5-2004

Voluntary and Involuntary Weight Change and Risk of Osteoporotic Hip Fracture in Men and Women of Utah

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VOLUNTARY AND INVOLUNTARY WEIGHT CHANGE AND RISK OF OSTEOPOROTIC HIP FRACTURE IN MEN AND WOMEN OF UTAH

by

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A thesis submitted in partial fulfillment
of the requirements for the degree

of

MASTER OF SCIENCE

in

Nutrition and Food Sciences

UTAH STATE UNIVERSITY
Logan, Utah

2004

ABSTRACT

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by

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Utah State University, 2004

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Change in body weight is an important determinant of risk of osteoporotic hip fracture in aging adults. Weight loss has been associated with an increased risk of hip fracture and weight gain has been associated with a decreased risk of hip fracture. Weight gain cannot be recommended as appropriate prevention against hip fracture, however, because it is associated with such adverse health outcomes as cardiovascular disease and diabetes, and weight loss is commonly recommended in the treatment of these types of diseases. Clarification of how weight loss is related to risk of hip fracture is needed to resolve this issue. An extensive review of published literature was completed to assess the relationships between hip fracture and body weight, weight change, and involuntary and voluntary weight loss. Change in body weight and weight loss that was either intentional or unintentional were then assessed for their effects on risk of hip fracture in a population-based case-control study of risk factors for osteoporotic

hip fracture in aging Utah residents. Analyses of risk of hip fracture by quintile of weight change since age 18 and according to weight loss intention were performed through logistic regression modeling. Weight loss after age 18 was associated with an increased risk of hip fracture in men and women, and above average weight gain after age 18 was protective against hip fracture in women. Involuntary weight loss of more than 20 pounds was associated with an increased risk of hip fracture in men and women aged 50 to 69 years, but was not related to risk of hip fracture in participants aged 70 to 89. Voluntary weight loss of more than 20 pounds did not significantly increase risk of hip fracture in either age group. It was concluded that involuntary weight loss may be an important predictor of risk of hip fracture in aging adults and that voluntary weight loss may be safely recommended to aging adults without increasing their risk of hip fracture.

(194 pages)

ACKNOWLEDGMENTS

I would like to thank my graduate committee for their support—Dr. Ron Munger for funding my education, allowing my constant requests for his time, and spending numerous hours reading and editing, Dr. Heidi Wengreen for her patience with my endless phone calls and questions, Dr. Chris Corcoran for his hours working through statistical analyses, and Dr. Richard Cutler for his always cheerful assistance. I also appreciate very much the support and encouragement of my wonderful parents, family, and close friends, and especially appreciate my beloved husband for getting me through this project. I will gratefully complete this work in loving memory of our dear brother and friend, "Rhino."

The Utah Study of Nutrition and Bone Health was supported by grant R01 AR43391 from the U.S. National Institute of Arthritis and Musculoskeletal and Skin Diseases (Dr. R.G. Munger, P.I.), and funding from the Agricultural Experiment Station and the Office of the Vice President for Research of Utah State University.

Megan Ruth McDonough

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CHAPTER 1

INTRODUCTION AND BACKGROUND

Abstract

Osteoporosis-related hip fractures in aging adults are a serious public health problem and contribute to excess morbidity and mortality and consequently to significant health care costs worldwide. Identification of factors that are associated with risk of hip fracture will aid in the prevention of these injuries. Weight change has been related to risk of hip fracture, with weight loss being associated with an increased risk. The distinction between involuntary and voluntary weight loss may be important in this context, because risk of hip fracture may differ depending on weight loss intention. The Utah Study of Nutrition and Bone Health will be used to explore these relationships in the Utah elderly population. Research goals and hypotheses are reviewed and plans for data analysis are summarized.

Introduction

Aging individuals worldwide face the possibility of developing chronic diseases or other health burdens that decrease quality of life and contribute significant health care costs to society. Epidemiologists and clinical researchers seek to help treat and even prevent these diseases and other health burdens by studying specific exposures and whether they lead to adverse health outcomes. Exposures may often be nutritional in nature; examples include a deficient intake of a vitamin or mineral, excessive consumption of saturated fatty acids, or inappropriate weight gain. Nutritional

epidemiologists frequently use population-based observational studies to establish relationships between specific nutritional exposures and health outcomes. Unfortunately, contradictory findings often arise from these studies, leading to delays in important community and national health recommendations and sometimes leaving the public confused and frustrated. It is only when results become relatively consistent in multiple studies and in a variety of populations that contradictions can be resolved and recommendations made to the public. One association that deserves attention in more observational studies is the relation between weight change and osteoporotic hip fracture. The Utah Study of Nutrition and Bone Health is a statewide case-control study of 50 to 89 year-old residents of Utah that can be used to clarify how weight change may affect an individual's likelihood of suffering a hip fracture.

Background

Fracture of the hip in older adults is a significant national and global public health problem (1-5). About one of every six white women and one of every 17 white men in the U.S. will experience a hip fracture in their lifetime (1, 6). The lengthy hospital stays, pain, and other physical impairments that result from hip fractures can lead to serious deterioration of physical and emotional health and severely limit social activities in surviving patients (7). A majority of patients do not return to their previous functional level (2, 8) and many will eventually be institutionalized in nursing care facilities (8, 9). The excess morbidity and mortality associated with hip fractures (7, 9-12) makes them a major contributor to national and global health care costs (1, 4, 10). Prevention of initial injury is the best way to reduce the morbidities and health care costs that are attributed to

hip fracture, so it is important to identify risk factors that make hip fractures more likely to occur. Several risk factors for hip fracture, such as low bone mineral density (3, 13-15), increased height (14, 16-20), and low levels of physical activity (14, 17), have been identified in case-control and other observational studies. Body weight (3, 7, 14, 16, 21-23) and weight change (14, 16, 21, 22, 24-28) are also both related to risk of hip fracture.

Numerous studies have documented that weight loss is associated with an increased risk of hip fracture (14, 16, 21, 22, 24-30) and that weight gain may be associated with a reduced risk (14, 16, 22, 24, 27). Researchers studying elderly adults have reported that weight loss since young adulthood, weight loss from a maximum weight, and weight loss in old age are all associated with an increased risk of hip fracture (14, 16, 21, 22, 24-29). Weight loss is common among the elderly, is associated with multiple adverse health outcomes (31), and has been shown to increase risk of all-cause mortality (32-34). In contrast, weight gain is also a well-known disadvantage to health. Obese or overweight persons have an increased risk of developing such chronic diseases as diabetes mellitus, cardiovascular disease, or hypertension (35-39). In general, weight loss is recommended to obese and overweight individuals as an effective preventive measure and treatment for these types of conditions (40-44), although more recent studies have reported that weight loss may not be warranted in moderately overweight adults over the age of 65 (32-34). Consequently, both weight loss and weight gain have been associated with adverse health outcomes and the risks and benefits of loss or gain of weight are unclear. Clarification of the association between weight loss and risk of hip fracture is needed to resolve this issue. Since weight change is related not only to risk of hip fracture, but also to a great number of other health outcomes, including many chronic

diseases and overall mortality (32-34, 40-43), more specific knowledge of how weight loss or gain affects an individual's risk of hip fracture would be helpful both in preventing future hip fractures, and when making public health recommendations that are related to other health burdens. A useful way to determine what specific aspects of weight loss contribute to an increased risk of hip fracture may be to distinguish between weight loss that is intentional and weight loss that is unintentional.

Weight loss can result from numerous conditions, including reduced caloric or nutrient intake, increased physical activity, illness, surgery, or poor mental health. One might reasonably argue that reducing caloric intake and increasing physical activity are behaviors associated with voluntary weight loss, and things such as disease, surgery, or mental illness are conditions that might cause involuntary weight loss. These behaviors and conditions may have different affects on risk of hip fracture. Some researchers have proposed that involuntary weight loss is an important predictor of hip fracture, and that voluntary weight loss does not contribute to risk of hip fracture (24, 45).

Three published reports, one from a case-control study of men and women aged 50 and over in Oslo, Norway (45), and two from the prospective Study of Osteoporotic Fractures on women aged 65 and over in the U.S. (24, 30), assessed the specific effect of weight loss intention on risk of hip fracture. In the Norwegian case-control study, men and women who experienced weight loss of any amount due to poor appetite in the previous year had a significant increase in risk of hip fracture when compared to subjects that did not lose weight (45). Weight loss reported to be for slimming purposes was not significantly related to risk of hip fracture (45). Similarly, in a report from the Study of Osteoporotic Fractures that documented weight loss over about six years and had an

average follow-up period of 1.6 years (24), women that reported an involuntary weight loss of at least ten percent of their baseline weight had an increased risk of hip fracture over women with stable weight, and a similar voluntary weight loss was not related to risk of hip fracture. A more recent analysis from the Study of Osteoporotic Fractures that used similar data as the previous study, but had an average follow-up period of 6.6 years (30), reported different findings. In this analysis (30), both intentional and unintentional weight loss of five percent or more from the baseline examination were associated with an increased risk of hip fracture and women with stable weight or that had weight gain shared a similar risk. The results of the first two analyses suggest that voluntary weight loss for the purpose of chronic disease prevention may be safely recommended to older patients without increasing their risk of hip fracture (24, 45), but researchers with the latter analysis concluded that the risks associated with weight loss in the elderly, whether intentional or not, outweighed any potential benefits that might be achieved with weight loss (30). Thus the issue of whether or not weight loss in elderly adults is beneficial or harmful, even when intention is accounted for, is still uncertain. It is likely that involuntary weight loss is a true risk factor for hip fracture, especially since it is a common sequela of illness and poor health, but the effect of voluntary weight loss is more equivocal. In the report that found an increased risk of hip fracture with voluntary weight loss, the researchers consented that voluntary weight loss that includes physical activity may still be beneficial for bone health (30). In a case-control study of Swedish women aged 50 to 81 (46), women who lost weight and participated in physical activity had a significantly reduced risk of hip fracture. Further study of the relationships between voluntary and involuntary weight loss and risk of hip fracture is certainly

needed. Such study should include investigation into what conditions that are associated with involuntary weight loss may contribute to an increased risk of hip fracture, and what types of behaviors that are associated with voluntary weight loss, if any, allow appropriate weight loss for health but also avoidance of hip fracture.

Risk of Hip Fracture in Utah Residents

The Utah Study of Nutrition and Bone Health, conducted between 1997 and 2001, can be used effectively to explore the relationships between weight change, weight loss intention, and risk of hip fracture. Weight change since age 18 and involuntary and voluntary weight loss of more than 20 pounds will be assessed for their effects on risk of hip fracture and results will be compared to other similar reports. Analysis of data gathered on 50 to 89 year old residents of Utah may add meaningfully to the results of existing analyses and may help provide stronger foundations for future public health recommendations. Research of the association between weight loss intention and risk of hip fracture may be especially important. In contrast to previous studies that reported weight loss intention over only one year, included even small amounts of weight loss, or that could not account for individuals that might have lost weight both intentionally and unintentionally (24, 30, 45), it will be possible in the Utah study to assess the effect of more extreme weight loss (at least 20 pounds) that was intentional or unintentional, and that could have occurred more than only a few years in the past. It will also be possible to account for participants that had both involuntary and voluntary weight loss or that had strictly one or the other. For analysis purposes, involuntary weight loss will be defined as weight loss that was reported to be due to illness, surgery, or feeling sad or depressed.

Voluntary weight loss will be defined as weight loss that was reported to result from dieting or increasing physical activity. These definitions will make it possible to study the effects of weight loss intention on risk of hip fracture and to examine how conditions that contribute to either intentional or unintentional weight loss contribute to risk. The following hypotheses will be tested in the Utah elderly population aged 50 to 89 years.

1. Weight change is associated with risk of hip fracture; persons with weight loss have an increased risk of hip fracture and persons with weight gain have a reduced risk of hip fracture.
2. Weight change is associated with risk of hip fracture even after controlling for the association between current weight or weight at age 18 and risk of hip fracture.
3. The association between weight change and risk of hip fracture is independent of other factors known to be associated with hip fracture, including age, gender, height, smoking habits, and estrogen use.
4. Of the participants who lost weight, those who lost weight involuntarily have an increased risk of hip fracture, and those who lost weight through voluntary means do not have an increased risk of hip fracture.

Logistic regression models will be used to quantify the risk of hip fracture by varying degrees of weight change and by weight loss intention. The logistic regression analysis will include determining whether involuntary weight loss that is related to illness, surgery, or depression is a predictor of fracture that is independent of other known risk factors for hip fracture. It may also be possible to determine if dieting or physical activity are factors that protect against hip fracture in individuals that voluntarily lose weight. Once these associations are clarified through appropriate analyses, it is hoped

that it will be feasible to make recommendations for how elderly adults can hope to prevent hip fractures by avoiding or treating involuntary weight loss, and how obese or overweight adults that wish to, can engage in appropriate weight loss that does not contribute to an increased risk of hip fracture.

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CHAPTER 2

WEIGHT CHANGE AND RISK OF OSTEOPOROTIC HIP FRACTURE: A REVIEW

Abstract

Osteoporotic hip fractures occur more frequently in elderly individuals that have lost weight. Weight loss is often recommended to obese or overweight adults, however, in an attempt to prevent chronic health burdens such as cardiovascular disease. Clarification of the association between weight change and risk of hip fracture is needed to better understand the risks and benefits associated with weight loss. Some factors that may account for the relationship between risk of hip fracture and weight loss include changes in bone mineral density, changes in mechanical loading of bone, alterations in the production of estrogen in adipose tissue, loss of muscle and fat mass, variations in smoking behavior, or changes in nutrient intake and health status. The association between weight loss and risk of hip fracture may become clearer by distinguishing between voluntary and involuntary weight loss. Involuntary weight loss may be an important indicator of risk of hip fracture and voluntary weight loss that includes physical activity may not contribute to risk of hip fracture. If these issues can be resolved through further research, prevention of both chronic diseases and osteoporotic hip fractures may be achievable.

Introduction

Risk of hip fracture has been related to changes in an individual's body weight. Weight loss is associated with an increased risk of hip fracture (1, 2) and weight gain is associated with a decreased risk (1). Weight gain cannot be recommended as protection against hip fracture, however, because obese and overweight persons, or persons who have gained weight, have increased risk of developing or dying from chronic conditions such as cardiovascular disease, diabetes mellitus, or hypertension (3-7). Although weight loss is associated with increased mortality in elderly adults and should not be routinely recommended to moderately overweight individuals over the age of 65 (8-10), weight loss is generally classified as an effective intervention for many chronic conditions, providing both short- (11-14) and long-term (14, 15) benefits in both men (12-15) and women (11-15). Since adverse health outcomes have been associated with both weight gain and weight loss, it is difficult to say which poses a greater risk to long-term health. Further research is needed to clarify the association between weight change and risk of hip fracture to help resolve this issue and to identify healthy behaviors that may enable individuals to reduce their risk of chronic health burdens while still avoiding an increased risk of hip fracture.

Background

Hip fractures in the elderly are often the result of osteoporosis, so it is common that only minor or moderate trauma is experienced prior to the fracture (16). Osteoporosis is a skeletal disease characterized by low bone mass and microarchitectural

deterioration of bone tissue, which results in increased bone fragility and susceptibility to fracture (17). Osteoporosis becomes clinically significant when a bone fracture occurs (18), and fracture of the hip is the most severe consequence of osteoporosis (17, 19, 20). Up to 33 percent of women and 17 percent of men in the U.S. will experience hip fracture by the time they reach 90 years of age (21). Hip fracture patients commonly develop chronic complications, comorbid conditions, malnutrition, decreased functional capacity, or loss of independence following fracture (22-25), and are two to five times more likely to die within one year of fracture than persons of the same sex and age without fracture (16). With increasing morbidities and health care costs being attributed to hip fractures, prevention of such injuries is of pivotal concern. The identification of risk factors that predispose elderly adults to hip fracture is important in order to distinguish high risk individuals and to develop public health recommendations aimed at hip fracture prevention.

Several risk factors for hip fracture have been identified. Some of these factors include low bone mineral density (BMD) (26-29), old age (16, 17, 28, 30-33), female gender (34), history of falls (17, 32), smoking (16, 29, 35-37), history of previous fractures (16, 17, 28, 32), family history of fracture (16, 28, 29), some medical conditions (26, 28, 37, 38), some medications (16, 26, 28, 34, 35, 37), increased height (1, 28, 37-40), and low levels of physical activity (28, 37). Weight (1, 16, 26, 28, 41-43) and weight change (1, 2, 28, 36, 41, 42, 44-46) are likewise both related to an individual's susceptibility to hip fracture.

Body Weight

Low body weight is associated with an increased risk of hip fracture (16, 26, 28, 41-43) and high body weight has been associated with a decreased risk (1). These relationships have been well established in women (1), and the results of most (37, 38, 40, 47), though not all (46) studies have shown these relationships to be important in men. Farahmand et al. (1) found that Swedish-born postmenopausal women weighing less than 58 kilograms (kg), when compared to women weighing more than 75 kg, had over six times the risk of hip fracture (odds ratio (OR) = 6.29, 95 percent confidence interval (CI): 4.82, 8.18) after controlling for age and height. White, elderly men from Rochester, Minnesota, were studied by Poór et al. (40), who found cases to weigh significantly less prior to hip fracture than control subjects (68.4 $\pm$ 13.9 kg versus 73.8 $\pm$ 12.4 kg), and reported that obesity in this population, defined as a relative weight greater than 1.2, reduced risk of hip fracture by half (OR = 0.50, 95 percent CI: 0.30, 0.90). Similar results were found when body mass index (BMI), a measurement of body mass that includes height (kg/M^2), was used as the anthropometric indicator. Grisso et al. (37) found that men aged 45 years and older residing in northern California or Philadelphia, Pennsylvania, who had a BMI less than 22.4, had almost four times the risk of hip fracture (OR = 3.80, 95 percent CI: 2.30, 6.40) when compared to men who had a BMI greater than 27.9. When studying middle-aged women and men in Norway, Meyer et al. found a threshold BMI value of 22, below which there was an increased risk of hip fracture (38). Likewise, Johnell et al. (39) and Kanis et al. (47), when studying men and

women aged 50 or older residing in Southern Europe, found that a low BMI (BMI $\leq$ 20) was significantly associated with an increased risk of hip fracture; a higher BMI was associated with a decreased risk and the relative risks (RR) of fracture in the highest quintiles of BMI were 0.44 (95 percent CI: 0.32, 0.62) in men and 0.37 (95 percent CI: 0.30, 0.45) in women. An association between body mass and hip fracture was also found using modified BMI, which uses height at a younger age instead of current height to account for any height loss that may have been experienced due to osteoporosis (44). Since the association between weight, body mass, and hip fracture is so important, clinicians have been advised that the measurement of weight is vital when assessing an individual's risk of hip fracture (48).

It is interesting that some researchers (39, 44, 47, 48) found that low weight or BMI were associated with increases in risk of hip fracture, but also noted that there seemed to be a threshold for the protective effect of high weight or BMI. Investigators for the MEDOS study of hip fracture in Southern Europe (39, 47) reported that an above-average BMI in men or a BMI of 26 or more in women were not associated with further decreases in fracture risk. Ensrud et al. (44) and Margolis et al. (48), for the Study of Osteoporotic Fractures, found that white, elderly women with average and heavier weights or body sizes shared similar risk of hip fracture. It may be that there is a U-shaped relationship between body weight and risk of hip fracture, or a plateau of risk at more extreme levels of body weight. Perhaps obesity should not be regarded as a protective factor against hip fracture, but rather leanness should be regarded as an important factor that increases risk of hip fracture (39, 47).

Weight Change

Weight change may be more strongly associated with risk of hip fracture than an individual's current body weight. For many elderly people, their current weight likely reflects whether they have gained or lost weight in adulthood, so an important role for weight change on bone health seems plausible. In the study by Farahmand et al. (1) on Swedish-born postmenopausal women, the risk of hip fracture for women weighing less than 58 kg went down by a factor of almost two after controlling for weight change (OR = 6.29, 95 percent CI: 4.82, 8.18 to OR = 3.54, 95 percent CI: 2.30, 5.46). Weight change accounted for at least part of the relationship between weight and risk of hip fracture. Furthermore, the investigators found that weight loss since age 18 was strongly and positively related to hip fracture risk, while the effect of weight gain was of the same magnitude in the opposite direction (1). The respective odds ratios for gain or loss of at least 12 kg were 0.35 (95 percent CI: 0.27, 0.45) and 3.29 (95 percent CI: 1.98, 5.48) (1). In the same study (1), as well as in one of elderly, nonblack women in the U.S. (2), the authors concluded that these associations were independent of either current weight or weight at age 18 because controlling for these factors did not alter the relationship between weight change and risk of hip fracture. As mentioned, Farahmand et al. (1) found that the association between current weight and hip fracture risk was attenuated after control for weight change, but in the study of elderly women in the U.S. (2), current weight and BMI were no longer associated with risk of frailty fracture after adjustment was made for percentage weight change. In addition, Langlois et al. (42) found that though weight loss in elderly, white women was significantly associated with increased risk of hip fracture, among women with little change in weight, risk of hip fracture did

not vary by BMI category, additional proof that weight loss, as opposed to current weight, better explains the relationship between weight and hip fracture risk. Weight loss has also been found to be associated with hip fracture in men (36, 45-47). Mussolino et al. (46) studied white men in the U.S. and found a significant association between weight loss and hip fracture, but found no significant relationship between hip fracture and BMI at baseline of the study. Weight loss, therefore, may be an important risk factor for hip fracture in both women and men.

Weight loss can be assessed in various ways—as weight loss since early adulthood, weight loss in old age, or weight loss from a maximum weight. In each case, weight loss has been found to increase risk of hip fracture. Cumming and Klineberg (36) reported that elderly, Australian men and women who had lost weight since age 20 had almost three and a half times the risk of hip fracture as men and women who had maintained or gained weight (OR = 3.40, 95 percent CI: 1.80, 6.40). Two reports from the Study of Osteoporotic Fractures also confirmed an effect of weight loss from a peak at a young age. Cummings et al. (28) and Ensrud et al. (44) reported that both absolute weight loss and percent weight loss since age 25 in elderly, nonblack women were related to an increased risk of hip fracture, though neither group could report with certainty whether current weight or weight change since age 25 had independent effects on risk of hip fracture. Other studies documented a relationship between hip fracture and weight loss in old age. In their study of elderly, Australian men and women, Cumming and Klineberg (36) found that people who had lost weight since age 50 had about two times the risk of hip fracture over people that had maintained or gained weight since age 50 (OR = 1.90, 95 percent CI: 1.10, 3.30). Langlois et al. (45), in a study of elderly, white

men in East Boston, Massachusetts and two counties in Iowa, found that older men who had lost ten percent or more of their body weight since age 50 had a risk of hip fracture nearly two times that of men with lesser weight loss or men with little change in weight, even after adjustment for other risk factors (RR = 1.85, 95 percent CI: 1.04, 3.31). Langlois et al. (42) also found this association in elderly, white women living in the same areas; women with a weight loss of ten percent or more since age 50 had about a three-fold increase in risk of hip fracture over women with minimal changes in weight after controlling for various other risk factors (RR = 2.9, 95 percent CI: 2.0, 4.1). Ensrud et al. (2), again for the Study of Osteoporotic Fractures, assessed weight change in old age and found that elderly, nonblack women in the lowest quartile of weight change (most weight lost) had nearly a two-fold increase in risk of frailty fracture when compared to women with stable weight (RR = 1.82, 95 percent CI: 1.02, 3.23). Using data from the NHANES I Epidemiologic Follow-up Study, Langlois et al. (41) and Mussolino et al. (46) assessed the relationship between hip fracture and weight loss from a maximum weight. The men and women from the NHANES who had at least a ten percent loss from their maximum weight had about a two-fold increase in risk of hip fracture over their stable weight counterparts (41, 46). The risk-adjusted relative risks for at least a 10 percent loss from maximum were 2.27 (95 percent CI: 1.13, 4.59) for men (46), 2.54 (95 percent CI: 1.10, 5.86) for women aged 50 to 64 years, and 2.04 (95 percent CI: 1.37, 3.04) for women aged 65 to 74 years (41). With such evidence for the association between weight loss and risk of hip fracture, clinicians have been advised that, along with current body weight, measurement of previous or recent weight change is also vital in assessing a person's risk of hip fracture (2).

Factors Related to Both Weight Loss and Hip Fracture

While weight change is associated with risk of hip fracture, it must also be acknowledged that some other factor or factors may account for the association, at least in part. In other words, weight change may affect hip fracture risk in it of itself, or it may be an indication of some other problem that is associated with risk of hip fracture. Weight loss in particular can be a sign of disease or some other change in health status that may be related to hip fracture. In addition, different mechanisms or relationships among factors related to both weight change and hip fracture could be important in one gender, but not the other (45). Some of these other factors that may account for the relationship between weight change and risk of hip fracture could include change in BMD, mechanical stresses on bones, hormone production, nutritional status, muscle mass, natural protective padding of bone, disease state, or smoking habits. These factors could be independently related to both weight change and hip fracture, or could occur somewhere along the causal pathway that relates weight loss to hip fracture. Some factors may be related to risk of hip fracture because they result from weight loss, some may be related because they cause weight loss, or some factors may be both causes and effects of weight loss. Changes in BMD, mechanical stress on bones, hormone production, muscle mass, and natural protective padding most likely occur as a result of weight loss, and factors like changes in nutritional status, disease state, or smoking habits could be causes or effects of weight loss. An amalgamation of all of these complicated relationships, as well as perhaps an independent effect of weight loss itself, may be the explanation for weight loss being associated with hip fracture risk.

Bone Mineral Density

Bone mineral density (BMD) is a very useful indicator for determining hip fracture risk (16, 17, 26). Authors of several studies have suggested that measurement of BMD is the best way to determine a person's risk of hip fracture because it is easily measured (16) and is strongly associated with fracture risk (16, 17, 49). Studies of both men (26, 32) and women (26, 28, 29) have documented that low BMD, especially when measured at the femoral neck (27), is a risk factor for hip fracture and that higher BMD is protective against hip fracture. BMD is also strongly correlated with body weight (2, 32, 43). Low body weight is associated with low BMD (23, 29, 50, 51) and higher body weight is associated with higher BMD (21, 32, 52, 53). Weight has been called the strongest determinant of BMD measured both peripherally and at the femur (43, 53-55), accounting for much of the individual variability in bone density measurements (23, 56, 57). If it were assumed that BMD was the principal determinant of hip fracture risk, and since body weight is so closely associated with BMD, it would be logical to conclude that low body weight increases hip fracture risk and high body weight decreases hip fracture risk.

Weight is a strong determinant of BMD in part due to gravitational or mechanical forces. Bone tissue is in a constant state of remodeling (23). The remodeling consists of osteoclasts resorbing old, dead, damaged, or underused bone, then osteoblasts replacing resorbed bone with new bone (23). In this way, bone is not only replenished after damage, but is constantly remodeled according to patterns of mechanical loading. In simple terms, bone can sense when it is being used, and adjusts by laying down more bone, thereby increasing BMD (23). Thus, mechanical forces must be present for bone

mass to be maintained (18), and disuse or immobilization reduces bone mass (18, 23). A person carrying a greater body weight puts more stress on their bones with each step than a person who is relatively lighter (23, 58); hence, total mechanical stress is greater in a person that weighs more and this may translate into greater BMD. The effect of weight-related stress on bones is likely greatest at weight-bearing sites, such as the femur (59). In a number of studies, weight-related variables, including weight loss, have been most associated with BMD at weight bearing sites, evidence that physical loading of bone is important (51, 59). When weight loss occurs, unless mechanical loading is maintained through increased physical activity, there is a subsequent decline in mechanical stresses on weight-bearing skeletal sites, which could influence the remodeling of bone (51, 60). Thus BMD is related to both weight and change in weight.

