DIETARY PATTERNS FROM CHILDHOOD TO EARLY ADULTHOOD AND THEIR ASSOCIATIONS WITH BONE HEALTH

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ABSTRACT

The amount of bone accrued during adolescence is an important determinant of later osteoporosis risk. I examined the role of adolescent dietary patterns (DPs) and food group intakes on the adult bone acquisition, and assessed the stability of DPs over time using the data from Saskatchewan Pediatric Bone Mineral Accrual Study (1991-2011).

Principal component analysis was used to derive adolescent DPs including "Vegetarian-style", "Western-like", "High-fat, high-protein", "Mixed" and "Snack" DPs. Associations between adolescent DPs and adolescent (age 12.7±2 years, n=125) or adult (age 28.2±3 years, n=115) bone mineral content (BMC) and areal bone mineral density (aBMD) were analyzed while adjusting for covariates. Mean adolescent total body aBMD and young adult total body BMC and aBMD and femoral neck BMC and aBMD were 5, 8.5, 6, 10.6 and 9% higher (P<0.05), respectively, in third quartile of "Vegetarian-style" DP compared to first quartile.

Associations between adolescents' intake of milk and alternatives (M&A) or fruit and vegetables (F&V) and adult bone structure and strength at tibia and radius were also investigated. Females with high M&A intake compared to low M&A intake group (mean 4 vs. 1.5 servings/d, respectively) had 14, 15 and 16% greater (P<0.05) adult ToA, CoA and CoC at radius shaft, respectively. Females with moderate F&V intake compared to low F&V intake group (mean 4 vs. 2 servings/d, respectively) had greater adult ToA (8.5%, P<0.05) at distal tibia.

The stability of DPs from childhood to adulthood were assessed by generalized estimating equations using the energy-adjusted applied DP scores. I found a moderate tracking for the "Vegetarian-style" (ß=0.44, P<0.001) and "High-fat, high-protein" (ß=0.39, P<0.001) DPs in females and "Vegetarian-style" DP (ß=0.30, P<0.001) in males; and a poor-to-fair tracking for remaining DPs, in both sexes. The "Western-like" DP was not stable in females. Adherence to "Vegetarian-style" DP increased and adherence to "High-fat, high-protein" DP decreased by age.

Higher adherence to "Vegetarian style" DP (in both sex) and higher intake of M&A or F&V (only in females) during adolescence was positively associated with bone health. Healthy dietary habits established during childhood and adolescence could moderately continue into adulthood.

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LIST OF ABBREVIATIONS

aBMD	Areal Bone Mineral Density
AHEI	Alternative Healthy Eating Index
BIA	Bioelectric Impedance Analysis
BMD	Bone Mineral Density
BMC	Bone Mineral Content
BMAD	Bone Mineral Apparent Density
BMI	Body Mass Index
CoA	Cortical Area
CoC	Cortical Content
CoD	Cortical Density
CSA	Cross Sectional Area
CV	Coefficient of Variance
DASH	Dietary Approaches to Stop Hypertension
DDS	Dietary Diversity Score
DXA	Dual-energy X-ray Absorptiometry
FFQ	Food Frequency Questionnaire
FN	Femoral Neck
FRAX	Fracture Risk Assessment Tool
HEIC	Healthy Eating Index of Canada
LS	Lumbar Spine
MDS/MD	Mediterranean Diet Score
μMR	Micro Magnetic Resonance
MRI	Magnetic Resonance Imaging
MuA	Muscle Area
NRS	Nutritional Risk Score
OHS	Oslo Health Study
OR	Odds Ratio
PA	Physical Activity
PAQ-A	Physical Activity Questionnaire in Children
PAQ-AD	Physical Activity Questionnaire in Adolescents
PAQ-C	Physical Activity Questionnaire in Adults
PBM	Peak Bone Mass
PBMAS	Pediatric Bone Mineral Accrual Study
PCA	Principal Component Analysis
PHV	Peak Height Velocity
pQCT	Peripheral Quantitative Computed Tomography
QCT	Quantitative Computed Tomography
QUS	Quantitative Ultra-Sound
RFS	Recommended Food Score
RRR	Reduced Ranked Regression
TB	Total Body
ToA	Total Area
ToC	Total Circumference
ToD	Total Density

TrA	Trabecular Area
TrC	Trabecular Circumference
TrD	Trabecular Density
vBMD	Volumetric Bone Mineral Density
WHO	World Health Organization

CHAPTER 1
INTRODUCTION

1.1.Background Information and Rationale

Bone changes over one's life. These changes are characterized predominantly by bone accrual during childhood and adolescence, and bone loss beginning in late adulthood (Anderson & Klemmer, 2012). Peak bone mass (PBM), defined as the amount of bone mass accrued at the end of skeletal maturity, is the main predictor of the risk of osteoporosis later in life (Bonjour et al, 2009). Therefore, it is important to identify the modifiable factors that can help to achieve one's highest potential PBM (Mughal & Khadilkar, 2011). The cumulative effect of nutrition over a life span (Kant, 2004; Wakimoto & Block, 2001), is one of the main factors associated with bone health. Nutritional modification impacts bone mass and bone density during critical periods of life (Cashman, 2007).

Diet is an intricate combination of nutrients that are correlated and likely to interact. Hence, the exclusive effect of a single nutrient is either difficult to assess or the effects might be too small to detect (Kant, 2004). To assess the influence of all the measured nutrients on a specific health outcome, multiple statistical tests are required. Multiple tests and comparisons can produce erroneous results (Moeller et al., 2007). Consequently in recent years, exploring the effect of overall diet, rather than single food items or nutrients, has attracted more attention (Jacobs & Steffen, 2003).

Because describing and quantifying diet through dietary patterns enables the study of the entire diet rather than individual foods or nutrients, assessing dietary patterns has emerged as a key component of a nutritional study (Kant, 2004). The association between one's current dietary pattern and bone health may be influenced or confounded by previous dietary intakes during critical periods of growth and development. Therefore, considering the evolution of a dietary pattern, using longitudinal studies, is vital for determining the association between dietary intake in adolescence and health outcomes in adulthood.

A longitudinal study measuring dietary intake during adolescence and tracking the changes into adulthood and evaluating the association between dietary patterns and bone health is required. The Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) is a mixed longitudinal study, which collected annual data on dietary intakes, physical activity, growth and

maturational factors and bone mineral accumulation from childhood to adulthood. The study was conducted from 1991 to 1997 (the original study; n= 113 males and 115 females), from 2003 to 2006 (the first follow-up study; n= 94 males and 88 females), and 2010 to 2011 (the second follow-up study; n= 48 males and 73 females). These longitudinal data from PBMAS provides an opportunity to investigate the relationship between dietary patterns and bone measurements from childhood to adulthood.

1.2.Purpose of the Study

(i) To determine the major dietary patterns consumed during adolescence

(ii) To investigate dietary pattern associations with bone measurements

(iii) To assess stability of dietary patterns from adolescence to adulthood

1.3.Research Questions and Hypothesis

Using the PBMAS data the following questions will be addressed:

- Research Question 1: How do dietary patterns, or food groups, associated with bone DXA and pQCT measurements from adolescence to adulthood?
- Hypothesis 1: A diverse and healthy dietary pattern including higher intakes of fruit and vegetables and milk and alternatives are associated with improved bone health.

- Research Question 2: Do dietary patterns change from adolescence to adulthood?
- Hypothesis 2: Dietary patterns do not change over the time from adolescence to adulthood.

1.4. Significance of the Study

The PBMAS provides a unique longitudinal data on dietary intake, physical activity, and bone measurements, from childhood to early adulthood in males and females (1991 to 2011). This study offers an exclusive opportunity for investigating the longitudinal effect of childhood diet on the bone during adulthood while controlling for other factors such as physical activity, fat mass and muscle mass, body measurements and maturity. There is a limited number of longitudinal studies on diet and bone measurements with a shorter follow-up period in comparison with the PBMAS. Furthermore, most existing studies on diet and bone focus on

females and only a few studies have included males. Therefore, using PBMAS data to investigate the relationship between diet and bone measurements can result in valuable findings that address a gap in the literature.

1.5. Thesis outline

In the next three chapters, I developed a literature review to represent the comprehensive image of the current knowledge in my research area. In Chapter 2, an overview on the bone as a tissue, bone measurement methods, factors associated with bone growth and mineral accrual, and dietary pattern approaches are presented. I also summarized previous PBMAS findings on the association of dietary intake and bone health. Current evidence on the association of dietary patterns and bone health indicators (bone mineral status, bone biomarkers, osteoporosis, and fracture) from 49 studies has been reviewed in Chapter 3. This scoping review has been published in "Advances in Nutrition" in 2017. In Chapter 4, I presented a literature review of studies that evaluated stability and tracking of dietary patterns over time during the lifespan. Findings of these studies were summarized as a scoping review manuscript. This manuscript is prepared for submission to "Nutrition Research Reviews" for publication. Methodology is represented in Chapter 5. The PBMAS data collection methods, study design and analytical approaches used in my research were provided in this chapter.

Findings of my research have been presented in three separate chapters, Chapters 6 to 8. Research Objective 1 has been addressed in Chapter 6 and Chapter 7. In Chapter 6, we derived dietary patterns during adolescence and evaluated their impact on adulthood bone measurements. The manuscript has been submitted to "Nutrition Journal" for publication. Chapter 7 represents a published manuscript in "Osteoporosis International" journal. In this study, we evaluated the impact of adolescent food group intake on adult bone structure and strength. Research Objective 2 has been addressed in Chapter 8. We assessed the stability of dietary patterns, which derived using adolescent dietary intake data, over the entire time from adolescent to young adulthood.

The final chapter, Chapter 9, discusses all findings from three studies while linking the findings to each other and the findings from previous studies. In this Chapter, we identified research gaps, limitations and future directions. The overall conclusion was established at the end of this Chapter.

CHAPTER 2

LITERATURE REVIEW 1

2.1. An Overview of Bone

2.1.1. Bone Tissue

Bone consists of an organic matrix (osteoid), within which minerals (calcium and phosphorous as hydroxyapatite) are deposited, and groups of cells, including: osteoclasts, osteoblasts, and osteocytes (Garner & Anderson, 2012). Osteoclasts resorb bone mineral content by creating an acidic environment and remove the remaining collagen matrix by releasing enzymes. Osteoblasts produce and deposit organic matrix called the osteoid in which minerals including calcium and phosphate begins to crystallize (Garner & Anderson, 2012). Some active osteoblasts become trapped in the matrix they secreted and thereby, become osteocytes. Osteocytes are important in maintaining viability and structural integrity of bone (Teti, 2011). There are two major types of bone tissue, cortical bone, and trabecular bone. Cortical bone, the harder shell of a bone, contributes to bone strength by resisting bending particularly at the long bone shaft. Trabecular bone, the spongy looking center, resist compression. Different bones and skeletal sites have different ratios of cortical-to-trabecular bone. For example, this ratio is 50:50 in the femoral head and 95:5 in the radial diaphysis. The adult human skeleton is composed of approximately 80% cortical bone and 20% trabecular bone (Gosman, Stout, & Larsen, 2011).

2.1.2. Bone Growth

Bone mass accrual velocity increases mainly during the first three years of life and then again during the puberty growth spurt (Perez-Lopez, Chedraui, & Cuadros-Lopez, 2010). In this period, long bone length increases by endochondral ossification at both proximal and distal growth plates of long bones, and bone width increases by a process named modeling. During modeling, osteoblasts deposit and subsequently mineralize bone matrix on the periosteal (outer) surface of bone leading to an increase in outer bone circumference. At the same time, osteoclasts resorb bone on the endocortical (inner) surface of bone resulting in an increase in the bone marrow circumference. During modeling, bone formation is quantitatively more than bone resorption (Schoenau et al., 2004). Remodeling plays an important role in bone maintenance. During remodeling activities of osteoclasts and osteoblasts are coupled. It means that, the same amount of the bone which is removed by osteoclasts is restored by osteoblasts on the same

surface. (Schoenau, 2006; Teti, 2011). Remodeling during adulthood is an important process for bone preservation (replacing the damaged bone with a new bone). In mature bones, remodeling leads to a gradual bone loss because of inequality in the rates of bone resorption and bone formation. In addition, remodeling plays an important role in calcium homeostasis and fracture healing (Kontulainen et al 2013).

2.1.3. Bone Accrual and Loss During Life Span

The skeleton changes during the human lifespan. This is characterized predominantly by bone development and growth during the intrauterine period, which continues throughout childhood and adolescence. The peak bone mass (PBM) is defined as the amount of bone mass accrued at the end of skeletal maturity, when long bones growth (length) has ceased and mineralization completed. The age of PBM achievement varies with the skeletal site and sex (Baxter-Jones 2011). More than 39% of total body PBM is acquired during the 4-year period around peak height velocity (PHV), defined as the greatest rate of stature increase, and more than 90 % is achieved by six years after PHV, by the end of the second or very early in the third, decade of life (Baxter-Jones 2011). There is a steady status of bone after PBM accrual which means there is no significant change in bone mineral content by age (a plateau) during this period. Gradual loss of bone content begins in late adulthood, by the age of 50 years (postmenopausal years in females) and is accelerated significantly in older ages. The amount of bone mass accrued from childhood to early adulthood is one the most important predictors of osteoporosis risk later in life; one standard deviation increase in PBM is associated with 50% reduced risk of osteoporosis (Bonjour et al, 2009). Nutrition and physical activity during the growth spurt may influence the PBM attained during late adolescence and early adulthood.

2.1.4. Sex Differences in Bone Mineral Accrual

There are sex differences in timing and the amount of PBM accrued at the end of the growth period (Karlberg, 2002). The sex differences in bone growth first emerge during puberty. Although females attain their PHV and peak bone mineral content velocity (PBMCV), defined as the greatest rate of bone accrual during adolescent, earlier than males, males have a prolonged period of bone maturation which results in an increase in bone size and cortical thickness (Karlberg, 2002). The PBMCV occurs at an average of 1 year after PHV, at mean age of 15 years in boys and 13 years in girls (Bailey et al 2000). However, evaluation of bone mineral accrual revealed that there is no sex difference in the bone mineral content from childhood to late

adolescence after controlling for age at PHV (as an indicator of somatic maturity) and body size and composition (Baxter-Jones, et al. 2003).

2.1.5. Bone Mass and Density

Bone mass and bone density are two different concepts, which should be recognized and interpreted based on biologic knowledge. Bone mass equals the weight of the bone mineral, which depends on bone size. Bone mineral content (BMC) reflects bone mineral mass. Volumetric bone mineral density (vBMD), represents the bone mineral content relative to outer bone volume and is independent of size (Perez-Lopez et al., 2010). However, areal bone mineral density (aBMD), which is determined by the attenuation of radiation beam by a 2-dimentional projected area of bone, depends on the size, as well as physical density, of the bone. A greater BMD or BMC might represent greater cortical thickness, a more compact trabecular bone, or the accumulation of a larger amount of minerals in the pre-existent organic matrix (Schoenau et al., 2004). During growth, an increase in bone size, which is characterized by the deposition of a new matrix followed by its mineralization, leads to an increase in aBMD but has little influence on vBMD (Bonjour, Chevalley, Ferrari, & Rizzoli, 2009). There are several available techniques to measure bone characteristics (Bonjour et al., 2009).

2.2. Bone Measurement Methods

Bone characteristics such as bone mass, bone density, bone strength, bone cross-sectional area, and microarchitecture can be measured using several techniques. Some of the most common noninvasive imaging techniques are described in this section, along with their advantages and limitations. Other approaches for evaluating bone health which was not included in this chapter are the assessment of fracture risk, biochemical markers of bone turnover, bone biopsy, and histomorphometry, quantitative ultrasound, and a genetic test (Wren & Gilsanz, 2006).

2.2.1. Dual-Energy X-Ray Absorptiometry (DXA)

DXA is the most widely used technique for bone assessment in all age groups. The fact that low-energy x-ray beam is much more attenuated by bone tissue than soft tissue and, high-energy beam attenuated less than low-energy beam by both soft and bone tissues, is the basis of bone measurement procedure by DXA which provides estimates for BMC (g) and aBMD (g/cm^2) (Wren & Gilsanz, 2006, Bauer, 2013). The primary sites of DXA scans are the lumbar

spine, femoral neck, and hip; all of which are important for the diagnosis of osteoporosis, estimation of fracture risk and assessment of treatment efficacy (Bauer, 2013). DXA owes its popularity to its short-term precision and low radiation exposure and short time of scan compared to other methods. In addition, the World Health Organization's (WHO) definition of osteoporosis is based on the DXA-measured aBMD. Femoral neck (FN) aBMD is one of the clinical risk factors included in Fracture Risk Assessment Tool (FRAX) WHO definition of fracture risk algorithm (Kanis, 2013). However, using DXA has some limitations. First, since DXA measures 2-dimensional aBMD in the projected area instead of volumetric BMD, variation in bone size and morphology may lead to erroneous interpretation of aBMD measured by DXA, especially in children. Larger bones yield higher BMC and aBMD measurements, independent of their real volumetric density (Schoenau et al., 2004; Wren & Gilsanz, 2006). Therefore, most childhood studies reported BMC and not aBMD. Another limitation is that soft tissue, a heterogeneous composition of lean and adipose tissue is considered as homogeneous in the procedure used for estimation of BMD by DXA. It may be problematic especially in overweight and obese individuals and those with recent considerable changes in weight and body composition (Bachrach, 2005; Wren & Gilsanz, 2006). The other limitation is that, bone geometry, structural properties and strength cannot be characterized using DXA (Bachrach, 2005; Wren & Gilsanz, 2006).

2.2.2. Quantitative Computed Tomography (QCT)

The QCT is a 3-dimentional imaging approach that measures true volumetric BMD, bone size, bone geometry and estimates of bone strength and differentiates cortical and trabecular bone separately. Since volumetric bone density measures are independent of bone size and body weight, the QCT values can be used for monitoring cortical and trabecular bone density development and growth in children and adolescents. Although radiation exposure in this method is more than DXA, especially for central versus peripheral assessments, it is still much lower than other CT imaging methods or radiographic tests such as dental X-ray. On the other hand, QCT is less available and more expensive and it has limited pediatric references norms (Bachrach, 2005; Gelfand & Dimeglio, 2005; Wren & Gilsanz, 2006). Although reference data on spinal single-slice QCT for L1-3 have been published for children and adults recently, image acquisition and analysis have not been standardized (Bauer, 2013).

2.2.3. Peripheral Quantitative Computed Tomography (pQCT)

To compensate the limitations of QCT, pQCT can be used to assess appendicular skeleton particularly tibia and radius with lower radiation exposure. In addition, the pQCT scanners are smaller and portable in comparison to QCT scanners. Bone parameters are determined in slices, which are defined based on a certain distance from an anatomical reference line. The cross-sectional area (CSA), cortical area (CoA), marrow area, cortical thickness, the outer and inner circumference of the bone shaft can all be determined at the proximal site. Proximal cortical density (CoD) is the other parameter that can be determined using pQCT. Bone mass can be calculated by multiplying total CSA (mm^2) by total density (ToD) (mg/cm^3) divided by 1000. In addition, pQCT can estimate bone strength by considering the geometry and mineral content of bone. The "Density weighted polar section modulus" (SSI_P, mm^3) is an indicator of resistance of bone diaphysis to bending and torsion. The bone strength index (BSI_C, mg^2/mm^2), estimated as $ToA*ToD^2$, is an index of compressive strength (Bonjour et al., 2009; Gelfand & Dimeglio, 2005; E Schoenau et al., 2004; Eckhard Schoenau, 2006; Wren & Gilsanz, 2006).

2.2.4. Magnetic Resonance Imaging (MRI)

Recently, MRI has taken on a role in bone measurement by its progress in producing high-resolution images, referred to as micro MR (μMR) (Bachrach, 2005; Wren & Gilsanz, 2006). Images of μMR are analyzed to obtain measures of trabecular and cortical bone macro- and microarchitecture. These measurements are made in peripheral locations including the distal radius, the distal tibia or more proximal sites such as the proximal femur using more strong magnets. Although MRI is of interest because of no radiation exposure, there are some limitations in use of MRI. This approach is technically challenging, expensive and takes longer measurement time during which participants must be still. However, by advancing new methods for analysis and establishing normative data, MRI could be used as one of the clinical approaches in the future (Bachrach, 2005; Wren & Gilsanz, 2006).

2.3. Factors Associated with Bone Mass Accrual and Bone Loss

The bone homeostatic system appears to be under genetic control (Baldock & Eisman, 2004). Results from twin and family studies indicate that genetics may explain 50% to 85% of the variance in peak bone mass, and 70% of the variance in aBMD (Ralston, 2006; Vicente-Rodríguez et al., 2008). In addition to heritable factors that control bone mass, environmental factors such as nutrition and physical activity have a strong influence on accumulation and

maintenance of bone mass during the evolving life cycle of bone (Langman, 2005). Achieving the highest genetically depicted potential peak bone mass is the main strategy for reducing the risk of osteoporosis later in life (Mughal & Khadilkar, 2011). Therefore, understanding the factors influencing bone mass development during childhood to early adulthood and bone loss in the following years is crucial to minimize the risk of osteoporosis.

