Untangling the Causality Knot: Another Tool for Clinical Researchers

Commentary on:
Chan MY, Frost SA, Center JR, Eisman JA, Nguyen TV. Relationship Between Body Mass Index and Fracture Risk Is Mediated By Bone Mineral Density. J Bone Miner Res 2014 in press.

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-- "Happy the man who has been able to learn the causes of things" (Virgil)

Clinical experience and a sound knowledge of pathophysiology are the traditional pillars of medicine. In recent years, new statistical methods have strengthened the ability of investigators to extract patterns from complex datasets that would otherwise remain hidden. Research to predict clinical events and the methods needed to support these analyses have evolved in tandem over the last few decades in a classical pas de deux. Indeed, the landscape of modern medicine would hardly be recognizable without such techniques. The recent development of fracture prediction tools is a prime example of one clinical application of powerful statistical methods (1).

When predicting an event is the sole objective, the existence of an association – whether causal or not – may be sufficient. However, to understand how that association arises, and to intervene appropriately, requires a deeper understanding of the cause and effect relationships. Obesity, defined from elevated body mass index (BMI), has generated much controversy in the osteoporosis literature, variably reported to be protective, neutral or a risk factor for osteoporosis and related fractures (2-4). Weight and BMI are both strongly correlated with bone mineral density (BMD) as measured form dual energy x-ray absorptiometry (DXA) in almost all studies, and it is no accident that weight or BMI are a component of virtually all fracture prediction tools (1). However, when weight is partitioned into its components of lean mass and fat mass, the associations become more complicated. Most studies find that lean mass is positively associated with higher BMD (5;6), whereas fat mass shows neutral or negative effects though there are exceptions to this generalization and a biphasic effect has even been reported (5;7-12). A recent meta-analysis found that among premenopausal women lean mass exerted a greater effect on

femoral neck BMD than fat mass (r = 0.45 vs r = 0.30), whereas in postmenopausal women the effects of lean mass and fat mass were similar (r = 0.33 vs r = 0.31) (13). The presence of large correlations amongst weight, BMI, lean mass and fat mass create collinearities that can pose a nightmare for data analysts and has fueled some of this controversy (4). For example, if one assumes that lean mass is solely responsible for BMD and that fat mass has no effect, then a model that includes weight and fat mass would actually show the latter as having an adverse (negative) effect on BMD simply because fat is interpreted as "not lean" in the model. Body composition is a major factor impacting on accuracy errors in DXA, effects that are amplified in longitudinal studies where weight, body composition and BMD (not to mention a myriad of other factors) are changing simultaneously (14-16).

A recent meta-analysis examined the association between BMI and fracture risk in prospective cohorts from 25 countries (398,610 women average age 63 years, 2.2 million person-years follow up) with a reported 22% prevalence of obesity (17). Risk for major osteoporotic fractures and hip fractures decreased monotonically with increasing BMI when the modifying effect of BMD was excluded. When BMD was considered, the effect of BMI was greatly reduced and, at least for major osteoporotic fractures, showed a biphasic response such that fracture risk decreased as BMI increased to the normal range and then slightly increased for overweight and obese individuals. Obese women were at lower risk for major osteoporotic fractures when BMD was not considered (hazard ratio 0.87 for BMI 35 kg/m^2 versus 25 kg/m^2) but at higher risk when BMD was considered (HR 1.16). In this analysis, low BMI was a risk factor for hip and all osteoporotic fractures, and was associated with lower risk for lower leg fractures; conversely, high BMI was a risk factor for upper arm fractures. Even after adjustment for BMD, low BMI was a risk factor for hip fracture and high BMI remained a risk factor for

upper arm fracture and also all osteoporotic fractures. Data from 52,939 women in the Global Longitudinal Study of Osteoporosis in Women (GLOW) found that relationships between fracture and weight, BMI, and height were site-specific (18;19). Despite this, there is evidence from the Study of Osteoporotic Fractures (SOF) that tools such as FRAX are still of value in predicting hip and major osteoporotic fractures in obese postmenopausal women, particularly when BMD contributes to the risk calculation (20). These observations clearly challenge our understanding of weight as a risk factor for osteoporosis and fractures, and have given rise to a plethora of basic, translational and clinical investigations into bone-fat-muscle interactions. If obesity is truly a risk factor for osteoporotic fractures, and not a protective factor as historically assumed, then this has major clinical implications given the epidemic crisis in obesity that is seen globally. It also begs the question of why something that is associated with preserved BMD would be a risk factor for fracture. Potential contributors include greater falls risk, adverse changes on skeletal biomechanics, alterations in energy metabolism, metabolic syndrome, overt type 2 diabetes mellitus or its associated treatments and comorbidities (21-25). Of course, this assumes that the association between obesity and fractures is causal. But what if the association is not causal at all? It is of scientific and public health importance to clarify the nature of the BMI-BMD correlation in order to more fully understand the "obesity paradox".