Weight may also be related to BMD through hormonal mechanisms. Women are known to lose BMD more quickly after menopause due to decreases in endogenous estrogen (61), and it has been suggested that androgen deficiency may have a similarly important role in the increased bone resorption in elderly men (21, 61). Postmenopausal women with an increased BMI have been found to have higher levels of free estradiol, albumin-bound estradiol, estrone, and estrone sulfate than women with a lower BMI (62). Obesity has been implicated in higher sex-related hormones due to a number of findings: first, obesity increases adrenal secretion of androgen precursors such as androstenedione, second, the aromatase enzyme that converts androstenedione to estrogen is present and works efficiently in peripheral adipose tissue, and third, sex hormone binding globulin (SHBG), which binds available estradiol, is decreased in obese subjects (63). These mechanisms in combination explain why obese, postmenopausal women have higher

amounts of available estrogens for target tissues than do postmenopausal women with less adipose tissue (63). Estrogens derived from these processes have been shown to be physiologically active (63). Grodin et al. (64), despite having studied only six postmenopausal women, concluded that the major source of estrogen in postmenopausal women was indeed the peripheral formation of estrone from androstenedione. Since estrogen has been shown to have several positive affects on bone (18) and bone loss accompanies estrogen loss in menopause (61), perhaps obese, postmenopausal women are somewhat protected from increased bone loss through the increased synthesis of estrogens in fat tissue. In a case-control study of hip fracture in postmenopausal women living in a Los Angeles retirement community (65), fracture patients had higher levels of SHBG and lower concentrations of estradiol and testosterone than control subjects and these levels were influenced by the difference in mean body size between the two groups. The study only included 25 fracture cases, but the researchers concluded that the levels of these hormones could influence the risk of hip fracture in elderly, postmenopausal women (65). This mechanism of hormone production in peripheral tissue may also be applicable in men. Kley et al. (66) compared obese and normal weight males aged 20 to 40 years of age and found that obese males had higher concentrations of plasma estrone and estradiol and lower concentrations of testosterone and SHBG, and that the plasma concentrations of all of these sex hormones were significantly correlated with degree of obesity. Thus the conversion rates of androstenedione to estrone and estradiol seemed to increase in obese males as well (66). In a study of major fractures in Australian, white men (67), Center et al. did not find a significant difference in levels of sex hormones between fracture and nonfracture subjects except that fracture subjects had higher levels

of SHBG. This study, however, had several acknowledged weaknesses, which included using a small sample size, grouping together several different types of fractures, testing total rather than free estradiol, and taking blood samples before fracture in some cases and after fracture in other cases (67). Other researchers further studied the relationship between weight, sex hormone levels, and hip fracture by looking at weight change, as weight loss may attenuate the protection of bone by adipose-derived sex hormones. O'Dea et al. (68) studied 12 obese, postmenopausal women that experienced short-term, significant weight loss with a very-low-calorie diet and found that weight loss was associated with significant decreases in total serum estradiol and increases in measures of SHBG, though the report did not specify whether weight loss included loss of adipose tissue. More evidence than this one study is needed, but it remains that weight loss that includes a decline in fat mass may result in decreases of hormones protective of bone mass or increases of SHBG that could be detrimental to bone density (60) and increase risk of hip fracture.

The relative contributions of mechanical and hormonal mechanisms to BMD may differ between men and women (57). Most researchers agree that total body weight is correlated with BMD in both men and women (59, 69, 70), yet when weight is divided into fat and fat-free components, findings between men and women diverge. A number of studies on postmenopausal women have shown that fat mass is more closely related to BMD than lean body mass (50, 59, 69, 71), leading some to conclude that the endocrine role of adipose conversion of androgens was more important in older women than the role of mechanical forces (50, 59, 71). In men, the most consistent finding has been that the relationship of weight and BMD was due predominantly to the lean component of

body mass (59, 70, 71). This led most investigators to conclude that mechanical forces were more important than hormonal factors in men (59, 71), though one research group proposed that aromatization of androstenedione may also occur in muscle tissue (59), and another group pointed out that any relationship in men between fat or muscle mass and BMD may be attenuated by the effect of testosterone on bone density (70). Most studies, however, agreed that hormonal mechanisms were important in women, while mechanical loading mechanisms were more important in men. In contrast, Reid et al. (69) concluded that neither of the mechanisms highlighted here, hormonal or mechanical, adequately explained the relationship between weight and BMD, at least in postmenopausal women. In a study of 140 white, postmenopausal women, it was found that while fat mass was more closely associated with BMD than lean body mass and lean body mass was not an independent predictor of BMD, estrogen and androgen levels were only marginally significantly associated with BMD (69). The investigators concluded that hormonal mechanisms were not an adequate predictor of BMD because the fat-BMD relationship was independent of serum levels of estrone (69). Mechanical mechanisms likewise did not adequately predict BMD because lean body mass was not independently related to BMD, and weight, a measure of total skeletal load from both fat and lean mass, was not more closely related to BMD than was fat mass (69). It is likely that, regardless of gender, BMD is determined by both hormonal and mechanical loading mechanisms (18, 59), and that neither mechanism alone (23, 61), or even in combination, is completely responsible for BMD in either gender. Weight change is likely to affect both fat and lean body masses and both hormonal and mechanical mechanisms, and thus cause some change in BMD.

Several studies have shown that decreases in body weight coincide with decreases in BMD. Three groups of researchers looked at the long-term effects of weight loss on femoral neck BMD by studying weight loss since early adulthood (57) or weight loss in old age (32, 51). All three groups found that weight loss in both men (32, 57) and women (51, 57) was inversely associated with BMD measured at the femoral neck. In men and women of the Framingham population (57), weight change was the strongest explanatory factor for the variance in BMD measurements within each gender at almost all sites that were evaluated and in the Dubbo Osteoporosis Epidemiology Study (32, 51), the effect of weight change on BMD seemed most pronounced in older, thinner subjects. In a report from the Study of Osteoporotic Fractures, Ensrud et al. looked at weight change in women over an average period of about 6 years (2). Increasing weight gain in nonblack, postmenopausal women was associated with higher femoral BMD and increasing weight loss was associated with an increasing rate of bone loss measured at the calcaneus (2). Other researchers measured the short-term effects of weight loss by measuring BMD soon after or during the weight loss period. Salamone et al. (60) conducted a lifestyle intervention trial that involved diet- and exercise-induced weight loss in premenopausal and early perimenopausal women and found decreases in hip BMD in the weight loss intervention group after a period of only 18 months, even after adjustment was made for baseline BMD and body weight. Women in the top quartile of weight loss had more than three times the rate of BMD loss over all other women (60). It must be pointed out, however, that these were not postmenopausal women and percentage weight change still only accounted for just over seven percent of the variance in hip BMD changes (60). Fogelholm et al. (72) in premenopausal women, and Chao et

al. (73) in postmenopausal women, also found decreases in total BMD after short periods of weight loss. Despite such evidence, there is disagreement about which measurement site is most important in relation to BMD loss and risk of hip fracture, and whether changes in BMD at different sites, according to amount of weight lost, are comparable. While some investigators found losses of femoral neck (32, 57, 60) or total body BMD (72, 73) with weight loss, others found decreases at the spine (74), but not at the femur (73, 74). Perhaps some of the studies (73, 74) were too short-term to detect changes at the femoral neck. There is also some disagreement about whether BMD is regained when weight is regained after a period of weight loss. Fogelholm et al. (72) reported regain of BMD after total regain in body weight, whereas Avenell et al. (74) reported no such finding. Additional research is needed to confirm the effects of weight loss on changes in BMD at additional sites and in different populations (73).

While it has been established that weight, weight change and BMD are related, one must also explore how these relationships are relevant in the context of hip fracture and determine the value of BMD measurements when predicting risk of hip fracture. Two separate analyses from the prospective Study of Osteoporotic Fractures, one in 1997 by Ensrud et al. (44), and one in 2000 by Margolis et al. (48), showed that of women examined at the baseline examination and then the second examination which started about three years later, women that were thin had up to a 2.5-fold increase in risk of hip fracture, even after adjustment for covariates related to body size. However, in both studies, adjustment for femoral BMD eliminated the increased risk, leading the researchers to conclude that the increased risk was explained completely by lower BMD and that if BMD was known, measurement of body weight did not contribute any

additional information (44, 48). Both research groups asserted that measurement of weight is useful only when measurement of BMD is not feasible (44, 48). In contrast, Cummings et al. (27), in an analysis from the Study of Osteoporotic Fractures that focused on bone density measurements, studied women who participated in the baseline and second examinations and found that while bone density was strongly related to risk of hip fracture among older women, declines in bone density with age did not entirely account for increased risk of hip fracture in these women. Since each 10-year increase in age was associated with a doubled risk of hip fracture even after adjustment for bone density, the investigators concluded that other factors were also important (27). One other analysis from the Study of Osteoporotic Fractures supports this assertion. In an analysis that was done concurrently with the one that found that BMD accounted for the relationship between weight and hip fracture risk, Ensrud et al. (2) studied women that had participated in the baseline examination and then the fourth examination which started about six years later. Weight change between the baseline and fourth examinations was related to risk of frailty fracture (including hip fracture) independently of current weight or BMI and independently of femoral BMD (2). No explanation was given for the contradictory findings of the former and latter groups of studies, especially in regards to the findings of the two analyses by Ensrud et al. Differences that are immediately apparent between the two studies by Ensrud et al. are that one (44) included women with data from the baseline examination and the second examination starting three years later, measured weight change between age 25 and the second examination, and focused on all weight variables in general. The other analysis (2) included data from women observed at the baseline examination and the fourth examination starting six

years later, measured weight change between the baseline and fourth examinations, and focused on weight change specifically. From these analyses it is difficult to conclude with certainty whether BMD accounts for the relationship between weight variables and hip fracture risk.

Other investigators have looked more closely at the value of BMD measurements for predicting risk of hip fracture. Steven R. Cummings reviewed case-control studies of risk factors for hip fracture (34) and reported that there did not seem to be any clear cut difference in BMD between case and control subjects. A review of 15 studies showed that patients with hip fractures had only slightly lower bone densities than those without hip fracture, and there was actually substantial overlap in the bone densities of cases and controls (34). Wardlaw (75) and Marshall et al. (76) documented similar conclusions. All adults gradually lose bone as they age, but only some ever actually experience hip fracture (34, 76). Wardlaw (75) concluded that evidence existed that there was at least an increasing gradient of risk of osteoporosis-related fractures with decreasing BMD, but in his review Cummings concluded that the difference in bone densities between cases and controls did not seem large enough for BMD to be the only measure that affected a person's risk of hip fracture (34). Consequently, BMD cannot be the only explanation for the association between weight change and hip fracture. Margolis et al. (48), for the Study of Osteoporotic Fractures Research Group, observed that if BMD were the sole etiologic mechanism behind fractures, weight should be related to all fractures that have been associated with low BMD. Their findings were unable to support this claim (48). Factors other than BMD must play some role in influencing hip fracture risk (23, 26) and accounting for the relationship between weight change and risk of hip fracture.

Nutrition

Another way to explain the relationship between weight change and hip fracture risk is that weight loss could be a marker for malnutrition or a nutritional deficiency that has an effect on risk of hip fracture. Good nutrition is important to prevent osteoporosis and its related fractures (17, 77), and although low body weight does not always imply that an individual is malnourished (50), hip fractures are prevalent among malnourished elderly (23). Fischer and Johnson declared that weight loss is a crucial and sensitive indicator for malnutrition and possibly an inadequate intake of nutrients in elderly persons (78). In a review of published literature, Slemenda (26) observed that the association between low body weight and hip fracture seems to occur most often when low body weight is the result of poor appetite or generally poor health. Meyer et al. (79) confirmed this association of poor appetite and risk of hip fracture in a study of men and women aged 50 years and older living in Oslo, Norway. Similarly, Kanis et al. (47) found that Southern European men aged 50 years or older that had a poor appetite in the recent past had a risk of hip fracture more than twice that of those that did not report a poor appetite (RR = 2.38, 95 percent CI: 1.57, 3.62) after adjustment for other risk factors. Nutritional deficiency is "strongly implicated in the pathogenesis and consequences of hip fracture in elderly patients with osteoporosis" (26), and malnutrition is considered to be a risk factor for osteoporotic fracture (80). Both Meyer et al. (79), studying elderly adults in Norway, and Huang et al. (77), using NHANES data on elderly, American women, found that elderly persons with hip fracture tended to have poorer dietary intakes, including low total daily food intakes. Serum albumin, another sensitive indicator of early nutritional inadequacy (77), was also found to independently increase

risk of hip fracture at low levels in elderly women (77). Unfortunately, poor nutritional status is common among elderly patients (78). Normal development and maintenance of bone requires a variety of nutrients, some of the most important being calcium, vitamin D, phosphorus, vitamin K, and protein (55, 81). Deficiency states of one or more of these nutrients could contribute to risk of osteoporosis and subsequent fracture (17). In particular, leanness, weight loss, and aging have all been associated with decreased or inadequate levels of calcium, vitamin D, and protein (21, 23, 50, 82).

Insufficient intakes of calcium and vitamin D have been implicated in reduced bone mass in the elderly (21, 23). Excessive leanness has been associated with low calcium intake (23) and vitamin D concentration has been shown to decrease with age (21). The requirement for calcium increases with age (23), but a combination of decreased absorption and decreased food intake makes calcium deficiency more common in the elderly (21, 23). The efficacy of calcium and vitamin D supplementation in reducing age-related bone loss has been shown in some studies (16, 17, 23). A review by Stone and Wolfe (81) cited results of a number of randomized trials that added positively to the evidence that increased calcium intake was effective in slowing bone loss rates in the elderly. Once again, however, it must be assessed whether this apparent protection from reduced bone loss translates into fewer fractures in malnourished elderly. In reviewing studies of risk factors for osteoporosis, Ross (16) found that adequate calcium and vitamin D intakes were associated with fewer osteoporotic fractures in some, but not all studies. Observational studies in elderly men and women of Oslo, Norway (79) and in elderly female participants of the NHANES (77) revealed that calcium intake was only marginally associated with risk of hip fracture. In a study of British men and women

aged 50 and over (83), hip fracture and calcium intake were not associated in women, and among men, only those with very high intakes had a lower risk of hip fracture, though the confidence intervals for this association were wide (RR = 6.20, 95 percent CI: 1.20, 32.70). In Australia, Nguyen et al. studied men aged 60 or older and discovered that while higher dietary calcium assessed through a food frequency questionnaire was associated with higher BMD at the spine and hip, this association did not translate into an apparent decrease in risk of osteoporotic fracture (32). Similar findings in white, U.S. women were reported by Cummings et al., specifically that dietary calcium intake was not related to risk of hip fracture, even in women with very low intakes, though the women were assessed for calcium intake only once with a short questionnaire (28). A trend of decreased risk of hip fracture with increasing calcium intake in both women and men (RR = 1.20, 95 percent CI: 0.80, 2.00 for women; RR = 1.50, 95 percent CI: 0.70, 3.20 for men with the highest intakes), was reported in a case-control study of elderly men and women in Hong Kong (84), but the confidence intervals crossed one and the mean daily intake of calcium in both cases and controls was much lower than is usually found in other populations. Vitamin D, which plays a major role in calcium absorption (81), has been shown to decrease risk of hip fracture in the elderly (79), but the evidence is still inconclusive (81). Thus, while adequate calcium and vitamin D is undeniably important in elderly populations, it is yet unclear whether their deficiency actually accounts for an increase in risk of hip fracture. Elderly individuals that have lost weight may also have inadequate intake of other nutrients, protein for one, which may be important when determining risk of hip fracture.

Individuals that have lost weight could reasonably have a history of low protein intake, and since protein makes up approximately one third of the mass of bone (85), it follows that low protein intake might have some effect on bone health and fracture risk. This issue is still controversial, however (81). Feskanich et al., for the Nurses' Health Study, found no significant relationship between total protein intake, animal protein intake, or vegetable protein intake and risk of hip fracture (RR = 0.79, 95 percent CI: 0.53, 1.19 for total protein intake). The number of hip fractures in the study was small and may have made a significant relationship difficult to detect, however it was clear that had the investigators found a significant association, they would have expected it to be one in which high protein intake was disadvantageous (86). Protein has been criticized in the past as being detrimental to bone at high levels due to its effect on calcium balance, but protein is nevertheless essential for a healthy skeleton (85). Reduced protein intake in hospitalized elderly patients has been associated with decreased femoral neck BMD (26), and protein intake greater than 1 g/kg was associated with higher femoral neck BMD in Swiss men and women aged 64 to 94 (80). Favorable effects of high protein intake on fracture risk have also been observed. Authors of an ancillary study to the Iowa Women's Health Study (87) reported a significant decreasing trend in adjusted relative risks of hip fracture with increasing total and animal protein intake, however only the highest level of animal protein intake was significantly protective with a confidence interval for the adjusted relative risk that did not cross one (of groups with the highest intake, RR = 0.44, 95 percent CI: 0.16, 1.22 for total protein; RR = 0.31, 95 percent CI: 0.10, 0.93 for animal protein). Similar findings were reported in a statewide case-control study in Utah (88). Though no association between total protein intake and risk of hip

fracture was found in participants aged 70 to 89 years, participants aged 50 to 69 years in the highest quartile of total protein intake had a 65 percent lower risk of hip fracture than those participants of the same age in the lowest quartile of intake (OR = 0.35, 95 percent CI: 0.21, 0.59) (88). In addition, it has been shown that protein supplementation after a hip fracture improves clinical outcomes and lessens femoral bone loss (89). Thus adequate protein intake does seem be important for bone health, as are other nutrients such as calcium and vitamin D. It is likely, however, that the relationship between weight loss and risk of hip fracture is due to more than just a few nutritive factors. Perhaps combinations of nutrients or general nutrition status are more important in determining risk of hip fracture (77).

Lean Body Mass

The association between weight loss and hip fracture may depend upon what specific type of body tissue is most involved. Weight loss can include lean body mass, body fat, or a combination of the two (78). Excessive loss of lean body mass often results in harmful muscle wasting (78). Such decreases in muscle mass may not only influence bone composition and loss (50), possibly through decreased mechanical loading of the skeleton (71), but may also impair muscle strength, gait, coordination, reaction time, and postural stability (23, 80). Generalized weakness and poor mobility have been related to risk of hip fracture (26, 90). Lessened quadriceps strength and postural instability in elderly, Australian men were related to risk of osteoporotic fracture (32), and a number of other research groups documented associations between increased risk of hip fracture and both upper and lower limb weakness (26, 37, 91). These effects of

decreased muscle mass, namely weakness, instability, impaired coordination, and poor gait and reflexes, are important with respect to hip fracture in the context of falls (23, 32), which are common antecedents of hip fractures (17, 20, 34).

Although only two to five percent of falls in the elderly result in a fracture (23), 85 to 90 percent of hip fractures occur due to a fall (34). This fact makes falls a risk factor for hip fracture that is independent of BMD (17, 32) and makes fall-related factors significant when determining hip fracture risk (16, 91). For example, Cummings et al. (28) found that the association between history of falls and hip fracture in elderly white women was attenuated by adjustments for ability to rise from a chair without using one's arms, amount of time spent on one's feet, and self-rated health, meaning factors that influenced a woman's likelihood of falling were more related to risk of hip fracture than falling itself. Poór et al. (40) found that hip fracture in men of Rochester, Minnesota was associated with diseases or conditions that were also related to likelihood of falling. Perhaps weight loss, or rather loss of muscle tissue, is another fall-related factor that is associated with risk of hip fracture. In an analysis of the relationship between falls and hip fracture, Cummings and Nevitt (92) implicated poor gait speed and inadequate protective reflexes as necessary components of a fall that will result in a hip fracture. These conditions are likely closely related to the resulting weakness that occurs with loss of muscle mass. Indeed weakness is a risk factor for falls, as well as for hip fractures (26). Langlois et al. (42, 45) reported that elderly men and women residing in Massachusetts, Iowa, or Connecticut, and who had lost weight, were more likely to have impaired mobility. A study by Ensrud et al. (2) for the Study of Osteoporotic Fractures Research Group showed that elderly women who lost weight had a slight increase in risk

of subsequent falls after adjustment was made for age; each 10 percent decrease in weight was associated with a 15 percent increase in risk of falling. Conversely, Grisso et al. studied elderly women in New York and Philadelphia and found that women with increased body mass had a significantly reduced risk of falling (20). Studies have shown conflicting findings on how the association between weight loss and falling relates to risk of hip fracture, however. Ensrud et al. (2), in the same study that showed an apparent increase in risk of falling with weight loss, also reported that adjustment for falls did not attenuate the association between weight change and risk of frailty or hip fracture. Two other analyses from the Study of Osteoporotic Fractures (44, 48) also showed that adjustment for falls did not significantly change the association between weight, body size, or weight change and risk of fracture, which prompted the investigators to suggest that the propensity to fall is not increased for those that are relatively thin (44, 48). Ensrud et al. (2) suggested, though, that weight change could still be related to certain types of falls, since some falls, such as falls to the side (93), are more likely to cause a hip fracture than others (23). It seems this issue is relatively unclear and that risk of falling due to weakness or loss of reflexes from decreased muscle mass may not completely account for the relationship between weight loss and risk of hip fracture.

Fat Mass

Changes in weight may include loss of lean body mass, fat tissue, or both, and the effects of decreased muscle mass on risk of falling have been discussed. Likewise, loss of fat tissue with weight loss may also be related to risk of hip fracture by its effect on whether falls result in fractures. In the report by Cummings and Nevitt (92) that explored

the relationship between falls and hip fracture, an important role for fat tissue concentrated around the hips was identified. A deficiency of local shock absorption from muscle and fat tissue around the hip may make hip fracture a more likely consequence of a fall, as reduced muscle and fat tissue means little available padding for absorption of fall energy away from the bone (92). This represents an additional role for loss of muscle tissue in the pathogenesis of hip fracture, and it has been suggested that low body weight is also related to hip fracture risk because it is a marker for insufficient fat padding around the hips (23, 26, 42). Other researchers support the hypothesis that fat mass concentrated around the hips and buttocks may help protect against hip fracture by cushioning the hip against impact from a fall (20, 23, 34, 93). This concept was the focus of a study by Bernstein and colleagues (94) who wanted to determine whether higher body mass was protective against hip fracture due to its relation to higher BMD from adipose conversion of estrogens, or whether it was protective due to the shock absorption effect of fat around the hips. White and black women aged 45 years and older from New York and Philadelphia were compared on the basis of having either hip or wrist fracture (94). Patients with wrist fracture had a mean body mass equal to or greater than the national mean for BMI, whereas the mean BMI of hip fracture patients was substantially below the average (94). Since normal or high body mass protected against hip fractures but not against wrist fractures, Bernstein et al. (94) concluded that the protective effect of fat mass must therefore be one of local energy absorption instead of a systemic effect on BMD. Other factors could have been responsible for these findings, however, including a possible selection bias by using only wrist fracture patients that required

surgery (94). Alternatively, the effects of adipose-derived estrogens may not be universally systemic throughout the skeleton.

The hypothesis concerning local energy absorption by fat tissue was also studied by Lauritzen et al. (95) who conducted a trial in nursing home residents aged 69 and over in Copenhagen using external hip protectors as an intervention to prevent fractures. Over a period of 11 months, the external hip protectors reduced the risk of hip fracture by about 53 percent (95). Those participants in the intervention group (those given hip protectors) that did experience hip fracture were not wearing their hip protectors at the time of fracture (95). Ekman and Mallmin (96) reported similar results after studying the effect of external hip protectors on residents of nursing homes in Uppsala, Sweden. It should be noted, however, that while external hip protectors do seem to be a helpful new development in the prevention of hip fractures (17), the hip protectors did not completely eliminate risk of hip fracture in either study (95, 96). It seems that loss of local energy absorption at the hip is just too simplistic an explanation to completely account for the association between weight loss and hip fracture risk. Recall that Ensrud et al. (44) found in their study of elderly, white women that adjustment for history of falls did not attenuate the association between weight and risk of hip fracture, leading to the conclusion that the propensity for falls or the absence of a cushioning effect on falling were not the explanations behind women with small body size or weight loss having an increased risk of hip fracture. In the words of Greenspan and colleagues (93), "falling appears to be necessary but not sufficient for the occurrence of a hip fracture."

Illness and Poor Health

An additional theory to explain why weight loss is associated with hip fracture is that weight loss could be a surrogate marker for general poor health or illnesses that are related to risk of hip fracture (2, 28, 42, 43, 45). Elderly individuals that have acute or chronic illnesses and those who have functional disability have a greater risk of nutrition-related problems such as poor nutrient intake, weight loss (78), and diminution of lean body mass (97). Weight loss is a common result of physical disease and psychiatric disorders such as depression and dementia (78). A number of studies of risk factors for hip fracture have documented that both male and female participants with weight loss were more likely to report having poor health or one or more medical conditions (2, 42, 43, 45). A wide variety of medical conditions, including diabetes, hyperthyroidism, multiple myeloma, stroke, senile dementia, and depression, and some surgical procedures, such as gastrectomy, have been implicated in increasing risk of hip fracture (17, 47, 98, 99). Use of some medications, which may cause weight loss (100), has also been related to risk of hip fracture in some studies (17, 98). In a study of white, U.S. women aged 65 years and older (28), poor self-rated health, history of hyperthyroidism, and use of long-acting benzodiazepines or anticonvulsant drugs were all predictors of hip fracture independent of other risk factors. In studies using NHANES data, the presence of one or more chronic diseases, including bronchitis, thyroid disease, diabetes, kidney disease, heart disease, and stroke, increased risk of hip fracture in both men and women (41, 46). Meyer et al. (79) found that of men and women participating in a case-control study in Oslo, Norway, those that had been admitted to the hospital at least twice in the previous two years had more than twice the risk of hip fracture after adjustment for other

risk factors when compared to participants who had no previous hospital admissions (OR = 2.21, 95 percent CI: 1.03, 4.76). Weight loss may affect risk of hip fracture even without the presence of illness, however, and poor health or chronic conditions may not be related to hip fracture simply because they can cause weight loss. Langlois et al. (41), using data from the NHANES on women aged 65 to 74, found that even though weight loss and history of chronic diseases were related in their study population, both measures were independent predictors of hip fracture. In a similar analysis from NHANES data (46) on men aged 45 and older, weight loss and presence of chronic conditions were each significantly related to hip fracture risk after adjustment for other risk factors. Investigators for this (46), and other studies of older white men (45), middle aged Norwegians (101), and U.S. women aged 65 years and older (2), found that weight loss was a risk factor for hip fracture even after adjustment for health status or the presence of chronic or medical conditions. Meyer et al. (79) reported an increased risk of hip fracture in Norwegians with a history of recent hospital admissions, but the adjusted odds ratio for hip fracture was not adjusted for weight or weight change. Finally, in a study of white women aged 67 years or older living in Massachusetts, Iowa, or Connecticut (42), weight loss was related to the report of a greater number of medical conditions, but hip fracture was not. While it may be that weight loss could be an indicator of subclinical disease or chronic inflammation that is not known to the patient (2, 102), it is still possible that weight loss affects an individual's risk of hip fracture in ways other than, or in addition to, an effect of medications or clinical conditions.

Smoking

Smoking may also be related to both weight loss and risk of hip fracture. Smoking has been called an independent risk factor for hip fracture in some (37, 79), though not all studies (32, 47). In a study of elderly men and women in Norway, Meyer et al. (79) found current smoking to increase risk of hip fracture by a factor of two (OR = 2.05, 95 percent CI: 1.17, 3.58), though this analysis was not adjusted for weight or weight change. Grisso et al. (37) found in men aged 45 years and over in Philadelphia, Pennsylvania and northern California, that risk of hip fracture was increased three-fold in those that currently smoked at least one pack per day when compared to nonsmokers (OR = 3.20, 95 percent CI: 1.70, 6.00). Smoking has been related to weight variability (103), and in most studies, was related to weight loss (42, 45, 59, 102), though in one study former smoking was related to weight gain (45). It has been suggested that weight loss and poorer health account for most of the relationship between smoking and risk of hip fracture (28). In studying white women 65 years and over, Cummings et al. (28) found that while smoking was associated with a two-fold increase in risk of hip fracture, smokers had also gained less or lost more weight, had poorer health, had more difficulty rising from a chair, spent less time on their feet, and were less likely to walk for exercise than nonsmokers. Adjustment for these factors explained most of the association between smoking and risk of hip fracture (28). The effect of smoking was reported to be independent of body mass in a study of men aged 45 or older in Pennsylvania and California (37), however others reported that weight loss in both men and women was related to risk of hip fracture independently of smoking (1, 2, 42, 45).

Weight Loss as an Independent Predictor of Hip Fracture

Weight loss precludes a number of conditions that could be related to risk of hip fracture and is the result of still other conditions that may be related to hip fracture. Factors related to both weight loss and risk of hip fracture include changes in BMD, changes of mechanical loading on bone, alterations in adipose tissue production of estrogen, decreases in nutrient intake, reductions in muscle mass with associated weakness, reductions of fat mass with decreases in local energy absorption, variations in health status, including generalized poor health or presence of illness, and differences in smoking behavior. Still other factors may exist that account for the relationship between weight loss and risk of hip fracture. This is a complex issue and there may be no straightforward explanation for the association. Many of these factors may be intertwined and a combination of them might be used to explain the true relationship. In addition, different factors may have more importance in one gender over another. Measurement of previous weight change is vital in assessing a person's risk of hip fracture (2) because it is easily assessed and is a common antecedent or sequela of other conditions that could be related to an individual's likelihood of suffering a hip fracture. Weight loss may be more than a disease outcome or indication of altered metabolic or mechanical processes, however. The more important issue, and aim of future research, should be to determine whether weight loss increases risk of hip fracture independently of other factors. The measurement of weight loss would then be important as an independent predictor of hip fracture. Many of the studies that were reviewed here

reported that weight loss had an effect on risk of hip fracture that was independent of some, though not all other known risk factors.