2.3.1. Physical Activity

It is believed that mechanical loading triggers differentiation and activity of osteoblasts to maintain or enhance bone matrix and change the bone shape and size to resist loadings (Clarke, 2008; Lanyon, 1993). Findings from various studies suggest that bone mass and strength benefit from physical activity in all periods of life (Bielemann, Martinez-Mesa, & Gigante, 2013). However, the strength of this relationship depends on several factors including sex, age, exercise characteristics, and bone site. Physical activity and exercise influence bone mass in males more than females, during prepubertal and early pubertal more than post puberty, in weight bearing skeleton sites, such as lumbar spine (LS) and femoral neck (FN), more than total body (TB), and more preferentially in cortical rather than trabecular bone (Bielemann et al., 2013; Hamilton, Swan, & Jamal, 2010; Lirani-Galvão & Lazaretti-Castro, 2010). Specific short and dynamic exercise characterized by specific intensity and frequency and imposing multi-directional mechanical loadings results in the greatest increase in bone strength (Lirani-Galvão & Lazaretti-Castro, 2010). Regular weight-bearing exercise can improve bone strength at the loaded sites by 1 to 8%. Improvement ranging from 0.5 to 2.5% has been reported in premenopausal women with high exercise compliance (Nikander et al., 2010). However, availability of adequate calcium, vitamin D and protein are essential for the positive effect of physical activity (Lirani-Galvão & Lazaretti-Castro, 2010).

2.3.2. Dietary Factors

Several key nutrients and foods play an important role in bone development and maintenance. Calcium, phosphorus, and protein are major components of bone. Other dietary components crucial for bone homeostasis are magnesium, zinc, copper, iron, fluoride and vitamins D, C, K and A (Nieves, 2013). Adequate dietary calcium intake is required for skeletal growth and mineralization during childhood and adolescence. During older ages, calcium is essential to offset the amount of bone loss associated with aging. However, calcium intake has a threshold level of which bone accumulation remain constant. In the other words, the threshold

level of calcium is the minimal calcium intake requirement at which the calcium retention is maximal (Mughal & Khadilkar, 2011; Vatanparast, Bailey, Baxter-Jones, & Whiting, 2010). Vitamin D influences bone health through its direct effect on bone cells and indirect effect on intestinal absorption of calcium. Dietary intake of vitamin D is limited, however, vitamin D supplements and production of vitamin D in the skin can help to meet the daily requirement (Bikle, 2012). To obtain an optimal serum level of 25-hydroxy vitamin D, supplementation is necessary for most Canadians (Hanley et al., 2010). Beside gamma-carboxylation of osteocalcin, vitamin K improves calcium balance, increase BMD and decrease fracture risk (Weber, 2001). It is believed that dietary potassium and magnesium induce an alkalis environment, which promotes renal calcium retention (Tucker et al., 1999a). In contrast, higher intake of salt has a negative effect on calcium retention in kidney and induces a hypercalciuric effect (Weaver, 2008). Other minerals such as zinc, copper, iron and fluoride may also buffer the metabolic acid load induced by animal proteins (Hunter, Skinner, & Lister, 2008). Vitamin C is involved in collagen formation for the organic matrix of bone. Moreover, antioxidant properties of vitamin C may be of benefit on bone health (Nieves, 2013). Omega-3 fatty acids also may have a positive effect on bone through their antioxidant effect and also by increasing the intestinal absorption of calcium (Nieves, 2013).

Since a variety of nutrients with complex relationships and interactions are essential for bone growth and maintenance, examining the effect of a single nutrient without considering the impact of other dietary components could misrepresent a real association. As a solution for this limitation, the dietary pattern approach has been emerged to elucidate associations between overall diet and health outcomes.

2.4. Dietary Pattern Assessment Approaches

The concept of the dietary pattern was first introduced about 35 years ago (Schwerin et al., 1981). Although there are different approaches for identification of dietary patterns, all of them aim to evaluate associations between dietary patterns and health outcomes. There are two major categories of dietary pattern approach.

(a) *a* priori-defined dietary pattern approach uses a dietary index, with different dietary variables constructed based on the theoretical nutritional knowledge, which usually assesses the compliance with dietary guidelines and recommendations. In this method, dietary variables are

marked different scores based on the existence of certain characteristics of diet and the final score represents the extent of exposure and can be further investigated for its relationship with a specific health outcome. Some examples of priory-defined dietary patterns are Mediterranean diet (MD), Dietary Diversity Score (DDS), Nutritional Risk Score (NRS), DASH, Oslo Health Study (OHS), Recommended Food Score (RFS) and Healthy Eating Index (HEI). More information is presented in section 2.5.

(b) Data-driven or posteriori-defined dietary pattern approach uses statistical methods to derive dietary patterns from collected data (Kant, 2004; Newby, Sc, Tucker, & Ph, 2004). Since dietary intake data are required as input variables, it is important to choose an appropriate method of data collection. A single 24-hour recall could not reflect day-to-day variations and may lead to erroneous results; and using food frequency questionnaire (FFQ) may obscure intake of special foods, which are collapsed into larger groups (Bailey et al., 2006; Moeller et al., 2007). After data collection, the first step in preparing the data is collapsing all food items into a reasonable number of food groups. Too few food groups would not be able to distinguish the actual intake of food items; too many food groups might produce a non-interpretable combination of food items in the pattern. Similarity measures to present food group intake include serving number or frequency of food group, gram weight of foods, percent of energy contribution and comparison with a predetermined cut-off amount (Bailey et al., 2006; Kant, 2004; Newby et al., 2004). A higher percent of energy contribution from one or two food groups would result in a lower percent of energy contribution from other groups and it would not permit non-caloric foods such as diet soda, tea, and coffee or low-caloric foods such as fruit and vegetables to be included in the analysis. In contrast, number of servings strategy is an absolute amount offering the advantage of being consistent and is not influenced by intake of other food groups; that is a high number of fat servings does not necessarily mean lower intake of other foods (Bailey et al., 2006; Newby et al., 2004). Next step is to use one of the statistical approaches including factor analysis, cluster analysis and reduced ranked regression (RRR) to generate dietary patterns from the prepared data.

2.4.1. Factor Analysis

Factor analysis is the most commonly used approach, which derives dietary patterns (factor) based on the inter-correlation between dietary items provided by the data (Newby et al., 2004). That is, correlated variables aggregated into a group, which are distinct from the other

groups of variables (Kant, 2004). Principal component analysis (PCA) is the usual factoring solution in most published studies. The number of factors generated might be as many as the number of variables. However, only a few factors are retained based upon their interpretability and extent of variance explained by the factor. This is determined by using eigenvalues or examining scree plots. The retained factors then are often rotated to derive more interpretable factor loadings. In the final step, factor loading for each variable is calculated and factor solutions are labeled (Kant, 2004). Each participant is assigned a factor score for each derived factor based on the factor loadings and the consumed amount of food groups. There are different methods for computing factor scores (DiStefano et al 2009). In the most common method, input variables are weighted by their factor loadings and then summed. Factor scores are continuous variables that usually are categorized into quartiles. Since a participant may have a high score for more than one factor, a relationship between one factor and health outcome would not necessarily reflect this relationship in participants. Rather, the relationship between health outcomes and a participant's overall dietary pattern, which is represented by the scores for all identified factors, should be investigated (Moeller et al., 2007; Newby et al., 2004).

2.4.2. Cluster Analysis

Cluster analysis derives dietary patterns based on the difference in dietary intake of participants. Participants are categorized into mutually exclusive clusters, such that, dietary intake characteristics of participants tend to be similar within a cluster and dissimilar between clusters (Moeller et al., 2007). Classification of subjects into clusters depends on the minimizing the Euclidean distance within a cluster and maximizing the difference between clusters (Bailey et al., 2006). Only the clusters with meaningful nutritional contents and less within-cluster variance compared to between-cluster variance are retained. In this regard, using available nutrition and biology knowledge, examining scree plots and using various statistical tests such as cubic cluster criterion can be helpful (Moeller et al., 2007; Tucker et al., 2002a). The small clusters which are the fragments of larger clusters and the clusters with too few participants fallen into them can be excluded (Bailey et al., 2006; Tucker et al., 2002a). Finally, clusters are labeled. The naming of the clusters is arbitrary; the common names of some reproducible dietary patterns are Western, healthy, traditional, sweets and alcohol (Moeller et al., 2007). Then, these clusters can be compared to each other with respect to different variables especially health outcomes.

2.4.3. Reduced Ranked Regression (RRR)

RRR derives dietary patterns from dietary intake data as predictors, by choosing disease related variables as response variables. The only difference between factor analysis and RRR is that factor analysis determines inter-correlation between dietary variables by maximizing the explained variance in the dietary variables, but RRR determines inter-correlation between dietary variables (predictors) by maximizing the explained variance in the health outcomes (intermediate response variables). Since the ultimate purpose of this method is to explain a high proportion of response variation, RRR-generated factors should be evaluated based on the response scores rather than factor scores (Hoffmann, 2004; Moeller et al., 2007).

In using data-driven dietary pattern assessment approaches investigators have to make decisions regarding how to collapse the foods into food groups, which factors or clusters should be retained and how to label them. Hence, all these methods are prone to the subjectivity. However, utilizing the nutritional knowledge in all decisions which should be made during statistical analysis might minimize the extent of errors (Moeller et al., 2007).

2.5. Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS)

Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) is a longitudinal study spanning the entire pubertal period in a group of normally active healthy Canadian children, to investigate the patterns of the growth and the magnitude and timing of bone mineral accrual during adolescence. This study was initially designed to answer the question "how did the patterns of growth cause a period during which the bone is the most susceptible to fracture during adolescent growth spurt?". Aligning children based on their age at peak BMC velocity, or age at peak height velocity, instead of chronologic age, allowed investigators to control for maturity differences. Therefore, children and adolescents would be compared to their peers in the similar stage of bone growth, rather than similar chronologic age. Serial bone measurements, body composition measurements, anthropometry, dietary intake and physical activity assessment were conducted across 7 years of original study (1991-1997). Subsequently, participants were tracked during the first follow-up study from 2003 to 2006 and again during the second follow-up study from 2009 to 2011. Detailed methodological information is provided in Chapter 5.

Longitudinal and cross-sectional analysis of PBMAS data has yielded to more than 40 publications in scientific journals which have primarily focused on the association between physical activity and bone mineral accrual and sex differences in bone mineral accrual, as well as

addressing some other questions such as muscle-bone growth, bone structural analysis, determining biologic maturity and relationships between nutrition and bone or fat mass. Since the present study aims to assess the dietary patterns in association with bone health, I am providing a summary of what is known about the relationship between nutrition and bone based on the published findings of PBMAS (Table 2.1).

Iuliano-Burns et al. (1999) assessed calcium intake and its main dietary sources in 226 participants in PBMAS, aged 8 to 19, analyzing food recalls completed over the seven years of study. After excluding the recalls with under- or over-reporting of energy intake, the major source of calcium was fluid milk, contributing 39-50% of total calcium intake. Girls decreased their calcium intake, especially from milk products' consumption, as they got older. In contrast, older boys consumed more calcium than younger boys. Assessing seasonal differences showed that total calcium intake and calcium intake from fluid milk was higher during summer compared with winter in younger girls.

Whiting et al. (2001) analyzed the relationship between different types of beverage intake and BMC and bone mineral accrual during the ± one-year around peak BMC velocity age in 59 boys and 53 girls participating in PBMAS. Beverages were categorized into milk, juice, cola beverages, non-cola carbonated beverages, total carbonated beverages, other sweetened beverages and total low nutrient dense beverages groups. In this category, noncarbonated beverages had a stronger inverse correlation with milk intake in both girls and boys. In girls, low nutrient dense and carbonated beverages were negatively correlated with total BMC. On the other hand, low nutrient dense and noncarbonated beverages were negatively correlated with BMC accrual over the two years. Milk intake was negatively correlated with low nutrient dense beverage intake in both boys and girls (Whiting et al., 2001).

Carter et al. (2001) compared calcium density (adjusted for energy intake) with unadjusted calcium intake as predictors of BMC in children and adolescents participating in PBMAS. Self-reported calcium intake of 227 children was used for this analysis. Multiple linear regression models indicated that there was a positive association between unadjusted calcium intake and total body BMC and L lumbar spine BMC in males but not females. When unadjusted calcium was substituted with calcium density, there was no significant improvement in the model (Carter et al., 2001).

Vatanparast et al. (2005) investigated the association between fruit and vegetable intake and total body BMC in 85 boys and 67 girls who were assessed during 7 years of PBMAS. Less than 30% of subjects met Canada's food guide recommendations for fruit and vegetable intake. After aligning subjects based on their biologic age, which is defined as the number of years before or after peak height velocity, Multilevel modeling showed that physical activity, calcium intake and fruit and vegetable intake were positively and significantly associated with total body BMC in boys but not girls (Vatanparast et al., 2005).

Vatanparast et al. (2006) examined the trend in calcium intake and beverage intake in grade 9 students at three time points: 98 subjects during 1991 to 1993 and 62 subjects during 1995 to 1997 who were participants of PBMAS, and 58 subjects during 2003-2004 who were participants of Fluids Used Effectively for Living (FUEL) Study, who had attended the same schools as PBMAS students over a decade earlier. Beverage intake was assessed using 24-h recall in both studies and classified as milk, fruit juice and/or soft drinks. Soft drinks were divided into carbonated and non-carbonated soft drinks. There was a descending trend in the contribution of milk intake and an ascending trend in the contribution of fruit juice intake of the total beverage intake in both sexes from 1991 to 2004. Milk intake and noncarbonated soft drinks were inversely correlated. Calcium intake was decreased significantly over the time in girls but not in boys (Vatanparast, et al., 2006).

Mundt et al. (2006) assessed the effect of physical activity and sugar-sweetened beverages on fat mass development in a subsample of PBMAS participants who had all the measurements done for this analysis. Fat mass was measured annually by DXA. To investigate the sole effect of sugar-sweetened beverages and control for total energy intake calories from these drinks were subtracted from total energy intake. Using multilevel random effects models, after controlling for maturation, fat-free mass and energy intake, physical activity was negatively associated with fat mass development in boys, but not in girls. However, sugar-sweetened beverages had no significant association with fat mass development in boys or girls (Mundt et al., 2006).

Vatanparast et al. (2007) investigated the relationship between protein intake and total body BMC, total body BMC net gain since PHV, and total body BMD in early adulthood. PBMAS participants who were followed-up during 2003-2006 were included in the analysis (59 males and 74 females). Calcium intake of 1000 mg/d were considered adequate intake for both

sexes. Participants were classified into four categories based on both adolescent and young adult calcium intake (Low/low, Adequate/low, low/ Adequate, Adequate / Adequate). Since calcium intake in most of the males was adequate it was not possible to control the effect of calcium intake on bone measurements. However, females had distributed within four groups based on calcium intakes. Multiple regression models revealed that protein intake is a significant predictor of total body BMC, total body BMC net gain since PHV, and total body BMD in all young adult women except for low/low group. These finding show that protein intake influence bone positively only when there is an adequate intake of calcium.

Vatanparast et al. (2010) estimated calcium requirements of adolescents in 9-13 y and 14-18y for both sex in accordance with DRIs sex-age groups, using the calcium accrual data from PBMAS. Annual total body BMC accrual was determined between age 9 to 18 and a factorial model approach was used to estimate the calcium requirements based on daily BMC accrual. Using this method, calcium requirement of Canadian boys and girls were determined to be 1000-1100 mg/d for 9-13y girls and boys, 1000 mg/d for 14-18 y girls and 1200 mg/d for 14-18 y boys (Vatanparast et al., 2007).

Table 2.1. Summary of publications of PBMAS on relationship between nutritional factors and bone or fat mass measurements

Objective (Reference)	Data used for analysis	Data analysis	Results
To assess calcium intake and its main dietary sources and seasonal differences (Iuliano-Burns et al. 1999)	Data collected during 1991-1997	Mann-Whitney test for comparisons between elementary schools and post-elementary schools and for seasonal comparisons between summer and winter	• The major source of calcium was fluid milk, contributing 39-50% of total calcium intake. • Girls decreased their calcium intake, especially from milk products' consumption, as they get older. • In contrast, older boys consumed more calcium than younger boys. • Total calcium intake and calcium intake from fluid milk are higher during summer compared with winter in younger girls.
To analyze the relationship between different types of beverage intake and BMC and bone mineral accrual (Whiting et al. 2001)	Data collected for two years spanning the time of peak BMC velocity for each subject	Pearson correlation between bone measurements (BMC, BMC accrual during ±one-year around peak BMC velocity) and different types of beverage intake	• Noncarbonated beverages and low nutrient dense beverage had a stronger inverse correlation with milk intake in both girls and boys. • In girls, low nutrient dense and carbonated beverages were negatively correlated with total BMC. • In girls, low nutrient dense and noncarbonated beverages were negatively correlated with BMC accrual over the two years.
To compare calcium density (adjusted for energy intake) to unadjusted	A cross-section of bone measurements and dietary	Multiple linear regression models to predict TBBMC and lumbar spine BMC with calcium intake	• There was a positive association between unadjusted calcium intake and TBBMC and lumbar

calcium intake as predictors of BMC in children and adolescents (Carter et al. 2001)	intake data during 1993	(adjusted / non-adjusted for EI) as predictor, and height, weight, bone area, maturity age, physical activity and EI as covariates.	spine BMC in males but not females. • When unadjusted calcium was substituted with calcium density, it was not able to make a significant improvement in the model.
To investigate the association between fruit and vegetable intake and TBBMC (Vatanparast et al. 2005)	Data collected during 1991-1997	Hierarchical linear models using random effects models to predict TBBMC with fruit and vegetable intake, height, BMI, physical activity, biologic maturity and calcium intake as predictors	• Fruit and vegetable intake, calcium intake and physical activity were positively and significantly associated with TBBMC in boys but not girls.
To determine the trend in calcium and beverage intake in the grade 9 students at three time points in the same elementary schools (Vatanparast et al. 2006)	Data collected between 1991-1993 and 1995-1997 in PBMAS, and 2003-2004 in FUEL Study	One-way analysis of variance or its nonparametric equivalent the Kruskal-Wallis test to assess the trend over the time	• There was a descending trend in contribution of milk intake and an ascending trend in contribution of fruit juice intake of the total beverage intake in both sexes from 1991 to 2004. • Milk intake and noncarbonated soft drinks were inversely correlated. • Calcium intake was decreased significantly over the time in girls but not in boys.
To assess the effect of physical activity and sugar-sweetened beverages on fat mass development (Mundt et al. 2006)	Data Collected during 1991-1997	Hierarchical linear modeling using random effects models to predict fat mass development with PA, sugar-sweetened beverages and adjusted total energy intake as predictors and fat-free mass and PHV as covariates	• After controlling for maturation, fat-free mass and energy intake, physical activity was negatively associated with fat mass development in boys, but not in girls. • Sugar-sweetened beverages had no significant association with fat mass development in boys or girls.

To investigate the relationship between protein intake and TBBMC, TBBMC net gain since PHV, and TBBMD in early adulthood, considering adequacy of calcium intake during adolescence and adulthood (Vatanparast et al. 2007)	Data collected during 1991-1997 and 2003-2006	Multiple regression models to predict TBBMC or TBBMD in early adulthood and TBBMC net gain, with height, weight, PA; and intakes of calcium, protein, fruit and vegetable as predictors.	• Protein intake is a significant positive predictor of TBBMC, TBBMC net gain since PHV, and TBBMD in all young adult women except for groups whose calcium intake was low in both adolescence and adulthood. • Height, weight, PA, and sex were significant predictors of TBBMC, TBBMC net gain since PHV, and TBBMD.
To estimate calcium requirements of Canadian adolescents in 9-13 y and 14-18y for both sex in accordance with DRIs sex-age groups (Vatanparast et al. 2010)	Bone accrual data during 1991-1997	Calcium requirements=(Calcium needs +Calcium losses)/38% Calcium needs were determined by plotting TBBMC values over time as distance and velocity curves. Calcium loss was based on what DRI used.	• Calcium requirement of Canadian boys and girls were determined to be 1000-1100 mg/d for 9-13y girls and boys, 1000 mg/d for 14-18 y girls and 1200 mg/d for 14-18 y boys.

BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; DRI, daily recommended intake; EI, energy intake; PA, physical activity; PHV, peak height velocity; TB, total body

To my knowledge, none of these studies focused on dietary patterns as an overall diet impact on bone. Instead, most of them evaluated the effect of a single nutrient like calcium and protein, or food groups such as fruit and vegetables, milk and alternatives and beverage consumption on bone. On the other hand, most of these studies have analyzed the data obtained during the 7 years of original study, but not follow-up studies. Therefore, there is no study investigating the effect of adolescent dietary intake on adulthood bone health. Before I conduct my research to address this question (Objective One), I reviewed all previous studies evaluating the association between data-driven or a priori dietary patterns and bone health indicators (bone mineral status, bone biomarkers, osteoporosis, and fracture). The scoping review is presented in Chapter 3.

