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Dietary protein and bone health across the life-course: an updated systematic review and meta-analysis over 40 years

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Online Resource

Abbreviations:

aBMD, areal Bone Mineral Density

ALP, Alkaline Phophatase

AP, Animal Protein

BAP, Bone Alkaline Phosphatase

BCE, Bovine Collagen Equivalents

BMC, Bone Mineral Content

BMD, Bone Mineral Density

BUA, Broadband Ultrasound Attenuation

BV, Bone Volume

Cr, Creatinine

CTX, C-telopeptide of Collagen

DPA, Dual Photon Absorptiometry

DPYD, Deoxypyridinoline

DXA, Dual X-ray Absorptiometry

FN, Femoral Neck

FNBA, Femoral Neck Bone Area

FNBMC, Femoral Neck Bone Mineral Content

FNBMD, Femoral Neck Bone Mineral Density

FNvBMD, Femoral Neck volumetric Bone Mineral Density

FSBMD, Femoral Shaft Bone Mineral Density

HBMD, Hand Bone Mineral Density

HCHP, High Calcium High Protein

HCLP, High Calcium Low Protein

HF, Hip Fracture

HPO, Hydroxyproline

HR, Hazard Ratio

IntertrochBMD, Intertrochanter Bone Mineral Density

LCHP, Low Calcium High Protein

LCLP, Low Calcium Low Protein

LS, Lumbar Spine

LSBMC, Lumbar Spine Bone Mineral Content

LSBMD, Lumbar Spine Bone Mineral Density

LSvBMD, Lumbar Spine volumetric Bone Mineral Density

MBP, Milk Basic Protein

NTX, N-terminal Peptide of Collagen

OC, Osteocalcin

OR, Odds Ratio

P1NP, Procollagen type 1 N-terminal Propeptide

PERI, Perimenopausal

PFBMD, Proximal Femur Bone Mineral Density

POM, Postmenopausal

PRE, Premenopausal

PYD, Pyridinoline

RBMC, Radial Bone Mineral Content

RBMD, Radial Bone Mineral Density

RR, Relative Risk

SOS, Speed of Sound

SP, Soy Protein

SSI, Strength-strain Index

TBBA, Total Body Bone Area

TBBMC, Total body Bone Mineral Content

TBBMD, Total body Bone Mineral Density

TEI, Total Energy Intake

THBMC, Total Hip Bone Mineral Density

TP, Total Protein

TRAP, Tartrate Resistant Acid Phosphatase

TrochBMD, Trochanter Bone Mineral Density

TSBMD, Total Spine Bone Mineral Density

vBMC, volumetric Bone Mineral Content

vBMD, volumetric Bone Mineral Density

VP, Vegetable Protein

[1] Supplementary Methods: Data extraction

Correlation coefficients (adjusted and unadjusted), n (number of participants), beta coefficients (standardized and unstandardized) for the relationship between protein intake (g/Kg/d or g/d) and bone outcomes were extracted, as well as bone outcomes by protein intake category. Data for calcium intakes were also extracted. For correlational studies looking at the association between change in bone outcomes over time and baseline protein intake, or assessing associations between protein intake and bone outcomes at different time points, all relevant data were extracted. This included mean and standard deviation (SD) for change in bone indices over time, or else r coefficients or beta coefficients for slope of bone loss in different protein intake groups. It also included bone outcomes by protein intake category.

For studies presenting data on risk of fracture or osteoporosis/osteopenia diagnosis, odds ratios, hazard ratios or relative risk estimates (with 95% confidence intervals) for the highest and lowest categories of protein intakes were extracted, with n and p if available. Mean and SD for protein intakes in cases and controls were extracted if no other data were presented (e.g. no risk estimates, no categories of intake data).

Finally, for the intervention studies, as subjects were randomized at baseline, only the mean, SD and n for follow up measurements were extracted for each relevant outcome in each study arm. Standard errors of the mean (SEM) were converted to standard deviations using the formula ($SEM=SD/\sqrt{n}$). Papers not providing complete data to calculate standardized size effects (i.e. not able to calculate the standard deviation, or the standard error of the mean) were excluded from the meta-analysis if this data could not be obtained from the relevant authors. Two authors of relevant articles with missing data were contacted. Neither of the authors replied so their papers were not included in the meta-analysis, but the general findings were included in the systematic review. Two other authors, whose papers had

missing data, or data only available in figures, was not contacted as previous contact when doing the original analysis in 2007 was not successful.

[2] Supplementary Results: Studies reporting correlation or regression coefficients for the relationship between dietary protein and bone indices

Study Characteristics

Of the 74 studies presenting data for correlation or regression coefficients, 18 studies were from South or East Asia (1-17), 21 from Europe(18-38), 2 from the Middle East (39, 40), 6 from Australia, Tasmania or New Zealand(41-46), 25 from USA or Canada (47-71) and 2 from South America(72, 73). Of these 74 studies, 12 were in children or adolescents (3, 17-21, 24, 25, 37, 38, 45, 48), with 1 study combining data from adults and children (44). Also, 13 studies were in premenopausal women (1, 4, 14, 15, 29, 30, 32, 43, 47, 52, 57, 62, 74), 21 in postmenopausal women (2, 6-8, 11, 12, 16, 22, 33, 39-42, 46, 55, 59, 61, 63, 65, 70, 72), 7 in both pre and postmenopausal women(9, 10, 27, 34, 49-51), 2 in both peri and postmenopausal women(5, 53), 5 in men(31, 36, 66, 67, 73), 1 in pre, peri or postmenopausal women(26) and 13 in both men and women(13, 23, 28, 35, 56, 58, 60, 64, 68, 69, 71, 75). Sixty-one studies assessed total protein intake only but 2 studies assessed both soy and total protein(5, 8), one study assessed soy protein only(6), 10 studies assessed animal and/or vegetable protein intake in addition to total protein(7, 15, 16, 19, 20, 34, 47, 54, 58, 71) and one study assessed soy, animal, vegetable and total protein(13).

Systematic Review: Studies reporting correlation or regression coefficients, or protein category data

Seventy-four studies presented correlation coefficient (r) or regression coefficient data (standardized (Beta) or unstandardized (B)) data (Table 1).

Cross-sectional data- BMD

In adults a large number of studies found an association between protein intake and Bone Mineral Density (BMD) at the hip (23, 27, 32, 36, 39, 41-43, 49, 55, 58, 60, 66, 72), radius (4, 49, 57, 58), spine(9, 23, 27, 32, 43, 52, 60, 62, 63, 66, 72), total body (27, 55, 56, 58, 62, 66, 68) or hand (HBMD) (55). Conversely, a large number of studies found that protein intake was not associated with BMD at the hip (1, 2, 9, 11, 22, 28-30, 35, 36, 47, 49, 50, 52, 58, 60, 63, 65, 72, 73), spine (1, 2, 8, 11, 22, 28-30, 35, 39, 47, 49, 50, 54, 58, 60, 65), radius (32, 49, 53, 61) or total body (50, 58, 64). See Supplemental Material for a review of adult studies assessing animal and vegetable protein intake specifically. In children, two studies found that total protein and animal protein intakes were not associated with femoral neck (FN) BMD or lumbar spine (LS) BMD(45). However, two other studies conflicted as to whether or not protein intake was associated with total body BMD (TBBMD) (45, 48).

Cross-sectional data- BMC and Bone Size

In children, seven studies showed that higher protein intake was associated with increased radial periosteal circumference, cortical area, volumetric BMC (vBMC) and polar SSI(18, 38), as well as TBBMC(3, 24, 48), total body bone area (TBBA)(3, 24), total radial BMC (RBMC)(21), radial metaphyseal BMC(21), femoral neck BMC (FNBMC)(21), femoral diaphysis BMC(21) and lumbar spine BMC (LSBMC)(21). Likewise, another study indicated that there was a positive association between dietary protein and forearm cortical BA but not forearm vBMC(25). However, one study found no association between child protein intake and radial diaphysis BMC or total hip BMC (THBMC)(21) and another found that total protein and animal protein intakes were not associated with total body BMC (TBBMC) or lumbar spine BMC (LSBMC)(19). In adults, a large number of studies found a

positive association between total protein intake and RBMC(10, 32, 33, 44, 57, 61), TBBMC(55, 62, 72), Spine BMC (62, 67), LSBMC(32) TBBMC(68) and HipBMC(32), but three studies found no association between protein intake and RBMC(33, 51, 67), humerus BMC(51) or Ulna BMC(51).

Cross-sectional data- quantitative ultrasound (QUS) and bone makers

There were no studies of BUA in children. In adults, four studies found that protein intake was positively associated with calcaneal BUA(15, 34, 41, 52). In one of these studies total protein intake was negatively associated with calcaneal BUA but the association disappeared when adjusting for animal: vegetable protein ratio(34). In terms of bone markers, in children the one study assessing bone markers found a positive association between protein intake and bone alkaline phosphatase (BAP), but found no association with osteocalcin (OC) or c-telopetide of collagen (CTx) (20). In adults, in four studies increased total protein intake was negatively associated with hydroxyproline (HPO) (premenopausal women only) (49), CTX(42), pyridinoline (PYD)(8, 26), deoxypyridinoline (DPYD)(26) and type 1 n-terminal procollagen (P1NP)(42). In contrast, one study found a positive association between total protein intake and CTX(31) and other studies found no association between total protein intake and HPO (postmenopausal women only)(49), OC(8, 12, 27, 49, 50, 59), n-terminal telopeptide (NTX)(12, 50, 59), DPYD(8, 12) or BAP(8, 12).

Systematic Review: Animal, vegetable or soy protein and bone health

Studies in adults

In four studies, animal protein intake was not associated with FNBMD (7, 47), LSBMD(7, 47), TBBMD(7) LSvBMD(54), THBMD(47) or calcaneal stiffness index (13). One study found a positive association between spine BMD and non-dairy animal protein intake in postmenopausal women aged 50 years or older, but conversely in premenopausal women

found a negative association (71). One study found increasing animal protein was associated with increased THBMD, FNBMD, TSBMD, TBBMD(58). One study found a negative association between BUA of the calcaneus with animal protein, the effect being modified by calcium intake (34). Finally, another study found that increased animal: vegetable protein ratio was a negative predictor of FNBMD (16).

Two studies found that vegetable protein was not associated with FNBMD and LSBMD(7) or calcaneal stiffness index(13). However a negative association was found in three studies between plant protein and spine BMD (16, 71) or TBBMD (7, 47) and hip BMD (47, 58, 71). Interestingly, one study found that higher vegetable protein intake was associated with reduced LSvBMD in persons of White (but not Chinese, Black or Hispanic) ethnicity (54). Increasing vegetable protein was associated in another study with reduced THBMD, FNBMD and TSBMD in women but not men (58). Conversely, one study found a positive association between vegetable protein intake and bone heath for calcaneal BUA (34).

In terms of soy protein, four studies showed no association with calcaneal stiffness index (13), LSBMD(5, 6) , FNBMD (5, 6), TBBMC(5, 6, 44), THBMC(5), THBMD(6), or TBBMD(6), Troch/intertroch BMD (6) or leg BMC(44). However, two studies found that increased soy protein intake was associated with lower DPYD(8) or higher LSBMD (8), but no association with PYD, ALP or OC(8).

Studies in children

In children, one study found no association between animal (meat) protein intake and TBBMC or LSBMC, but did find a positive association between BAP and animal protein intake (19). However, there was no association between animal or vegetable protein intake and OC or CTX, or between vegetable protein and BAP(20). Conversely, another paper from

the same group found a positive association between animal protein intake and OC, CTX and BAP(19). There were no studies of soy protein intake in children or adolescents.

Systematic Review: Studies reporting r values for slope of change in bone mass

In children, one study in boys found that baseline protein intake (age 7 years) was not associated with FN vBMD, Total hip vBMD, distal tibia vBMD, FNBA, FN width, total hip aBMD or FN aBMD at age 15 years when physical activity levels were lower (37), but protein intake was positively associated when physical activity levels were higher (37). Another study, in pre-pubertal girls with low calcium intakes, found increased animal protein intake was associated with lower gain in Radial BMC and TBBMC from age 10 to 15 years (17).

In adults, one study found no relationship between baseline intake of total, animal or vegetable protein and 3 year change in hip, spine or TBBMD(47) with another finding no association between protein intake and bone loss, also over 3 years (59). Another study found no association between protein intake and loss of LSBMD, FNBMD, THBMC or TBBMC over 30 months (5).

Similarly, one study found no association between protein intake during adolescence (15 years old) and subsequent LSBMD or FNBMD in young adulthood (20-25y old)(28). Finally, another found no association between BUA, BV or SOS in 18-19 year old women and previous protein intake at 9-11 years old (74). No relationship between protein intake and total hip BMD(75). Sahni 2014 found a negative association in men between protein intake and % change in TrochBMD but not % change in LS or FN BMD in men, but there were no associations at any site for women (60).

However, some studies have found an association between protein intake and change in bone mass. One study found increased protein intake at age 20-25 years was retrospectively

associated with increased gain in TBBMC from peri-adolescence to the present day, in females with adequate calcium intake as well as all males regardless of calcium intake (64). One study found that for every 20% increase in % of total energy from dietary protein, over a 6 year period, there was an increase of 0.003 to 0.004g/cm^2 for TBBMD, HipBMD and Spine BMD(70). Another study found reduced FNBMD and LS BMD loss (but no change in radial shaft BMD) over a 4 year period in those in with the highest (vs. lowest) quartile of protein intake(69). Finally, another study found an association between higher protein intake and reduced radial bone loss (BMD) in both pre and postmenopausal women(51). Another study in elderly women found a positive association between baseline protein intake and BMC 5 years later with the highest daily protein intake tertile (>87g/d) being associated with higher appendicular and whole body BMC than the lowest quartile (<66g/d)(46). Finally, in one study of men and women aged ≥50 years old, there was a positive association between baseline total protein intake and BMD 5 years later at the hip, as well as a positive association between protein intake and Spine BMD for both men and women, and with Hip BMD for the women only (71).

Conversely, one study found increased bone loss in men with higher protein intake (60). A negative association between vegetable protein intake and % change in LSBMD, as well as between AP:VP ratio and FNBMD(16). Another study found increased bone loss in women consuming high animal: vegetable protein ratio diets than those consuming low animal: vegetable protein ratio diets (76). One study found that higher quartiles of soy protein intake were associated with protection against loss of TBBMC(5). Another study found no association between soy intake and loss of LSBMD, FNBMD, THBMC or TBBMC over 30 months (5).

Meta-analysis: Funnel Plots and Sensitivity analyses for FNBMD and LSBMD models

Funnel plots were conducted for the following models: FNBMD (unadjusted and adjusted); LSBMD (unadjusted and adjusted), BMD in postmenopausal women and BMD in premenopausal women. The FNBMD plot showed all studies within the 95% confidence interval boundaries but there were a lack of smaller studies showing a negative effect estimate. The LSBMD plot had 3 out of 18 studies outside the 95% confidence interval boundary (strong positive effect sizes) showing, as with FNBMD, a lack of smaller studies in the negative effect estimate area. The funnel plot for postmenopausal women BMD showed few small studies with a negative effect, and the premenopausal women BMD plot showed 3 studies out of 10 outside the 95% confidence interval area (strong positive effect sizes) and a lack of medium sized studies in the negative effect estimate area. Taken together, this suggests potential publication bias in terms of smaller to medium studies, particularly those with negative associations between protein and bone health, not being published.

In terms of sensitivity analyses, removal of each study in turn for the FNBMD analysis (confounder adjusted data only) had little effect on the above results. Sensitivity analyses show effect sizes as follows when each study excluded in turn: Chan 2009 r(random)=0.07 (-0.04 to 0.18) R^2=0.005 (0.5%) P=0.21, I^2=47% $P_{(heterogeneity)}$=0.15; Cooper 1995 Postmenopausal data $r_{(random)}$=0.05 (-0.06 to 0.17) R^2=0.003 (0.3%), P=0.37, I^2=63% $P_{(heterogeneity)}$=0.07; Cooper 1995 Premenopausal data $r_{(fixed)}$=0.01(-0.05 to 0.07) R^2=<0.001 (<0.1%) P=0.33, I^2=0% $P_{(heterogeneity)}$=0.67; Ho2003 $r_{(random)}$=0.05 (-0.08 to 0.19) R^2=0.003 (0.3%) P=0.43, I^2=62% $P_{(heterogeneity)}$=0.07. However, removal of the Cooper et al. (1995)(49) premenopausal data reduced heterogeneity to 0%, suggesting this study contributed strongly to the heterogeneity. Exclusion of this study also reduced the effect size from 0.07 to 0.01, suggesting it was increasing the effect size substantially. However, the R^2 was still very small (<0.1% to 0.5%) and not statistically significant when any of the studies were removed,

or all included (0.2%). Therefore removal of studies had little overall effect on the pooled effect size.

In terms of sensitivity analyses for LSBMD (confounder adjusted data only), the following pooled effect sizes were found when each study in turn were excluded: Ho 2003(6) $r_{(fixed)}$=-0.021 (-0.14 to 0.10) R^2=<0.001 (0.1%) P=0.73, I2=0% $P_{(heterogeneity)}$=0.39; Cooper 1995(49) Postmenopausal r(fixed)= 0.02 (-0.06 to 0.11) R^2<0.001 (0.1%) P=0.60, I^2=0% $P_{(heterogeneity)}$=0.68; Cooper 1995(49) Premenopausal $r_{(fixed)}$ = -0.01 (-0.08 to 0.07) R^2=<0.001 (0.1%) P=0.88, I^2=0% $P_{(heterogeneity)}$=0.43. The pooled effect size was unchanged by the elimination of any studies in the model, suggesting no studies were having a strong impact on the overall effect size.

Meta-analysis: Associations with protein and calcium dose, as well as calcium: protein ratio

Linear, quadratic and cubic regression models (not controlling for confounders) showed that neither the calcium: protein ratio (calcium mg/protein g), nor the protein (g/kg/d) or calcium (mg/kg/d) dose, were associated with correlation (r) coefficients for the association between protein intake and bone health for either LSBMD or FNBMD (P values were P >0.05 or did not survive multiple testing adjustment (revised cutoff of P>0.001)). There was a positive association between protein intake and both FNBMD and LSBMD in the linear model (both P=0.02, b=0.33-0.39) and a negative association in the cubic models (P=0.01 (b= -0.90) for FNBMD and P=0.009 (b= -0.84) for LSBMC) but these models did not survive adjustment for multiple testing (P>0.001). See Supplemental Table 6 for full details of these analyses.

[3] Supplementary Results: Studies reporting fracture or osteoporosis risk

Study Characteristics

Of the 29 studies (including six studies already reported in correlation coefficient or bone slope sections), 4 were from Asia (2, 14, 77, 78), 11 were from the USA or Canada (70, 71, 76, 79-86) , 2 were from the Middle East (40, 87) 1 was from New Zealand(42) and 9 were from Europe (36, 88-95). In addition, 2 studies were by authors from the USA but reported data from multiple countries (96, 97).

In terms of study design, 13 studies were cohort studies (70, 71, 76, 78-84, 88, 92, 94), 2 were ecological studies (96, 97), 3 were of cross-sectional design (2, 36, 42) and 11 were case-control studies (14, 40, 77, 85-87, 89-91, 93, 95). Of the latter, only 2 were prospective (nested) case-control studies (89, 93). In terms of fracture type, of the 13 cohort studies, 7 assessed hip fracture only(70, 76, 80-83, 94), 1 assessed hip, spine and forearm/wrist fracture (84), one study assessed hip and forearm/wrist fractures (79), two studies assessed all fragility fractures combined (71, 88) and two studies assessed all fractures (fragility and non-fragility)(78, 92). The 2 ecological studies assessed just hip fracture incidence (96, 97).

For the 11 case-control studies, 1 study was in children, assessing dietary protein intake in children with fracture compared with children without fracture (93). The other 10 studies were all in adults, 1 assessing odds of hip fracture(86), 1 assessing odds of all fragility fractures by protein intake(91), 4 assessing differences in protein intake in hip, spine or wrist fracture cases and controls (89) or between osteoporotic/osteopenic cases vs. controls (14, 40, 87), 2 assessing odds of hip fracture only by protein intake(85, 95) and 2 assessing odds of osteoporosis diagnosis by protein intake category(77, 90).

In terms of population studied, 6 of the 13 cohort studies were in postmenopausal women(70, 76, 78, 81, 84, 88), 1 in pre and postmenopausal women(79), 5 in men and women(71, 80, 83, 92, 94) and 1 in men only(82). In the 11 case-control studies, 1 was in children(93), 3

studied men and women(86, 89, 91), 1 studied premenopausal women(14) and 6 studied postmenopausal women(40, 77, 85, 87, 90, 95).

Six cohort studies and the 3 cross-sectional studies assessed total dietary protein only (2, 36, 42, 70, 71, 80, 82, 84, 92), 1 studied animal protein only(94), 1 studied soy protein only(78) and 5 studied total dietary protein, animal protein and vegetable protein(76, 79, 81, 83, 88). The 2 cross cultural studies assessed the relationship between protein intake and fracture risk in 16 (96) to 33(97) countries worldwide, with Abelow et al.(1992)(96) studying animal protein only and Frassetto et al. (2000)(97) studying animal, vegetable and total protein intake. In the case-control studies, 7 studies assessed total protein only(14, 40, 85, 87, 89, 93, 95), whilst 4 assessed total, animal and vegetable protein(77, 86, 90, 91).

Exclusion of studies from fracture risk meta-analysis

Studies were excluded from the quantitative meta-analysis of fracture risk if they were cross-cultural studies(96, 97), had only data on risk of osteoporosis or osteopenia (2, 36, 40, 42, 77, 87, 90), had effect statistics that were incompatible with other studies(70, 92) were the only fracture study in children (93) or reporting soy protein(78), only had results that were stratified by calcium (84), had missing data (76) or were case-control studies not reporting odds ratios (14, 89, 95). Case-control studies were analysed separately from cohort studies due to methodological differences. Cohort studies presenting data on RR and HR were analysed separately.

Systematic Review: Studies reporting fracture or osteoporosis risk

Twenty-nine studies reported data on fracture and/or osteoporosis diagnosis (**Table 2**), of which 28 studies were in adults and one in children (93). All studies provided multivariate adjusted estimates adjusted for multiple confounders (see Table 2) except for one cohort

study (76) which controlled for only 2 confounders, 2 ecological studies (96, 97) which were only adjusted for age, 2 cross-sectional studies which were only adjusted for BMI or energy intake(36, 42), 5 of the case-control studies(14, 40, 87, 89, 93) which presented only unadjusted data, and another case-control study which presented categories of intake (non-statistically analysed) so confounder adjustment was not required (90).

Cohort studies- total protein intake

Three studies found no association between total protein and risk of hip (80, 82) or spine fractures. In terms of fracture type, three studies found no association between total protein intake and either risk of combined fragility and non-fragility fractures (92), just all fragility fractures (71, 88) or hip fracture specifically (79, 81, 94). One study found an increased risk with higher total protein intake (79) and another found the reduced risk with higher protein intake(70). Finally, another study found increased odds of fracture when calcium intake was high and protein intake was low, but this association was attenuated when both calcium and protein were high (84). One study found the relationship between protein intake and fracture risk depended on calcium intake(83).