Weight Loss Intention

There are numerous reasons why weight loss occurs in adults, so it may be prudent to ask one question—is all weight loss the same? One might argue that individuals who lose weight from a heavier starting point may not have the same magnitude of increased risk of hip fracture as those who lose weight from a lighter starting point, or perhaps certain behaviors employed by some individuals to lose weight have differing effects on hip fracture risk. To help answer these questions it might be useful to define weight-losers by separate categories instead of defining all weight loss as the same. One possible scheme is to dichotomize weight-losers into those that lost weight voluntarily and those that lost weight involuntarily. It has been proposed by some researchers (2, 79) that involuntary weight loss is more important than voluntary weight loss in relation to risk of hip fracture.

Involuntary Weight Loss

Two separate studies on white American women (41, 42) showed that the highest risk of hip fracture occurred in those women that were in the lowest BMI group that then lost 10 percent or more of their weight. In other words, risk was greatest in those women who were the thinnest to begin with and lost the most weight (41, 42). In both instances, the risk of hip fracture was more than two times that of the reference group (OR = 2.37, 95 percent CI: 1.32, 4.27 and OR = 2.30, 95 percent CI: 1.10, 4.80) (41, 42). Nguyen et

al. (51) found that weight loss in women who were thinner at the baseline of their study had an effect on femoral neck BMD; thinner subjects with greater weight loss had considerably more loss of BMD at the femoral neck than the average, and three to five times more than subjects whose weight increased. An analysis of NHANES data on elderly, white men (46) also revealed a greater effect of weight loss on hip fracture risk in thinner subjects, however it was less clear in this study whether the categorization of thin versus not thin subjects was before weight loss occurred. These studies share the relatively consistent finding that weight loss among thin participants contributes more to risk of hip fracture than among more average or overweight subjects; it is possible that weight loss in these subjects was unintentional since they were already relatively thin. Perhaps unintentional weight loss, rather than intentional loss, was more directly related to increased risk of hip fracture in these studies. This cannot be asserted with certainty since these studies did not account for weight loss intention (41, 42, 46, 51), and it must be acknowledged that even overweight or obese individuals may lose weight unintentionally. It cannot be ignored, however, that there may be some difference in risk depending on whether weight loss was or was not intentional.

The association between low body weight and hip fracture risk possibly "occurs when low body weight results from poor appetite or generally poor health (as opposed to intentional weight loss)" (26). Kanis et al. (47) found that men aged 50 years and more from Southern Europe with poor appetite in the recent past had more than a two-fold increase in risk of hip fracture. Illness, surgery, or decreased nutrient intake from poor appetite are conditions that may contribute to weight loss; perhaps these are the combined causes of hip fracture risk among weight losers and explain why involuntary weight loss

may have more of an effect than voluntary weight loss. Involuntary weight loss is common in the elderly (78, 100), is associated with harmful health behaviors (102), and can be a sequela of subclinical diseases (2, 102). It is also possible that a person who has lost weight voluntarily maintains their weight only because of some underlying illness (100). Indeed it is difficult to account for weight loss intention without accounting for at least some of these other factors that are likewise associated with risk of hip fracture. Results of several studies (2, 41, 45, 46) have shown that participants who reported significant weight loss also reported poorer health and more medical conditions, but the effect of weight loss on hip fracture risk remained after adjustments for illness or poor health. An independent effect of involuntary weight loss, apart from illness, cannot be ruled out.

Only three published reports to date were found that assessed the specific effect of weight loss intention on risk of hip fracture, one from a case-control study of men and women aged 50 and over in Oslo, Norway (79), and two from the prospective Study of Osteoporotic Fractures on U.S. women aged 65 and over (2, 104). Meyer et al. (79) asked elderly participants of the case-control study in Norway if they had lost weight in the last year and whether that weight loss was for slimming purposes, due to poor appetite, or was for other reasons. Those that lost any amount of weight for slimming purposes or for "other reasons" had an increased risk of hip fracture, but the relationships were not significant (OR = 2.03, 95 percent CI: 0.62, 6.66 for slimming reasons; OR = 1.36, 95 percent CI: 0.73, 2.55 for other reasons). Participants that lost any amount of weight due to a poor appetite in the last year had a significant three and a half-fold increase in risk of hip fracture compared to those that did not lose weight (OR = 3.42, 95

percent CI: 1.40, 8.36). These relationships were independent of the presence of diabetes mellitus, current smoking, number of years of education, and triceps skinfold measurements. Ensrud and colleagues (2) reported similar findings in an analysis from the Study of Osteoporotic Fractures that documented weight loss from the baseline to the fourth examinations of the study (an interval of about six years), and had an average follow-up period of 1.6 years. The effect of weight loss on risk of frailty and hip fracture in ambulatory, nonblack women aged 65 years or older was dependent on whether or not a woman had reported trying to lose weight in the previous year (2). A 10 percent loss of weight since the baseline examination was a predictor of frailty and hip fracture in women who were not trying to lose weight (RR = 1.81, 95 percent CI: 1.26, 2.61), while among women who were trying to lose weight, weight change was protective, but was not significantly related to risk of frailty or hip fracture (RR = 0.85, 95 percent CI: 0.37, 1.94) (2). The relative risks reported in this study were multivariate relative risks, and while multivariate models for general weight loss included adjustment for smoking and select medical conditions, it was not clear whether the same multivariate models were used in assessing the relationship between hip fracture and weight loss intention. It appears that the association between involuntary weight loss and risk of hip fracture in this study was independent of smoking status and some medical conditions, but this cannot be surmised with complete confidence. Another more recent analysis by Ensrud et al. (104) used similar data as the previous study except for an average follow-up period of 6.6 years, but reported different findings. In this case, both unintentional and intentional weight loss of five percent or more between the baseline and fourth examinations were associated with an increased risk of hip fracture (multivariate hazard

ratio (HR) = 2.34, 95 percent CI: 1.41, 3.90 for women trying to lose weight; multivariate HR = 1.66, 95 percent CI: 1.29, 2.13 for women not trying to lose weight) and women with stable weight or with weight gain shared a similar risk of hip fracture (104). A few small differences between these two analyses by Ensrud et al. (2, 104) may help explain the inconsistent findings. In the first analysis that found no effect of voluntary weight loss on risk of frailty or hip fracture (2), relative risks were used to estimate risk of hip fracture, the average follow-up period was much shorter (only 1.6 years), and comparisons were made using weight loss of ten percent or more of baseline weight. In the second analysis that found that even voluntary weight loss increased risk of hip fracture (104), hazard ratios were used to estimate risk of hip fracture, the average follow-up period was longer (6.6 years), and comparisons were made using weight loss of only five percent or more of baseline weight. Perhaps the first study does not adequately predict long-term risk of hip fracture, or perhaps more extreme weight loss than that reported in the second study is needed to adequately assess the effect of weight loss intention on risk of hip fracture. In both studies (2, 104), weight loss was recorded over a period of about six years (from the baseline to the fourth examination), but weight loss intention was only assessed for the year previous to the fourth examination. This would make it hard to assess whether some individuals might have lost weight both intentionally and unintentionally over the entire six-year period. More research is certainly needed to determine if involuntary weight loss is truly an independent predictor of hip fracture and whether voluntary weight loss does or does not contribute to risk of hip fracture in elderly patients. The distinction between involuntary and voluntary weight loss has important clinical and public health implications. The findings of Meyer

et al. (79) and the first analysis by Ensrud et al. (2) imply that voluntary weight loss may still be recommended to overweight patients without fear of unnecessarily increasing their risk of hip fracture later in life. If voluntary weight loss does not contribute to risk of hip fracture, desirable knowledge would be to know exactly what behaviors might be included in a voluntary weight loss program that would allow reduction in risk of chronic diseases, but would not increase risk of hip fracture.

Healthy Weight Loss Behaviors

Voluntary Weight Loss

Voluntary weight loss is commonly initiated in an effort to avoid heart disease, hypertension, diabetes, or other chronic medical conditions. Reducing overweight and maintaining a lower weight are effective in preventing or alleviating these diseases and have benefits in both the short- (11-14, 105) and long-term (14). Although some studies of elderly adults past the age of 55 reported that intentional weight loss was not significantly protective against increased mortality, moderate intentional weight loss has been associated with reduced mortality in overweight and obese middle-aged adults (102). Even though maintenance of an appropriate weight is undoubtedly the best course to longevity (8, 10, 106), it would still be prudent to identify healthy behaviors that might allow for the beneficial effects of weight loss, but are not detrimental to bone health or risk of hip fracture. Although many schemes can, and have been employed for weight loss purposes, a number of possible behaviors may be identified that separate intentional and unintentional weight-losers. Some behaviors are not easily measured and have not been extensively studied. These may include an overall healthier lifestyle, better access

and utilization of health care (102), or increased awareness of dietary intake, including intake of nutrients that are most important for bone health, among those that lose weight voluntarily. Other behaviors are more measurable and can be studied further. Increased physical activity in particular is a behavior associated with voluntary weight loss that demands attention as it has been extensively studied in relation to its effect on BMD and risk of hip fracture.

Physical Activity

Physical activity has been identified as a healthy lifestyle behavior that may have profound benefits in the prevention and treatment of osteoporosis (18, 107, 108). Physical activity can be defined in a variety of ways, including low versus high intensity, short versus long duration, as leisure or work activity, or as activity at a younger age versus activity in the recent past. All of these aspects of physical activity have been investigated (107). In men or women, in one study population or another, physical activity, regardless of how it has been measured, has consistently been found to have positive effects on BMD, at least in loaded areas, to help reduce risk of falls in the elderly, and to reduce overall risk of hip fracture (18, 107, 108).

The relationship between physical activity and BMD is relatively well established (16). Immobility is a risk factor for bone loss (16, 17, 23) and activity has been found to increase or at least maintain BMD at weight-bearing skeletal sites (16, 17). Physical activity contributes to mechanical loading on bone and maintains or increases lean muscle mass (58). These effects of loading and increased muscle contraction contribute to a balance between bone formation and resorption that favors bone deposition (55).

Speaking of exercise that is vigorous in nature, the 1993 Consensus Development Conference on osteoporosis declared "exercise augments BMD in adults as long as it is continued" (17). Benefits of physical activity on bone have been shown with both aerobic and strength-training exercises. For example, a cross-sectional analysis of NHANES III data on men aged 20 to 59 years showed that self-report of frequency of jogging was associated with significantly higher femoral BMD (109). In a 1-year clinical trial of high-intensity strength-training in postmenopausal women, Nelson et al. (110) found that strength-training had a protective effect on femoral neck and lumbar spine BMD. There is evidence, however, that there can be too much of a good thing. A U-shaped relationship may exist between BMD and frequency or intensity of physical activity. While disuse is well known to cause reduced bone mass (23), too much high-intensity exercise may negate the favorable effects of activity (111). An analysis of white, postmenopausal women residing in Pittsburgh showed that the "best" BMD appeared in active, nonathletic women, as opposed to athletic or endurance trained women (111). Hagberg et al. (111) concluded that prolonged low- to moderate-intensity weight-bearing activity, but not higher-intensity training in postmenopausal women was independently associated with higher BMD. This seems to be a unique finding, however. A critic of the study by Hagberg et al. pointed out some differences, including more years beyond menopause and use of hormone replacement therapy for a smaller proportion of the postmenopausal period, in the higher-intensity exercise group when compared to the moderate-intensity group (112). Vigorous exercise in postmenopausal women should not be discouraged as the optimal intensity, frequency, and duration of weight-bearing exercise is yet unknown (112).

Since it was established previously that weight also has profound effects on BMD, it would be prudent to review the combined effects of weight change and physical activity on BMD. A small clinical trial of 30 postmenopausal women in Maryland (113) was designed to assess the affect of weight loss and weight loss plus exercise on bone over a 6-month period. Ryan et al. found that femoral neck BMD decreased in the weight loss group, but not in the weight loss plus exercise group and that the percentage change in femoral neck BMD was significantly different between the groups (113). This study, however, was of a short-duration, had a small sample size, and did not control for various confounding factors, including no control for weight loss when testing the difference in femoral neck BMD between groups (113). Fogelholm et al. (72) reported slightly different results in a clinical trial of longer duration. The trial involved studying premenopausal women for three years, during which participants first underwent a three-month weight loss intervention, then a nine-month period of either no exercise or a moderate or higher-intensity walking program, and then a two-year follow-up period (72). Femoral neck BMD remained unchanged during the weight loss period while total body BMD decreased significantly. Weight regain during follow-up was associated with regain of BMD, though both total body and femoral neck BMD were significantly lower than baseline measurements at the completion of follow-up. Inclusion of exercise did not affect the results of weight loss or weight regain on BMD (72). These results may not be generalizable to postmenopausal women, however. Nguyen et al. (51), in the prospective Dubbo Osteoporosis Epidemiology Study, observed Australian women aged 60 and over and found that a sedentary lifestyle was associated with significant reductions in BMD measured at the femoral neck and that no significant bone loss occurred among active

women. These associations were independent of age and baseline BMD, but were dependent on baseline weight and weight change (51). The protective effect of physical activity on bone loss was more prominent in thinner women or women who lost weight, but among women with higher weight or who gained weight, the effect of physical activity was attenuated (51). It seems the issue of whether physical activity protects against the BMD loss associated with weight loss is still unclear. Further research is needed in this area, though a positive effect of physical activity seems likely. In addition, Nguyen et al. (51) noted that, in the postmenopausal women they studied, the combination of age, baseline BMD, weight, weight change, and physical activity still only explained about 13 percent of the variance in rate of BMD loss with age, so there were still other factors unaccounted for that affected BMD loss. In a review that focused on the relationship between physical activity, risk of falls, and osteoporotic fractures, Gregg and colleagues (108) noted that for physical activity to have a profound influence on risk of hip fracture, it must have multifactorial effects, meaning benefits in addition to its affect on BMD.

Physical activity may also be beneficial by improving muscle strength and coordination and thus reducing risk of falls (16, 108). Gregg et al. (108), in their review of published literature, found an accumulation of evidence to indicate that physical activity may help maintain mobility and physical functioning and improve muscle strength and balance, thus helping to prevent falls and osteoporotic fractures in the elderly. A meta-analysis of eight independent trials making up the Frailty and Injuries Cooperative Studies of Intervention Techniques (FICSIT) used a variety of exercise interventions, including flexibility, balance, lower extremity resistance training, and

multidisciplinary physical therapy, to test if the various interventions had any influence on fall and injury reduction (108, 114). The results from these trials for any one treatment modality were largely inconclusive, though there was a 10 percent reduction in risk of falls associated with exercise intervention in general, and a 17 percent reduction in risk of falls associated with balance training (114). The investigators were unable to conclude whether these reductions in risk of falling were actually effective in reducing injuries, however (114). A separate review of these trials proposed that perhaps interventions such as these have more pronounced effects in high-risk persons or those who tend to fall frequently, rather than in those individuals who have only occasional events that are associated with movement in general (108). The same review cited a number of more recent clinical trials, some of which found beneficial effects of exercise training on risk of falls, a couple of which did not (108). It should be noted that some forms of very vigorous physical activity might actually increase the risk of falls, which may be part of the reason why the association between physical activity and risk of falls seems unclear and is difficult to study (108). In a prospective cohort study, Gregg et al. (115) studied nonblack women aged 65 and over living in Maryland, Minnesota, Oregon, or Pennsylvania and found that the proportion of women who fell twice or more per year was greater among the least active and most active women than among women in the middle quintiles of activity. As with BMD and intensity of physical activity, a U-shaped relationship may exist between amount of physical activity and risk of falls, in which the most inactive and the most active individuals have the highest risk of falling (108). Perhaps only specific types, amounts, and intensities of physical activity are effective protection against falls. Cummings and Nevitt (92) reported that the slowing of gate that

occurs in many elderly individuals reduces forward momentum when walking and is partially responsible for falls to the side, which precede a majority of hip fractures. Exercise regimens that can help prevent this slowing of gait and maintain the forward momentum associated with normal movement may be of critical importance in reducing risk of falls, or at least altering the orientation of falls, so that fracture of the hip may be avoided (92). As can be asserted from review of the FICSIT trials, it is not known exactly what kind of exercise intervention is helpful for reducing falls in the elderly, specifically the types of falls that result in hip fracture (108).

A combination of different types of exercise interventions is probably most helpful in reducing risk of falls in the elderly. Some recent controlled trials have shown especially promising effects of balance and strength-training programs (108). Two such trials were conducted in the Boston, Massachusetts area (110, 116). One of these trials (110) consisted of randomizing postmenopausal white women into control and resistance-training groups. Results showed that one year of high-intensity strength training had positive effects on muscle mass, muscle strength, dynamic balance, and overall physical activity level, all of which may be related to risk of falls. The authors stressed the importance of maintaining muscle mass into old age, which their intervention appeared to be able to do, and concluded that resistance training was capable of simultaneously altering multiple risk factors for falls (110). The other controlled trial was conducted in a long-term care facility in the Boston area on men and women aged 70 and over (116). The participants in the intervention groups were assigned to high-intensity resistance training of the hip and knee extensors for 10 weeks (116). Resistance training improved muscle strength and size in the frail, elderly subjects and these changes were associated

with improvements in mobility (116). Though more research is needed, the assertion that physical activity, especially strength training, has an effect on risk of falling in the elderly seems justified.

The beneficial effects of physical activity, including its effects on BMD and risk of falling, as well as other potential benefits not reviewed here, likely all combine to explain the potential favorable impact of physical activity on overall risk of hip fracture in elderly populations. In a review of observational and clinical studies on the relationship between physical activity and risk of hip fracture, Gregg et al. cited strong evidence that a physically active lifestyle is protective against hip fractures (108). Authors of another review of case-control and prospective studies reached similar conclusions (107). In both reviews, the researchers found activity in leisure time, as opposed to occupational activity, to be the most related to risk of hip fracture (107, 108). In addition, the association was present both for physical activity in childhood and young adulthood and for recent activity in older adults, and both research groups observed that there seemed to be strong evidence for a dose-response reduction in risk of hip fracture associated with increasing levels of physical activity (107, 108). The magnitude of effect seen, and the consistency in findings of the association in many diverse populations, strongly suggested to the investigators that a causal protective effect of physical activity against hip fracture existed and that the relationship was not confounded by other factors (107, 108). Authors of a more recent study (77) used data from NHANES I on white women aged 45 years and older and found that physical activity was not significantly related to a reduced risk of hip fracture, however this study was cross-sectional in nature and the researchers commented that misclassification of reported activity could have

occurred. Other recent studies in women have been more positive in relation to the benefits of physical activity. An analysis of women aged 65 and over from the Study of Osteoporotic Fractures (115) showed protective effects of increased total physical activity, increased intensity of energy expenditure, decreased amount of time spent sitting, and even increased hours per week spent doing heavy chores. The researchers reported a 36 percent reduction in risk of hip fracture among women in the highest two quintiles of total physical activity (RR = 0.64, 95 percent CI: 0.45, 0.89) and a 42 percent reduction in risk of hip fracture in women who did moderately intense or vigorous recreational activities (RR = 0.58, 95 percent CI: 0.42, 0.80) (115). These reductions in risk of hip fracture were not explained by effects of physical activity on bone mass or muscle strength, neither were the associations confounded by health status, functional status, history of falling, intake of calcium, or smoking (115). In a prospective study of postmenopausal women that participated in the Nurses' Health Study (117), investigators measured the effect of metabolic equivalent scores (MET) on risk of hip fracture and found total physical activity from exercise and leisure-time activities to be associated with a significant reduction in risk of hip fracture. Every 3 MET-hour per week increase in activity (equivalent to a 1 hour per week walk at an average pace) was associated with a six percent (95 percent CI: 4 percent, 9 percent) decrease in risk of hip fracture (117). The protective effect of physical activity was independent of BMI, age, smoking, postmenopausal hormone use, and intakes of calcium, vitamin D, retinol, protein, vitamin K, alcohol, and caffeine (117). Similar protective effects were seen when the analysis was limited just to the activity of walking (117). Recent studies also confirm the protective effects of physical activity in men (37, 47, 118). A case-control study of men

aged 45 or over in California and Philadelphia (37) showed that participation in at least seven hours of physical activity per week, including activities such as gardening, indoor chores, or recreational exercise, reduced the risk of hip fracture by 40 percent after exclusions for premorbid lower limb or upper limb dysfunction (OR = 0.60, 95 percent CI: 0.40, 0.80). Authors of another case-control study of risk factors for hip fracture in men of Southern Europe aged 50 years or over (47) also found physical activity to be associated with a reduction in risk of hip fracture. Participants of the study were assigned a recreational physical activity score (based on a 5-point scale of amount of activity per week) and even those with at least some activity were protected against hip fracture (OR = 0.67, 95 percent CI: 0.48, 0.95). There was a significant dose-dependent reduction in risk of hip fracture with increasing amounts of activity so that the men that reported frequent physical activity had a 36 percent reduction in risk of hip fracture after adjustment for age, center of risk factor measurement, and BMI (OR = 0.64, 95 percent CI: 0.21, 0.53) (47). Finally, Kujala et al, in a recent prospective study (118) that assessed the effect of physical activity on risk of hip fracture in twin men aged 44 years and over, found a protective effect of vigorous physical activity on risk of hip fracture. Men participating in vigorous activity had a significant 62 percent reduction in risk of hip fracture (HR = 0.38, 95 percent CI: 0.16, 0.91) after adjustment for height, BMI, diseases at baseline, smoking, use of alcohol, work-related physical activity, and occupational group (118). Thus, physical activity appears to be significantly protective against hip fracture in both women and men.

A small number of research groups (117, 119, 120) have studied how change in amount of physical activity over a few years or from teenage years to old age affects risk

of hip fracture and reported interesting findings. In an analysis from the Nurses' Health Study restricted to postmenopausal women (117), Feskanich et al. reported the effects of changing activity levels over a six-year period. Women who reported less than one hour per week of activity that then increased their activity to four hours per week or more reduced their risk of hip fracture by almost half when compared to those who remained in the low-activity category, though the confidence interval crossed one in this case (RR = 0.53, 95 percent CI: 0.27, 1.04) (117). In contrast, those women who reported four hours per week or more of activity that then decreased their activity to less than one hour per week more than doubled their risk of hip fracture (RR = 2.08, 95 percent CI: 1.20, 3.61) when compared to women who maintained their high activity level (117). The authors noted that it could not be dismissed that decreases in activity could have been a result of underlying diseases that confounded the relationships they reported, however, control for chronic disease did not alter their findings (117). A separate analysis based on pooled data from three population studies of men and women in Denmark (119) also showed that subjects who reduced their physical activity had increases in risk of hip fracture. Participants who went from being moderately active to being sedentary between baseline and follow-up examinations about six years later had a 50 percent higher risk of subsequent hip fracture than those individuals who remained moderately physically active (RR = 1.53, 95 percent CI: 1.12, 2.08). Similar results were found for those individuals who became sedentary after being highly active, though the results were not significant in this case (RR = 1.61, 95 percent CI: 0.97, 2.51) (119). Exclusion for baseline and incident disease only strengthened these relationships (119). One additional population-based case-control study of Swedish women aged 50 to 81

years reported by Farahmand et al. (120) showed that women with a high level of physical activity and those who maintained their high activity level at both younger and older ages had the lowest risks of hip fracture. These relationships, however, were completely accounted for by the effect of recent activity (activity in old age) on risk of hip fracture (120). In addition, activity earlier in life had no effect on risk of hip fracture after adjustment for recent activity, and change in activity level after ages 18 to 30 was not associated with risk of hip fracture after adjustment for recent activity (120). The results of these three studies suggest two important points. First, the effect of recent activity seems to be the most important in relation to risk of hip fracture, so even individuals who have been inactive previously may receive substantial benefits from beginning an exercise program (120). It appears it is never too late to integrate regularly planned activity into an individual's lifestyle (120). Second, once a program of activity is initiated, maintenance of a particular activity level is crucial. Maintenance of one's activity level appears to provide the greatest protection from hip fracture (117, 119).

One last important topic for this review in regard to physical activity is whether increased activity has the same potential to reduce risk of hip fracture in those individuals who have lost weight. The combined effect of physical activity with weight loss has already been discussed in relation to BMD. Their combined affect must also be addressed in relation to risk of hip fracture. This issue is key to being able to identify a healthy behavior that allows evasion of chronic health burdens through weight loss, while avoiding increased risk of hip fracture as well. In the analysis from the Nurses' Health Study by Feskanich et al. (117), high levels of activity among postmenopausal women were protective against hip fracture in both lean (BMI < 25) and overweight (BMI ≥ 25)

women. Even the leanest (BMI < 21) and heaviest (BMI ≥ 30) women had reduced risk of hip fracture with increasing levels of activity (117). These results, however, still do not address whether activity that is concurrent with weight loss, not just lean body size, is still protective. Likewise in men, studies assessing the relationship between physical activity and risk of hip fracture have controlled for weight or BMI in multivariate analyses, but the possible interaction between activity and weight loss was not explored (47, 107, 118, 119). Unfortunately, this issue surrounding weight loss specifically has only been studied in detail among postmenopausal women. In a case-control study of Swedish women aged 50 to 81 years, Farahmand et al. (120) found a significant interaction between physical activity and weight change since age 18. Among women who lost three or more kg after age 18, women participating in three or more hours of recreational activity per week had a 76 percent reduction in risk of hip fracture (OR = 0.24, 95 percent CI: 0.14, 0.42) when compared to women who were inactive (120). Similar levels of activity among women who gained three or more kg after age 18 were associated with only a 38 percent decrease in risk of hip fracture (OR = 0.62, 95 percent CI: 0.46, 0.82) (120). Among those with unchanged weight, participation in three or more hours of activity per week was associated with a 67 percent decrease in risk (OR = 0.33, 95 percent CI: 0.20, 0.57) (120). Thus, the protective effect of physical activity on risk of hip fracture was greatest in women who lost weight after age 18 and the authors concluded that those women who lost weight during adult life were also those that might actually benefit the most from exercise (120). Perhaps decreased mechanical loading from weight loss is made up through increased mechanical loading associated with physical activity. These are very encouraging findings for women who wish to lose

weight in later life for potential health benefits. This issue deserves further attention in research, especially in elderly male populations. It could be that physical activity is a crucial factor that would allow voluntary weight-losers to avoid increasing their risk of hip fracture because of weight loss.

Recommendations for Avoiding Hip Fracture

After extensive review of evidence relating weight, weight change, physical activity, and risk of hip fracture, some potentially modifiable behaviors can be identified that may help elderly individuals maintain a favorable hip fracture risk profile. Substantial evidence has been provided to indicate weight loss as an important risk factor for hip fracture and it has been further suggested that involuntary weight loss increases risk of hip fracture while voluntary weight loss that includes healthy lifestyle behaviors may not. As a result, some important recommendations can be made that can aid hip fracture prevention. First, involuntary weight loss should be treated and prevented when possible. This may involve treating underlying diseases, psychological conditions, functional disabilities, or social problems that cause or contribute to weight loss (100). In addition, harmful behaviors such as smoking should be discouraged. Nutritional deficiencies should be treated, adequate intake should be stressed, intake should be supplemented when necessary, and if possible, gradual increases in physical activity should be encouraged to stimulate appetite and improve strength and function in the frail elderly. Second, middle- and older-aged men and women who are not overweight should be encouraged to maintain their weight in order to best promote good skeletal health (42, 45). Of course, weight gain (increased fat mass) for added protection against hip fracture

in those already at an appropriate level of body weight cannot be recommended due to its association with chronic health burdens (26, 42, 45). Recall that obesity should not necessarily be regarded as protective against hip fracture, but leanness, or reduced fat and muscle mass, should be regarded as a risk factor for hip fracture (39). Third, voluntary weight loss should be undertaken cautiously, and only with the inclusion of healthy lifestyle behaviors.

Healthy lifestyle behaviors that should be included in any hip fracture prevention plan include intake of a healthy diet adequate in nutrients and regular maintenance of an appropriate physical activity level. Adequate intake of those nutrients discussed previously to be of utmost importance for skeletal health is crucial. For example, calcium must be sufficient and other nutrition factors should be optimal for normal bone development if any other intervention is to be successful (18, 45, 107). Inclusion of physical activity is likewise essential, especially when dietary restriction is initiated for weight loss (58). The protective effects of physical activity are evident (107). An individualized exercise program should be tailored to each person's ability and should include both weight-bearing activities and appropriate strength training (107). Even if individuals have been inactive in the past, substantial benefit can be derived from beginning a program of physical activity (120). Walking is a common way to increase physical activity, is feasible for many elderly adults (26), and is suitable for lowering fracture risk (117). Most importantly, it is vital that once a certain level of physical activity is achieved, it is maintained throughout life as much possible (108). In summary, eating a healthful diet and participating in physical activity is appropriate advice for almost any relatively healthy adult (14). Physical activity can be routinely recommended

for its benefits in conditions such as cardiovascular disease, diabetes, insulin resistance, cancer, and hypertension (121). Thus exercise and intake of a healthy diet are lifestyle behaviors that should be strongly encouraged in all adult populations, regardless of their potential affect on general fracture incidence (107).

