

Chapter 7

Nutritional Epidemiology: Nutritional Assessment and Analysis

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Key Points

- Dietary assessment can determine the amount of foods, nutrients, energy, and other dietary components consumed.
- Methods include the 24-h recall, diet record, food frequency questionnaire, and others.
- Cross-sectional and longitudinal studies of the skeleton have used assessment methods to determine if any benefits accrue from defined diets or from single or multiple nutrient supplements
- Randomized controlled trials for one or more years designed to test nutrients besides calcium are needed for advancing our knowledge of skeletal effects and recommending dietary intakes of nutrients across the life cycle.

Keywords Food frequency • 24 h recall • Nutritional epidemiology • Diet assessment • Calcium • Phosphorus • Vitamin D

7.1 Introduction

This overview of nutritional assessment is a revised version of the chapter (Chap. 7) in the first edition [1]. Better understandings of diet–bone linkages help in both the promotion of bone health and the prevention of osteopenia, osteoporosis, and skeletal fractures in late life. Many nutritional factors contribute to skeletal development during the first two decades of life, to the maintenance of the adult skeleton, and to attempts to bolster bone mass and bone density in late life. Many nutrients are of importance for adults and the elderly, notably calcium, phosphorus, and vitamin D, but also protein, magnesium, vitamins C and K, carotenoids, and others. On the other hand, although phosphorus and vitamin A are both essential for bone status, too much of these nutrients may have negative consequences, and care to avoid excess intakes in the context of the US diet is advised. Several trace

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minerals found in bone likely exist by their omnipresence in the earth's crust including silicon, an under-researched, but important mineral for bone status [2] and an increasing number of phytonutrients, such as carotenoids, are understood to protect bone with aging.

Prior reports of nutrient intakes of older adults show that major changes in nutrient consumption begin at approximately 70 years of age, when older men and women start to have marked reductions in both macronutrient and micronutrient intakes from foods [3–5]. Since micronutrient requirements do not generally decrease, and in some cases increase, with aging, the selection of micronutrient-dense foods remains of major importance throughout adulthood.

Several chapters in this book provide information on other risk factors for bone health, including nutritional variables and lifestyle factors. The use of data on dietary intakes of calcium, for example, permits statistical analyses that uncover associations or linkages between assessments of dietary variables and measurements of bone mass (bone mineral content, BMC) or density (bone mineral density, BMD) by dual energy X-radiography (DXA). DXA is the main device used today for assessing adult bone status. Epidemiological and biostatistical methods, using both linear and nonlinear techniques, generate statistical meaning of any diet–bone associations, but not of the mechanistic aspects of the linkages that require biological information.

This chapter covers methods used in nutritional assessment with selected references to published reports that utilize the types of nutritional assessments that relate dietary nutrients to bone status.

7.2 Dietary Intake Assessment

Capturing the intake of nutrients across a 24-h period or longer is much more difficult than it may appear [6]. Validity of dietary data varies by method and by nutrient, depending on time period to be assessed. Common dietary methodologies include the diet record, where individuals record detail on everything they eat or drink, the 24-h recall (24HR), where respondents are asked to report everything they ate or drank the day before with detail on preparations and recipes, and the food frequency questionnaire (FFQ), where individuals report their usual pattern of intake over the past year for different types of foods, with or without additional information on portion sizes and preparation. For epidemiologic analyses relating dietary intake to bone status or fracture outcome, we are usually interested in usual long-term intake, which may be estimated with multiple individual days or with one or more food frequency questionnaires. Because diet records require educated and compliant volunteers, they are less useful in large population-based epidemiologic studies. The respondent burden is high, and poor completion rates and variable completion quality limit their validity. Further, dietary records have been shown to underestimate and misrepresent usual intake, as individuals tend to consume less when focused on recording their intake. For these reasons, we discuss only the 24-h recall (24HR) and food frequency questionnaire (FFQ) methods below.

7.2.1 24-Hour Recall

The 24HR is widely used in large surveys, including the National Health and Nutrition Examination Survey (NHANES) in the USA. An interviewer asks each participant to recall everything ingested as a food or beverage, or taken as a supplement, during the previous 24 h. Although incomplete information is always a concern with this method because of memory lapses or lack of knowledge of specific recipes of dishes consumed, recent advances in data entry, such as the USDA automated multiple pass system, along with food models, booklets or other portion size aids [7, 8], have greatly improved

completeness and validity [9]. Because the recall is open-ended, it allows for diverse foods and preparations and is, therefore, an excellent choice for multiethnic groups or new populations, for whom specific questionnaires have not been developed. Recalls are usually interviewer-administered, with direct input into a computer system, either in person or over the telephone [10, 11]. New programs, such as the National Cancer Institute (NCI) computer-assisted 24HR, (ASA24), allow compliant individuals enter their own data [12].