CHAPTER 3
LITERATURE REVIEW 2

Published paper:

Movassagh EZ, Vatanparast H. **Current evidence on the association of dietary patterns and bone health: a scoping review.** Advances in Nutrition 2017; 8: 1-16*

**format and structure of the original manuscript has been revised to provide a better flow within the thesis and be consistent with the format of previous chapters*

In this chapter, we assessed and summarized current evidence on the association of data-driven and a priori dietary patterns and bone health. Results from a total of 49 studies, published as English full-text articles from 2002 to June 2016, were included in this literature review. Thirty-two of these articles used the data-driven dietary pattern method (Okubo et al., 2006; Kontogianni et al., 2009; Fairweather et al., 2011; McNaughton et al. 2011; Hardcastle et al. 2011; Sugiura et al. 2011; Whittle et al. 2012; Karamati et al. 2012; Karamati et al. 2014; Chen et al. 2015; Shin et al 2015; Franca et al 2016; Langstemo et al. 2010; Langestemo et al 2016; Shin and Joung 2013; Mu et al. 2014; Park et al 2012; Zeng et al 2013; Monma et al. 2010; Langstemo et al. 2011; Samieri et al 2013; Dai et al 2014; Fung and Feskanich 2015; Tucker et al. 2002; Mangano et al. 2015; Pedone et al. 2011; Ward et al 2016; Shin et al. 2013; Monjardino et al. 2015; Wosje et al. 2010; Noh et al. 2011; Hooven et al 2015) and 20 of them utilized *a* priori dietary pattern approach (Kontogianni et al., 2009; Whittle et al. 2012; Dai et al 2014; Hostmark et al 2011; Zagarins et al. 2012; Rivas et al. 2013; Shivappa et al. 2016; Chen et al 2016; Aparicio et al. 2016; de Jonge et al. 2015; Hamidi et al. 2014; Lee et al. 2013; Go et al 2014; Zeng at al. 2014; Feart et al. 2013; Benetou et al. 2013; Haring et al. 2016; Byberg et al. 2016; Monjardino et al. 2012; Seiquer et al. 2008). Three articles assessed both dietary pattern approaches in association with bone (Kontogianni et al., 2009; Whittle et al. 2012; Dai et al 2014). Most of the studies had cross-sectional design (*n*=26) Okubo et al., 2006; Kontogianni et al., 2009; Fairweather et al., 2011; McNaughton et al. 2011; Hardcastle et al. 2011; Sugiura et al. 2011; Whittle et al. 2012; Karamati et al. 2012; Karamati et al. 2014; Chen et al. 2015; Shin et al 2015; Franca et al 2016; Shin and Joung 2013; Mu et al. 2014; Tucker et al. 2002; Mangano et al. 2015; Shin et al. 2013; Hostmark et al 2011; Zagarins et al. 2012; Rivas et al. 2013; Shivappa

et al. 2016; Chen et al 2016; Aparicio et al. 2016; Hamidi et al. 2014; Lee et al. 2013; Go et al 2014) and remaining had case-control (*n*=2) (Zeng et al 2013, Zeng at al. 2014), longitudinal (*n*=20) (Langstemo et al. 2010; Langestemo et al 2016; Park et al 2012; Monma et al. 2010; Langstemo et al. 2011; Samieri et al 2013; Dai et al 2014; Fung and Feskanich 2015; Pedone et al. 2011; Ward et al 2016; Monjardino et al. 2015; Wosje et al. 2010; Noh et al. 2011; Hooven et al 2015; de Jonge et al. 2015; Feart et al. 2013; Benetou et al. 2013; Haring et al. 2016; Byberg et al. 2016; Monjardino et al. 2012) or clinical trial (*n*=1) (Seiquer et al. 2008) design.

3.1. Characteristics of Participants

The smallest sample size was 20, in the Spanish male adolescents clinical trial (Seiquer et al. 2008). Other studies had a larger sample size, numbers varied from 156 (Franca et al 2016) to 188,795 (Benetou et al. 2013) participants. Twenty studies enrolled only females (Okubo et al., 2006; Kontogianni et al., 2009; Fairweather et al., 2011; McNaughton et al. 2011; Hardcastle et al. 2011; Sugiura et al. 2011; Karamati et al. 2012; Karamati et al. 2014; Chen et al. 2015; Franca et al 2016; Shin and Joung 2013; Park et al 2012; Pedone et al. 2011; Noh et al. 2011; Zagarins et al. 2012; Rivas et al. 2013; Shivappa et al. 2016; Aparicio et al. 2016; Go et al 2014; Haring et al. 2016), two studies enrolled only males (Mu et al. 2014, Seiquer et al. 2008) and the remaining recruited both sexes (*n*=27) (Whittle et al. 2012; Shin et al 2015; Langstemo et al. 2010; Langestemo et al 2016; Zeng et al 2013; Monma et al. 2010; Langstemo et al. 2011; Samieri et al 2013; Dai et al 2014; Fung and Feskanich 2015; Tucker et al. 2002; Mangano et al. 2015; Ward et al 2016; Shin et al. 2013; Monjardino et al. 2015; Wosje et al. 2010; Hooven et al 2015; Hostmark et al 2011; Chen et al 2016; de Jonge et al. 2015; Hamidi et al. 2014; Lee et al. 2013; Zeng at al. 2014; Feart et al. 2013; Benetou et al. 2013; Byberg et al. 2016; Monjardino et al. 2012) as participant. The age range of participants varied among studies. Most of the studies recruited participants from all age groups ≥18 years old. Summary of studies in adult and elderly population (aged ≥18 y) are presented in Table 3.1 (data-driven dietary pattern studies) and Table 3.2 (*a* priori dietary patterns studies). Only two studies included children (aged 4 to 11 years) (Wosje et al. 2010; Noh et al. 2011) and five studies included adolescents (aged 12 to 18 years) (Shin et al. 2013; Monjardino et al. 2015; Hooven et al 2015; Monjardino et al. 2012; Seiquer et al. 2008). Summary of the studies conducted in children and adolescents (aged <18 y) are presented in Table 3.3.

Table 3.1. Summary of studies evaluating the association between bone preclinical and clinical outcomes and dietary patterns, derived using *a* posteriori dietary pattern approaches in participants aged ≥18 years

Study, location and design (reference)	Participants Number, gender and age	Bone outcome(s) and method of measurement(s)	Dietary patterns: foods positively associated with them	Results
Factor analysis				
aBMD/BMC				
Japanese Multi-Centered Environmental Toxicant Study, Japan, cross-sectional (Okubo et al. 2006)	291 females, 40-55 y	Distal radius and ulna aBMD and BMC by DXA	1) "Healthy": green and white vegetables, mushrooms, fish and shellfish, fruit, processed fish, seaweed and soy ; 2) "Japanese traditional": rice, miso soup and soy products; 3) "Western": fats and oils, meat, processed meats and seasoning; 4) "Beverage and Meats": coffee, soft drinks, dairy products, sugary foods and meats.	Pattern (1) was directly associated with BMD.
Greek women study, Greece, cross-sectional (Kontogianni et al. 2009)	196 pre- and peri-menopausal females, (48±2)	LSaBMD and TBBMC by DXA	Component (1): dairy, cereals, red meat and olive oil; Component (2): vegetables, fruits and olive oil; Component (3): fish, olive oil; Component (4): poultry and nuts; Component (5): alcohol; Component (6): legume; Component (7): sweet; Component (8): fruit drink; Component (9): coffee	Pattern (3) was directly associated with LSBMD and TBBMC.
Co-twin controlled study, UK, cross-sectional,	4928 post-menopausal females, 56±12 y	FNaBMD, Total hip aBMD, LSaBMD by DXA	1) "Fruit & Vegetables": fruit, Allium and cruciferous vegetables; 2) "High alcohol":	Pattern (3) was inversely associated with FNBMD.

(Fairweather et al. 2011)			beer, wine and allium vegetables; 3) “Traditional English”: fried fish, fried potatoes, legumes, red and processed meats, savory pies and cruciferous vegetables (e.g. cabbage and cauliflower); 4) “Dieting”: low-fat dairy products, low sugar soda; 5) “Low meat”: baked beans, pizza, soy foods	
Twin and Sister Bone Research Program, Australia, cross-sectional (McNaughton et al. 2011)	527 females, 18-68 y	Total hip aBMD, LSaBMD, TBBMC by DXA	Pattern (1) Refined cereals, soft drinks, fried potatoes, sausages and processed meat, vegetable oils; Pattern (2) Vegetables (potatoes, carrot, peas and beans, brassica vegetables, zucchini and squash) red meat, butter and cream; Pattern (3) Leafy vegetables, tomato and tomato products, milk and yogurt (<1% fat), fruit, cheese, eggs, and fish; Pattern (4) Legumes, seafood, seeds and nuts, wine, rice and rice dishes, and other vegetables and vegetable dishes; Pattern (5) Chocolate, confectionary and added sugar, fruit drinks and cordials, dairy milk and yogurt (>1% fat)	Pattern (1) was inversely associated TBBMC; pattern (4) was directly associated with total hip BMD, LSBMD and TBBMC; pattern (5) was inversely associated with LSBMD

The Aberdeen Prospective Osteoporosis Screening Study, Scotland, cross-sectional (Hardcastle et al. 2011)	3236 females 50-59 y	FNaBMD, LSaBMD by DXA	1) “Healthy foods”: fruit & vegetables, rice and pasta, white meat, oily fish and dairy products (excluding milks); 2) “Processed foods”: processed foods with cakes and desserts; 3) “Bread and butter”: bread and fats or oils; 4) “Fish and chips”: fish, fish dishes, potatoes, bread and fats or oils; 5) “Snack food”: confectionary, crisps or nuts and sauces	Patterns (2) & (5) were inversely associated with FNBMD and LSBMD.
Annual health check-up program, Japan, cross-sectional (Sugiura et al. 2011)	293 post-menopausal females, 60±6 y	33% Radial aBMD by DXA	1) “Carotene”: β-carotene, α-carotene, lutein, lycopene and vitamins C and E; 2) “Retinol”: preformed retinol, zeaxanthin, vitamin E, lutein, vitamin C, and β-carotene; 3) “β-cryptoxanthin”: β-cryptoxanthin and vitamin C	Pattern (2) was inversely and pattern (3) was directly associated with radial BMD.
Northern Ireland Young Heart Project, Ireland, cross-sectional (Whittle et al. 2012)	238 females and 251 males, 20-25 y	FNaBMD, FNBMC, LSaBMD, LSBMC by DXA	1) “Healthy”: fruit, vegetables, brown bread, rice and pasta; 2) “Traditional”: white bread, fats and hot drinks; 3) “Social”: alcohol; in men, 4) “Refined”: puddings, crisps, chips, confectionery, chocolate and soft drinks; in women, 4) “Nuts and Meat”: nuts, chocolate, red meat, meat dishes and poultry.	Pattern (4) in men was inversely associated with FNBMC. Pattern (4) in women was directly associated with FNBMD and FNBMC.
Iranian Menopausal Women Study,	160 females 50-85 y	FNBMD, LSaBMD by DXA	Pattern (1): high-fat dairy products, organ meats, red or processed meats and non-refined	The Patterns (1) was inversely associated with LSBMD and

Iran, cross-sectional (Karamati et al. 2012)			cereals; Pattern (2): French fries, mayonnaise, sweets and desserts, and vegetable oils; Pattern (3): hydrogenated fats, pickles, eggs and soft drinks; Pattern (4): vegetables, low-fat dairy products, fruits and fruit juices, legumes and fish; Pattern (5): condiment and potatoes; Pattern (6): snacks, tea and coffee, poultry and nuts	Patterns (2) was inversely associated with FNBMD.
Postmenopausal Iranian women, Iran, cross-sectional (Karamati et al. 2014)	160 females, 50-85 y	LSaBMD and FNaBMD by DXA	Pattern (1): Folate, total fiber, vitamin B_6, potassium, vitamins A, C and K, β-carotene, magnesium, copper and manganese; Pattern (2): vitamin B_2, protein, calcium, phosphorus, zinc, vitamin B_{12} and vitamin D and low vitamin E; Pattern (3): total fat, MUFA, SFA, PUFA and low carbohydrate and vitamin B_1	Pattern (1) was directly associated with LSBMD.
The 2-year prospective study of postmenopausal women, China, cross-sectional (Chen et al. 2015)	282, 212 and 202 females at baseline, year 1 and year 2, respectively 50-65 y at baseline	Hip aBMD (FN, trochanter and Ward's) LSaBMD, TBaBMD by DXA	Pattern (1): rice, cooked wheaten food, fried food and other grains and fruits; Pattern (2): milk and root vegetables	Pattern (1) was inversely associated with hip and LSBMD; Pattern (2) was directly associated with hip BMD.
Healthy Twin Cohort, Korea,	1102 females, (46±12 y), 716 males, (47±13 y)	Whole arm aBMD, whole leg aBMD, whole pelvis aBMD,	1) "Rice and kimchi": white rice, kimchi, garlic and onions, fish and shellfish, legumes and	Pattern (3) was inversely associated with risk of low TBBMD in both sex, and

cross-sectional (Shin et al 2015)		LSaBMD, TBaBMD by DXA	vegetables and mushrooms; 2) "Eggs, meat and flour": oil and seasonings, eggs, processed meats, meat and poultry, noodles and dumplings, and bread and snacks; 3) "Fruit, milk and whole grains": fruits, potatoes, whole grains, dairy foods, vegetables, and mushrooms and nuts; 4) "Fast food and soda": pizza, hamburgers, French fries, soda and coffee and sweet fruit juice	directly associated with whole leg, arm, TBBMDs in females and whole leg, pelvis and LSBMDs in males; pattern (1) was directly associated with whole arm BMD in both sex.
Brazilian postmenopausal women with osteoporosis, Brazil, cross-sectional (Franca et al 2016)	156 females, 45 y ≤ (68±9 y)	LSaBMD, total femur aBMD, FNBMD, TBaBMD by DXA	1) "Healthy": vegetables, fruits and fresh juices, tubers and tuberous roots; 2) "Red meat and refined cereals": refined cereals and their baked products, beef and pork; 3) "Low-fat dairy": low-fat dairy products; 4) "Sweet foods, coffee and tea": sugar, sugary products, coffee and tea; 5) "Western": snacks, pizza, pie, soft drinks, and fruit drinks	Pattern (4) was inversely associated with total femur and TBBMD.
Canadian Multicenter Osteoporosis Study, Canada, longitudinal (Langstemo et al. 2010)	4611 females and 1928 males, 25 y ≤ at baseline	FNaBMD by DXA	1) "Nutrient dense" (prudent): Fruit, vegetables and whole grains; 2) "Energy dense" (Western): Soft drinks, patio chips and French fries, certain meats (hamburgers, hot dog, lunch meat, smoked meat, bacon and sausage), certain desserts (doughnuts, chocolate, ice cream)	Pattern (2) was inversely associated with FNBMD in men aged 50+ y old and postmenopausal women. Pattern (1) was directly associated with FNBMD in men aged 25-49 y old.

Bone biomarkers				
The Aberdeen Prospective Osteoporosis Screening Study, Scotland, cross-sectional (Hardcastle et al. 2011)	3236 females 50-59 y	bone resorption biomarkers: urine fPYD:Cr and fDPD:Cr ratios; bone formation biomarker: serum P1NP	1) "Healthy foods": fruit & vegetables, rice and pasta, white meat, oily fish and dairy products (excluding milks); 2) "Processed foods": processed foods with cakes and desserts; 3) "Bread and butter": bread and fats or oils; 4) "Fish and chips": fish, fish dishes, potatoes, bread and fats or oils; 5) "Snack food": confectionary, crisps or nuts and sauces	Pattern (1) was inversly associated with bone resorption biomarkers.
Canadian Multicenter Osteoporosis Study (CaMos), Canada, longitudinal (Langestemo et al 2016)	754 females, 318 males, (63±11 y)	bone resorption biomarkers: CTX; bone formation biomarker: BAP; PTH; blood samples collected in 5th year of study	1) "Prudent": Fruit, vegetables, whole grains, fish and legumes; 2) "Western": Soft drinks, potato chips and French fries, certain meats (hamburgers, hot dog, lunch meat, smoked meat, bacon and sausage), certain desserts (doughnuts, chocolate, ice cream)	Pattern (1) was inversely associated with CTX in women and PTH in men; pattern (2) was directly associated with BAP and CTX in women.
Osteoporosis				
Korean Health and Nutrition Examination Survey 2008-10, Korea, cross-sectional (Shin and Joung 2013)	3735 postmenopausal females (64±9 y)	Osteoporosis by LS and femur (FN, trochanter, inter-trochanter, ward's and total) aBMD T-score by DXA	1) "Meat, alcohol and sugar"; 2) "Vegetables and soya sauce"; 3) "White rice, kimchi and seaweed"; 4) "Dairy and fruit"	Pattern (4) was inversely associated with and pattern (3) was directly associated with risk of osteoporosis
The college freshmen study,	1319 males, 16-20 y, (18±1 y)	Osteoporosis/osteopenia by SOS T-score	1) "Western": hamburger and fried food, nuts, snack food, cola,	The "Calcium" and "Chinese traditional" were inversely

China, cross-sectional (Mu et al. 2014)		on the right calcaneus by ultrasound	coffee, sugars; 2) "Animal protein": pork, mutton, beef, poultry meat, animal liver; 3) "Calcium": milk and dairy products, beans, and bean products, fresh fruit, egg, fish and shrimp, kelp laver and sea fish; 4) "Chinese traditional": grains, fresh vegetables and fruits, and pork	associated with risk of osteopenia/osteoporosis.
Korean Genome and Epidemiology Study, Korea, longitudinal (Park et al 2012)	1,464 postmenopausal females, 4 y follow-up	Osteoporosis incidence by SOS T-score at the mid-radius and tibia shaft by ultrasound	1) "Traditional": rice, kimchi and vegetables, and fruits; 2) "Dairy": milk, dairy products, and green tea; 3) "Western": sugar, fat noodles, and bread	Pattern (2) was inversely associated with and pattern (1) and pattern (3) were directly associated with risk of osteoporosis
Fractures				
China, matched case-control (Zeng et al 2013)	433 female pairs, 148 male pairs, 55-80 y (71 ± 7 y)	Hip fracture incident within the previous 2 weeks recruited in hospital	1) "Healthy": fruit, vegetables, eggs and fresh water fish; 2) "Prudent": nuts, mushrooms, algae, sea foods and white vegetables; 3) "Traditional": Chinese herbal tea and double-stewed soup, processed meat and fish and animal organ meat; 4) "High-fat": red meat, poultry with skin, animal organ meat and cooking oil	Pattern (1) and pattern (2) were inversely associated with and pattern (4) was directly associated with risk of hip fracture
Population-based prospective	877 females and males, 70+ y at	Frequency of fall-related fracture by	1) "Vegetable": vegetables, sea-weeds, soy products and salt; 2)	Pattern (2) was inversely associated with and pattern (1)

survey, Japan, longitudinal, (Monma et al. 2010)	baseline, followed up for 4 years	insurance claim records	"Meat": meat (chicken, pork, beef), processed meat, sea food; 3) "Traditional Japanese": rice and miso soup, Natto soup (fermented soy product)	was directly associated with risk of fall-related fracture.
Canadian Multicenter Osteoporosis Study (CaMos), Canada, longitudinal (Langstemo et al. 2011)	3539 postmenopausal females (67±8 y) and 1649 males, 50≤ y (64±10 y)	Low-trauma fractures by 10^{th} year of study by self-reported interviews	1) "Nutrient dense" (prudent): Fruit, vegetables and whole grains; 2) "Energy dense" (Western): Soft drinks, potato chips and French fries, certain meats (hamburgers, hot dog, lunch meat, smoked meat, bacon and sausage), certain desserts (doughnuts, chocolate, ice cream)	Pattern (1) was inversely associated with risk of fracture in men and women
Bordeaux sample of Three-City (3C) Study, France, longitudinal (Samieri et al 2013)	934 females, 548 males, 68-95 y	Hip, wrist and vertebrae fracture, self-reported incidence	Pattern (1) "Nutrient dense": all macro- and micronutrients specially manganese, potassium, phosphorous, calcium, iron and vitamin B12 and folate and vitamin C and E, alcohol; Pattern (2): retinol, vitamin B12, folate, iron; Pattern (3)/ "South-Western French": proteins, fats, alcohol, phosphorous, calcium, vitamin D and B12 and retinol	Pattern (1) was inversely associated with risk of wrist and overall fractures. Pattern (3) was inversely associated with risk of hip fracture
Singapore Chinese Healthy Study, China, longitudinal (Dai et al 2014)	35,241 females, 27,913 males, 45-74 y	Hip fracture from nationwide hospital discharge database	1) "Vegetable-fruit-soy": 23 vegetables, 5 soy foods, and 5 fruits; 2) "Meat-dim-sum": 7 meat items, 12 dim sum items (5 meat and 7 "other"), 4 starch items, 3	Pattern (1) was inversely associated with risk of hip fracture.

			combined meat-starch items, and 1 egg item	
Nurses' Health Study and Health Professionals Follow-up Study, USA, longitudinal (Fung and Feskanich 2015)	74,540 menopausal females and 35,451 males, 50< y, 20 y follow-up	Hip fracture, self-reported incidenc in biennial questionnaires	1) "Prudent": fruits, vegetables, whole grains, and poultry and low-fat dairy products; 2) "Western": red and processed meats, sweets and desserts, refined grains and full-fat dairy products.	No significant association
Cluster analysis				
Framingham Osteoporosis Study, USA, cross-sectional (Tucker et al. 2002)	562 females and 345 males, 69-93 y	FNaBMD, Ward's area aBMD and trochanter aBMD by Lunar dual-photon absorptiometry; 33% radius shaft aBMD by Lunar single-photon absorptiometry	1) "Meat, dairy and bread": Meat, poultry and fish, milk and dairy products and bread; 2) "Meat and sweet baked products": Meat, processed meats, sweet baked products; 3) "Sweet baked products": cakes, pies, doughnuts, and cookies; 4) "Alcohol": Liquor, red meat; 5) Candy; 6) "Fruit, vegetables and cereal": Fruit and vegetables and breakfast cereals	Cluster (6) was directly associated with FNBMD, Ward's BMD and trochanter BMD when compared to clusters 2-4 in men. Cluster (5) was inversely associated with FNBMD, Ward's BMD and radius BMD when compared to cluster (6) in men. Cluster (5) was negatively associated with radius BMD when compared to clusters 1,2,4 and 6 in women.
Framingham Offspring Study, The USA, cross-sectional (Mangano et al. 2015)	1534 females and 1206 males, 29-86 y (61±9 y)	FNaBMD, total femur aBMD, trochanter aBMD and LSaBMD by DXA Cluster analysis	1) "Chicken": chicken; 2) "Fish": fish; 3) "Processed food": pizza, French fries, snacks, white grains, and cheese products; 4) "Red meat": red meat; 5) "Low-fat milk": low-fat milk	Clusters (3) and (4) were inversely associated with FNBMD compared to cluster (5).