Conclusion

Osteoporotic fracture of the hip is a serious public health concern. Since such fractures are major contributors to health care costs (19, 22, 122) and are associated with excess morbidity and mortality (16, 22-25), prevention of such injuries is important. Key to fracture prevention is the identification of risk factors that are amenable to intervention. Increased awareness of risk factors and the practice of preventive interventions could help decrease the incidence of hip fractures and reduce health care costs to society (17, 22, 26, 122, 123). Substantial evidence has been provided to link weight loss to increased risk of hip fracture and to show that involuntary and voluntary weight loss may have differing effects on risk. This distinction between types of weight loss has many clinical and public health implications given that weight loss is commonly recommended to overweight or obese patients. Important goals for future research should include establishing whether involuntary weight loss independently increases risk of hip fracture and identifying what specific traits of involuntary weight loss contribute to an increased risk of fracture. In addition, the issue of whether voluntary weight loss contributes to an increased risk of hip fracture, is associated with no increase in risk, or whether it may actually be protective against hip fracture should be explored, and additional evidence for a protective effect of physical activity among individuals who

lose weight is needed. These relationships need to be explored in various populations, including elderly men. If it can be shown that involuntary weight loss, as opposed to voluntary weight loss, is the more important indicator of hip fracture risk in elderly adults, and if physical activity is indeed found to be protective against hip fracture in those that lose weight, the relationship between weight loss and risk of hip fracture will no longer be in conflict with current public health recommendations regarding chronic diseases such as cardiovascular disease, diabetes, and hypertension. Perhaps then clinicians may more confidently prescribe weight loss to their overweight patients without being fearful of increasing their patients' risk of hip fracture. In addition, prevention of more hip fractures may be possible by urging clinicians to put greater emphasis on the importance of recognizing and treating involuntary weight loss. More precise knowledge of the relationships between weight loss, physical activity, and hip fracture may help men and women with goals for health maintenance or weight loss be fully informed of all the risks and benefits associated with their lifestyle choices, and possibly strategies could be developed that support prevention of both chronic diseases and osteoporotic hip fractures.

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CHAPTER 3

VOLUNTARY AND INVOLUNTARY WEIGHT CHANGE AND RISK OF OSTEOPOROTIC HIP FRACTURE IN MEN AND WOMEN OF UTAH[1]

Abstract

Weight change is associated with risk of osteoporotic hip fracture and involuntary and voluntary weight loss may affect risk of hip fracture differently. The associations between weight change, weight loss intention, and risk of hip fracture were assessed in adults aged 50 to 89 in a case-control study conducted in Utah from 1997 to 2001. Weight history and other characteristics were collected from 1159 cases (330 men, 829 women) and 1332 controls (452 men, 880 women) and logistic regression models were used to estimate risk of hip fracture. Weight loss and below average weight gain since age 18 increased risk of hip fracture in men and women. Above average weight gain after age 18 was protective against hip fracture in women. Involuntary weight loss significantly increased risk of hip fracture in participants aged 50 to 69, and risk increased with increasing amounts of weight loss. Involuntary weight loss was not associated with risk of hip fracture in participants aged 70 to 89. Voluntary weight loss was not associated with risk of hip fracture in either age group. Involuntary weight loss may be an important predictor of hip fracture and voluntary weight loss might still be safely recommended to aging adults.

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Introduction

Risk of hip fracture, the most severe consequence of osteoporosis (1-3), is increased in men and women who have lost weight (4-13), and weight gain has been associated with a reduced risk of hip fracture (4, 5, 7, 10, 11). Weight gain is a clear disadvantage to health for other reasons, however. Obese or overweight persons have an increased risk of developing or dying from such chronic conditions as cardiovascular disease, diabetes mellitus, or hypertension (14-18), and although weight loss may not be warranted in moderately overweight adults over the age of 65 (19-21), it is nevertheless classified as an effective intervention for these types of conditions (22-26). Thus both weight gain and weight loss are associated with undesirable health outcomes, including hip fracture (4-13), chronic diseases (14-18), and overall mortality (19-21, 27, 28), and weight gain cannot be a prudent recommendation for protection against hip fracture. More specific knowledge of exactly what aspects of weight loss contribute to an increased risk of hip fracture would be helpful both in preventing future hip fractures and when making public health recommendations that are related to other health burdens.

Weight loss occurs for many reasons, including reduced caloric intake, increased physical activity, illness, surgery, or poor mental health. Some of these factors may be associated with weight loss that occurs intentionally, while others may precede weight loss that occurs unintentionally. Risk of hip fracture may vary depending on whether or not weight loss was intentional. Involuntary weight loss has been reported to increase risk of hip fracture (5, 29), perhaps because it often results from factors such as poor appetite, illness, surgery, depression, or general poor health. The effect of voluntary

weight loss on risk of hip fracture is more equivocal. Voluntary weight loss or weight loss for slimming purposes were found to contribute little to risk of hip fracture in two studies (5, 30), while in another report (29), voluntary weight loss was associated with an increased risk of hip fracture. Further research of the association between weight change and risk of hip fracture is needed, specifically to determine whether involuntary weight loss is indeed an important predictor of hip fracture and whether voluntary weight loss also increases risk of hip fracture, or whether its benefits on risk factors for chronic diseases may still be achieved without affecting an individual's likelihood of suffering a hip fracture.

The associations between weight gain and loss, weight loss intention, and risk of hip fracture were explored in aging men and women of Utah. Weight change since age 18 was calculated and used to examine the association between weight change and risk of hip fracture. To test the hypothesis that involuntary weight loss increases risk of hip fracture and that voluntary weight loss is not significantly related to risk of hip fracture, weight loss of 20 pounds or more due to illness, surgery, or sadness, and weight loss of 20 pounds or more due to dieting or physical activity were assessed for their contribution to risk of hip fracture.

Materials and Methods

Study Participants

Utah residents aged 50 to 89 years were recruited for the Utah Study of Nutrition and Bone Health, a statewide case-control study of risk factors for osteoporotic hip fracture conducted between 1997 and 2001. Cases were hip fracture patients identified

through surveillance of 18 Utah hospitals that were responsible for the treatment of 98 percent of hip fractures in the state. In total, 1,371 cases were interviewed an average of 4.2 months after their fracture. Control subjects for the study were randomly selected from the Utah Driver's License and Medicare databases and 1, 369 were interviewed after being frequency-matched to cases by gender and five-year age intervals. All study protocols were reviewed and approved by the Institutional Review Boards of each respective hospital and participating university. Written-informed consent was obtained from each of the 2,740 participants.

The percentage of subjects who refused to complete an interview was similar for cases and controls (23.2 percent and 24.0 percent, respectively). More cases than controls failed to complete interviews due to frailty, illness, cognitive impairment, or death (37.2 percent and 16.8 percent, respectively). In addition, 2.8 percent of cases and 3.4 percent of controls could not be located. Consequently, the overall participation rate was 36.9 percent for cases and 55.8 percent for controls.

Data Collection

Data for cases and controls was self-reported and was collected via in-person interviews. (See Appendix A for complete interview booklet.) Weight and height variables that were reported included current weight and height for controls (weight and height at the time of interview) and weight and height at the time of hip fracture for cases. Weight and height at age 18, maximum weight (other than pregnancy weight), and age at maximum weight were also reported. Each participant's body mass index (BMI) was calculated by dividing their current weight or weight at hip fracture in kilograms (kg) by

their squared current height or height at hip fracture in meters (M) (kg/M^2). Weight and height at age 18 were used to calculate BMI at age 18 for each participant, and a modified BMI was calculated using each participant's current weight or weight at hip fracture and their height at age 18 to account for any height lost during adulthood. Participants were also asked whether they had ever lost more than 20 pounds in a period of one year or less (other than following a pregnancy). Those that gave an affirmative answer to this question were asked to report the greatest amount of weight they had ever lost at one time, and whether this weight loss was due to dieting, increased physical activity, surgery, illness, or feeling sad or depressed.

Other characteristics of the study population that were assessed included race and ethnicity, education status (<12 or ≥ 12 years of education), medical history, participation in physical activity, smoking status, alcohol use, estrogen use in women, dietary intake, and cognitive function. Participants were characterized as having a history of at least one of a selected list of medical conditions or not having a history of any of the conditions. The selected medical conditions were chosen based on the availability of information in the Utah data and by identifying conditions that were important covariates in other studies of risk factors for hip fracture (5, 7, 31). The conditions selected for inclusion were emphysema, myocardial infarction, stroke, diabetes mellitus, cancer (except for skin cancer), thyroid disease, and Parkinson's disease. To account for physical activity, participants were asked to report whether they regularly participated in selected recreational activities (jogging, swimming, bicycling, yoga, dancing, skiing, exercise classes, weight lifting, tennis, or calisthenics), house work (vacuuming, scrubbing floors, or moving furniture) or yard work (weeding, cutting grass, digging, or snow shoveling).

Participation in physical activity was characterized as no participation in any of the activities or regular participation in one, two, or all three types of activities. Respondents were also characterized as current smokers (smoked regularly in the past year for controls or year before hip fracture for cases), former smokers, or never smokers, as well as current users of alcohol (regularly drank one or more drinks per month over the past year for controls or year before hip fracture for cases), former users, or never users. Estrogen use was defined as having ever used estrogen in pills, patches, or creams other than for contraception, and women were divided into current, former, or never users of estrogen. Dietary intake was assessed during the interview by a food frequency questionnaire (Appendix B) (32). Cognitive function was measured by the Mini-Mental State Examination (MMSE) and each MMSE was scored and adjusted for sensory impairment.

A number of exclusions were applied to the 2,740 participants and are listed in the order that they were applied. Cases with hip fractures caused by high impact trauma (n=117), such as a car accident or a fall from greater than a standing height, were first excluded. Data collection in the oldest-old proved difficult, so interviews of participants aged 90 or above were discontinued, and participants aged 90 and above that were initially interviewed (n=37) were excluded. Participants with an adjusted MMSE score of 17 or less (n=31), indicating severe cognitive impairment (33), were next excluded from the analysis. Cases that included weight loss due to their hip fracture (n=32) or their hip fracture surgery (n=24) in their responses were also excluded. Finally, cases that suffered hip fracture during hip replacement surgery (n=2) and controls that had previously experienced hip fractures (n=6) were excluded. The remaining 2,491 participants (1,159 cases and 1,332 controls) were included in analyses.

Statistical Analysis

Descriptive analyses were performed to compare characteristics between cases and controls within each gender and to compare weight change variables between cases and controls within different age groups (50 to 69 years and 70 to 89 years). Analysis of variance (ANOVA) was used to evaluate differences in means of continuous variables and differences between categorical variables were evaluated through chi-square tests. Confounding relationships were explored using ANOVA, chi-square tests, and correlations to determine what variables were significantly related to both hip fracture and weight loss.

Weight change since age 18 was calculated as the ratio of current weight or weight at time of hip fracture and weight at age 18 to obtain percent weight loss or gain since age 18 (0.95 represented a five percent loss, 1.05 represented a five percent gain, etc.). Weight change was expressed as a percentage of weight at age 18 to facilitate comparisons of weight change between participants that gained or lost weight from different starting points. Participants who had ever lost more than 20 pounds within a one-year period were included in analyses of weight loss intention. Involuntary weight loss was defined as loss due to illness, surgery, sadness and depression, or a combination of these reasons. Voluntary weight loss was defined as loss due to dieting, increased physical activity, or both. Weight loss was classified as mixed if it was due to both involuntary and voluntary reasons. There were relatively few participants in the mixed weight loss group (about four percent of the total sample), so further analysis of this group is not included.

The associations between weight change, weight loss intention, and risk of hip fracture were evaluated using logistic regression analyses with case-control status as the dependent variable. Weight change since age 18 was included in logistic regression models as quintiles of percent weight change. Most participants gained weight after age 18 (mean weight change since age 18 was a gain of 22 percent), so quintile three of weight change since age 18, representing a gain of 12.6 to 25 percent, was used as the reference group. Quintile one represented weight loss (less than zero percent weight change since age 18), quintile two represented lower than average weight gain (zero to 12.5 percent weight gain), and quintiles four (26 to 39.8 percent weight gain) and five (greater than 39.8 percent weight gain) represented higher than average weight gain. Other logistic regression models included weight loss of more than 20 pounds within a one-year period as a binary, independent variable. Weight loss intention was included in logistic regression models as an independent, categorical variable that included involuntary and voluntary weight loss. Additional regression models included either involuntary or voluntary weight loss as independent, binary variables to test the individual effects of involuntary or voluntary weight loss, specific reasons for weight loss (illness, dieting, etc.), and amount of weight loss ($<$ or $\geq$ 15 percent loss from maximum weight). In models that included weight loss of more than 20 pounds or weight loss intention as independent variables, a reference group was chosen that represented participants that had neither extreme weight loss nor extreme weight gain, and included participants who had never lost more than 20 pounds in a year or less and that were also in the third quintile of weight change (average weight change) since age 18.

Variables that could potentially confound the relationship between weight change and risk of hip fracture were identified by reviewing published literature and through analysis of the Utah data. These variables were added to logistic regression models and included age, smoking, alcohol use, education status, gender, estrogen use, participation in physical activity, and history of one or more of the selected medical conditions. Age was accounted for by dividing participants into two groups—those aged 50 to 69 and those aged 70 to 89. Smoking and alcohol use were correlated in this population ($r = 0.58$), but both were included in logistic regression models because they were both individually related to risk of hip fracture. Gender and estrogen use were included in models that evaluated men and women together by creating a gender-estrogen variable with four levels, with one level for males, and three levels for women divided into current, former, or never users of estrogen. In models that included weight change since age 18, the variables representing medical history and physical activity participation were included as covariates. Models that included both involuntary and voluntary weight loss were unadjusted for medical history or physical activity because illness and physical activity were used in the definitions of involuntary and voluntary weight loss. Participation in physical activity was included as a covariate in separate models that assessed the effect of only involuntary weight loss, and history of one or more of the selected medical conditions was included in separate models that assessed the effect of only voluntary weight loss. Total protein, calcium, and vitamin D intake were not significantly related to both weight change and hip fracture and thus were not included as potential confounding factors in the logistic regression models.

To assess whether weight change and weight loss intention were related to risk of hip fracture independently of other measures of body size, current BMI or BMI at time of hip fracture, BMI at age 18, and modified BMI were evaluated as covariates in the logistic regression models. Each measure of BMI was at least somewhat linearly related to risk of hip fracture, and since comparison of likelihood ratio statistics revealed no significant evidence for the need to include measures of BMI as categorical variables, each measure was included in regression models as a continuous variable. Results using modified BMI were not appreciably different than those obtained using current BMI or BMI at time of hip fracture, so modified BMI was not used in subsequent models. Body mass index at age 18 was included as a covariate in models that assessed the effect of weight change since age 18 to evaluate whether weight change was related to risk of hip fracture independent of body mass at the starting point of the weight change. Logistic regression models that included weight loss of more than 20 pounds or weight loss intention variables were not adjusted for BMI at age 18, but were adjusted for current BMI or BMI at time of hip fracture.

Possible interactions between age group, gender, estrogen use, weight change since age 18, weight loss of more than 20 pounds, and weight loss intention were explored. Marginal associations between weight change variables and risk of hip fracture were inspected for differences by gender or age group and comparisons of likelihood-ratio statistics for models with and without interaction terms were used to determine which interaction terms should be included in multivariate models. For weight change since age 18, results are presented stratified by gender as there was evidence that the effect of higher than average weight gain (quintiles four and five of weight change since

age 18) was modified by gender. The associations between lower than average weight gain (quintile two), weight loss (quintile one), and risk of hip fracture appeared to be similar in men and women, however these associations were modified by age group (p = 0.002 for the interaction in the multivariate model), so estimates for risk of hip fracture based on the lower two quintiles of weight change since age 18 are also presented stratified by age group. There were no significant interactions between gender and weight loss of more than 20 pounds or weight loss intention, and results from logistic regression models including these variables are presented with men and women combined. In models that included weight loss of more than 20 pounds, overall weight loss intention, and involuntary weight loss alone, there were significant two-way interactions between age group and weight loss ($p < 0.01$ in all multivariate models), so results from these models are presented stratified by age group. In separate logistic regression models that assessed the individual effects of voluntary weight loss, there was less evidence that the association between voluntary weight loss and risk of hip fracture was modified by age ($p = 0.08$), however these results are also presented stratified by age group. A significant two-way interaction between age group and the gender-estrogen variable was discovered and included in models assessing weight loss of more than 20 pounds ($p = 0.03$), overall weight loss intention ($p = 0.01$), and models assessing the individual effects of voluntary weight loss ($p = 0.02$).

Odds ratios and 95 percent confidence intervals for risk of hip fracture were obtained from each logistic regression model. In addition, higher than average weight gain, lower than average weight gain, and weight loss were assessed for dose-response relationships with risk of hip fracture by comparing the likelihood-ratio statistics of

multivariate models that included the upper and lower quintiles of weight change since age 18 as continuous variables to models without these variables. Similar methods were used to test for dose-response relationships between risk of hip fracture and amount of involuntary or voluntary weight loss. All analyses were performed using SPSS software, version 11.0 (SPSS, Chicago, IL, USA) and SAS software, version 8 (SAS Institute, Cary, NC, USA).

Results

Characteristics of 1,709 female participants (829 cases and 880 controls) and 782 male participants (330 cases and 452 controls) are listed in table 3-1. The overall study population was 97 percent white, not of Hispanic origin. Among women, more cases than controls were current or former smokers or users of alcohol, had never taken estrogen other than for contraception, were less physically active, and had a history of medical conditions. Female cases also weighed less and were taller than female controls. In men, more cases than controls were current or former smokers or users of alcohol, were less physically active, and had a history of medical conditions. Male cases weighed less, were taller, and weighed more at age 18 than male controls. As shown in table 3-2, male and female cases gained less weight after age 18 than did controls, and more cases than controls were in the bottom two quintiles of weight change since age 18.

Table 3-3 includes comparisons by age group of weight change variables between cases and controls. In both age groups, cases gained significantly less weight after age 18 than controls. In those aged 50 to 69 years, more cases than controls were in the lowest two quintiles of weight change since age 18, ever lost more than 20 pounds in a one-year

Table 3-1. Characteristics by gender of 1,159 cases and 1,332 controls from the Utah Study of Nutrition and Bone Health: 1997 - 2001[†]

Covariates	Women		Men	
	Case (n = 829)	Control (n = 880)	Case (n = 330)	Control (n = 452)
Mean (SD) age, y	76.4 (9.1)	75.8 (9.3)	74.6 (9.5)	73.5 (10.5)
Age groups, No. (%)				
50 – 69 years	168 (20.3)	189 (21.5)	96 (29.1)	146 (32.3)
70 – 89 years	661 (79.7)	691 (78.5)	234 (70.9)	306 (67.7)
No. (%)				
White race	811 (97.8)	860 (97.7)	319 (96.7)	424 (93.8)
Education status				
< 12 years	127 (15.3)	108 (12.3)	58 (17.6)	87 (19.3)
≥ 12 years	702 (84.7)	771 (87.7)	272 (82.4)	364 (80.7)
Smoking				
Never	633 (76.5)	734 (83.4)***	145 (43.9)	238 (52.7)*
Former	135 (16.3)	122 (13.9)	148 (44.9)	177 (39.2)
Current	59 (7.1)	24 (2.7)	37 (11.2)	37 (8.2)
Regular alcohol use				
Never	593 (72.0)	699 (79.6)***	144 (43.8)	222 (49.2)
Former	127 (15.4)	78 (8.9)	108 (32.8)	126 (27.9)
Current	106 (12.8)	101 (11.5)	77 (23.4)	103 (22.8)
Estrogen user				
Never	407 (50.3)	365 (42.1)***		
Former	211 (26.1)	223 (25.7)		
Current	192 (23.7)	279 (32.2)		
No. of physical activities[‡]				
None	204 (24.6)	109 (12.4)***	44 (13.3)	41 (9.1)***
One	230 (27.7)	180 (20.5)	104 (31.5)	96 (21.2)
Two	247 (29.8)	354 (40.3)	108 (32.7)	188 (41.6)
Three	148 (17.9)	236 (26.8)	74 (22.4)	127 (28.1)
≥ 1 medical conditions[§]	541 (65.3)	502 (57.0)***	217 (65.8)	230 (50.9)***
Mean (SD)				
Weight[#] (kg)	63.4 (14.0)	68.9 (14.5)***	79.6 (14.7)	82.6 (15.1)**
Height[#] (cm)	162.1 (6.6)	161.4 (6.4)*	178.8 (6.9)	176.6 (7.5)***
Weight at age 18 (kg)	55.1 (8.3)	54.4 (7.3)	70.2 (11.4)	68.3 (10.4)*
BMI[#] (kg/M^2)	24.2 (5.1)	26.5 (5.1)***	24.9 (4.0)	26.4 (4.3)***

Asterisks indicate significant differences between cases and controls within gender:
* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

[†] Some covariates have a slightly smaller sample size due to missing data. Subjects with missing data were excluded from individual analyses. Some percentages do not add to 100 due to rounding.

[‡] Regular participation in none, exactly one, exactly two, or all three of yard work, house work, or recreational activities.

[§] History of 1 or more medical conditions, including emphysema, myocardial infarction, stroke, diabetes, non-skin cancer, thyroid disease, and Parkinson's disease.

[#] Current weight and height for controls, weight and height at time of hip fracture for cases.

Table 3-2. Comparison by gender of weight change since age 18 between 1,159 cases and 1,332 controls in the Utah Study of Nutrition and Bone Health: 1997 - 2001[†]

	Women		Men	
	Case (n = 829)	Control (n = 880)	Case (n = 330)	Control (n = 452)
Mean (SD) percent weight change since age 18[‡]	16.2 (25.5)	28.3 (26.2)***	15.6 (24.2)	22.6 (22.8)***
No. (%)[§]				
Quintiles of percent weight change since age 18 (range)[‡]				
Q1 (< 0%)	184 (22.2)	80 (9.1)***	71 (21.5)	50 (11.1)***
Q2 (0 to 12.5%)	192 (23.2)	164 (18.6)*	99 (30.0)	101 (22.4)*
Q3 (12.6 to 25%)	166 (20.0)	173 (19.7)	61 (18.5)	113 (25.0)*
Q4 (26 to 39.8%)	116 (14.0)	181 (20.6)***	46 (13.9)	106 (23.5)***
Q5 (> 39.8%)	125 (15.1)	235 (26.7)***	40 (12.1)	76 (16.8)

Asterisks indicate significant differences between cases and controls within gender: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

[†] Some covariates have a slightly smaller sample size due to missing data. Subjects with missing data were excluded from individual analyses.

[‡] Negative numbers represent weight loss since age 18, positive numbers represent weight gain since age 18.

[§] Percentages do not add to 100 due to rounding.

Table 3-3. Comparison by age group of weight change variables between 1,159 cases and 1,332 controls in the Utah Study of Nutrition and Bone Health: 1997 - 2001[†]

Covariates	50 – 69 years		70 – 89 years	
	Case (n = 264)	Control (n = 335)	Case (n = 895)	Control (n = 997)
Mean (SD) percent weight change since age 18[‡]	19.5 (27.7)	33.7 (25.5)***	15.0 (24.2)	23.8 (24.6)***
No. (%)				
Quintiles of percent weight change since age 18 (range)[‡§]				
Q1 (< 0%)	54 (20.5)	11 (3.3)***	201 (22.5)	119 (11.9)***
Q2 (0 to 12.5%)	59 (22.4)	49 (14.6)*	232 (25.9)	216 (21.7)*
Q3 (12.6 to 25%)	47 (17.8)	83 (24.8)*	180 (20.1)	203 (20.4)
Q4 (26 to 39.8%)	45 (17.1)	79 (23.6)*	117 (13.1)	208 (20.9)***
Q5 (> 39.8%)	51 (19.3)	107 (31.9)***	114 (12.7)	204 (20.5)***
Ever lost > 20 lbs in ≤ 1 year	147 (55.7)	153 (45.7)*	294 (33.0)	332 (33.3)
No loss of > 20 lbs in ≤ 1 year and in middle quintile of weight change[#]	24 (9.1)	53 (15.8)*	123 (13.7)	136 (13.6)
Involuntary weight loss[††]	82 (31.1)	38 (11.3)***	155 (17.3)	151 (15.2)
Loss due to just illness	40 (15.2)	18 (5.4)***	71 (7.9)	80 (8.0)
Loss due to just surgery	11 (4.2)	10 (3.0)	30 (3.4)	27 (2.7)
Loss due to illness and surgery	15 (5.7)	3 (0.9)***	31 (3.5)	23 (2.3)
Loss due in part to depression[‡‡]	16 (6.1)	7 (2.1)*	23 (2.6)	21 (2.1)
< 15% involuntary loss[§§]	25 (9.5)	19 (5.7)***	66 (7.4)	60 (6.0)
≥ 15% involuntary loss[§§]	57 (21.6)	19 (5.7)	83 (9.3)	88 (8.8)
Voluntary weight loss[††]	50 (18.9)	88 (26.3)*	98 (11.0)	140 (14.0)*
Loss due to just dieting	26 (9.9)	39 (11.6)	51 (5.7)	68 (6.8)
Loss due to just physical activity	5 (1.9)	11 (3.3)	10 (1.1)	14 (1.4)
Loss due to both	19 (7.2)	38 (11.3)	37 (4.1)	58 (5.8)
< 15% voluntary loss[§§]	22 (8.3)	37 (11.0)	32 (3.6)	59 (5.9)*
≥ 15% voluntary loss[§§]	28 (10.6)	50 (14.9)	63 (7.0)	77 (7.7)

period, and experienced involuntary weight loss. More controls than cases were in the highest two quintiles of weight change and experienced voluntary weight loss. In participants aged 70 to 89 years, more cases than controls were in the lowest two quintiles of weight change since age 18, and more controls than cases were in the highest two quintiles of weight change since age 18 and experienced voluntary weight loss.

Odds ratios for hip fracture based on quintile of weight change since age 18 and stratified by gender are listed in table 3-4. In multivariate analysis, risk of hip fracture in women increased with decreasing amounts of weight gain (quintile two) or increasing amounts of weight loss (quintile one) (p trend < 0.0001); however, risk of hip fracture was increased significantly only with weight loss (odds ratio (OR) = 2.34, 95 percent confidence interval (CI): 1.62, 3.38). In men, lower than average weight gain and weight loss were both associated with a significant increase in risk of hip fracture (OR = 1.91, 95 percent CI: 1.24, 2.95 for quintile two; OR = 2.65, 95 percent CI: 1.58, 4.47 for quintile one) and risk increased with decreasing amounts of weight gain or increasing amounts of weight loss (p trend = 0.0001). Higher than average amounts of weight gain decreased risk of hip fracture in women (OR = 0.61, 95 percent CI: 0.44, 0.85 for quintile four; OR = 0.46, 95 percent CI: 0.33, 0.64 for quintile five) and risk of hip fracture decreased with increasing amounts of weight gain (p trend < 0.0001). Above average weight gain in men decreased risk of hip fracture slightly, but was not significantly protective.

Odds ratios for hip fracture based on the lower quintiles of weight change since age 18 and stratified by age group are presented in table 3-5. In men and women aged 50 to 69 years, multivariate analysis showed that lower than average weight gain and weight loss were associated with a significant increase in risk of hip fracture (OR = 2.11, 95

Table 3-4. Odds ratios (OR) with 95% confidence intervals (CI) for hip fracture by quintile of percent weight change since age 18* and stratified by gender in 1,159 cases and 1,332 controls in the Utah Study of Nutrition and Bone Health: 1997 - 2001

Quintiles (range)	Women				Men			
	Age-adjusted model		Multivariate† model		Age-adjusted model		Multivariate† model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Q1 (< 0%)	2.41	1.72, 3.38	2.34‡	1.62, 3.38	2.63	1.63, 4.24	2.65§	1.58, 4.47
Q2 (0 - 12.5%)	1.22	0.91, 1.65	1.20	0.87, 1.64	1.81	1.19, 2.75	1.91	1.24, 2.95
Q3 (12.6 – 25%)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Q4 (26 - 39.8%)	0.67	0.49, 0.92	0.61#	0.44, 0.85	0.80	0.50, 1.28	0.76**	0.47, 1.22
Q5 (> 39.8%)	0.55	0.41, 0.75	0.46	0.33, 0.64	0.98	0.60, 1.60	0.77	0.45, 1.31

* Negative numbers (Q1) represent weight loss since age 18, positive numbers represent weight gain since age 18.

† Multivariate models were simultaneously adjusted for age group, BMI at age 18, smoking, alcohol use, education status, history of one or more select medical conditions (including emphysema, myocardial infarction, stroke, diabetes, non-skin cancer, thyroid disease, and Parkinson's disease), and regular participation in none, exactly one, exactly two, or all three of yard work, house work, or recreational activities. Point estimates for women were additionally adjusted for estrogen use.

‡ p trend < 0.0001 for decreasing amounts of weight gain or increasing amounts of weight loss (Q2 and Q1) among women.

