Association Between Lean Mass, Fat Mass, and Bone Mineral Density: A Meta-analysis

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Context: Body weight is the most important anthropometric determinant of bone mineral density (BMD). Body weight is mainly made up of lean mass (LM) and fat mass (FM), and which component is more important to BMD has been a controversial issue.

Objective: This study sought to compare the magnitude of association between LM, FM, and BMD by using a meta-analytic approach.

Data Source: Using an electronic and manual search, we identified 44 studies that had examined the correlation between LM, FM, and BMD between 1989 and 2013. These studies involved 20 226 men and women (4966 men and 15 260 women) aged between 18 and 92 years. We extracted the correlations between LM, FM, and BMD at the lumbar spine, femoral neck, and whole body. The synthesis of correlation coefficients was done by the random-effects meta-analysis model.

Results: The overall correlation between LM and femoral neck BMD (FNBMD) was 0.39 (95% confidence interval, 0.34 to 0.43), which was significantly higher than the correlation between FM and FNBMD (0.28; 95% confidence interval, 0.22 to 0.33). The effect of LM on FNBMD in men ($r = 0.43$) was greater than that in women ($r = 0.38$). In premenopausal women, the effect of LM on BMD was greater than the effect of FM ($r = 0.45$ vs $r = 0.30$); however, in postmenopausal women, the effects of LM and FM on BMD were comparable ($r = 0.33$ vs $r = 0.31$).

Conclusion: LM exerts a greater effect on BMD than FM in men and women combined. This finding underlines the concept that physical activity is an important component in the prevention of bone loss and osteoporosis in the population. **(*J Clin Endocrinol Metab* 99: 30–38, 2014)**

Low bone mineral density (BMD) is the most robust risk factor for fracture (1, 2). Each SD decrease in BMD is associated with a 2- to 3-fold increase in the risk of fracture (2), and this magnitude of association is equivalent to the association between blood pressure and cardiovascular events (3). Therefore, measurement of BMD is commonly used as a tool for the diagnosis of osteoporosis (4). Body weight is an important determinant of BMD, such that individuals with higher body weight have higher BMD (5) and reduced fracture risk (6). Between-individual variation in body weight accounts for about 30% of variation in BMD, making it one of the best determinants of BMD (7, 8).

Body weight is largely made up of two components: fat mass (FM) and lean mass (LM; or fat-free mass). The relative contribution of each of the two components to BMD variation has been highly contentious. Although some studies have suggested that LM, not FM, is associated with

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received August 16, 2013. Accepted October 29, 2013.

Abbreviations: BMD, bone mineral density; FM, fat mass; LM, lean mass.

BMD (9–18), other studies (19–22) have shown that FM, not LM, is an important determinant of BMD. Still, other studies have found that both FM and LM were significant predictors of BMD (23–25). Taken together, these studies suggest that the relative contribution of body composition parameters to BMD could be dependent on gender, ethnicity, and age. Although most studies found that LM significantly predicted BMD in both genders (26, 27), some studies observed that FM was associated with BMD for men under 50 years but not for women and men over

Table 1. Characteristics of Individual Studies Included in the Meta-Analysis

						Correlation of LM			Correlation of FM		
First Author (Ref.)	Year	Ethnicity	Sex	Age, y	N	LS	FN	WB	LS	FN	WB
Bevier (53)	1989	Caucasian	Men	61–84	36	0.15					
			Women	61–84	55	0.19					
Reid (65)	1992	Caucasian	Men	31	51			0.51			0.26
			Women	33	68			0.55			0.6
Reid (20)	1992	Caucasian	Women	45–78	140	0.20	0.18	0.18	0.34	0.38	0.55
Compston (59)	1992	Caucasian	Women	49–65	97	0.28		0.58			
Edelstein (68)	1993	Caucasian	Men	55–84	597	0.3			0.3		
			Women		895	0.34			0.36		
Reid (19)	1994	Caucasian	Women	47–73	140	0.21			0.43		
Reid (66)	1995	Caucasian	Women	36	36	0.47	0.59	0.6	0.34	0.47	0.5
				33	63	0.33	0.38	0.44	0.14	−0.15	0.18
Salamone (16)	1995	Caucasian	Women	40–50	334	0.44	0.40	0.45	0.16	0.16	0.19
Douchi (41)	1997	Asian	Women	20–54	128	0.33		0.38	0.38		0.27
					196	0.47		0.39	0.31		0.23
Chen (58)	1997	Caucasian	Women	<65	50	0.11	0.10	0.23	0.05	0.07	0.25
Barondess (55)	1997	Caucasian	Men	33–64	42			0.58			0.35
		Black	Men	33–64	37			0.51			0.60
Ohmura (50)	1997	Asian	Women	20–79	1006			0.42			0.41
Nguyen (9)	1998	Caucasian	Women	53	112	0.38	0.27	0.32	0.37	0.26	0.59
Taaffe (17)	2000	Caucasian	Women	60–86	62	0.34	0.33	0.29	0.28	0.31	0.27
		Hispanic	Women	60–86	54	0.33	0.21	0.40	0.18	0.19	0.34
Nakaoka (52)	2001	Asian	Women	48–84	205	0.34	0.34		0.25	0.38	0.11
Lee (46)	2001	Asian	Women	20–69	178	0.21		0.3	0.09		0.18
Van Langendonck (67)	2002	Caucasian	Men	60	156	0.33		0.24	0.24		0.20
Reid (21)	2002	Caucasian	Women	60	119	0.21			0.43		
Ijuin (24)	2002	Asian	Women	Post	193	0.36	0.38	0.38	0.32	0.38	0.31
		Asian	Women	Pre	360	0.30	0.39	0.34	0.04	0.33	0.09
Douchi (42)	2003	Asian	Women	<60	123	0.31	0.33	0.32			
		Asian	Women	>65	102	0.38	0.51	0.42			
Douchi (11)	2003	Asian	Women		45	0.42			0.15		
		Asian	Women		89	0.23			0.25		
Douchi (10)	2003	Asian	Men		93	0.38		0.56	−0.03		−0.09
Li (14)	2004	Caucasian	Women	40–55	43	0.41	0.52	0.09	0.37	0.49	0.02
Liu (15)	2004	Asian	Women	20–55	282	0.28	0.34	0.36	0.05	0.14	0.10
Wang (18)	2005	Mixed	Women	20–25	921	0.38	0.37	0.41	0.18	0.23	0.33
Mizuma (29)	2006	Asian	Women	30–49	302	0.30		0.35	0.18		0.10
	2006	Asian	Women	50–69	197	0.42		0.30	0.19		0.20
Gnudi (23)	2007	Caucasian	Women	62	770		0.33	0.42		0.26	0.35
Kim (45)	2009	Asian	Women	<50	1694	0.12			0.02		
Lee (88)	2009	Asian	Women	22–72	60	0.35	0.47	0.75	0.25	0.16	−0.04
Lekamwasam (47)	2009	Asian	Women	30–54	106	0.22	0.40	0.28	0.21	0.43	0.19
Benetos (54)	2009	Caucasian	Men	60–85	169	0.34	0.52	0.35			
Ho-Pham (43)	2010	Caucasian	Women	50–85	210	0.76	0.63	0.89	0.03	0.03	0.04
Bogl (56)	2011	Caucasian	Women	23–31	147	0.35		0.43	0.46		0.24
			Men	23–31	154	0.37		0.51	0.43		0.38
Ho-Pham (44)	2011	Asian	Men	18–85	353	0.45	0.55	0.47	0.19	0.16	0.05
			Women	18–85	863	0.32	0.32	0.29	0.09	0.05	0.01
Liu (48)	2011	Asian	Women	40–67	244	0.3	0.24		0.24	0.25	
					298	0.41	0.25		0.25	0.24	
Dytfeld (60)	2011	Caucasian	Women	52–86	92	0.23	0.33		0.13	0.36	
Moseley (27)	2011	Caucasian	Men	40–65	78	0.16	0.42	0.42	0.03	0.11	0.27
			Women	40–65	56	0.21	0.38	0.48	0.20	0.41	0.57
Chantler (57)	2012	Caucasian	Women	18–45	187	0.09	0.45	0.53	0.13	0.27	0.26
		Black	Women	18–45	240	0.33	0.59	0.41	0.29	0.53	0.30
Park (51)	2012	Asian	Men + Women	44	1782	0.12		0.31	0.06		0.20
Kim (26)	2012	Asian	Men	>40	1284			0.78			0.48
			Women	>40	362			0.61			0.58
			Women	>40	1396			0.64			0.61
El Hage (61)	2012	Lebanese	Men	65–84	70		0.48	0.52		0.44	0.27
Gomez-Cabello (63)	2013	Caucasian	Women	65–92	159	0.41	0.31	0.47	0.29	0.25	0.30
			Men	65–92	64	0.31	0.11	0.18	0.01	−0.02	−0.12
Namwongprom (49)	2013	Asian	Women	40–90	1579	0.47	0.53	0.40	0.38	0.40	0.18
Nur (64)	2013	Caucasian	Women	46–75	202	0.24	0.26		0.29	0.33	