Data from 24HR provide valid group and subgroup nutrient intake means and, as such, is an excellent tool for population surveillance. For use in relation to individual outcomes such as bone mineral density or incidence of fracture, however, the 24HR has important limitations. Primarily, the day-to-day variation in individual intake limits the 24HR as a measure of usual intake [13, 14]. To the extent that intraindividual variation exceeds interindividual variation in the population under study, large numbers of individuals may be grossly misclassified relative to their usual intake, resulting in attenuation of or complete inability to see associations with outcome variables. For example, if someone who rarely eats meat happens to be interviewed the day after going out for an annual steak dinner, their recorded intake will not even closely represent their usual intake. At the population level, this variation can be assumed to be random error. Therefore, the group mean will be reasonably valid, but misclassification of individuals will weaken the ability to detect true associations. This variation differs by nutrient [14, 15], depending on whether they are concentrated in infrequently consumed foods (like vitamin A in liver), or if part of a regular daily pattern (like milk intake with meals). As an example, using data from Finland, 7–14 days were considered adequate to classify most nutrients, but nutrients with high variability may require 21 days or more [16].

Most large studies cannot afford to collect multiple days of intake to stabilize the within person estimates toward their usual intake. To the extent that the day-to-day variability is truly random, statistical corrections may be used when at least 2 days of intake are available to estimate intraindividual or interindividual variation. This ratio can then be used to better estimate the true association in linear models with continuous outcome variables [13, 17]. Because the effect of this random error is always toward the null, this means that most observed associations will underestimate the truth. The application of a correction for this can then provide evidence for an association that may not be seen directly.

In addition to this correction for random error, the National Cancer Institute (NCI) designed a method to improve nutrient intake estimates from recalls, by adding a propensity (frequency) questionnaire to record intake of episodically consumed foods (like liver). This approach will help to avoid the extreme misclassification in cases where low nutrient intakes are captured on the 2 days of recorded recall, but where an individual reports relatively frequent consumption of an important source of that nutrient on other days. An example would be low retinol intakes on two random days that did not include weekly consumption of liver (a high retinol food). To consider this information, the NCI developed a two step model to (1) estimate the probability of intake from 2 recalls, and (2) fit a model with the transformed recall data, adjusted for episodically consumed foods from the FFQ [18]. Although this approach improves estimates, it still does not allow precise assignment of nutrient intake to individuals. A further limitation of corrections for intraindividual/interindividual variation is that the within-to-between variability is not constant across populations, so that adjustments for the full sample may bias estimates of subgroups [19].

Addition concerns for validity in the 24HR include differential underreporting [20] by certain subgroups in the population, including obese individuals [21–23], smokers [21], women [22], and restrained eaters [24, 25]. Although some statisticians have experimented with adjustment for this nonrandom error in reporting behavior, it will vary by population and is unlikely to be easily corrected. To the extent that the underreporting represents portion sizes rather than exclusion of specific food groups, adjustment for total energy intake will help to improve ranking in nutrient intake distributions relative to total intake or requirement, thereby improving ability to detect associations with outcomes.

7.2.2 *Food Frequency Questionnaire (FFQ)*

Because of the need for repeat measures and rather complex post-measurement statistical adjustment with the 24HR, the food frequency questionnaire (FFQ) is the main tool used in large epidemiologic studies. Unlike 24HR, FFQ capture usual intake over a period of time, usually the past year, in a single administration. The FFQ consists of a food list, where like foods are grouped together to minimize length. Respondents are then asked to note the frequency of consumption of each food type, for example, “red meat (beef, pork, and lamb) and meat dishes”. Responses include a range of options such as: rarely or never; less than once/month; two to three times/month; one to two times/week; three to six times/week; once/day; twice/day; three or more times/day. Portion size options may be provided or, in the Willett FFQ, may be assumed from other population-based data. Nutrient intake is calculated by multiplying the frequency by the portion size to obtain an amount, and then calculated from the weighted nutrient content for key foods within the food line item. For red meat in the US population, this may include a heavy weighting for ground beef, lower weightings for steak or beef stew, pork chops or roast, and lower still for lamb, which together add to 100 % to form a composite food with appropriate nutrient content.