Case-control, cross-sectional and ecological studies- total protein intake

The one case-control study in children was of prospective (nested within-cohort) design and found no difference in protein intake between fracture cases and controls (93). All case-control studies in adults were of retrospective design, with the exception of 1 study that was prospective (89). Four adult case-control studies found no significant difference between protein intakes in cases with osteoporosis vs. non-osteoporotic controls(90) or

osteoporotic/osteopenic cases vs. healthy controls (14, 40, 87). In contrast, one study found increased odds of osteoporosis diagnosis with higher total protein intake (77). Three studies found no reduction in odds of being a fracture case in persons with higher protein intake compared with low protein intake (85, 91, 95). However, one study found lower total protein intake (non-adjusted for confounders) in cases with fragility fractures than in controls(89), and two studies found an increased odds of fracture(36) or reduced odds of fracture (50-69 year old subgroup) in persons with higher protein intake (86). The two cross-cultural (ecological) studies found a positive association between hip fracture and total protein intakes (97) and a positive association between hip fracture and animal protein intake (96), both studies controlling for age only. Two of the 3 cross-sectional studies found that protein intake was a predictor of odds for LS osteopenia(2) or hip BMD below 0.83g/cm2 (men)(36), however the 3rd study found that protein intake was not associated with diagnosis of osteoporosis or osteopenia(42).

Systematic Review: Animal, Vegetable and Soy Protein and Fracture risk

In studies that presented data on animal and vegetable protein, one study found no association between animal or vegetable protein and fragility fracture(88). Similarly, 2 studies found no association between animal or vegetable protein and hip fractures (79, 94), or found an association between animal protein intake and hip fracture in persons with lower calcium intakes only (83). Other studies found no association between hip fracture risk and animal or vegetable protein intake (86), or no difference in odds of being a fragility fracture case in persons with varying animal or vegetable protein intake (91).

However, two other studies did find a significant association between animal protein intake and risk of forearm(79) and hip fractures(81), but one study found no association between vegetable protein intake and fracture risk(81). In addition, 1 study found an association

between increased animal protein intake and increased hip fracture risk, as well as increased risk of hip fracture with increased animal: vegetable protein ratio, and a reduced risk of hip fracture with increased vegetable protein intake (76). One study found increased odds of osteoporosis with higher animal protein intake, but lower odds with increased vegetable protein intake(77). Finally, the 2 cross cultural studies(96, 97) found a positive association between animal protein intake and hip fracture incidence as well as a negative association between hip fracture incidence and increasing vegetable protein intake(97). The one cohort study assessing the relationship between soy protein intake and fracture risk (all fractures) found a reduced risk of fracture in the highest intake quintile of soy protein compared with the lowest(78).

Quality Analysis

Twelve cohort studies were assessed for quality using the Newcastle-Ottawa Cohort study assessment tool(98) (scored out of 9). Three studies scored 4-5 (44-55%)(79, 88, 94), 8 studies scored 6-7 (66-78%)(70, 71, 76, 78, 80, 81, 83, 92) and 1 study scored 8 (89%)(82). In addition, 6 case-control studies were assessed using the Newcastle-Ottawa case-control study assessment tool (scored out of 10), with 3 studies scoring 3-5(77, 91, 95) and 2 studies scoring 6-7 (85, 86). The nested case-control study by Samieri et al. (2013) (89) (score=8 out of 9) was assessed using the cohort study tool as it was deemed more appropriate for the study design. As discussed previously, the cross-sectional studies were not analysed for quality due to the very large numbers of studies. It was not possible to formally assess the quality of the 2 ecological studies (96, 97) as there is no specific tool for this.

Fracture risk meta-analysis: Sensitivity and subgroup analysis

Subgroup analysis showed that when removing Dargent-Molina et al 2008, (which was the only study to include non-hip fracture results), pooled estimates were as follows: animal protein intake, ($RR_{(random)}$=0.83 (0.54 to 1.30, p=0.42, n=3 studies, I^2=48% $P_{(heterogenity)}$=0.14)), vegetable protein intake ($RR_{(fixed)}$=1.20 (0.82 to 1.73, p=0.35, n=2 studies, I^2=4% $P_{(heterogenity)}$=0.34)), and total protein intake ($RR_{(random)}$=0.75 (0.47 to 1.21, p=0.24, n=3 studies, I^2=22% $P_{(heterogenity)}$=0.28)).

In terms of sensitivity analysis, the effect sizes when each study were removed in turn were: (see estimates above for removal of Dargent-Molina): Animal Protein: Feskanich: $RR_{(random)}$=0.91 (0.61 to 1.37, p=0.67, n=3 studies, I^2=63% $P_{(heterogenity)}$=0.07); Meyer: $RR_{(random)}$=0.93 (0.63 to 1.37, p=0.71, n=3 studies, I^2=63% $P_{(heterogenity)}$=0.07); Munger: $RR_{(fixed)}$=1.09 (0.97 to 1.21, p=0.73, n=3 studies, I^2=0% $P_{(heterogenity)}$=0.73). For Vegetable Protein: Feskanich: $RR_{(random)}$=1.13 (0.63 to 2.05, p=0.68, n=2 studies, I^2=48% $P_{(heterogenity)}$=0.68); Munger: $RR_{(fixed)}$=0.96 (0.86 to 1.08, p=0.51, n=2 studies, I^2=0% $P_{(heterogenity)}$=0.48). For Total Protein: Feskanich: $RR_{(random)}$=0.76 (0.42 to 1.39, p=0.38, n=3 studies, I^2=54% $P_{(heterogenity)}$=0.12); Munger: $RR_{(fixed)}$=1.05 (0.93 to 1.17, p=0.43, n=3 studies, I^2=0% $P_{(heterogenity)}$=0.43); Mussolino: $RR_{(random)}$=0.99 (0.77 to 1.27, p=0.90, n=3 studies, I^2=33% $P_{(heterogenity)}$=0.22). Therefore, for all protein types the removal of Munger rendered the heterogeneity down to zero, suggesting this study was the cause of the heterogeneity observed. Overall statistical significance of the models, for all types of protein, were not affected by the removal of any study.

For the cohort studies reporting hazard ratios, removal of each study in turn led to pooled estimates as follows: Langsetmo (Men): $HR_{(random)}$=0.87 (0.57 to 1.34, p=0.54, n=4 studies, I^2=47% $P_{(heterogenity)}$=0.13); Langsetmo (Women): $HR_{(random)}$=0.82 (0.47 to 1.44, p=0.50, n=4 studies, I^2=50% $P_{(heterogenity)}$=0.11); Misra: $HR_{(random)}$=0.89 (0.58 to 1.37, p=0.60, n=4 studies,

I^2=41% $P_{(heterogenity)}$=0.16); Sahni(High Calcium): HR $_{(random)}$=0.84 (0.58 to 1.22, p=0.36, n=4 studies, I^2=49% $P_{(heterogenity)}$=0.12), Sahni(Low Calcium): HR $_{(fixed)}$=0.79 (0.64 to 0.97, p=0.02, n=4 studies, I^2=0% $P_{(heterogenity)}$=0.66). The removal of Sahni (Low Calcium) data led to a statistically significant reduction in fracture risk when protein intake was higher. Heterogeneity was also reduced to 0%, suggesting this result was leading to a masking of an association between protein and fracture risk shown in the low calcium arm of the Sahni study and the other studies in the meta-analysis.

For case control studies reporting odds ratios the following effect sizes were obtained when studies were removed as follows: Martinez-Ramirez: OR $_{(random)}$=0.65 (0.26 to 1.65, p=0.36, n=3 studies, I^2=73% $P_{(heterogenity)}$=0.03); Nieves: OR $_{(random)}$=0.57 (0.23 to 1.44, p=0.23, n=3 studies, I^2=47% $P_{(heterogenity)}$=0.15); Wengreen (50-69years old: OR $_{(fixed)}$=1.10 (0.53 to 2.26, p=0.81, n=3 studies, I^2=0% $P_{(heterogenity)}$=0.98); Wengreen (70-89years old: OR $_{(random)}$=0.61 (0.25 to 1.51, p=0.29, n=3 studies, I^2=70% $P_{(heterogenity)}$=0.04). All results were still not statistically significant when studies were removed in turn. Of note, the removal of Wengreen (50 to 59 years old group) did make heterogeneity go down to zero suggesting this study was the cause of the heterogeneity observed. There were not enough studies to perform funnel plots for each of the fracture meta-analyses.

[4] Supplementary Results: Intervention Studies

Study Characteristics

The 30 intervention studies included 2 studies in peri-menopausal women(99, 100), 6 in premenopausal women(101-106), 12 in postmenopausal women(107-118), 6 in both men and women, of which 4 were elderly groups (119-122) and 2 younger or middle-aged(123, 124), as well as 2 studies in men alone(125, 126) and 2 in children(127, 128). Seventeen of the 30 studies were from USA or Canada (99, 101, 102, 107-109, 112-117, 119, 120, 123-

125), with 2 from Switzerland(121, 122), 2 from Australia(111, 118), 1 from Brazil(110), 1 from Spain(128), 1 from New Guinea(127), 5 from Japan(100, 103, 104, 106, 126) and 1 from China(105). Eight of the 30 studies presented data on soy protein intervention vs. non-soy protein control (99, 107, 111, 112, 114, 116, 117, 125), 6 presented data on milk basic protein (MBP) vs. control (100, 103-106, 126), and 7 studies presented data on other protein types (110, 118, 120-122, 127, 128). Finally, 9 studies assessed dietary interventions, comparing higher vs. lower protein intakes (101, 102, 108, 109, 113, 115, 119, 123, 124).

Jadad Scores

See Supplementary Table x for full details of study quality and risk of bias in the 30 intervention studies. In terms of Jadad scores (0-5, 5=highest quality), 16 studies were scored as 0-2(101, 102, 104-106, 108, 111, 113, 115, 116, 119, 121, 123, 126-128), 7 studies as 3-4(99, 100, 107, 114, 120, 124, 125) and 7 studies as 5(103, 109, 110, 112, 117, 118, 122). Some studies (101, 102, 108, 109, 113, 115, 119, 124) may have scored lower than expected due to being dietary intervention studies, whereby it is difficult to undertake participant blinding as the different diets are difficult to conceal. Indeed, the Jadad scale is really intended for quality assessment of studies were participants and investigators can feasibly be blinded to treatment allocation. Study quality was variable, with many studies having significant methodological flaws.

Intervention Studies

Non-dietary Studies- Bone markers

In soy protein (vs. non-soy protein control) studies, six studies found no effect of soy protein on BAP(99, 107, 114, 125), NTX(114, 117), DPYD or PYD(107, 111, 125). However there

was an effect of soy protein vs. milk protein on reducing both BAP and CTx in one study(112) and in another study there was a positive effect of soy protein on raising BAP and OC, but no effect on NTX(116). Of the three MBP studies reporting bone marker data, one study found no effect of MBP supplementation vs. inactive placebo on NTX and OC concentration(100), another study found a lower NTX and higher OC in the MBP group than the inactive placebo control(126) and the final study found lower NTX and DPYD in the MBP group than inactive placebo(106).

For total protein (vs non-protein control), protein supplementation was associated with increases in type 1 N-terminal procollagen (P1NP)(120), HPO(124), DPYD(122, 124) and PYD(122, 124). There were conflicting results for CTX and OC with three studies finding no effect (110, 120, 122) one study finding a reduction in CTX (120) and one finding an increase in OC (121). Finally, one study found no statistically significant for an effect of protein supplementation on BAP (110). The only study in children found no statistically significant difference in BAP or OC or tartrate-resistant acid phosphatase (TRAP), but there was a higher increase in CTX over the study period in controls (increase by 6% of baseline value) than in the collagen supplemented group (increase by 3% of baseline value).

Dietary Studies- Bone markers

Seven diet studies found no differential effect of high and low protein diets on CTX (109, 115), OC(101, 102, 109, 115, 119), DPYD(108) or NTX(108). Four studies found a lower NTX (101, 102, 119, 123) and two studies found that DPYD was lower(113) or HPO was higher(115) in those taking a high protein diet (compared with a low protein diet). Finally, two studies conflicted in that they found either a higher BAP(102) or no difference in BAP(123) in those with a low protein compared with those with moderate or high protein diets.

Soy and MBP protein and BMD/BMC

In all supplementation studies no differential effect of soy protein vs. non-soy protein was seen for LSBMD(99, 112, 114, 117), LSBMC(99), FNBMD(112, 114, 117), RBMD(114) or TBBMD(112, 114, 117). Also, in a food based study (107) there was no differential effect of soy or non-soy protein on both BMD and BMC at the LS, TB and TH. (107). For MBP, a statistically significant effect of MBP supplementation in increasing LSBMD was found in two studies by 1 - 1.6%(100, 103) and in one study increasing TBBMD by 2%(105). However other results for MBP were conflicting, with studies finding either increased RBMD(104) or no effect on RBMD LSBMD or TBBMD (105).

Total protein and BMD/Bone size

For total protein, in malnourished New Guinea children aged 7-13 years, one study found an effect of 20g/d milk protein supplementation (vs. no supplement) for increased periosteal breadth, but not endosteal or compact bone breadth (127). In adults, no effect was seen for protein supplementation vs. non-protein control on LSBMD(120-122), THBMD(118, 120), FNBMD(118, 120, 121) FSBMD(121, 122) or TBBMD(122). Finally, one study found no differential effect of high vs low protein supplement drink on TH vBMD or FN vBMD(118).

Meta-analysis: MBP and Soy Protein Sensitivity analysis

Elimination of each MBP study in turn gave the following pooled estimates: Aoe 2005 $MD_{(fixed)}$= 0.01 (-0.04 to 0.07) R^2<0.001 P=0.69, I^2=0% $P_{(heterogenity)}$=0.69; Uenishi 2007 $MD_{(fixed)}$=0.02 (-0.003 to 0.04) R^2=0.0004 P=0.10, I^2=0% $P_{(heterogenity)}$=0.63; Zou 2009 $MD_{(fixed)}$= 0.02 (-0.002 to 0.04) R^2=0.04 P=0.07, I^2=0% $P_{(heterogenity)}$=0.07. Elimination of

each soy protein study in turn gave the following pooled effect sizes: Alekel 2000 $MD_{(random)}$=0.02 (-0.07 to -0.12, P=0.61) I^2=52% $P_{(heterogenity)}$=0.15; Kenny2009 $MD_{(fixed)}$= -0.03 (-0.07 to 0.02, P=0.23) I^2=8% $P_{(heterogenity)}$=0.30; Vupadhyahula 2009 $MD_{(random)}$=0.01 (-0.14 to 0.15, P=0.93) I^2=75% $P_{(heterogenity)}$=0.04. Removal of Kenny 2009 reduced heterogeneity from 51% to 8%, suggesting this study was contributing to the heterogeneity to a large degree. There were not enough studies to produce funnel plots for these meta-analyses.

Table S1: Characteristics and outcomes of 74 cross-sectional and/or longitudinal correlational studies

Study	Mean Protein **	Method	Population	n	Outcome	Coefficient*	P
Alexy et al, 2005, Germany	Prepubescent (M and F)- 2.0+/-0.3 g/Kg/d Pubescent (M)- 1.6+/-0.3 gKg/d Pubescent(F)- 1.4+/-0.3 g/Kgd	pQCT	Prepubescent and pubescent boys and girls	229		Standardized Beta: protein g/d, adjusted for age, sex, energy intake	
					Periosteal Circumference	0.170.27	0.0014
					Cortical Area	0.26	0.0001
					BMC	0.29	0.0011
					Polar SSI		<0.0001
Alissa et al, 2011, Saudi Arabia	1.03 g/Kg/d	DXA	Women aged 46-70 years old	122	Protein intake	Mean (SEM): g/d Control: 77.5 (3.15) n 61 Osteopenic: 76.6 (2.92) n 61	NS
Alissa et al, 2014, Saudi Arabia	71.4+/-1.55 g/d	DXA	Postmenopausal women, aged 46-88 years	300		Energy adjusted protein intake: r values:	
					LSBMD	-0.021	0.722
					FNBMD* used pooling	0.182	0.002
					TotalHipBMD	0.244	<0.0001
Beasley et al. 2010, USA	TP: 5.7 - 27.6% energy AP:45g/d VP:19g/d	DXA	Females aged 14-40 years	560		Tertile of protein intake %total energy BMD:(Mean, 95% CI)	
					TP:	T1 (lowest) T3 (highest)	0.94
					TotalHipBMD	0.93(0.91,0.95) 0.93 (0.91,0.96)	0.37
					LSBMD	1.00 (0.98,1.02) 1.02(1.00,1.04)	0.98
					TBBMD	1.08(1.07, 1.09) 1.08(1.06,1.10)	
					AP		
					TotalHipBMD	0.93(0.91,0.95) 0.94(0.92,0.96)	0.99
					LSBMD	1.00(0.98,1.02) 1.02(1.00,1.04)	0.40
					TBBMD	1.08(1.07,1.09) 1.08(1.07,1.10)	0.80
					VP		
					TotalHipBMD	0.92(0.90,0.94) 0.94(0.92,0.96)	0.03
					LSBMD	1.00(0.98,1.01) 1.01(0.99,1.04)	0.10
					TBBMD	1.07(1.06,1.11) 1.08(1.06,1.09)	0.04
						Beta for increment of protein as an extra 1% energy, adjusted for age, BMI,	

						physical activity, smoking, contraception, energy intake, phosphorus, magnesium.	
					N 224: 3 year change in: HipBMD SpineBMD TBBMD HipBMD SpineBMD TBBMD HipBMD SpineBMD TBBMD	TP % energy (Year 3)Beta= -0.0002 Beta= 0.0004 Beta= -0.0012 AP % energy (Year 3) Beta= -0.0002 Beta= 0.0005 Beta= -0.0011 VP % energy (Year 3) Beta= -0.0023 Beta= -0.0019 Beta= 0.0009	P value 0.88 0.71 0.19 0.87 0.69 0.21 0.40 0.50 0.69
Beasley et al. 2014, USA	15% total energy	DXA	Postmenopausal women 50-79 years	144,580		Change in mean BMD per 20% increase in %of calories from protein:	
					TBBMD	At 6 y (n=6552), change in BMD of 0.004 (0.001, 0.007) g/cm2	-
					Hip BMD	At 6 y (n=6553) change in BMD of 0.003 (0.000, 0.005)	-
					Spine BMD	At 6y (n=6457), change in BMD of 0.003(0.000,0.008)	-
Bounds et al, 2005, USA	55g/d (1.9g/Kg/d)	DXA	6-8 year old children	25 Boys, 27 Females	 TBBMC TBBMD TBBMC TBBMD	Unadjusted r values- Pearson's 0.37 0.33 Stand.Beta=2.40* Stand. Beta=0.001** *adjusted for Height,Weight, age and sex **adjusted for Sex	 ≤0.05 ≤0.05 0.008 0.04

Budek et al. 2007a, Denmark	2.67	Bone turnover markers	N=81 pubertal boys	81	TP	Standardized beta: Age and BMI adjusted	
					sOC microg/L	0.09	0.68
					sBAP U/L	0.89	0.01
					sCTX microg/L	<-0.01	0.59
					VP		
					sOC microg/L	0.24	
					sBAP U/L	-0.16	0.36
					sCTX microg/L	<-0.01	0.72
							0.29
					Dairy protein		
					sOC microg/L	-0.45	0.05
					sBAP U/L	0.53	0.16
					sCTX microg/L	-0.01	0.51
					Meat protein		
					sOC microg/L	0.44	0.11
					sBAP U/L	0.86	0.04
					sCTX microg/L	-0.01	0.35
Budek et al. 2007b, Denmark	TP: 1.2 (Girls), 1.3 (Boys) AP: 0.4 (Girls), 0.5 (Boys) DP: 0.4 (Both Girls and Boys)	DXA	17-year-olds: 63 girls and 46 boys	109	TP: TBBMC LSBMC AP: TBBMC LSBMC	Standardized Beta(adj*): -0.02 -0.08 0.01 -0.01 *adjusted for bone area, weight, height, sex, calcium, energy intake, physical activity	0.78 0.46 0.62 0.78
Chan et al, 2009, Hong Kong/Beijing	77.5g/d Hong Kong 65.4g/d Beijing	DXA	Premenopausal women	441	 TotalHipBMD FNBMD TotalSpineBMD	R Protein (g/d): (adjusted for age and BMI) 	 0.359 ns ns
Chan et al. 2011, Hong Kong	1.3 g/Kg/d	DXA	Older men and women	2217	Energy adjusted protein intake	B coefficient (adjusted for age, weight, height, education, alcohol, smoking, physical activity, calcium supplement,	

						energy adjusted calcium and vitamin D	
					% change Hip BMD	intakes)	0.147
					% change FNBMD	Men:	0.006
						B= -0.007	
						B= -0.013	
						Women: data not reported (all ns)	
Chevalley et al. 2008, Switzerland	47.3 g/d, 1.78 g/Kg/d	DXA	Prepubertal boys	232		Protein intake g/d:	P
						r (not adjusted)	
					Radial Metaphysis BMC	0.26	0.0001
					Radial Diaphysis BMC	0.21	0.002
					Total Radius BMC	0.27	0.0001
					FNBMC	0.20	0.002
					Total Hip BMC	0.18	0.005
					Femoral Diaphysis BMC	0.23	0.0003
					LSBMC	0.24	0.0002
						Standardized Beta (adjusted for physical activity and calcium intakes)	
					Radial Metaphysis BMC	0.201	0.013
					Radial Diaphysis BMC	0.120	0.146
					Total Radius BMC	0.199	0.013
					FNBMC	0.187	0.028
					Total Hip BMC	0.122	0.136
					Femoral Diaphysis	0.190	0.025
					LSBMC	0.217	0.009
						Data for <median physical activity only shown:	
					Mean(SD)	Protein>median vs. <median:	
					Radial Metaphysis BMC	649(82) vs. 663(103)	-
					Radial Diaphysis BMC	919(104) vs. 937(104)	-
					Total Radius BMC	2679(379) vs. 2807(422)	-
					FNBMC	1980(321) vs. 1988(321)	-
					Total Hip BMC	10342(1958) vs. 10535(1973)	-
					Femoral Diaphysis	17575(3698) vs. 18431(3486)	-
					LSBMC	15652(2080) vs. 15839(2505)	-