InCHIANTI Study, Italy, longitudinal (Pedone et al. 2011)	434 females, 65-94 y (75±7 y)	Total and trabecular BMD at 4% and cortical BMD at 38% tibia by pQCT; BMD variation over 6 years	Cluster (1): lower intake of energy (30 kcal/kg IBW) and bone-related nutrients (animal and vegetal protein, calcium, phosphorus, vitamin D, magnesium, folate, PUFA and alcohol); Cluster (2): higher intake of energy (44 kcal/kg IBW) and bone-related nutrients	Cluster (2) was directly associated with cortical BMD and inversely associated with cortical BMD loss over 6 years compared to cluster (1).
Reduced rank regression				
MRC National Survey of Health and Development, England, Scotland, and Wales, longitudinal (Ward et al 2016)	661 females, 602 males, 36 y at baseline	Total and trabecular aBMD at distal radius, total and medullary CSA, cortical aBMD and bone strength (SSI) at radius shaft by pQCT; spine and hip and TBaBMD and area by DXA; RRR with protein, calcium and potassium densities as predictor variable	1) "PrCaK-rich": low-fat milk, low-fat yogurt, fruit and vegetables, whole meal bread, fish and fish dishes, coffee and tea	Pattern (1) was directly associated with size-adjusted BMC (total, spine, and hip) and total and trabecular BMD at distal radius in women.

BAP, bone-specific alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; Cr, creatinine; CSA, cross-sectional area; CTX, serum c-terminal telopeptide; DXA, dual-energy X-ray absorptiometry; FN, femoral neck; fDPD, free deoxypyridinoline; fPYD, free pyridinoline; LS, lumbar spine; P1NP, N-terminal propeptide of type 1 collagen; PQCT, peripheral quantitative computed tomography; PrCaK, protein, calcium, potassium; PTH, parathyroid hormone; RRR, reduced rank regression; SOS, speed of sound; TB, total body

Table 3.2. Summary of studies evaluating the association between bone preclinical and clinical outcomes and dietary patterns derived using the *a* priori-defined dietary pattern approaches in participants aged ≥18 years

Study, location and design (reference)	Participants Number, gender and age	Bone outcome(s) and method of measurement(s)	Dietary pattern score or index	Results
BMD/BMC				
Greek women study, Greece, cross-sectional (Kontogianni et al. 2009)	196 pre- and peri-menopausal females, (48±2 y)	LSaBMD and TBBMC by DXA	MDS (total score 0-55): discrete scores from 0 to 5 assigned to frequency of intake from each of non-refined cereals, potatoes, fruits, vegetables, legumes, fish, red meat and products, poultry, full-fat dairies, olive oil and alcohol based on the recommendations of the Greek ministry of health	No significant association
Oslo Health Study, Norway, cross-sectional (Hostmark et al 2011)	1255 females, 871 males, 30-60y	Distal and ultra-distal forearm, by SXA	OHS index (total score 0.08-2.5): sum of intake frequency categories of two items (range 2-10): 'colas', and 'non-cola soft drinks', divided by the sum of intake frequency categories of 4 items (range 4–23): 'raw vegetables/salads' (fresh or cooked), 'cooked vegetable soup' and 'fruit/berries' and 'fruit juice'	Inversely associated with distal forearm BMD
Northern Ireland Young Heart Project, Ireland, cross-sectional (Whittle et al. 2012)	238 females and 251 males, 20-25 y	FNaBMD, FNBMC, LSaBMD, LSBMC by DXA	MDS (total score of 0-9): fruits, vegetables, nuts, legumes and fish (score 1 vs. 0 for above sex-specific intake median); meat and meat products and dairy (score 0 vs. 1 for above sex-specific intake median); MUFA/SFA (score 1 vs. 0 for above sex-specific intake median); Alcohol	No significant association

			consumption of 10-50 g for men and 5-25g for women (score of 1 vs. 0)	
			DDS (total score of 0-5): counting the number of foods in five food groups including dairy and grains (with a minimum of 15g of solids and 30g of liquids) and meat, fruit and vegetables (with a minimum of 30g of solids and 60g of liquids).	Directly associated with FNBMD in women, but not in men
			NRS (total score): rankings of the 19 nutrient intakes (energy, protein, total fat, MUFA and SFA, alcohol, cholesterol, sodium, carbohydrate, PUFA, fiber, calcium, selenium, vitamins C, B6, B12 and E, folate and b-carotene) from 1 to the number of all subjects was summed and transformed.	No significant association
The UMass Vitamin D Status Study, USA, cross-sectional (Zagarins et al. 2012)	226 females, 18-30 y	TBaBMD and bone mineral apparent density [BMAD=BMC/ (bone area^2/ height)]	RFS (total score range of 0-51): one point for each recommended food item that was consumed at least once a week: vegetables (23 items), fruits (16 items), protein foods (6 items), grains (5 items), Dairy (1 item) (McCullough et al. 2002)	Inversely associated with BMAD
			AHEI (total scores of 2.5-87.5): A proportion between 0 and 10 score: vegetables (0 to 5 serv./d), fruit (0 to 4 servings/d), nuts and soy protein (0 to 1 servings d), ratio of weight of white to red meat (0 to 4), cereal fiber (0 to15g/d), % of energy from *trans* fats (≥4to ≤0.5), PUFA/SFA ratio *(*≤0.1 to ≥1), alcohol (0 or	No significant association

			> 3.5 to 1.5-2.5 serv./d) and alcohol for women (0 or > 2.5 to 0.5-1.5 serv./d) and dichotomous no and yes multivitamin and mineral use (McCullough et al. 2002)	
Southern Spain women study, Spain, cross-sectional (Rivas et al. 2013)	100 premenopausal (34±7 y) 100 postmenopausal (54±6 y) female, 18-65 y	Calcaneus aBMD by DXA	MDS (total score of 0-9): fruits, vegetables, nuts, legumes and fish (score 1 for above sex-specific intake median); meat and meat products and dairy (score 0 for above sex-specific intake median); MUFA/SFA (score 1 for above sex-specific intake median); Alcohol consumption of 5-25g for women (score of 1)	Directly associated with BMD in all subjects
The postmenopausal women, Iran, cross-sectional (Shivappa et al. 2016)	160 postmenopausal females, 50-85 y	FNaBMD and LSaBMD by DXA	DII: sum of z-scores of 25 food parameters intakes in DII compared to world standard database: energy, carbohydrate, protein, total fat, fiber, cholesterol, saturated fat, monounsaturated, fat, polyunsaturated fat, niacin, thiamin, riboflavin, vitamin B12, vitamin B6, iron, magnesium, selenium, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, β-carotene, and caffeine.	Inversely associated with LSBMD
Community-based Chinese adults, China, cross-sectional (Chen et al 2016)	1678 females, 693 males, 40-75y	TBaBMD, FNaBMD, LSaBMD, all hip sites aBMD by DXA	aMed score (total score of 0-9): energy-adjusted intake of whole grains, fruits, vegetables, nuts, legumes and fish (score 1 vs. 0 for above sex-specific intake median); meat and meat products (score 0 vs. 1 for above sex-specific intake	Directly associated with BMD at all sites.

			median); MUFA/SFA (score 1 vs. 0 for above sex-specific intake median); Alcohol consumption of 10-50 g for men and 5-25g for women (score of 1 vs. 0)	
The FLAMENCO project, Spain, cross-sectional (Aparicio et al. 2016)	197 females, 45-60 y	TBaBMD by DXA	MDS (total score 0-55): discrete scores from 0 to 5 assigned to frequency of intake from each of non-refined cereals, potatoes, fruits, vegetables, legumes, fish, red meat and products, poultry, full-fat dairies, olive oil and alcohol based on the recommendations of the Greek ministry of health	No significant association
The Rotterdam Study, Netherlands, longitudinal and cross-sectional (de Jonge et al. 2015)	2932 females and 2211 males, 55≤ y at baseline (median: 67 y and interquartile range 61-73 y)	FNaBMD by DXA, at baseline and 3 subsequent visits	BMD Diet-Score (total score 0-30): based on quartiles of intake of 8 food groups; for "High BMD" components (vegetables, fruits, dairy products, whole grain products, fish and legumes & beans) ascending values for quartiles (1,2,3,4) and for "Low-BMD" components (meat including red, processed and organ meat and confectionary including candy, cakes and cookies) descending values for quartiles (4,3,2,1)	Directly associated with FNBMD
			HDI (total score 0-120): A proportion between 10 and 0 scores should be assigned between optimal intake and lower/upper limit respectively: moderate intake of SFA, mono- and disaccharides, cholesterol, trans fat and sodium; intake for PUSA, protein, total fat, n-6 PUFAs and n-3 PUFAs within recommended levels;	Directly associated with FNBMD, but 3 times weaker than BMD Diet-Score

			adequate intake of fiber and fruit and vegetables	
Biomarkers				
NHANES 1999-2002, USA, cross-sectional (Hamidi et al. 2014)	827 postmenopausal females ≥45 y	Bone formation: serum BAP; bone resorption: urinary N-telopeptide/creatinie	HEI-2005 (0-100): A proportion between 0 and 5 score for total fruit (0 to 1.6 servings/1000kcal), whole fruit (0 to 0.8 servings/1000kcal), total vegetables (0 to 2.2 servings/1000kcal), dark green and orange vegetables and legumes (0 to 0.8 servings/1000kcal), total grain (0 to 85 g/1000kcal), whole grains (0 to 40 g/1000kcal); a proportion between 0 and 10 score for milk (0 to 1.3 servings/1000kcal), meat and beans (0 to 70 g/1000kcal), oils (0 to 12 g/1000kcal), %energy from saturated fat (≥15 to ≤7), %energy from solid fat, alcohol and added sugar (score 0 for ≥50 to score 20 for ≤20), sodium (score 0 for heavy, 5 for moderate and 10 for light use)	No association was found
Osteoporosis				
4th Korean National Health and Nutritional Examination Survey (2007 & 2008), Korea, cross-sectional (Lee et al. 2013)	5,320 females and males, 30-80 y	Osteoporosis history	KDS (total score of 0-60): A proportion between 0 and 10 score for the degree of correspondence with the Korean recommendations for each of six food group intakes including grain dishes, fish and meat dishes, vegetable dishes, fruits, milk, oils and sugars; proportional negative	Inversely associated with risk of osteoporosis

			score for exceeding the recommended intake.	
5th Korean National Health and Nutritional Examination Survey (2010) Korea, cross-sectional (Go et al 2014)	847 postmenopausal females	Osteoporosis and osteopenia based on WHO aBMD T-score criteria	MAR (maximum score 1.0): NAR is the ratio of amount of certain nutrient (energy, protein, vitamin A, vitamin C, Thiamin, riboflavin, niacin, calcium, phosphorus, and iron) intake relative to KDRI and MAR is the average of all NARs.	No association was found
			DDS (total score of 0-5): 1 point for consumption of designated amount of foods from each of five food groups including dairy, grains, meat, fruit and vegetables	Inversely associated with risk of osteoporosis and osteopenia
			Calcium source assessment: average weekly consumption of nine major calcium sources (milk, kimchi, anchovy, bean curd (tofu), radish leaves, yogurt, sea mustard, egg, bean)	Milk, anchovy, and sea mustard were inversely associated with risk of osteoporosis and osteopenia
			Food group intake pattern: consuming foods from all five food groups including Grain, Meat, Dairy, Vegetable, and Fruit; for dairy and grains (minimum of 15g of solids and 30g of liquids) and meat, fruit and vegetables (minimum of 30g of solids and 60g of liquids) was considered.	-
Fractures				

China, case-control (Zeng at al. 2014)	726 pairs of gender- and age-matched; 55-80 y	Hip fracture	HEI-2005: A proportion between 0 and 5 score for total fruit (0 to 1.6 servings/1000kcal), whole fruit (0 to 0.8 servings/1000kcal), total vegetables (0 to 2.2 servings/1000kcal), dark green and orange vegetables and legumes (0 to 0.8 servings/1000kcal), total grain (0 to 85 g/1000kcal), whole grains (0 to 40 g/1000kcal); a proportion between 0 and 10 score for milk (0 to 1.3 servings/1000kcal), meat and beans (0 to 70 g/1000kcal), oils (0 to 12 g/1000kcal), %energy from saturated fat (≥15 to ≤7), %energy from solid fat, alcohol and added sugar (score 0 for ≥50 to score 20 for ≤20), sodium (score 0 for heavy, 5 for moderate and 10 for light use)	Inversely associated with hip fracture risk
Three-City study, France, longitudinal (Feart et al. 2013)	1482 females and males, 67≤ at baseline, 8 y follow-up	Hip, vertebral and wrist fractures, self-reported every biennial interview	MeDi score (total score of 0-9): fruits, vegetables, nuts, legumes and fish (score 1 vs. 0 for above sex-specific intake median); meat and meat products and dairy (score 0 vs. 1 for above sex-specific intake median); MUFA/SFA (score 1 vs. 0 for above sex-specific intake median); Alcohol consumption of 10-20 g for men and 1.4-5.7 g for women (score of 1 vs. 0)	No significant association
European prospective investigation into cancer and nutrition (EPIC) study, 10 European countries,	139,981 females, 48,814 males, 35-70 y at baseline (48.6 y)	Hip fracture incident over 9 years	MDS (total score of 0-9): vegetables, nuts and fruits together, cereals, legumes and fish (score 1 vs. 0 for above sex-specific intake median); meat and meat products and dairy (score 0 vs. 1 for above sex-	Inversely associated with hip fracture risk

longitudinal (Benetou et al. 2013)			specific intake median); (MUFA+PUFA)/SFA (score 1 vs. 0 for above sex-specific intake median); Alcohol consumption of 10-50 g for men and 5-25g for women (score of 1 vs. 0)	
Singapore Chinese Healthy Study, China, longitudinal (Dai et al 2014)	35,241 females, 27,913 males, 45-74 y	Hip fracture from nationwide hospital discharge database	AHEI 2010 (total score of 0-100): A proportion between 0 and 10 score for 10 components including vegetables (0 to ≥5 serving/d), fruit (0 to ≥4 servings/d), whole grains (score 10 for 75 g/d in females and 90 g/d for males), sugar-sweetened drinks and fruit juice (≥1 to 0 servings d), nuts legumes (0 to ≥1 servings d), red/processed meat (≥1.5 to 0 servings/d), EPA+DHA (0 to 250 mg/d), % of energy from PUFA (≤0.1 to ≥1), sodium (highest decile to lowest decile), alcohol (≥2.5 to 0.5-1.5 drinks/d for females; ≥3.5 to 0.5-2 drinks/d for males)	Inversely associated with hip fracture risk
			AHEI (total scores of 2.5-87.5): A proportion between 0 and 10 score: vegetables (0 to ≥5 serving/d), fruit (0 to ≥4 serving/d), nuts and soy protein (0 to ≥1 serving/d), ratio of weight of white to red meat (0 to ≥4), cereal fiber (0 to ≥15g/d), PUFA/SFA ratio (0 to ≥1), alcohol for men (0 or > 3.5 to 1.5-2.5 serv./d) and alcohol for women (0 or > 2.5 to 0.5-1.5 serv./d), long-term multivitamin regular use (≥5 y score 7.5, otherwise score 2.5)	Inversely associated with hip fracture risk

	DQI-I: 1) variety (total 0-20 scores): ≥1 serving/d from each food group (meat/poultry/fish/eggs, dairy/beans, grains, fruits, vegetables); within group variety for protein source (≥0.5 serving from any 3 of meat, poultry, fish, eggs, dairy, beans); 2) adequacy (total 0-40 scores; score 5, 3, 1, 0 for ≥100%, 50 to <100%, 0 to <50% and 0% RNI or AI for each item, respectively): vegetables (RNI: ≥2-5 serving/d), fruit (RNI: ≥1-4 serving/d), grains (RNI: ≥3-11 serving/d), fiber (RNI: 15-30 g/d), protein (RNI: ≥10% of energy), iron (AI: 15 mg/d for men and 20 mg for women), calcium (AI: 800 mg/d), vitamin C (AI: 100 mg/d); 3) Moderation (total 0-30 score; score 6, 3 and 0 for light, moderate and heavy use of each item, respectively): total fat, saturated fat, cholesterol, sodium, Empty calorie foods (oils, alcohol, starch); 4) overall balance (total 0-10 score): % energy from macronutrient (highest score for carbohydrate %55-65: protein %10-15: fat %15-25) and fatty acid ratio (highest score for PUFA/SFA or MUFA/SFA: 1-1.5)	Inversely associated with hip fracture risk
	aMed (total score of 0-9): whole grains, vegetables, fruits, legumes, nuts, fish and MUFA/SFA (score 1 vs. 0 for above sex-specific intake median); red and processed meats (score 0 vs. 1 for above sex-specific intake median); Alcohol consumption of	Inversely associated with hip fracture risk

			15-25 g for men and 5-15g for women (score of 1 vs. 0)	
Women's Health Initiative observational study, USA, longitudinal (Haring et al. 2016)	90,014 postmenopausal females, 50 to 79 y at (63±7) baseline, 16-21 y follow-up	Total and hip fracture	aMED score (total score of 0-9): whole grains, vegetables, fruits, legumes, nuts, fish and MUFA/SFA (score 1 vs. 0 for above sex-specific intake median); red and processed meats (score 0 vs. 1 for above sex-specific intake median); Alcohol consumption of 15-25 g for men and 5-15g for women (score of 1 vs. 0)	Inversely associated with hip fracture risk
			HEI-2010 (total score of 0-100) A proportion between 0 and 5 score for total fruit (0 to ≥0.8 cup/1000kcal), whole fruit (0 to ≥0.4 cup/1000kcal), total vegetables (0 to ≥1.1cup/1000kcal), greens and beans (0 to ≥0.2 cup/1000kcal), total protein foods (0 to ≥2.5 oz/1000kcal), sea food and plant proteins (0 to ≥0.8 oz/1000kcal); a proportion between 0 and 10 score for whole grains (0 to ≥1.5 oz/1000kcal), low-fat dairy (0 to ≥1.3 cup/1000kcal), (PUFAs + MUFAs) /SFAs ratio (<1.2 to ≥ 2.5), refined grains (≥4.3 to <1.8 oz/1000kcal), sodium (≥2.0 to <1.1 g/1000kcal), empty calories form solid, alcohol and added sugar (≥50% to ≤19% of total kcal, maximum 20 score)	No significant association
			AHEI 2010 (total score of 0-110): A proportion between 0 and 10 score for 11 components including vegetables (0 to ≥5 serving/d), fruit (0 to ≥4 servings/d), whole	No significant association

			grains (score 10 for 75 g/d in females and 90 g/d for males), sugar-sweetened drinks and fruit juice (≥1 to 0 servings d), nuts and legumes (0 to ≥1 servings d), red/processed meat (≥1.5 to 0 servings/d), EPA+DHA (0 to 250 mg/d), % of energy from PUFA (≤0.1 to ≥1), % of energy from *trans* fats (≥4to ≤0.5), sodium (highest decile to lowest decile), alcohol (≥2.5 to 0.5-1.5 drinks/d for females; ≥3.5 to 0.5-2 drinks/d for males)	
			DASH: scores 1 to 5 for each item based on the assignment to the quintiles of intake: higher scores for higher intake of fruit, vegetables, nuts and legumes, low-fat dairy products and whole grains; higher scores for lower intake of sodium, red and processed meat and sweetened beverages	No significant association
Swedish men and women cohort, longitudinal (Byberg et al. 2016)	33403 females, 37903 males, 60 y	Hip fracture by national patient register between 1998 to 2012	Modified MED (total score of 0-8): high intake of fruits and vegetables, legumes and nuts, whole grains, fermented dairy products, fish, and olive/rapeseed oil, moderate intake of alcohol, and low intake of red and processed meat	Inversely associated with hip fracture risk

AHEI, alternative healthy eating index; aMed/aMED, alternate Mediterranean diet; BAP, bone-specific alkaline phosphatase; BMAD, bone mineral apparent density; BMC, bone mineral content; BMD, bone mineral density; DASH, dietary approach to stop hypertension; DDS, dietary diversity score; DHA, docosahexaenoic acid; DQI-I, dietary quality index-international; DII, dietary inflammatory index; DPD, deoxypyridinoline; DXA, dual-energy X-ray absorptiometry; EPA, eicosapentaenoic acid; FN, femoral neck; HDI, healthy diet indicator; KDS, Korean diet score; KRDI, Korean dietary reference intake; KIDMED, kids Mediterranean diet score; LS, lumbar spine; MAR, mean nutrient adequacy ratio; MDS, Mediterranean diet score; MeDi, Mediterranean diet; MUFA, monounsaturated fatty acid; NAR, nutrient adequacy ratio; NRS, nutritional risk score; OHS, Oslo health study; PUFA, polyunsaturated fatty acid; RFS, recommended food score; RNI, recommended nutrient intake; SFA, saturated fatty acid; SXA, Single-energy X-ray absorptiometry; TB, total bod

Table 3.3. Summary of studies evaluating the association between bone preclinical and clinical outcomes and dietary patterns derived using *a* posteriori or *a* priori-defined dietary pattern approaches in participants <18 years of age

Study, location and design (reference)	Participants Number, gender and age	Bone outcome(s) and method of measurement(s)	Dietary patterns: foods positively associated with them	Results
Factor analysis				
Korean adolescents study, Korea, cross-sectional (Shin et al. 2013)	196 female and male, 12-15 y	FNaBMD, LSaBMD by DXA	1) "Traditional Korean": rice and other grains, fish and shellfish, legumes, soy sauce and soybean pastes, seaweed, and Kimchi; 2) "Fast food": carbonated drinks, French fries, hamburgers, biscuits and cookies, pizza, and fried chicken; 3) "Milk and cereals": milk and yogurt, cereal, and bread; 4) "Snacks": Sauce and seasonings, chocolate, ice cream, gum and candy, seeds and nuts, fruits and vegetables, sandwiches, and simple sugars	Pattern (3) was directly associated with LSBMD
Cluster analysis				
EPITeen Cohort, Portugal, longitudinal and cross-sectional (Monjardino et al. 2015)	543 females and 464 males; 13 y at baseline, follow-up to 17 y	Distal radius aBMD by DXA	1) "Healthier": fish vegetables, added fats, fruits, and pasta/potatoes/rice; 2) "Dairy products": dairy food and intermediate intake of other foods; 3) "Fast foods and sweets": sweets, fast foods and soft drinks and coffee and tea; 4) "Lower intake": low intake of red meat, fish, fruits, pasta/potatoes/rice, dairy products, cereals and added fat.	No association observed between BMD at age 13 y and any of clusters. Cluster (4) was inversely associated with BMD increase from age 13 to 17 years compared to other clusters.
Reduced rank regression				