As is evident from this example, FFQ will contain measurement error due to limitations in the food list, individual food weighting assumptions, and un-captured variation in portion size. Despite these limitations in individual specificity, however, FFQ have been shown to rank intakes well after total energy intake adjustment [15], particularly when developed for and validated with a specific population [26, 27]. What is important to note is that the assumptions included in the food list and specific food weightings within each line item are based on the most frequently consumed foods and recipes in either national data or another data set. Therefore, when a subgroup varies considerably in their dietary pattern, the use of FFQ developed for the majority US population will misclassify them. In fact, the most commonly used FFQ have shown poor results in minority populations. For example, validity coefficients for energy intake in the Block FFQ were 0.44 for non-Hispanic white women, but only 0.14 for Hispanic women [28].

For this reason, it is important that the FFQ selected for use has been calibrated for use and validated in each group with different dietary patterns targeted for study analyses.

7.3 **Dietary Recall vs. Food Frequency Questionnaire: Focus on Micronutrients**

Given the limitations discussed above, the choice of 24HR vs. FFQ ultimately depends on the goals of the specific study. 24HR estimate both macro and micronutrients more precisely than do FFQ in the short term, while FFQ obtain data on usual intake over a longer period of time, but lack the precision of individual portion sizes and recipes. Energy-adjustment usually improves the accuracy of micronutrient intake ranking in populations for which the questionnaire has been designed and validated, but captures less accurate quantitative estimates of actual micronutrient intakes. The extent of misclassification from a few recalls will depend on the intraindividual variation of intake in the population under study. To illustrate this, we will discuss a few specific micronutrients of importance to bone health: calcium, phosphorus and vitamin D.

7.3.1 *Calcium Intake Assessment*

Assessment of total calcium intake requires quantification of the amounts of calcium naturally in foods, of calcium used in foods as a fortificant, and lastly as supplemental calcium. A recent estimate of total

calcium intake by adults, using NHANES data from 2003 to 2006 showed that intakes ranged from a mean of 728 mg/day in men 81 year of age and older to 968 mg/day in men 31–40 year, and from 581 mg/day in women 81 year and older to 730 mg/day in those 31–40 year [29]. These data suggest that most adults do not meet the Recommended Allowances of 1,000 mg/day for ages 19–50 year (both genders), 1,000 mg/day for males between 50 and 70 year, and 1,200 for females beyond age 50, of the Institute of Medicine [30]. The same analysis by Mangano et al. [29], noted that from 33 % of younger to 56 % of older men, and from 42 % of younger to 69 % of older women take supplements containing some amount of calcium—adding an average of 74 (younger men) to 393 (older women) mg/day to their intakes. Importantly, however, non-supplement users tended to also have lower dietary intake than supplement users, and thus constitute a large group with clearly low calcium exposure.

The means reported above are for specific age and sex groups, based on 24HR data in the national survey. Estimates for individuals in the NHANES recalls, whether a single day in earlier surveys, or the average of 2 days in more recent years, will be limited and subject to misclassification from intra-individual day to day variation. For calcium, the coefficients of variation within (CVw) and between (CVb) individuals, calculated from the NHANES 2007–2008 data, were 52 %:37 % for adult men and 46 %:38 % for adult women [15]. To the extent that within-person variation exceeds the variance between-individuals (as it does here), more days will be needed to obtain a stable estimate for individual usual intake. With only a few days, individuals are likely to be misclassified in the distribution, making it difficult to find significant associations with outcome measures, such as bone mineral density. Still, the practice of consuming milk and dairy products, the major sources of calcium, tends to be reasonably regular and the ratios described above (1.2–1.4) are not extreme relative to many other nutrients. High intraindividual and interindividual variability in micronutrient intakes is another reason why most epidemiologic studies use the FFQ, rather than the 24 HR, and adjust for total energy intake to standardize relative to likely individual requirement.

Regardless of the method for data collection, the frequent use of calcium supplements by a large subset of the population will distort the distribution for total calcium intake. For this reason, it is common practice to add supplement use in statistical models separately from linear measures of dietary intake. This may be done either as a yes/no variable or in categories of intake levels (0=no supplement use; 1=some-250 mg (the amount that may be in a multivitamin-mineral supplement; and 2=>250 mg (suggesting specific calcium supplement use). Another approach is to calculate total calcium intake by summing diet and supplement intakes, but then to perform analyses in quartile or quintile categories (understanding that the highest categories will be due largely to supplement use).