Chevalley et al. 2014, Switzerland	Age 7: 1.8; Age 15: 1.1 (g/Kg/d)	High resolution pQCT	Adolescent boys	176	Bone outcomes at 15 years:	Protein intake at Age 7 years: Higher (n=36) vs lower protein (n=52) (lower physical activity)	0.176
					FN vBMD	4645±788 vs. 4411±795	0.233
					TotalHipvBMD	36389±7995 vs. 34381±7493	0.341
					FNBA	5.28±0.50 vs. 5.18±0.47	0.341
					FN width	3.49±0.33 vs. 3.43±0.31	0.178
					FNBMD (DXA)	879±109 vs. 846±112	0.169
					TotalHipBMD (DXA)	976±127 vs. 937±130	0.063
					DistalTibia Total vBMD	276±39 vs. 259±44	
						Higher (n=49) v s lower protein(n=38) (higher physical activity)	0.0006
					FN vBMD	5075±894 vs. 4405±858	0.002
					TotalHipvBMD	40913±8451 vs. 35303±7863	0.030
					FNBA	5.46±0.36 vs. 5.26±0.47	0.030
					FN width	3.61±0.24 vs. 3.48±0.31	0.0009
					FNBMD (DXA)	932±139 vs. 834±122	0.009
					TotalHipBMD (DXA)	1011±140 vs. 929±144	0.336
					DistalTibia Total vBMD	273±41 vs. 263±53	
Chiu et al, 1997, Taiwan	1.09	DPA (BMD)	Older post F	258		r Protein g/d (unadjusted- Pearson's values)	0.09
					LSBMD		0.18
					FNBMD	0.107	
						0.085	
Coin et al, Italy, 2008	75.8+/-22.1 g/d Weight=74.2+/-13.4	DXA	Males, mean age 73.9+/-5.6 years	136	Male data only for protein (no data for females) n=136	R squared	Controlling for BMI, albumin, skeletal muscle, age
	So 1.02 g/Kg/d				Total Hip BMD	0.12(non adj) p<0.001	
						0.06(adj) p<0.01 r(adj)=0.25	
					FNBMD* chosen for pooling men as same as other studies	0.03(nonadj) p<0.05	
						0.01(adj) p>0.05 r(adj)=0.1	
					TrochBMD	0.10(nonadj)p<0.001	
						0.08(adj) p<0.01 r(adj)=0.28	

Cooper et al, 1996, USA	72g/d	DPA/SPA (BMD)	Pre (72) and post (218) F	290		Adjusted for age, weight, physical activity	P for unadj data
							Ns
					LSBMD(pre)	0.20 adj=0.07 ns	<0.01
					TrochBMD (pre)	0.36 adj=0.35 p<0.01	<0.05
					FNBMD(Pre)	0.26 adj=0.27 p<0.05	<0.01
					DRBMD (pre)	0.35 adj=0.28 p<0.01	<0.05
					MRBMD(pre)	0.27 adj=0.21 p<0.05	Ns
					FSBMD(pre)	0.22 adj=0.16 ns	Ns
					LSBMD(post)	0.13 adj=-0.05 ns	<0.01
					TrochBMD(post)	0.20 adj= -0.06 ns	<0.001
					FNBMD(post)	0.25 adj=0.02 ns	<0.01
					DRBMD (post)	0.19 adj=-0.08 ns	<0.01
					MRBMD(post)	0.21 adj=-0.05 ns	<0.001
					FSBMD(post)	0.24 adj=0.01 ns	
						* age adjusted:	
					HPO(pre)*	-0.25 p<0.01	
					HPO(post)*	-0.01 p>0.05	
					OC(pre)*	0.20 p>0.05	
					OC(post)*	0.05 p>0.05	
Dawson-Hughes et al, 2002, USA	79g/d	DXA	184 men and women(>=65 years old) in placebo (inactive) arm of calcium supplementation trial	184		Tertile protein intake, % of energy	
					TBBMD	Tertile 1 1.12(0.13)	
						Tertile 2 1.10(0.11)	ns
						Tertile 3 1.07(0.14)	
					FNBMD	Tertile 1 0.89(0.14)	
						Tertile2 0.86(0.12)	ns
						Tertile3 0.86(0.14)	
					LSBMD	Tertile 1 1.17(0.23)	
						Tertile2 1.17(0.20)	ns
						Tertile 2 1.11 (0.25)	
					sOC (nmol/L)	Tertile 1 1.1(0.3)	
						Tertile2 1.1(0.4)	ns
						Tertile3 1.1(0.4)	
					uNTX (nmol)		
						Tertile 1 231(172)	
						Tertile2 218(115	ns
						Tertile3 232(218)	

Devine et al, 2005, Australia	1.2	DXA , QUS	Elderly F mean age 75y+/-3y Caucasian	1077	TP: Total Hip BMD BUA calcaneus	r values (unadjusted) 0.138 0.136				- -
					TP: TotalHipBMD FNBMD TrochBMD IntertrochBMD BUA calcaneus SOS Stiffness	Unstandardized Beta (SE): 0.31 (0.07) 0.26 (0.07) 0.32 (0.08) 0.32 (0.06) 0.02 (0.08) Not shown 0.02 (-0.06)				<0.01 <0.05 <0.01 <0.05 <0.01 NS NS
						BUA (db/Hz): <66 g/d: 99.6 ± 0.4 (n = 357) 66-87 g/d: 100.8 ± 0.4 (n = 337) >87 g/d: 101.2 ± 0.4 (n = 341)				
						BMD at Hip Sites (mg/cm^2) Tertile 1 <66 g/d (n = 374) Tertile 2 66-87 g/d (n = 350) Tertile 3 >87 g/d (n = 351)				
							Mean	SE	95%CI	
					Total Hip BMD	Tertile 1	0.798	0.006	0.79,	0.81
						Tertile 2	0.815	0.006	0.80,	0.83
						Tertile 3	0.823	0.006	0.81,	0.84
					Femoral Neck BMD	Tertile 1	0.679	0.005	0.67,	0.69
						Tertile 2	0.695	0.005	0.69,	0.71
						Tertile 3	0.701	0.005	0.69,	0.71
					Trochanter BMD	Tertile1	0.625	0.005	0.62,	0.64
						Tertile 2	0.640	0.005	0.63,	0.65
						Tertile 3	0.649	0.005	0.64,	0.66
					Intertrochanter BMD	Tertile 1	0.937	0.007	0.92,	0.95
						Tertile 2	0.957	0.007	0.94,	0.97
						Tertile 3	0.964	0.007	0.95,	0.98
Ekbote et al, 2011, India	18.6g/d-normal and malnourished children combined	DXA	2-3 year old children	71	Normal children: TBBMC TBBA	 0.62* 0.65*				 <0.01 <0.01

					Malnourished Children:		
					TBBMC	0.44*	
					TBBA	0.57*	<0.05
							<0.01
					All children:		
					TBBMC	0.55*	
					TBBA	0.58*	<0.01
						*remained statistically significant when adjusted for energy intake	<0.05
Fairweather-Tait et al, 2011, UK	81.3g/d	DXA	Postmenopausal female twin pairs (Monozygotic or dizygotic twins)	2464 pairs	Energy adjusted protein intake (g):	Beta(adjusted for age, BMI, smoking, physical activity), Including variables for individual diet and twin difference:	P (adjusted for multiple comparisons)
							0.651
					LSBMD (n=1232 pairs)	0.029 (-0.014, 0.072)	0.964
					HipBMD(n=1218 pairs)	-0.013 (-0.047, 0.022)	0.365
					FNBMD (n=1019 pairs)	-0.033 (-0.071, 0.005)	
						Individual intakes only in model:	0.502
					LSBMD (n=1232 pairs)	0.012 (-0.023, 0.046)	0.738
					HipBMD(n=1218 pairs)	-0.005 (-0.036, 0.025)	0.102
					FNBMD (n=1019 pairs)	-0.027 (-0.060, 0.005)	
Freudenheim et al, 1986, USA	1.02	SPA	Pre and post F, 35-65y, Caucasian	84 (17 pre F, 67 post F)		r, p	Adjusted for bone width
					RBMC (pre)	0.384, 0.128	
					HumBMC (pre)	0.157, 0.546	
					UBMC (pre)	0.282, 0.272	
					RBMC (post)	-0.017, 0.889	
					HumBMC (post)	0.138, 0.267	
					UBMC (post)	0.044, 0.725	
						Slope of bone loss:	
					TP	Pre F: r, p	
						RBMD 0.742, 0.022	
						HuBMD 0.518, 0.153	
						Ulna 0.428, 0.250	
					TP	Post F: r, p	
						RBMD 0.493, 0.004	
						HuBMD 0.258, 0.147	

						Ulna -0.095, 0.597	
Geinoz et al, 1993, Switzerland	Mean Intake in g/d by group: 37.8-59.4	DXA	Elderly M and F Mean age 82y(F); 80(M)	74	Gender, protein intake	Mean +/-SD	P
					F,>1g/Kg/d		
					FNBMD	0.679+/-0.09	Ns
					FSBMD	1.288+/-0.35	Ns
					SpineBMD	0.935+/-0.24	Ns
					F<1g/Kg/d		
					FBBMD	0.574+/-0.13	p<0.05
					FSBMD	1.120+/-0.33	ns
					SpineBMD	0.877+/-0.36	ns
					M,>1g/Kg/d		
					FNBMD	0.761+/-0.12	ns
					FSBMD	1.516+/-0.19	ns
					SpineBMD	1.094+/-0.26	ns
					M,<1g/Kg/d		
					FNBMD	0.643+/-0.14	p<0.05
					FSBMD	1.318+/-0.34	ns
					Spine BMD	0.847+/-0.18	p<0.05
Genaro et al, 2015, Brazil	66g/d	DXA	Women over 65 years old	200		Protein:g/Kg/d <0.8 (n=73)	P for trend:
					TBBMCg/cm2	0.988	0.011
					LSBMD g/cm2	0.903	0.014
					FNBMD g/cm2	0.760	0.017
					TrochBMD g/cm2	0.679	0.071
					Total Femur BMD g/cm2	0.807	0.026
						0.8-1.2 (n=84)	Posthoc tests:
					TBBMCg/cm2	1.025	>1.2 vs. <0.8
					LSBMD g/cm2	0.965	P<0.05 at all sites
					FNBMD g/cm2	0.795	
					TrochBMD g/cm2	0.689	>1.2 vs 0.8-1.2
					Total Femur BMD g/cm2	0.833	P<0.05 for TBBMC,
						>1.2 (n=43)	LSBMD and
					TBBMCg/cm2	1.039	FNBMD
					LSBMD g/cm2	0.983	

					FNBMD g/cm2	0.813	
					TrochBMD g/cm2	0.727	
					Total Femur BMD g/cm2	0.868	
Gregg et al, 1999, USA	0.9	QUS	Middle aged (premenopausal) F- mean age= 45.5y	393		Unadjusted coefficients (non adjusted)	
					BUA Calc	3.15	0.0008
					SOS Calc	0.96	0.02
					LSBMD	0.015	0.02
					FNBMD	0.010	0.09
					Dietary protein: per 87kcal	Controlling for lean body mass, physical activity, race, menopausal status, BMI:	
					BUA	0.14 SD increase	0.004
Gunn et al, 2014, New Zealand	79g/d	Bone markers, DXA	Postmenopausal women, 60 years of age	142		Energy adjusted protein: (not adjusted for other confounders)	
					FNBMD	0.19	<0.05
					FN T-Score	0.17	<0.05
					sCTX	-0.18	<0.05
					sP1NP	-0.23	<0.05
Hannan et al. 2000, USA	68g/d (16% of total energy) 0.97 g/kg/d	DXA	Older men and women	615	TP	Change in BMD by protein quartile:	*= p<0.05 Q1 compared with Q4
					FNBMD		
					QI	-4.61 +/- 070*	
					Q4	-2.32 +/-0.74	Adjusted for total energy intake, age, sex, weight, weight change, height, alcohol intake and smoking (current or former).
					TrochBMD		
					Q1	-8.00 +/- 0.84	
					Q4	-6.65+/-0.90	
					Wards BMD		
					Q1	-7.05+/-1.0	
					Q4	-4.39+/-1.1	
					LSBMD		
					Q1	-3.72+/-0.97	
					Q4	-1.11+/-1.1	
					RBMD		

					Q1 Q4 <u>AP</u> FNBMD QI Q4 TrochBMD Q1 Q4 Wards BMD Q1 Q4 LSBMD Q1 Q4 RBMD Q1 Q4	-4.21+/-0.71 -4.31+-0.76 -3.95 +/- 0.69* -2.15+/-0.73 -2.57+/-0.86 -1.95+/-0.92 -4.02+/-1.0 -1.97+/-1.1 -3.79+/-0.99 -1.65+/-1.1 -4.60+/-0.71 -4.52+/-0.76	
Henderson et al, 1995 , Australia	1.0	DXA	Pre F- mean age=18y	115	 FNBMD IntertrochBMD TrochBMD DTB BMD TFBMD FSBMD LSBMD	Unadjusted r values 0.22 0.19 0.27 0.05 0.21 0.09 0.05	 p<0.05 p<0.05 p<0.005 p>0.05 p<0.05 p>0.05 p>0.05
Hernandez et al, 1993, USA	76g/d	SPA	Pre- and Perimenopausal Women (50-60 years old)	281	Ultradistal R BMD	Beta=0.0108 SE=0.259 (unstandardized beta) Adjusted for dietary nutrients, alcohol and caffeine.	NS
Hirota et al, 1992, Japan	1.13	SPA (BMD)	Young pre F: 19-25y	161	Forearm BMD	r=0.0017 (adjusted for sports, BMI, milk intake in childhood, dieting, skipping meals)	0.03 Adjusted for sports, BMI,

							childhood milk intake, dieting, skipping meals
						Dietary intakes g/d by Forearm BMD category (BMD % of mean) <=85% 50.7+/-13.6 86-100% 56.8+/-13.3 101-114% 60.1+/-18.2* >=115% 64.2+/-19.7* *significantly different from the <=85% group (lowest)	
Ho et al, 2003, China Soy protein	1.01 SP	DXA	<12y post F(48-62y), Asian	454 (269 <4 y post F 185 >4 y post F)	<u>ALL WOMEN</u>	Quartile of soy protein intake:	
						Q1 Q4	
					Spine BMD	0.825±0.118 0.844±0.133	
					FNBMD	0.668±0.103 0.694±0.099	
					TrochBMD	0.581±0.098* 0.606±0.095	
					IntertrochBMD	0.945±0.145* 0.981±0.130	
					TotalHipBMD	0.781±0.118* 0.815±0.111	
					TBBMD	0.958±0.088 0.966±0.084	
					TBBMC	1601±255 1649±228	
					Spine BMD	Standardized beta (SE)	
					FNBMD	0.0034(0.005)	0.497
					TrochBMD	0.0048(0.004)	0.200
					IntertrochBMD	0.0056(0.004)	0.119
					TotalHipBMD	0.0069(0.005)	0.162
					TBBMD	0.0070(0.004)	0.087
					TBBMC	0.0071(0.004)	0.842
						5.974 (8.784)	0.497
						Controlling for soy protein intake quartile, weight, years since menopause, calcium intake quartile, soy protein- calcium interaction, total protein intake, and energy intake	
Ho et al, 2008, China	5.2g/d SP 48.6 g/d TP	DXA	Pre and perimenopaus	438		r(adj)=adjusted for age-menopause stage and energy intake	

	al women 45-55 years old	TP:		
		LSBMD	r=0.064	ns
			r(adj)=0.016	ns
		FNBMD	r=0.088	ns
			r(adj)=0.037	ns
		TotalHipBMC	r=0.084	ns
			r(adj)=0.053	ns
		WBBMC	r=0.075	ns
			r(adj)=0.024	ns
		SP:		
		LSBMD	r= -0.043	ns
			r(adj)= -0.05	ns
		FNBMD	r=0.020	ns
			r(adj)= -0.004	ns
		TotalHipBMC	r= -0.001	ns
			r(adj)= -0.027	ns
		WBBMC	r= -0.002	ns
			r(adj)= -0.017	ns
		Quartile of soy protein intake:	Standardized beta (SE)	
		WBBMC	Q1(<1.07)=Reference	-
			Q2(1.07-)=0.19 (0.3282)	ns
			Q3(2.85-)=0.73 (0.3340)	<0.05
			Q4(5.72+)=0.73 (0.3225)	<0.05
		Change from baseline: (30 months) TBBMC	Quartile of soy protein intake vs TBBMC: Unst. Beta* SE	
		Q1 <1.07 g/d Reference	1.0000	
		Q2 1.07-2.84 g/d	0.1932 0.3282	ns
		Q3 2.85-5.72 g/d	0.7306 0.3340	<0.05
		Q4 >5.72 g/d	0.7303 0.3225	<0.05
			*Controlling for baseline BMC, lean mass, change in weight, number of pregnancies, walking and menopausal status.	

Ho-Pham et al, 2009, Vietnam	g/d: TP= 35.4(11.6) Vegans, 62.6(18.3) Omnivores AP=2.1(3.2) Vegans, 34.6(15.8) Omnivores VP=33.2(11.6)Vegans, 28.0(8.4) Omnivores	DXA	105 Post F Buddhist vegan Nuns and 105 omnivorous women 62+/- 10 years old	210	 FNBMD LSBMD TBBMD FNBMD LSBMD TBBMD	AP: +10g Beta 0.008 (0.006) 0.013 (0.008) 0.006 (0.006) VP:+10g Beta -0.008 (0.007) 0.014 (0.009) -0.014(0.006)	 0.175 0.108 0.313 0.261 0.128 0.033
Ho-Pham et al, 2012, Vietnam	TP: 36g/d Vegans 62g/d Omnivores	DXA	105 Buddhist vegan Nuns and 105 omnivorous women Mean(SD) age 61(9.2)	181	 Change in: LSBMD FNBMD	Beta: (adjusted for age, anthropometry, fat intake) VP: -0.075(0.035) AP:VP ratio: -0.244 (0.094)	 0.036 0.01
Hoppe et al. 2000, Denmark	82g/d (Boys) 73g/d(Girls)	DXA	10 year old children	105	WBBMC WBBA	0.327 (unadjusted r values) 0.311 Has linear regression but only p values, not effect size p1027	<0.001 <0.01
Horiuchi et al, 2000, Japan	Total- 62.5g/d Soy-12.6g/d	DXA	Post F, 52-83y	85	Soy LSBMD Osteocalcin ALP Pyridinoline Deoxypyd Total Protein LSBMD Pyridinoline Deoxypyd Osteocalcin ALP Z score for LSBMD Total protein Soy protein	r values (unadjusted) 0.251 -0.097 -0.017 -0.132 -0.229 0.223 -0.229 -0.218 -0.131 -0.09 Beta (standardized): -0.03 (no SE or p value given)* used in SR 0.225 (no SE given)	 p<0.05 ns ns ns p<0.05 p<0.05 p<0.05 ns ns ns ns 0.038

Hu et al, 2014, USA	TP: 12.0-19.0 % energy intake (F) TP: 11.6-20.4% energy intake (M)	QCT	801 women and 857 men enrolled on the Multi-Ethnic Study of Atherosclerosis (age 62+/-10 years)	1658	LS vBMDmg/cm^3 n1658	Quartile of protein intake: Q1 115+/-40 Q2 115+/-38 Q3 116+/-42 Q4 112+/-39	P=0.88
					LSBMD ZScore: n801	Standardized Beta, p	
					TP:		
					White	-0.06 0.75	
					Chinese	-0.07 0.84	
					Black	0.35 0.2	
					Hispanic	0.16 0.55	
					AP:		
					White	-0.13 0.51	
					Chinese	-0.65 0.06	
					Black	0.29 0.37	
					Hispanic	0.40 0.16	
					VP:		
					White	0.44 0.02	
					Chinese	0.22 0.49	
					Black	-0.36 0.27	
					Hispanic	0.06 0.9	
						Model adjusted for age, BMI, physical activity, sedentariness, smoking, education, hormone therapy use, age at menopause, and intakes of total energy, dietary carbohydrate as a percentage of energy, Ca, P, Mg and alcohol.	
						Quartiles of protein intake: Q4 mean (96% CI)	
					LS trabecular vBMD		
					Female, AP	97.3 (87.7, 106.8)	
					White	107.5 (68.0, 146.9)	
					Chinese	134.9 (117.3, 152.4)	
					Black	120.5 (105.2, 135.8)	

					Hispanic		
					Male AP	110.3 (100.8, 119.7)	
					White	115.9 (99.5, 132.2)	
					Chinese	155.7 (135.3, 176.1)	
					Black	128.8 (117.3, 140.3)	
					Hispanic		
					Female, VP	107.4 (98.6, 116.2)	
					White	139.4 (102.5, 176.2)	
					Chinese	125.8 (110.3, 141.4)	
					Black	112.8 (100.5, 125.2)	
					Hispanic		
					Male VP	105.0 (97.1, 112.9)	
					White	109.6 (94.8, 124.4)	
					Chinese	141.6 (122.9, 160.3)	
					Black	123.6 (112.6, 134.6)	
					Hispanic		
Ilich et al, 2003, USA	1.04	DXA	Older F, >5 post, Caucasian, mean age 68.7+/-7.1y	136		Unstandardized. Beta (adjusted for age, lean body mass, total body fat, and height (in TBBMC model), past physical activity, present mode of walking, and energy intake	
					TBBMD	1 $x10^{-3}$ (also adjusted for Ca intake)	0.027
					TBBMC	2.9	0.03
					WBMD	$1.4x10^{-3}$ (also adj for ca and vit C intake)	0.021
					HBMD	$4.1x10-^{4}$ (also adjusted for ca intake)	0.021
Iuliano-Burns et al, 2005, Australia	76g/d	DXA	7-20 year old Male twins (Monozygotic n=30) and Dizygotic (n=26)	56		Beta coefficient: Within pair difference in protein intake, adjusted for anthropometric and lifestyle factors.	
					TBBMC (g)	1.3	ns
					Arm BMC (g)	0.7	<0.05
					Leg BMC (g)	0.3	ns
					LSBMC (g)	0.0	ns
Jaime et al, 2006, Brazil	1.2	DXA	Men- Over 50y	277 (n=31 Black and		Energy adjusted protein intake (not adjusted for other confounders)	
					FNBMD (Black)	0.359	0.040
					FNBMD (White)	0.055	0.505

				n=246 white)		Beta: (Unadjusted, standardized.)	
					FNBMD(black)	0.00192	0.261
					FNBMD (white)	0.00058	0.299
Jones et al. 2001, Tasmania	83g/d	DXA	Boys and Girls Aged 8 years old	330 (n=262 in analysis)		Non adjusted r values:	
					FNBMD	-0.05	>0.05
					LSBMD	0.00	>0.05
					TBBMD	-0.09	>0.05
Knurick et al. 2015, USA	Omnivore: 97g/d Lacto-ovo Vegetarian: 68g/d Vegan: 69g/d	DXA	Adult men and women, 18-50 y (combined data only)	81	TBBMD, TP	Pearson's correlations (unadjusted):	
					All	0.274- used in TBBMD pooling	0.017
					Omnivores	0.190	ns
					Lacto-ovo Vegetarian	0.262	ns
					Vegans	0.434	<0.05
Kumar et al, 2010, Northern India	45.7g/d	DXA	Women aged 20-69 years	225		Dietary protein: (non-adjusted r values)	
					LSBMD	0.224	0.0001
					FNBMD	0.040	0.529
					WardsBMD	-0.039	0.536
						Q1, Q4 (Mean, SD)	
					LSBMD	1.05(0.20), 1.15(0.18)	-
					FNBMD	0.96(0.20), 0.93(0.15)	-
					WardsBMD	0.87(0.27), 0.80(0.18)	-
Lacey et al, 1991, Japan	1.35	SPA	Asian pre F(35-40y) and post F (55-60y)	178 (89 pre F, 89 post F)	MRBMC	% protein in diet vs. radial BMC	
					PreF	0.22	0.04
					Post F	0.19	0.05
Langsetmo et al., 2015 Canada	0.79g/Kg/d	DXA	Men and women aged over 25 years old	6510	(n not given for subgroups)	Adjusted for age, BMI, energy intake AP (Non-dairy) Beta (95%CI)	
					Men 25-49 y		
					Hip BMD	-0.001 -0.016, 0.013	
					HipBMD change:	0.000 -0.004, 0.004	
					LSBMD	-0.012 -0.026, 0.003	
					LSBMD change:	-0.001 -0.006, 0.005	
					Premenopausal Women 25-49 y		