Abbreviations: N, number of subjects; LS, lumbar spine; FN, femoral neck; WB, whole body; Pre, premenopause; Post, postmenopause.

50 years (28). It has been suggested that LM is more important than FM in premenopausal women, and FM a more important than LM in postmenopausal women (24, 28, 29), but other studies showed that only LM was associated with BMD in both premenopausal and postmenopausal women (25, 26). The inconsistent findings may be due to the strong correlation between FM and LM (9) and that body fat in Caucasian populations are generally greater than in Asian populations (30). Many past studies had relatively low sample sizes, which could contribute to the inconsistency of findings.

In the presence of conflicting findings and variability in sample sizes in individual studies, a meta-analysis may be helpful to resolve the association between body composition and bone density. Two research questions guided this study: 1) what is the real magnitude of association between body composition components and BMD; and 2) what are the effects of gender, age, and ethnicity on the association. The present study took a meta-analytical approach to address the two questions by estimating the correlation between LM, FM, and BMD.

Materials and Methods

As mentioned above, this study is a systematic review and meta-analysis that involved the synthesis of data from past studies. The study was conducted in accordance with the methods of the Cochrane Collaboration (31).

Search strategy and study inclusion

An electronic search of the literature was carried out using PubMed, Ovid, and ISI Web of Knowledge resources (all-year timespan) to identify studies relating body composition and BMD. The initial keywords used for the search included "body composition*" OR "lean mass*" OR "fat-free mass*" OR "fat mass*" concatenated with "BMD" OR "bone mass" OR "bone health." In addition, we hand-searched review articles and checked reference lists of original articles to identify studies that might have been missed from the electronic search. The inclusion criteria were: 1) original studies published in English language journals, reporting data on body composition and BMD; 2) observational studies; 3) using dual-energy x-ray absorptiometry technology; and 4) human studies on individuals aged 18+ years. We excluded review papers, case-control and interventional studies, animal studies, and studies on children or adolescents. Two reviewers (L.T.H.-P. and T.V.N.) independently identified eligible articles according to the above criteria. Discrepancies in opinion as to whether studies should be included in the analysis were resolved by discussion.

Data extraction and synthesis

Data extraction was also done independently by two reviewers. For each study, we extracted data relating to study characteristics and outcomes. Specifically, the following data were extracted: authors, journal, year of publication, study design, ethnicity, age group, gender, number of participants, and correlation coefficient of LM/FM with BMD. If more than one paper with the same data was identified, only the one that contained the definitive data was included. The primary analysis variable was the correlation coefficient between body composition measures and BMD. The two measures were LM and FM. Three BMD sites

Table 2. Correlation Between LM, FM, and BMD: Analysis by Gender, Ethnicity, and Menopausal Status

	Lumbar Spine BMD	Femoral Neck BMD	Whole Body BMD
Overall, men and women (n = 20 226; no. of studies = 44)			
LM	0.33 (0.29–0.36)	0.39 (0.34–0.43)	0.46 (0.41–0.51)
FM	0.24 (0.20–0.28)	0.28 (0.22–0.33)	0.28 (0.21–0.31)
By gender			
Men (n = 4966; no. of studies = 13)			
LM	0.36 (0.29–0.43)	0.43 (0.27–0.60)	0.53 (0.40–0.67)
FM	0.23 (0.11–0.35)	0.18 (0.003–0.36)	0.23 (0.07–0.40)
Women (n = 15 260; no. of studies = 31)			
LM	0.33 (0.29–0.37)	0.38 (0.33–0.42)	0.44 (0.39–0.49)
FM	0.24 (0.20–0.29)	0.29 (0.23–0.34)	0.29 (0.22–0.37)
By ethnicity			
Asians (n = 13 730; no. of studies = 19)			
LM	0.34 (0.29–0.39)	0.41 (0.34–0.47)	0.48 (0.39–0.56)
FM	0.19 (0.14–0.25)	0.29 (0.14–0.40)	0.21 (0.11–0.31)
Caucasians (n = 5174; no. of studies = 23)			
LM	0.31 (0.27–0.35)	0.35 (0.29–0.41)	0.44 (0.37–0.50)
FM	0.29 (0.23–0.35)	0.26 (0.18–0.33)	0.34 (0.25–0.42)
By menopausal status			
Premenopause (n = 5087; no. of studies = 14)			
LM	0.31 (0.24–0.37)	0.45 (0.37–0.53)	0.46 (0.39–0.52)
FM	0.19 (0.10–0.27)	0.30 (0.15–0.45)	0.29 (0.19–0.40)
Postmenopause (n = 7640; no. of studies = 22)			
LM	0.34 (0.30–0.39)	0.33 (0.26–0.40)	0.42 (0.34–0.50)
FM	0.31 (0.26–0.35)	0.31 (0.25–0.36)	0.36 (0.25–0.47)