7.3.2 Phosphorus Intake Assessment

In contrast to calcium, phosphorus is found in practically all foods and, increasingly, is added to processed foods to improve flavor or texture and to increase shelf life [31, 32]. Public health concern has surfaced because of the excess amounts of phosphorus consumed in the USA and the resulting lower dietary calcium to phosphorus ratio (Ca:P). The addition of numerous phosphorus compounds to our food supply is becoming an important public health concern [33, 34]. Although adequate phosphorus intake is necessary for healthy bone formation, excess phosphorus may pose significant risk. Most of the research on the damaging effects of high phosphorus exposure has been conducted with kidney patients, where it is known that high serum phosphate is associated with elevated risk for heart disease and mortality [35–37]. However, it is now believed that high phosphorus exposure may contribute to cardiovascular disease (CVD) in the general population. It has been shown to stimulate fibroblast growth factor-23, secreted by osteocytes, and parathyroid hormone, secreted by the parathyroid gland, both of which have been associated with elevated CVD risk [38–41]. High levels of added

phosphorous compounds may also contribute to low bone mineral density. For example, regular cola consumption has been linked with lower bone mass in adult women [42].

Research in this area remains limited in part, because it is difficult to accurately assess the usual long-term exposure to added phosphorus compounds in individuals. Food composition tables are currently incomplete for phosphate additives, and vary considerably in actual content even within category. For example, poultry, which is widely consumed, may be sold without additives, or it may be basted in a plastic shrink-wrap package, with phosphate compounds in the liquid. This information is not currently collected in most dietary methods. Even without this information, however, using the known food composition of phosphorus currently in the database, US adults obtain considerably more than the RDA of 700 mg per day for men and women [43]. Data from the NHANES, 2005–2006 show that many adults exceed twice that amount (ranging from a mean of 1,270 mg for men aged 71 year and older, to almost 1,730 mg in men 31–50 year; and from 985 in women aged 71 year and older, to about 1,200 in women aged 31–50 year [44]. Even more concerning is that we know that these intakes are underestimates. Several studies compared estimated intake from the national nutrient database with direct chemical analysis of food and found that phosphorus intake was likely underestimated by 25–30 % [9, 45–47]. In addition, it is important to note that the phosphorus from additive salts is highly absorbed and bioavailable relative to that found in foods.

Given the rather large error in our current estimates of actual phosphorus exposure, it is also difficult to estimate the actual day-to-day variability in intake. However, as measured in the NHANES 2007–2008, the CVw /CVB for phosphorus intake were reported as 37 %/30 % in adult men and 37 %/29 % in adult women, similar to those for calcium [15]. This suggests that the intraperson variation exceeds between-person variation, but not to an extreme degree, so that rankings would be possible with several days of recall or, as is usually done, with a single good quality FFQ measure. To the extent that individuals tend to consume processed foods vs. not on a regular basis, the actual values for phosphorus intake may have an extended distribution and the true intra/inter person variation may be lower than currently estimated.

For all these reasons, it is important to continue to improve the status of the national nutrient databank to keep up with rapid changes in the food supply. In addition, future analyses with phosphorus intake may benefit from methods similar to those used with supplements or other nutrients added to the food supply vs. naturally in the food matrix (such as natural folate vs added folic acid), to account for these differences in bioavailability [48]. Further long-term investigations are needed to understand the potentially adverse effects of high serum PTH under high phosphorus intake conditions or when the phosphorus to calcium intake ratios continue to exceed 2:1, as is already true for most US adults.

7.3.3 *Vitamin D Intake Assessment*

Vitamin D has recently gained enormous attention due to increasing understanding of its importance to numerous systems for maintaining health. This vitamin is unique in that it has historically largely been obtained endogenously, by activation of 7-dehydrocholesterol in the skin by sunlight to provitamin D₃, which is then converted to cholecalciferol. This process works well only with regular direct sun exposure and in northern latitudes, clear seasonal variation in vitamin D status is apparent, with drops in the winter and spring in the Northeastern United States [49]. Surprisingly, however, many recent surveys have shown low or deficient vitamin D status in populations even in lower latitude sunny areas [50, 51]. Concern for skin cancer, increasing use of sunscreen, and availability of air-conditioned cars and buildings has led to lower sun exposure throughout the world. Because of this, more attention has been given to vitamin D intake from both food and supplements. However, vitamin D is in very few foods. In the USA, most of our vitamin D intake comes from fortified milk, fatty fish, eggs, some fortified yogurts, and fortified breakfast cereals. Still, dietary intake of vitamin

D, as measured by FFQ, does associate significantly with serum concentration, as has been shown in the Framingham Heart Study [52]. Because vitamin D is found in high concentration in limited foods, like fatty fish, within person day to day variation will be much larger than between-person variation. Therefore, a few 24HR are unlikely to rank usual intake well and use of an FFQ is advisable.