	Hip BMD	-0.004 -0.015, 0.006
	HipBMD change:	0.001 -0.002, 0.005
	LSBMD	-0.012* -0.024, 0.000
	LSBMD change:	0.001 -0.005, 0.003
	Men 50+ y	
	Hip BMD	-0.002 -0.011, 0.006
	HipBMD change:	0.001 -0.001, 0.004
	LSBMD	0.000 -0.011, 0.011
	LSBMD change:	0.000 -0.003, 0.004
	Postmenopausal Women 50+ y	
	Hip BMD	0.004 -0.001, 0.009
	HipBMD change:	0.000 -0.002, 0.002
	LSBMD	0.010* 0.003, 0.016
	LSBMD change:	0.001 -0.001, 0.003
	Men 25-49 y	
	Hip BMD	-0.010 -0.024, 0.003
	HipBMD change:	0.001 -0.003, 0.005
	LSBMD	-0.013 -0.027, 0.001
	LSBMD change:	0.000 -0.005, 0.005
	Premenopausal Women 25-49	
	Hip BMD	-0.011* -0.022, -0.001
	HipBMD change:	-0.003 -0.006, 0.001
	LSBMD	-0.005 -0.017, 0.007
	LSBMD change:	-0.002 -0.006, 0.003
	Men 50+	
	Hip BMD	-0.007 -0.016, 0.001
	HipBMD change:	0.001 -0.002, 0.003
	LSBMD	-0.009 -0.020, 0.002
	LSBMD change:	0.001 -0.002, 0.005
	Postmenopausal Women 50+ y	-0.006* -0.011, -0.001
	Hip BMD	0.000 -0.002, 0.002

					HipBMD change: LSBMD LSBMD change: *=CI indicates exclusion of null effect	-0.012* -0.019, -0.005 -0.003* -0.005, 0.000	
Lau et al, 1998, China	0.65 (vegetarians)	DXA	Post F, 70-89y	76		Unadjusted r values	-
					LSBMD	0.09	-
					FNBMD	0.13	-
					IntertrochBMD	0.084	-
					WBMD	0.042	
						Beta coefficient- adjusted for energy intake, age, calcium intake, urinary Na:Cr ratio	
					LSBMD	7.9x10-4	>0.05
					FNBMD	-6.8x10-4	>0.05
					IntertrochBMD	-3.6x10-3	>0.05
					WBMD	-1.0x10-3	>0.05
Libuda et al. 2008, Germany	1.3 g/Kg/d	pQCT	Children and adolescents 8-14 years old	228		Standardized (Beta) coefficient: Total Protein	
					BMC	1.02	0.03
					Cortical Area:	0.97	0.01
					PC:	0.28	0.02
					SSI:	5.23	0.01
Libuda et al. 2011, Germany	Median protein: Boys: 46.1g/d Girls: 42.7g/d	pQCT	Pre-pubertal children	107 (N=57 Boys N=50 Girls)	Diaphyseal bone Forearm : vBMC mg/mm Cortical Area mm^2	Coefficients: Controlling for muscle area and androstenediol Beta=1.49 Beta (stand)=0.11 Beta=1.37 Beta(stand)=0.11	 0.073 0.056
Loenekke et al. 2010, USA	91.3+/- 45.15 g/d 71.72 +/- 13.95 kg	DXA	Males and Females, 22+/-3 years	27		r values, controlling for body mass:	
					TBBMD	0.607	0.001
					TBBMC	0.557	0.003
MacDonald et al, 2005, UK	79.4g/d	Bone Markers, DXA	45-54y women, pre, peri or post menopausal	5119	DPD/Cr n=2929	Mean (g/d) by Quartile (Q) Q1 69.0 Q2 76.4 Q3 84.3	ANCOVA: (confounder adjusted)

						Q4 99.3	P=0.02
					PYD/Cr n=2929	Data not shown	P=0.01
					LSBMD n=3226	Data not shown	ns
					FNBMD n=3226	Data not shown	ns
Meng et al. 2009 Australia	80.6g/d	DXA	862 elderly women 75 ± 3 (SD) yr of age of white origin.	862	TBBMC	r=0.15 Unadjusted correlation between baseline protein intake and 5 year BMC	<0.001
					TBBMC AppendicularBMC	Q1 n=287, <66g/d 1352±236 1 388±242	
					TBBMC AppendicularBMC	Q2 n=287, 66-87g/d 1433±262 888±162	
					TBBMC AppendicularBMC	Q3 n=288, >87g/d 918±164 942±177	
						Whole body BMC (mg/cm2, headless) <66 g/d: 1357 ± 17 (n = 287) 66-87 g/d: 1387 ± 13 (n = 287) >87 g/d: 1429 ± 18 (n = 288)	
						Appendicular BMC (mg/cm2) <66 g/d: 889 ± 11 (n = 287) 66-87 g/d: 917 ± 9 (n = 287) >87 g/d: 942 ± 12 (n = 288)	
Metz et al, 1993, USA	1.24	SPA	Pre F Caucasian (24-28y)	38		Unstandardized B (SEM) adjusted for calcium intake, physical activity, lean body mass	
					DRBMC	-0.450 (0.183)	0.019
					DRBMD	-0.434 (0.194)	0.032
					MRBMC	-0.503 (0.180)	0.009
					MRBMD	-0.251(0.214)	0.248
Michaelsson et al, 1995, Sweden	59g/d	DXA (Dietary Records	F 28-74y, Caucasian	175		Standardized Beta (adjusted for BMI, energy intake, physical activity, menopausal status, menopausal age,	

		data used, not FFQ)				smoking, diabetes, cortisone, HRT, athletic activity	
						Dietary records	
					TBBMD	0.00086	0.28
					LSBMD	-0.0010	0.51
					FNBMD	0.0028	0.04
						Food frequency records:	
					TBBMD	0.0020	0.005
					LSBMD	0.0013	0.36
					FNBMD	0.0024	0.06
						Unadjusted r values:	
					TBBMD	0.189	0.018
					LSBMD	0.058	0.474
					FNBMD	0.117	0.151
					OC	-0.036	0.669
Nakamura et al, 2004, Japan	1.29	Bone markers	Elderly post F, mean age=68.3y , range 43-79	43		Unadjusted r values:	
					OC	-0.197	p>0.05
					Bone ALP	-0.039	p>0.05
					Deoxypyd.	-0.241	p>0.05
					NTX	-0.205	p>0.05
Neville et al, 2002, UK	98g/d (M) and 66g/d(F)	DXA	238 M and 205 F, at both 15 and 20-25 years of age	443	Young adult (20-25y old) BMD:	Standardized Beta(adjusted for dietary, anthropometric and lifestyle parameters):	
					MALES:	Young adult protein intake:	
					LSBMD	-0.62	0.13
					FNBMD	-0.57	0.16
					FEMALES:	Young adult protein intake:	
					LSBMD	-0.11	0.61
					FNBMD	-0.04	0.87
					Young adult (20-25y old) BMD:	Standardized Beta(adjusted for dietary, anthropometric and lifestyle parameters)	

					MALES: LSBMD FNBMD	Adolescent protein intake: 0.53 -0.08	 0.13 0.83
					FEMALES: LSBMD FNBMD	Adolescent protein intake: 0.12 0.47	 0.76 0.27
New et al, 1997, UK	81+/-22 g/d	DXA	Women aged 44-50 years (Premenopausal)	994	 LSBMD FNBMD TrochBMD WardsBMD	Energy adjusted protein intake 0.03 0.02 0.04 0.02:	 P>0.05 ns P>0.05 ns P>0.05 ns P>0.05 ns
Oh et al, 2013, Korea	TP 52.3g/d (Men) 45.0g/d(Women) AP 15.8g/d(Men) 12.0g/d(Women) SP 3.1g/d(Men) 2.8g/d(Women) VP 35.5g/d(Men) 32.2g/d(Women)	Ultrasound Calcaneal bone density (stiffness index only)	Men and Postmenopausal Women aged 50-70 years	3330 (2575 in analysis)	Bone Stiffness	Spearmans Rho (Adjusted for age, energy intake, BMI, alcohol, smoking, HRT use, exercise, calcium intake): Men: TP 0.027 AP 0.044 VP -0.026 SP -0.013 VP:AP ratio -0.036 Women: TP 0.030 AP 0.035 VP -0.012 SP -0.014 VP:AP ratio -0.027	 0.347 0.136 0.379 0.656 0.220 0.257 0.195 0.657 0.592 0.318

Orozco et al, 1998, Spain	TP: 73.4(17.9) g/d AP: 49.7(15.3)g/d VP: 23.7(8.7)g/d	DXA	Premenopausal women aged 42years old	76		Unadjusted r values	
					LS BMD	-0.03	ns
					FN BMD	-0.03	ns
					TrochBMD	-0.04* chosen for troch-intertroch analysis	ns
					IntertrochBMD	-0.08	ns
					WardsBMD	-0.05	ns
					Normal (n=64) vs. Osteopenic (n=12): LSBMD	73.5(18.1) g/d vs. 72.8(17.4)g/d	0.9
					Normal (n=64) vs. Osteopenic (n=10): TotalHipBMD	72.8(18.4)g/d vs 77.0(17.7)g/d	0.5
Orwoll et al, 1987, USA	-	CT (vertebrae), SPA (radius)	Study 1: Men Study 2: Men 30-90y	62 92		Unadjusted r values:	
					PRBMC- 1	0.20	Ns
					DRBMC- 1	0.03 *chosen for radius pooled analysis	Ns
					Vertebral BMC-1	0.27 * chosen for men BMC analysis	<0.05
					DRBMC- 2	0.22* chosen for radius pooled analysis	Ns
					PRBMC- 2	0.15	Ns
					Vertebral BMC-2	0.30*chosen for men BMC analysis	<0.01
Pearce et al. 2010, UK	Median: 87.7g/d	Bone Markers	Men aged 49-52 years	412	sCTX	r (95% CI) 0.04 (0.001, 0.1) Unadjusted linear regression coefficient, daily protein intake (per 100g)	0.04
Promislow et al, 2002 USA	72.5g/d	DXA	M/F 55-92y 572F 388M	960		Standardized Beta coefficients (95% CI) Controlling for age, body mass index, calcium intake, years menopausal (women only), diabetes status, current exercise, and current use of estrogen (women only), steroids, cigarettes, alcohol, thiazides, and thyroid hormones	
					TP: per 15g		
					THBMD(F)	0.0094 (-0.0025, 0.0214)	0.12
					FNBMD(F)	0.0063 (-0.0039, 0.0165)	0.22
					TotalSpineBMD(F)	0.0084 (-0.0090, 0.0258)	0.34
					TBBMD(F)	0.0081 (-0.0017, 0.0179)	0.11
					THBMD(M)	-0.0003 (-0.0180, 0.0174)	0.97
					FNBMD(M)	-0.0045 (-0.0202, 0.0112)	0.57
					TotalSpineBMD(M)	-0.0095 (-0.0345, 0.0155)	0.45

					TBBMD(M)	-0.0078 (-0.0212, 0.0057)	0.26
					AP: per 15g		
					THBMD(F)	0.0162 (0.0049, 0.0275)	0.005
					FNBMD(F)	0.0115 (0.0019, 0.0211)	0.02
					TotalSpineBMD(F)	0.0149 (-0.0016, 0.0314)	0.08
					TBBMD(F)	0.0098 (0.0005, 0.0191)	0.04
					THBMD(M)	0.0059(-0.0112,0.0230)	0.50
					FNBMD(M)	0.0007 (-0.0145,0.0159)	0.93
					TotalSpineBMD(M)	-0.0007(-0.0249,0.0235)	0.96
					TBBMD(M)	-0.0036(-0.0167,0.0095)	0.59
					VP: per 5g		
					THBMD(F)	-0.0133 (-0.0219, -0.0047)	0.002
					FNBMD(F)	-0.0102(-0.0175, -0.0028)	0.01
					TotalSpineBMD(F)	-0.0129 (-0.0255, -0.0003)	0.04
					TBBMD(F)	-0.0047 (-0.0121, 0.0026)	0.20
					THBMD(M)	-0.0206(-0.0357,-0.0054)	0.01
					FNBMD(M)	-0.0131 (-0.0267, 0.0006)	0.06
					TotalSpineBMD(M)	-0.0327(-0.0542,-0.0112)	0.003
					TBBMD(M)	0.0124 (-0.0243,-0.0004)	0.04
Quintas et al, 2003, Spain	1.4g-1.7	DPA	Pre F	164		Unadjusted r values	
					RBMC	0.236	P<0.05
					RBMD	0.070	ns
					LSBMC	0.434	p<0.05
					HipBMC	0.412	<0.05
					LSBMD	0.317	<0.05
					HipBMD	0.301	<0.05
Rapuri et al, 2003, USA	53.7-71.2	DXA	Post F-65-77y	473		r values:	
					MRBMD	0.097	0.036
					FNBMD	0.092	0.047
					TrochBMD	0.155	0.001
					TFBMD	0.136	0.003
					LSBMD	0.065	0.163
					TBBMD	0.129	0.005
					NTX	-0.022	0.641
					OC	0.01	0.832

					Baseline:	Protein tertile data:	
					OC (g/L)	4.07±0.012 Q1	0.50
						3.74±0.012 Q2	
						3.81±0.012 Q3	
						3.57±0.012 Q4	
					NTX:Cr ratio	56.2±2.45 Q1	0.50
						51.82±2.45 Q2	
						50.56±2.47 Q3	
						44.35±2.46 Q4	
Rubinacci et al, 1992, Italy	Recent menopause (less than 9 years ago, median age 51y)- 83+/-21.7 g/d	SPA	Post F	120		N=81, recent menopause, unadjusted r	
					Total Protein Intake:	values	<0.001
					DRBMC	0.305* used for pooling	ns
					DRBMC/BW	-0.062	<0.05
					Ultradistal RBMC	0.281	
	Distant menopause (more than 15 years ago, median age 68y) - 68+/-17.6 g/d					N=39 distant menopause, unadjusted r	ns
					DRBMC	values	ns
					DRBMC/BW	0.041 * used for pooling	ns
					Ultradistal RBMC	-0.031	
						-0.111	
Sahni et al. 2013, USA	81g/d (Men) 77g/d (Women)	DXA	1,280 men and 1,639 women	2919		Model 2- adjusted for energy intake, age, height, weight, dietary vitamin D intake (IU/d), vitamin D supplement use (yes/no), Ca supplement use (yes/no), dietary Ca intake (,800 mg/d or $800 mg), current smoking (yes/no), menopausal status (yes/no), current oestrogen use (yes/no) in women alone, caffeine intake (g/d), Physical Activity Scale in the Elderly (PASE), osteoporosis medication use (yes/no) and alcohol intake (none, moderate and heavy intake	
					Cross sectional data:	Standardized coefficients:	
					FNBMD	MEN (N=1268):	0.31
					TrochBMD	Beta (SE)=0.00115 (0.001)	0.28
					LSBMD	Beta(SE)=0.00129 (0.001)	0.72

						Beta(SE)=0.00065 (0.001)	
					FNBMD TrochBMD LSBMD	WOMEN (N=1614): Beta (SE)=0.00185 (0.001) Beta(SE)=0.00200(0.001) Beta(SE)=0.00280 (0.001)	0.04 0.02 0.04
						Model 2- adjusted for energy intake, age, height, weight, dietary vitamin D intake (IU/d), vitamin D supplement use (yes/no), Ca supplement use (yes/no), dietary Ca intake (,800 mg/d or $800 mg), current smoking (yes/no), menopausal status (yes/no), current oestrogen use (yes/no) in women alone, caffeine intake (g/d), Physical Activity Scale in the Elderly (PASE), osteoporosis medication use (yes/no) and alcohol intake (none, moderate and heavy intake).	
						Beta(SE)	
					Bone change data: FNBMD TrochBMD LSBMD	MEN (N=493): Beta (SE)=-0.0052(0.019) Beta(SE)=-0.0498 (0.020) Beta(SE)=-0.0062(0.019)	 0.78 0.01 0.75
					FNBMD TrochBMD LSBMD	WOMEN (N=673): Beta (SE)=-0.0131(0.017) Beta(SE)=-0.0288(0.21) Beta(SE)=0.0042 (0.018)	 0.44 0.21 0.81
Tanaka et al, 2001, Japan	1.3	Ultrasonic Bone Absorptiometry	Pre F-18-22y	965		Regression B (Unstandardized) Coefficient, adjusted for age, weight, height, exercise, menstrual	

						status and daily nutrient intakes (energy,	
					OSI calcaneus	Ca, Phosphorus, Sodium)	0.009
						0.234	
Teegarden et al, 1998, USA	1.21	DXA	Young pre F	215		Unadjusted r values:	
					TBBMD	0.11	Ns
					RBMD	0.16	<0.05
					LSBMD	0.19	<0.05
					FNBMD	0.08	Ns
					TrochBMD	0.10	Ns
					WBMD	0.08	Ns
					TBBMC	0.12	Ns
					RBMC	0.08	Ns
					Spine BMC	0.23	<0.05
						Unstandardized B (SE) adjusted for postmenarchal age, lean and fat mass,:	
					TBBMD	0.0016+/-0.0006	<0.05
					TBBMC	6.95+/-2.09	<0.05
					SpineBMD	0.0029+/-0.0013	<0.05
					SpineBMC	0.1823+/-0.068	<0.05
Thorpe et al, 2008, USA	74.7g/d	DXA	Postmenopausal women mean age 68+/-6 years	161	LSBMD	-0.01	0.94
					TotalHipBMD (non adjusted, Spearmans)	0.08	0.30
						Unstandardized correlation coefficient:	
					LSBMD	B(SE): controlling for body weight and sulphur intake	0.04
						1.35x10-3 (6x10-4)	
Tylavsky and Anderson, 1988, USA	1.01	SPA	60-98y elderly F	375		□ coefficient	
					DRBMC	2.72	0.03
					DRBMD	0.63	0.25
					MRBMC	2.96	0.003
					MRBMD	1.36	0.06
Vatanparast et al, 2007, Canada	20-25 years: 68+/-22(F) and 119+/-53 (M)	DXA	Young adults (59 males, 74 females). Measured at	133		Unstandardized Beta+/-SE (adjusted for sex, current height and weight, physical activity level, and other dietary nutrients)	
	Periadolescence: 64.2+/-17 (F) and 79.6+/-17 (M)		both periadolesence and young			<u>Current protein intake (young adult)</u>	
					TBBMC	NS (not entered into stepwise model)	ns
					TBBMD	NS (not entered into stepwise model)	ns

			adulthood (20-25 y)		TBBMC net gain	0.33 +/- 0.042	<0.001
						Unstandardized Beta+/-SE (adjusted for sex, current height and weight, physical activity level, and other dietary nutrients) Females only with adequate calcium at pert-adolescence/early adulthood	
						0.21+/- 0.095	
					TBBMC	0.21+/-0.080	<0.05
					TBBMC net gain	0.32+/-0.32	<0.05
					TBBMD		<0.05
Wang et al, 1997, USA	0.97	DXA	Older post F	125	LSBMD	0.04	Ns
					FNBMD	-0.01	Ns
						Spearmans correlations	
Wang et al. 1999, USA	1.05 g/Kg/d	QUS	18-18 year old women	63	Bone indices at18-19 years	Protein intake when aged 9-11 years:	
						Spearmans Rho	
					BUA	0.16	ns
					BV	0.27	<0.05
					SOS	0.25	Ns
						Pearson's:	
					BUA	0.11	Ns
					BV	0.21	Ns
					SOS	0.17	Ns
						Coefficients not shown for multiple regression as ns for protein (adjusted for calcium, magnesium, vitamin C, race, height and weight)- no effect size	
Weikert et al, 2005, Germany	67.9g/d	QUS/BUA	F 35-67y	8178	Os calcis	Beta (Standardized) coefficient	
					TP	-0.03 (0.013)	0.017
					AP	-0.03 (0.012) (controlling for VP)	0.010
					VP	0.11 (0.042) (controlling for AP)	0.007
					AP:VP ratio	-1.12 (0.31) (controlling for TP)	<0.001
					TP	0.014 (0.017) (controlling for AP:VP ratio)	0.41
						Pearson's Correlations: r	

					VP	0.03	0.009
					AP	0.02	0.015
					TP	0.03	0.002
Whiting et al, 2002, Canada	1.15	DXA	M 39-42y	57		Pearson's correlations:	
					TBBMD	0.383(adj)	<0.01
					LSBMD	0.419 (adj)	<0.01
					THBMD	0.322 (adj)* chosen for pooling men as closest to Jaime -controlling for anthropometry and energy intake	<0.05
					TBBMD	Linear regression: (non-standardized B) 0.00193 (0.00065) Adjusted for lean body mass, height, fat mass, energy intake	<0.01
Yazdanpanah et al, 2007, The Netherlands	81.3g/d , 1.1g/Kg/d	DXA	Men and Women aged 55 years and over	5304		Standardized Beta coefficient (adjusted for age, BMI, other dietary nutrients, sex) Protein intake:	
					FNBMD	-0.03	0.29
					LSBMD	-0.03	0.27
Zhang et al. 2010, China	1.7 g/Kg/d	DXA	Girls (Mean age 10 years)	757		Beta(adjusted for baseline bone mass, tanner stage, age, physical activity). Beta represents % change with doubling of protein intake: All participants:	
					DRBMC	-4.82	
					DRBMD	-3.18	<0.01
					DRBA	~	<0.01
					PRBMC	-10.2	-
					PRBMD	~	<0.01
					PRBA	-9.11	- <0.01
					TBBMC	-1.92	
					TBBMD	~	0.02
					TBBA	~	-
						~=not entered into stepwise regression	-

* simple r coefficients unless otherwise stated; for r2 the brackets indicate if corresponding regression coefficient + or - ** total protein in g/Kg/d unless otherwise stated. ALP= Alkaline Phosphatase; AP=animal protein; BMC=Bone Mineral Content; BMD=Bone Mineral Density; BUA-Broadband Ultrasound Attenuation; BV=Bone Volume; Calc=Calcaneus; Cr=Creatinine; Deoxypyd=Deoxypyridinoline; DRBA=Distal Radial Bone Area; DRBD=Distal Radial Bone Density; DTB=Distal Tibial; DXA=Dual X-ray Absorptiometry; FN=Femoral Neck; FNBA=Femoral Neck Bone Area; FNBMD=Femoral Neck Bone Mineral Density; FNvBMD=Femoral Neck volumetric Bone Mineral Density; FSBMD=Femoral Shaft Bone Mineral Density; HBMD=Humerus Bone Mineral Density; HPO=Hydroxyproline; HumBMC=Humerus Bone Mineral Content ;IntertrochBMD=Intertrochanter Bone Mineral Density; LSBMC=Lumbar Spine Bone Mineral Content; LSBMD=Lumbar Spine Bone Mineral Density; MRBMC Midradial Bone Mineral Content; MRBMD Midradial Bone Mineral Density; OC=Osteocalcin; P1NP= Procollagen type 1 N-terminal propeptide; PC=Periosteal Circumference; pQCT=Peripheral Quantitative Computed Tomography; PRBMC=Proximal Radial Bone Mineral Content; PYD=Pyridinoline; QUS=Quantitative Ultrasound; R=Radial RBMC=Radial Bone Mineral Content; sBAP=serum Bone Alkaline Phosphatase; sCTX serum C-telopeptide of collagen; sOC serum Osteocalcin; SP=Soy Protein; SSI=Stength Strain Index; Stand.=Standardised; TBBA=Total Body Bone Area; TBBMD Total Body Bone Mineral Density; TP=Total Protein; TrochBMD=Trochanter Bone Mineral Density; UBMC=Ulna Bone Mineral Content; uNTX=Urinary n-telopeptide of collagen; vBMD=volumetric Bone Mineral Density; VP=Vegetable Protein; WBBMC=Whole Body Bone Mineral Content; WBBMD=Whole Body Bone Mineral Density