Young children study, USA, longitudinal (Wosje et al. 2010)	325 female and male, 3.8-7.8 y	TBBMC (except the skull) and Fat mass by DXA; RRR with TBBMC and fat mass as predictor variable	Pattern (1): non-whole grains, cheese, processed meats, eggs, fried potatoes, discretionary fats, and artificially sweetened beverages; Pattern (2): Dark-green vegetables, deep-yellow vegetables and processed meats	Pattern (1) directly associated with fat mass and bone mass independent of energy intake; Pattern (2) inversely associated with fat mass and positively with bone mass independent of energy intake
School girls study, Korea, longitudinal (Noh et al. 2011)	198 females, 9-11 y at baseline	Calcaneus aBMD, BMC by DXA; RRR with change in BMI, body fat, aBMD, and BMC during 22 months as predictor variables	1) "Fruit, Nuts, Milk Beverage, Egg, Grain": fruit, nuts and seeds, milk and dairy products, other beverages, eggs, fruit juice, eastern grains; 2) "Egg and Rice": egg and rice	Pattern (1) was directly associated with an increase in BMI, fat mass and BMC. Pattern (2) was directly associated with increase in BMI and fat mass and inversely associated with increase in BMC
Young adults born to mothers in the Western Australian Pregnancy Cohort, Australia, longitudinal	500 females and 524 males; 14 y at baseline	TBaBMD, TBBMC and bone area by DXA at age 20 y; RRR (PLS procedure) with protein, calcium and potassium as predictor variable	Pattern 1 (positively associated with protein, calcium and potassium): low-fat dairy, whole grains, and vegetables; Pattern 2 (positively associated with protein but negatively associated with calcium and potassium intake): meat, poultry, fish and eggs	Pattern 1 at age 14 y was directly associated with BMD and BMC at age 20 y

(Hooven et al 2015)				
Dietary indexes				
The EPITeen Cohort, Portugal, longitudinal and cross-sectional (Monjardino et al. 2012)	673 females and 591 males, 13y at baseline and 17y at follow-up	Distal radius aBMD by DXA	KIDMED: +1 each of fruit and vegetables (at least 1 serving/d), nuts and fish (at least 2-3 serving/wk.), pulses (more than 1 serving/wk.), pasta and rice (at least 5 times/wk.), daily consumption of grain and cereals, dairy products (3 serving/d), olive oil for culinary use; -1 for frequent intake of sweets, candy, commercially baked goods, pastries, and fast foods.	Directly associated with BMD at age 13 y in males, but not with its annual variation or BMD at age 17y
			DASH: scores 1 to 5 for each item based on the assignment to the quintiles of intake: higher scores for higher intake of fruit, vegetables, nuts, legumes, dairy products and whole grains; higher scores for lower intake of Na, red and processed meat and sweetened beverages	No significant association
			OHS index: sum of intake frequency categories of three items (range 3–27): 'colas', 'ice tea soft drinks' and 'other soft drinks', divided by the sum of intake frequency categories of three items (range 3–27): 'vegetables' (fresh or cooked), 'vegetable soup' and 'fruit' (fresh, canned or juice)	No significant association
Spain, Clinical trial (Seiquer et al. 2008)	Intervention group: 20 males aged	Bone resorption biomarkers: urinary DPD; bone formation biomarker: serum BAP;	Mediterranean-based dietary pattern: 28-day intervention with a including meat and eggs 1.5 serving/d, fish 0.5 serving/d, dairy products 3 serving/d, pasta, rice and cereals	Directly associated with calcium absorption and retention and urinary

	11-14 (13±1 y) No control group	calcium absorption and retention at baseline and after 28d intervention	4.5 serving/d, legumes 0.4 serving/d, vegetables 1.7 serving/d, fruits 2 serving/d and olive oil as the main fat.	DPD; no significant association with BAP

BAP, bone-specific alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; DASH, dietary approach to stop hypertension; DPD, deoxypyridinoline; DXA, dual-energy X-ray absorptiometry; FN, femoral neck; KIDMED, kids Mediterranean diet score; LS, lumbar spine; OHS, Oslo health study; TB, total body

3.2. Bone Outcome Measurements

Our search retrieved four classes of bone outcomes: bone mineral status, bone formation and resorption biomarkers, osteoporosis and fracture incidence.

3.2.1. Bone Mineral Status

The aBMD was the most common bone outcome measured in the majority of studies. The most frequent measurement sites were lumber spine (Kontogianni et al., 2009; Fairweather et al., 2011; McNaughton et al. 2011; Hardcastle et al. 2011; Sugiura et al. 2011; Whittle et al. 2012; Karamati et al. 2012; Karamati et al. 2014; Chen et al. 2015; Shin et al 2015; Franca et al 2016; Mangano et al. 2015; Ward et al 2016; Shin et al. 2013; Shivappa et al. 2016; Chen et al 2016), femoral neck (Fairweather et al., 2011; Hardcastle et al. 2011; Whittle et al. 2012; Karamati et al. 2012; Karamati et al. 2014; Chen et al. 2015; Langstemo et al. 2010; Tucker et al. 2002; Mangano et al. 2015; Shin et al. 2013; Shivappa et al. 2016; Chen et al 2016; de Jonge et al. 2015) and total body (Chen et al. 2015; Shin et al 2015; Ward et al 2016; Hooven et al 2015; Zagarins et al. 2012; Chen et al 2016; Aparicio et al. 2016). Some studies also measured BMD at trochanter (Chen et al. 2015; Tucker et al. 2002; Mangano et al. 2015; Chen et al 2016) , ward's area (Chen et al. 2015; Tucker et al. 2002; Chen et al 2016), total hip (Fairweather et al., 2011; McNaughton et al. 2011; Ward et al 2016), distal radius (Okubo et al., 2006; Monjardino et al. 2015; Ward et al 2016; Monjardino et al. 2012), radius shaft (Sugiura et al. 2011; Tucker et al. 2002; Ward et al 2016), total femur (Franca et al 2016; Mangano et al. 2015), calcaneus (Noh et al. 2011; Rivas et al. 2013), intertrochanteric area (Chen et al 2016), distal ulna (Okubo et al., 2006), whole arm, whole leg and whole pelvis (Shin et al 2015), distal and ultra-distal forearm (Hostmark et al 2011), and distal tibia and tibia shaft (Pedone et al. 2011). Bone mineral content (BMC) was also measured in some studies (n=7) (Okubo et al., 2006; Kontogianni et al., 2009; McNaughton et al. 2011; Whittle et al. 2012; Wosje et al. 2010; Noh et al. 2011; Hooven et al 2015).

Bone mineral status was primarily assessed by dual-energy X-ray absorptiometry (Okubo et al., 2006; Kontogianni et al., 2009; Fairweather et al., 2011; McNaughton et al. 2011; Hardcastle et al. 2011; Sugiura et al. 2011; Whittle et al. 2012; Karamati et al. 2012; Karamati et al. 2014; Chen et al. 2015; Shin et al 2015; Franca et al 2016; Langstemo et al. 2010; Mangano et al. 2015; Shin et al. 2013; Monjardino et al. 2015; Wosje et al. 2010; Noh et al. 2011; Hooven et al 2015; Zagarins et al. 2012; Rivas et al. 2013; Shivappa et al. 2016; Chen et al 2016; Aparicio

et al. 2016; de Jonge et al. 2015; Monjardino et al. 2012). Two studies used peripheral quantitative computed tomography to measure trabecular and cortical BMD at distal tibia and tibia shaft (Pedone et al. 2011) and distal radius and radius shaft (Ward et al 2016). Only limited number of studies used other methods such as lunar dual-photon and single-photon absorptiometry (*n*=1) (Tucker et al. 2002) and single energy X-ray absorptiometry (*n*=1) (Hostmark et al 2011).

3.2.2. Bone Biomarkers

Four studies evaluated dietary patterns in association with bone resorption and formation biomarkers. The bone resorption biomarkers measured in these studies includes urinary deoxypyridinoline (Seiquer et al. 2008), free pyridinoline: creatinine and free deoxypyridinoline: creatinine ratios (Hardcastle et al. 2011), serum C-terminal telopeptide (Langestemo et al 2016) and urinary N-telopeptide: creatinine ratio (Hamidi et al. 2014). The bone formation biomarker included serum N-terminal propeptide of type 1 collagen (Hardcastle et al. 2011) and bone-specific alkaline phosphatase (Langestemo et al 2016; Hamidi et al. 2014; Seiquer et al. 2008).

3.2.3. Osteoporosis and Osteopenia Incidence

Five studies examined the association between dietary patterns and osteoporosis in cross-sectional (Shin and Joung 2013; Mu et al. 2014; Lee et al. 2013; Go et al 2014) and longitudinal (Park et al 2012) studies. Osteoporosis was defined as T-score less than -2.5 standard deviations for BMD measured by dual-energy X-ray absorptiometry in lower spine and/or hip (Shin and Joung 2013; Lee et al. 2013; Go et al 2014) or speed of sound measured by ultrasound method in upper or lower limbs (Mu et al. 2014; Park et al 2012).

3.2.4. Fracture Incidence

Eleven studies evaluated dietary patterns in association with fracture incidence in case-control (*n*=2) (Zeng et al 2013; Zeng at al. 2014) and longitudinal studies (*n*=8) (Monma et al. 2010; Langstemo et al. 2011; Samieri et al 2013; Dai et al 2014; Fung and Feskanich 2015; Feart et al. 2013; Benetou et al. 2013; Haring et al. 2016; Byberg et al. 2016). The follow-up period varied from 4 (Monma et al. 2010) to 21 years (Haring et al. 2016). Hip fracture incidence was the main outcome measured in the studies (Zeng et al 2013; Samieri et al 2013; Dai et al 2014; Fung and Feskanich 2015; Zeng at al. 2014; Feart et al. 2013; Benetou et al. 2013; Haring et al. 2016; Byberg et al. 2016). Some studies measured the overall incidence of fall-related or low-trauma fractures (Monma et al. 2010; Langstemo et al. 2011; Haring et al. 2016) and some also

included wrist and vertebrae fractures in the analysis (Samieri et al 2013; Feart et al. 2013). Fracture incidences were measured using insurance claim records (Monma et al. 2010), hospital database (Zeng et al 2013; Dai et al 2014; Zeng at al. 2014), or self-reported interview (Langstemo et al. 2011; Samieri et al 2013; Fung and Feskanich 2015; Feart et al. 2013; Haring et al. 2016).

3.3. Data-Driven Dietary Patterns

In most studies after data collection, all food items were collapsed into a reasonable number of food groups ranging from 13 to 46, before analysis. Only two studies used all food items from a 165-item FFQ (Dai et al 2014) and a131-item FFQ (Fairweather et al., 2011) in dietary pattern analysis without aggregating them into a smaller number. Similarity measurements to indicate food group intake were daily intake as weight (g) (energy adjusted or non-adjusted), frequency (servings per day or week or month), percent of total energy intake contribution or percent of total protein intake contribution in different studies. Four studies included bone-related nutrients or antioxidants intake as an alternative for food items in dietary pattern analysis (Sugiura et al. 2011; Karamati et al. 2014; Samieri et al 2013; Pedone et al. 2011). Food items (or nutrients) with higher loading factors in the derived dietary patterns represented the dietary pattern components (Tables 3.1 and Table 3.3).

3.3.1. Data-driven Dietary Patterns in Adults and Elderly Populations

Factor analysis in adults and elderly populations. The most common data-driven dietary pattern approach used in the studies was factor analysis via PCA procedure (*n*=19, Table 3.1) (Okubo et al., 2006; Kontogianni et al., 2009; Fairweather et al., 2011; McNaughton et al. 2011; Hardcastle et al. 2011; Sugiura et al. 2011; Whittle et al. 2012; Karamati et al. 2012; Karamati et al. 2014; Chen et al. 2015; Shin et al 2015; Franca et al 2016; Langstemo et al. 2010; Langestemo et al 2016; Shin and Joung 2013; Mu et al. 2014; Park et al 2012; Zeng et al 2013; Monma et al. 2010; Langstemo et al. 2011; Samieri et al 2013; Dai et al 2014; Fung and Feskanich 2015). Two to nine dietary patterns were derived from different study populations using this method. Naming of the retained dietary patterns was arbitrary and the common names of some reproducible dietary patterns were “healthy” (*n*=7) (also called as “Nutrient dense” or “prudent”) (Okubo et al., 2006; Hardcastle et al. 2011; Whittle et al. 2012; Franca et al 2016; Langstemo et al. 2010; Langestemo et al 2016; Zeng et al 2013; Langstemo et al. 2011; Fung and

Feskanich 2015), "traditional" (*n*=7) (Okubo et al., 2006; Fairweather et al., 2011; Whittle et al. 2012; Mu et al. 2014; Park et al 2012; Zeng et al 2013; Monma et al. 2010), and "Western" (*n*=6) (also called "Energy-dense") (Okubo et al., 2006; Franca et al 2016; Langstemo et al. 2010; Langestemo et al 2016; Mu et al. 2014; Park et al 2012; Langstemo et al. 2011; Fung and Feskanich 2015) dietary patterns. These dietary patterns were repeatedly extracted along with a variety of other dietary patterns in the studies (Table 3.1).

The "Healthy" dietary pattern, mainly characterized by high intake of fruit, vegetables, whole grains, poultry and fish, nuts and legumes and low-fat dairy products was directly associated with BMD (Okubo et al., 2006, Langstemo et al. 2010) and lower risk of fracture (Langstemo et al. 2011, Zeng et al 2013), and inversely associated with bone resorption biomarkers (Hardcastle et al. 2011; Langestemo et al 2016). The Dietary patterns representing some aspects of "Healthy" dietary pattern such as "high fish and olive oil" (Kontogianni et al., 2009), "Legumes, seafood, seeds and nuts, wine, rice, and vegetables" (McNaughton et al. 2011) "Nuts and Meats" (Whittle et al. 2012), "milk and root vegetables" (Chen et al. 2015) and "Fruit, milk and whole grains" (Shin et al 2015) were found to have beneficial impact on BMD and/or BMC. The "Vegetable-fruit-soy" (Dai et al 2014) dietary pattern was associated with lower risk of fracture. The "Dairy" (Park et al 2012), "Dairy and fruit" (Shin and Joung 2013) and "Calcium" (Mu et al. 2014) were associated with lower risk of osteoporosis. Conversely, the "Vegetable" dietary pattern, reflecting high intake of vegetables, seaweeds, soy products and salt, was associated with increased risk of fracture in Japanese elderly men and women (Monma et al. 2010).

The "traditional" dietary pattern characteristics varied among different study populations including Irish (Whittle et al. 2012), Korean (Park et al 2012), English (Fairweather et al., 2011), Japanese (Okubo et al., 2006; Monma et al. 2010) and Chinese (Mu et al. 2014; Zeng et al 2013) traditional dietary patterns. The "English traditional" dietary pattern characterized by high intake of fried fish, fried potatoes, legumes, red and processed meats, savory pies and cruciferous vegetables (e.g. cabbage and cauliflower) was inversely associated with BMD (Fairweather et al., 2011), however "Chinese traditional" dietary pattern which was rich in grains, fresh vegetables, fresh fruits, and pork was inversely associated with risk of osteopenia/osteoporosis (Mu et al. 2014).

The “Western” dietary pattern, mainly characterized by high intake of soft drinks, fried foods, meat and processed products, sweets and desserts and refined grains, was inversely associated with BMD (Langstemo et al. 2010) and directly associated with bone resorption and formation biomarkers (Langestemo et al 2016) and risk of osteoporosis (Park et al 2012).

The Dietary patterns representing some aspects of unhealthy diet such as “processed food” (Hardcastle et al. 2011), “snack food” (Hardcastle et al. 2011), “refined” (Whittle et al. 2012) and “sweet foods, coffee, and tea” (Franca et al 2016) were also associated with lower BMD and/or BMC. As well, dietary patterns that have not been labeled by the investigator but was reflecting frequent intake of “refined cereals, soft drinks, fried potatoes, sausages and processed meat, vegetable oils” (McNaughton et al. 2011); “chocolate, confectionary and added sugar, fruit drinks and cordials, dairy milk and yogurt (>1% fat)” (McNaughton et al. 2011); “high-fat dairy products, organ meats, red or processed meats and non-refined cereals” (Karamati et al. 2012); or “French fries, mayonnaise, sweets and desserts, and vegetable oils” (Karamati et al. 2012) were negatively related to BMD and/or BMC. The “High-fat” dietary pattern was associated with higher risk of fracture (Zeng et al 2013). Conversely, the “Meat” dietary pattern characterized by high intake of chicken, pork, beef, processed meat, and seafood was associated with lower risk of fracture in Japanese elderly men and women (Monma et al. 2010).

Investigating the association between bone outcomes and the dietary patterns that mainly contained rice has yielded mixed results (Chen et al. 2015; Shin et al 2015; Shin and Joung 2013). The “Rice and kimchi” dietary pattern (Shin et al 2015) was positively and the “rice, cooked wheaten food, fried food and other grains and fruits” dietary pattern (Chen et al. 2015) was negatively associated with BMD and/or BMC in two different studies. The “White rice, kimchi, and seaweed” dietary pattern (Shin and Joung 2013) was associated with higher osteoporosis risk.

Three studies derived nutrient dietary patterns using factor analysis and examined their relationship with bone outcomes (Sugiura et al. 2011; Karamati et al. 2014; Samieri et al 2013). Results showed that the “Retinol” pattern determined by high intake of “preformed retinol, zeaxanthin, vitamin E, lutein, vitamin C, and β-carotene” antioxidants was negatively associated with BMD (Sugiura et al. 2011). In contrast, the “β-cryptoxanthin” pattern rich in “β-cryptoxanthin and vitamin C” (Sugiura et al. 2011) and the dietary pattern high in “folate, total fiber, vitamin B6, potassium, vitamins A, C and K, β-carotene, magnesium, copper and

manganese" (Karamati et al. 2014) were positively associated with BMD. The "Nutrient dense" dietary pattern high in "all macro- and micronutrients specially manganese, potassium, phosphorous, calcium, iron, vitamins B-12, folate, C and E, and alcohol" and the "South-Western French" dietary pattern reflecting high "proteins, fats, alcohol, phosphorous, calcium, vitamin D, B-12 and retinol" were associated with lower risk of fractures (Samieri et al 2013). The "Nutrient dense" dietary pattern was associated with high intake of fruit and vegetables, meats, fish, cheese, milk, charcuteries, cereals, rice, pasta and potatoes and the "South-Western French" dietary pattern was associated with high intake of cheese, milk, and charcuteries (Samieri et al 2013).

Cluster analysis in adults and elderly populations. The cluster analysis has been employed less frequently than factor analysis. In the studies that conducted cluster analysis (n=3) to derive dietary patterns (Tucker et al. 2002; Mangano et al. 2015; Pedone et al. 2011), participants were classified into two to six dietary pattern clusters; then bone outcomes were compared across the clusters (Table 3.1). Results showed that participants in "Processed food" and "Red meat" clusters compared to those in "Low-fat milk" cluster (Mangano et al. 2015); and participants in "Candy" cluster compared to those in "Meat, dairy and bread", "Meat and sweet baked products", "Fruit, vegetables, and cereal", and "Alcohol" clusters (Tucker et al. 2002) had lower BMD. In contrast, participants in "Fruit, vegetables, and cereal" cluster had greater BMD compared to those in "Meat and sweet baked products", "Sweet baked products" or "Alcohol" (Tucker et al. 2002). In the study of extracting dietary patterns from energy and bone-related nutrients (protein, calcium, phosphorus, vitamin D, magnesium, folate, PUFA and alcohol), participants in the cluster with higher intake of energy (44 kcal/kg ideal body weight) and other nutrients compared to the cluster with lower intake of energy (30 kcal/kg ideal body weight) and other nutrients had greater cortical BMD (Pedone et al. 2011).

Reduced-rank regression in adults and elderly populations. The RRR method derives dietary patterns in association with intermediate response variables. The number of retained dietary patterns could have been as many as the number of response variables. Only one study conducted RRR to derive dietary patterns in older adults using bone-related nutrients (protein, calcium, and potassium) as response variables (Ward et al 2016). Results showed that "protein, calcium, and potassium rich" dietary pattern was positively associated with BMC and BMD (Ward et al 2016).

Overall, the most reproducible dietary patterns in the studies of adult and elderly population included in this review were “healthy”, “Western” and “traditional” dietary patterns. Though, “traditional” dietary pattern was reflecting different dietary characteristics across study populations from different countries. The “healthy” dietary pattern and those reflecting some aspects of healthy diet were associated directly (Okubo et al., 2006; Kontogianni et al., 2009; McNaughton et al. 2011; Hardcastle et al. 2011; Whittle et al. 2012; Chen et al. 2015; Shin et al 2015; Langstemo et al. 2010; Langestemo et al 2016; Shin and Joung 2013; Mu et al. 2014; Park et al 2012; Zeng et al 2013; Langstemo et al. 2011; Dai et al 2014; Tucker et al. 2002; Ward et al 2016) and the “Western” dietary pattern and those featuring some aspects of unhealthy diet were associated inversely with bone health (McNaughton et al. 2011; Hardcastle et al. 2011; Whittle et al. 2012; Karamati et al. 2012; Franca et al 2016; Langstemo et al. 2010; Langestemo et al 2016; Park et al 2012; Zeng et al 2013; Tucker et al. 2002; Mangano et al. 2015). Other dietary patterns reported mixed results.