Data are shown as coefficient of correlation (95% confidence limit).

were considered, namely, lumbar spine, femoral neck (or total hip), and whole body. Thus, a maximum of six correlation coefficients were extracted and analyzed. The correlation coefficients were initially transformed to Fisher's z-scores for meta-analysis, and then back-transformed into the original correlation coefficient in the final result.

The synthesis of z-scores across studies was done by the random-effects model (32, 33). The National Research Council 1992 (34) considers the random-effects model to be more appropriate in fitting real-world data that come from populations with varying average effect sizes with a strong assumption of representativeness. Briefly, study-level z-score (denoted by z_i) is assumed to be normally distributed with a "true" but unknown mean θ_i and a within-study variance σ^2. The collection of θ_i across studies is assumed to follow a normal distribution with unknown mean θ and between-study variance τ^2. The classical random-effects method recognizes that the possibility of heterogeneity of between-study variation (ie, τ^2) could be difference from zero but with a fixed value. All parameters of the random-effects model were estimated by the inverse variance weighting method as implemented by the "metafor" package (35) within the R language (36).

The heterogeneity of correlations across studies was assessed by the Cochran's Q statistic (37) and the coefficient of inconsistency (I^2). The latter is an estimate of the proportion of total variation in study estimates that is due to heterogeneity (38). Subgroup analyses by age, gender, and ethnicity were also carried out as specified in the analysis protocol. Publication bias was examined by a funnel plot (39). Furthermore, the radial plot (Galbraith plot) and the standardized residuals plot were used to assess asymmetry and publication bias (40).

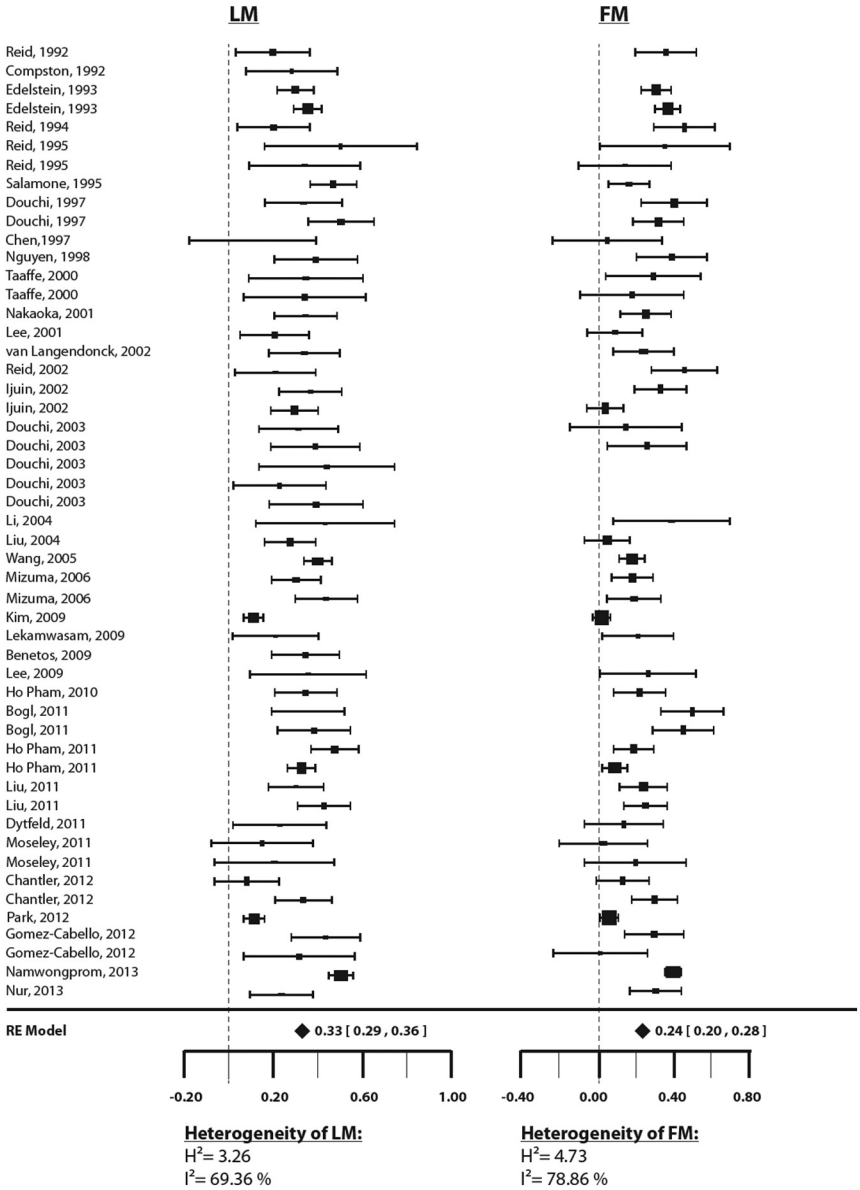

Figure 1. Correlation (and 95% confidence interval) between lumbar spine BMD and LM (left panel) and FM (right panel). The size of the dots was proportional to sample size. The overall effect size (solid diamond) was derived from the random-effects model.

Results

Characteristics of studies

An initial search yielded 3065 articles written in English with contents relating to the body composition and BMD. However, after excluding articles that did not met the inclusion criteria, only 44 studies were included in the analysis. The 44 studies involved 20 226 individuals (15 260 women and 4966 men) with means of age ranging from 18 to 92 years. Twenty studies were conducted on Asian populations (10, 11, 15, 18, 24, 26, 29, 41–52) and 24 studies were on Caucasians (9, 14, 16, 17, 19–21, 27, 53–68) (Table 1). Thirty studies were conducted on women, five studies on men (10, 54, 55, 61, 67), and nine studies included both men and women (26, 27, 44, 51, 53, 56, 63, 65, 68).