The most recent Institute of Medicine (IOM) Panel set the RDA for vitamin D at 600 IU (15 mg)/day for most individuals, and at 800 IU (20 mg)/day for those 71 year and older. They further recommended that serum 25(OH)-vitamin D concentration should be above 20 ng/mL (50 nmol/L), although many researchers argue that concentrations much greater than this may offer better protection against chronic disease [53]. Because of the attention to this nutrient, increasing numbers of individuals are taking supplements either the year round, or during the winter months and the self-dosing ranges greatly. Therefore, as described above for calcium, it is advisable to create a three-level categorical variable, to indicate no use, relatively low use, or high dose supplement use per day. Some studies of vitamin D include questions about sunlight exposure, such as walking or sitting outside, and whether they travel to the south during winter months. The best assessment of vitamin D status, however, is the measurement of serum 25(OH)-vitamin D.

7.3.4 *Intake Assessments of Other Micronutrients*

Three of the more critical micronutrients that affect bone status have been highlighted above, but the active investigation of nutrient–bone linkages in recent decades has demonstrated that many micronutrients and macronutrients are important, including protein, vitamins C and K, magnesium, and carotenoids and other phytonutrients [54–59]. For this reason, a full dietary assessment is optimal in order to obtain information on the full complement of nutrients and foods, rather than to use a brief screener. The use of brief screeners for calcium and vitamin D have been popular, but have been shown to have many limitations, including limitations in the food list that lead to biased intake assumptions, lack of ability to include lower amounts of calcium intake from commonly consumed foods, like bread, that can add up to important amounts, lack of ability to adjust for total energy to improve ranking estimates and importantly, and lack of ability to consider the role of other nutrients, either as additional important dietary components in preserving bone mineral density or in fracture risk reduction, or as potentially confounding variables in the analysis.

One important issue with dietary variables is collinearity of nutrients in common foods. To some extent we have this with dairy products, which are the major sources not only of calcium, but also of vitamin D (fortified) and to a large extent, phosphorus. In addition, they contain protein, potassium and other nutrients that likely work together to improve the effect of calcium on the bone. Therefore, testing adjusted regression models with a full array of micronutrients is recommended before declaring a significant effect of a specific nutrient on the outcome. For this reason, more studies are examining whole foods and dietary patterns as well as single nutrients [60].

7.4 **Examples of Bone Studies Using Nutritional Assessments**

Relationships between diet, nutritional status and bone status or fracture risk have been studied in many different ways. Population based epidemiologic approaches include cross-sectional studies, to examine associations at a single point in time and prospective cohort studies, to improve estimates of likely causality, by measuring the dietary exposure prior to either change in bone status or to future fracture. Because there may be considerable variation across studies due to socio-economic, cultural and genetic differences in distributions of risk or to issues of study design, no single study is definitive. Therefore, after many studies are done, summary reviews help to assess the cumulative strength

of observed associations, using methods such as systematic review or meta-analysis. Below are just a few examples of these.

7.4.1 Cross-Sectional Studies

The strength of epidemiologic results depends on study design as well as the validity of the measures. Many studies, including the NHANES, are cross-sectional surveys that assess correlations between nutritional intake measures and outcomes, like BMD, at the same point in time. As an example, an analysis of NHANES 2005–2006 data did not show a significant association between concurrent calcium intake and BMD of the hip or lumbar spine in adults aged 50 and older. In this case, calcium