3.3.2. Data-driven Dietary Patterns in Children and Adolescents

Factor analysis in children and adolescents. Of a total number of studies conducted data-driven approaches in children and adolescents (*n*=5), only one study in Korean adolescents used factor analysis to derive dietary patterns. A positive association was found between “Milk and cereals” dietary pattern and lumbar spine BMD. However, there was no relationship between “Traditional Korean”, “Fast food” and “Snacks” dietary patterns and BMD (Shin et al. 2013).

Cluster analysis in children and adolescents. In the only study employed cluster analysis to derive dietary patterns, participants were classified into “Healthier”, “Dairy products”, “Fast foods and sweets”, and “lower intake” clusters (Monjardino et al. 2015). Results showed that the participants in “Lower intake” cluster (low intake of red meat, fish, fruits, pasta/potatoes/rice, dairy products, cereals and added fat) compared to their peers in “Healthier”, “Dairy products”, and ”Fast foods and sweets” clusters had smaller increase in BMD from age 13 to 17 years (Monjardino et al. 2015).

Reduced-rank regression in children and adolescents. Two studies used bone and body composition variables (Wosje et al. 2010; Noh et al. 2011) and one study used bone-related nutrients intake as intermediate response variables (Hooven et al 2015). Two dietary patterns were derived using total body BMC and fat mass as response variables in children aged 4 to 8 years. The dietary pattern high in dark-green and deep-yellow vegetables and processed meats

was positively associated with bone mass and negatively associated with fat mass (Wosje et al. 2010). However, the dietary pattern characterized by high intake of non-whole grains, cheese, processed meats, eggs, fried potatoes, discretionary fats, and artificially sweetened beverages were positively associated both bone mass and fat mass (Wosje et al. 2010). In another study, change in BMI, body fat, BMD, and BMC over 22 months were used as outcome variables in the analysis. The "Fruit, Nuts, Milk Beverage, Egg, Grain" dietary pattern was positively associated with an increase in BMI, fat mass, and BMC; (Noh et al. 2011) while the "Egg and rice" pattern was positively associated with an increase in BMI and fat mass and negatively associated with increase BMC (Noh et al. 2011).

Two dietary patterns derived using protein, calcium, and potassium as intermediate response variables in the prospective study of adolescents (Hooven et al 2015). Findings suggested that higher adherence to "protein, calcium, and potassium" dietary pattern at age 14, was related to higher BMD at age 20 y (Hooven et al 2015).

Overall, in children and adolescents, the limited number of studies employing data-driven dietary pattern approach yielded mixed results. Dietary patterns representing some aspects of a healthy diet including "Milk and cereals" (Shin et al. 2013), "Fruit, Nuts, Milk Beverage, Egg, Grain" (Noh et al. 2011) and "protein, calcium, and potassium" (Hooven et al 2015) were positively associated with BMD. Mixed dietary patterns including "dark-green and deep-yellow vegetables and processed meats" and "non-whole grains, cheese, processed meats, eggs, fried potatoes, discretionary fats, and artificially sweetened beverages" were also positively associated with bone mass in children (Wosje et al. 2010). However, dietary patterns featuring some aspects of Western diet such as "Fast foods" (Shin et al. 2013), "Snacks" (Shin et al. 2013), "Fast food and snacks" (Monjardino et al. 2015) and "meat, poultry, fish and egg" (Hooven et al 2015) were not associated with BMD in children and adolescents. In contrast, "Lower intake" (Monjardino et al. 2015) and "egg and rice" (Noh et al. 2011) dietary patterns were associated negatively with BMD in children and adolescents.

3.4. The *a* Priori Dietary Patterns

Adherence to *a* priori dietary indices in association with bone outcomes was also examined using a variety of dietary indices and scoring methods. The dietary indices used for scoring dietary intake of study populations were "Mediterranean diet score" (Kontogianni et al.,

2009; Whittle et al. 2012; Rivas et al. 2013; Shivappa et al. 2016; Aparicio et al. 2016; Zeng at al. 2014; Feart et al. 2013; Benetou et al. 2013; Haring et al. 2016; Byberg et al. 2016; Monjardino et al. 2012; Seiquer et al. 2008), "alternate healthy eating index" (AHEI) (Dai et al 2014; Zagarins et al. 2012; Zeng at al. 2014; Haring et al. 2016), HEI (Hamidi et al. 2014; Zeng at al. 2014; Haring et al. 2016), "diet quality index-international" (Zeng at al. 2014), "dietary diversity score" (Whittle et al. 2012; Go et al 2014), "food group intake pattern" (Go et al 2014), "Korean dietary score" (Lee et al. 2013), DASH (Monjardino et al. 2012, Haring et al. 2016), "recommended food score" (Zagarins et al. 2012), "Oslo health study index" (Hostmark et al 2011; Monjardino et al. 2012), "nutritional risk score" (Whittle et al. 2012), "mean nutrient adequacy ratio" (Go et al 2014),"healthy diet indicator" (de Jonge et al. 2015), "dietary inflammatory index" (Shivappa et al. 2016), and "BMD-diet score" (de Jonge et al. 2015). (Table 3.2 and Table 3.3)

3.4.1. The a Priori Dietary Patterns in Adults and Elderly Populations

Ten studies investigated the adherence to Mediterranean diet in relation to bone outcomes (Kontogianni et al., 2009; Whittle et al. 2012; Rivas et al. 2013; Chen et al 2016; Aparicio et al. 2016; Zeng at al. 2014; Feart et al. 2013; Benetou et al. 2013; Haring et al. 2016; Byberg et al. 2016). Findings indicated that the higher Mediterranean diet scores the higher BMD (Rivas et al. 2013, Chen et al 2016), and the lower risk of fracture (Zeng at al. 2014; Benetou et al. 2013; Haring et al. 2016; Byberg et al. 2016) were in the study populations.

The HEI was evaluated in association with bone outcomes in three studies (Zeng at al. 2014; Haring et al. 2016; Hamidi et al. 2014). The HEI was associated with decreased risk of hip fracture in one study (Zeng at al. 2014). Four studies examined adherence to AHEI (Dai et al 2014, Zagarins et al. 2012, Zeng at al. 2014; Haring et al. 2016) in association with bone outcomes. Two studies showed that AHEI was associated with decreased risk of hip fracture (Dai et al 2014; Zeng at al. 2014).

The "dietary quality index-international", which is assessing variety, adequacy, moderation and overall balance of diet, was associated with decreased risk of hip fracture (Zeng at al. 2014). The "dietary diversity score" that measures the diversity of intake from five food groups was directly associated with BMD (Whittle et al. 2012) and inversely associated with risk of osteoporosis and osteopenia (Go et al 2014). Adherence to the "Food group intake pattern", assessing the diversity of intake from five food groups, was not related to osteoporosis and

osteopenia risk in Korean population (Go et al 2014). Participants with higher "Korean diet score", assessing the correspondence with the Korean recommendations for six food group intakes, were likely to have a lower risk of osteoporosis (Lee et al. 2013). Adherence to DASH dietary pattern was not associated with hip fracture risk (Haring et al. 2016).

The "recommended food score", constructed on the basis of recommended intakes of 51 food items was negatively associated with BMD (Zagarins et al. 2012). The adherence to "Oslo health study index", which is the ratio of soft drinks to fruit and vegetable intake, had a negative relationship with BMD in one study (Hostmark et al 2011).

Some studies investigated the association between bone outcomes and dietary indices that were primarily scoring the energy and nutrient intakes instead of food intakes. These dietary indices included "nutritional risk score" (Whittle et al. 2012), "mean nutrient adequacy ratio" (Go et al 2014), "healthy diet indicator" (de Jonge et al. 2015), and "dietary inflammatory index" (Shivappa et al. 2016). Investigators found no association between the "nutritional risk score" and BMD or BMC (Whittle et al. 2012) and between "mean nutrient adequacy ratio" and osteoporosis and osteopenia risk (Go et al 2014). The "healthy diet indicator", primarily measuring the adherence to recommended intakes of macronutrients, sodium, fiber and fruit, and vegetables, was positively associated with BMD (de Jonge et al. 2015). Participants with higher scores for "dietary inflammatory index" were likely to have lower BMD (Shivappa et al. 2016).

BMD diet score was developed to reflect the beneficial diet for BMD in the Rotterdam Study in Netherlands (de Jonge et al. 2015). Scoring method was based on ascending values for quartiles for "High BMD" components (vegetables, fruits, dairy products, whole grain products, fish and legumes & beans) and descending values for quartiles of "Low-BMD" components (red meat, processed and organ meat and confectionary). Adherence to BMD diet score was positively associated with BMD (de Jonge et al. 2015).

Overall, in adult and elderly populations, findings revealed a beneficial impact of higher adherence to Mediterranean diet in 6 of 10 studies (Rivas et al. 2013; Chen et al 2016; Zeng at al. 2014; Benetou et al. 2013; Haring et al. 2016; Byberg et al. 2016), HEI or AHEI in 3 of 7 studies (Dai et al 2014; Hostmark et al 201; Zeng at al. 2014), "dietary diversity score" in 2 of 2 studies (Whittle et al. 2012; Go et al 2014) and "diet quality index-international" (Zeng at al. 2014), "BMD-diet score" (de Jonge et al. 2015), "healthy diet indicator" (de Jonge et al. 2015) and "Korean diet score" (Lee et al. 2013) in the sole studies evaluating their effects on bone health. A

negative impact of higher adherence to "Oslo health study index" (Hostmark et al 2011), "dietary inflammatory index" (Shivappa et al. 2016) and "recommended food score" (Zagarins et al. 2012) on bone outcomes was reported in the studies evaluating their impact. No association was detected between bone outcomes and higher scores for DASH (Haring et al. 2016), "food group intake score" (Go et al 2014), "nutritional risk score" (Whittle et al. 2012) and "mean nutrient adequacy ratio" (Go et al 2014) in individual studies.

3.4.2. The a Priori Dietary Patterns in Children and Adolescents

Only two studies in adolescents evaluated a priori dietary patterns in association with bone outcomes. Adherence to a modified Mediterranean diet score for children was associated with higher distal radius BMD in male adolescents at age 13 y (Monjardino et al. 2012). In a clinical trial, Mediterranean-based dietary intake modification over 28 days increased urinary bone resorption biomarker and improved calcium absorption and retention compared to baseline measurements (Seiquer et al. 2008). The adherence to "Oslo health study index" and DASH dietary patterns were not associated with BMD in adolescents (Monjardino et al. 2012).

3.5. Conclusion

Studies based on dietary pattern approaches, which take into account contributions from various aspects of diet, have been increasing during the last decades. Findings from these studies not only could complement those from studies of single nutrient and food on bone health but also can be more beneficial with regards to knowledge translation and recommendations for practice. The data-driven dietary pattern approach has the advantage of assessing real dietary patterns of populations, although subjectivity and low reproducibility are the limitations of this method. The *a* priori dietary index is more reproducible, however; the association with bone outcomes might be indistinct or weakened because of some components of the dietary index that are not causally associated with bone. Most of the dietary indices evaluated in the studies have been developed aiming to improve overall health. In this respect, a bone-specific dietary index would be desirable. Recently "BMD-diet score" has been built and examined in association with bone in a single study. Due to the limitations of BMD, studies should consider using other robust measures of bone strength when evaluating the dietary patterns in association with bone health. To further advance this newly developed dietary index in different populations and age groups; more research is required. In both *a* priori and data-driven dietary pattern studies, a dietary pattern

which emphasized intake of fruit, vegetables, whole grains, poultry and fish, nuts and legumes and low-fat dairy products and deemphasized intake of soft drinks, fried foods, meat and processed products, sweets and desserts and refined grains has been implicated as being beneficial for bone health. These findings warrant further prospective studies and clinical trials specifically designed to evaluate the impact of dietary patterns, using standardized approaches, on robust measures of bone quality.

In assessing the impact of early life dietary intake on later life bone quality and health, it is not clear whether dietary patterns established during adolescence were continued throughout the entire follow-up period until adulthood or not. Therefore, it is important to assess tracking and change in dietary patterns from adolescence to adulthood (Objective Two). Before conducting our research to address this question, we reviewed the current findings from previous studies which investigated the stability of dietary patterns over time. Chapter 4 presents the scoping review we conducted to summarize these results.

CHAPTER 4
LITERATURE REVIEW 3

Movassagh E, Vatanparast H. **Current evidence on how dietary patterns evolve over the lifespan: a scoping review.**

Early modification in eating habits and behaviors during adolescence might promote health, and decrease the risk of developing certain health conditions later in life (Bennet et al, 2015). It is important to investigate how dietary patterns are formed and maintained throughout the lifespan. To address this question, I reviewed the literature to assess current evidence on how dietary patterns change or are maintained from childhood to adulthood. I retrieved fourteen longitudinal studies published between 2005 to 2016 as English full text articles, evaluating the change in data-driven dietary patterns over time, by age (Mikkila et al. 2005; Weismayer et al 2006; Mishra et al. 2006; Borland et al. 2008; Northstone et al. 2009; Asghari et al. 2012; Dekker et al. 2013; Harrington et al. 2014; Jankovic et al. 2014; Ambrosini et al. 2014; Batis et al. 2014; Johns et al. 2014; Lioret et al. 2015; Schneider et al. 2016). Table 4.1. summarizes the information from fourteen studies evaluating the change in data-driven dietary patterns.

4.1. Characteristics of Participants

Sample sizes in these cohort studies ranged from 94 participants in the Southampton women's survey to 9253 participants in the China Health and Nutrition Survey (Batis et al. 2014). Age of participants at baseline at the youngest was 2 years old and at the oldest was 85 years old. Most of the studies in children and adolescents followed participants over a short period ranging from 3 years (Lioret et al. 2015, Scheneider et al. 2016) to 6 years (Northstone et al. 2008, Ambrosini et al. 2014). Only one study followed participants over a longer period; in the study by Milkkila et al. (2005) participants aged 3 to 18 years were followed for 21 years. Remaining studies (n=9) were assessing change in dietary patterns in adults (older than 18 years old) (Weismayer et al 2006; Mishra et al. 2006; Borland et al. 2008; Asghari et al. 2012; Harrington et al. 2014; Jankovic et al. 2014; Batis et al. 2014; Johns et al. 2014; Dekker et al. 2014). The follow-up length in these studies ranged from 2 years (Borland et al. 2008) to 18 years (Batis et al. 2014).

Table 4.1 Summary of studies evaluating change in data-driven dietary patterns over time

Study (Reference)	Participants' age at baseline (n)	Dietary patterns	Analysis	Results
Children and Adolescents				
• **Factor analysis**				
Cardiovascular Risk in Young Finns Study (Mikkila et al. 2005)	Aged 3–18 years (n=1768 at t0) (n=1200 at t6) (n=1037 at t21)	DPs at each time point 1) Traditional Finnish; 2) Health-conscious	Change through t0, t6, and t21 - Spearman correlation - Chi-square test, dependent distribution between quintiles between time points - Separate analysis for children (3-12 y) and adolescents (15-18 y)	Traditional Finnish - $r_{(t0\ to\ t21)}$ =0.32 - % remained in $Q5_{(t0\ to\ t21)}$ = in children 28%, in adolescents 41% - Dependent distributions for each pair of t0 and t6 or t21 Health-conscious - $r_{(t0\ to\ t21)}$ =0.38 - % remained in $Q5_{(t0\ to\ t21)}$ = in children 29%, in adolescents 38% - Dependent distributions for each pair of t0 and t6 or t21, except in children between t0 and t6
Avon Longitudinal Study of Pregnancy and Childhood (Northstone & Emmet 2008)	Aged 3 years (n=6177)	DPs at each time point 1) Processed; 2) Traditional; 3) Health conscious (at t6 modified version); 4) snack at t0	Change through t0, t1, t4 and t6 -Spearman correlation -Weighted kappa for partial agreement between quintile -Paired t-tests	Processed - $r_{(between\ each\ pair\ of\ t)} = 0.46_{(t0\ to\ t6)}$ to $0.65_{(t4\ to\ t6)}$ - Weighted $k_{(between\ each\ pair\ of\ t)} = 0.30_{(t0\ to\ t6)}$ to $0.47_{(t4\ to\ t6)}$ - Significant increase in DP scores over time Traditional - $r_{(between\ each\ pair\ of\ t)} = 0.35_{(t0\ to\ t6)}$ to $0.61_{(t1\ to\ t4)}$ - Weighted $k_{(between\ each\ pair\ of\ t)}$

				= 0.25 $_{(t1 \text{ to } t6)}$ to 0.44$_{(t1 \text{ to } t4)}$ Health conscious - r $_{(\text{between each pair of t})}$ = 0.41$_{(t0 \text{ to } t6)}$ to 0.69$_{(t1 \text{ to } t4)}$ - Weighted k $_{(\text{between each pair of t})}$ = 0.34 $_{(t1 \text{ to } t6)}$ to 0.47$_{(t1 \text{ to } t4)}$
EDEN mother–child cohort (Lioret et al. 2015)	Aged 2 years (n=989, 53% boys)	DPs at each time point 1)Processed and fast foods; 2) Guidelines (at age 5: Protein-rich and diversified); 3) baby food (at age 2)	Change through t0, t1, and t3 -Spearman correlation	Processed and fast foods - r $_{(\text{between each pair of t})}$ = 0.13$_{(t1 \text{ to } t3)}$ to 0.40$_{(t0 \text{ to } t1)}$ Guidelines - r $_{(\text{between each pair of t})}$ = 0.16$_{(t1 \text{ to } t3)}$ to 0.53$_{(t0 \text{ to } t1)}$
Reduced-rank regression				
The Avon Longitudinal Study of Parents and Children (Ambrosini et al. 2014)	Aged 7 years (n=7078, 50% boys)	DPs at each time point (energy, fat and fiber intakes as intermediate factors) 1)Adiposity	Change through t0, t3 and t6 -GEE for tracking coefficient (applied scores at t3 and t6 were calculated using loading at t0 and converted to z-scores) -%remained in the same quartiles	Adiposity - Tracking $_{(\text{for all time points})}$ = 0.48 boys and 0.38 girls - % remained in Q1$_{(t0 \text{ to } t6)}$ = 41% in boys, 43% in girls, - % remained in Q4$_{(t0 \text{ to } t6)}$ = 45% in boys, 32% in girls
Latent class analysis				
1993 Pelotas (Brazil) birth cohort (Schneider et al. 2016)	Age 15 years (n=3,823, 48% boys)	DPs at each time point 1) Varied; 2) Traditional; 3) Dieting; 4) Processed meats at t0; 4) Fish, fast food, and alcohol at t3	Change through t0 and t3 -Transition of individuals between classes $_{(t0, t3)}$	- %remained in the Varied class: 33% boys, 30.6% girls - %remained in the Traditional class: 30% boys, 33.5% girls

				- %remained in the Dieting class: 33.5% boys, 38.5% girls - The most frequent change was from the Processed Meats to the Dieting = 38.1%
Adults **Factor analysis**				
The Swedish Mammography Cohort (Weismayer et al. 2006)	Aged 49-70 years (four subsamples of 1000 women)	DPs at each time point 1) Healthy; 2) Western; 3) Alcohol	Change through t0 to t4, t5, t6, or t7 - Spearman correlation with t0 - Internal stability test: by assessing changes in the covariance matrix between t0 and follow-up.	Healthy - $r_{(\text{between each pair of t0 and follow-ups})} = 0.50_{(t0 \text{ to } t7)}$ to $0.59_{(t0 \text{ to } t4)}$ Western - $r_{(\text{between each pair of t0 and follow-ups})} = 0.39_{(t0 \text{ to } t7)}$ to $0.47_{(t0 \text{ to } t4)}$ Alcohol - $r_{(\text{between each pair of t0 and follow-ups})} = 0.46_{(t0 \text{ to } t7)}$ to $0.54_{(t0 \text{ to } t4)}$ - At t4 and t5 3 internally stable patterns; at t6 and t7 western and at t7 alcohol pattern were internally unstable
1946 British Birth Cohort (Mishra et al. 2006)	Aged 36 years (n=1265)	for women:1) fruit, vegetable and dairy; 2) ethnic foods and alcohol; 3) meat, potatoes, and sweets for men:1) ethnic foods and alcohol; 2) mixed	Change through t0, t7, and t17 -Applied scores for t0and t7 based on DPs at t17) -random effects models (change in scores by age) -Weighted kappa for partial agreement between tertiles	Change in DP scores (from t0 to t7 and t17): increase in all DP scores in men and women; decrease in meat, potatoes and sweets scores in women Fruit, vegetable, and dairy: - weighted k (between each pair of t): $0.36_{(t0 \text{ to } t17)}$ to $0.41_{(t0 \text{ to } t7)}$