§ p trend = 0.0001 for decreasing amounts of weight gain or increasing amounts of weight loss (Q2 and Q1) among men.

p trend < 0.0001 for increasing amounts of weight gain (Q4 and Q5) among women.

** p trend = 0.2 for increasing amounts of weight gain (Q4 and Q5) among men.

Table 3-5. Odds ratios (OR) with 95% confidence intervals (CI) for hip fracture by quintile 1 and 2 of percent weight change since age 18* and stratified by age group in 1,159 cases and 1,332 controls in the Utah Study of Nutrition and Bone Health: 1997 - 2001

Quintiles (range)	50 – 69 years				70 – 89 years			
	Age & gender-adjusted† model		Multivariate‡ model		Age & gender-adjusted† model		Multivariate‡ model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Q1 (< 0%)	8.56	4.07, 17.99	8.25§	3.76, 18.12	1.92	1.41, 2.60	1.92#	1.38, 2.66
Q2 (0 - 12.5%)	2.16	1.28, 3.65	2.11	1.22, 3.65	1.23	0.93, 1.62	1.25	0.94, 1.67
Q3 (12.6 – 25%)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent

* Negative numbers (Q1) represent weight loss since age 18, positive numbers represent weight gain since age 18.

† Age and gender-adjusted models include an interaction term for age group and weight change.

‡ Multivariate models were simultaneously adjusted for gender, age group, estrogen use, BMI at age 18, smoking, alcohol use, education status, history of one or more select medical conditions (including emphysema, myocardial infarction, stroke, diabetes, non-skin cancer, thyroid disease, and Parkinson's disease), regular participation in none, exactly one, exactly two, or all three of yard work, house work, or recreational activities, and an interaction term for age group and weight change.

§ p trend < 0.0001 for decreasing amounts of weight gain or increasing amounts of weight loss (Q2 and Q1) among ages 50 – 69 years.

p trend = 0.0002 for decreasing amounts of weight gain or increasing amounts of weight loss (Q2 and Q1) among ages 70 – 89 years.

percent CI: 1.22, 3.65 for quintile two; OR = 8.25, 95 percent CI: 3.76, 18.12 for quintile one). In men and women aged 70 to 89 years, lower than average weight gain was associated with a slight increase in risk of hip fracture that was not significant (OR = 1.25, 95 percent CI: 0.94, 1.67), and weight loss significantly increased risk of hip fracture (OR = 1.92, 95 percent CI: 1.38, 2.66). In both age groups, risk of hip fracture increased with decreasing amounts of weight gain and increasing amounts of weight loss (p trend < 0.0001 for participants aged 50 to 69 years, p trend = 0.0002 for participants aged 70 to 89 years).

The associations between weight loss of more than 20 pounds in a one-year period, weight loss intention, and risk of hip fracture differed depending on age group (table 3-6). In multivariate analysis, weight loss of more than 20 pounds was associated with a significant increase in risk of hip fracture in participants aged 50 to 69 years (OR = 2.28, 95 percent CI: 1.28, 4.07), but was not significantly associated with risk of hip fracture in participants aged 70 to 89 years (OR = 0.90, 95 percent CI: 0.67, 1.20). Involuntary weight loss among those aged 50 to 69 years was associated with a significantly increased risk of hip fracture (OR = 4.73, 95 percent CI: 2.45, 9.13), but among those aged 70 to 89 years, involuntary weight loss was not associated with risk of hip fracture (OR = 1.03, 95 percent CI: 0.73, 1.46). In men and women aged 50 to 69, voluntary weight loss was associated with an increase in risk of hip fracture that was not significant (OR = 1.81, 95 percent CI: 0.96, 3.45), and in men and women aged 70 to 89, voluntary weight loss was associated with a slight decrease in risk of hip fracture that was not significant (OR = 0.89, 95 percent CI: 0.61, 1.29).

Table 3-6. Odds ratios (OR) with 95% confidence intervals (CI) for hip fracture based on weight loss of more than 20 pounds in a year or less and intent of weight loss* and stratified by age group in 1,159 cases and 1,332 controls in the Utah Study of Nutrition and Bone Health: 1997 - 2001

	50 – 69 years				70 – 89 years			
	Age & gender-adjusted model		Multivariate model		Age & gender-adjusted model		Multivariate model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No loss of > 20 lbs in ≤ 1 year and in middle quintile of weight change	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Ever lost > 20 lbs in ≤ 1 year[†‡]	2.12	1.24, 3.61	2.28	1.28, 4.07	0.98	0.73, 1.31	0.90	0.67, 1.20
Involuntary weight loss[§#]	5.04	2.69, 9.42	4.73	2.45, 9.13	1.13	0.81, 1.58	1.03	0.73, 1.46
Voluntary weight loss[§#]	1.25	0.68, 2.27	1.81	0.96, 3.45	0.77	0.54, 1.10	0.89	0.61, 1.29

* Involuntary or voluntary weight loss of more than 20 pounds in a year or less.

† Age and gender-adjusted model includes an interaction term for age group and weight loss.

‡ Multivariate model was simultaneously adjusted for gender, age group, estrogen use, BMI, smoking, alcohol use, education status, history of one or more select medical conditions (including emphysema, myocardial infarction, stroke, diabetes, non-skin cancer, thyroid disease, and Parkinson's disease), regular participation in none, exactly one, exactly two, or all three of yard work, house work, or recreational activities, and interaction terms for age group and weight loss and age group and the gender-estrogen variable.

§ Age and gender-adjusted model includes interaction terms for age group and weight loss and age group and the gender-estrogen variable.

Multivariate model was simultaneously adjusted for gender, age group, estrogen use, BMI, smoking, alcohol use, education status, and interaction terms for age group and weight change and age group and the gender-estrogen variable.

Multivariate odds ratios obtained from logistic regression models used to assess the individual effects of involuntary weight loss, reason for involuntary weight loss, and amount of involuntary weight loss on risk of hip fracture are presented stratified by age group in table 3-7. The estimates for risk of hip fracture based on whether or not weight loss was involuntary are slightly different from those in table 3-6 because they are additionally adjusted for participation in physical activity. Involuntary weight loss was associated with an increased risk of hip fracture among participants aged 50 to 69 (OR = 4.17, 95 percent CI: 2.18, 7.97), but was not associated with risk of hip fracture among participants aged 70 to 89 (OR = 0.95, 95 percent CI: 0.67, 1.36). Among men and women aged 50 to 69 years, weight loss due to only surgery was not significantly related to risk of hip fracture (OR = 2.52, 95 percent CI: 0.92, 6.97) and weight loss due to a combination of both illness and surgery appeared to be the most harmful (OR = 10.87, 95 percent CI: 2.74, 43.20), though the CI for this association was wide. Weight loss of equal to or more than 15 percent of maximum weight was associated with a higher increase in risk of hip fracture than was weight loss of less than 15 percent of maximum weight (OR = 5.39, 95 percent CI: 2.57, 11.32 for weight loss of at least 15 percent of maximum weight; OR = 2.80, 95 percent CI: 1.24, 6.32 for weight loss less than 15 percent of maximum weight), and risk of hip fracture increased with increasing amounts of involuntary weight loss (p trend < 0.0001). Among men and women aged 70 to 89 years, no specific reason for involuntary weight loss or amount of involuntary weight loss was significantly related to risk of hip fracture.

Table 3-8 includes multivariate odds ratios for hip fracture that are stratified by age group and that were obtained from logistic regression models evaluating the

Table 3-7. Multivariate* odds ratios (OR) with 95% confidence intervals (CI) for hip fracture based on involuntary weight loss of more than 20 pounds in a year or less, reason for involuntary loss, and amount of involuntary loss and stratified by age group in 1,159 cases and 1,332 controls in the Utah Study of Nutrition and Bone Health: 1997 - 2001

	50 – 69 years		70 – 89 years	
	OR	95% CI	OR	95% CI
No loss of > 20 lbs in ≤ 1 year and in middle quintile of weight change	1.00	Referent	1.00	Referent
Involuntary weight loss[†]	4.17	2.18, 7.97	0.95	0.67, 1.36
Reason for involuntary weight loss				
Just illness	4.24	1.93, 9.29	0.82	0.53, 1.26
Just surgery	2.52	0.92, 6.97	1.00	0.54, 1.86
Illness and surgery	10.87	2.74, 43.20	1.43	0.77, 2.64
Just depression and depression in combination with other reasons[‡]	3.43	1.15, 10.21	0.86	0.43, 1.73
Amount of involuntary weight loss[§]				
< 15% loss	2.80[#]	1.24, 6.32	1.05	0.66, 1.66
≥ 15% loss	5.39	2.57, 11.32	0.85	0.56, 1.29

* Multivariate models were simultaneously adjusted for gender, age group, estrogen use, BMI, smoking, alcohol use, education status, regular participation in none, exactly one, exactly two, or all three of yard work, house work, or recreational activities, and an interaction term for age group and weight loss.

[†] Point estimates are slightly different from those in table 3-6 because they are additionally adjusted for regular participation in none, exactly one, exactly two, or all three of yard work, house work, or recreational activities

[‡] Includes loss due to just depression, illness and depression, surgery and depression, or all three of illness, surgery, and depression.

[§] Most weight ever lost at one time as a percent of maximum weight.

[#] p trend < 0.0001 for increasing amounts of involuntary weight loss among ages 50 to 69 years.

Table 3-8. Multivariate* odds ratios (OR) with 95% confidence intervals (CI) for hip fracture based on voluntary weight loss of more than 20 pounds in a year or less, reason for voluntary loss, and amount of voluntary loss and stratified by age group in 1,159 cases and 1,332 controls in the Utah Study of Nutrition and Bone Health: 1997 - 2001

	50 – 69 years		70 – 89 years	
	OR	95% CI	OR	95% CI
No loss of > 20 lbs in ≤ 1 year and in middle quintile of weight change	1.00	Referent	1.00	Referent
Voluntary weight loss[†]	1.73	0.88, 3.39	0.89	0.60, 1.31
Reason for voluntary weight loss				
Just dieting	2.06	0.93, 4.53	0.91	0.57, 1.47
Just physical activity	1.25	0.33, 4.68	0.92	0.37, 2.27
Both	1.56	0.68, 3.55	0.86	0.51, 1.45
Amount of voluntary weight loss[‡]				
< 15% loss	1.89	0.85, 4.22	0.65	0.38, 1.10
≥ 15% loss	1.58	0.73, 3.42	1.05	0.66, 1.65

* Multivariate models were simultaneously adjusted for gender, age group, estrogen use, BMI, smoking, alcohol use, education status, history of one or more select medical conditions (including emphysema, myocardial infarction, stroke, diabetes, non-skin cancer, thyroid disease, and Parkinson's disease), and interaction terms for age group and weight loss and age group and the gender-estrogen variable.

[†] Point estimates are slightly different from those in table 3-6 because they are additionally adjusted for history of one or more select medical conditions (including emphysema, myocardial infarction, stroke, diabetes, non-skin cancer, thyroid disease, and Parkinson's disease).

[‡] Most weight ever lost at one time as a percent of maximum weight.

individual effects of voluntary weight loss, reason for voluntary weight loss, and amount of voluntary weight loss. The estimates for risk of hip fracture based on voluntary weight loss are slightly different than those in table 3-6 because they are additionally adjusted for history of medical conditions. Though voluntary weight loss did not significantly increase risk of hip fracture in either age group, estimates of risk did differ by age group. Voluntary weight loss among men and women aged 50 to 69 years was associated with an increased risk of hip fracture that was not significant (OR = 1.73, 95 percent CI: 0.88, 3.39) and voluntary weight loss among participants aged 70 to 89 years was associated with a slight decrease in risk of hip fracture that was not significant (OR = 0.89, 95 percent CI: 0.60, 1.31). Risk of hip fracture based on reason for voluntary weight loss or amount of voluntary weight loss differed similarly by age group and was not significantly increased or decreased in either group.

Discussion

In the Utah elderly population, above average weight gain since age 18 was significantly protective against hip fracture among women, but not among men. Lower than average weight gain and weight loss since age 18 appeared to increase risk of hip fracture in both men and women and in participants aged 50 to 69 years and 70 to 89 years. Involuntary weight loss caused by illness, surgery, or depression was associated with over a four-fold increase in risk of hip fracture in men and women 50 to 69 years of age (OR = 4.73, 95 percent CI: 2.45, 9.13) and risk increased with higher amounts of weight loss. In men and women aged 70 to 89, involuntary weight loss was not associated with risk of hip fracture. Voluntary weight loss that was the result of dieting

or increased physical activity did not significantly increase risk of hip fracture in either age group.

The increased risk of hip fracture associated with weight loss since young adulthood that was seen in men and women of all ages in this Utah study is consistent with the results of other studies of weight loss from a peak at a young age (6-8). Likewise, many studies have reported that women who gained weight at various stages in their life had a decreased risk of hip fracture (4, 5, 7, 10) and in aging women of Utah, above average weight gain since age 18 was associated with a significant decrease in risk of hip fracture. Other studies of men have reported that weight gain after age 50 (11) and high BMI or obesity (34, 35) were associated with a decrease in risk of hip fracture, however in this study, above average weight gain after age 18 in men was not associated with a significant decrease in risk of hip fracture. Perhaps weight change since age 18 is not a meaningful measure of weight change in men, or perhaps our study lacked the sufficient sample size among men to detect a significantly protective effect.

Our finding that involuntary weight loss significantly increased risk of hip fracture in participants aged 50 to 69 years corroborates the findings of Meyer et al. (30) and Ensrud et al. (5), that weight loss that is unintentional or due to poor appetite increases risk of hip fracture in elderly adults. Our finding that involuntary weight loss did not significantly increase risk of hip fracture in participants aged 70 to 89 years is unique, however. Cases and controls in the older age group gained less weight after age 18 (table 3-2) than did the younger age group, so perhaps older participants were less likely to have extreme weight loss, or it is possible that men and women aged 70 to 89 who did gain high amounts of weight after age 18 were not included in our study because

they had already died from illnesses related to extreme weight gain. Alternatively, it may be that illness, surgery, and depression are so common among the oldest-old that it is difficult to evaluate how their effects may differ between older cases and controls. Lack of a significant finding could also be attributed to the poorer participation rate among older cases in our study. When comparing the proportions of cases and controls that failed to complete interviews due to illness, frailty, cognitive impairment, or death, there was a bigger difference between case and control proportions among the older age group. In participants aged 50 to 69 years, 17.5 percent of cases and 3.5 percent of controls failed to complete interviews due to illness, frailty, cognitive impairment, or death. Among participants aged 70 to 89 years, 39.3 percent of cases and 18.0 percent of controls failed to complete interviews for the same reasons. This limitation could have resulted in a group of older cases that had less weight loss due to illness, surgery, or depression than what truly occurs in the Utah elderly population and could have biased our associations toward the null in the older age group.

We found that voluntary weight loss was not significantly associated with risk of hip fracture. Although risk was slightly elevated in participants aged 50 to 69, and there may have been an insufficient sample size in this age group to detect a significant relationship in our study, Meyer et al. (30) and Ensrud et al. (5) also found that voluntary weight loss or weight loss for slimming purposes did not significantly increase or decrease risk of hip fracture. Our lack of a significant relationship between voluntary weight loss and risk of hip fracture is inconsistent with results from another study by Ensrud et al. (29), however, who when using similar prospective data as their former study, only using a longer follow-up period, reported that both intentional and

unintentional weight loss increased risk of hip fracture in postmenopausal women. Both studies by Ensrud et al. (5, 29) assessed weight loss over a period of about six years, but only asked about weight loss intention in the last year of assessment. Inaccuracies may have been introduced because they were not able to account for weight loss intention over the entire weight loss period. In the Utah study, our analysis of weight loss intention included one major weight loss event, and we were able to completely account for the reasons for that weight loss, including respondents that may have had both intentional and unintentional aspects included in their weight loss. This may make the measurement of weight loss intention more meaningful in our study.

There are a number of ways that weight loss, and more specifically involuntary weight loss, may contribute to risk of hip fracture. Weight loss is associated with reduced femoral neck bone mineral density (BMD) in aging men and women (36-38), in part because weight loss that is not accompanied with increased physical activity results in a subsequent decline in mechanical stresses on weight-bearing skeletal sites, which could influence the remodeling of bone (37, 39, 40). In addition, estrone converted from androstenedione in peripheral adipose tissue is a source of estrogen in postmenopausal women (41) and weight loss that includes reductions in fat tissue may result in greater BMD loss in postmenopausal women by depriving them of the bone-protecting effects of adipose-derived estrogen (42, 43). Weight reduction may also contribute to risk of hip fracture through the loss of fat and muscle tissue, which may affect risk of falling in the elderly and whether or not falls result in fractures. Excessive losses of lean body mass may cause harmful muscle wasting (44). Such decreases in muscle mass may impair muscle strength, gait, coordination, reaction time, and postural stability (39, 45) and

make falls more likely to occur in the elderly (36, 39). Loss of fat and muscle tissue around the hips and buttocks may also result in a loss of the protective padding that helps to absorb the energy of a fall or other impact away from the proximal femur, thus making a fracture more likely to occur (3, 39, 46-48). Finally, involuntary weight loss may also contribute to an increased risk of hip fracture by being a marker for malnutrition or for illness and poor health. Weight loss can be an important indicator of an inadequate intake of nutrients in the elderly (44) and since nutritional deficiency is implicated in the pathogenesis and consequences of hip fracture in elderly patients (46), it is plausible that involuntary weight loss may contribute to an increased risk of hip fracture when it results from poor intake of nutrients that are important for bone health, including calcium, vitamin D, and protein (2, 39, 49-52). Furthermore, poor nutrient intake and involuntary weight loss often result from acute or chronic illnesses (44), and in studies of risk factors for hip fracture, participants with weight loss were far more likely to report poor health or one or more medical conditions (5, 10, 11, 53). A wide variety of medical conditions have been associated with an increased risk of hip fracture (2, 9, 12, 13, 54, 55). Weight loss that was the result of illness or otherwise poor health certainly contributed to the increase in risk of hip fracture seen with involuntary weight loss in our study because weight loss associated with illness, surgery, or depression was used to define involuntary weight loss. Some or all of these other factors, including decreases in BMD and reductions in muscle and fat mass, could also have contributed to the association between involuntary weight loss and risk of hip fracture among men and women of Utah.

The finding in our study that voluntary weight loss did not significantly increase risk of hip fracture is encouraging. Voluntary weight loss is commonly initiated in an

attempt to avoid the burdens of such chronic diseases as heart disease, hypertension, or diabetes. Although intentional weight loss was not found to significantly predict or protect against increased mortality in one elderly population (56), reducing overweight and maintaining a lower weight have nonetheless been shown to be effective in preventing or alleviating these diseases (22-25, 57) and have been shown to reduce mortality in overweight and obese middle- to older-aged adults (27). A crucial factor that may enable voluntary weight-losers to avoid increasing their risk of hip fracture because of weight loss is physical activity. We could not show in our study that voluntary weight loss was unrelated to risk of hip fracture because it resulted from increased physical activity, but it is still possible that physical activity helps voluntary weight-losers avoid increasing their risk of hip fracture. Physical activity has consistently been found to have positive effects on BMD, at least in weight-bearing areas, to help reduce risk of falls in the elderly, and to reduce overall risk of hip fracture (42, 58, 59). In a Swedish case-control study of women aged 50 to 81 years (60), women who had lost three or more kg since age 18 and participated in three or more hours of recreational activity per week had a 76 percent reduction in risk of hip fracture when compared to women who were inactive. Similar levels of activity in women who gained three or more kg since age 18 were associated with only a 38 percent decrease in risk of hip fracture (60). Perhaps physical activity helps maintain the otherwise reduced mechanical loading that is associated with weight loss and preserves valuable lean body mass in elderly adults, thus facilitating a reduction in risk of falls and overall risk of hip fracture. If voluntary weight loss is indeed unassociated with risk of hip fracture in elderly adults, the relationship between weight loss and risk of hip fracture will no longer be in conflict with current

public health recommendations regarding weight loss to prevent and treat chronic diseases, and clinicians may more confidently prescribe weight loss to their overweight patients without being fearful of increasing their patients' risk of hip fracture.

There are a number of limitations in this study. One limitation was mentioned previously, and was that more cases than controls failed to complete interviews due to illness, frailty, cognitive impairment, or death, and this difference was most apparent among older participants. Another limitation was that values obtained for percent weight loss since age 18 likely did not reflect strictly increasing or decreasing weight since young adulthood; participants could have experienced wide fluctuations in weight prior to the measurement of weight change for our study. This may have attenuated some of the results reported in our study. A third limitation of our study was that the weight loss of more than 20 pounds in a year or less reported by respondents in our study represented only one episode of weight loss and could have occurred at any time in the respondents' past. However, researchers studying elderly adults have reported that weight loss since young adulthood, weight loss from a maximum weight, and weight loss in old age are all associated with an increased risk of hip fracture (4-13). There was also no information collected in our study regarding whether weight loss was maintained, how long it was maintained, or if and how much weight was regained. In addition, although great pains were taken to account for any participants that may have included weight loss due their hip fracture in their responses, the involuntary weight loss category used in our analysis could still have included some cases that lost weight due to their hip fracture surgery. Analyses that did not include weight loss due to surgery produced similar results, however (data not shown), and weight loss due to only surgery was not more strongly

related to risk of hip fracture than was involuntary weight loss that was the result of illness or depression. Our study was also prone to the normal limitations and biases of case-control studies, including limitations in self-report of height and weight or possible biases in the amount of weight loss reported depending on the participants' intent of weight loss. Finally, our Utah sample was predominantly Caucasian, so these results may not be applicable to other races or ethnicities.

Our study also has a number of strengths. By including only one weight loss episode of more than 20 pounds, we were able to account for intention of the entire weight loss episode and could separate those participants who had characteristics of both voluntary and involuntary weight loss. We could also examine specific traits of weight loss intention, i.e. whether weight loss due to dieting, increased physical activity, illness, surgery, or depression had differing effects on risk of hip fracture. Although other studies have examined the effect of weight loss intention over a period of a year, this is the first study to examine more extreme weight loss (at least 20 pounds) and how the reasons for that weight loss affected risk of hip fracture. Our choice of reference group was also a strong point in our study. Due to the fact that the average weight change since age 18 among participants in our study was a gain of 22 percent, the reference group used in models assessing weight change included participants in the middle quintile of weight change since age 18 (12.6 to 25 percent weight gain), and the reference group used in all weight loss intention models was made up of participants who responded that they had never lost more than 20 pounds in a year or less and that were also in the middle quintile of weight change since age 18. Many studies of the effect of weight change on risk of hip fracture use a reference group that includes participants with stable weight or little

change in weight (4, 9-12), however in our study, it was unusual for participants to have little change in weight. Although comparing participants with weight loss to participants with weight gain results in higher estimates of the effect of weight loss on risk of hip fracture, these estimates are likely more meaningful in a population in which it is common to gain weight in adulthood.

In summary, weight loss or below average weight gain since age 18 were associated with an increased risk of hip fracture in men and women of Utah and above average weight gain was protective against hip fracture in women. Involuntary weight loss significantly increased risk of hip fracture in men and women aged 50 to 69 years and voluntary weight loss was not significantly associated with risk of hip fracture. These results suggest that prevention of more hip fractures may be possible by urging clinicians to focus greater emphasis on the recognition and treatment of involuntary weight loss and that voluntary weight loss might be safely recommended to aging adults without increasing their risk of hip fracture. Further research of the relationship between weight loss intention and risk of hip fracture is needed to verify that involuntary weight loss is associated with an increased risk of hip fracture and to determine whether voluntary weight loss does indeed contribute little to risk of hip fracture. Additional evidence for a protective effect of physical activity among individuals who lose weight is also needed. If these associations can be confirmed in additional studies, more precise knowledge of the relationships between weight gain and loss, weight loss intention, and risk of hip fracture will be available and it may be possible to develop strategies that support prevention of both chronic diseases and osteoporotic hip fractures.

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CHAPTER 4

SUMMARY AND CONCLUSION

Summary

The general purpose of this thesis project was to learn how observational studies were used by nutritional epidemiologists to establish relationships between nutritional exposures and health outcomes, to review published literature in order to learn how weight change is associated with risk of hip fracture in aging adults, and to contribute original research findings to the body of already published research on this topic. After thorough study of how observational studies are designed, the different strengths and weaknesses for their use in the study of nutritional exposures, and how conclusions are drawn from such studies, an extensive review of published literature was completed to better understand the relationships between body weight, weight change, and risk of hip fracture, and to deduce possible ways through which weight loss makes hip fractures more likely to occur in the elderly (chapter 2). Data from a state-wide case-control study of risk factors for osteoporotic hip fracture in aging residents of Utah was then analyzed to examine the association between weight change and risk of hip fracture and to test the hypothesis that involuntary weight loss increases risk of hip fracture and that voluntary weight loss does not increase risk of hip fracture. Results from this analysis were presented and compared to previous analyses of the relationships between weight change and risk of osteoporotic hip fracture (chapter 3).

Weight Change and Risk of Osteoporotic Hip Fracture: A Review

Weight change has consistently been found to be associated with risk of osteoporotic hip fracture in both men and women. Weight gain has been associated with a reduced risk of hip fracture and weight loss has been associated with an increased risk of fracture. Weight loss, therefore, has been called an important risk factor for hip fracture and clinicians have been advised that its measurement is important when assessing risk of hip fracture in elderly patients. In studies of aging adults, weight loss since young adulthood, weight loss from a maximum weight, and weight loss in old age have all been related to risk of hip fracture. Other recent studies of the association between weight loss and risk of hip fracture have looked more closely at how reasons for weight loss may affect risk, more specifically, whether involuntary weight loss increases risk of hip fracture and whether voluntary weight loss, especially when it results from increased physical activity, does not contribute to risk of hip fracture. There is growing evidence that involuntary weight loss is an important risk factor for hip fracture, but there is less agreement about the effect of voluntary weight loss. Weight loss is commonly recommended to overweight or obese patients, so further research of the distinction between voluntary and involuntary weight loss as it relates to risk of hip fracture is needed to determine if all aspects of weight loss contribute to risk of hip fracture.

Voluntary and Involuntary Weight Change and Risk of Osteoporotic Hip Fracture in Men and Women of Utah

The associations between osteoporotic hip fracture and weight change and weight loss intention were assessed in men and women aged 50 to 89 years in a population-based

case-control study in Utah. Data on weight history and other characteristics of participants in the study were obtained via in-person interviews.

Logistic regression models that included case-control status as the dependent variable and weight change or weight loss intention as independent, categorical variables were used to evaluate risk of hip fracture. In logistic regression models that were stratified by gender, weight loss since age 18 significantly increased risk of hip fracture in both men and women. Above average weight gain was significantly protective against hip fracture in women, but was not significantly protective in men. In logistic regression models that were stratified by age in two groups, involuntary weight loss of more than 20 pounds in a one-year period was associated with a significant increase in risk of hip fracture in men and women aged 50 to 69 years, but was not significantly associated with risk of hip fracture in men and women aged 70 to 89. Voluntary weight loss was not significantly related to risk of hip fracture in either age group.

Similar studies of the relationship between weight change and risk of hip fracture in men and women have found that weight loss since age 18 and involuntary weight loss increased risk of hip fracture and that weight gain appeared to be protective against hip fracture. The analysis of the Utah participants is unique in that weight gain in men was not significantly protective against hip fracture and involuntary weight loss among participants aged 70 to 89 years did not significantly increase risk of hip fracture. In regards to the lack of a significant relationship between weight gain and risk of hip fracture among men, it may be that there were not enough men in the study to be able to detect a significant relationship, or it may be that weight gain does not provide the same benefits in men that it does in women. As for the lack of a significant association

between involuntary weight loss and risk of hip fracture among participants aged 70 to 89, it is possible that associations in the oldest age group were biased by the fact that more older cases than older controls failed to complete interviews due to death, illness, cognitive impairment, or frailty. It is also possible that the effect of involuntary weight loss on risk of hip fracture does in fact differ depending on age, and this is the first study to examine this modification by age of the association between weight loss intention and risk of hip fracture. The finding in the Utah study that voluntary weight loss did not significantly increase risk of hip fracture is similar to some, though not all studies of the relationship between weight loss intention and risk of hip fracture.

Conclusion

Changes in body weight are related to a variety of health outcomes. Weight gain has been related to an increase in risk of chronic diseases, but a decrease in risk of osteoporotic hip fracture. Weight loss is recommended as an effective treatment for chronic diseases, but is also associated with an increased risk of hip fracture. Thus the distinction between how involuntary and voluntary weight loss affect risk of hip fracture in aging adults is important in helping to resolve whether weight loss is harmful in some situations and beneficial in others.