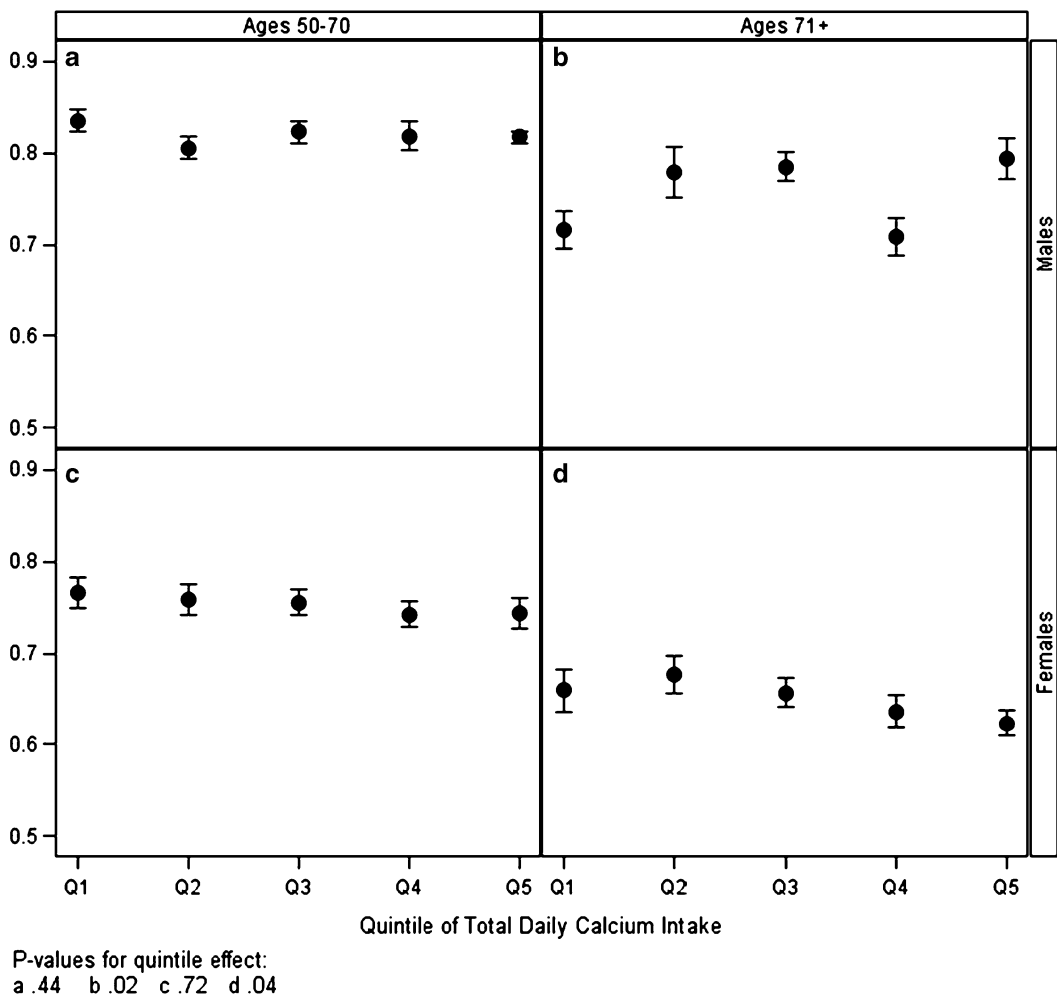


Fig. 7.1 Calcium intake and bone mineral density of the hip (proximal femur) adjusted for body mass index in a sample of older US men and women. (Permission to reproduce this figure is given by the Journal of Clinical Endocrinology and Metabolism: Anderson, J.J.B., Roggenkamp, K.J., and Suchindran, C.M. Calcium intakes and femoral and lumbar bone density of elderly U.S. men and women: National Health and Nutrition Examination Survey 2005–2006 analysis. J Clin Endocrinol Metab 97: 4531–4539, 2012.)

intake was analyzed as quintile categories and the only adjustment in the analysis was for BMI [61]. Data for the hip are shown in Fig. 7.1. As noted above, with this model, most individuals in the highest categories will be calcium supplement users. In other words, the data presented in this report from a representative national survey of older US adults confirms earlier understandings that suggest that calcium loading, i.e., high dose provided by a single supplement, has little or no effect on femoral or lumbar bone density in older adults. Cross sectional studies provide good evidence of association, but on their own, do not imply causation. Because both the calcium intake and the BMD are measured at the same period of time, the possibility always remains of confounding by other variables, such as age, medication use, or physical activity (among others), or by reverse causality, where individuals with a poor outcome have changed their dietary intake in response to the problem, rather than developing the problem due to long term low intake of the nutrient.

7.4.2 *Prospective Studies*

Stronger evidence is obtained with prospective studies. Dietary intake is measured at a baseline time point and either loss in bone over time, or incident fracture is assessed. In this case, the exposure is measured before the outcome so there is stronger likelihood that the intake may be contributing to the outcome. One example is a study [62] of prospective data from the Swedish Mammography Cohort that were used to assess fracture rates in older women over a 19-year follow-up period. Calcium intake was measured by FFQ at baseline and women were divided into quintiles of intake. In this study, the association of fracture with dietary calcium was nonlinear, with higher risk of any fracture in the lowest intake quintile (<751 mg/day) relative to the third quintile (882–996 mg/day) (Hazard Ratio=1.18 (95 % confidence interval 1.12–1.25); of first hip fracture (HR=1.29 (1.17–1.43) and development of osteoporosis (HR=1.47 (1.09–2.00)). However, higher intake of calcium above the third quintile did not reduce the risk of fractures of any type, or of osteoporosis, and the highest intake quintile (>1,137 mg/day) was actually associated with greater risk of hip fracture, hazard ratio 1.19 (1.06 to 1.32). The authors suggest that moderate intake of calcium combined with adequate intake of other micronutrients is likely to be sufficient to meet the structural and functional demands of the skeleton, while high levels of intake may increase the rate of hip fractures. However, they caution that high levels are likely result from supplement use, which may be more common in individuals who perceive themselves to be at high risk.