LM, FM, and BMD

Results of random-effects analysis (Table 2) showed that the correlation between LM and BMD was greater than that between FM and BMD in men and women of all ages and ethnicities. For instance, the overall correlation between LM and BMD ranged between 0.33 (for lumbar spine BMD) to 0.46 (for whole body BMD), whereas the correlation between FM and BMD ranged between 0.24 (for lumbar spine BMD)

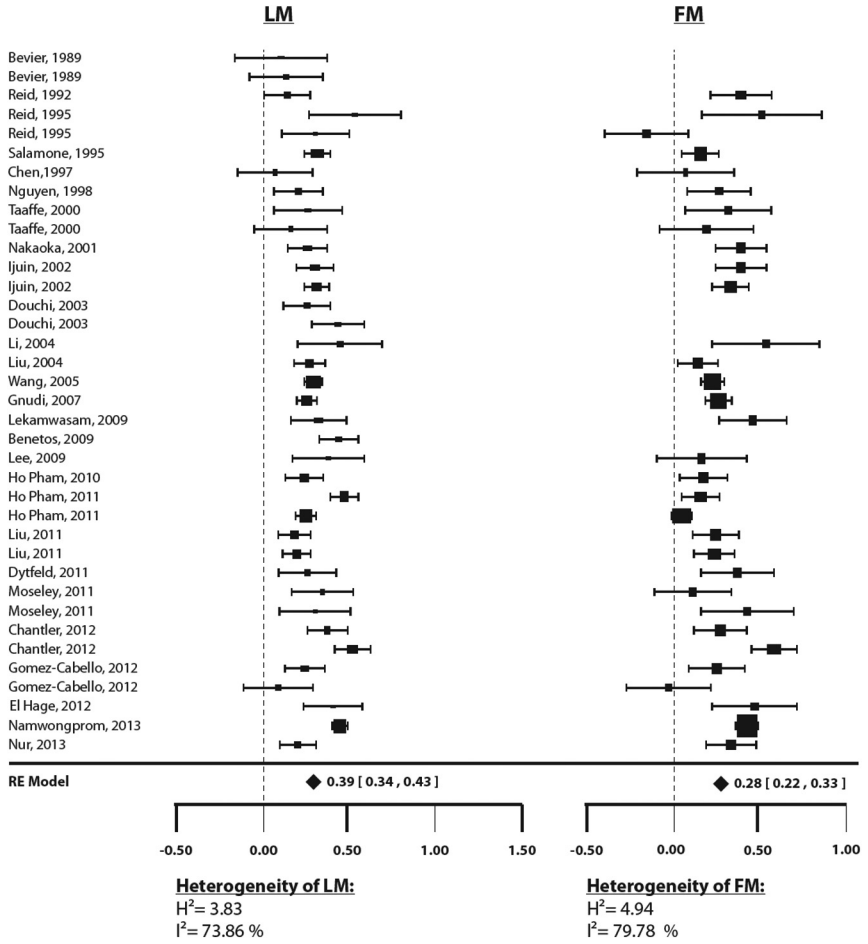

Figure 2. Correlation (and 95% confidence interval) between femoral neck BMD and LM (left panel) and FM (right panel). The size of the dots was proportional to sample size. The overall effect size (solid diamond) was derived from the random-effects model.

to 0.28 (for whole body BMD) (Figures 1–3). Measured by the correlation coefficient, it appears that the "effect" of LM on femoral neck and whole body BMD was greater than that on lumbar spine BMD. The same trend was observed in both men and women, and both Asians and Caucasians (Table 2).

Analysis by menopausal status suggested that the correlation between FM and BMD was dependent on skeletal site and menopausal status (Table 2). At the lumbar spine, the contributions of LM and FM to BMD were equivalent in postmenopausal women, but LM exerted a stronger correlation than FM in premenopausal women. For femoral neck and whole body BMD, the correlation between LM and BMD in premenopausal women (r = 0.45–0.46) was greater than that in postmenopausal women (r = 0.33–0.42).

There was a significant heterogeneity in the correlations, with the index of inconsistency (I^2) ranging from 69 to 89% for LM, and 79 to 92% for FM. However, funnel plots show no systematic trend of publication bias (Figure 4).

Discussion

For more than two decades, it is has not been clear whether LM is more important than FM as a determinant of BMD. Although some studies have suggested that LM has a more pronounced effect on BMD than FM, other studies found that FM was a better determinant of BMD than LM. The discrepancy of findings is expected because previous studies have been based on different study designs with variability in sample sizes, age groups, and ethnicities. In such a context, meta-analysis offers an attractive way to resolve the issue. In this study, by using a meta-analytic approach, we have demonstrated that both LM and FM are significantly associated with BMD, but LM is more important than FM in men and women combined. We estimated that the variation in LM accounts for 21% of differences in whole body BMD, and the variation in FM explains approximately 8% of differences in BMD.

The finding that LM exerts a stronger effect on BMD than FM in men and women combined is consistent with most previous studies. Indeed, out of 57 pairs of correlation coefficients between body composition measures and BMD, 43 coefficients showed that the correlation between LM and BMD was greater than between FM and BMD. However, the association between LM and BMD appears to be dependent on gender and age group, such that the effect of LM on BMD was stronger in men than in women, probably reflecting that the effect of muscle mass and physical activity in men is more apparent than in women. At the weight-bearing site (eg, femoral neck), the effect of LM observed in premenopausal women was greater than in postmenopausal women. In postmenopausal women, the magnitude of correlation between FM and BMD was equivalent to that between LM and BMD.

The delineation of effects of LM and FM on BMD is not easy, because LM and FM are correlated and the correlation could be different among studies due to sample size and sampling variability. If the correlation is null or low, then it is possible to estimate the contribution of each factor; if the correlation is high, the esti-