It is against this backdrop that Chan et al. (26) shed new light on the topic using causal mediation analysis. Mediation occurs when part or all of the effect of an exposure on an outcome operates through an intermediate causal pathway. In the current issue of *JBMR*, Chan et al. explore the role of BMD in mediating the relationship between BMI and risk of fracture for hip, vertebrae, upper limb, and lower limb sites, as well as for all fracture sites. The authors examined

the mediating effect of BMD in the longitudinal, observational Dubbo Osteoporosis Epidemiology Study (DOES) that has followed more than 3,500 men and women since 1989.

In order for a variable to be identified as a mediator, it is assumed to have an association with both exposure and outcome variables. Furthermore, adjustment for the mediator attenuates the relationship between these variables. While the same assumptions apply to a confounding variable, the key difference between mediator and confounding variables is that the mediator model is adopted when a causal mechanism is assumed to exist in the data. The directional arrows in Figure 2 of Chan et al. (26) imply that BMI has a causal relationship with BMD and also that BMD has a causal relationship with fracture risk.

Timing of variable relationships and the existence of a known or suspected mechanism for causality are key issues to be addressed when identifying a plausible mediator variable. Mediation models are widely used in experimental studies, because the temporal relationships amongst the exposure, mediator, and outcome are typically easy to establish. For example, Ten Have and Joffe (27) describe a clinical study in which prescription medication use was investigated as a mediator of the causal relationship between a suicide prevention program (collaborative care versus usual care) and scores on the Hamilton depression scale.

Mediation models are increasingly being used in observational studies as researchers seek to test causal hypotheses that advance theory (28). However, mediation models are challenging to defend in observational studies, particularly cross-sectional studies. When the exposure and mediator variables are inherent attributes of the individual, as is the case with both BMI and BMD, it is more difficult to unequivocally argue for the presence of mediation than when the variables are external characteristics of the individuals, such as medication use or program participation. The Figure 2 model in Chan et al.(26) implies that change in BMI “precedes”

change in BMD. This is plausible given the absence of a biological model whereby change in BMD would affect BMI, but does not exclude the possibility of true confounding (e.g., frailty, malnutrition) or technical factors related to DXA alluded to earlier. The role of BMD as a major determinant of fracture risk is consistent with a wealth of clinical and experimental data. Thus, there are a sound clinical and biological arguments to defend BMD's role as a as a mediator variable. The assumption of a linear association between BMI and BMD is more tenuous, however, and recent evidence suggests that this relationship plateaus at higher levels of BMI (29).

Baron and Kenny's (30) mediation model testing strategy for linear models has been widely adopted in psychological and other social science research. Extensions of this testing strategy for non-linear models, including the logistic model adopted by Chan et al. (26), are more recent (31;32). Three models are fit to the data. The first model tests the association between BMI and fracture risk, to provide an estimate of the direct BMI effect. The second model tests the association between BMI and BMD, while the third model tests the association of both BMD and BMI with fracture risk in a multiple logistic regression model. The first two models are used to establish the presence of univariate linear relationships amongst the variables; if one or more of these relationships are not statistically significant, one can conclude that a mediation effect is unlikely to occur. With respect to the third model, if the association between BMI and fracture risk is not statistically significant after controlling for BMD, one can conclude that full mediation has occurred. If BMI remains statistically significant after including the mediator variable in the model, one can conclude that partial mediation has occurred.

For both men and women, Chan et al. (26) found increased BMI was associated with reduced overall fracture risk, and this association was stronger for men (hazard ratio [HR] per

standard deviation [SD] = 0.77; 95% confidence interval [CI]: 0.67 – 0.88) than for women (HR per SD = 0.92; 95% CI: 0.85 – 0.99). The association for site-specific fractures was statistically significant amongst women for hip and amongst men for hip and vertebral sites. An association between BMD and BMI of moderate size was also observed for both sexes. Thus, the univariate relationships amongst the variables were established. For any fracture, the inverse relationship between BMI and fracture risk disappeared amongst women after adjusting for BMD, but remained statistically significant for men. As Table 4 reveals, the effect of BMI on fracture risk that adjusted for the causal effect of BMD was statistically significant for all fracture sites. These results lend support to the role of BMD as a mediator variable. For all analyses, the authors used Sobel's (33) test of statistical significance for the indirect effect, as well as adopting a robust bootstrap procedure to produce 95% confidence intervals. The former is sensitive to small sample sizes, while MacKinnon et al. (34) observed, via simulation, that the bootstrap maintains good Type I error and power, and thus is frequently recommended to measure precision of estimates.