7.4.3 *Systematic Reviews and Meta-Analyses*

The history of nutritional sciences has been to focus on the single nutrients that may contribute to reduced risk of disease, and this has been true for bone health as well. The most often studied of these are calcium and vitamin D. When multiple observational cross-sectional and prospective studies show congruent protective associations between a nutrient and an outcome, such as fracture risk, randomized clinical trials have been implemented with supplements vs. placebo to determine with more confidence whether or not the result is causal and therefore may be used in clinical practice. Trials themselves have limitations and multiple trials in differing populations are needed to show effectiveness. Once the body of literature has advanced to include sufficient numbers of trials, it is helpful to evaluate the sum total of results to get a better idea of what the evidence suggests in its totality.

An early review, that examined the relationship between calcium supplementation and bone, was based on 15 trials, but with a small number of participants $n=1,806$) [63]. The authors concluded that calcium had small, though weak, benefit to bone, but no fracture reduction was demonstrated.

The small size of this analysis limited its statistical strength for drawing conclusions. A more recent review of both prospective studies and meta-analysis of clinical trials is based on larger numbers of older adults in prospective cohort studies [64]. However, the conclusion was essentially the same—that high calcium consumption or use of calcium supplements was not significantly related to risk of hip fracture in either men or women. Neither the pooled results from prospective cohort studies nor those from randomized controlled trials supported an association between calcium intake or supplementation and fracture risk in women or men.

7.5 Discussion

Nutritional assessments of calcium have been especially helpful in bone studies of older adults and the elderly, but the few investigations examining phosphorus and vitamin D intakes have been less insightful, largely because of methodological issue, such as inadequate food compositions tables for foods fortified with phosphate additives and of vitamin D skin production in those exposed to sunlight (UVB) in critical times of the year. Despite relatively large errors of measurement in micronutrient assessments, consistency of micronutrient–bone linkages across studies, especially meta-analyses, suggest that ball-park estimates of intakes have provided reasonable data to support current thought about the importance of micronutrients for the promotion of health and the reduction of osteoporosis and fractures, especially of the hip (Table 7.1).

Calcium Intakes: Early thinking was that calcium supplements would increase measurements of bone mineral content and density and several studies did report skeletal benefits of calcium supplements. One early report, however, clearly did not [65]. Calcium assessments over the last 10 years or so have generated important understandings of calcium requirements during the later decades of life, long after peak bone development in the second decade of life and consolidation by the end of the third decade. Older adults, both male and female, need smaller amounts of calcium each day in order to maintain bone mass or density [61, 62] and to prevent hip fractures [62, 64]. The maintenance of

Table 7.1 Calcium, vitamin D, and phosphorus: effects on bone health and food sources

Nutrient	RDA and UL for most adults	Too little	Sources to encourage	Too much	Sources to avoid
Calcium	RDA: 1,000–1,200 mg/day UL: 2,000 mg/day	Low BMD	Milk Yogurt Sardines or fish with bones Tofu Fortified soy milk	Brittle bones	Excess supplements
Vitamin D	RDA: 600 IU/day UL: 4,000 IU/day	Low BMD	Fatty fish Fortified milk, yogurt or breakfast cereal Supplements as needed	Brittle bones	Excess supplements
Phosphorus	RDA: 700 mg/day UL: 4,000 mg/day	Poor bone development	Milk Yogurt Tofu Beans Nuts Lean meats and fish	Brittle bones	Cola Processed or basted meats Commercial baked products or salad dressing Processed cheese

BMD also applies to both women who were omnivorous or lacto-ovo-vegetarian [66]. The cited reports used food frequency questionnaires or repeat recall measures.

A major finding emerged from the recent publications using the appropriate assessment tools: routine calcium intakes that maintained bone mass or density typically did not reach recommended intake amounts (RDAs) in large percentages of study participants. After a minimal daily intake of calcium, i.e., about 600 mg per day, was achieved, hip fracture rates were prevented; intakes higher than the RDAs had no additional benefits in terms of BMD or fracture prevention, except for the highest quintile in the prospective study of older Swedish women which had an increase in fracture rate [62]. In the USA at least, the high intakes of calcium in NHANES populations and other national surveys have resulted from calcium supplement use [61, 67]. Most studies published over a decade or more ago supported the benefit of calcium supplements for older adults in increasing bone mass and density, but, since the first meta-analysis [63, 68], the preponderance of studies have not shown such robust skeletal benefits, if any [61, 62, 64]. Calcium supplements are no longer recommended by the US Preventive Services Task Force [69].