The finding in this analysis that involuntary weight loss in men and women aged 50 to 69 years was associated with an increased risk of hip fracture suggests that involuntary weight loss is an important predictor of hip fracture, at least in this age group, and that the burdens and costs associated with osteoporotic hip fracture could be eased by putting greater focus on the recognition and treatment of unintentional weight loss. It is

encouraging that voluntary weight loss was not associated with risk of hip fracture in this analysis, which suggests that voluntary weight loss is a safe recommendation to aging adults who wish to avoid both chronic diseases and hip fractures. The results of this project contribute meaningfully to existing reports of the effects of weight change and weight loss intention on risk of hip fracture and may perhaps be helpful in developing strategies that support both the treatment of chronic diseases and the prevention of hip fractures.

APPENDICES

Appendix A. USNBH Interview Booklet

The Utah Hip Fracture Study
Interview Questionnaire

NIH Grant Number R01-AR43391

Department of Nutrition and Food Sciences
Utah State University
Logan, UT 84322-4450

Revised 8-5-98

START TIME: ☐☐:☐☐ AM or PM

A. INTERVIEW INFORMATION		
A1.	DATE OF INTERVIEW:	MONTH:☐☐ DAY:☐☐ YEAR:☐☐☐☐
A2.	NAME OF INTERVIEWER:	_____
A3.	ID CODE OF INTERVIEWER:	..... ☐☐
A4.	SETTING OF INTERVIEW:	HOME OF PARTICIPANT ..... 1 HOME OF FRIEND/RELATIVE ..... 2 HOSPITAL ..... 3 SPECIFY: _____ SKILLED NURSING FACILITY ..... 4 SPECIFY: _____ OTHER INSTITUTION ..... 5 SPECIFY: _____ OTHER ..... 6 SPECIFY: _____
A5.	COMPLETE THE INTERVIEW SITE ADDRESS IF DIFFERENT FROM THE FACE SHEET:	_____ STREET ADDRESS _____ CITY _____ STATE _____ ZIP CODE ☐☐☐ - ☐☐☐ - ☐☐☐☐ TELEPHONE

B. DEMOGRAPHICS:
First, I'd like to ask you a few background questions.

B1. In what state were you born?	UTAH ..... 1 OTHER (SPECIFY BELOW) ..... 2 SPECIFY STATE OR COUNTRY: _____ ☐☐
B2. How many years have you lived in Utah?	NUMBER OF YEARS ..... ☐☐
a. Are you a permanent resident of Utah?	YES ..... 1 NO 2
b. How long have you lived in your current residence? (COUNT THE TIME AT RESIDENCE BEFORE HIP FRACTURE FOR CASES.)	NUMBER OF YEARS ..... ☐☐
B3. What best describes your main residence in the (year before your hip fracture/past year)? Was it...	On a farm ..... 1 Rural area, but not a farm or ..... 2 City or town 3
B4. What was your <u>main source</u> of drinking water in the (year before your hip fracture/past year)? Was it a...	City system ..... 1 Rural or county system ..... 2 Private well ..... 3 Bottled water or ..... 4 Something else? (SPECIFY BELOW) ..... 5 _____
B5. During your life, in what city and state have you lived the longest?	CITY_____ ☐☐☐ STATE_____ ☐☐ COUNTRY_____ ☐☐
a. What year did you move there or were you born there?	YEAR ..... ☐☐☐☐
b. What year did you move away?	YEAR ..... ☐☐☐☐ (CODE CURRENT YEAR IF STILL THERE.)

B6. What is your marital status? Are you ...	Married ..... 1 Living with someone as married ..... 2 Separated or divorced ..... 3 Widow/widower ..... 4 Never married ..... 5 RF 7
B7. What is your race or ethnic group?	WHITE, NOT OF HISPANIC ORIGIN ..... 1 AFRICAN AMERICAN ..... 2 ASIAN AMERICAN OR PACIFIC ISLANDER .. 3 (SPECIFIC GROUP:_____) MEXICAN-AMERICAN OR CHICANO ..... 4 PUERTO RICAN, CUBAN, OR OTHER HISPANIC 5 NATIVE AMERICAN OR NATIVE ALASKAN ... 6 (SPECIFIC TRIBE: _____) OTHER OR MIXED ..... 7 (SPECIFIC GROUPS:_____) RF 97
B8. How many years of school did you complete?	1-8 YEARS ..... 1 9-11 YEARS ..... 2 HIGH SCHOOL GRADUATE OR GED ..... 3 VOCATIONAL EDUCATION AFTER HIGH SCHOOL ..... 4 SOME COLLEGE (INCLUDES AA DEGREE) .... 5 COLLEGE GRADUATE (BS, BA) ..... 6 GRADUATE DEGREE (MS, MA, PH.D, MD, JD, DVM) ..... 7 RF 97
B9. What is your religious preference?	CATHOLIC ..... 1 EASTERN ORTHODOX (GREEK OR RUSSIAN) . 2 JEWISH ..... 3 LDS (MORMON) ..... 4 PROTESTANT ..... 5 SEVENTH DAY ADVENTIST ..... 6 OTHER ..... 7 SPECIFY: _____ NO RELIGIOUS PREFERENCE ..... 8 RF 97
B10. About how often did you attend religious services or activities in the (year before your hip fracture/past year)? Would you say ...	Never ..... 1 Less than once a month ..... 2 Once or twice a month ..... 3 Once a week ..... 4 More than once a week ..... 5 RF 7

C. MINI-MENTAL STATE EXAMINATION:

Now, I would like to ask you some questions to check your memory and concentration. Some of the questions may be easy and some will be harder. Take your time if you need to. Just relax and do your best. WRITE DOWN RESPONSES AND CIRCLE RESPONSE CODE AT RIGHT.

C1.	What is the year NOW? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C2.	What is the season of the year? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C3.	What is the month? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C4.	What is the date? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C5.	What is the day of the week? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C6.	What state are we in? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C7.	What county are we in? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C8.	What city or town are we in? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____

C9.	What floor of the building are we on? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C10.	What building are we in? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____

C11. I am going to name three objects. After I have said them, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes. The three objects are: **apple, table, and penny.** Please repeat the names for me now.

SCORE THE FIRST TRY. IF INCORRECT, REPEAT OBJECTS AND ALLOW R TO RECALL FOR UP TO THREE TRIALS ONLY.

	OBJECT	CORRECT	ERROR	RF	NOT ASSESSED
a.	APPLE	 1	 2	 7	 8
b.	TABLE	 1	 2	 7	 8
c.	PENNY	 1	 2	 7	 8
d.	HOW MANY TRIALS WERE NEEDED?			NUMBER OF TRIALS ..... ☐	

C12. Now I am going to give you a word and ask you to spell it forwards and backwards. The word is "world." First, will you spell "world" forwards for me?

REPEAT OR HELP R SPELL WORLD FORWARDS, IF NECESSARY.

Now spell the word "world" backwards.

WRITE LETTERS EXACTLY AS R RECITES THEM TO YOU.
SCORE 1 POINT FOR EACH LETTER IN CORRECT BACKWARD ORDER, BEFORE THE FIRST MISTAKE.
ENTER SCORE IN OPEN BOX (MAXIMUM = 5)

RECORD LETTERS HERE AS GIVEN:

___ ___ ___ ___ ___
(forwards)

___ ___ ___ ___ ___ ..... ☐
(backwards)
NOT ASSESSED (EXPLAIN) 8
_____

C13. What were the three objects I asked you to remember? (SCORE RECALL ONLY. OBJECTS DO NOT HAVE TO BE IN ORDER)

	CORRECT	ERROR	RF	NOT ASSESSED
a. APPLE	1	2	7	8
b. TABLE	1	2	7	8
c. PENNY	1	2	7	8

C14.	POINT TO YOUR WATCH What is this called? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C15.	SHOW YOUR PENCIL What is this called? _____	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C16.	I would like you to repeat a phrase after me. The phrase is, "No ifs, ands, or buts." Please repeat it to me now. SCORE FIRST RESPONSE, MAY REPEAT INSTRUCTIONS UP TO TWO TIMES.	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____
C17.	HOLD UP THE SHEET WITH "CLOSE YOUR EYES" STATEMENT IN FRONT OF R. Please read the words on this page and then do exactly what it says. CODE CORRECT IF R CLOSES EYES.	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____

C18. I am going to give you a piece of paper. When I do, take the paper in your right hand, fold the paper in half with both hands, and place it on your lap.

READ THE FULL STATEMENT THEN HAND OVER THE "CLOSE YOUR EYES" PAPER. DO NOT REPEAT INSTRUCTIONS OR COACH. SCORE EACH PART BELOW.

		CORRECT	ERROR	RF	NOT ASSESSED
a.	RIGHT HAND	 1	 2	 7	 8
b.	FOLDS	 1	 2	 7	 8
c.	ON LAP	 1	 2	 7	 8

C19.	Please write any complete sentence on that piece of paper for me.	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____ ☐☐
C20.	Here is a drawing. Please copy the drawing on the same paper exactly as it appears.	CORRECT ..... 1 ERROR ..... 2 RF ..... 7 NOT ASSESSED (EXPLAIN) ..... 8 _____ ☐☐

D. ACTIVITIES OF DAILY LIVING AND PHYSICAL ACTIVITY Now, I'd like to ask you about activities that we often do as part of our daily lives. I would like to know if during the (month before your hip fracture/past month) you needed help with these activities, or if you could do them without any help.	
D1. Did you need help with eating, for example, serving your food, using utensils, or drinking from a glass or cup?	YES ..... 1 NO 2
D2. Did you need help preparing meals for yourself, for example making a hot meal, a sandwich, or a TV dinner or microwaving food?	YES ..... 1 NO 2
D3. Did you need help bathing, including running the water, washing any part of your body, washing your hair, getting in or out of the tub or shower?	YES ..... 1 NO 2
D4. Did you need help using the toilet, including adjusting clothing, cleaning yourself, getting onto or off of the toilet, or reminders to use the toilet?	YES ..... 1 NO 2
D5. Did you need help dressing yourself, including getting out of clothes, putting clothes on, fastening clothes together, or putting on shoes?	YES ..... 1 NO 2
D6. Did you need help getting into or out of bed or a chair?	YES ..... 1 NO 2
D7. Did you use a cane, walker, or some other form of assistance to help you walk?	YES ..... 1 NO 2
D8. Could you walk short distances by yourself within your own home or inside a building? This would include assistance with a cane or walker.	YES ..... 1 NO 2
D9. Could you walk longer distances by yourself, that is a block or more? This would include assistance with a cane or walker.	YES ..... 1 NO 2
D10. Were you able to climb 10 or more stairs without help?	YES ..... 1 NO 2
D11. Did you need help doing light housework such as dusting, washing dishes, sweeping, or doing laundry?	YES ..... 1 NO 2
D12. Did you need any kind of help using the telephone, either answering the phone or placing calls? This would include use of an amplifier or larger push button numbers.	YES ..... 1 NO 2
D13. Did you need help with shopping for groceries or prescriptions?	YES ..... 1 NO 2
D14. Did you need help or reminders to take your medications, other than a pill box?	YES ..... 1 NO 2

D15.	Did you need anyone to help with managing your finances, such as paying the bills or balancing your checkbook?	YES ..... 1 NO 2
D16.	Could you drive a car by yourself?	YES ..... 1 NO 2
D17.	Did you receive home delivered meals such as Meals on Wheels?	YES ..... 1 NO 2
D18.	Did you attend a senior center?	YES ..... 1 NO 2
D19.	Did you eat lunch at a center or participate in a congregate meal service?	YES ..... 1 NO 2
D20.	Did you feel that you had enough contacts with other people?	YES ..... 1 NO 2

E. WEIGHT AND HEIGHT HISTORY: The next series of questions is about your weight and height.		
E1.	CASES: What was your weight at the time of your hip fracture? CONTROLS: What is your current weight?	..... POUNDS ☐☐☐
E2.	CASES: What was your height at the time of your hip fracture? CONTROLS: What is your current height?	..... FEET ☐ ..... INCHES ☐☐
E3.	What was your weight at age 18, around the time that you may have finished high school?	..... POUNDS ☐☐☐
E4.	What was your height at age 18?	..... FEET ☐ ..... INCHES ☐☐
E5.	What was the most you ever weighed? OTHER THAN WHEN PREGNANT.	..... POUNDS ☐☐☐
a.	How old were you at your maximum weight?	AGE IN YEARS ..... ☐☐☐
E6.	Have you ever lost more than 20 pounds in one year or less for any reason? OTHER THAN FOLLOWING A PREGNANCY.	YES ..... 1 NO (SKIP TO SECTION F) 2
a.	What was the most weight that you have ever lost at one time?	..... POUNDS ☐☐☐
b.	Was that weight loss a result of your dieting?	YES ..... 1 NO (SKIP TO E8) ..... 2 DK (SKIP TO E8) 8
E7.	At times that you lost 20 pounds or more, what types of diets did you use?	_____ ☐☐ _____ ☐☐ _____ ☐☐

E8.	Was your weight loss of 20 pounds or more ever a result of increased physical activity, work, or exercise?	YES (SPECIFY ACTIVITIES BELOW) ..... 1 NO ..... 2 DK ..... 8 TYPE OF ACTIVITIES: _____ ☐☐ _____ ☐☐ _____ ☐☐
E9.	Was your weight loss of 20 pounds or more ever a result of ...	
a.	... surgery?	YES ..... 1 NO 2
b.	... feeling blue, sad or depressed?	YES ..... 1 NO 2
c.	... illness?	YES (SPECIFY ILLNESS BELOW) ..... 1 NO ..... 2 TYPE OF ILLNESS: _____ ☐☐ _____ ☐☐

F. PHYSICAL ACTIVITY: The next questions are related to physical activity.	
F1. In the (year before your hip fracture/past year), how many hours each day did you <u>sit</u> while watching TV, a VCR, reading, or while doing other seated activities? Would you say it was ...	Less than 5 hours per day, or . . . 1 Between 5-10 hours per day, or . 2 More than 10 hours per day 3
F2. In the (year before your hip fracture/ past year) did you ever go for walks? This would include times that you walked for exercise, to visit, shop or while hiking, fishing, hunting, or golfing.	YES . . . . . 1 NO (SKIP TO F3) 2
a. How <u>often</u> did you take walks?	NUMBER OF WALKS . . . . . ☐☐ PER { DAY . . . . . 1 WEEK . . . . . 2 MONTH 3
b. How <u>long</u> did you walk each time, on average?	MINUTES . . . . . ☐☐☐
c. How <u>far</u> did you walk each time, on average? (8 CITY BLOCKS = 1 MILE)	MILES . . . . . ☐☐.☐☐

I'd now like to ask you about several kinds of active work or recreation you may have done at any time in your adult life, meaning since the age of 18. Since the age of 18 did you ever regularly...														
		(IF NO SKIP TO NEXT ACTIVITY)		a. Did you do (ACTIVITY) in the (year before your hip fracture/past year)? (IF NO GO TO C)		b. During that year, how much time did you spend doing (ACTIVITY) per day, week, month or year? (GO TO NEXT ACTIVITY)					c. At what age did you stop doing (ACTIVITY)?	
	ACTIVITY	YES	NO	YES	NO	MIN.		D	W	M	Y	AGE
F3.	... do heavy housework including vacuuming, mopping, scrubbing floors or sidewalks, moving furniture or boxes?	1	2	1	2	☐☐☐		D	W	M	Y	☐☐☐ years
F4.	... ever do garden or yard work including digging, weeding, cutting grass, raking, or snow shoveling?	1	2	1	2	☐☐☐		D	W	M	Y	☐☐☐ years
F5.	... ever jog or run?	1	2	1	2	☐☐☐		D	W	M	Y	☐☐☐ years
F6.	... ever use an exercise bike, treadmill, or other exercise machine?	1	2	1	2	☐☐☐		D	W	M	Y	☐☐☐ years
F7.	... ever ride a bicycle outside?	1	2	1	2	☐☐☐		D	W	M	Y	☐☐☐ years

	Since the age of 18, did you ever regularly... ACTIVITY	(IF NO SKIP TO NEXT ACTIVITY) YES	NO	a. Did you do (ACTIVITY) in the (year before your hip fracture/past year)? (IF NO GO TO C) YES	NO	b. During that year, how much time did you spend doing (ACTIVITY) per day, week, month or year? (GO TO NEXT ACTIVITY) MIN. D W M Y	c. At what age did you stop doing (ACTIVITY)? AGE
F8.	... swim laps?	1	2	1	2	☐☐☐ D W M Y	☐☐☐ years
F9.	... ever do aerobics classes or aerobic dance?	1	2	1	2	☐☐☐ D W M Y	☐☐☐ years
F10.	... ever do other kinds of dancing including square dancing, country western swing dance, ballroom dancing or other kinds?	1	2	1	2	☐☐☐ D W M Y	☐☐☐ years
F11.	... ever do calisthenics or other similar exercises?	1	2	1	2	☐☐☐ D W M Y	☐☐☐ years
F12.	... ever do yoga, Tai-chi exercise, or other similar exercise?	1	2	1	2	☐☐☐ D W M Y	☐☐☐ years
F13.	... ever ski downhill or cross-country ski?	1	2	1	2	☐☐☐ D W M Y	☐☐☐ years
F14.	... ever play tennis, racquet ball, or squash?	1	2	1	2	☐☐☐ D W M Y	☐☐☐ years
F15.	... ever lift weights?	1	2	1	2	☐☐☐ D W M Y	☐☐☐ years

G. OCCUPATIONAL HISTORY

The next group of questions is about work you have had during your life time.

G1. What kind of work have you done for the majority of your working life, for example, homemaker, farmer, rancher, electrical engineer, typist, sales clerk?	_____ KIND OF WORK ☐☐☐☐☐☐☐☐
a. How old were you when you started doing this type of work?	AGE IN YEARS . . . . . ☐☐☐
b. How many years did you do this type of work?	NUMBER OF YEARS . . . . . ☐☐ (IF HOMEMAKER, SKIP TO G1e)
c. What was the name of the company or business?	_____ ☐☐☐☐ NAME OF COMPANY OR BUSINESS
d. What kind of business or industry was this (for example, TV and radio manufacturing, retail store or work at home or on a farm)?	_____ ☐☐☐☐ KIND OF BUSINESS
e. What were your most frequent activities or duties (for example, typing, keeping account books, selling cars, keeping house)?	1._____ _____ ☐☐☐☐ 2._____ _____ ☐☐☐☐ 3._____ _____ ☐☐☐☐
f. I'd like to know about the activity level of this job. Did you ... RESPONSE 3: WOULD CAUSE A SLIGHT INCREASE IN HEART RATE AND LIGHT PERSPIRATION. RESPONSE 4: WOULD CAUSE A SUBSTANTIAL INCREASE IN HEART RATE AND HEAVY PERSPIRATION	Usually sit with only minimal standing and walking, or . . . . . 1 Stand or walk most of your working time, or . . . . . 2 Carry loads less than ten pounds or walk continuously most of your working hours, or . . . . . 3 Carry loads of ten pounds or more, walk briskly, climb or dig most of your working hours 4

G2. Has there been another kind of work you have done for 5 or more years? (NOT NECESSARILY CONSECUTIVE YEARS)	YES ..... 1 NO (SKIP TO G4) 2
a. What kind of work was that?	_____ KIND OF WORK ☐☐☐☐☐☐☐☐
b. How old were you when you started doing this type of work?	AGE IN YEARS ..... ☐☐☐
c. How many years did you do this type of work?	NUMBER OF YEARS ..... ☐☐ (IF HOMEMAKER, SKIP TO G2f)
d. What was the name of the company or business?	_____ ☐☐☐☐ NAME OF COMPANY OR BUSINESS
e. What kind of business or industry was this (for example, TV and radio manufacturing, retail store or work at home or on a farm)?	_____ ☐☐☐☐ KIND OF BUSINESS
f. What were your most frequent activities or duties (for example, typing, keeping account books, selling cars, keeping house)?	1._____ _____ ☐☐☐☐ 2._____ _____ ☐☐☐☐ 3._____ _____ ☐☐☐☐
g. I'd like to know about the activity level of this job. Did you ... RESPONSE 3: WOULD CAUSE A SLIGHT INCREASE IN HEART RATE AND LIGHT PERSPIRATION. RESPONSE 4: WOULD CAUSE A SUBSTANTIAL INCREASE IN HEART RATE AND HEAVY PERSPIRATION	Usually sit with only minimal standing and walking, or ..... 1 Stand or walk most of your working time, or ..... 2 Carry loads less than ten pounds or walk continuously most of your working hours, or ..... 3 Carry loads of ten pounds or more, walk briskly, climb or dig most of your working hours 4

G3. Has there been another kind of work you have done for 5 or more years?	YES ..... 1 NO (SKIP TO G4) 2
a. What kind of work was that?	_____ KIND OF WORK ☐☐☐☐☐☐☐☐
b. How old were you when you started doing this type of work?	AGE IN YEARS ..... ☐☐
c. How many years did you do this type of work?	NUMBER OF YEARS ..... ☐☐ (IF HOMEMAKER, SKIP TO G3f)
d. What was the <u>name</u> of the company or business?	_____ ☐☐☐☐ NAME OF COMPANY OR BUSINESS
e. What <u>kind</u> of business or industry was this (for example, TV and radio manufacturing, retail store or work at home or on a farm)?	_____ ☐☐☐☐ KIND OF BUSINESS
f. What were your most frequent activities or duties (for example, typing, keeping account books, selling cars, keeping house)?	1._____ _____ ☐☐☐☐ 2._____ _____ ☐☐☐☐ 3._____ _____ ☐☐☐☐
g. I'd like to know about the activity level of this job. Did you ... <u>RESPONSE 3</u>: WOULD CAUSE A SLIGHT INCREASE IN HEART RATE AND LIGHT PERSPIRATION. <u>RESPONSE 4</u>: WOULD CAUSE A SUBSTANTIAL INCREASE IN HEART RATE AND HEAVY PERSPIRATION	Usually sit with only minimal standing and walking, or ..... 1 Stand or walk most of your working time, or ..... 2 Carry loads less than ten pounds or walk continuously most of your working hours, or ..... 3 Carry loads of ten pounds or more, walk briskly, climb or dig most of your working hours 4
G4. What was your employment status (at the time of your hip fracture/during the last month)? Were you...	Employed ..... 1 Retired ..... 2 A homemaker ..... 3 Able to work but unemployed ..... 4 Disabled and unable to work ..... 5 Or something else ..... 6 SPECIFY: _____ ☐☐

H. NUTRITIONAL ASSESSMENT
The next part of the interview is an activity that will help us find out about your diet.

H1.	ADMINISTER PICSORT FOOD FREQUENCY QUESTIONNAIRE	
H2.	What kind of oil, fat or shortening do you usually cook with? (MARK 1 CHOICE.)	OIL (LIST MAIN TYPE) ..... 1 TYPE OF OIL: _____ SOFT OR TUB MARGARINE ..... 2 STICK MARGARINE ..... 3 BUTTER ..... 4 LARD, FATBACK, BACON FAT ..... 5 VEGETABLE SHORTENING ..... 6 PAM OR NO OIL ..... 7 DON'T COOK ..... 8 DK 98
H3.	What kind of oil, fat or shortening do you usually add to vegetables, potatoes, and breads or rolls? (MARK 1 CHOICE.)	OIL (LIST MAIN TYPE) ..... 1 TYPE OF OIL: _____ SOFT OR TUB MARGARINE ..... 2 STICK MARGARINE ..... 3 BUTTER ..... 4 LARD, FATBACK, BACON FAT ..... 5 PAM OR NO OIL ..... 6 DON'T ADD FAT ..... 7 DK 98
H4.	Thinking back to your younger years, how often per week did you drink an 8 ounce glass of milk when you were 18 years old, or around the time you may have finished high school?	GLASSES PER WEEK ..... ☐☐
H5.	Please tell me if you have ever avoided any of the following foods in your diet, for any reason, for a year or more. Have you ever avoided ...	
a.	... all red meat, that is beef, pork, and lamb?	YES (SPECIFY NUMBER OF YEARS) . 1 NO ..... 2 NUMBER OF YEARS ..... ☐☐
b.	... chicken and turkey?	YES (SPECIFY NUMBER OF YEARS) . 1 NO ..... 2 NUMBER OF YEARS ..... ☐☐
c.	... fish?	YES (SPECIFY NUMBER OF YEARS) . 1 NO ..... 2 NUMBER OF YEARS ..... ☐☐

d. ... eggs?	YES (SPECIFY NUMBER OF YEARS) . 1 NO . . . . . 2 NUMBER OF YEARS . . . . . ⌊⌋⌋
e. ... milk?	YES (SPECIFY NUMBER OF YEARS) . 1 NO . . . . . 2 NUMBER OF YEARS . . . . . ⌊⌋⌋
f. ... other dairy products, that is cheese, yogurt and ice cream?	YES (SPECIFY NUMBER OF YEARS) . 1 NO . . . . . 2 NUMBER OF YEARS . . . . . ⌊⌋⌋

J. DIETARY SUPPLEMENTS:
Now, I would like to ask you about your use of dietary supplements in the (year before your hip fracture/past year). Would you please take out any bottles of vitamins, minerals, or other dietary supplements that you have taken.