					Ethnic foods and alcohol: - weighted k (between each pair of t): $0.28_{(t0 \text{ to } t17)}$ to $0.36_{(t7 \text{ to } t17)}$ Meat, potatoes, and sweets - weighted k (between each pair of t): $0.14_{(t0 \text{ to } t7/t17)}$ to $0.20_{(t7 \text{ to } t17)}$ Ethnic foods and alcohol - weighted k (between each pair of t): $0.38_{(t0 \text{ to } t7)}$ to $0.41_{(t07 \text{ to } t7)}$ Mixed - weighted k (between each pair of t): $0.38_{(t0 \text{ to } t17)}$ to $0.44_{(t7 \text{ to } t17)}$
	Southampton Women's Survey (Borland et al.2008)	Aged 20-34 y (n=94 women)	DPs at each time point 1) Prudent; 2) High energy	Change from t0 to t2 -Spearman's rank correlation -Bland-Altman plots for change in DP scores	Prudent - $r_{(\text{from t0 to t2})} = 0.81$ - Increase in DP score (0.13 SD) High-energy - $r_{(\text{from t0 to t2})} = 0.64$ - no change in DP score
	Tehran lipid glucose study (Asghari et al. 2012)	Aged 20-50 years (n=132, 46% men)	DPs at each time point 1)Iranian traditional; 2) Western; 3) combined (at t8)	change through t0 to t1.2 (14 mon) and t8 -Intra class correlation -Weighted kappa for agreement between quintiles	Iranian traditional - $ICC_{(t1.4 \text{ to } t8)}$ = non-significant - Weighted $k_{(t1.4 \text{ to } t8)}$ = non-significant Western - $ICC_{(t1.4 \text{ to } t8)} = 0.49$ - Weighted $k_{(t1.4 \text{ to } t8)} = 0.20$

The China Health and Nutrition Survey (Batis et al. 2014)	Aged 18-65 years (n=9,253, 47.8% men)	DPs at each time point 1) traditional southern; 2) modern high-wheat	Change through t0, t2, t6, t9, t13, t15 and t18 Applied scores based on factor loading in t9. -Pearson correlation for each pair of years -GEE for tracking coefficient (t9 against all other years)	Traditional southern - r $_{\text{(between each pair of t)}}$ = 0.67$_{\text{(t13/t15 to t18)}}$ to 0.81$_{\text{(t2 to t6)}}$ - Tracking $_{\text{(for all time points)}}$ = 0.71 Modern high-wheat - r $_{\text{(between each pair of t)}}$ = 0.46$_{\text{(t0 to t18)}}$ to 0.63$_{\text{(t0 to t2)}}$ - Tracking $_{\text{(for all time points)}}$ = 0.55 - More increase in DP score over time compared to DP1
Reduced-rank regression				
Zutphen Elderly Study (Jankovic et al. 2014)	Aged 64-85 years (n=467 men)	DPs at each time six cardiovascular risk factors as intermediate factors 1)Low in cereal fiber; 2) alcohol; 3) inconsistent	Change from t0 to t5 -Pearson correlation coefficient	Low in cereal fiber - r $_{\text{(t0 to t5)}}$ = 0.47 Alcohol - r $_{\text{(t0 to t5)}}$ =0.34 Inconsistent - r $_{\text{(t0 to t5)}}$ = non-significant
Swedish obese subjects (SOS) study (Johns et al. 2014)	Aged 46-53 years (n=2037, 29% men)	DPs at each time Energy, saturated fats, and fiber as intermediate factors 1)energy dense, high saturated fat, low fiber density	Change through registration, t0, 0.5, 1, 2, 3, 4, 6, 8, and 10-years -Applied DP score based on factor loading of DP in $t_{registration}$ - GEE for tracking coefficient (t9 against all other years)	Energy dense, high saturated fat, low fiber density - Tracking $_{\text{(for all time points from registration to t10)}}$ = 0.40 for women and 0.38 for men
Cluster analysis				

Doetinchem Cohort Study (Dekker at al. 2013)	aged 46 years (n=6113 at t0) (n=4916 at t5) (n=4520 at t10) (50% males)	DPs at each survey 1)low fiber bread 2) high fiber bread	Change through t0, t5, and t10 - reproducibility for food groups in clusters by comparing the contribution of foods to total energy intake in two clusters -Transition of individuals between clusters $_{(t0,\ t10)}$	- Good reproducibility - % remained in the same cluster $_{(t0,\ t5\ and\ t10)}$= 41.8%
Latent class analysis				
Cork and Kerry Diabetes and Heart Disease Study (Irish) (Harrington et al. 2014)	Aged 50-69 years (n=303)	DPs at each time 1) Western; 2) Healthy; 3) Low-energy	Change from t0 to t10 -Transition of individuals between classes $_{(t0,\ t10)}$	- %remained in the Western Class: 39% - %remained in the Healthy Class: 74% - %remained in the Low-energy class: 44%

t0, baseline; tn, n years after baseline. DP, dietary pattern

4.2. Data-Driven Dietary Patterns

Different dietary pattern approaches were used in these studies to derive dietary patterns at baseline. Eight studies conducted factor analysis using PCA approach (Mikkila et al. 2005; Weismayer et al 2006; Mishra et al. 2006; Borland et al. 2008; Northstone et al. 2009; Asghari et al. 2012; Batis et al. 2014; Lioret et al. 2015), three studies used RRR (Jankovic et al. 2014; Ambrosini et al. 2014; Johns et al. 2014) and three studies used cluster analysis (Dekker et al. 2013) or latent class analysis (LCA) (Harrington et al. 2014; Schneider et al. 2016).

A variety of dietary patterns were derived among study populations in different studies. The "healthy", "traditional" and "Western" dietary patterns were the most common dietary patterns derived using data-driven approaches. The "healthy" dietary pattern (Weismayer et al. 2006; Harrington et al. 2014), also labeled as "health-conscious" (Mikkila et al. 2005; Northstone & Emmet 2008), "prudent" (Borland et al.2008), "guidelines" (Lioret et al. 2015) or "fruit, vegetable and dairy" (Mishra et al. 2006), was mainly characterized by higher intakes of fruit and vegetables, dairy products, poultry and fish, nuts and legumes. The "traditional" dietary pattern characteristics varied among different study populations including Finnish (Mikkila et al. 2005), British (Northstone & Emmet 2008), Brazilian (Schneider et al. 2016), Iranian (Asghari et al. 2012) and Southern Chinese (Batis et al. 2014). The "Western" dietary pattern (Weismayer et al. 2006; Asghari et al. 2012; Harrington et al. 2014), was mainly characterized by high intake of red meat and processed products, soft drinks, fried foods, sweets and desserts and refined grains. Some studies derived dietary patterns representing some characteristics of "Western" dietary pattern and labeled them as "processed" (Northstone & Emmet 2008), "processed and fast food" (Lioret et al. 2015), "adiposity" (Ambrosini et al. 2014), "meat, potatoes, sweets" (Mishra et al. 2006), "high-energy" (Borland et al.2008), "modern high-wheat" (Batis et al. 2014), "low in cereal fiber" (Jankovic et al. 2014), "energy dense, high saturated fat, low fiber density" (Johns et al. 2014), "low fiber bread" (Dekker at al. 2013) and " processed meats" (Schneider et al. 2016). Table 4.2. represents the data-driven dietary patterns and associated food groups in fourteen studies evaluating the change in dietary patterns over time.

Table 4.2. Data-driven dietary patterns and associated food groups in studies evaluating change in dietary patterns over time

Reference	Dietary pattern	Food groups associated with dietary patterns
Children and Adolescents		
• **Factor analysis**		
Cardiovascular Risk in Young Finns Study (Mikkila et al. 2005)	Traditional Finnish	Positive loadings for rye, potatoes, milk, butter, sausages and coffee in each study year; negative loadings for fruit and berries, and other dairy products in 1980 and 2001
	Health- conscious	Positive loadings rye (but less than in pattern 1), vegetables, legumes and nuts, tea, cheese and other dairy products at all study points, and with alcoholic beverages in 2001; negative loadings for milk
the Avon Longitudinal Study of Pregnancy and Childhood (Northstone & Emmet 2008)	Processed	Positive loadings for foods with high fat and sugar content, and processed and convenience foods
	Traditional	Positive loadings for meat, poultry, potato and vegetable consumption at all time-points.
EDEN mother–child cohort (Lioret et al. 2015)	Processed and fast foods	Positive loadings for French fries, processed meat, carbonated soft drinks, chocolate, chips, cookies, pizza, fruit juice, meat, dairy desserts, and ice cream
	Guidelines	Positive loadings for cooked vegetables, rice, fresh fruit, raw vegetables, low-fat fish, potatoes, ham, stewed fruit, and meat.
• **Reduced-rank regression**		
The Avon Longitudinal Study of Parents and Children (ALSPAC) UK (Ambrosini et al. 2014)	high energy, high fat, low fiber	Positive loadings for confectionery, crisps, low fiber bread, cakes, and biscuits; negative loadings for fruit, vegetables and high fiber breakfast cereals
• **Latent class analysis**		

1993 Pelotas (Brazil) birth cohort (Schneider et al. 2016)	Varied	Positive loadings for all food groups (except alcohol, coffee, and tea at age 15)
	Traditional	Positive loadings for rice, pasta, potatoes, beans, bread, vegetables, coffee, and tea
	Dieting	Negative loadings for all food groups
	Processed meats	Positive loadings for sausages and processed meats
	Fish, fast food and alcohol	Positive loadings for fish, fast food, and alcohol
Adults		
• **Factor analysis**		
the Swedish Mammography Cohort (Weismayer et al. 2006)	Healthy	Positive loadings for fruits, tomatoes, vegetables, cereal, and fish
	Western	Positive loadings for meat, processed meat, fried potatoes, soft drinks, and sweets
	Alcohol	Positive loadings for beer, wine, and liquor consumption as well as snack consumption
1946 British Birth Cohort (Mishra et al. 2006)	fruit, vegetable, and dairy (in women)	Positive loadings for low-fat/reduced-fat dairy products, fruit, some vegetables and wholemeal bread; negative loadings for meat, meat products and white bread.
	Ethnic foods and alcohol (in women)	Positive loadings for Indian and Chinese meals, rice and pasta, oily fish and shellfish, olive oil, some vegetables and alcoholic beverages
	Meat, potatoes and sweets (in women)	Positive loadings for red meat, bacon, and ham, all types of potato and potato dishes, sweet pies, cakes, puddings and desserts; negative loadings for pasta and skimmed milk

	Ethnic foods and alcohol (in men)	Positive loadings for Indian and Chinese meals, rice and pasta, shellfish, olives, some vegetables and legumes, and alcoholic beverages; negative loadings for meat pies, fried chips and animal fats
	Mixed (in men)	Positive loadings for fruits and vegetables, low-fat/low-calorie yogurt and soya milk and a range of sweet foods including cakes, sweet biscuits, sweet pies, puddings, desserts, confectionery and ice cream
Southampton Women's Survey (Borland et al. 2008)	Prudent	Positive loadings for vegetables, fruit, wholemeal bread, rice/pasta, yoghurt and breakfast cereals frequently; negative loadings for white bread, roast potatoes/chips, red/processed meat, full-fat milk, full-fat spread, crisps, confectionery, sugar, tea/coffee and Yorkshire puddings/pancakes, tinned vegetables, cakes and biscuits and soft drinks
	High energy	Positive loadings for all foods including Puddings, cakes/biscuits, potatoes/chips, vegetables, fruit, red/processed meat, fish, eggs, oils and full-fat spreads
Tehran lipid glucose study (Asghari et al. 2012)	Iranian traditional,	Positive loadings for vegetables, fruits, potatoes, dairy products, legumes and nuts, whole grains, tea and coffee, olive, eggs, red meat and organ meat
	Western	Positive loadings for carbonated drinks, salty snacks and salty vegetables, sugars, sweets, desserts, vegetable oil, animal fat, fast foods, poultry, fish and other seafood and refined grains
	combined	Positive loadings for potatoes, tea and coffee, vegetable oils, eggs, legumes and nuts, sugars, whole grains and salty snacks
The China Health and Nutrition Survey (Batis et al. 2014)	traditional southern	Positive loadings for intake of rice, fresh leafy vegetables, low-fat red meat, low- and high-fat pork, organ meats, poultry and fish/seafood; negative loadings for wheat flour, corn/coarse grains

	modern high-wheat	Positive loadings for wheat buns/bread, cakes/cookies/pastries, deep-fried wheat, nuts/seeds, starchy roots/tubers products, fruits, eggs/eggs products, soy milk and animal-based milk
• **Reduced-rank regression**		
Zutphen Elderly Study (Jankovic et al. 2014)	Low in cereal fiber	Positive loadings for fruit juices and sugar-sweetened beverages; negative loadings for high-fiber bread and cereals
	Alcohol	Positive loadings for beer wine and strong alcoholic beverages
	Inconsistent	No consistent food groups at baseline and follow-up
Swedish obese subjects (SOS) study (Johns et al. 2014)	Energy-dense, high saturated fat, low fiber density	Positive loadings for chocolate, low fiber bread, full fat spread, cheese, fast food, cake, white bread, candy, fatty meat; negative loadings for fruit, vegetables, low-fat yogurt
• **Cluster analysis**		
Doetinchem Cohort Study (Dekker et al. 2013)	High-fiber bread	Positive loadings for high-fiber bread, cakes and cookies, and cheese
	high-fiber bread	Positive loadings for low-fiber bread, sugar-sweetened beverages, other alcoholic drinks, and fries
• **Latent class analysis**		
Cork and Kerry Diabetes and Heart Disease Study (Irish) (Harrington et al. 2014)	Western	Positive loadings for cereals, bread and potatoes, dairy products, meats (red and processed meats) and foods from the top shelf of the food pyramid, especially sweet snacks
	Healthy	Positive loadings for fruits and vegetables, higher intakes of low-fat dairy products
	Low-energy	Negative loadings for red meat, sweet snacks, and overall energy

4.3. Methodology Approaches and Findings

Adherence of each participant to a specific dietary pattern, derived using factor analysis or RRR, could be determined by calculating their dietary pattern score. Higher scores show higher adherence to a specific dietary pattern. To assess change in dietary pattern scores, several studies used applied dietary pattern scores (Mishra et al 2006, Borland et al 2009, Ambrosini et al 2014, Jankovic et al 2014, Batis et al 2014, Johns et al 2014), meaning that, scores were calculated at each time point based on the factor loadings of the food groups in each dietary pattern derived at reference time point. Remaining studies derived dietary patterns and calculated scores at each time point (Mikkila et al. 2005; Weismayer et al 2006; Northstone et al. 2009; Asghari et al. 2012; Lioret et al. 2015). Different statistical analysis methods were used in the studies to evaluate the change in dietary patterns over time. Determining the tracking coefficient over the entire period (Batis et al, 2014; Johns et al. 2014; Ambrosini et al 2014), correlation coefficient for dietary pattern scores between two time points (Mikkila et al. 2005, Northstone et al. 2008; Jancovic et al. 2014) or assessing the proportion of participants who remained in the same quartile/quintile of dietary pattern scores were the common methods.

Studies that used cluster analysis or LCA are not score-based. Therefore, investigators should conduct the same baseline analysis at the follow-up to evaluate transition of individuals between clusters/classes (Dekker et al. 2013; Harrington et al. 2014; Schneider et al. 2016).

4.3.1. Tracking Dietary Patterns

Some studies examined the consistency of dietary patterns at the individual level by calculating the tracking coefficients over the entire time using generalized estimating equation (GEE) models (Batis et al, 2014; Johns et al. 2014; Ambrosini et al 2014). This approach estimates how individuals maintained their position in the study population distribution for dietary pattern scores in the subsequent follow-up measurements (Twisk et al. 2003). One study in children (Ambrosini et al 2014) and two studies in adults (Batis et al, 2014; Johns et al. 2014) used GEE for tracking dietary pattern scores over time. In the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK, a “high energy, high fat, low fiber” dietary pattern identified by RRR method in 7027 children aged 7 years at baseline were tracked 3 years and 6 years later. They reported a moderate tracking, 0.38 in girls and 0.48 in boys, from 7 to 13 years of age (Ambrosini et al, 2014). In the China health and nutrition survey, applied scores for “traditional southern” and “modern high-wheat” dietary patterns, derived using PCA, were

tracked in 9253 participants aged ≥18 years from 1991 to 2009. Dietary intake data were collected using 3-day 24-hour recalls at 7 time-points over 18 years. Both dietary patterns were remarkably stable over time, with stronger tracking for traditional southern compared to modern high-wheat dietary patterns (0.71 vs. 0.55) (Batis et al 2014). In Swedish obese subjects (SOS) study, the "energy-dense, high saturated fat and low fiber density" dietary pattern derived using reduced-rank regression (RRR) method, were tracked in 2037 severely obese subjects aged 47±6 years at baseline. A semi-quantitative diet questionnaire was used to assess dietary intake at 10 time-points over ten years. They found a moderate tracking, 0.40 in women and 0.38 in men (John et al. 2014). The small number of studies, which used GEE to track dietary patterns, and diversity in population characteristics among studies make it difficult to draw a general conclusion. However, from the available evidence, it seems that dietary patterns are more stable during adulthood, compared to younger ages.

4.3.2. Correlation in Dietary Pattern Scores between Two Time-points

The correlation coefficient between baseline and follow-up dietary pattern scores was the most commonly used indicator to assess stability in dietary patterns in children and adults' studies. Three studies in children assessed change in dietary patterns by determining the correlation in dietary pattern scores between two time-points (Mikkila et al. 2005; Northstone & Emmett 2008; Lioret et al. 2015). Mikkila et al (2005) assessed change in two dietary patterns derived using PCA in 1768 participants (aged 3-18 years at baseline). The "traditional Finnish" and "health-conscious" dietary patterns showed a moderate correlation (0.32 and 0.38, respectively) between baseline and 21-year follow-up, with higher tracking in adolescents (aged 15-18 years) compared to children (aged 3-14 years) (Mikkila et al. 2005). In the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC), dietary patterns were derived using PCA in 6177 participants aged 3 years old, at baseline and follow-up years (1, 4 and 6 years later). Three dietary patterns were consistently derived at each time point including "processed", "traditional" and "health conscious" dietary patterns. The correlation coefficients for dietary pattern scores between baseline and follow-up at age 9 years old were 0.46 for "processed", 0.41 for "health conscious" and 0.35 for "traditional" dietary patterns (Northstone & Emmett 2008). In EDEN mother-child cohort, PCA was used to derive dietary patterns in 989 participants at their age at 2, 3 and 5 years old. The "processed and fast food" and "guidelines" dietary patterns were derived consistently at each age. A correlation coefficient of 0.35 for "processed and fast

food" and 0.33 for "Guidelines" dietary patterns was reported from age 2 to 5 years old (Lioret et al. 2015).

Four studies in adult and elderly people assessed change in dietary patterns by determining the correlation in dietary pattern scores between two time-points (Weismayer et al. 2006; Borland et al. 2008; Jancovic et al. 2014; Batis et al. 2014). In the Swedish mammography cohort of women aged 49-70 years at baseline (n=1000), the correlation between scores of three dietary patterns ("healthy", "Western" and "alcohol") derived by factor analysis at baseline and follow-up years was estimated. The correlation coefficient between baseline and 4-year follow-up or baseline and 7-year follow-up were 0.59 and 0.50 for "healthy", 0.47 and 0.39 for "Western" and 0.54 and 0.46 for "alcohol" dietary pattern scores (Weismayer et al. 2006). In Southampton women's survey, scores of "prudent" and "high-energy" dietary patterns derived by factor analysis (PCA) in women aged 20 to 34 years, were highly correlated after 2 years (0.81 and 0.64, respectively) (Borland et al. 2008). In Zutphen elderly study of 467 men aged 64 to 85, RRR was used to derive three dietary patterns associated with cardiovascular risk factors including "low in cereal fiber", "alcohol" and "inconsistent" dietary patterns. Exploratory correlation coefficients for dietary pattern scores between baseline and 5-year follow-up were 0.47 for "low in cereal fiber" and 0.34 for "alcohol" dietary patterns. There was no correlation between "inconsistent" dietary pattern between two time-points (Jancovic et al. 2014). In the China Health and Nutrition Survey in 9253 adults (18 to 65 years old), correlation between applied dietary pattern scores for two "traditional southern" and "modern high-wheat" PCA-derived dietary pattern was determined for each pair of study years (1991, 1993, 1997, 2000, 2004, 2006 and 2009). They reported a higher correlation for "traditional southern" compared to "modern high-wheat" (0.67 to 0.81 vs. 0.46 to 0.63) for each pair of study years (Batis et al. 2014).

Overall, due to the diversity of dietary patterns derived from different populations, and different baseline and follow-up age of participants, these crude correlation values, without adjustments for age and sex and characteristics of participants, are not comparable between studies.

4.3.3. Transition between Dietary Pattern Score Categories

Some investigators categorized participants into non-overlapping groups using quintiles, quartiles or tertiles of dietary pattern scores as cut-off point at each time point, indicating

participants in the top category as having strictest adherence and those in the bottom category having poor adherence to dietary patterns. Then, they determined the proportion of participants who remained in the same category or calculated the level of agreement (kappa statistics) to assess the stability of dietary patterns. The level of the agreement indicates the percent of participants who remained in the same category in the follow-up, after removing the chance of random allocation to a group. Three studies in children and adolescents and two studies in adults assessed the stability of dietary patterns using this method (Mikkila et al. 2005; Northstone & Emmett 2008; Lioret et al. 2015; Mishra et al. 2006; Asghari et al 2012). Assessing the transition between quintiles of dietary pattern scores in participants of Cardiovascular Risk in Young Finns Study (aged 3-18 years at baseline, n=1768) showed that 41% and 38% of participants remained in the top quintile of "traditional Finnish" and "health-conscious", respectively, after 21 years (Mikkila et al, 2005). In the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK, the transition of 7027 children between quartiles of an RRR-derived dietary pattern scores from age 7 to age 13 years was assessed. Proportion of participants who maintained their position in the same quartile of "high energy, high fat, low fiber" dietary pattern scores, were 43% of females and 41% of males in the lowest quartile and 32% of females and 45% of males in the highest quartile (Ambrosini et al, 2014). In the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC), 6177 participants (aged 3 years old at baseline) were categorized based on the quintiles of dietary pattern scores at each time point (baseline and 1-, 4- and 6-year follow-ups). The proportion of participants remained in the same quintile in the follow-ups were determined. The level of agreement (kappa coefficient) for different time pairs varied from 0.30 to 0.47 for "processed", from 0.25 to 0.44 for "traditional" and from 0.34 to 0.47 for "health conscious" dietary patterns (Northstone & Emmett 2008).