Table S2 Pooled r values for protein intake and bone health for gender and age subgroups (non-adjusted data)

Parameter	Model	r	R^2	Lower limit	Upper limit	p	I^2	Total n	Included Studies
MEN BMD	Fixed	0.1201	0.01	0.0291	0.2091	0.010	44%	470	Coin, Jaime(Black), Jaime(White), Whiting
	Random	0.1549	0.02	0.0184	0.2858	0.026			
MEN BMC	Fixed	0.2881	0.08	0.1346	0.4281	0.0003	0%	154	Orwoll(group 1), Orwoll (group 2)
	Random	0.2881	0.08	0.1346	0.4281	0.0003			
POST F BMD	Fixed	0.1148	0.01	0.0791	0.1502	<0.001	1%	2987	Alissa 2014, Cooper, Chiu, Devine, Gunn, Horiuchi, Lau, Rapuri, Thorpe 2008, Wang 1997
	Random	0.1147	0.01	0.0787	0.1503	<0.001			
POST F BMC	Fixed	0.181	0.03	0.0618	0.2941	0.003	0%	267	Freudenheim, Lacey, Rubinacci (Early Post), Rubinnacci (Late Post)
	Random	0.181	0.03	0.0618	0.2941	0.003			
PRE F BMD	Fixed	0.0748	0.01	0.0384	0.1111	<0.001	74%	2896	Chan 2009, Chiu, Cooper, Gregg, Henderson, Hirota, Lau, New, Orozco, Quintas
	Random	0.1158	0.01	0.0376	0.1925	0.004			
PRE F BMC	Fixed	0.2834	0.08	0.1986	0.3640	<0.001	47%	485	Freudenheim, Lacey, Teegarden, Quintas
	Random	0.2748	0.08	0.1442	0.3959	<0.001			
OLDER ADULT (OVER 60 YEARS) M/F BMD	Fixed	0.1131	0.01	0.0736	0.1522	<0.001	0%	2448	Chiu, Coin, Devine, Gunn, Lau, Rapuri, Thorpe2008, Wang1997
	Random	0.1131	0.01	0.0736	0.1522				
CHILD M/F BMC*	Fixed	0.3154	0.10	0.2251	0.4003	<0.001	0%	416	Bounds, Chevalley 2008, Ekbote, Hoppe

Random	0.3154	0.10	0.2251	0.4003	<0.001

BMD=Bone Mineral Density BMC=Bone Mineral Content n=number of partipcnats in analysis *only radius BMC and total body BMC available for pooling. Where studies have multiple outcomes eligible for inclusion, choice of measures for pooling was as follows: Hip indices (first choice), Spine indices (2nd choice), Radial indices (3rd choice).

Table S3: Pooled r values for protein intake and bone health by outcome (non-adjusted data)

Parameter	Model	r	R^2	Lower limit	Upper limit	p	I^2	Total n	Included Studies
ADULTS									
TBBMC	Fixed	0.12	0.01	0.0662	0.1683	<0.001	73%	580	Ho, Loenekke, Meng, Teegarden,
	Random	0.14	0.02	0.0133	0.2622	0.0304			
DEPYD	Fixed	-0.23	0.05	-0.3859	-0.052	0.01	0%	128	Horiuchi, Nakamura
	Random	-0.23	0.05	-0.3859	-0.052	0.01			
FNBMD	Fixed	0.07	0.00	0.0374	0.0942	<0.001	26%	4786	Alissa 2014, Chan 2009, Chiu, Coin, Cooper (post), Cooper (pre),
	Random	0.07	0.00	0.0391	0.1090	<0.001			Gunn, Henderson, Ho, Jaime(Black), Jaime (White), Kumar, Lau, Michaelsson, New, Orozco, Rapuri, Teegarden, Wang
FEMORAL SHAFT BMD	Fixed	0.06	0.00	-0.0394	0.1563	0.240	0%	405	Cooper(post), Cooper(pre), Henderson
	Random	0.06	0.00	-0.0394	0.1563	0.240			
TROCH/INTTROCH BMD	Fixed	0.09	0.008	0.0528	0.1330	<0.001	68%	2375	Coin, Cooper (post), Cooper (pre), Henderson, Lau, New, Orozco, Rapuri, Teegarden
	Random	0.12	0.014	0.0401	0.2027	0.004			
TOTAL HIP BMD	Fixed	0.09	0.008	0.0389	0.1491	0.001	86%	1259	Alissa 2014, Chan 2009, Coin, Quintas, Thorpe M, Whiting
	Random	0.14	0.02	-0.0118	0.2919	0.07			
WARDS BMD	Fixed	0.02	0.0004	-0.0325	0.0654	0.51	0%	1616	Kumar, Lau, New, Orozco, Teegarden
	Random	0.02	0.0004	-0.0325	0.0654	0.51			
HUMERUS BMC	Fixed	0.16	0.03	-0.0613	0.3648	0.16	0%	84	Freudeneheim (Post), Freudenheim (Pre)
	Random	0.16	0.03	-0.0613	0.3648	0.16			
HYDROXYPROLINE	Fixed	-0.07	0.00	-0.1838	0.0466	0.24	68%	290	Cooper (post), Cooper (pre)
	Random	-0.11	0.01	-0.3363	0.1240	0.35			
LSBMD	Fixed	0.07	0.005	0.0410	0.1012	0.0001	58%	4257	Chiu, Cooper (post), Cooper (pre), Henderson, Ho, Horiuchi, Kumar,
	Random	0.09	0.008	0.0373	0.1385	0.0007			Lau, Michaelsson, Quintas, Rapuri, Thorpe M, Teegarden, Wang, Whiting
LSBMC	Fixed	0.31	0.10	0.2329	0.3876	<0.001	41%	533	Orwoll (group 1), Orwoll (group 2), Teegarden, Quintas
	Random	0.31	0.10	0.2057	0.4146	<0.001			
RADBMD	Fixed	0.07	<0.01	0.0180	0.1267	0.009	53%	795	Cooper (post), Cooper (pre), Hirota, Quintas, Rapuri, Teegarden
	Random	0.07	<0.01	-0.0101	0.1574	0.084			
OSTEOCALCIN	Fixed	0.00	0.00	-0.0817	0.0809	0.99	40%	593	Cooper (post), Cooper (pre), Horiuchi, Nakamura, Michaelsson
	Random	-0.01	0.00	-0.1175	0.1039	0.90			
RADBMC	Fixed	0.16	0.026	0.0987	0.2268	<0.001	0%	915	Freudeneheim (Post), Freudenheim (Pre), Lacey (Pre), Lacey (Post),
	Random	0.16	0.026	0.0987	0.2268	<0.001			Orwoll (group 1), Orwoll (group 2), Quintas, Rubinacci (early post), Rubinacci (late post), Teegarden
TOTAL BODY BMD	Fixed	0.17	0.03	0.114	0.2334	<0.001	59%	1028	Knurick, Loenekke, Michaelsson, Rapuru, Teegarden, Whiting

	Random	0.22	0.05	0.0114	0.3263	<0.001			
ULNABMC	Fixed	-0.02	0.00	-0.2395	0.197	0.84	0%	84	Freudeneheim (Post), Freudenheim (Pre)
	Random	-0.02	0.00	-0.2395	0.197	0.84			
TOTALHIP BMC	Fixed	0.16	0.026	0.0766	0.2330	0.001	94%	602	Ho, Quintas
	Random	0.24	0.06	-0.1358	0.5494	0.211			
	Random	0.13	0.02	0.0771	0.1913	<0.001			
CHILDREN									
ALL BMC*	Fixed	0.32	0.10	0.2251	0.4003	<0.001	0%	416	Bounds, Chevalley 2008, Ekbote, Hoppe
	Random	0.32	0.10	0.2251	0.4003	<0.001			
TBBMC	Fixed	0.37	0.14	0.2386	0.4927	<0.001	0%	184	Bounds, Ekbote, Hoppe
	Random	0.37	0.14	0.2386	0.4927	<0.001			
TBBA	Fixed	0.48	0.23	0.3591	0.5892	<0.001	79%	176	Ekbote, Hoppe
	Random	0.46	0.21	0.1641	0.6821	0.003			
TBBMD	Fixed	-0.02	0.0004	-0.1322	0.0901	0.71	87%	314	Bounds, Jones
	Random	0.11	0.01	-0.3055	0.4853	0.62			

All pooled effects calculated in R using 'meta' and 'metacor' packages, which use the inverse variance method, DerSimonian and Laird (random effects models) and Fisher's Z Transformation. BMD=Bone Mineral Density DEPYD=Deoxypyridinoline FNBMD= Femoral Neck Bone Mineral Density INTTROCH=Intertrochanter LSBMC=Lumbar Spine Bone Mineral Content LSBMD=Lumbar Spine Bone Mineral Density RADBMC= Radial Bone Mineral Content RADBMD= Radial Bone Mineral Density TBBA=Total Body Bone Area, TBBMC=Total Body Bone Mineral Content, TBBMD=Total Body Bone Mineral Density TROCH=Trochanter ULNABMC=Ulna Bone Mineral Content

Table S4 Associations between protein dose, calcium dose and calcium:protein ratio and FNBMD and LSBMD (non-adjusted for confounders)

Linear Model

X	**r for FNBMD**				**r for LSBMD**				**Actual FNBMD**				**Actual LSBMD**			
Model	Estimate*	SE	Model P	N studies	Estimate *	SE	Model P	N studies	Estimate *	SE	Model P	N studies	Estimate *	SE	Model P	N studies
Protein (g/kg/d)	-0.05	0.16	0.76	16	0.25	0.18	0.19	14	0.39	0.15	0.02	19	0.33	0.13	0.02	16
Calcium (mg/kg/d)	-0.01	0.008	0.17	16	0.007	0.01	0.57	17	0.02	0.010	0.06	19	0.02	0.010	0.06	17
Ca:Prot ratio (mg/g/d)	-0.01	0.01	0.20	18	-0.008	0.02	0.63	17	0.0005	0.013	0.97	19	0.005	0.01	0.74	17

*Intercept not shown for clarity. Equation: y=x+c (where c=intercept, y=dependent variable). Note: No results were statistically significant after Bonferroni correction (36 tests, 0.05/36=0.001) Note: some studies had Ca:Prot ratio but not protein or calcium. This is because for some studies the body weight was not given so protein in g/Kg/d was not calculated. However, if studies gave Ca mg/d and Protein g/d the Ca:Prot ratio could still be calculated for these studies. Ca=Calcium FNBMD=Femoral Neck Bone Mineral Density LSBMD= Lumbar Spine Bone Mineral Density N Studies =Number of studies Prot=Protein SDE=Standard Error

Quadratic model

X^2	r for FNBMD				r for LSBMD				Actual FNBMD				Actual LSBMD			
Model	Estimate*	SE	Model P	N studies	Estimate *	SE	Model P	N studies	Estimate *	SE	Model P	N studies	Estimate *	SE	Model P	N studies
Protein^2 (g/kg/d)	-1.28	1.16	0.53	16	1.26	0.87	0.17	14	0.33	0.77	0.06	19	0.28	0.70	0.08	16
Calcium^2 (mg/kg/d)	-0.0007	0.003	0.40	16	0.002	0.004	0.75	17	0.0003	0.003	0.18	19	-0.0004	0.003	0.19	17
Ca:Prot ratio^2 (mg/g/d)	-0.002	0.003	0.38	18	-0.003	0.004	0.75	17	-0.002	0.004	0.89	19	1.3×10^{-5}	4.4×10^{-3}	0.95	17

*Other model estimates not shown for clarity. Ca=Calcium, Prot=Protein. Equation: $y=x+x^2+ c$ (where c=intercept, y=dependent variable). Note: No results were statistically significant after Bonferroni correction (36 tests, 0.05/36=0.001). Note: some studies had Ca:Prot ratio but not protein. This is because for some studies the body weight was not given so protein in g/Kg/d was not calculated. However, if studies gave Ca mg/d and Protein g/d the Ca:Prot ratio could still be calculated for these studies. Ca=Calcium FNBMD=Femoral Neck Bone Mineral Density LSBMD= Lumbar Spine Bone Mineral Density N Studies =Number of studies Prot=Protein SDE=Standard Error

Cubic model

X^3	r for FNBMD				r for LSBMD				Actual FNBMD				Actual LSBMD			
Model	Estimate*	SE	Model P	N studies	Estimate *	SE	Model P	N studies	Estimate *	SE	Model P	N studies	Estimate *	SE	Model P	N studies
Protein^3 (g/kg/d)	0.06	0.40	0.74	16	-0.10	0.46	0.33	14	-0.90	0.36	0.01	19	-0.84	0.29	0.009	16
Calcium^3 (mg/kg/d)	-0.0006	0.001	0.56	16	-0.0008	0.002	0.86	17	4.9 x 10-5	1.4 x 10 -3	0.35	19	-0.0003	0.001	0.35	17
Ca:Prot ratio^3 (mg/g/d)	-0.001	0.001	0.51	18	-0.0002	0.002	0.91	17	-0.001	0.002	0.84	19	-0.003	0.002	0.58	17

*Other model estimates not shown for clarity. Ca=Calcium, Prot=Protein. Equation: $y=x+x^2+x^3+ c$ (where c=intercept, y=dependent variable) Note: No results were statistically significant after Bonferroni correction (36 tests, 0.05/36=0.001). Note: some studies had Ca:Prot ratio but not protein. This is because for some studies the body weight was not given so protein in g/Kg/d was not calculated. However, if studies gave Ca mg/d and Protein g/d the Ca:Prot ratio could still be calculated for these studies. Ca=Calcium FNBMD=Femoral Neck Bone Mineral Density LSBMD= Lumbar Spine Bone Mineral Density N Studies =Number of studies Prot=Protein SDE=Standard Error

Table S5: Characteristics and outcomes of the 29 studies reporting fracture or osteoporosis diagnosis data (6 of which also in Table 1)
a) 14 Cohort studies

Study	Mean Protein *	Population	Length	Total n	Fracture / BMD site	Protein type	RR **≠	95% CI	P value	Confounder Adjustments
Beasley et al. 2014, USA	<13.3% to ≥15.6% of energy intake from protein	Women aged 50-79 y at baseline	6y	144,580	Any Hip Spine Forearm	TP TP TP TP	HR: 0.99 0.91 1.05 0.93	(0.97, 1.02) (0.84, 1.00) (0.98, 1.13) (0.88, 0.98)	- - - -	Age, BMI, race-ethnicity, calibrated energy intake, general health, physical activity, history of fracture at age 55 y, history of parental fracture, current smoking, corticosteroid use, glucocorticoid use, treated diabetes, rheumatoid arthritis, and hormone use
Dargent-Molina et al, 2008, France E3N study	TP: 46(7.5)g/d AP:29 (8.8) g/d VP: 12(3.0)g/d	Postmenopausal women	8.37 (1.73) y	36217 (2408 with incident fracture, 33809 fracture free)	Any low impact fracture	Energy adjusted TP AP VP	1.06 1.10 0.95	0.94-1.19 0.98-1.24 0.85-1.06	- - -	(Also has calcium intake stratification data) Adjusted for BMI, physical activity, parity, maternal history of hip fracture, HT use, smoking status, and alcohol intake
Feskanich et al, 1996, USA	79.6g/d median	Caucasian F, 35-59y	12y	85,900	FF HF	AP TP VP AP TP VP	1.25 1.22 0.9 0.98 0.96 1.11	1.07-1.46 1.04-1.43 0.77-1.06 0.65-1.47 0.64-1.45 0.75-1.66	0.004 0.01 0.17 0.7 0.7 0.58	Adjusted for questionnaire time period; age (5-year intervals), BMI and hours of vigorous activity per week (qulntjles); menopause) status and use of postmenopausal hormones (premenopausal, postmenopausal-never user, postmenopausal-past user, postmenopausal-current user); cigarette smoking (never, past, current); use of thyroid hormone medication and thiazlde diuretics (yes or no); and alcohol and caffeine Intakes (quintiles).

Study	Mean Protein *	Population	Length	Total n	Fracture / BMD site	Protein type	RR **≠	95% CI	P value	Confounder Adjustments
Gunn et al, 2014, New Zealand	79g/d	Bone markers, DXA	POM women, 60 years of age	142	Osteoporosis diagnosis)	TP Mean(SD) Protein intake by category:	BMD: Normal 79(21) Mild Osteopenia 83(18) Significant osteopenia 77(22) Osteoporosis 76(21)	n 51 21 53 17	NS	Non confounder adjusted
Key et al, 2007, UK	Women: 73.1 (21.6) g/d 77.8(22.6)g/d	26 749 women and 7947 men aged 20–89 years.	5.2y	26 749 women, 7947 men, aged 20–89 years	All sites, incident fractures (including high trauma fractures, but still 72% from a fall)	TP: Women n=362 fractures Men n=76 fractures	Incident Rate Ratio: 0.97 1.29	0.74-1.27 0.72-2.31	0.55 0.68	Confounder adjusted: Method of recruitment and adjusted for age, smoking, intakes of energy and each other nutrient, alcohol consumption, body mass index, walking, cycling, vigorous exercise, other exercise, physical activity at work, marital status and, for women, parity and use of hormone replacement therapy
Langsetmo et al, 2015, Canada	TP: 0.79(0.60-1.03) AP (Non-dairy): 17.6(12.8-23)g/d	Men and Women, aged 25-49 and ≥50 years	5y	6510	Fragility fracture: n=4543	TP: Men Women :	HR= 0.66 0.85	0.35-1.24 0.67-1.09	-	Confounder adjusted: Age, height, TEI, center (women only), education, smoking, alcohol intake, physical activity, sedentary hours, calcium and vitamin D supplement use, hormone therapy (women only), bisphosphonate use (women only), and diagnosis of osteoporosis (women only);

Study	Mean Protein *	Population	Length	Total n	Fracture / BMD site	Protein type	RR **≠	95% CI	P value	Confounder Adjustments
	VP: 24.3(18.8-31.0)g/d				Main fracture: n=4570	TP: Men Women:	0.55 0.90	0.28-1.09 0.69-1.19	-	
Meyer et al, 1997, Norway	0.8	M/F (mean age 47.1y)	11.4y	19752 F 20035 M	HF- F HF-M	 AP AP	 0.96 1.3	Q4= highest: 0.62-1.49 0.63-2.68 Q1=reference, RR=1, lowest	 0.37 0.48	Adjusted for age at screening, body height, body mass index, serf-reported physical activity at work and during leisure time, diabetes mellltus, disability pension, marital status, and smoking
Misra et al, 2011, USA	64g/d (energy adjusted)	Men and women mean age=75 years	11.6y	946 (n=100 had hip fracture)	HF	TP: M/F (n=100) F (n=80)	HR= 0.63 0.82	 0.37-1.09 0.44-1.51	 - -	Confounder adjusted: age, sex, weight, height and total energy intake
Munger et al, 1999, USA	1.2	Postmenopausal F (55-69y)	1-3y	32 050	HF	 AP TP VP	RR= 0.31 0.44 1.92	 0.10-0.93 0.16-1.22 0.72-5.11	 0.037 0.049 0.11	Age, body mass index, number of pregnancies, smoking, alcohol use, estrogen use, and physical activity.
Mussolino et al, 1998, USA	<56g/d - >98g/d	Caucasian M (45-74y)	22y	2879	HF	 TP	RR: 0.55	 0.20-1.55	 -	BMI, previous fracture, smoker, physical activity, alcohol, chronic health condition, calcium intake, weight loss.
Sahni et al, 2010, USA **Framingham Offspring Study**	Men TP: 79.0(27) g/d AP: 54.3(22) VP: 24.6(9)	Men and women aged mean= 55 (9.9)years	7 to 14 years	3656	HF	Low calcium intake (<800 mg/d) n=2124:	HR for highest tertile of protein intake:			Adjusted for sex and menopause status (group 1: men; group 2: premenopausal women; group 3: postmenopausal women), age (years), weight at baseline (kg), height at baseline (m), physical activity index, intake of energy (MJ/day) and total vitamin D (IU/day), and smoking status (current versus former/never) and calcium intake

Study	Mean Protein *	Population	Length	Total n	Fracture / BMD site	Protein type	RR **≠	95% CI	P value	Confounder Adjustments
	Women: TP:75.7(27) AP: 52.5(22) VP: 23.1(9)					Energy adjusted TP: g/d AP:g/d VP:g/d AP:VP ratio	2.20 3.17 0.60 1.81	0.88-5.54 1.30-7.78 0.20-1.85 0.68-4.86	0.09 0.01 0.34 0.29	
						High calcium intake (≥800 mg/d) n=1532				
							0.54	0.12-1.30	0.38	
						Energy adjusted TP: g/d AP:g/d VP:g/d AP:VP ratio	0.32 0.23 2.02	0.05-2.08 0.05-1.03 0.37-11.05	0.33 0.06 0.32	
Sellmeyer et al, 2001, USA	49.8g/d	Caucasian F aged over 65y	7.0y +/- 1.5y	1035	Hip Fracture	VP Ratio AP:VP AP	0.3 3.7 2.7	- - -	0.03 0.04 0.04	Age and body weight
Zhong et al, 2009 USA	Mean(SE)=61+/-0.8 g/d	Postmenopausal women at least 50 y of age	<7y	2006	All fragility fractures (hip, wrist, spine)	TP	OR data	Data in Figure Only	-	Age, race, body mass index (underweight/normal, overweight, obese), physical activity level, smoking status, alcohol use (heavy, moderate/none), hormone use, general health status, osteoporosis, arthritis, vision impairment, and stroke.