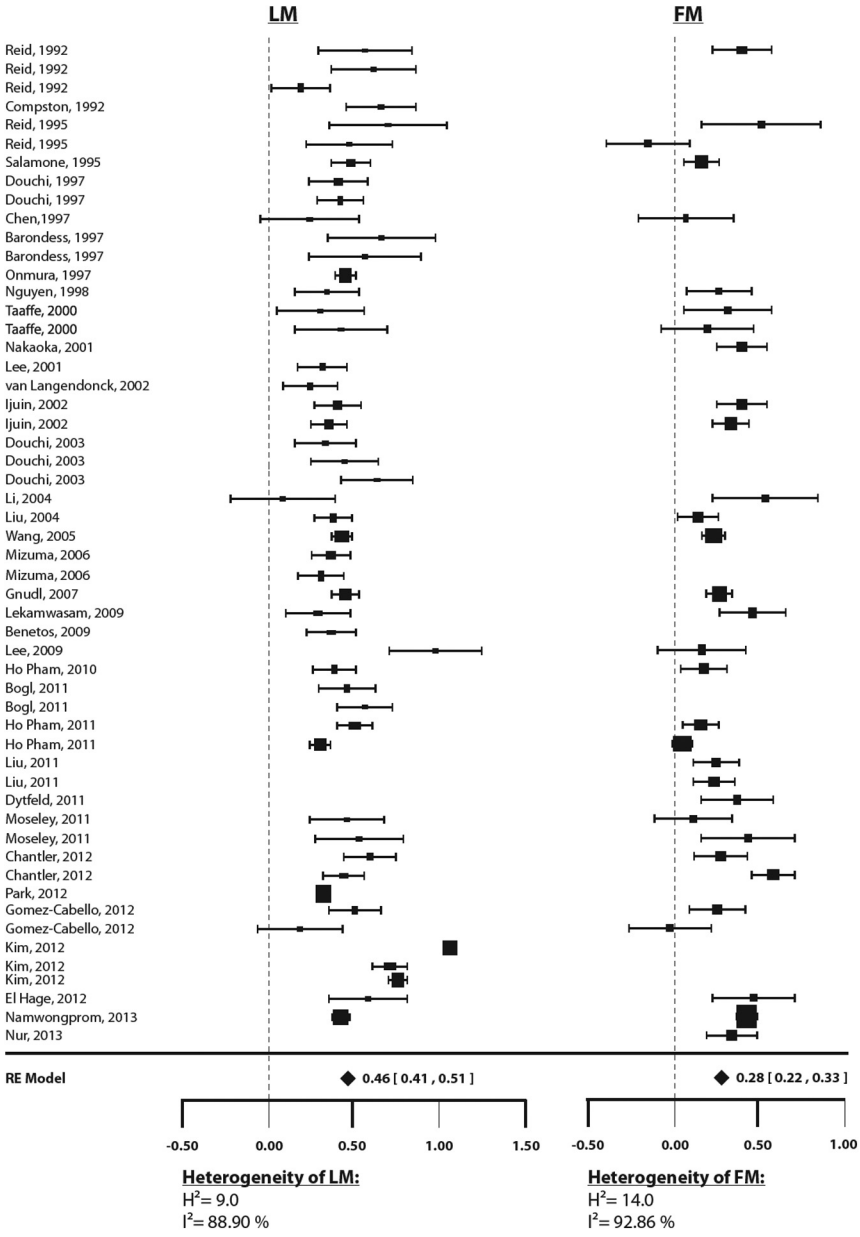

Figure 3. Correlation (and 95% confidence interval) between whole body BMD and LM (left panel) and FM (right panel). The size of the dots was proportional to sample size. The overall effect size (solid diamond) was derived from the random-effects model.

mation of contribution of any factor can be confounded by another factor. In a recent study (43), by using simulation method, it was shown that studies with sample sizes of more than 200 individuals have a much better chance of detecting the real effects of both LM and FM. These results are in broad agreement with the literature so far, in which the effects of both LM and FM were reported in studies with at least 300 individuals, and only small studies reported the effect of FM alone on BMD. In such a heuristic situation, our finding from the meta-analysis in 20 226 individuals has important implications for the identification and delineation of the effects of LM and FM on BMD.

In this study, we found that in relative terms the contribution of LM on BMD in Asians was more pronounced than in Caucasians. Based on the assumption that body fat in Caucasian populations is generally greater than in Asian populations (29), the results from some of the Caucasian studies found that FM was a strong determinant of BMD (19–21, 68), whereas most studies in Asians showed that LM was more important than FM in the association with BMD (10, 11, 15, 29, 43, 44, 49, 52). However, results from a recent study suggested that although Caucasian women have greater body weight and FM than Asian women, their percentage of body fat is similar (69), which seems to be in agreement with the finding in this study. Furthermore, it is noted that the sample size of studies on Caucasian populations was much lower than that in Asian populations. Because small sample size studies tended to yielded larger and more unstable effect size than large studies, it is possible that the differential effect was purely due to sample size issue rather than biological factors.

This study also shows that there are gender-related differences in the associations between body composition and BMD. Generally, LM has a stronger relationship with BMD than FM in both genders, but this trend was more apparent in men than in women. Among women, the association between body composition and BMD is also dependent on menopausal status. In premenopausal women, LM is more important than FM as a determinant of BMD, but in postmenopausal women, the contribution of FM to BMD variation is equivalent to that of LM.

Several hypotheses have been proposed to account for the associations between LM and FM with BMD. Both FM and LM may contribute to an increase in BMD by causing increased mechanical loading (70). In addition, the impact of LM on BMD has been attributed in part to the influence of biomechanical usage on bone development (71). According to this theory, bone strength is in-

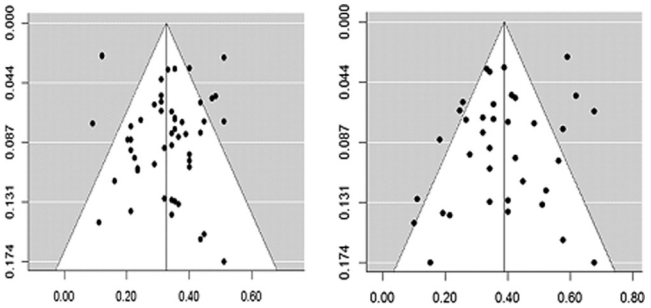

Figure 4. Funnel plot of correlation coefficients (x-axis) and SE (y-axis) for LM and femoral neck BMD (right panel) and lumbar spine BMD (left panel) vs SE.

fluenced by mechanical muscle force and hormonal factors. The force that muscle exerts against bone is influenced by how much body mass the muscles and bones support (72), and this could lead to a positive relationship between the masses of muscles and bones. As a result, physical activity seems to be important for bone mass in all periods of life and in both of genders (73), and the observed association between LM and BMD seems to be consistent with that hypothesis.

Recent data suggest that sclerostin (an osteocyte-expressed inhibitor of Wnt signaling pathway) may play a key role in the relationship between body composition and bone mass (74). Serum levels of sclerostin are positively associated with BMD and FM (75, 76). Sclerostin is regulated by estrogen and PTH (74). Postmenopausal women treated with PTH (1–34) have circulating levels of sclerostin decreased (77). Collectively, these findings suggest that the association between FM and BMD is likely mediated through sclerostin.