It is important to note that throughout the three-step modeling strategy a number of confounding covariates were included in the mediation models, including age, history of falls, prior fracture, history of smoking, physical activity level, and use of pharmacologic therapies. There is the potential for spurious tests of the association amongst the exposure, outcome, and mediator variables if confounders are not taken into account. In developing a mediation model for observational data, selection and inclusion of covariates is therefore critically important. Covariates can be included directly in the multiple regression model or, if appropriate, via a propensity-score or matching methodology. It is important to note that it is possible for a variable to serve as a mediator in one model and a confounder in another model, depending on the

exposure and outcome of interest. Thus, it is important that investigators not to apply a “one size fits all” modeling strategy to causal mediation models.

Another requirement for identifying a mediator variable is the lack of an interaction between exposure and mediator variables. This can be assessed by a multiple (linear or non-linear) regression model containing main effect and two-way interaction effect terms. Chan et al. tested the two-way interaction effect between BMI and BMD and found that it was not statistically significant. Also important in the model is establishing a linear relationship between BMI and BMD.

Fitting a series of linear or non-linear multiple regression models to one’s data is a common approach to test for a mediation effect, but a structural equation modeling (SEM) approach might also be considered. SEM is used to simultaneously solve for estimates of direct and indirect effects (35); an advantage is that measures of overall model goodness-of-fit are produced, offering the opportunity to compare the fit of different mediation models. SEM was initially developed for linear models, models that accommodate continuous and discrete variables have been proposed (32;36); but may require specialized software. Mediation models that accommodate multiple potential mediation variables and repeated measurements of exposure, outcome, and mediation variables over time (37)can be applied to complex observational data.

Does Chan et al. (26) prove that obesity is not a risk factor for fracture and that the effects of BMI are largely (if not completely) mediated through BMD? No single study would be able to establish this and, inevitably, it is the totality of the evidence that will lead us in the correct direction. Causal mediation analysis provides another analytical tool to attach to the researcher’s tool belt to test complex relationships in a variety of contexts, including fracture risk

prediction models, that is new to this field of inquiry (38). However, the use of this tool must be tempered with careful thought for the theoretical implications of the underlying models.

References

1. Rubin KH, Friis-Holmberg T, Hermann AP, Abrahamsen B, Brixen K. Risk assessment tools to identify women with increased risk of osteoporotic fracture: complexity or simplicity? A systematic review. J Bone Miner Res 2013;28(8):1701-17.

2. Compston J. Obesity and fractures. Joint Bone Spine 2013;80(1):8-10.

3. Gower BA, Casazza K. Divergent effects of obesity on bone health. J Clin Densitom 2013;16(4):450-4.

4. Reid IR. Fat and bone. Arch Biochem Biophys 2010;503(1):20-7.

5. Beck TJ, Petit MA, Wu GL, Leboff MS, Cauley JA, Chen Z. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the Women's Health Initiative-Observational Study. J Bone Miner Res 2009 Aug;24(8):1369-79.

6. Petit MA, Beck TJ, Shults J, Zemel BS, Foster BJ, Leonard MB. Proximal femur bone geometry is appropriately adapted to lean mass in overweight children and adolescents. Bone 2005;36(3):568-76.

7. Travison TG, Araujo AB, Esche GR, Beck TJ, McKinlay JB. Lean mass and not fat mass is associated with male proximal femur strength. J Bone Miner Res 2008;23(2):189-98.

8. Leslie WD, Weiler HA, Lix LM, Nyomba BL. Body composition and bone density in Canadian White and Aboriginal women: the First Nations Bone Health Study. Bone 2008;42(5):990-5.

9. Zhao LJ, Liu YJ, Liu PY, Hamilton J, Recker RR, Deng HW. Relationship of obesity with osteoporosis. J Clin Endocrinol Metab 2007;92(5):1640-6.

10. Hsu YH, Venners SA, Terwedow HA, Feng Y, Niu T, Li Z, 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(1):146-54.

11. Reid IR, Ames R, Evans MC, Sharpe S, Gamble G, France JT, 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(1):45-51.

12. Viljakainen HT, Pekkinen M, Saarnio E, Karp H, Lamberg-Allardt C, Makitie O. Dual effect of adipose tissue on bone health during growth. Bone 2011;48(2):212-7.

13. Ho-Pham LT, Nguyen UD, Nguyen TV. Association between lean mass, fat mass, and bone mineral density: a meta-analysis. J Clin Endocrinol Metab 2014;99(1):30-8.

14. Blake GM, Fogelman I. How important are BMD accuracy errors for the clinical interpretation of DXA scans? J Bone Miner Res 2008;23(4):457-62.