Study	Mean Protein *	Population	Length	Total n	Fracture / BMD site	Protein type	RR **≠	95% CI	P value	Confounder Adjustments
Zhang 2005	SP: 9.6g/d Non Soy: 134g/d	Women aged 40-70 years old	4.5 y	24403	All fractures	SP	<4.98 g/d (Reference) ≥13.27 g/d 0.63	0.53-0.76	<0.001	Age, body mass index, hours of exercise per week, cigarette smoking, alcohol consumption, history of diabetes mellitus, level of education, family income, season of recruitment, and intakes of total calories, calcium, non-soy protein, fruits, and vegetables

AP, Animal Protein; BMD, Bone Mineral Density; DXA, Dual X-ray Absorptiometry; HF, Hip Fracture; HR, Hazard Ratio; POM, Postmenopausal; RR, Relative Risk; SP, Soy protein; TEI, Total Energy Intake; TP, Total Protein; VP, Vegetable Protein

4b.2 Cross cultural studies

Study	Mean Protein **	Method	Population	n	Outcome	Coefficient*	p	Confounders
Abelow et al, al1992, USA cross cultural	10.4g/d-77.8g/d AP	Fracture	F over 50y	34 studies 16 countries	Hip fracture and animal protein	r2=0.66(+) (by study) r2=0.67 (+) (by country)	<0.001 <0.001	Age adjusted
Frassetto et al, 2000, USA Cross Cultural	48 to 110.9 g/d	Fracture	F aged over 50y	33 countries	Hip fracture TP AP VP	 0.67; 0.82; -0.370;	 p<0.001 p<0.001 p<0.04	Age. Also, for AP, TP and VP

AP, Animal Protein; TP, Total Protein; VP, Vegetable Protein

4c 13 Case control studies

Study	Protein intake*	Population	n	Site	Group/outcome	OR**≠	p	Confounders
Alissa et al, 2011, Saudi Arabia Non-Prospective	77g/d	DXA	Postmenopausal women, aged 50-60 years	122	Normal BMD Osteopenic	Dietary protein intake g/d 77.5 76.6	 ns	Non adjusted for confounders
Chevalley et al. 2011, Switzerland	Age 7.4 (0.4): 1.78 (0.46) Age 15.2(0.5): 1.08 (0.41)	DXA	Caucasian boys- measured during pre-puberty and adolescence	176	Age 7: Without Fracture: n=89 With Fracture: n=87 Age 15: Without Fracture :n=89 With Fracture: n=87	Dietary Intake, (g/d) 48.5 (13.3) 45.2(11.1) 65.4 (24.1) 61.2 (23.1)	 0.08 0.24	Non adjusted for confounders
Chiu et al, 1997, Taiwan **Non-Prospective**	1.09	DPA (BMD)	Older POM F	258	Osteopenia of: Lumbar Spine Femoral Neck	Energy intake from protein (%) 0.51 (0.30-0.89) 0.71 (0.33-1.54)	- Significant NS	Adjusted for age, BMI, physical activity, calcium intake, non-protein energy intake, long term vegan/vegetarianism
Coin et al, Italy, 2008 **Non-Prospective**	75.8+/-22.1 g/d Weight=74.2+/-13.4 So 1.02 g/Kg/d	DXA	Males, mean age 73.9+/-5.6 years	136	Only data for men included protein in model: MEN Protein<65.7g/d Protein>=65.7g/d	OR (95% CI) of low total hip BMD<=0.83h/cm2) 3.69 (1.40-9.70) 1.00	 0.008 -	Adjusted for BMI
Farrin et al. 2008, Iran	81.4g/d	DXA	Postmenopausal Women	58	LSBMD based diagnosis: Normal Osteopenic	Mean (SD) Protein intake:g/d 68.7 +/- 5.0 95.5+/- 67.6	One way ANOVA p<0.05	Unadjusted

Non-prospective					Osteoporotic	67.6+/-5.3	Post hoc tests: Normal-Osteopenia: P=0.009 Normal-Osteoporotic P=0.75	
Kim et al, 2008, Korea **Non-prospective**	TP= 60g/d AP= 19g/d VP= 40g/d	DXA	Postmenopausal women, 134 osteoporotic cases and 137 non-osteoporotic controls	271	Osteoporotic (n=134) Non-Osteoporotic (n=137)	OR for Osteoporosis by protein intake: TP: g/d Lowest 1.0(reference) Middle 0.91 (0.68-1.21) Highest 1.47 (1.03-2.05)	P=0.004	Adjusted for age, smoking, alcohol drinking, BMI, exercise, family history of osteoporosis, and energy intakes
					Osteoporotic (n=134) Non-Osteoporotic (n=137)	AP: g/d Lowest=1.0 (reference) Middle= 1.21(0.58-2.52) Highest= 1.62(1.03-3.92)	P=0.03	
					Osteoporotic (n=134) Non-Osteoporotic (n=137)	VP: g/d Lowest=1.0(reference) Middle=0.62(0.31-1.23) Highest=0.42(0.23-0.83)	P=0.011	
Martinez-Ramirez et al, 2012, Spain	TP:105 (1.0) g/d AP:66-70 (1.3) g/d VP: 38 (0.63)g/d	Aged 65 years or over, cases from hospital record and	167 cases and 167 controls	All low energy fractures (e.g. from a fall)	TP AP VP AP:VP ratio	OR: 1.10 (0.18, 6.80) 0.38 (0.10-1.41) 0.52(0.16-1.65) 0.75(0.14-3.99)	0.291 0.115 0.460 0.121	Adjusted for age, sex, energy intake, vegetable protein intake or animal protein intake (according to the analysis), serum vitamin C, calcium intake, underlying

Non-Prospective	AP:VP ratio: 2 (0.1) g/d	controls drawn from local community population, 80% female						chronic disease, home access, Katz's index, physical activity (METS), HDL cholesterol, and MUFA/PUFA intake.
Nieves et al, 1992, USA **Non-prospective**	<24g/d to >55g/d	F 50 to 103y	329 (161 cases, 168 controls)	Hip (OR)	Hip fracture	1.04 (0.43, 2.55)	ns	Hospital, age, BMI, oestrogen use, chronic disease status
Park et al, 2014, Korea **Non-prospective**	81.93+/-52.31 g/d	Z score from DXA	Young Women	1157	Z-Score ≥0 (n=171) Z-score<0 (n=986)	Protein Intake g/d: 85.96+/-55.81 81.23+/-51.67	 0.276	Non-adjusted
Perez-Durillo et al, 2011, Spain **Non-prospective**	Cases 60 (19)g/d; controls 94 (19) g/d	Women older than 65 y, medical outpatients	44 cases and 42 controls	HF	% energy TP TP intake: (n=86)	16.7 (4.7)% (cases (3.0)%) vs 18.3 (control) OR of being a case: (continuous protein intake) 0.96	0.07 0.92-1.00	Non adjusted BMI, carbohydrate intake and calcium intake
Preisinger et al, 1995, Austria **Non-prospective**	15 % total energy, 45-96 g/d	Osteoporosis diagnosis	Post F 50-70 years old	23	 Group 1-Osteoporotic n=12 Group 2 Non-osteoporotic n=11	<u>Protein intake % mean+/-SEM</u> <u>TP</u> 15.5+/-0.9 15.4+/-0.9 AP (g/d) 46.9+/-4.1	 NS	Non adjusted

					Group 1- Osteoporotic n=12 Group 2 Non-osteoporotic n=11 Group 1- Osteoporotic n=12 Group 2 Non-osteoporotic n=11	42.8+/-3.3 VP (g/d) 25.0+/-4.1 25.4+/-2.3		
Samieri et al, 2013, France **Prospective**	70-76 g/d	Men and women 65y and over	1482	Incident fracture of hip, spine or wrist	Cases (n=155) Controls(n=1327)	70.4 (26.3) g/d 75.8 (26.8) g/d Baseline protein intake	0.02	Not adjusted for confounders
Wengreen et al, 2004, USA **Non-prospective**	1.2g/Kg/d	50-89y M/F	2501 (1157 cases, 1334 controls	Hip (OR)	50-69y (TP) 70-89y (TP) 50-69y (AP) 70-89y (AP) 50-69y (VP) 70-89y (VP)	0.35 1.28 0.43 1.54 0.52 0.79	<0.001 0.06 0.21 0.95 0.19 0.46	BMI, smoking, alcohol, physical activity, oestrogen use, gender, total Calcium and Vitamin D intakes (diet and supplements), potassium intake, age. AP model also adjusted for VP intake, VP model also adjusted for AP intake.

*in g/Kg/d unless otherwise stated, * *(Highest Quartile/Quintile of intake, lowest quartile=1),≠OR unless otherwise stated

AP, Animal Protein; BMD, Bone Mineral Density; DPA, Dual Photon Absorptiometry; DXA, Dual X-ray Absorptiometry; LSBMD, Lumbar Spine Bone Mineral Density; OR, Odds Ratio; POM, Postmenopausal; TP, Total Protein; VP, Vegetable Protein

TableS6: Characteristics and outcomes of the 30 intervention studies

Study, Country,	Design	Baseline protein intake	Supp. (g/d) vs control	Subject Total n	Outcomes Measured	n (I)	Mean, SD(I)	n(p)	Mean/SD(p)	p
Alekel et al, 2000, USA, 24wks	Parallel	No information in paper	Soy vs Whey	2002 PERI F	LSBMC LSBMD BAP	24 24 24	52.96+/-8.72 0.933+/-0.12 15.05+/-5.11	21 21 21	56.57+/-9.74 0.989+/-0.132 12.51+/-4.3	Ns Ns -
Aoe et al, 2001, Japan	Parallel	No information in paper	40mg/d MBP vs Placebo	PRE F	% change in Calcaneal BMD	17	3.42+/-2.05 %	16	2.01+/-1.75 %	0.042
Aoe et al 2005, Japan, 6mo	Parallel	No information in paper	MBP vs Inactive placebo	27 PERI F	NTX OC LSBMD	14 14 14	47.3+/-8.3 5.73+/-0.59 1.11+/-0.03	13 13 13	58.7+/-8.3 5.82+/-0.59 1.09+/-0.03	Ns Ns <0.05
Arjmandi et al, 2003, USA, 3mo	Parallel	Mean (SE)	40g/d Soy protein vs MBP	42 POM F	BAP DPYD	20 20	0.41+/-0.14 7.19+/-3.31	22 22	0.35+/-0.15 6.79+/-3.24	- -
Cao et al, 2011, USA	Crossover-7 weeks in each arm	Soy group – 60(6)g/d	61g/d (‘lower protein control- US daily recommendation) vs. 118g/d (‘higher protein’ group)	N=16 40-75 year old postmenopausal women,	NTX Log DPYD	16 16	270 +/- 153 3.7+/-0.61	16 16	227+/-153 3.5+/-0.61	0.41 0.20

Ceglia et al, 2009 41 d	Cross-over study	MBP group (75(9) g/d	0.5g/Kg/d (low) vs. 1.5g/Kg/d (high)	M/F 54-82 years old N=10 (placebo group used)	OC (ng/mL) Urinary NTX/Cr (nmol/mmol)	10 10	6.2+/-2.6 41.0+/-15.2	10 10	6.9+/-4.3 40.4+/-19.1	Ns ns
Cuneo et al, 2010, Brazil	Parallel	No information in paper	Hydrolysed collagen (10g/d protein) vs. maltodextrin placebo	N=36 collagen, N=35 placebo 45-65 year old post women	BAP CTX OC	36 36 36	26.2(7.2) 0.48(0.1) 29.0(8.5)	35 35 35	32.0(10.6) 0.57(0.2) 31.8(10.5)	- - -
Dalais et al, 2003, AUS, 3mo	Parallel	Mean (SD): 69.1 (22.1) g/d	40g Soy protein vs casein placebo	106 POM F 50-75 y	PYD DPYD	38 38	70+/-24.97 14.48+/-8.15	40 40	72.72+/-21.31 14.19+/-6.58	Ns ns
Dawson-Hughes et al 2004,USA, 63d	Parallel	Mean (SD)	High (0.75g/Kg/d) vs low (0.04 g/kg/d) protein	32 Elderly M/F	NTX OC	16 16	High protein 102.3+/-34.5 3.4+/-0.9	16 16	Low protein 170+/-118.4 3.2+/-1.5	0.038 0.795
Evans et al, 2007, USA 9 mo	Cross-over	67(18.8) g/d (placebo)	Soy protein isolate (I) vs. Milk protein isolate (p), exercise counterbalanced across groups (1/2 in each group exercise, ½ in each group no exercise)	Postmenopausal women N=22, Mean age 63 years	Change in: TBBMD; LSBMD ProximalFemur BMD FNBMD TrochBMD IntertrochBMD BAP CTX	 21 21 21 21 21 21 21 21	 −0.009 ± 0.013 −0.011 ± 0.028 0.002 ± 0.016 0.003 ± 0.022 0.004 ± 0.013 0.000 ± 0.025 -2.1 ± 4.0 −0.08 ± 0.09	 22 22 22 22 22 22 22 22	 −0.011 ± 0.018 −0.014 ± 0.022 −0.003 ± 0.015 −0.006 ± 0.025 −0.002 ± 0.018 −0.002 ± 0.023 1.2 ± 4.7 −0.02 ± 0.11	 0.72 0.65 0.29 0.20 0.23 0.74 0.02 0.02

Hunt et al, 2009, USA 7wk each arm	Cross-over	61.9(24) g/d (collagen)	Low Calcium (LC)(670mg/d) Low protein (10%of total energy, 0.8g/Kg/d) vs. High protein (20% of total energy, 1.6g/Kg/d) . HighCalcium (HC) (1500mg/d) Low protein (10%of total energy, 0.9g/Kg/d) vs. High protein (20% of total energy1.7g/Kg/d) .	N=13 in two LC arms, n=14 in two HC arms POM F	Group 1 LC: LCLP (p) vs. LCHP (I) Log DPYD Log OC BAP TRAP Group 2 HC: HCLP (p) vs. HCHP(I) Log DPYD Log OC BAP TRAP	13 13 13 13 14 14 14 14	2.3 (0.2) 1.74(0.74) 0.55(0.08) 52.5(8.0) 2.2(0.2) 1.90(0.74) 0.58(0.02) 57.6(8.0)	13 13 13 13 14 14 14 14	2.4 (0.2) 1.94(0.74) 0.52(0.08) 55.1(8.0) 2.3(0.2) 1.73(0.74) 0.53(0.02) 55.7(8.0)	- - - - - - - -
Ince et al 2004, USA, 2wks	Cross-over	109(7) g/d Soy group	High (1.1g/Kg/d) vs low (0.8g/Kg/d) protein diet	39 Pre F, 22-39y	NTX OC	39 39	High protein 442+/-124.9 15.8+/-8.74	39 39	Low protein 360+/-99.9 13.4+/-8.1	<0.001 0.166
Kenny et al, 2009, USA, 1y	Parallel	112(6)g/d Placebo	Soy protein (I) vs. Mixed control protein (Casein,	Women over 60 years old (mean= 71y)	Change in FNBMD Change in LSBMD	24 24	Mean(SEM) 0.001+/-0.005 0.001+/-0.008	22 22	Mean(SEM) -0.003(0.005) 0.010+/-0.007	0.317 0.181

			Whey and Egg) (p).		BAP	24	18.8+/-1.07	22	25.2+/-2.03	0.050
			No isoflavones in these two study arms		NTX	24	30.2+/-2.74	22	35.0+/-3.21	0.50
Kerstsetter et al, 2015, USA, 18mo	Parallel	No information in g	45g Whey protein (I) or isocaloric maltodextrin (p)	Men over 70 y and women over 60 years, n=121			Mean(SEM)		Mean(SEM)	
					LSBMD	106	1.05(1.10+/-0.01)	102	1.02(1.11+/-0.02)	-
					TotalHipBMD	106	1.06(0.88+/-0.01)	102		-
					FNBMD	106	1.06(0.80+/-0.01)	102	1.02(0.89+/-0.01)	-
					LSBMD	106	45(99.3+/-4.29)	102	1.02(0.82+/-0.01)	-
					P1NP nmol/L	61	1.32+/-0.06	60		0.395
					CTX ng/L	61	480+/-30	60		0.041
					OC nmol/L	61	1.12+/-0.05	60	44(106+/-4.07)	0.775
									1.35+/-0.07	
									440+/-30	
									1.18+/-0.06	
Kerstetter et al, 1999, USA, 4d	Cross-over	(17-18% of total energy)	High (2.1g/kg/d)vs low (0.7g/kg/d) protein	16 Pre F, 20-40g			Mean+/-SEM		Mean+/-SEM	
					OC	-	5.7+/-0.8	-	7.6+/-1.4	Ns
					BAP	-	57.2+/-7.8	-	69.4+/-8.8	Ns
					NTX	-	48.2+/-7.2se	-	32.7+/-5.3	<0.05
Khalil et al, 2002, US, 3mo	Parallel	No information in paper	Soy vs Milk protein (40g)	64 M, 59.2+/-17.6y	BAP	24	-	22	-	Ns
					DPYD	24	-	22	-	ns
Jenkins et al, 2003, USA, 2mo Crossover	Cross-over	63(15) g/d	Vegetable diet (27% protein) vs Control diet(16% protein)	20 Middle aged M/F	NTX	20	584+/-340	20	461+/-259	-
					BAP	20	20+/-4.5	20	19+/4.5	-
Lampl et al. 1978, New Guinea, 8 mo	Parallel	69(17) g/d	Normal diet (11g/d)(p) vs. normal diet plus 20g/d milk protein	7-13 year old children with low	Periosteal breadth (mm)	26	5.9+/-0.1	30	5.7+/-0.1	<0.05
					Endosteal breadth (mm)	26	2.8+/-0.1	30	2.8+/-0.1	ns
					Compact bone breadth (mm)	26	3.1+/-0.1	30	2.8+/-0.1	ns

			supplement(I)	protein intakes					Mean+/-SEM	
Martin-Bautista, 2011, Spain 4 mo	Parallel	1.1 kg/d	Collagen (without calcium) group vs. Placebo	38			GP 2		GP 1	
					BAP	20	2.35+/-42.6	18	-28.6+/-29.9	NS
					OC	20	-4.0+/-8.1	18	-2.1+/-14.3	NS
					TRAP	20	-1.2+/-4.0	18	1.6+/-4.2	NS
					CTX	20	0.03+/-0.44	18	0.07+/-0.43	<0.05
Roughead et al, 2003, USA, 8wk	Cross-over	No information in g	High meat (20% of energy) versus low meat(12% of energy) diet	15 POM F			High		Low	
					HPO	15	71.5	15	64.5	0.001
					OC	15	4.01	15	3.94	Ns
					NTX	15	3.79	15	3.83	Ns
					BAP	15	18.1	15	18.3	Ns
Schurch et al, 1998 Switzerland, 6mo	Parallel	(18% of total energy)	Total protein (20g/d) vs placebo	82 Elderly M/F 80.7y+/-7.4	%change					
					DPYD	-	-9.2	-	1.4	>0.2
					FSBMD	-	-1.61	-	-1.23	>0.2
					LSBMD	-	-3.05	-	-6.11	>0.2
					OC	-	7.9	-	6.9	>0.2
					PFBMD	-	-2.95	-	-3.37	>0.2
					PYD	-	6.6	-	17	>0.2
					TrochBMD	-	-3.02	-	-3.65	>0.2
					TBBMD	-	-3.77	-	-3.1	>0.2
Shapses et al, 1995, USA, 5d	Cross-over	Mean +/-SD	LPHC(0.44g/Kg/D protein, p) vs. HPHC (2.71g/kg/d, I) Calcium in both groups=1600 mg/d	21-42 year old males and females	HPO (mol/mol)	15	0.011+/-0.008	13	0.010 +/-0.007	-
Spence et al, 2005, USA, 28d per phase	Cross-over	Soy group-62.5 (13.7) g/d	Soy protein isolate without isoflavones (I) vs.	N=15 POM F	BAP ng/mL	15	14.8+/-4.5	15	14.3+/-4.0	<0.05
					OC ng/mL	15	10.2+/-3.9	15	8.1+/-3.8	<0.05
					NTX nmolBCE/mmol Cr	15	48.0+/-22.6	15	55.6+/-29.0	ns

			casein-whey protein (p)							
Tkatch et al, 1992, Switzerland, 38days	Parallel	Mixed control group- 57.0(21.9)	20.4g/d Protein in nutritional supplement vs. the same nutritional supplement without protein	62 M/F elderly, mean age 82y	Change: FNBMD FSBMD LSBMD OC	25 24 25 24	0.569+/-0.105 0.24+/-0.049 0.88+/-0.18 6.94+/-2.45	23 22 23 18	0.579+/-0.12 1.257+/-0.3 0.81+/-0.17 4.96+/-2.93	 <0.05
Toba et al 2001, Japan, 16d	Parallel	1.0g/Kg/d	MBP (30mg/d) vs inactive placebo	30 M, 36.2y+/-8.5	NTX OC	30 30	26.8+/-9.6 5.4+/-1.8	30 30	31.5+/-10.2 3.7+/-1.8	<0.001 <0.001
Uenishi et al, 2007, Japan, 6mo	Parallel	Mean (SEM):	40mg/d MBP vs inactive placebo	35 Pre F	LSBMD %change in LSBMD	17 17	1.16+/-0.14 +1.75%	18 18	1.13+/-0.16 +0.13%	- 0.042
Vupadhyahula et al, 2009, USA	Parallel	72.9(1.8) Maltodextrin Group	25g soy protein (no isoflavones), 25g milk (casein, whey) protein	203 POM F Mean (SE) age 64 0.6)y	SpineBMD FNBMD TrochBMD TotalFemoralBMD TBBMD %change from baseline: NTX:Cr	48 48 48 48 48 22	Mean+/-SE 1.068+/- 0.02 0.845+/-0.01 0.741+/-0.01 0.892+/-0.02 1.078+/-0.01 2.27+/-2.1	52 52 52 52 52 30	Mean+/-SE 1.082+/-0.02 0.869+/-0.01 0.747+/-0.01 0.897+/-0.01 1.094+/-0.01 -1.86+/-2.3	- - - - - -
Yamamura et al, 2002, Japan	Parallel	73.9(1.9) Whey Group	MBP(40mg) vs inactive placebo	33 Pre F	RBMD	17	-Missing data	16	-Missing data	-
Zhu et al, 2011, AUS, 2y	Parallel	No information in paper	High protein drink (I) vs.	219 70-80 year	Total Hip vBMD	67	Mean(SEM) -3.63+/-1.10	66	Mean(SEM) -3.82+/-1.43	- -

			low protein drink (p)	old women	FN vBMD	67	-2.39+/-1.25	66	-0.24+/-1.19	
					Baseline FN aBMD	91	0.70+/-0.010	88	0.71+/-0.012	0.35
					2 yr FN aBMD	91	0.69+/-0.010	88	0.70+/-0.012	0.33
Zou et al 2009, China, 8 mo	Parallel	11g/d	Milk with 40mg MBP (I) vs. Milk without MBP (p)	57 women, 20 years old	TBBMD	29	0.946+/-0.064	28	0.913+/-0.053	-
					LSBMD	29	1.041+/-0.118	28	0.995+/-0.068	-
					DistalRadius/Ulna BMD	29	0.351+/-0.041	28	0.341+/-0.036	-

aBMD, areal Bone Mineral Density; BAP, Bone Specific Alkaline Phosphatase; BCE, Bovine Collagen Equivalents; BMD, Bone Mineral Density; Cr, Creatinine; CTX, C-terminal telopeptide of collagen; DPYD, Deoxypyridinoline; FNBMD, Femoral Neck Bone Mineral Density; FSBMD, Femoral Shaft Bone Mineral Density; GP, Group; HCHP, High Calcium High Protein; HCLP, High Calcium Low Protein; HPO, Hydroxyproline; IntertrochBMD, Intertrochanter Bone Mineral Density; LCHP, Low Calcium High Protein; LCLP, Low Calcium Low Protein; LSBMC, Lumbar Spine Bone Mineral Content; LSBMD, Lumbar Spine Bone Mineral Density; NTX, N-terminal telopeptide of collagen; OC, Osteocalcin; P1NP, Procollagen type 1 N-terminal propeptide; PERI, Perimenopausal; PFBMD, Proximal Femur Bone Mineral Density; POM, Postmenopausal; PRE, Premenopausal; RBMD, Radial Bone Mineral Density; TBBMD, Total Body Bone Mineral Density; TRAP, Tartrate Resistant Alkaline Phosphatase; TrochBMD, Trochanter Bone Mineral Density; vBMD, volumetric Bone Mineral Density