Distinguishing the role of LM vs FM as a determinant of BMD has clinical relevance. Physical activity is a strong determinant of bone mass acquisition during growth (78) and maintenance during postmenopause (79, 80) or late decades of life (81). A healthy dietary regime with rich vegetables is associated with healthy fat and bone accrual in children (82), but fast food and/or saturated fat intakes are adversely associated with bone health (83, 84). Thus, an association between BMD and LM suggests that an increase in physical activity may directly translate into protection against osteoporosis (85), whereas an association between BMD and FM implies that sex hormones and good nutrition may have a protective effect against bone loss (86). Results of this study seem to suggest that muscle strength and physical activity have a more prominent effect on bone health than hormones, particularly in men and premenopausal women.

As with any meta-analysis, exclusion of pertinent unpublished studies represents a threat to the validity of the result. However, in this analysis, we found no evidence of systematic publication bias by all methods (funnel, radial, and standardized residual histogram). Nevertheless, there was a significant heterogeneity among the studies included in the analysis, and we dealt with this problem by a random-effects analysis and subgroup analysis (34). Possible heterogeneity expected in included studies could be due to the discrepancy of sample sizes and measurement of variables that were not the case in the random-effects analysis of correlation coefficients (87). Another threat of validity is that the association between LM, FM, and BMD might not be linear. However, in all original studies, the assumption of linearity appears to be tenable.

In conclusion, we have shown that whereas both LM and FM are associated with BMD, LM is more important than FM as a determinant of BMD in men and women of all ages and ethnicity. However, in postmenopausal women, the effects of LM and FM on BMD are equivalent. The importance of LM as a determinant of BMD underlines the concept that muscle mass or physical activity is an important component in the prevention of bone loss and osteoporosis in the general population. However, the significant association between FM and BMD suggests that sex hormones and nutrition also play an important role in the growth and maintenance of bone mass.

Acknowledgments

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There was no funding for this study. T.V.N. was supported by a senior research fellowship from the Australian National Health and Medical Research Council.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Nguyen ND, Pongchaiyakul C, Center JR, Eisman JA, Nguyen TV.** Identification of high-risk individuals for hip fracture: a 14-year prospective study. *J Bone Miner Res*. 2005;20:1921–1928.
2. **Marshall D, Johnell O, Wedel H.** Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ*. 1996;312:1254–1259.
3. **Lewington S, Clarke R, Qizilbash N, Peto R, Collins R.** Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
4. **Writing Group for the ISCD Position Development Conference.** Diagnosis of osteoporosis in men, premenopausal women, and children. *J Clin Densitom*. 2004;7(1):17–26.
5. **Nguyen TV, Kelly PJ, Sambrook PN, Gilbert C, Pocock NA, Eisman JA.** Lifestyle factors and bone density in the elderly: implications for osteoporosis prevention. *J Bone Miner Res*. 1994;9:1339–1346.
6. **Nguyen TV, Eisman JA, Kelly PJ, Sambrook PN.** Risk factors for