J1. Did you regularly take multi vitamin/mineral supplements in the (year before your hip fracture/past year)?	YES ..... 1 NO (SKIP TO J2) 2
a. What specific brand or brands of multivitamin/minerals do you use? ASK FOR THE BOTTLES AND RECORD FULL NAME OF BRAND AND TYPE.	BRAND AND TYPE: _____ ☐☐☐☐ _____ ☐☐☐☐ _____ ☐☐☐☐
b. How many years have you taken multivitamin/minerals?	NUMBER OF YEARS ..... ☐☐
c. How often did you take them?	NUMBER OF TIMES ..... ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8
J2. Other than a multivitamin/mineral, did you regularly take any combination of two or more vitamins or minerals that came in a single pill in the (year before your hip fracture/past year)?	YES ..... 1 NO (SKIP TO J5) 2
a. What specific brand and type of combination dietary supplement do you use? ASK FOR THE BOTTLES AND RECORD FULL NAME OR BRAND AND TYPE.	BRAND AND TYPE: _____ ☐☐☐☐ _____ ☐☐☐☐
b. How many years have you taken this combination dietary supplement?	NUMBER OF YEARS ..... ☐☐
c. How often did you take them?	NUMBER OF TIMES ..... ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8

J3. Did you regularly take any other combination dietary supplement in the (year before your hip fracture/past year)?	YES ..... 1 NO (SKIP TO J5) 2
a. What specific brand and type of combination dietary supplement do you use? ASK FOR THE BOTTLES AND RECORD FULL NAME OR BRAND AND TYPE.	BRAND AND TYPE: _____ ☐☐☐☐ _____ ☐☐☐☐
b. How many years have you taken this combination dietary supplement?	NUMBER OF YEARS ..... ☐☐
c. How often did you take them?	NUMBER OF TIMES ..... ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8
J4. Did you regularly take any other combination dietary supplement in the (year before your hip fracture/past year)?	YES ..... 1 NO (SKIP TO J5) 2
a. What specific brand and type of combination dietary supplement do you use? ASK FOR THE BOTTLES AND RECORD FULL NAME OR BRAND AND TYPE.	BRAND AND TYPE: _____ ☐☐☐☐ _____ ☐☐☐☐
b. How many years have you taken this combination dietary supplement?	NUMBER OF YEARS ..... ☐☐
c. How often did you take them?	NUMBER OF TIMES ..... ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8

Now, I am going to ask you about individual vitamins, minerals, and other dietary supplements that you take by themselves. I would also like to know the strength or dose of the dietary supplement and how often you took them. You don't need to tell me again about the vitamins, minerals, and other dietary supplements we've already recorded.

a. In the (year before your hip fracture/past year) did you regularly take... IF NO SKIP TO NEXT VITAMIN	b. How many years have you taken (VITAMIN)?	c. How often did you take them?	d. What dose did you usually take each time?
J5. YES ..... 1 NO ..... 2 Vitamin A	NUMBER OF YEARS .. ☐☐.☐	NUMBER OF TIMES ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN IU .. ☐☐☐☐☐ Less THAN 8000 IU ..... 1 8,000 TO 13, 000 IU ..... 2 13,001 TO 22,000 IU ..... 3 22,001 IU OR MORE ..... 4 DK 8
J6. YES ..... 1 NO ..... 2 Beta carotene	NUMBER OF YEARS .. ☐☐.☐	NUMBER OF TIMES ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN IU .. ☐☐☐☐☐ LESS THAN 5,000 IU ..... 1 5,000 TO 10,000 IU ..... 2 10,001 TO 25,000 IU ..... 3 25,001 IU OR MORE ..... 4 DK 8
J7. YES ..... 1 NO ..... 2 Vitamin C	NUMBER OF YEARS .. ☐☐.☐	NUMBER OF TIMES ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN MG . ☐☐☐☐ LESS THAN 400 MG ..... 1 400 TO 700 MG ..... 2 701 TO 1300 MG ..... 3 1301 MG OR MORE ..... 4 DK 8
J8. YES ..... 1 NO ..... 2 Vitamin E	NUMBER OF YEARS .. ☐☐.☐	NUMBER OF TIMES ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN IU .. ☐☐☐☐☐ LESS THAN 100 IU ..... 1 100 TO 500 IU ..... 2 501 TO 1000 IU ..... 3 1001 IU OR MORE ..... 4 DK 8

a. In the (year before your hip fracture/past year) did you regularly take... IF NO SKIP TO NEXT VITAMIN	b. How many years have you taken (VITAMIN)?	c. How often did you take them?	d. What dose did you usually take each time?
J9. YES ..... 1 NO ..... 2 Calcium	NUMBER OF YEARS .. ☐☐.☐	NUMBER OF TIMES ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN MG . ☐☐☐☐☐ LESS THAN 400 MG ..... 1 400 TO 900 MG ..... 2 901 TO 1300 MG ..... 3 1301 MG OR MORE ..... 4 DK 8
J10. YES ..... 1 NO ..... 2 Vitamin D	NUMBER OF YEARS .. ☐☐.☐	NUMBER OF TIMES ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN IU .. ☐☐☐☐☐ LESS THAN 200 IU ..... 1 200 TO 400 IU ..... 2 401 TO 1,000 IU ..... 3 1,001 IU OR MORE ..... 4 DK 8
J11. YES ..... 1 NO ..... 2 Vitamin B6	NUMBER OF YEARS .. ☐☐.☐	NUMBER OF TIMES ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN MG ... ☐☐☐ LESS THAN 10 MG ..... 1 10 TO 50 MG ..... 2 51 TO 100 MG ..... 3 101 MG OR MORE ..... 4 DK 8
J12. YES ..... 1 NO ..... 2 Vitamin B12	NUMBER OF YEARS .. ☐☐.☐	NUMBER OF TIMES ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE MCG .... ☐☐☐☐ LESS THAN 20 MCG ..... 1 20 TO 100 MCG ..... 2 101 TO 250 MCG ..... 3 251 MCG OR MORE ..... 4 DK 8
J13. YES ..... 1 NO ..... 2 Niacin	NUMBER OF YEARS .. ☐☐.☐	NUMBER OF TIMES ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN MG ... ☐☐☐ LESS THAN 20 MG ..... 1 20 MG TO 50 MG ..... 2 51 TO 100 MG ..... 3 101 MG OR MORE ..... 4 DK 8

a. In the (year before you hip fracture/past year) did you regularly take... IF NO SKIP TO NEXT VITAMIN	b. How many years have you taken (VITAMIN)?	c. How often did you take them?	d. What dose did you usually take each time?
J14. YES ..... 1 NO ..... 2 Folic Acid	NUMBER OF YEARS .. ⌊⌊⌋.⌊⌋	NUMBER OF TIMES ⌊⌊⌋ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE MCG . ⌊⌊⌋⌊⌊⌋⌊⌊⌋ LESS THAN 300 MCG .... 1 300 TO 400 MCG ..... 2 401 TO 800 MCG ..... 3 801 MCG OR MORE ..... 4 DK 8
J15. YES ..... 1 NO ..... 2 Selenium	NUMBER OF YEARS .. ⌊⌊⌋.⌊⌋	NUMBER OF TIMES ⌊⌊⌋ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE MCG .... ⌊⌊⌋⌊⌊⌋ LESS THAN 80 MCG ..... 1 80 TO 130 MCG ..... 2 131 TO 250 MCG ..... 3 251 MCG OR MORE ..... 4 DK 8
J16. YES ..... 1 NO ..... 2 Iron	NUMBER OF YEARS .. ⌊⌊⌋.⌊⌋	NUMBER OF TIMES ⌊⌊⌋ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN MG ..... ⌊⌊⌋⌊⌋ LESS THAN 25 MG ..... 1 25 TO 75 MG ..... 2 76 TO 100 MG ..... 3 101 MG OR MORE ..... 4 DK 8
J17. YES ..... 1 NO ..... 2 Magnesium	NUMBER OF YEARS .. ⌊⌊⌋.⌊⌋	NUMBER OF TIMES ⌊⌊⌋ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN MG ... ⌊⌊⌋⌊⌋ LESS THAN 200 MG ..... 1 200 TO 300 MG ..... 2 301 TO 400 MG ..... 3 401 MG OR MORE ..... 4 DK 8
J18. YES ..... 1 NO ..... 2 Zinc	NUMBER OF YEARS .. ⌊⌊⌋.⌊⌋	NUMBER OF TIMES ⌊⌊⌋ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8	DOSE IN MG ... ⌊⌊⌋⌊⌋ LESS THAN 25 MG ..... 1 25 TO 75 MG ..... 2 76 TO 100 MG ..... 3 101 MG OR MORE ..... 4 DK 8

J19.	In the (year before your hip fracture/past year) did you regularly take herbal preparations?	YES ..... 1 NO (SKIP TO J20) 2
a.	What specific brand and type of herbal preparation do you use? ASK FOR THE BOTTLES AND RECORD FULL NAME OR BRAND AND TYPE.	BRAND AND TYPE: _____ ☐☐☐☐ _____ ☐☐☐☐ _____ ☐☐☐☐
b.	How many years did you take herbal preparations?	NUMBER OF YEARS ..... ☐☐.☐
c.	How often did you take them?	NUMBER OF TIMES ..... ☐☐ PER{ DAY ..... 1 WEEK ..... 2 MONTH ..... 3 YEAR ..... 4 DK 8
J20.	In the (year before your hip fracture/past year) did you regularly take...	
a.	Any other nutritional supplement?	YES (SPECIFY BELOW) ..... 1 NO ..... 2 BRAND AND TYPE: _____ ☐☐☐☐ _____ ☐☐☐☐ _____ ☐☐☐☐

K. MEDICATION HISTORY:
Now I would like to ask you about medications you have taken.

K1.	During the (year before your hip fracture/past year), have you taken any medications that were prescribed for you or were prescribed for someone else and given to you by family members or friends?	YES ..... 1 NO ..... 2 RF ..... 7 DK 8
K2.	We are also interested in other medications that do not require a prescription, such as aspirin, other pain killers, laxatives, cold medicines, or herbal medicines. During the (year before your hip fracture/past year), have you taken any non-prescription medications?	YES ..... 1 NO ..... 2 RF ..... 7 DK 8
	INTERVIEW CHECKPOINT: IS K1 OR K2 = Yes?	YES (CONTINUE) ..... 1 NO (SKIP TO K6) 2
K3.	May I please see all the prescription and non-prescription medication (containers) that you used in the (year before your hip fracture/past year)? LET R GATHER MEDICATIONS. Let's put them into two separate piles.	
	SEPARATE THE PRESCRIPTION FROM THE NON-PRESCRIPTION DRUGS. LIST ALL PRESCRIPTION MEDICATIONS ACROSS ROW A ON THE MEDICATION INVENTORY.	
K4.	Are there any other prescription medications you've used in the (year before your hip fracture/past year) that you don't have here?	
	LIST ANY ADDITIONAL PRESCRIPTION MEDICATIONS ACROSS ROW A ON THE MEDICATION INVENTORY. RECORD OR ASK B-H FOR ALL PRESCRIPTION MEDICATIONS LISTED.	

K5.	Now I would also like to ask you about the non-prescription medications that you have taken in the (year before your hip fracture/past year). First, let me list the non-prescription medications you have here.	
	LIST ALL NON-PRESCRIPTION MEDICATIONS PROVIDED ON THE MEDICATION INVENTORY.	
K5a.	Are there any other non-prescription medications that you've taken in the (year before your hip fracture/past year) that you don't have a bottle for?	
	LIST ANY ADDITIONAL NON-PRESCRIPTION MEDICATIONS ACROSS ROW A AND RECORD OR ASK B-H FOR ALL NON-PRESCRIPTION MEDICATIONS.	
K6.	I would like you to think very carefully over your past and try to remember if you have ever been bothered by any of these illnesses or problems...	
a.	...headaches or migraine headaches?	YES ..... 1 NO 2
b.	... joint pain or back pain, including arthritis, gout, bursitis, rheumatism, or other joint pain?	YES ..... 1 NO 2
c.	...pain from injuries or operations, or other medical procedures or chronic conditions?	YES ..... 1 NO 2
	INTERVIEWER CHECKPOINT: IF SUBJECT ANSWERED NO TO ALL CONDITIONS IN K6, SKIP TO K9.	
	SHOW DRUG CARD I	
K7.	Please look at this card. It is a list of medications that are often taken for the painful or inflammatory conditions that we just discussed. Can you read the names of the drugs without difficulty?	YES (ALLOW SUBJECT TO LOOK AT LIST) . 1 NO (READ ALOUD TO SUBJECT) 2

K8.	You don't have to tell me again about your medications that we already recorded. Could you please tell me if, in the (year before your hip fracture/past year), you have ever used any of the medications on this card regularly?	YES ..... 1 NO (SKIP TO K9) 2
	AS EACH MEDICATION IS REPORTED BY RESPONDENT, RECORD ON MEDICATION INVENTORY AND ASK QUESTIONS B-H FOR EACH MEDICATION.	
	IF RESPONDENT CAN NOT READ, CONTINUE TO READ ENTIRE LIST UNTIL R REPORTS ALL USAGE FOR DRUGS ON THIS CARD.	
K9.	Now I would like to ask you about some stomach, bowel or gastrointestinal problems. Have you ever had a problem with...	
a.	...ulcers, heartburn or indigestion?	YES ..... 1 NO 2
b.	...gastritis, esophagitis, reflux or hiatal hernia?	YES ..... 1 NO 2
c.	...irritable bowel syndrome, constipation, diarrhea or other stomach or bowel problems?	YES ..... 1 NO 2
	INTERVIEWER CHECKPOINT: IF SUBJECT ANSWERED NO TO ALL CONDITIONS IN K9, GO TO K11.	

	SHOW DRUG CARD II	
K10.	Remember, you don't have to tell me about the medications we have already recorded. After we have read this list, could you please tell me if, in the (year before your hip fracture/past year), you have ever used any of the medications on this card regularly for any of the stomach, bowel, or digestive conditions we just talked about?	YES ..... 1 NO 2
	AS EACH MEDICATION IS REPORTED BY RESPONDENT, RECORD ON MEDICATION INVENTORY AND ASK QUESTIONS B-H FOR EACH MEDICATION.	
K11.	Have you ever had problems with...	
a.	...hay fever, seasonal allergies or asthma?	YES ..... 1 NO 2
b.	...chronic colds, bronchitis, sinus problems or pneumonia?	YES ..... 1 NO 2
c.	Have you had emphysema or chronic obstructive pulmonary disease?	YES ..... 1 NO 2
	INTERVIEWER CHECKPOINT: IF SUBJECT ANSWERED NO TO ALL CONDITIONS IN K11 GO TO K13.	
	SHOW DRUG CARD III	
K12.	Here is another drug card. Remember, you don't have to tell me again about the medications we have already recorded. After we have read this list, could you please tell me if, in the (year before your hip fracture/past year), you have ever used any of the medicines on this card regularly?	YES ..... 1 NO 2
	AS EACH MEDICATION IS REPORTED BY RESPONDENT, RECORD ON MEDICATION INVENTORY AND ASK QUESTIONS B-H FOR EACH MEDICATION.	

K13.	Now, I would like to ask about problems people often have with sleep, their nerves, or their mood. Have you ever ...	
a.	... had sleep problems, anxiety or nerve problems?	YES ..... 1 NO 2
b.	... been sad, felt blue, down or depressed for two weeks or more?	YES ..... 1 NO 2
c.	...had manic-depression, bipolar disorder, schizophrenia or other mental health problems?	YES ..... 1 NO 2
d.	...had seizures or convulsions?	YES ..... 1 NO 2

IF NO TO ALL CONDITIONS IN K13, SKIP TO SECTION L.

SHOW DRUG CARD IV

K14.	Here is another drug card. After we have read this list, could you please tell me if, in the (year before your hip fracture/past year), you have ever used any of the medications on this card regularly?	YES ..... 1 NO 2

AS EACH MEDICATION IS REPORTED BY RESPONDENT, RECORD ON MEDICATION INVENTORY AND ASK QUESTIONS B-H FOR EACH MEDICATION.

L. MEDICAL HISTORY:	
L1. Has a doctor ever told you that you had osteoporosis or bone loss? Osteoporosis includes broken bones due to bone loss and thinning of bones that occurs with aging, loss of height because of bone loss in the spine, or a "Dowager's hump" in the spine because of bone loss.	YES ..... 1 NO (SKIP TO L2) ..... 2 DK (SKIP TO L2) 8
a. How old were you when you were told that you had osteoporosis?	AGE IN YEARS ..... ☐☐☐
b. Did you receive medical treatment or medication for osteoporosis?	YES ..... 1 NO (SKIP TO L2) ..... 2 DK 8
c. Are there any medications that you have taken for osteoporosis (in the year before your hip fracture/past year) that you have not told me about?	YES (GO TO MI) ..... 1 NO 2
L2. Has a doctor ever told you that you had arthritis?	YES ..... 1 NO (SKIP TO L3) ..... 2 DK (SKIP TO L3) 8
a. What type of arthritis did you have? Was it...	Osteoarthritis ..... 1 Rheumatoid arthritis ..... 2 Both osteoarthritis and rheumatoid arthritis ..... 3 Other (SPECIFY BELOW) ..... 4 _____ ☐☐☐ DK 8
b. Did you have arthritis in your hip joint(s)?	YES ..... 1 NO ..... 2 DK 8
c. Did you have arthritis in your knee(s)?	YES ..... 1 NO ..... 2 DK 8
d. Did you have arthritis in your feet?	YES ..... 1 NO ..... 2 DK 8
d. Did you have arthritis in your hand(s)?	YES ..... 1 NO ..... 2 DK 8

e. Did you have arthritis in your elbow(s)?	YES ..... 1 NO ..... 2 DK 8
f. Did you have arthritis in your shoulder(s)?	YES ..... 1 NO ..... 2 DK 8
g. Did you have arthritis in your spine or back?	YES ..... 1 NO ..... 2 DK 8
h. How old were you when you were first told that you had arthritis?	AGE IN YEARS ..... ⌊⌊⌊
i. Did you receive medical treatment or medication for your arthritis?	YES ..... 1 NO (SKIP TO L3) ..... 2 DK 8
j. Are there any medications that you have taken for arthritis (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2
L3. Has a doctor ever told you that you had high blood pressure or hypertension?	YES ..... 1 NO (SKIP TO L4) ..... 2 DK (SKIP TO L4) 8
a. How old were you when you were told that you had high blood pressure or hypertension?	AGE IN YEARS ..... ⌊⌊⌊
b. Did you receive medical treatment or medication for high blood pressure or hypertension?	YES ..... 1 NO (SKIP TO L4) ..... 2 DK 8
c. Are there any medications that you have taken for high blood pressure (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2
L4. Has a doctor ever told you that you had a heart attack?	YES ..... 1 NO (SKIP TO L5) ..... 2 DK (SKIP TO L5) 8
a. How old were you when you were told that you had a heart attack?	AGE IN YEARS ..... ⌊⌊⌊
b. Did you receive medical treatment or medication for your heart attack?	YES ..... 1 NO (SKIP TO L5) ..... 2 DK 8
c. Are there any medications you have taken for your heart attack (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2

L5. Has a doctor ever told you that you had a stroke?	YES ..... 1 NO (SKIP TO L6) ..... 2 DK (SKIP TO L6) 8
a. How old were you when you were told that you had a stroke?	AGE IN YEARS ..... ⌊⌊⌊⌋
b. Did you receive medical treatment or medication for your stroke?	YES ..... 1 NO (SKIP TO L6) ..... 2 DK 8
c. Are there any medications you have taken for your stroke (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2
L6. Has a doctor ever told you that you had diabetes?	YES ..... 1 NO (SKIP TO L7) ..... 2 DK (SKIP TO L7) 8
a. How old were you when you were told that you had diabetes?	AGE IN YEARS ..... ⌊⌊⌊⌋
b. Did you receive medical treatment or medication for your diabetes?	YES ..... 1 NO (SKIP TO L7) ..... 2 DK 8
c. Are there any medications you have taken for your diabetes (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2

L7.	Has a doctor ever told you that you had cancer?	YES . . . . . 1 NO (SKIP TO L8) . . . . . 2 DK (SKIP TO L8) 8
a.	What type of cancer was it (PRIMARY SITE)?	_____ ☐☐☐
b.	How old were you when you were told that you had this type of cancer?	AGE IN YEARS . . . . . ☐☐☐
c.	Did you receive medical treatment for this type of cancer?	YES . . . . . 1 NO 2
d.	Did you have another type of cancer?	YES . . . . . 1 NO (SKIP TO L7l) 2
e.	What type of cancer was it (PRIMARY SITE)?	_____ ☐☐☐
f.	How old were you when you were told that you had this type of cancer?	AGE IN YEARS . . . . . ☐☐☐
g.	Did you receive medical treatment for this type of cancer?	YES . . . . . 1 NO 2
h.	Did you have another type of cancer?	YES . . . . . 1 NO (SKIP TO L7l) 2
i.	What type of cancer was it (PRIMARY SITE)?	_____ ☐☐☐
j.	How old were you when you were told that you had this type of cancer?	AGE IN YEARS . . . . . ☐☐☐
k.	Did you receive medical treatment for this type of cancer?	YES . . . . . 1 NO 2
l.	Are there any medications you have taken for your cancer (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) . . . . . 1 NO 2
L8.	Has a doctor ever told you that you had kidney disease?	YES . . . . . 1 NO (SKIP TO L9) . . . . . 2 DK (SKIP TO L9) 8
a.	How old were you when you were told that you had kidney disease?	AGE IN YEARS . . . . . ☐☐☐
b.	Did you receive medical treatment or medication for your kidney disease?	YES . . . . . 1 NO (SKIP TO L9) . . . . . 2 DK 8
c.	Are there any medications you have taken for your kidney disease (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) . . . . . 1 NO 2

L9. (WOMEN ONLY) Has a doctor ever told you that you had endometriosis?	YES ..... 1 NO (SKIP TO L10) ..... 2 DK (SKIP TO L10) 8
a. How old were you when you were told that you had endometriosis?	AGE IN YEARS ..... ⌊⌊⌊⌋
b. Did you receive medical treatment or medication for your endometriosis?	YES ..... 1 NO (SKIP TO L10) ..... 2 DK 8
c. Are there any medications you have taken for your endometriosis (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2
L10. Has a doctor ever told you that you needed "blood thinners?"	YES ..... 1 NO (SKIP TO L11) ..... 2 DK (SKIP TO L11) 8
a. How old were you when you were told that you needed "blood thinners?"	AGE IN YEARS ..... ⌊⌊⌊⌋
b. Did you receive medical treatment or medication to thin your blood?	YES ..... 1 NO (SKIP TO L11) ..... 2 DK 8
c. Are there any medications you have taken to thin your blood (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2
L11. Has a doctor ever told you that you had thyroid disease or goiter?	YES ..... 1 NO (SKIP TO L12) ..... 2 DK (SKIP TO L12) 8
a. How old were you when you were told that you had thyroid disease or goiter?	AGE IN YEARS ..... ⌊⌊⌊⌋
b. Did you receive medical treatment or medication for your thyroid disease or goiter?	YES ..... 1 NO (SKIP TO L12) ..... 2 DK 8
c. Are there any medications you have taken for your thyroid disease or goiter (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2

L12. Has a doctor ever told you that you had parathyroid disease?	YES ..... 1 NO (SKIP TO L13) ..... 2 DK (SKIP TO L13) 8
a. How old were you when you were told that you had parathyroid disease?	AGE IN YEARS ..... ⌊⌊⌊
b. Did you receive medical treatment or medication for your parathyroid disease?	YES ..... 1 NO (SKIP TO L13) ..... 2 DK 8
c. Are there any medications you have taken for your parathyroid disease (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2
L13. Has a doctor ever told you that you had cataracts?	YES ..... 1 NO (SKIP TO L14) ..... 2 DK (SKIP TO L14) 8
a. How old were you when you were told that you had cataracts?	AGE IN YEARS ..... ⌊⌊⌊
b. Did you receive medical treatment or medication for your cataracts?	YES ..... 1 NO (SKIP TO L14) ..... 2 DK 8
c. Are there any medications you have taken for your cataracts (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2
L14. Has a doctor ever told you that you had glaucoma?	YES ..... 1 NO (SKIP TO L15) ..... 2 DK (SKIP TO L15) 8
a. How old were you when you were told that you had glaucoma?	AGE IN YEARS ..... ⌊⌊⌊
b. Did you receive medical treatment or medication for your glaucoma?	YES ..... 1 NO (SKIP TO L15) ..... 2 DK 8
c. Are there any medications you have taken for your glaucoma (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2

L15. Has a doctor ever told you that you had memory loss?	YES ..... 1 NO (SKIP TO L16) ..... 2 DK (SKIP TO L16) 8
a. How old were you when you were told that you had memory loss?	AGE IN YEARS ..... ⌊⌊⌊⌋
b. Did you receive medical treatment or medication for your memory loss?	YES ..... 1 NO (SKIP TO L16) ..... 2 DK 8
c. Are there any medications you have taken for your memory loss (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2
L16. Has a doctor ever told you that you had Parkinson's disease?	YES ..... 1 NO (SKIP TO L17) ..... 2 DK (SKIP TO L17) 8
a. How old were you when you were told that you had Parkinson's disease?	AGE IN YEARS ..... ⌊⌊⌊⌋
b. Did you receive medical treatment or medication for your Parkinson's disease?	YES ..... 1 NO (SKIP TO L17) ..... 2 DK 8
c. Are there any medications you have taken for your memory loss (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2
L17. Has a doctor ever told you that you had multiple sclerosis?	YES ..... 1 NO (SKIP TO SECTION M) ..... 2 DK (SKIP TO SECTION M) 8
a. How old were you when you were told that you had multiple sclerosis?	AGE IN YEARS ..... ⌊⌊⌊⌋
b. Did you receive treatment for your multiple sclerosis?	YES ..... 1 NO (SKIP TO SECTION M) ..... 2 DK 8
c. Are there any medications you have taken for your multiple sclerosis (in the year before your hip fracture/past year) you have not told me about?	YES (GO TO MI) ..... 1 NO 2
RECORD ADDITIONAL MEDICATIONS TAKEN IN THE (YEAR BEFORE HIP FRACTURE/PAST YEAR) ON THE MEDICATION INVENTORY AND ASK QUESTIONS B-H FOR EACH ADDITIONAL MEDICATION.	

M. HISTORY OF BONE FRACTURES:
Now I'd like to ask you some questions about your personal history of bone fractures.

M1.	Have you ever broken your hip? This includes your hip joint or the top of your femur or thigh bone, near your hip.	YES ..... 1 NO (SKIP TO M7) ..... 2 DK (SKIP TO M7) 8
M2.	Which side of your hip did you fracture?	LEFT ..... 1 RIGHT ..... 2 BOTH ..... 3 DK 8
M3.	What was the date of your most recent hip fracture?	MONTH:☐☐ DAY:☐☐ YEAR:☐☐☐☐
M4.	I'd like to ask you some questions about your hip fracture.	
	a. Did it happen because of a fall?	YES (SKIP TO M5) ..... 1 NO 2
	b. How did you fracture your hip, if other than a fall?	_____ ☐☐ _____ ☐☐ _____ ☐☐ (SKIP TO M6)
M5.	Now I'd like to ask you some questions about your fall.	
	a. What were you doing at the time of the fall? Were you...	Lying still ..... 1 Sitting still ..... 2 Standing still ..... 3 Transferring or changing position ..... 4 Walking on a level surface ..... 5 Stepping up or down ..... 6 Running or other vigorous activity .... 7 Other (SPECIFY BELOW) ..... 8 _____ ☐☐ DK 98

b. How far did you fall? Was it...	From bed to the floor ..... 1 From a seated position ..... 2 From a standing position ..... 3 A standing fall from the height of one step or curb ..... 4 A standing fall from the height of two steps ..... 5 A standing fall from the height of a chair or stool ..... 6 A standing fall from a height greater than a chair or stool ..... 7 Other (SPECIFY INCLUDING HEIGHT) ... 8 _____ ☐☐ DK 98
c. What type of surface did you hit when you fell? Was it ...	A thick, padded rug or carpet ..... 1 A rug without padding ..... 2 A bare wood floor ..... 3 Linoleum or soft tile ..... 4 Ceramic (hard) tile ..... 5 Concrete, cement, or asphalt ..... 6 Dirt, grass, or soft snow ..... 7 Hard ice or packed snow ..... 8 Other (SPECIFY BELOW) ..... 9 _____ ☐☐ DK 98
d. What direction did you fall? Was it... CIRCLE ONE RESPONSE. IF SIDEWAYS, PROBE FOR RIGHT OR LEFT AND CIRCLE APPROPRIATE CODE. USE CODE 2 ONLY IF SIDEWAYS AND R DOES NOT KNOW IF THEY FELL TO THE RIGHT OR LEFT.	Forward ..... 1 Sideways (DK RIGHT OR LEFT) ..... 2 To the right ..... 3 To the left ..... 4 Backward ..... 5 Other (SPECIFY BELOW) ..... 6 _____ ☐☐ DK 8
e. Just before the fall did you feel dizzy or weak?	YES ..... 1 NO ..... 2 DK 8
f. Just before the fall did you feel faint or lose consciousness?	YES ..... 1 NO ..... 2 DK 8
g. Just before the fall was your vision impaired for any reason?	YES (SPECIFY BELOW) ..... 1 _____ ☐☐ NO ..... 2 DK 8

h. Just before the fall did you trip on an object?	YES (SPECIFY BELOW) . . . . 1 ________________ □□ NO . . . . 2 DK 8
M6. Did you fracture your hip another time before your last fracture?	YES . . . . 1 NO (SKIP TO M7) 2
a. Please tell me the date of each earlier time that you broke your hip.	. . . . MONTH:□□ YEAR:□□□□ . . . . MONTH:□□ YEAR:□□□□
M7. I'd like to ask you about other bones that you may have broken. Have you broken any other bones since you were 18 years old?	YES . . . . 1 NO (SKIP TO SECTION N) 2

M8. Please tell me the dates of fractures, the bones fractured, and how the fracture occurred. Let's start with the most recent time that you broke one or more bones.

What was the date of your fracture(s)?	Which bones were fractured?	How did the fracture(s) occur?
MONTH:□□ YEAR:□□□□	________ □□ ________ □□ ________ □□	________ ________ ________ ________ □□□
MONTH:□□ YEAR:□□□□	________ □□ ________ □□ ________ □□	________ ________ ________ ________ □□□
MONTH:□□ YEAR:□□□□	________ □□ ________ □□ ________ □□	________ ________ ________ ________ □□□
MONTH:□□ YEAR:□□□□	________ □□ ________ □□ ________ □□	________ ________ ________ ________ □□□

N. FAMILY HISTORY OF BONE FRACTURE AND BONE DISEASE:

I would like to ask you about your blood relatives and whether or not any of them have ever had a hip fracture or other problems with their bones known as osteoporosis.

Osteoporosis includes broken bones due to bone loss and thinning of bones that occurs with aging, loss of height because of bone loss in the spine, or a "Dowager's hump" in the spine because of bone loss.