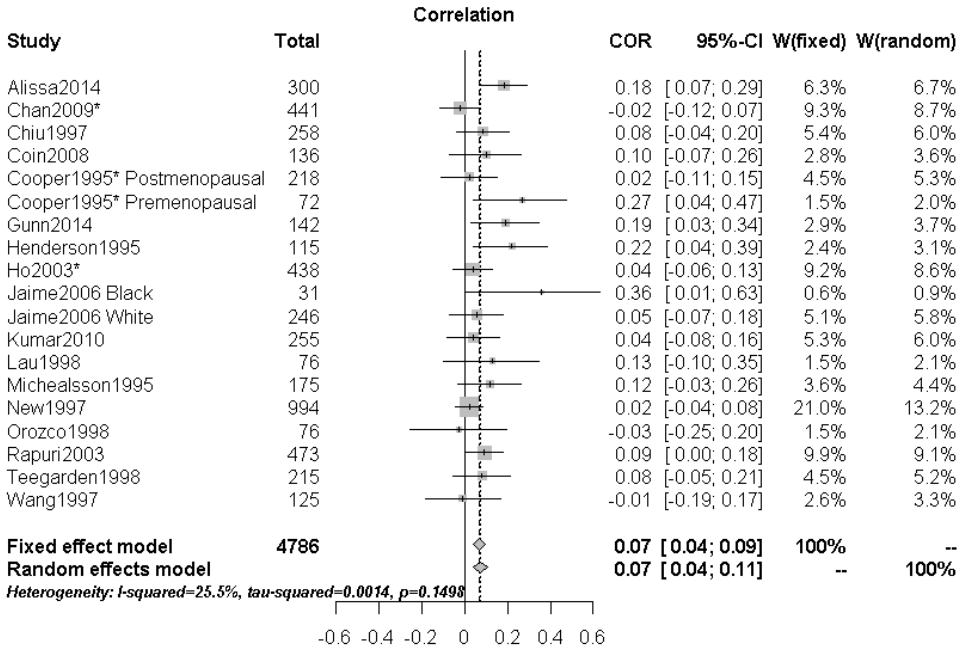

Figure S1 Femoral Neck Bone Mineral Density- correlation coefficients for association with dietary protein intake*=multivariate adjusted data

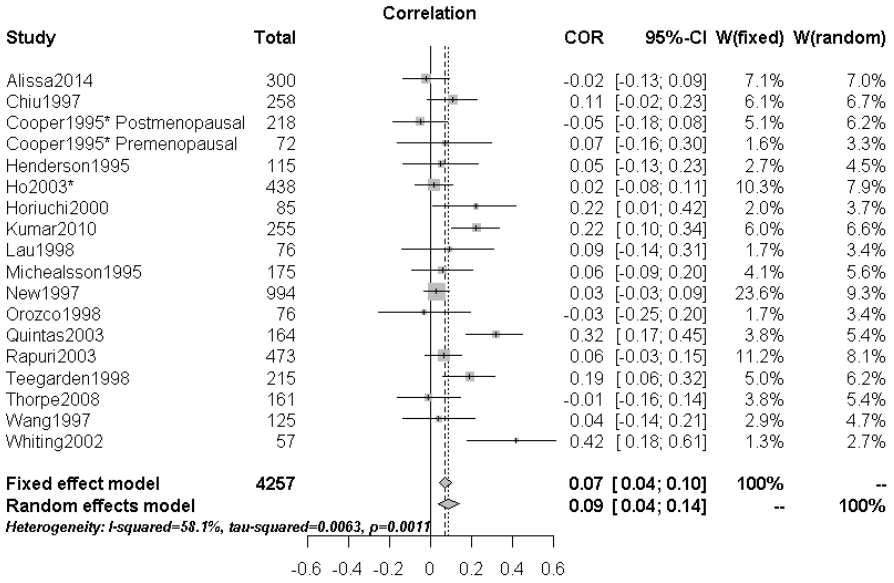

Figure S2 Lumbar Spine Bone Mineral Density- correlation coefficients with dietary protein intake *=multivariate adjusted data

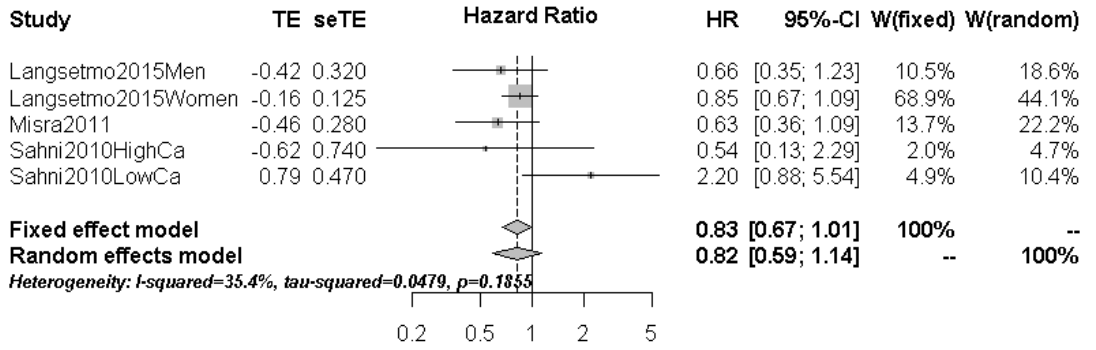

Figure S3 Total Protein intake and Hazard Ratio for Fracture (cohort studies) Lowest intake category=reference (OR=1)

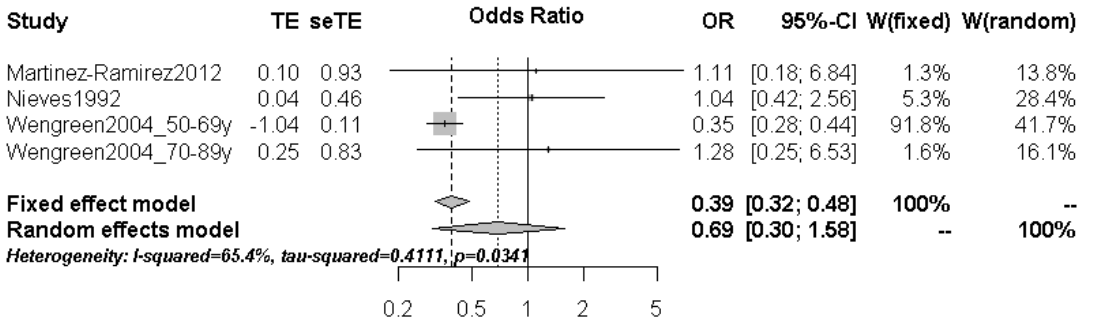

Figure S4 Protein intake and Odds Ratio of Fracture (case control studies) Lowest intake category=reference (OR=1)

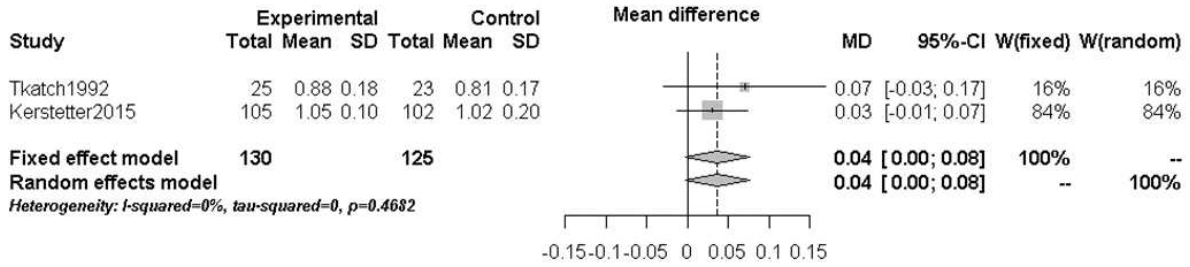

Figure S5 Effects of Total Protein intake on areal Lumbar Spine Bone Mineral Density in randomized controlled trials

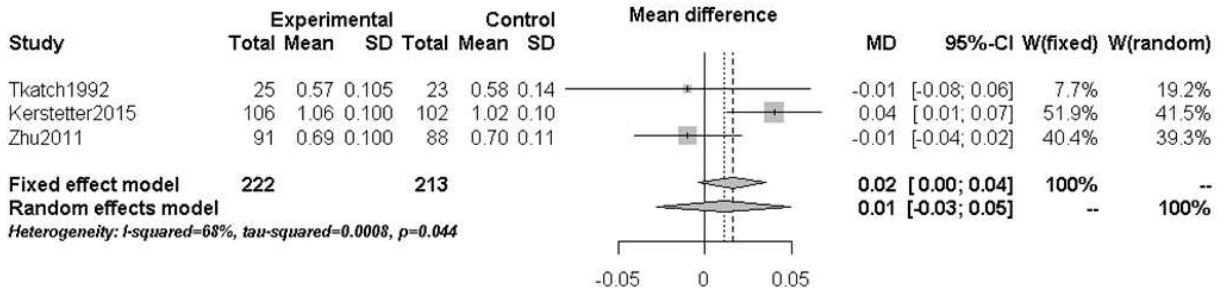

Figure S6: Effects of Total Protein intake on areal Femoral Neck Bone Mineral Density in randomized controlled trials

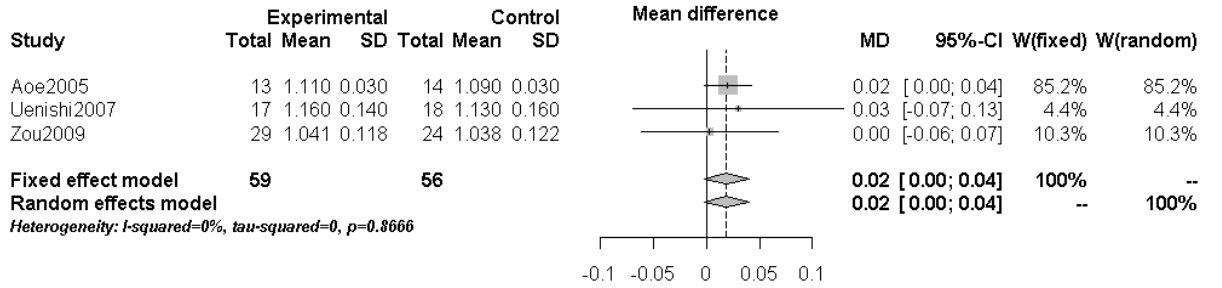

Figure S7: Milk Basic Protein supplementation: Effects on Lumbar Spine Bone Mineral Density

Supplementary References

1. Chan R, Woo J, Lau W, Leung J, Xu L, Zhao XH, Yu W, Lau E, Pocock N. Effects of lifestyle and diet on bone health in young adult Chinese women living in Hong Kong and Beijing. Food Nutr Bull 2009;30(4):370-8.
2. Chiu JF, Lan SJ, Yang CY, Wang PW, Yao WJ, Su LH, Hsieh CC. Long-term vegetarian diet and bone mineral density in postmenopausal Taiwanese women. Calcif Tissue Int 1997;60(3):245-9.
3. Ekbote VH, Khadilkar AV, Chiplonkar SA, Khadilkar VV. Determinants of bone mineral content and bone area in Indian preschool children. J Bone Miner Metab 2011;29(3):334-41. doi: 10.1007/s00774-010-0224-x.
4. Hirota T, Nara M, Ohguri M, Manago E, Hirota K. Effect of diet and lifestyle on bone mass in Asian young women. Am J Clin Nutr 1992;55(6):1168-73.
5. Ho SC, Chan SG, Yip YB, Chan CSY, Woo JLF, Sham A. Change in bone mineral density and its determinants in pre- and perimenopausal Chinese women: the Hong Kong perimenopausal women osteoporosis study. Osteoporosis Int 2008;19(12):1785-96. doi: 10.1007/s00198-008-0614-2.
6. Ho SC, Woo J, Lam S, Chen Y, Sham A, Lau J. Soy protein consumption and bone mass in early postmenopausal Chinese women. Osteoporosis Int 2003;14(10):835-42. doi: 10.1007/s00198-003-1453-9.
7. Ho-Pham LT, Nguyen PLT, Le TTT, Doan TAT, Tran NT, Le TA, Nguyen TV. Veganism, bone mineral density, and body composition: a study in Buddhist nuns. Osteoporosis Int 2009;20(12):2087-93. doi: 10.1007/s00198-009-0916-z.
8. Horiuchi T, Onouchi T, Takahashi M, Ito H, Orimo H. Effect of soy protein on bone metabolism in postmenopausal Japanese women. Osteoporos Int 2000;11(8):721-4. doi: 10.1007/s001980070072.
9. Kumar A, Mittal S, Orito S, Ishitani K, Ohta H. Impact of dietary intake, education, and physical activity on bone mineral density among North Indian women. J Bone Miner Metab 2010;28(2):192-201. doi: 10.1007/s00774-009-0118-y.
10. Lacey JM, Anderson JJB, Fujita T, Yoshimoto Y, Fukase M, Tsuchie S, Koch GG. Correlates of Cortical Bone Mass among Premenopausal and Postmenopausal Japanese Women. Journal of Bone and Mineral Research 1991;6(7):651-9.
11. Lau EMC, Kwok T, Woo J, Ho SC. Bone mineral density in Chinese elderly female vegetarians, vegans, lacto-vegetarians and omnivores. Eur J Clin Nutr 1998;52(1):60-4. doi: DOI 10.1038/sj.ejcn.1600516.
12. Nakamura K, Hori Y, Nashimoto M, Okuda Y, Miyazaki H, Kasai Y, Yamamoto M. Dietary calcium, sodium, phosphorus, and protein and bone metabolism in elderly Japanese women: a pilot study using the duplicate portion sampling method. Nutrition 2004;20(4):340-5. doi: 10.1016/j.nut.2003.12.004.
13. Oh SM, Kim HC, Rhee Y, Park SJ, Lee HJ, Suh I, Feskanich D. Dietary protein in relation to bone stiffness index and fat-free mass in a population consuming relatively low protein diets. J Bone Miner Metab 2013;31(4):433-41. doi: 10.1007/s00774-013-0427-z.
14. Park YJ, Lee SJ, Shin NM, Shin H, Kim YK, Cho Y, Jeon S, Cho I. [Bone mineral density, biochemical bone turnover markers and factors associated with bone health in young Korean women]. J Korean Acad Nurs 2014;44(5):504-14. doi: 10.4040/jkan.2014.44.5.504.
15. Tanaka M, Itoh K, Abe S, Imai K, Masuda T, Koga R, Itoh H, Kinukawa N, Matsuyama T, Nakamura M. Relationship between nutrient factors and osteo-sono assessment index in calcaneus of young Japanese women. Nutr Res 2001;21(12):1475-82. doi: Doi 10.1016/S0271-5317(01)00363-3.
16. Ho-Pham LT, Vu BQ, Lai TQ, Nguyen ND, Nguyen TV. Vegetarianism, bone loss, fracture and vitamin D: a longitudinal study in Asian vegans and non-vegans. Eur J Clin Nutr 2012;66(1):75-82. doi: 10.1038/ejcn.2011.131.
17. Zhang Q, Ma GS, Greenfield H, Zhu K, Du XQ, Foo LH, Hu XQ, Fraser DR. The association between dietary protein intake and bone mass accretion in pubertal girls with low calcium intakes. Brit J Nutr 2010;103(5):714-23. doi: 10.1017/S0007114509992303.
18. Alexy U, Remer T, Manz F, Neu CM, Schoenau E. Long-term protein intake and dietary potential renal acid load are associated with bone modeling and remodeling at the proximal radius in healthy children. American Journal of Clinical Nutrition 2005;82(5):1107-14.
19. Budek AZ, Hoppe C, Ingstrup H, Michaelsen KF, Bugel S, Molgaard C. Dietary protein intake and bone mineral content in adolescents-The Copenhagen Cohort Study. Osteoporos Int 2007;18(12):1661-7. doi: 10.1007/s00198-007-0422-0.

20. Budek AZ, Hoppe C, Michaelsen KE, Bugel S, Molgaard C. Associations of total, dairy, and meat protein with markers for bone turnover in healthy, prepubertal boys. J Nutr 2007;137(4):930-4.
21. Chevalley T, Bonjour JP, Ferrari S, Rizzoli R. High-protein intake enhances the positive impact of physical activity on BMC in prepubertal boys. Journal of Bone and Mineral Research 2008;23(1):131-42. doi: 10.1359/Jbmr.070907.
22. Fairweather-Tait SJ, Skinner J, Guile GR, Cassidy A, Spector TD, MacGregor AJ. Diet and bone mineral density study in postmenopausal women from the TwinsUK registry shows a negative association with a traditional English dietary pattern and a positive association with wine. American Journal of Clinical Nutrition 2011;94(5):1371-5. doi: 10.3945/ajcn.111.019992.
23. Geinoz G, Rapin CH, Rizzoli R, Kraemer R, Buchs B, Slosman D, Michel JP, Bonjour JP. Relationship between Bone-Mineral Density and Dietary Intakes in the Elderly. Osteoporosis Int 1993;3(5):242-8. doi: Doi 10.1007/Bf01623827.
24. Hoppe C, Molgaard C, Michaelsen KF. Bone size and bone mass in 10-year-old Danish children: effect of current diet. Osteoporos Int 2000;11(12):1024-30.
25. Libuda L, Wudy SA, Schoenau E, Remer T. Comparison of the effects of dietary protein, androstenediol and forearm muscle area on radial bone variables in healthy prepubertal children. Br J Nutr 2011;105(3):428-35. doi: 10.1017/S0007114510003508.
26. Macdonald HM, New SA, Fraser WD, Campbell MK, Reid DM. Low dietary potassium intakes and high dietary estimates of net endogenous acid production are associated with low bone mineral density in premenopausal women and increased markers of bone resorption in postmenopausal women. American Journal of Clinical Nutrition 2005;81(4):923-33.
27. Michaelsson K, Holmberg L, Mallmin H, Wolk A, Bergstrom R, Ljunghall S. Diet, bone mass, and osteocalcin: a cross-sectional study. Calcif Tissue Int 1995;57(2):86-93.
28. Neville CE, Robson PJ, Murray LJ, Strain JJ, Twisk J, Gallagher AM, McGuinness M, Cran GW, Ralston SH, Boreham CAG. The effect of nutrient intake on bone mineral status in young adults: The Northern Ireland Young Hearts project. Calcified Tissue Int 2002;70(2):89-98. doi: 10.1007/s00223-001-1023-0.
29. New SA, BoltonSmith C, Grubb DA, Reid DM. Nutritional influences on bone mineral density: A cross-sectional study in premenopausal women. American Journal of Clinical Nutrition 1997;65(6):1831-9.
30. Orozco Lopez P, Ruiz Gil E, Nolla Sole JM. [Are food intake and life styles related with bone mass in fertile women?]. An Med Interna 1998;15(2):63-9.
31. Pearce MS, Relton CL, Groom A, Peaston RT, Francis RM. A lifecourse study of bone resorption in men ages 49-51years: the Newcastle Thousand Families cohort study. Bone 2010;46(4):952-6. doi: 10.1016/j.bone.2010.01.369.
32. Quintas ME, Ortega RM, Lopez-Sobaler AM, Garrido G, Requejo AM. Influence of dietetic and anthropometric factors and of the type of sport practised on bone density in different groups of women. Eur J Clin Nutr 2003;57 Suppl 1:S58-62. doi: 10.1038/sj.ejcn.1601817.
33. Rubinacci A, Porrini M, Sirtori P, Galli L, Tessari L. [Nutrients, anthropometric characteristics and osteoporosis in women in the recent and late postmenopausal period]. Minerva Med 1992;83(9):497-506.
34. Weikert C, Walter D, Hoffmann K, Kroke A, Bergmann MM, Boeing H. The relation between dietary protein, calcium and bone health in women: Results from the EPIC-Potsdam cohort. Ann Nutr Metab 2005;49(5):312-8. doi: 10.1159/000087335.
35. Yazdanpanah N, Zillikens MC, Rivadeneira F, De Jong R, Lindemans J, Uitterlinden AG, Pols HAP, Van Meurs JBJ. Effect of dietary B vitamins on BMD and risk of fracture in elderly men and women: The Rotterdam Study. Bone 2007;41(6):987-94. doi: 10.1016/j.bone.2007.08.021.
36. Coin A, Perissinotto E, Enzi G, Zamboni M, Inelmen EM, Frigo AC, Manzato E, Busetto L, Buja A, Sergi G. Predictors of low bone mineral density in the elderly: the role of dietary intake, nutritional status and sarcopenia. Eur J Clin Nutr 2008;62(6):802-9. doi: 10.1038/sj.ejcn.1602779.
37. Chevalley T, Bonjour JP, van Rietbergen B, Ferrari S, Rizzoli R. Tracking of Environmental Determinants of Bone Structure and Strength Development in Healthy Boys: An Eight-Year Follow Up Study on the Positive Interaction Between Physical Activity and Protein Intake From Prepuberty to Mid-Late Adolescence. Journal of Bone and Mineral Research 2014;29(10):2182-92. doi: 10.1002/jbmr.2247.
38. Libuda L, Alexy U, Remer T, Stehle P, Schoenau E, Kersting M. Association between long-term consumption of soft drinks and variables of bone modeling and remodeling in a sample of healthy German children and adolescents. American Journal of Clinical Nutrition 2008;88(6):1670-7. doi: 10.3945/ajcn.2008.26414.