osteoporotic fractures in elderly men. *Am J Epidemiol*. 1996;144: 255–263.
7. **Nguyen TV, Eisman JA.** Genetics of fracture: challenges and opportunities. *J Bone Miner Res*. 2000;15:1253–1256.
8. **Hannan MT, Felson DT, Anderson JJ.** Bone mineral density in elderly men and women: results from the Framingham Osteoporosis Study. *J Bone Miner Res*. 1992;7:547–553.
9. **Nguyen TV, Howard GM, Kelly PJ, Eisman JA.** Bone mass, lean mass, and fat mass: same genes or same environments? *Am J Epidemiol*. 1998;147:3–16.
10. **Douchi T, Kuwahata R, Matsuo T, Uto H, Oki T, Nagata Y.** Relative contribution of lean and fat mass component to bone mineral density in males. *J Bone Miner Metab*. 2003;21:17–21.
11. **Douchi T, Matsuo T, Uto H, Kuwahata T, Oki T, Nagata Y.** Lean body mass and bone mineral density in physically exercising postmenopausal women. *Maturitas*. 2003;45:185–190.
12. **Hsu YH, Venners SA, Terwedow HA, et al.** Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. *Am J Clin Nutr*. 2006;83:146–154.
13. **Leslie WD, Weiler HA, Nyomba BL.** Ethnic differences in adiposity and body composition: the First Nations Bone Health Study. *Appl Physiol Nutr Metab*. 2007;32:1065–1072.
14. **Li S, Wagner R, Holm K, Lehotsky J, Zinaman MJ.** Relationship between soft tissue body composition and bone mass in perimenopausal women. *Maturitas*. 2004;47:99–105.
15. **Liu JM, Zhao HY, Ning G, et al.** Relationship between body composition and bone mineral density in healthy young and premenopausal Chinese women. *Osteoporos Int*. 2004;15:238–242.
16. **Salamone LM, Glynn N, Black D, et al.** Body composition and bone mineral density in premenopausal and early perimenopausal women. *J Bone Miner Res*. 1995;10:1762–1768.
17. **Taaffe DR, Villa ML, Holloway L, Marcus R.** Bone mineral density in older non-Hispanic Caucasian and Mexican-American women: relationship to lean and fat mass. *Ann Hum Biol*. 2000;27:331–344.
18. **Wang MC, Bachrach LK, Van Loan M, Hudes M, Flegal KM, Crawford PB.** The relative contributions of lean tissue mass and fat mass to bone density in young women. *Bone*. 2005;37:474–481.
19. **Reid IR, Evans MC, Ames RW.** Volumetric bone density of the lumbar spine is related to fat mass but not lean mass in normal postmenopausal women. *Osteoporos Int*. 1994;4:362–367.
20. **Reid IR, Ames R, Evans MC, et al.** Determinants of total body and regional bone mineral density in normal postmenopausal women–a key role for fat mass. *J Clin Endocrinol Metab*. 1992;75:45–51.
21. **Reid IR.** Relationships among body mass, its components, and bone. *Bone*. 2002;31:547–555.
22. **Reid IR, Ames RW, Evans MC, Sharpe SJ, Gamble GD.** Determinants of the rate of bone loss in normal postmenopausal women. *J Clin Endocrinol Metab*. 1994;79:950–954.
23. **Gnudi S, Sitta E, Fiumi N.** Relationship between body composition and bone mineral density in women with and without osteoporosis: relative contribution of lean and fat mass. *J Bone Miner Metab*. 2007;25:326–332.
24. **Ijuin M, Douchi T, Matsuo T, Yamamoto S, Uto H, Nagata Y.** Difference in the effects of body composition on bone mineral density between pre- and postmenopausal women. *Maturitas*. 2002;43: 239–244.
25. **Khosla S, Atkinson EJ, Riggs BL, Melton LJ 3rd.** Relationship between body composition and bone mass in women. *J Bone Miner Res*. 1996;11:857–863.
26. **Kim JH, Choi HJ, Kim MJ, Shin CS, Cho NH.** Fat mass is negatively associated with bone mineral content in Koreans. *Osteoporos Int*. 2012;23:2009–2016.
27. **Moseley KF, Dobrosielski DA, Stewart KJ, De Beur SM, Sellmeyer DE.** Lean mass and fat mass predict bone mineral density in middle-aged individuals with noninsulin-requiring type 2 diabetes mellitus. *Clin Endocrinol (Oxf)*. 2011;74:565–571.
28. **Lee KG, Lee H, Ha JM, et al.** Increased human tumor necrosis factor-α levels induce procoagulant change in porcine endothelial cells in vitro. *Xenotransplantation*. 2012;19:186–195.
29. **Mizuma N, Mizuma M, Yoshinaga M, et al.** Difference in the relative contribution of lean and fat mass components to bone mineral density with generation. *J Obstet Gynaecol Res*. 2006;32:184–189.
30. **Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RN Jr.** Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. *Am J Clin Nutr*. 1994;60:23–28.
31. **Higgins JP, Green S.** Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. Meta-analysis of Observational Studies in Epidemiology: A Proposal. The Cochrane Collaboration. www.cochrane-handbook.org. Published March 2011.
32. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
33. **Normand SL.** Meta-analysis: formulating, evaluating, combining, and reporting. *Stat Med*. 1999;18:321–359.
34. **National Research Council.** *Combining Information: Statistical Issues and Opportunities for Research*. Washington DC: National Academy Press; 1992
35. **Viechtbauer W.** Conducting meta-analyses in R with the metafor package. *J Stat Software*. 2010;36:1–48.
36. **R Development Core Team.** *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2007.
37. **Cochran WG.** The combination of estimates from different experiments. *Biometrics*. 1954;10:101–129.
38. **Higgins JP, Thompson SG.** Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
39. **Sterne JA, Gavaghan D, Egger M.** Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol*. 2000;53:1119–1129.
40. **Bax L, Ikeda N, Fukui N, Yaju Y, Tsuruta H, Moons KG.** More than numbers: the power of graphs in meta-analysis. *Am J Epidemiol*. 2009;169:249–255.
41. **Douchi T, Oki T, Nakamura S, Ijuin H, Yamamoto S, Nagata Y.** The effect of body composition on bone density in pre- and postmenopausal women. *Maturitas*. 1997;27:55–60.
42. **Douchi T, Iemura A, Matsuo T, et al.** Relationship of head lean mass to regional bone mineral density in elderly postmenopausal women. *Maturitas*. 2003;46:225–230.
43. **Ho-Pham LT, Nguyen ND, Lai TQ, Nguyen TV.** Contributions of lean mass and fat mass to bone mineral density: a study in postmenopausal women. *BMC Musculoskelet Disord*. 2010;11:59.
44. **Ho-Pham LT, Nguyen UD, Pham HN, Nguyen ND, Nguyen TV.** Reference ranges for bone mineral density and prevalence of osteoporosis in Vietnamese men and women. *BMC Musculoskelet Disord*. 2011;12:182.
45. **Kim CJ, Oh KW, Rhee EJ, et al.** Relationship between body composition and bone mineral density (BMD) in perimenopausal Korean women. *Clin Endocrinol (Oxf)*. 2009;71:18–26.
46. **Lee JS, Kawakubo K, Sato H, Kobayashi Y, Haruna Y.** Relationship between total and regional bone mineral density and menopausal state, body composition and life style factors in overweight Japanese women. *Int J Obes Relat Metab Disord*. 2001;25:880–886.
47. **Lekamwasam S, Weerarathna T, Rodrigo M, Arachchi WK, Munidasa D.** Association between bone mineral density, lean mass, and fat mass among healthy middle-aged premenopausal women: a cross-sectional study in southern Sri Lanka. *J Bone Miner Metab*. 2009;27:83–88.
48. **Liu S, Li J, Sheng Z, Wu X, Liao E.** Relationship between body composition and age, menopause and its effects on bone mineral density at segmental regions in Central Southern Chinese postmenopausal elderly women with and without osteoporosis. *Arch Gerontol Geriatr*. 2011;53:e192–e197.
49. **Namwongprom S, Rojanasthien S, Mangklabruks A, Soontrapa S, Wongboontan C, Ongphiphadhanakul B.** Effect of fat mass and lean