N1. First, did your own biological mother ever have a hip fracture?	YES ..... 1 NO (SKIP TO N2) ..... 2 DK (SKIP TO N2) 8
a. What was your mother's age at the time of her first hip fracture?	AGE IN YEARS ..... ☐☐☐
b. How did the fracture occur?	_____ ☐☐ _____ ☐☐
N2. Did a doctor ever tell your mother that she had osteoporosis?	YES ..... 1 NO (SKIP TO N3) ..... 2 DK (SKIP TO N3) 8
a. At what age was your mother told that she had some problems due to osteoporosis?	AGE IN YEARS ..... ☐☐☐
N3. Did your biological father ever have a hip fracture?	YES ..... 1 NO (SKIP TO N4) ..... 2 DK (SKIP TO N4) 8
a. What was your father's age at the time of his first hip fracture?	AGE IN YEARS ..... ☐☐☐
b. How did the hip fracture occur?	_____ ☐☐ _____ ☐☐
N4. Did a doctor ever tell your father that he had osteoporosis?	YES ..... 1 NO (SKIP TO N5) ..... 2 DK (SKIP TO N5) 8
a. At what age was your father told that he had some problems due to osteoporosis?	AGE IN YEARS ..... ☐☐☐
N5. How many daughters do you have?	NUMBER OF DAUGHTERS ..... ☐☐ (IF NONE, ENTER 00 AND SKIP TO N8)

N6.	Have any of your daughters had a hip fracture?	YES ..... 1 NO (SKIP TO N7) ..... 2 DK (SKIP TO N7) 8
a.	How many of your daughters had a hip fracture?	NUMBER OF DAUGHTERS WITH HIP FRACTURE ..... ⌊⌊⌋⌋
N7.	Did a doctor ever tell (any of) your daughter(s) that she had osteoporosis?	YES ..... 1 NO (SKIP TO N8) ..... 2 DK (SKIP TO N8) 8
a.	How many of your daughters had this condition?	NUMBER OF DAUGHTERS WITH THIS CONDITION ..... ⌊⌊⌋⌋
N8.	How many sons do you have?	NUMBER OF SONS ..... ⌊⌊⌋⌋ (IF NONE, ENTER 00 AND SKIP TO N11)
N9.	Have any of your sons had a hip fracture?	YES ..... 1 NO (SKIP TO N10) ..... 2 DK (SKIP TO N10) 8
a.	How many of your sons had a hip fracture?	NUMBER OF SONS WITH HIP FRACTURE ..... ⌊⌊⌋⌋
N10.	Did a doctor ever tell (any of) your son(s) that he had osteoporosis?	YES ..... 1 NO (SKIP TO N11) ..... 2 DK (SKIP TO N11) 8
a.	How many of your sons had this condition?	NUMBER OF SONS WITH THIS CONDITION ..... ⌊⌊⌋⌋
I would now like to ask you the same questions about your brothers and sisters. I will first ask you about your full brothers, that is, those brothers who have the same parents as you.		
N11.	How many full-brothers do you have?	NUMBER OF FULL-BROTHERS ..... ⌊⌊⌋⌋ (IF NONE, ENTER 00 AND SKIP TO N14)
N12.	Have any of your full-brothers had a hip fracture?	YES ..... 1 NO (SKIP TO N13) ..... 2 DK (SKIP TO N13) 8
a.	How many of your full-brothers had a hip fracture?	NUMBER OF FULL-BROTHERS WITH A HIP FRACTURE ..... ⌊⌊⌋⌋
N13.	Did a doctor ever tell (any of) your full-brother(s) that he had osteoporosis?	YES ..... 1 NO (SKIP TO N14) ..... 2 DK (SKIP TO N14) 8
a.	How many of your full-brothers had this condition?	NUMBER OF FULL-BROTHERS WITH THIS CONDITION ..... ⌊⌊⌋⌋

	I would now like to ask you about your half-brothers, that is, those brothers who have only the same mother or only the same father as you.	
N14.	How many half-brothers do you have?	NUMBER OF HALF-BROTHERS ..... ⌊⌋⌋ (IF NONE, ENTER 00 AND SKIP TO N17)
N15.	Have any of your half-brothers had a hip fracture?	YES ..... 1 NO (SKIP TO N16) ..... 2 DK (SKIP TO N16) 8
a.	How many of your half-brothers had a hip fracture?	NUMBER OF HALF-BROTHERS WITH A HIP FRACTURE ..... ⌊⌋⌋
N16.	Did a doctor ever tell (any of) your half-brother(s) that he had osteoporosis?	YES ..... 1 NO (SKIP TO N17) ..... 2 DK (SKIP TO N17) 8
a.	How many of your half-brothers had this condition?	NUMBER OF HALF-BROTHERS WITH THIS CONDITION ..... ⌊⌋⌋
N17.	How many full-sisters do you have?	NUMBER OF FULL-SISTERS ..... ⌊⌋⌋ (IF NONE, ENTER 00 AND SKIP TO N20)
N18.	Have any of your full-sisters had a hip fracture?	YES ..... 1 NO (SKIP TO N19) ..... 2 DK (SKIP TO N19) 8
a.	How many of your full-sisters had a hip fracture?	NUMBER OF FULL-SISTERS WITH A HIP FRACTURE ..... ⌊⌋⌋
N19.	Did a doctor ever tell (any of) your full-sister(s) that she had osteoporosis?	YES ..... 1 NO (SKIP TO N20) ..... 2 DK (SKIP TO N20) 8
a.	How many of your full-sisters had this condition?	NUMBER OF FULL-SISTERS WITH THIS CONDITION ..... ⌊⌋⌋
N20.	How many half-sisters do you have?	NUMBER OF HALF-SISTERS ..... ⌊⌋⌋ (IF NONE, ENTER 00 AND SKIP TO SECTION P)
N21.	Have any of your half-sisters had a hip fracture?	YES ..... 1 NO (SKIP TO N22) ..... 2 DK (SKIP TO N22) 8
a.	How many of your half-sisters had a hip fracture?	NUMBER OF HALF-SISTERS WITH A HIP FRACTURE ..... ⌊⌋⌋

N22.	Did a doctor ever tell (any of) your half-sister(s) that she had osteoporosis?	YES ..... 1 NO (SKIP TO SECTION P) ..... 2 DK (SKIP TO SECTION P) 8
a.	How many of your half-sisters had this condition?	NUMBER OF HALF-SISTERS WITH THIS CONDITION ..... ⌊⌊⌋⌋

P. PERSONAL HISTORY OF FALLS:		
P1.	In the (year before your hip fracture/past year), have you fallen? (FOR CASES, EXCLUDE FALL THAT CAUSED HIP FRACTURE, IF APPLICABLE)	YES ..... 1 NO (SKIP TO SECTION Q) 2
P2.	How many times in the (year before your hip fracture/past year), have you fallen?	NUMBER OF FALLS ..... ☐☐☐
P3.	What were the main reasons for your falls?	_____ ☐☐☐ _____ ☐☐☐ _____ ☐☐☐

INTERVIEWER CHECK POINT:	IF RESPONDENT IS FEMALE →CONTINUE ..... 1 IF RESPONDENT IS MALE → SKIP TO SECTION S 2

Q. REPRODUCTIVE HISTORY (WOMEN ONLY) Now I would like to ask some questions about your menstrual history and pregnancies.		
Q1.	Have you ever been pregnant? I would like to know about all of your pregnancies, even if the pregnancy did not result in the birth of a live baby.	YES ..... 1 NO (SKIP TO SECTION R) ..... 2 DK (SKIP TO SECTION R) 8
Q2.	Including all live births, stillbirths, miscarriages, and abortions, how many times have you been pregnant?	NUMBER OF PREGNANCIES ..... ⌊⌊⌋
Q3.	How many live births did you have?	NUMBER OF LIVE BIRTHS ..... ⌊⌊⌋ (IF NONE CODE 00 AND SKIP TO Q6)
Q4.	How many children did you breast feed?	NUMBER OF CHILDREN BREAST FED ..... ⌊⌊⌋ (IF NONE CODE 00 AND SKIP TO Q6)
Q5.	How many months did you (usually) breast feed your child (children)?	NUMBER OF MONTHS ..... ⌊⌊⌋
Q6.	How old were you when you <u>first</u> became pregnant?	AGE IN YEARS ..... ⌊⌊⌊⌋
Q7.	How old were you when you were <u>last</u> pregnant?	AGE IN YEARS ..... ⌊⌊⌊⌋
Q8.	How often per week did you drink a cup of milk during your pregnancies?	NUMBER OF TIMES PER WEEK ..... ⌊⌊⌋

R. MENOPAUSE AND ESTROGEN USE (WOMEN ONLY)

Now I would like to ask questions about menopause and hormone or estrogen use.

R1. Have you gone through your menopause or change of life? (That is, have your menstrual periods stopped completely for at least one year?)	YES ..... 1 NO (SKIP TO R2) ..... 2 DK (SKIP TO R2) 8
a. How old were you when your menstrual periods stopped completely?	AGE IN YEARS ..... ⌊⌊⌊
b. What was the reason that your menstrual periods stopped completely? Was it due to ...	Natural menopause; "change of life" ..... 1 A hysterectomy (uterus and/or ovaries were removed in surgery) ..... 2 Taking medication that stopped periods ... 3 Or something else? (SPECIFY) ..... 4 SPECIFY:_____
R2. Has your uterus (womb) been surgically removed?	YES ..... 1 NO (SKIP TO R3) ..... 2 DK (SKIP TO R3) 8
a. How old were you when your uterus was surgically removed?	AGE IN YEARS ..... ⌊⌊⌊
R3. Have your ovaries been surgically removed?	YES (ONE OVARY) ..... 1 YES (BOTH OVARIES) ..... 2 NO (SKIP TO R4) ..... 3 DK (SKIP TO R4) 8
a. How old were you when your last ovary was removed?	AGE IN YEARS ..... ⌊⌊⌊
R4. Have you ever taken estrogen pills or tablets, also called female hormone pills, other than for contraception?	YES ..... 1 NO (SKIP TO R5) ..... 2 DK (SKIP TO R5) 8
a. How old were you when you first started taking estrogen pills?	AGE IN YEARS ..... ⌊⌊⌊
b. Are you still taking estrogen pills?	YES (SKIP TO R5) ..... 1 NO 2
c. How old were you when you stopped taking estrogen pills?	AGE IN YEARS ..... ⌊⌊⌊

R5. Did your doctor ever prescribe a progesterone pill, such as Provera, either alone or to go along with your estrogen prescription?	YES (SPECIFY, IF KNOWN) ..... 1 _____ ☐☐ NO (SKIP TO R6) 2
a. How many days a month did you take this pill?	DAYS PER MONTH ..... ☐☐
R6. Have you ever used estrogen in a patch on your skin such as Estraderm?	YES ..... 1 NO (SKIP TO R7) 2
a. How old were you when you started using the estrogen patch?	AGE IN YEARS ..... ☐☐☐
b. Are you still using the estrogen patch?	YES (SKIP TO R7) ..... 1 NO 2
c. How old were you when you stopped using the estrogen patch?	AGE IN YEARS ..... ☐☐☐
R7. Have you ever used any type of estrogen cream such as Premarin cream or Estrace cream?	YES ..... 1 NO (SKIP TO R8) 2
a. How old were you when you started using the estrogen cream?	AGE IN YEARS ..... ☐☐☐
b. Are you still using the estrogen cream?	YES (SKIP TO R8) ..... 1 NO 2
c. How old were you when you stopped using the estrogen cream?	AGE IN YEARS ..... ☐☐☐
R8. Have you ever used any other form of estrogen (other than for contraception) including herbal products, such as wild yam cream?	YES ..... 1 NO (SKIP TO R9) 2
a. What kind(s) of estrogen did you use?	SPECIFY: _____ ☐☐☐ SPECIFY: _____ ☐☐☐
b. How old were you when you started using (medication listed in R8a)?	AGE IN YEARS ..... ☐☐☐
c. Are you still using (medication listed in R8a)?	YES ..... 1 NO (SKIP TO R9) 2
d. How old were you when you stopped using (name of medication listed in R8a)?	AGE IN YEARS ..... ☐☐☐

R9.	Have you ever taken oral contraceptives or birth control pills for any reason?	YES ..... 1 NO (SKIP TO SECTION S) 2
a.	How old were you when you first started taking oral contraceptives or birth control pills?	AGE IN YEARS ..... ⌊⌊⌊
b.	How old were you when you stopped taking oral contraceptives or birth control pills?	AGE IN YEARS ..... ⌊⌊⌊

S. SMOKING/TOBACCO HISTORY:
The next few questions are about the use of tobacco.

S1.	In your lifetime, have you ever smoked cigarettes, cigars, a pipe, chewed tobacco, or dipped snuff?	YES ..... 1 NO (SKIP TO SECTION T) ..... 2 RF (SKIP TO SECTION T) ..... 7 DK (SKIP TO SECTION T) 8
S2.	Have you ever smoked 100 cigarettes or more in your lifetime?	YES ..... 1 NO (SKIP TO S3) ..... 2 RF (SKIP TO S3) ..... 7 DK (SKIP TO S3) 8
	a. How old were you when you started to smoke cigarettes regularly?	AGE IN YEARS ..... ⌊⌊⌋⌋
	b. Do you smoke cigarettes now?	YES (SKIP TO d) ..... 1 NO ..... 2 RF 7
	c. How old were you when you last smoked cigarettes regularly?	AGE IN YEARS ..... ⌊⌊⌋⌋
	d. How many cigarettes (do/did) you usually smoke per day? 20 CIGARETTES = 1 PACK	CIGARETTES PER DAY ..... ⌊⌊⌋⌋
S3.	Was there ever a time when you smoked cigars once a week or more?	YES ..... 1 NO (SKIP TO S4) ..... 2 RF (SKIP TO S4) ..... 7 DK (SKIP TO S4) 8
	a. How old were you when you started to smoke cigars regularly?	AGE IN YEARS ..... ⌊⌊⌋⌋
	b. Do you smoke cigars now?	YES (SKIP TO d) ..... 1 NO ..... 2 RF 7
	c. How old were you when you last smoked cigars regularly?	AGE IN YEARS ..... ⌊⌊⌋⌋
	d. How many cigars (do/did) you usually smoke per week?	CIGARS PER WEEK ..... ⌊⌊⌋⌋

S4. Was there ever a time when you smoked a pipe once a week or more?	YES ..... 1 NO (SKIP TO S5) ..... 2 RF (SKIP TO S5) ..... 7 DK (SKIP TO S5) 8
a. How old were you when you started to smoke a pipe regularly?	AGE IN YEARS ..... ⌊⌊⌊
b. Do you smoke a pipe now?	YES (SKIP TO d) ..... 1 NO ..... 2 RF 7
c. How old were you when you last smoked a pipe regularly?	AGE IN YEARS ..... ⌊⌊⌊
d. How many pipefuls (do/did) you usually smoke per day?	PIPEFULS PER DAY ..... ⌊⌊⌊
S5. Was there ever a time when you chewed tobacco or dipped snuff once a week or more?	YES ..... 1 NO (SKIP TO SECTION T) ..... 2 RF (SKIP TO SECTION T) ..... 7 DK (SKIP TO SECTION T) 8
a. How old were you when you started to chew tobacco or dip snuff regularly?	AGE IN YEARS ..... ⌊⌊⌊
b. Do you chew tobacco or dip snuff now?	YES (SKIP TO d) ..... 1 NO ..... 2 RF 7
c. How old were you when you last chewed tobacco or dipped snuff regularly?	AGE IN YEARS ..... ⌊⌊⌊
d. How many chews or dips of tobacco/snuff (do/did) you usually chew per day?	CHEWS/DIPS PER DAY ..... ⌊⌊⌊

T. USE OF ALCOHOL:

The next few questions are about the use of alcoholic beverages, like beer, wine, or liquor that people drink at meals, special occasions, or when just relaxing.

T1.	Have you ever had a can or glass of beer, a glass of wine, or a shot of liquor or a mixed drink during your lifetime?	YES ..... 1 NO (SKIP TO SECTION U) ..... 2 RF (SKIP TO SECTION U) ..... 7 DK (SKIP TO SECTION U) 8
T2.	Have you ever regularly drank one or more of these alcoholic beverages a month?	YES ..... 1 NO (SKIP TO T3) ..... 2 RF (SKIP TO T3) ..... 7 DK (SKIP TO T3) 8
	a. At what age did you begin?	AGE IN YEARS ..... ⌊⌊⌊
	b. Did you drink alcohol in the (year before your hip fracture/past year)?	YES ..... 1 NO (SKIP TO T3) ..... 2 RF (SKIP TO T3) ..... 7 DK (SKIP TO T3) 8
	c. How often did you drink alcohol per week?	TIMES PER WEEK ..... ⌊⌊
	d. When you drank, how many drinks would you have each time?	DRINKS EACH TIME ..... ⌊⌊

1 DRINK = 1 CAN OR 12 OZ BEER, 1 GLASS OR 4 OZ WINE, OR 1 SHOT OF HARD LIQUOR OR A MIXED DRINK.

T3.	From time to time, people may have occasion to drink more than usual. Have there been any days when you drank 12 or more drinks in one 24-hour period? (Twelve drinks is about one pint of liquor, or two bottles of wine, or two six-packs of beer.)	YES ..... 1 NO (SKIP TO SECTION U) ..... 2 RF (SKIP TO SECTION U) ..... 7 DK (SKIP TO SECTION U) 8
	a. How many times in the (year before your hip fracture/past year) did you drink this amount?	NUMBER OF TIMES ..... ⌊⌊
	b. Thinking back over your life, how many times did you drink this much alcohol in one day?	1-3 ..... 1 4-10 ..... 2 11 OR MORE 3

U. CONTACTS, FOLLOW-UP INFORMATION, AND CLOSING OF INTERVIEW

U1. In the future, it may become necessary to contact you for additional information. We may need to gather more information on your health or on other topics important to our study. In the event that we cannot reach you, is there a relative or close friend, who does not live with you, who will always know where to contact you?

YES 1
NO 2
RESPONDENT REFUSED TO GIVE FUTURE CONTACT 7

U2a.	U2b.
First name	First name
Last name	Last name
Relationship to participant	Relationship to participant
Street Address	Street Address
City, State	City, State
Zip Code	Zip Code
☐☐☐ - ☐☐☐ - ☐☐☐☐ Telephone number	☐☐☐ - ☐☐☐ - ☐☐☐☐ Telephone number

U3.	Please tell me your Social Security Number. This is important for helping us to contact you again. This will be kept confidential like the rest of the information from this interview.	☐☐☐ - ☐☐ - ☐☐☐☐ RF ..... 7 DK 8
U4.	**FOR CONTROLS ONLY.** READ THE FFQ FOLLOW-UP STUDY CONSENT FORM TO THE RESPONDENT. DID R AGREE TO PARTICIPATE IN FFQ FOLLOW-UP STUDY?	YES ..... 1 NO 2
U5.	TIME INTERVIEW WAS COMPLETED:	☐☐:☐☐ AM PM (CIRCLE ONE)
U6.	COMPLETE PHLEBOTOMY	
U7.	CLOSING STATEMENT AND "THANK YOU" TO PARTICIPANT	
U8.	INTERVIEWER ASSESSMENT OF QUALITY OF INTERVIEW	GOOD ..... 1 FAIR ..... 2 UNSATISFACTORY 3

V. ADDITIONAL INTERVIEWER OBSERVATION:		
V1.	COULD THE RESPONDENT HEAR YOU CLEARLY?	YES ..... 1 HAD SOME DIFFICULTY BUT COULD COMPLETE INTERVIEW ..... 2 NO 3
V2.	WAS THE RESPONDENT'S SPEECH CLEAR?	YES ..... 1 HAD SOME DIFFICULTY BUT COULD COMPLETE INTERVIEW ..... 2 NO 3
V3.	WAS THE RESPONDENT WELL-ORIENTED TO TIME AND PLACE?	YES ..... 1 SOMEWHAT CONFUSED BUT COULD COMPLETE INTERVIEW ..... 2 NO, VERY DISORIENTED 3
V4.	WAS THE RESPONDENT'S VISION GOOD ENOUGHT TO READ THE MEDICATION CARDS AND TO SEE THE FOOD PICTURES?	YES ..... 1 HAD SOME DIFFICULTY BUT COULD COMPLETE INTERVIEW ..... 2 NO 3
V5.	WAS THERE ANYTHING UNUSUAL ABOUT THIS INTERVIEW THAT YOU WOULD LIKE TO DESCRIBE?	_____ _____ _____ _____ _____

Appendix B. Utah Picture Sort Food Frequency Questionnaire

RESPONDENT ID: ☐☐☐☐-☐☐☐☐

BEVERAGES

FOOD NAME	FOOD NO.	FREQ	PERIOD 1 2 3 4 5
Plain water from a tap or bottled	001	☐☐	D W M Y N
Milk (SPECIFY TYPE BELOW)	002	☐☐	D W M Y N
What type of milk do you drink most often?	SKIM/NO FAT ..... 1 LOW FAT (1-2%) ..... 2 WHOLE ..... 3 BUTTERMILK 4		
Ensure or other supplemental beverages (SPECIFY TYPE)	003	☐☐	D W M Y N
What types and brands of supplemental beverages do you drink most often?	_____ ☐☐☐ _____ ☐☐☐ _____ ☐☐☐		
Chocolate milk or hot cocoa	005	☐☐	D W M Y N
Orange juice	006	☐☐	D W M Y N
Other fruit juices	007	☐☐	D W M Y N
Diet cola with caffeine	008	☐☐	D W M Y N
Coke, Pepsi and other regular colas	009	☐☐	D W M Y N
Coffee, regular	010	☐☐	D W M Y N
Hot tea or iced tea	011	☐☐	D W M Y N
Beer	012	☐☐	D W M Y N
Red wine	013	☐☐	D W M Y N
White wine	014	☐☐	D W M Y N
Liquor, whiskey, gin, mixed drinks	015	☐☐	D W M Y N

FRUITS

FOOD NAME	FOOD NO.	FREQ	PERIOD 1 2 3 4 5
Orange	016	☐☐	D W M Y N
Grapefruit	017	☐☐	D W M Y N
Banana	018	☐☐	D W M Y N
Cantaloupe	019	☐☐	D W M Y N
Prunes	020	☐☐	D W M Y N
Apple or pear	021	☐☐	D W M Y N
Applesauce	022	☐☐	D W M Y N
Peach, apricot, plum, nectarine	023	☐☐	D W M Y N
Watermelon	024	☐☐	D W M Y N
Fresh, frozen, or canned strawberries	025	☐☐	D W M Y N
Fruit cocktail or jell-o salad with fruit	026	☐☐	D W M Y N
Raisin or grapes	027	☐☐	D W M Y N
Avocado	028	☐☐	D W M Y N

VEGETABLES

FOOD NAME	FOOD NO.	FREQ	PERIOD 1 2 3 4 5
Fresh tomatoes	029		D W M Y N
Canned tomatoes or tomato sauce	030		D W M Y N
Tomato juice, V-8 juice, vegetable juice	031		D W M Y N
Raw carrots	032		D W M Y N
Cooked carrots or carrot juice	033		D W M Y N
Corn	034		D W M Y N
Green or string beans	035		D W M Y N
Peas	036		D W M Y N
Baked, pinto, refried, kidney, or lima beans	037		D W M Y N
Mixed vegetables	038		D W M Y N
Broccoli	039		D W M Y N
Cauliflower	040		D W M Y N
Brussels sprouts	041		D W M Y N
Cabbage, cole slaw, or sauerkraut	042		D W M Y N
Red beets, not greens	043		D W M Y N
Sweet green, red, or yellow peppers	044		D W M Y N
Iceberg or head lettuce in salad	045		D W M Y N
Romaine or leaf lettuce in salad	046		D W M Y N
Raw spinach leaves in salad	047		D W M Y N
Cooked spinach	048		D W M Y N
Mustard, turnip, collard greens, chard	049		D W M Y N
Eggplant, zucchini, or summer squash	050		D W M Y N
Acorn, butternut, or other dark orange winter squash	051		D W M Y N
Onion as a cooked vegetable	052		D W M Y N
French fries, or other fried potatoes	053		D W M Y N
Baked, boiled, or mashed potatoes	054		D W M Y N
Yams or sweet potatoes	055		D W M Y N

OTHER DAIRY FOODS

FOOD NAME	FOOD NO.	FREQ	PERIOD 1 2 3 4 5
Cottage or ricotta cheese	056		D W M Y N
Cheddar, jack, swiss, mozzarella cheese	057		D W M Y N
Yogurt	058		D W M Y N
Cream cheese	059		D W M Y N

MEATS AND MAIN DISHES

FOOD NAME	FOOD NO.	FREQ	PERIOD 1 2 3 4 5
Hamburger	060		D W M Y N
Meatloaf	061		D W M Y N
Beef steak, roast beef, or beef brisket	062		D W M Y N
Casserole with beef and noodles	063		D W M Y N

FOOD NAME	FOOD NO.	FREQ	PERIOD 1 2 3 4 5
Roast beef or barbecue sandwich	064	⌊⌋⌊⌋	D W M Y N
Beef or pork ribs	065	⌊⌋⌊⌋	D W M Y N
Beef stew or potpie with vegetables	066	⌊⌋⌊⌋	D W M Y N
Chili with meat and beans	067	⌊⌋⌊⌋	D W M Y N
Beef, calf, or pig liver	068	⌊⌋⌊⌋	D W M Y N
Lamb, roast, chops, or in stew	069	⌊⌋⌊⌋	D W M Y N
Pork roast or pork chops	070	⌊⌋⌊⌋	D W M Y N
Ham or ham sandwich	071	⌊⌋⌊⌋	D W M Y N
Pork stew or pork pie	072	⌊⌋⌊⌋	D W M Y N
Pork sausage in patties or links	073	⌊⌋⌊⌋	D W M Y N
Bacon	074	⌊⌋⌊⌋	D W M Y N
Eggs	075	⌊⌋⌊⌋	D W M Y N
Venison, elk, or other game meat	076	⌊⌋⌊⌋	D W M Y N
Pheasant, duck, or other game bird	077	⌊⌋⌊⌋	D W M Y N
Fried chicken	078	⌊⌋⌊⌋	D W M Y N
Baked or roasted chicken or turkey	079	⌊⌋⌊⌋	D W M Y N
Chicken or turkey liver	080	⌊⌋⌊⌋	D W M Y N
Chicken or turkey vegetable potpie	081	⌊⌋⌊⌋	D W M Y N
Chicken or turkey sandwich	082	⌊⌋⌊⌋	D W M Y N
Chicken salad or chef salad	083	⌊⌋⌊⌋	D W M Y N
Tuna sandwich, salad, or casserole	084	⌊⌋⌊⌋	D W M Y N

FOOD NAME	FOOD NO.	FREQ	PERIOD 1 2 3 4 5
Canned salmon, sardine, or oysters	085	⌊⌋⌊⌋	D W M Y N
Fried fish or fish sticks	086	⌊⌋⌊⌋	D W M Y N
Broiled or baked white-meat fish	087	⌊⌋⌊⌋	D W M Y N
Fish sandwich	088	⌊⌋⌊⌋	D W M Y N
Salmon, sardine, bluefish, swordfish	089	⌊⌋⌊⌋	D W M Y N
Shrimp, lobster, or scallops	090	⌊⌋⌊⌋	D W M Y N
Spaghetti or other pasta in tomato sauce	091	⌊⌋⌊⌋	D W M Y N
Pizza	092	⌊⌋⌊⌋	D W M Y N
Macaroni and cheese	093	⌊⌋⌊⌋	D W M Y N
Enchilada	094	⌊⌋⌊⌋	D W M Y N
Taco or tostada	095	⌊⌋⌊⌋	D W M Y N
Burrito	096	⌊⌋⌊⌋	D W M Y N
Hot dog	097	⌊⌋⌊⌋	D W M Y N
Bologna, processed lunch meats, salami	098	⌊⌋⌊⌋	D W M Y N
Polish sausages, brats	099	⌊⌋⌊⌋	D W M Y N
Liverwurst	100	⌊⌋⌊⌋	D W M Y N
Canned meats, spam or vienna sausages	101	⌊⌋⌊⌋	D W M Y N
Soup (SPECIFY TYPE BELOW)	102	⌊⌋⌊⌋	D W M Y N
What type of soup do you eat most often?			_____ ⌊⌋⌊⌋⌊⌋ _____ ⌊⌋⌊⌋⌊⌋ _____ ⌊⌋⌊⌋⌊⌋

CEREALS AND BREADS

FOOD NAME	FOOD NO.	FREQ	PERIOD 1 2 3 4 5
Cold breakfast cereal	103	☐☐	D W M Y N
What types and brands of cold breakfast cereal do you eat most often? _____ _____ _____		☐☐☐ ☐☐☐ ☐☐☐	
Oatmeal	104	☐☐	D W M Y N
Other cooked breakfast cereal	105	☐☐	D W M Y N
Instant breakfast beverage or bar	106	☐☐	D W M Y N
Pancakes or waffles	107	☐☐	D W M Y N
White bread	108	☐☐	D W M Y N
Dark bread	109	☐☐	D W M Y N
Dinner rolls, bagels, or pita bread	110	☐☐	D W M Y N
White rice	111	☐☐	D W M Y N
Corn bread or corn muffin	112	☐☐	D W M Y N
Corn tortilla	113	☐☐	D W M Y N
Flour tortilla	114	☐☐	D W M Y N
Potato chips, corn	115	☐☐	D W M Y N
Crackers: saltines, triscuit, wheat-thins	116	☐☐	D W M Y N

OTHER FOODS

FOOD NAME	FOOD NO.	FREQ	PERIOD 1 2 3 4 5
Peanut Butter	117	☐☐	D W M Y N
Peanuts	118	☐☐	D W M Y N
Other nuts	119	☐☐	D W M Y N
Butter	120	☐☐	D W M Y N
Tub or liquid margarine	121	☐☐	D W M Y N
Stick margarine	122	☐☐	D W M Y N
Ice cream	123	☐☐	D W M Y N
Ice milk, frozen yogurt, sorbet	124	☐☐	D W M Y N
Chocolate candy	125	☐☐	D W M Y N
Hard candy	126	☐☐	D W M Y N
Cookies	127	☐☐	D W M Y N
Pie	128	☐☐	D W M Y N
Cake	129	☐☐	D W M Y N
Doughnut, scones	130	☐☐	D W M Y N
Jam, jellies, syrup	131	☐☐	D W M Y N
Oat Bran	132	☐☐	D W M Y N
Other Bran	133	☐☐	D W M Y N
Wheat germ	134	☐☐	D W M Y N
Olive oil	135	☐☐	D W M Y N
Other oil dressing	136	☐☐	D W M Y N
Mayonnaise	137	☐☐	D W M Y N
Salad dressing	138	☐☐	D W M Y N