39. Alissa EM, Alnahdi WA, Alama N, Ferns GA. Relationship Between Nutritional Profile, Measures of Adiposity, and Bone Mineral Density in Postmenopausal Saudi Women. Journal of the American College of Nutrition 2014;33(3):206-14.
40. Alissa EM, Qadi SG, Alhujaili NA, Alshehri AM, Ferns GA. Effect of diet and lifestyle factors on bone health in postmenopausal women. J Bone Miner Metab 2011;29(6):725-35. doi: 10.1007/s00774-011-0274-8.
41. Devine A, Dick IM, Islam AFM, Dhaliwal SS, Prince RL. Protein consumption is an important predictor of lower limb bone mass in elderly women. American Journal of Clinical Nutrition 2005;81(6):1423-8.
42. Gunn CA, Weber JL, Kruger MC. Diet, weight, cytokines and bone health in postmenopausal women. J Nutr Health Aging 2014;18(5):479-86. doi: 10.1007/s12603-014-0002-x.
43. Henderson NK, Price RI, Cole JH, Gutteridge DH, Bhagat CI. Bone-Density in Young-Women Is Associated with Body-Weight and Muscle Strength but Not Dietary Intakes. Journal of Bone and Mineral Research 1995;10(3):384-93.
44. Iuliano-Burns S, Stone J, Hopper JL, Seeman E. Diet and exercise during growth have site-specific skeletal effects: a co-twin control study. Osteoporosis Int 2005;16(10):1225-32. doi: 10.1007/s00198-004-1830-z.
45. Jones G, Riley MD, Whiting S. Association between urinary potassium, urinary sodium, current diet, and bone density in prepubertal children. American Journal of Clinical Nutrition 2001;73(4):839-44.
46. Meng X, Zhu K, Devine A, Kerr DA, Binns CW, Prince RL. A 5-year cohort study of the effects of high protein intake on lean mass and BMC in elderly postmenopausal women. J Bone Miner Res 2009;24(11):1827-34. doi: 10.1359/jbmr.090513.
47. Beasley JM, Ichikawa LE, Ange BA, Spangler L, LaCroix AZ, Ott SM, Scholes D. Is protein intake associated with bone mineral density in young women? American Journal of Clinical Nutrition 2010;91(5):1311-6. doi: 10.3945/ajcn.2009.28728.
48. Bounds W, Skinner J, Carruth BR, Ziegler P. Current research - The relationship of dietary and lifestyle factors to bone mineral indexes in children. J Am Diet Assoc 2005;105(5):735-41. doi: 10.1016/j.jada.2005.02.046.
49. Cooper C, Atkinson EJ, Hensrud DD, Wahner HW, O'Fallon WM, Riggs BL, Melton LJ, 3rd. Dietary protein intake and bone mass in women. Calcif Tissue Int 1996;58(5):320-5.
50. Dawson-Hughes B, Harris SS. Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. Am J Clin Nutr 2002;75(4):773-9.
51. Freudenheim JL, Johnson NE, Smith EL. Relationships between Usual Nutrient Intake and Bone-Mineral Content of Women 35-65 Years of Age - Longitudinal and Cross-Sectional Analysis. American Journal of Clinical Nutrition 1986;44(6):863-76.
52. Gregg EW, Kriska AM, Salamone LM, Wolf RL, Roberts MM, Ferrell RE, Anderson SJ, Kuller LH, Cauley JA. Correlates of quantitative ultrasound in the women's healthy lifestyle project. Osteoporosis Int 1999;10(5):416-24. doi: DOI 10.1007/s001980050248.
53. Hernandezavila M, Stampfer MJ, Ravnikar VA, Willett WC, Schiff I, Francis M, Longscope C, Mckinlay SM. Caffeine and Other Predictors of Bone-Density among Premenopausal and Perimenopausal Women. Epidemiology 1993;4(2):128-34. doi: Doi 10.1097/00001648-199303000-00008.
54. Hu T, Rianon NJ, Nettleton JA, Hyder JA, He J, Steffen LM, Jacobs DR, Criqui MH, Bazzano LA. Protein intake and lumbar bone density: the Multi-Ethnic Study of Atherosclerosis (MESA). Brit J Nutr 2014;112(8):1384-92. doi: 10.1017/S0007114514002220.
55. Ilich JZ, Brownbill RA, Tamborini L. Bone and nutrition in elderly women: protein, energy, and calcium as main determinants of bone mineral density. Eur J Clin Nutr 2003;57(4):554-65. doi: 10.1038/sj.ejcn.1601577.
56. Knurick JR, Johnston CS, Wherry SJ, Aguayo I. Comparison of Correlates of Bone Mineral Density in Individuals Adhering to Lacto-Ovo, Vegan, or Omnivore Diets: A Cross-Sectional Investigation. Nutrients 2015;7(5):3416-26. doi: 10.3390/nu7053416.
57. Metz JA, Anderson JJ, Gallagher PN, Jr. Intakes of calcium, phosphorus, and protein, and physical-activity level are related to radial bone mass in young adult women. Am J Clin Nutr 1993;58(4):537-42.
58. Promislow JH, Goodman-Gruen D, Slymen DJ, Barrett-Connor E. Protein consumption and bone mineral density in the elderly : the Rancho Bernardo Study. Am J Epidemiol 2002;155(7):636-44.
59. Rapuri PB, Gallagher JC, Haynatzka V. Protein intake: effects on bone mineral density and the rate of bone loss in elderly women. American Journal of Clinical Nutrition 2003;77(6):1517-25.

60. Sahni S, Broe KE, Tucker KL, McLean RR, Kiel DP, Cupples LA, Hannan MT. Association of total protein intake with bone mineral density and bone loss in men and women from the Framingham Offspring Study. Public Health Nutrition 2014;17(11):2570-6. doi: 10.1017/S1368980013002875.
61. Tylavsky FA, Anderson JJ. Dietary factors in bone health of elderly lactoovovegetarian and omnivorous women. Am J Clin Nutr 1988;48(3 Suppl):842-9.
62. Teegarden D, Lyle RM, McCabe GP, McCabe LD, Proulx WR, Michon K, Knight AP, Johnston CC, Weaver CM. Dietary calcium, protein, and phosphorus are related to bone mineral density and content in young women. Am J Clin Nutr 1998;68(3):749-54.
63. Thorpe M, Mojtahedi MC, Chapman-Novakofski K, McAuley E, Evans EM. A positive association of lumbar spine bone mineral density with dietary protein is suppressed by a negative association with protein sulfur. J Nutr 2008;138(1):80-5.
64. Vatanparast H, Bailey DA, Baxter-Jones ADG, Whiting SJ. The effects of dietary protein on bone mineral mass in young adults may be modulated by adolescent calcium intake. J Nutr 2007;137(12):2674-9.
65. Wang MC, Villa ML, Marcus R, Kelsey JL. Associations of vitamin C, calcium and protein with bone mass in postmenopausal Mexican American women. Osteoporosis Int 1997;7(6):533-8. doi: Doi 10.1007/Bf02652558.
66. Whiting SJ, Boyle JL, Thompson A, Mirwald RL, Faulkner RA. Dietary protein, phosphorus and potassium are beneficial to bone mineral density in adult men consuming adequate dietary calcium. J Am Coll Nutr 2002;21(5):402-9.
67. Orwoll ES, Weigel RM, Oviatt SK, Meier DE, McClung MR. Serum protein concentrations and bone mineral content in aging normal men. Am J Clin Nutr 1987;46(4):614-21.
68. Loenneke JP, Balapur A, Thrower AD, Syler G, Timlin M, Pujol TJ. Short report: Relationship between quality protein, lean mass and bone health. Ann Nutr Metab 2010;57(3-4):219-20. doi: 10.1159/000321736.
69. Hannan MT, Tucker KL, Dawson-Hughes B, Cupples LA, Felson DT, Kiel DP. Effect of dietary protein on bone loss in elderly men and women: the Framingham Osteoporosis Study. J Bone Miner Res 2000;15(12):2504-12. doi: 10.1359/jbmr.2000.15.12.2504.
70. Beasley JM, LaCroix AZ, Larson JC, Huang Y, Neuhouser ML, Tinker LF, Jackson R, Snetselaar L, Johnson KC, Eaton CB, et al. Biomarker-calibrated protein intake and bone health in the Women's Health Initiative clinical trials and observational study. Am J Clin Nutr 2014;99(4):934-40. doi: 10.3945/ajcn.113.076786.
71. Langsetmo L, Barr SI, Berger C, Kreiger N, Rahme E, Adachi JD, Papaioannou A, Kaiser SM, Prior JC, Hanley DA, et al. Associations of Protein Intake and Protein Source with Bone Mineral Density and Fracture Risk: A Population-Based Cohort Study. J Nutr Health Aging 2015;19(8):861-8. doi: 10.1007/s12603-015-0544-6.
72. Genaro PD, Pinheiro MD, Szejnfeld VL, Martini LA. Dietary Protein Intake in Elderly Women: Association With Muscle and Bone Mass. Nutr Clin Pract 2015;30(2):283-9. doi: 10.1177/0884533614545404.
73. Jaime PC, Latorre Mdo R, Florindo AA, Tanaka T, Zerbini CA. Dietary intake of Brazilian black and white men and its relationship to the bone mineral density of the femoral neck. Sao Paulo Med J 2006;124(5):267-70.
74. Wang MC, Moore EC, Crawford PB, Hudes M, Sabry ZI, Marcus R, Bachrach LK. Influence of pre-adolescent diet on quantitative ultrasound measurements of the calcaneus in young adult women. Osteoporosis Int 1999;9(6):532-5. doi: DOI 10.1007/s001980050181.
75. Chan R, Woo J, Leung J. Effects of Food Groups and Dietary Nutrients on Bone Loss in Elderly Chinese Population. Journal of Nutrition Health & Aging 2011;15(4):287-94.
76. Sellmeyer DE, Stone KL, Sebastian A, Cummings SR. A high ratio of dietary animal to vegetable protein increases the rate of bone loss and the risk of fracture in postmenopausal women. Study of Osteoporotic Fractures Research Group. Am J Clin Nutr 2001;73(1):118-22.
77. Kim J, Lim SY, Kim JH. Nutrient intake risk factors of osteoporosis in postmenopausal women. Asia Pac J Clin Nutr 2008;17(2):270-5.
78. Zhang X, Shu XO, Li H, Yang G, Li Q, Gao YT, Zheng W. Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. Arch Intern Med 2005;165(16):1890-5. doi: 10.1001/archinte.165.16.1890.
79. Feskanich D, Willett WC, Stampfer MJ, Colditz GA. Protein consumption and bone fractures in women. Am J Epidemiol 1996;143(5):472-9.

80. Misra D, Berry SD, Broe KE, McLean RR, Cupples LA, Tucker KL, Kiel DP, Hannan MT. Does dietary protein reduce hip fracture risk in elders? The Framingham osteoporosis study. Osteoporosis Int 2011;22(1):345-9. doi: 10.1007/s00198-010-1179-4.
81. Munger RG, Cerhan JR, Chiu BC. Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. Am J Clin Nutr 1999;69(1):147-52.
82. Mussolino ME, Looker AC, Madans JH, Langlois JA, Orwoll ES. Risk factors for hip fracture in white men: the NHANES I Epidemiologic Follow-up Study. J Bone Miner Res 1998;13(6):918-24. doi: 10.1359/jbmr.1998.13.6.918.
83. Sahni S, Cupples LA, McLean RR, Tucker KL, Broe KE, Kiel DP, Hannan MT. Protective effect of high protein and calcium intake on the risk of hip fracture in the Framingham offspring cohort. J Bone Miner Res 2010;25(12):2770-6. doi: 10.1002/jbmr.194.
84. Zhong Y, Okoro CA, Balluz LS. Association of total calcium and dietary protein intakes with fracture risk in postmenopausal women: the 1999-2002 National Health and Nutrition Examination Survey (NHANES). Nutrition 2009;25(6):647-54. doi: 10.1016/j.nut.2008.12.002.
85. Nieves JW, Grisso JA, Kelsey JL. A Case-Control Study of Hip Fracture - Evaluation of Selected Dietary Variables and Teenage Physical-Activity. Osteoporosis Int 1992;2(3):122-7. doi: Doi 10.1007/Bf01623818.
86. Wengreen HJ, Munger RG, West NA, Cutler DR, Corcoran CD, Zhang J, Sassano NE. Dietary protein intake and risk of osteoporotic hip fracture in elderly residents of Utah. J Bone Miner Res 2004;19(4):537-45. doi: 10.1359/JBMR.040208.
87. Farrin N, Ostadrahimi AR, Mahboob SA, Kolahi S, Ghavami M. Dietary intake and serum bone related chemistry and their correlations in postmenopausal Iranian women. Saudi Med J 2008;29(11):1643-8.
88. Dargent-Molina P, Sabia S, Touvier M, Kesse E, Breart G, Clavel-Chapelon F, Boutron-Ruault MC. Proteins, dietary acid load, and calcium and risk of postmenopausal fractures in the E3N French women prospective study. J Bone Miner Res 2008;23(12):1915-22. doi: 10.1359/jbmr.080712.
89. Samieri C, Ginder Coupez V, Lorrain S, Letenneur L, Alles B, Feart C, Paineau D, Barberger-Gateau P. Nutrient patterns and risk of fracture in older subjects: results from the Three-City Study. Osteoporos Int 2013;24(4):1295-305. doi: 10.1007/s00198-012-2132-5.
90. Preisinger E, Leitner G, Uher E, Alacamlioglu Y, Seidl G, Marktl W, Resch KL. [Nutrition and osteoporosis: a nutritional analysis of women in postmenopause]. Wien Klin Wochenschr 1995;107(14):418-22.
91. Martinez-Ramirez MJ, Delgado-Martinez AD, Ruiz-Bailen M, de la Fuente C, Martinez-Gonzalez MA, Delgado-Rodriguez M. Protein intake and fracture risk in elderly people: a case-control study. Clin Nutr 2012;31(3):391-5. doi: 10.1016/j.clnu.2011.11.016.
92. Key TJ, Appleby PN, Spencer EA, Roddam AW, Neale RE, Allen NE. Calcium, diet and fracture risk: a prospective study of 1898 incident fractures among 34 696 British women and men. Public Health Nutr 2007;10(11):1314-20. doi: 10.1017/S1368980007696402.
93. Chevalley T, Bonjour JP, van Rietbergen B, Ferrari S, Rizzoli R. Fractures during childhood and adolescence in healthy boys: relation with bone mass, microstructure, and strength. J Clin Endocrinol Metab 2011;96(10):3134-42. doi: 10.1210/jc.2011-1445.
94. Meyer HE, Pedersen JI, Loken EB, Tverdal A. Dietary factors and the incidence of hip fracture in middle-aged Norwegians. A prospective study. Am J Epidemiol 1997;145(2):117-23.
95. Perez Durillo FT, Torio Durantez J, Villarejo Villar AB, Sanchez Vico AB, Cueto Camarero Mdel M, Durillo JP. [Comparative study of dietary intake and nutritional status in elderly women with and without hip fracture]. Aten Primaria 2011;43(7):362-8. doi: 10.1016/j.aprim.2010.06.006.
96. Abelow BJ, Holford TR, Insogna KL. Cross-cultural association between dietary animal protein and hip fracture: a hypothesis. Calcif Tissue Int 1992;50(1):14-8.
97. Frassetto LA, Todd KM, Morris RC, Jr., Sebastian A. Worldwide incidence of hip fracture in elderly women: relation to consumption of animal and vegetable foods. J Gerontol A Biol Sci Med Sci 2000;55(10):M585-92.
98. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. Internet: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed April 11, 2017.
99. Alekel DL, St Germain A, Pererson CT, Hanson KB, Stewart JW, Toda T. Isoflavone-rich soy protein isolate attenuates bone loss in the lumbar spine of perimenopausal women. American Journal of Clinical Nutrition 2000;72(3):844-52.

100. Aoe S, Koyama T, Toba Y, Itabashi A, Takada Y. A controlled trial of the effect of milk basic protein (MBP) supplementation on bone metabolism in healthy menopausal women. Osteoporosis Int 2005;16(12):2123-8. doi: 10.1007/s00198-005-2012-3.
101. Ince BA, Anderson EJ, Neer RM. Lowering dietary protein to U.S. Recommended dietary allowance levels reduces urinary calcium excretion and bone resorption in young women. J Clin Endocrinol Metab 2004;89(8):3801-7. doi: 10.1210/jc.2003-032016.
102. Kerstetter JE, Mitnick ME, Gundberg CM, Caseria DM, Ellison AF, Carpenter TO, Insogna KL. Changes in bone turnover in young women consuming different levels of dietary protein. J Clin Endocr Metab 1999;84(3):1052-5. doi: DOI 10.1210/jc.84.3.1052.
103. Uenishi K, Ishida H, Toba Y, Aoe S, Itabashi A, Takada Y. Milk basic protein increases bone mineral density and improves bone metabolism in healthy young women. Osteoporos Int 2007;18(3):385-90. doi: 10.1007/s00198-006-0228-5.
104. Yamamura J, Aoe S, Toba Y, Motouri M, Kawakami H, Kumegawa M, Itabashi A, Takada Y. Milk basic protein (MBP) increases radial bone mineral density in healthy adult women. Biosci Biotechnol Biochem 2002;66(3):702-4. doi: 10.1271/bbb.66.702.
105. Zou ZY, Lin XM, Xu XR, Xu R, Ma L, Li Y, Wang MF. Evaluation of milk basic protein supplementation on bone density and bone metabolism in Chinese young women. Eur J Nutr 2009;48(5):301-6. doi: 10.1007/s00394-009-0014-1.
106. Aoe S, Toba Y, Yamamura J, Kawakami H, Yahiro M, Kumegawa M, Itabashi A, Takada Y. Controlled trial of the effects of milk basic protein (MBP) supplementation on bone metabolism in healthy adult women. Biosci Biotech Bioch 2001;65(4):913-8. doi: DOI 10.1271/bbb.65.913.
107. Arjmandi BH, Khalil DA, Smith BJ, Lucas EA, Juma S, Payton ME, Wild RA. Soy protein has a greater effect on bone in postmenopausal women not on hormone replacement therapy, as evidenced by reducing bone resorption and urinary calcium excretion. J Clin Endocr Metab 2003;88(3):1048-54. doi: 10.1210/jc.2002-020849.
108. Cao JJ, Johnson LK, Hunt JR. A diet high in meat protein and potential renal acid load increases fractional calcium absorption and urinary calcium excretion without affecting markers of bone resorption or formation in postmenopausal women. J Nutr 2011;141(3):391-7. doi: 10.3945/jn.110.129361.
109. Ceglia L, Harris SS, Abrams SA, Rasmussen HM, Dallal GE, Dawson-Hughes B. Potassium bicarbonate attenuates the urinary nitrogen excretion that accompanies an increase in dietary protein and may promote calcium absorption. J Clin Endocrinol Metab 2009;94(2):645-53. doi: 10.1210/jc.2008-1796.
110. Cuneo F, Costa-Paiva L, Pinto-Neto AM, Morais SS, Amaya-Farfan J. Effect of dietary supplementation with collagen hydrolysates on bone metabolism of postmenopausal women with low mineral density. Maturitas 2010;65(3):253-7. doi: 10.1016/j.maturitas.2009.10.002.
111. Dalais FS, Ebeling PR, Kotsopoulos D, McGrath BP, Teede HJ. The effects of soy protein containing isoflavones on lipids and indices of bone resorption in postmenopausal women. Clin Endocrinol (Oxf) 2003;58(6):704-9.
112. Evans EM, Racette SB, Van Pelt RE, Peterson LR, Villareal DT. Effects of soy protein isolate and moderate exercise on bone turnover and bone mineral density in postmenopausal women. Menopause 2007;14(3 Pt 1):481-8. doi: 10.1097/01.gme.0000243570.78570.f7.
113. Hunt JR, Johnson LK, Fariba Roughead ZK. Dietary protein and calcium interact to influence calcium retention: a controlled feeding study. Am J Clin Nutr 2009;89(5):1357-65. doi: 10.3945/ajcn.2008.27238.
114. Kenny AM, Mangano KM, Abourizk RH, Bruno RS, Anamani DE, Kleppinger A, Walsh SJ, Prestwood KM, Kerstetter JE. Soy proteins and isoflavones affect bone mineral density in older women: a randomized controlled trial. Am J Clin Nutr 2009;90(1):234-42. doi: 10.3945/ajcn.2009.27600.
115. Roughead ZK, Johnson LK, Lykken GI, Hunt JR. Controlled high meat diets do not affect calcium retention or indices of bone status in healthy postmenopausal women. J Nutr 2003;133(4):1020-6.
116. Spence LA, Lipscomb ER, Cadogan J, Martin B, Wastney ME, Peacock M, Weaver CM. The effect of soy protein and soy isoflavones on calcium metabolism in postmenopausal women: a randomized crossover study. Am J Clin Nutr 2005;81(4):916-22.
117. Vupadhyayula PM, Gallagher JC, Templin T, Logsdon SM, Smith LM. Effects of soy protein isolate on bone mineral density and physical performance indices in postmenopausal women--a 2-year randomized, double-blind, placebo-controlled trial. Menopause 2009;16(2):320-8. doi: 10.1097/gme.0b013e3181844893.

118. Zhu K, Meng X, Kerr DA, Devine A, Solah V, Binns CW, Prince RL. The effects of a two-year randomized, controlled trial of whey protein supplementation on bone structure, IGF-1, and urinary calcium excretion in older postmenopausal women. J Bone Miner Res 2011;26(9):2298-306. doi: 10.1002/jbmr.429.
119. Dawson-Hughes B, Harris SS, Rasmussen H, Song LY, Dallal GE. Effect of dietary protein supplements on calcium excretion in healthy older men and women. J Clin Endocr Metab 2004;89(3):1169-73. doi: 10.1210/jc.2003-031466.
120. Kerstetter JE, Bihuniak JD, Brindisi J, Sullivan RR, Mangano KM, Larocque S, Kotler BM, Simpson CA, Cusano AM, Gaffney-Stomberg E, et al. The Effect of a Whey Protein Supplement on Bone Mass in Older Caucasian Adults. J Clin Endocrinol Metab 2015;100(6):2214-22. doi: 10.1210/jc.2014-3792.
121. Tkatch L, Rapin CH, Rizzoli R, Slosman D, Nydegger V, Vasey H, Bonjour JP. Benefits of oral protein supplementation in elderly patients with fracture of the proximal femur. J Am Coll Nutr 1992;11(5):519-25.
122. Schurch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998;128(10):801-9.
123. Jenkins DJ, Kendall CW, Vidgen E, Augustin LS, Parker T, Faulkner D, Vieth R, Vandenbroucke AC, Josse RG. Effect of high vegetable protein diets on urinary calcium loss in middle-aged men and women. Eur J Clin Nutr 2003;57(2):376-82. doi: 10.1038/sj.ejcn.1601530.
124. Shapses SA, Robins SP, Schwartz EI, Chowdhury H. Short-term changes in calcium but not protein intake alter the rate of bone resorption in healthy subjects as assessed by urinary pyridinium cross-link excretion. J Nutr 1995;125(11):2814-21.
125. Khalil DA, Lucas EA, Juma S, Smith BJ, Payton ME, Arjmandi BH. Soy protein supplementation increases serum insulin-like growth factor-I in young and old men but does not affect markers of bone metabolism. J Nutr 2002;132(9):2605-8.
126. Toba Y, Takada Y, Matsuoka Y, Morita Y, Motouri M, Hirai T, Suguri T, Aoe S, Kawakami H, Kumegawa M, et al. Milk basic protein promotes bone formation and suppresses bone resorption in healthy adult men. Biosci Biotechnol Biochem 2001;65(6):1353-7. doi: 10.1271/bbb.65.1353.
127. Lampl M, Johnston FE. The effects of protein supplementation on the growth and skeletal maturation of New Guinean school children. Ann Hum Biol 1978;5(3):219-27.
128. Martin-Bautista E, Martin-Matillas M, Martin-Lagos JA, Miranda-Leon MT, Munoz-Torres M, Ruiz-Requena E, Rivero M, Quer J, Puigdueta I, Campoy C. A nutritional intervention study with hydrolyzed collagen in pre-pubertal spanish children: influence on bone modeling biomarkers. J Pediatr Endocrinol Metab 2011;24(3-4):147-53.