0 | 6 | 0 | 0 | 3 |
| **Grant B**[16] | | | | | | |
| Treatment (n = 1294) | 800 | 535 | 539 | 1000 | 668 | 669 |
| Controls (n = 1294) | 0 | 0 | 6 | 1000 | 680 | 683 |
| **Jackson 2005**[17] | | | | | | |
| Treatment (n = 6925) | 400 | 330 | 528 | 1000 | 825 | 1106 |
| Controls (n = 6905) | 0 | 0 | 199 | 0 | 0 | 290 |
| **Lyons 2007**[21] | | | | | | |
| Treatment (n = 1715) | 821 | 657 | 657 | 0 | 0 | 0 |
| Controls (n = 1707) | 0 | 0 | 0 | 0 | 0 | 0 |
| **Pfeifer 2009**[19] | | | | | | |
| Treatment (n = 122) | 800 | 720 | 720 | 1000 | 900 | 900 |
| Controls (n = 120) | 0 | 0 | 0 | 1000 | 900 | 900 |
| **Bischoff-Ferrari 2010**[13] | | | | | | |
| Treatment (n = 86) | 2000 | 1949 | 1949 | 1000 | 975 | 975 |
| Controls (n = 87) | 800 | 728 | 728 | 1000 | 909 | 909 |

**Legend Appendix 1:** The difference between treatment dose and actual vitamin D intake (accounting for adherence and supplement use outside the study protocol) was most pronounced for the Grant A and Grant B trials. For the Jackson trial (WHI trial)[17], the inclusion of the supplement dose outside the study protocol almost doubled the actual intake of vitamin D. The data set as published originally by Chapuy et al. included only adherent individuals. Two trials (Flicker and Lyons) tested vitamin D2, all other trials tested vitamin D3.

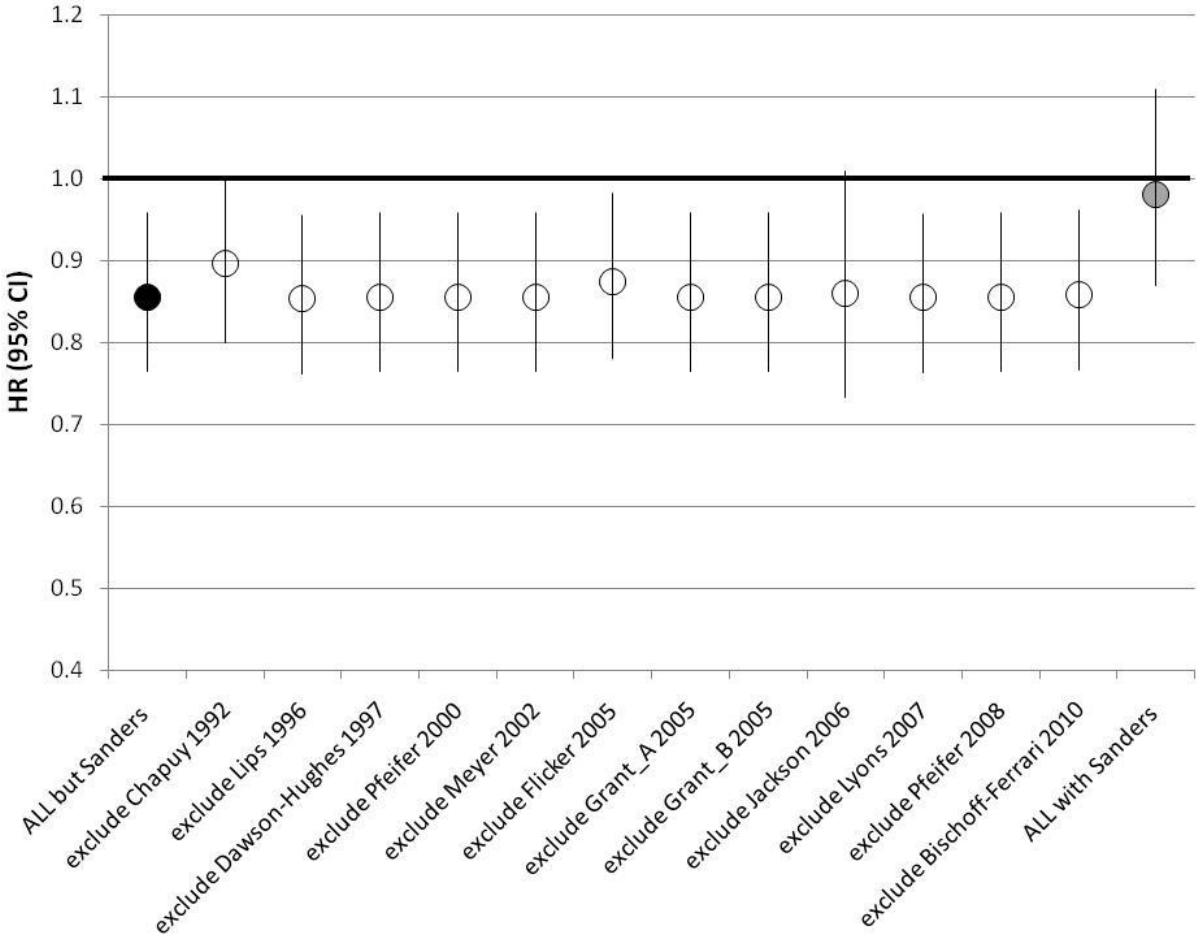
**Appendix 2**: Influence of individual trials on fracture reduction at the highest actual vitamin D intake level