mass on bone mineral density in postmenopausal and perimenopausal Thai women. *Int J Womens Health*. 2013;5:87–92.
50. **Ohmura A, Kushida K, Yamazaki K, Okamoto S, Katsuno H, Inoue T.** Bone density and body composition in Japanese women. *Calcif Tissue Int*. 1997;61:117–122.
51. **Park JH, Song YM, Sung J, et al.** The association between fat and lean mass and bone mineral density: the Healthy Twin Study. *Bone*. 2012;50:1006–1011.
52. **Nakaoka D, Sugimoto T, Kaji H, et al.** Determinants of bone mineral density and spinal fracture risk in postmenopausal Japanese women. *Osteoporos Int*. 2001;12:548–554.
53. **Bevier WC, Wiswell RA, Pyka G, Kozak KC, Newhall KM, Marcus R.** Relationship of body composition, muscle strength, and aerobic capacity to bone mineral density in older men and women. *J Bone Miner Res*. 1989;4:421–432.
54. **Benetos A, Zervoudaki A, Kearney-Schwartz A, et al.** Effects of lean and fat mass on bone mineral density and arterial stiffness in elderly men. *Osteoporos Int*. 2009;20:1385–1391.
55. **Barondess DA, Nelson DA, Schlaen SE.** Whole body bone, fat, and lean mass in black and white men. *J Bone Miner Res*. 1997;12:967–971.
56. **Bogl LH, Latvala A, Kaprio J, Sovijärvi O, Rissanen A, Pietiläinen KH.** An investigation into the relationship between soft tissue body composition and bone mineral density in a young adult twin sample. *J Bone Miner Res*. 2011;26:79–87.
57. **Chantler S, Dickie K, Goedecke JH, et al.** Site-specific differences in bone mineral density in black and white premenopausal South African women. *Osteoporos Int*. 2012;23:533–542.
58. **Chen Z, Lohman TG, Stini WA, Ritenbaugh C, Aickin M.** Fat or lean tissue mass: which one is the major determinant of bone mineral mass in healthy postmenopausal women? *J Bone Miner Res*. 1997;12:144–151.
59. **Compston JE, Bhambhani M, Laskey MA, Murphy S, Khaw KT.** Body composition and bone mass in post-menopausal women. *Clin Endocrinol (Oxf)*. 1992;37:426–431.
60. **Dytfeld J, Ignaszak-Szczepaniak M, Gowin E, Michalak M, Horst-Sikorska W.** Influence of lean and fat mass on bone mineral density (BMD) in postmenopausal women with osteoporosis. *Arch Gerontol Geriatr*. 2011;53:e237–e242.
61. **El Hage R, Mina F, Ayoub ML, Theunynck D, Baddoura R.** Relative importance of lean mass and fat mass on bone mineral density in a group of Lebanese elderly men. *J Med Liban*. 2012;60:136–141.
62. **Gnudi S, Malavolta N, Lisi L, Ripamonti C.** Bone mineral density and bone loss measured at the radius to predict the risk of nonspinal osteoporotic fracture. *J Bone Miner Res*. 2001;16:1130–1135.
63. **Gómez-Cabello A, Ara I, González-Agüero A, Casajús JA, Vicente-Rodríguez G.** Fat mass influence on bone mass is mediated by the independent association between lean mass and bone mass among elderly women: a cross-sectional study. *Maturitas*. 2013;74:44–53.
64. **Nur H, Toraman NF, Arica Z, Sarier N, Samur A.** The relationship between body composition and bone mineral density in postmenopausal Turkish women. *Rheumatol Int*. 2013;33:607–612.
65. **Reid IR, Plank LD, Evans MC.** Fat mass is an important determinant of whole body bone density in premenopausal women but not in men. *J Clin Endocrinol Metab*. 1992;75:779–782.
66. **Reid IR, Legge M, Stapleton JP, Evans MC, Grey AB.** Regular exercise dissociates fat mass and bone density in premenopausal women. *J Clin Endocrinol Metab*. 1995;80:1764–1768.
67. **Van Langendonck L, Claessens AL, Lefevre J, et al.** Association between bone mineral density (DXA), body structure, and body composition in middle-aged men. *Am J Hum Biol*. 2002;14:735–742.
68. **Edelstein SL, Barrett-Connor E.** Relation between body size and bone mineral density in elderly men and women. *Am J Epidemiol*. 1993;138:160–169.
69. **Ho-Pham LT, Lai TQ, Nguyen ND, Barrett-Connor E, Nguyen TV.** Similarity in percent body fat between white and Vietnamese women: implication for a universal definition of obesity. *Obesity (Silver Spring)*. 2010;18:1242–1246.
70. **Wu CH, Yao WJ, Lu FH, Yang YC, Wu JS, Chang CJ.** Sex differences of body fat distribution and cardiovascular dysmetabolic factors in old age. *Age Ageing*. 2001;30:331–336.
71. **Rauch F, Schoenau E.** The developing bone: slave or master of its cells and molecules? *Pediatr Res*. 2001;50:309–314.
72. **Schoenau E, Neu MC, Manz F.** Muscle mass during childhood–relationship to skeletal development. *J Musculoskelet Neuronal Interact*. 2004;4:105–108.
73. **Bielemann RM, Martinez-Mesa J, Gigante DP.** Physical activity during life course and bone mass: a systematic review of methods and findings from cohort studies with young adults. *BMC Musculoskelet Disord*. 2013;14:77.
74. **Mödder UI, Hoey KA, Amin S, et al.** Relation of age, gender, and bone mass to circulating sclerostin levels in women and men. *J Bone Miner Res*. 2011;26:373–379.
75. **Amrein K, Amrein S, Drexler C, et al.** Sclerostin and its association with physical activity, age, gender, body composition, and bone mineral content in healthy adults. *J Clin Endocrinol Metab*. 2012;97:148–154.
76. **Sheng Z, Tong D, Ou Y, et al.** Serum sclerostin levels were positively correlated with fat mass and bone mineral density in central south Chinese postmenopausal women. *Clin Endocrinol (Oxf)*. 2012;76:797–801.
77. **Drake MT, Srinivasan B, Mödder UI, et al.** Effects of parathyroid hormone treatment on circulating sclerostin levels in postmenopausal women. *J Clin Endocrinol Metab*. 2010;95:5056–5062.
78. **Vicente-Rodriguez G, Ara I, Perez-Gomez J, Dorado C, Calbet JA.** Muscular development and physical activity as major determinants of femoral bone mass acquisition during growth. *Br J Sports Med*. 2005;39:611–616.
79. **Mason C, Xiao L, Imayama I, et al.** Influence of diet, exercise, and serum vitamin D on sarcopenia in postmenopausal women. *Med Sci Sports Exerc*. 2013;45:607–614.
80. **Hansen RD, Allen BJ.** Habitual physical activity, anabolic hormones, and potassium content of fat-free mass in postmenopausal women. *Am J Clin Nutr*. 2002;75:314–320.
81. **Starling RD, Ades PA, Poehlman ET.** Physical activity, protein intake, and appendicular skeletal muscle mass in older men. *Am J Clin Nutr*. 1999;70:91–96.
82. **Wosje KS, Khoury PR, Claytor RP, et al.** Dietary patterns associated with fat and bone mass in young children. *Am J Clin Nutr*. 2010;92:294–303.
83. **Corwin RL, Hartman TJ, Maczuga SA, Graubard BI.** Dietary saturated fat intake is inversely associated with bone density in humans: analysis of NHANES III. *J Nutr*. 2006;136:159–165.
84. **Ernersson A, Nystrom FH, Lindström T.** Long-term increase of fat mass after a four week intervention with fast food based hyperalimentation and limitation of physical activity. *Nutr Metab (Lond)*. 2010;7:68.
85. **Beavers KM, Beavers DP, Nesbit BA, et al.** Effect of an 18-month physical activity and weight loss intervention on body composition in overweight and obese older adults [published online ahead of print September 20, 2013]. *Obesity (Silver Spring)*. doi:10.1002/oby.20607.
86. **Macdonald HM, New SA, Golden MH, Campbell MK, Reid DM.** Nutritional associations with bone loss during the menopausal transition: evidence of a beneficial effect of calcium, alcohol, and fruit and vegetable nutrients and of a detrimental effect of fatty acids. *Am J Clin Nutr*. 2004;79:155–165.
87. **Field AP.** Meta-analysis of correlation coefficients: a Monte Carlo comparison of fixed- and random-effects methods. *Psychol Methods*. 2001;6:161–180.
88. **Lee N, Radford-Smith GL, Forwood M, Wong J, Taaffe DR.** Body composition and muscle strength as predictors of bone mineral density in Crohn's disease. *J Bone Miner Metab*. 2009;27:456–463.