Phosphorus Intakes: The major concern about phosphorus is excessive intake from additives [34]. Deficient intake is rarely a problem and it typically results because of poor protein nutrition and starvation (marasmus) or semi-starvation status. Phosphate salt additives are not available for processed foods in food composition tables. So, assessing phosphorus amounts in the diet is basically not possible; only the phosphate content of unprocessed (or raw) foods can be totaled. Even without food additive phosphates, typical estimated phosphorus intakes are twice as great as calcium intakes, on average. Therefore, a calcium-phosphorus ratio of 0.5 certainly contributes to an acute intake of PTH following meals. The long-term effects of such diets on bone mass and density has not been investigated.

Vitamin D Intakes: Vitamin D consumption from foods can be reasonably assessed using food composition tables, but the unknown quantity of vitamin D skin production during the months with UVB exposure has been difficult to obtain by skin film badges or other methods. So, overall vitamin D status remains a mystery. The best tool so far to assess vitamin D status is the serum 25-hydroxyvitamin D concentration with the three arbitrary classes of deficiency, insufficiency, and sufficiency [70]. Sufficiency is arbitrarily classified as having serum 25-hydroxyvitamin D concentrations greater than 30 ng/mL (or 75 nmol/L). Insufficiency is within the range from 21 to 29 ng/mL and deficiency is a measurement less than 20 ng/mL. In his previous review [53, 70] he only used two classes: deficiency (<20 ng/mL) and sufficiency (20 ng/mL and greater). Using these definitions, large percentages of adults have been shown to be deficient or insufficient in surveys of populations of the USA and other western nations. The meaning of such widespread low serum concentrations has been difficult to establish without evident clinical signs of osteomalacia. Theoretically, any concentration of serum 25-hydroxyvitamin D above zero should provide sufficient substrate for renal production of serum 1,25-dihydroxyvitamin D, the hormonal form that enhances both intestinal calcium absorption and osteoblastic bone formation.

Since the utility of dietary assessment of vitamin D is extremely limited, vitamin D status is now primarily based on serum 25-hydroxyvitamin D measurements. Presumably an adequate status for bone health is a serum concentration of 20 ng/mL or greater.

Intakes of Other Nutrients: The evidence for the importance of intakes of other nutrients such as protein, vitamins C, K, certain B vitamins, magnesium, potassium and carotenoids and other nutrients is much more recent and remains active. Together, however, the evidence is coalescing toward the importance of a high quality nutrient-rich diet for the protection of bone status and prevention of fracture, rather than the use of calcium supplements, as has been widely promoted in the past.

7.6 Conclusions

Nutritional assessments have been essential for the analysis of the association between the usual intake of a nutrient, such as calcium, and bone parameters, such as BMD, during the later stages of life. Most studies have examined postmenopausal women because of the greater incidence of osteoporosis and hip fractures in this gender, but men if they live long enough will suffer from osteoporosis and hip fractures as well. Calcium intake has relatively little impact at superannuated ages as long as consumption exceeds approximately 600 mg a day, according to findings of the prospective study of Swedish women [62]. In western nations phosphorus intakes are substantially increased by food additives, and high total P intakes that are almost twice as large as calcium may have adverse skeletal effects. Vitamin D intakes contribute to vitamin D status, as assessed chemically by measuring serum 25-hydroxyvitamin D, but sun exposure to UVB apparently has a greater benefit than vitamin D intake from foods, including D-fortified foods. Individuals with a serum 25-hydroxyvitamin D deficiency clearly need to improve their intake to support calcium metabolism and balance, but it remains unclear whether insufficient individuals need vitamin D supplements. Nutritional assessments of calcium have been very helpful to researchers, but so far the same cannot be said for nutritional assessments of phosphorus and vitamin D.

Assessing dietary intake accurately for use in epidemiologic studies poses significant challenges. Despite this, many advances have been made. Whereas early work concentrated almost exclusively on calcium, we now know that many nutrients contribute to optimal bone health and fracture prevention. Unfortunately, calcium supplements alone have not proven to be the panacea originally expected. Rather, adequate intake of many different nutrients appears to be necessary, within an overall healthy dietary pattern, to maintain optimal bone health. Future work will continue to explore the optimal combinations of foods and an expanding range of nutrients and phytochemicals that may optimize healthy aging, including maintenance of bone status.

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