A) Hip fracture reduction at the highest actual intake level of vitamin D per day (range 792-2000 IU/day)



**Legend Figure Appendix 2 A:** The black dot shows the pooled effect of the highest actual intake level of vitamin D (range: 792-2000 IU per day) compared to placebo in all trials of the primary analysis with a 30% reduction of hip fractures (HR = 0.70; 95% CI 0.58-0.86). The unfilled dots indicate the same effect if an individual trial is excluded. The effect of vitamin D at the highest actual intake level is significant if any individual trial is excluded from the primary analysis. All analyses control for age group (65-74,75-85,85+), sex, institutionalized (yes/no) and study. If in a sensitivity analysis the Sanders trial[11] with a large yearly dose of vitamin D is added to the primary analysis (grey filled dot), the benefit at the highest actual intake level of vitamin D is somewhat attenuated (HR = 0.81; 95% CI 0.66-1.00).

B) Any non-vertebral fracture at the highest actual intake level of vitamin D (range 792-2000IU/day)



**Legend Appendix 2 B:** The black dot shows the pooled effect of the highest actual intake level of vitamin D (range: 792-2000 IU per day) compared to placebo in all trials of the primary analysis with a 14% reduction of non-vertebral fractures (HR = 0.86; 95% CI 0.76-0.96). The unfilled dots indicate the same effect if an individual trial is excluded. The effect of vitamin D at the highest actual intake level is significant if most individual trials are excluded, with some attenuation of the effect if the trials of Chapuy[10] or Jackson (WHI)[17] are excluded. All analyses control for age group (65-74, 75-85, 85+), sex, institutionalized (yes/no) and study. If in a sensitivity analysis the Sanders trial[11] with a large yearly dose of vitamin D is added to the primary analysis (grey filled dot), the benefit at the highest actual intake level of vitamin D is attenuated (HR = 0.98; 95% CI 0.87-1.11).

**Appendix 3**: Influence of Sanders Trials at the intent-to-treat level and the highest actual vitamin D intake quartile

If one additional trial that gave vitamin D at a very high annual dose (500,000 IU) was added to the primary pooled analyses[11], fracture benefits were attenuated among the total group of 33,277 seniors age 65 and older. Comparing 16,657 seniors treated with vitamin D to 16,620 controls, vitamin D treatment reduced the risk of hip fracture non-significantly by 9% (HR = 0.91; 0.81-1.02) and the risk of any non-vertebral fracture non-significantly by 6% (HR = 0.94; 0.89-1.01). Based on our refined comparison by actual intake of vitamin D, treatment benefits were also attenuated at the highest intake level (792-2000 IU/day), both at the hip (HR = 0.81; 0.66-1.00) and at any non-vertebral fracture site (HR= 0.98; 0.87-1.11; see **Appendix 2 A and B**).

**Appendix 4:** Further sensitivity analyses

Findings at the highest intake level did not change appreciably if supplement use outside the study protocol was not adjusted for adherence (hip fracture: HR = 0.72; 0.59-0.87; any non-vertebral fracture: HR = 0.87; 0.78-0.97), or if we added an estimated 100 IU vitamin D as a supplement dose outside the study protocol to the treatment dose of participants from 2 trials where additional vitamin D intake was allowed but not documented (hip fracture: HR = 0.70; 0.57-0.86; any non-vertebral fracture: HR = 0.85; 0.76-0.96).