15. Bolotin HH, Sievanen H, Grashuis JL. Patient-specific DXA bone mineral density inaccuracies: Quantitative effects of nonuniform extraosseous fat distributions. J Bone Miner Res 2003;18(6):1020-7.

16. Yu EW, Bouxsein ML, Roy AE, Baldwin C, Cange A, Neer RM, et al. Bone loss after bariatric surgery: Discordant results between DXA and QCT bone density. J Bone Miner Res 2014;29(3):542-50.

17. Johansson H, Kanis JA, Oden A, McCloskey E, Chapurlat RD, Christiansen C, et al. A meta-analysis of the association of fracture risk and body mass index in women. J Bone Miner Res 2014;29(1):223-33.

18. Compston JE, Watts NB, Chapurlat R, Cooper C, Boonen S, Greenspan S, et al. Obesity is not protective against fracture in postmenopausal women: GLOW. Am J Med 2011;124(11):1043-50.

19. Compston JE, Flahive J, Hosmer DW, Watts NB, Siris ES, Silverman S, et al. Relationship of weight, height, and body mass index with fracture risk at different sites in postmenopausal women: the Global Longitudinal Study of Osteoporosis in Women (GLOW). J Bone Miner Res 2014;29(2):487-93.

20. Premaor M, Parker RA, Cummings S, Ensrud K, Cauley JA, Lui LY, et al. Predictive value of FRAX for fracture in obese older women. J Bone Miner Res 2013;28(1):188-95.

21. Rosenblatt NJ, Grabiner MD. Relationship between obesity and falls by middle-aged and older women. Arch Phys Med Rehabil 2012;93(4):718-22.

22. Kim T, Park S, Pak YS, Lee S, Lee EH. Association between metabolic syndrome and bone mineral density in Korea: the Fourth Korea National Health and Nutrition Examination Survey (KNHANES IV), 2008. J Bone Miner Metab 2013;31(6):652-62.

23. Sornay-Rendu E, Boutroy S, Vilayphiou N, Claustrat B, Chapurlat RD. In obese postmenopausal women, bone microarchitecture and strength are not commensurate to greater body weight: the Os des Femmes de Lyon (OFELY) study. J Bone Miner Res 2013;28(7):1679-87.

24. Sealand R, Razavi C, Adler RA. Diabetes mellitus and osteoporosis. Curr Diab Rep 2013;13(3):411-8.

25. Lecka-Czernik B. Safety of anti-diabetic therapies on bone. Clin Rev Bone Miner Metab 2013;11(1):49-58.

26. Chan MY, Frost SA, Center JR, Eisman JA, Nguyen TV. Relationship between body mass index and fracture risk is mediated by bone mineral density. J Bone Miner Res forthcoming 2014.

27. Ten Have TR, Joffe MM. A review of causal estimation of effects in mediation analyses. Stat Methods Med Res 2012;21(1):77-107.

28. Mascha EJ, Dalton JE, Kurz A, Saager L. Statistical grand rounds: understanding the mechanism: mediation analysis in randomized and nonrandomized studies. Anesth Analg 2013;117(4):980-94.

29. Leslie WD, Orwoll ES, Nielson CM, Morin SN, Majumdar SR, Johansson H, et al. Estimated lean mass and fat mass differentially affect femoral bone density and strength index but are not FRAX independent risk factors for fracture. J Bone Miner Res forthcoming 2014.

30. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51(6):1173-82.

31. MacKinnon DP, Dwyer JH. Estimating mediated effects in prevention studies. Evaluation Review 1993;17(2):144-58.

32. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. Psychol Methods 2010;15(4):309-34.

33. Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. In: Leinhardt S, editor. Sociological Methodology. Washington,DC: American Sociological Association; 1982. p. 290-312.

34. MacKinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect: distribution of the product and resampling methods. Multivariate Behav Res 20041;39(1):99-128.

35. Kline R. Principles and practice of structural equation modeling. 3rd ed. New York: The Guilford Press; 2010.

36. Hayes AF, Preacher KJ. Quantifying and testing indirect effects in simple mediation models when the constituent paths are nonlinear. Multivariate Behav Res 2010;45(4):627-60.

37. Cole DA, Maxwell SE. Testing mediational models with longitudinal data: Questions and tips in the use of structural equation modeling. J Abnorm Psychol 2003;112(4):558-77.

38. Sritara C, Thakkinstian A, Ongphiphadhanakul B, Chailurkit L, Chanprasertyothin S, Ratanachaiwong W, et al. Causal relationship between the AHSG gene and BMD through fetuin-A and BMI: Multiple mediation analysis. Osteoporos Int 2014;25(5):1555-62.