Two studies in adults assessed the stability of dietary patterns by determining the transition of participants across tertiles or quintiles of dietary patterns and calculating the level of agreement (Mishra et al. 2006; Asghari et al 2012). In the 1946 British Birth Cohort, the level of agreement for the proportion of participants who remained in the same tertiles of dietary pattern scores from age 36 to 43 and 53 was determined (n=1265). In females, the level of agreement for all pairs of times were higher for "fruit, vegetable and dairy" compared to "ethnic foods and alcohol" or "meat, potatoes and sweets" (kappa value of 0.36-0.41 vs. 0.28-0.36 vs. 0.14-0.20, respectively). In males, kappa value varied from 0.38 to 0.44 for "ethnic foods and alcohol" and

0.38 to 0.41 for “Mixed” (Mishra et al. 2006). In the Tehran Lipid Glucose Study, the proportion of participants remained in the same quintile of PCA-derived dietary pattern scores were determined in adults aged 20-50 years old (n=132). After 8 years of follow-up, 20% and 27% of participants remained in the same quintiles of “Iranian traditional” and “Western” dietary pattern scores, respectively. However, there was no significant level of agreement for “Iranian traditional” dietary pattern. The kappa statistic was 0.20 for “Western” dietary pattern (Asghari et al 2012).

Overall, the limitation of using this method is that by classifying participants into a few categories, investigators are losing so much information at the individual level. In addition, reporting the percent of participants remaining in the same categories without reporting kappa statistic would not be useful in terms of assessing the stability of dietary patterns.

4.3.4. Transition between Dietary Pattern Clusters/Classes

Cluster analysis or LCA are two dietary pattern approaches that derive dietary patterns by classifying individuals into a non-overlapping clusters/classes based on similarity in their dietary intake. Despite PCA or RRR methods, no dietary pattern score is calculated in cluster analysis/LCA. Therefore, the only method to assess the stability of these dietary patterns is to assess transition of participants among different dietary pattern clusters/classes. One study in children and adolescents (Schneider et al. 2016) and two studies in adults (Dekker et al. 2013; Harrington et al. 2014) evaluated the stability of dietary patterns derived using cluster or LCA approach. In Pelotas birth cohort study, change in dietary patterns of 3823 adolescents in Brazil was investigated from age 15 to 18 years. Using LCA, participants were categorized into four dietary pattern classes including “varied”, “traditional” and “dieting” at both time points, and “processed meats” at age 15 years or “fish, fast food, and alcohol” at age 18 years. The most frequent change was a transition of participants from “processed meat” to “dieting” class (38%). However, 36% of participants in “dieting” class at age 15 remained in the same class at age 18 years (Schneider et al 2016). In Doetinchem cohort study in Netherlands, the stability of two dietary patterns, “low-fiber bread” and “high-fiber bread”, derived using cluster analysis was investigated in adults aged 46 years (n=6113) after 5 years (n=4916) and 10 years (n=4520). Results of the study showed that there was a good reproducibility for food groups at each cluster and almost 42% of participants remained in the same cluster of dietary patterns after 10 years (Dekker et al, 2013). Harrington et al. (2014) used LCA to derived dietary patterns in 303 Irish

participants of Cork and Kerry Diabetes and Heart Disease Study at baseline (aged 50-69 years) and 10 years later. Three dietary patterns were derived including "Western", "healthy" and "low-energy" and participants were categorized into these classes. Based on the proportion of participants remained in the same class after 10 years (74%, 44% and 39% stable in "healthy", "low-energy" and "Western", respectively), they found that "healthy dietary pattern" was more stable compared to "low-energy" or "Western" dietary patterns (Harrington 2014).

Overall, the limitation of using cluster analysis or LCA for assessing the stability of dietary patterns over time is that conducting the same analysis at the follow-up does not always yields the same dietary patterns (clusters/classes). However, these methods are useful in exploring new dietary patterns which emerge over time. The small number of cluster analysis or LCA studies and different age group of participants and follow-up period in these studies make it difficult to synthesize new knowledge based on these findings.

4.4. Conclusion

Overall a higher correlation or tracking coefficient was reported in adults (aged >18 years) compared to children and adolescents. This might imply that children and adolescents compared to adults are more likely to change their dietary patterns over time. In most studies, the "healthy" dietary pattern showed a higher stability compared to the other ones including "Western" dietary pattern (Mishra et al, 2006; Borland et al, 2008; Milkkila et al, 2005; Weismayer et al, 2006; Harrington et al, 2014; Lioret et al, 2015). However, in the young children study (3 years old at baseline) dietary patterns rich in processed and fast foods had higher tracking compared to "healthy" dietary patterns (Northstone & Emmet 2008). Only one study has evaluated the change in dietary patterns from childhood and adolescence (aged 3-18 years) to adulthood (after 21 years) (Mikkila et al, 2005). They reported a moderate tracking for "traditional Finnish" and "health-conscious" dietary patterns.

LITERATURE REVIEW SUMMARY

A number of gaps in knowledge are apparent from the literature review. Most of the studies evaluating the association between bone health and dietary patterns had a cross-sectional design which were not able determine a cause-and-effect relationship between them. The number of studies examining childhood and adolescence dietary pattern in relation to bone was limited. To our knowledge, there was no study examining the long-term impact of the adolescent dietary pattern on adult bone. Adolescence is a critical period during bone mineral accrual and any adaptation in bone might continue into adulthood. Longitudinal studies, which follow up the same participants from childhood to adulthood and elderly, help bridge the gap in knowledge. However, it is not clear whether dietary patterns established during adolescence could continue throughout the entire follow-up period until adulthood or not. Therefore, it is important to assess tracking and change in dietary patterns from adolescence to adulthood. Findings from the studies evaluating the stability of dietary patterns over time were inconsistent due to variations in age at baseline, the length of follow-up periods, the number of measurements, different dietary pattern approaches and statistical analysis. There are no standard cut-offs for tracking dietary pattern scores between two time-points or over the entire period. However, most studies reported a correlation between 0.3 and 0.6 as moderate tracking. Findings from these studies suggest that established healthy dietary habits during adolescence could be moderately maintained into adulthood. However, more longitudinal research is needed to bridge the gap in knowledge and address this question.

As Objective One of my thesis, I aimed to investigate the association between data-driven dietary patterns and bone mineral accrual from adolescence to young adulthood. This study would help bridge the gaps and add to the current knowledge. The related manuscript has been presented in Chapter 6. We also investigated the impact of adolescence food group intake on adult bone structure and strength. This study (Chapter 7) is published in “Osteoporosis International” journal in 2017. To address Objective Two of my thesis, we evaluated the stability of adolescent dietary patterns over the entire time from adolescence to adulthood. The manuscript of this study is presented in Chapter 8.

Next chapter, Chapter 5, represents PBMAS data collection methods, study design and analytical approaches used in my research.

CHAPTER 5
METHODOLOGY

5.1. Data Collection

5.1.1. Participants

Participants were recruited from two elementary schools, only two blocks away from each other, as a population-based sample of children, in the city of Saskatoon, Saskatchewan. Almost all participants were Caucasian, living in the middle-class area of the Saskatoon. This sample of participants from two schools will be considered homogeneous in all analysis. Only those children with a written consent form signed by child and parents with no history of chronic disease, no chronic medication use, and no medical conditions, allergies, or medication use known to influence bone metabolism or calcium balance were enrolled in the study. In 1991, data collection was conducted on 228 students (113 boys and 115 girls), from 8 age cohorts (aged 8 to 15 years). In the following years, 23 children joined the ongoing study. A total of 251 students enrolled in the first phase of the study from 1991 to 1997. Of this number, 230 students (109 males and 121 females) had been measured on two or more occasions. The age range of the sample was 12 to 21 after 6 years of follow-up. Of the original cohort of 113 boys and 115 girls, 94 males and 88 females with available longitudinal data were invited to participate in a further follow-up study between 2002 and 2005. A total of 169 participants were measured on at least one occasion in the first follow-up study. The follow-up age was between 18to 27 years. In the second follow-up study, which conducted between 2009 and 2012, 48 males and 73 females aged 24 to 34 years were assessed. Table 5.1 shows the number of subjects who had bone scans and other measurements by test year.

5.1.2. Dietary Intake Assessment

During 1991 to 1997, dietary intake information was collected by administering 24-hour dietary recall both at the participation schools and in the hospital setting at the time of bone scans at least three times per year during the first three years of study and at least two times per year thereafter. All days of the week, except Friday and Saturday, were included. For all subjects, 24-hour recalls were self-administered, except for the younger children from grades 2 and 3 for which the interviewer wrote down the verbally provided information. A training session on food portion sizes conducted for children at the beginning of the study. In addition, display boards of

life-size pictures of foods and portion sizes were presented at each administration of 24-hour recall helping subjects make accurate estimates of their dietary intake. Dietary information derived from 24-hour recalls was coded for nutritional content based on the type of food and serving size. The coded data was analyzed using NUTS nutritional assessment software (version 3.7 Quilchena Consulting Ltd., Victoria, BC), which used the 1988 Canadian Nutrient File information. This software categorized every food into food groups based on the 1982 Canada's Food Guide, which was like the current version of Food Guide, apart from names and recommended servings of the food groups and graphic to illustrate the Guide (Iuliano-Burns et al., 1999). Food items were categorized into main food groups including "fruit and vegetables", "milk and alternatives", "meat and alternatives", "grain products" and "other foods". For foods categorized as "other foods", two separate groups were used: "fats and oils", and "sweets and desserts". Nutrient supplement use was included in nutrient intake data when supplement use was considered consistent, that is at least two-thirds of the time (Iuliano-Burns et al., 1999). The same individual coded and checked all the forms, and analyzed dietary intake data. To obtain usual intake of subjects, intake of food and nutrients from serial 24-hour recalls were averaged for each year of study.

Only one 24-hour recall per year was collected during follow-up years. During the first follow-up study (2002-2005), at least three 24-hour recalls, two at the time of bone scans and one through a phone interview, were obtained. Food intake was analyzed using Food Processor (Version 8.0, ESHA Research Inc, Salem OR) that contained food from the 1997 Canadian Nutrient File. During second follow-up (2010-2011) two 24-hour recalls collected and data were analyzed using Food Processor (Version 10.0, ESHA Research) that contained foods from the 2007 Canadian Nutrient File.

Table.5.1. Age and gender distribution of PBMAS participants during study years from 1991 to 2011

	Years of study (Sequences)															
Age	**1991 (2)**	**1992 (4)**	**1993 (6)**	**1994 (8)**	**1995 (10)**	**1996 (12)**	**1997 (14)**	**1998 (16)**	**2002 (24)**	**2003 (26)**	**2004 (28)**	**2005 (30)**	**2010 (40)**	**2011 (42)**	**Male (female)**	**Total**
8	3 (7)	5 (10)	- (2)												8 (19)	27
9	12 (16)	3 (10)	5 (9)	- (2)											20 (37)	57
10	17 (14)	9 (17)	3 (11)	5 (10)	- (2)										34 (54)	88
11	17 (13)	19 (15)	11 (18)	3 (9)	5 (10)	- (2)									55 (67)	122
12	19 (18)	17 (12)	19 (14)	13 (14)	3 (10)	5 (10)	- (2)								76 (80)	156
13	20 (23)	21 (17)	16 (12)	15 (15)	12 (14)	3 (10)	5 (7)								92 (98)	190
14	19 (15)	14 (19)	19 (15)	12 (11)	13 (15)	10 (12)	3 (9)	- (2)							90 (98)	188
15	5 (15)	19 (15)	14 (20)	14 (15)	12 (11)	10 (16)	7 (8)	- (5)							81 (105)	186
16		3 (8)	18 (14)	13 (13)	13 (14)	10 (7)	9 (11)								66 (67)	133
17			3 (7)	13 (11)	14 (12)	12 (13)	9 (5)		- (2)						51 (50)	101
18				3 (6)	12 (8)	13 (12)	8 (10)		3 (3)	- (2)					39 (41)	80
19					3 (5)	7 (6)	7 (8)		4 (13)	3 (2)	- (2)				24 (36)	60
20						3 (4)	5 (3)		6 (13)	2 (12)	5 (4)				21 (36)	57
21							2 (2)		6 (9)	5 (7)	2 (9)	- (2)			15 (29)	44
22									12 (9)	6 (11)	6 (10)	4 (7)			28 (37)	65
23									8 (10)	10 (8)	7 (9)	3 (7)			28 (34)	62
24									14 (13)	9 (12)	10 (7)	7 (11)	- (2)		40 (45)	85
25									8 (6)	11 (13)	8 (14)	5 (12)	1 (1)		33 (46)	79
26									3 (5)	9 (6)	10 (11)	7 (8)	1 (8)	1 (1)	31 (39)	70
27									1 (-)	4 (5)	9 (5)	12 (11)	2 (4)	1 (3)	29 (28)	57
28											3 (3)	11 (14)	8 (8)	3 (8)	25 (33)	58
29												9 (5)	7 (10)	4 (3)	20 (18)	38
30												2 (2)	4 (5)	6 (4)	12 (11)	23
31													9 (11)	2 (4)	11 (15)	26
32													4 (8)	12 (7)	16 (15)	31
33													5 (7)	5 (7)	10 (14)	24
34													1 (-)	5 (3)	6 (3)	9
35														1 (1)	1 (1)	2
Male (female)	112 (121)	110(123)	108(122)	91 (106)	87 (101)	73(92)	55(65)	0 (7)	65 (83)	59(78)	60 (74)	60 (79)	42(64)	40 (36)	902(1148)	
Total	223	233	230	197	188	165	120	7	148	137	134	139	108	76		2050

PBMAS, Pediatric Bone Mineral Accrual Study.

5.1.3. Bone Measurements

Bone measurements including total body BMC, poster-anterior lumbar spine (L1-L4) BMC, and the femoral neck BMC were obtained annually by DXA using the Hologic 2000 QDR (Hologic, Inc., Waltham, MA, U.S.A.). The same operator conducted DXA scans during the original and follow-up study and the same person analyzed all the scans to minimize operator-related variability. Array mode was used for all bone scans and employed enhanced global software version 7.10 for analysis. Total body scans were analyzed using software version 5.67 A. Coefficient of variation in vivo for total body, lumbar spine and femoral neck scans (0.60, 0.61 and 0.91, respectively) were comparable to the values from other studies that employed the QDR 2000 in the array mode.

One pQCT scan (Stratec XCT 2000, Stratec Medical, Pforzheim, Germany) for each participant was obtained during 2010 or 2011, performing at the 4% (distal) and 66% (diaphysis) of the tibia length in the ipsilateral lower leg; and 4% (distal) and 65% (diaphysis) of the radius length of the non-dominant forearm. We measured trabecular bone properties in distal tibia and radius, and cortical bone properties in tibia and radius shafts, which are the dominant bone structures at the respective bone sites. Bone structural and densitometry characteristics were assessed using pQCT manufacturer's software (stratec Medical, Pforzheim, Germany, version 6). Total bone area (ToA, mm^2), cortical bone area (CoA, mm^2), density (CoD, mg/cm^3) and content (CoC, mg/mm) were calculated at the shaft sites; and total bone area (ToA, mm^2) and density (ToD, mg/cm^3), trabecular bone area (TrA, mm^2), density (TrD, mg/cm^3) and content (TrC, mg/mm) were estimated at the distal sites. "Density weighted polar section modulus" (SSI_P, mm^3) was estimated as an indicator of resistance of bone diaphysis to twisting force. In addition, bone strength index (BSI_C, mg^2/mm^2), an index of compressive strength, was derived as $ToA*ToD^2$. The short-term precision error coefficient of variation (CV_{rms}) for the bone measures in my study ranged from 1.4 to 6.1% at the radius and 0.7 to 2.1% at the tibia.

5.1.4. Fat Mass and Muscle Mass Measurements

Total body fat mass, trunk fat, and muscle mass were estimated annually using DXA scans and expressed as gram and proportion (%). Muscle area (MuA, mm^2) was estimated using pQCT scan in 2010 or 2011 for each participant in the shaft site of both forearm and lower leg. In pQCT scans, muscle tissue was recognized as the tissue with a density greater than 40 mg/cm^3

(to be distinguished from subcutaneous fat) and less than 280 mg/cm^3 (to be distinguished from bone) with CV_{rms} of 1.4% in the forearm and 3.7% in the lower leg in duplicate measures.

5.1.5. Anthropometrics

Trained personnel following standard protocols measured height and weight. Stand-up height was measured using a wall-mounted stadiometer to the nearest 0.1 cm; and weight was measured on a SECA electronic scale during original and first follow-up study, and using a calibrated mechanical scale during the second follow-up study, to the nearest 0.01 kg. Participants were asked to wear light clothes (shorts and T-shirts) and remove their shoes and jewelry before anthropometric measurements. The length of lower leg, measured as "the distance from the tibial joint line to the distal edge of the medial malleolus", and length of forearm, measured as "the distance from distal aspect of radial styloid process to the proximal head of radius", was taken by an anthropometric tape measure, to the nearest 0.1 cm.

5.1.6. Physical Activity

Physical activity was defined as "sports, games, or dance that make you breathe hard, make your legs feel tired or make you sweat". The Physical Activity Questionnaire for Children (PAQ-C) in elementary schools and the Physical Activity Questionnaire for Adolescents (PAQ-A) in high schools were used to assess physical activity during spare time in the previous 7 days by rating nine items in the questionnaire, scored on a five-point scale. The average score derived from each questionnaire ranged from one to five, with higher scores indicating higher levels of physical activity. The PAQ-A was the modified version of the PAQ-C after omitting the item regarding activity at recess. The questionnaire administered at least three times per year during first 3 years and two times per year thereafter. The Physical Activity Questionnaire for Adults (PAQ-AD), the 7-item version of PAQ-C, was used in the follow-up study to assess physical activity during spare time in the previous 7 days by the same scoring system as PAQ-C/A. The PAQ-C and PAQ-A have shown good test-retest reliability and in the validity study, it was shown that self-reported PAQ-AD correlated significantly to direct measurement of physical activity in adults (Copeland et al., 2005). The average score of the two or three administrations was considered as the score of individual's physical activity for the year.

5.1.7. Maturational Assessment

To control the effect of biological maturity on bone and body composition measurements, age at PHV was calculated as the age at the maximum rate of height increase during the

adolescent growth spurt (Bailey et al, 1999). Biological age was computed using the age at PHV as 0, then negative values were assigned to the years before PHV, and positive values were assigned to the years after PHV.

5.2. Analytical approaches

Study design and statistical analysis used for analysis of the data were presented for each of three studies separately in the following chapters (Chapters 4, 5 and 6). To address objective one, I evaluated the association between adolescence fruit and vegetable intake or milk and alternatives intake with adult cortical and trabecular bone structure, bone density, and strength in study one. I also derived dietary patterns during the adolescent growth spurt and examined their impact on adult BMC and BMD in study two. To address objective two, I evaluated the stability of adolescent dietary patterns over 20 years from childhood to adulthood, in study three.

5.3. Ethical Approval

Ethical approval for the original PBMAS study and ethical re-approval to monitor the PBMAS cohort in the first and second follow-up studies were received from the University of Saskatchewan and Royal University Hospital Advisory Committee on Ethics in Human Experimentation in 1991, 2001 and 2009 respectively.

In the next three chapters, Chapters 6 to 8, findings of my research have been presented. Research Objective 1 has been addressed in Chapter 6 and Chapter 7. In Chapter 6, we derived dietary patterns during adolescence and evaluated their impact on adulthood bone measurements. The manuscript has been submitted to “Nutrition Journal” for publication. Chapter 7 represents a published manuscript in “Osteoporosis International” journal. In this study, we evaluated the impact of adolescent food group intake on adult bone structure and strength. Research Objective 2 has been addressed in Chapter 8. We assessed the stability of dietary patterns, which derived using adolescent dietary intake data, over the entire time from adolescent to young adulthood.

CHAPTER 6

STUDY 1

Movassagh EZ, Baxter-Jones A, Kontulainen S, Whiting S, Szafron M, Vatanparast H.

Vegetarian style dietary pattern during adolescence has a long-term positive impact on the bone from adolescence to young adulthood.

6.1. Introduction

Peak bone mass (PBM) attained by the end of adolescence is an early determinant of osteoporosis risk in older populations (Bonjour et al, 2009). During adolescence, bone linear growth and subsequent mineral deposition increase substantially. The greatest rate of growth in height during this time is termed as peak height velocity (PHV) (Bailey et al, 1999). The PHV is considered as one of the main indicators of somatic maturation, the stage during which males and females are at a comparable sexual development milestone (Bailey et al, 1999; Baxter-Jones et al, 2003). More than 39% of total body PBM is acquired during a 5-year period around PHV, and around 99% is attained by six years after attainment of PBM (Baxter-Jones et al, 2011). This suggests that modification of the factors that contribute to PBM attainment during adolescence might impact the risk of osteoporosis later in life (Bonjour et al, 2009).

Nutrition is an important modifiable factor, which could influence bone accrual, maintenance, and loss during one's lifetime (New, 2001). Diet is a complex combination of nutrients and dietary components that correlate or interact with each other. Even though the separate role of key nutrients, or foods, on bone health has been reported previously, these associations might be confounded by any change in the other dietary components. Dietary pattern approaches describe and quantify the whole diet and take into account contributions from various dietary aspects (Kant, 2004). Findings from dietary pattern studies could complement those from studies of single nutrients and foods on bone accrual and may be translated into public health recommendations, which better suit real world dietary habits.

In adults and elderly, several studies have investigated the association between dietary patterns derived by an exploratory method, mainly factor analysis, and bone health (Tucker et al, 2002; Okubo et al, 2006; Kontogianni et al, 2009; Langestmo et al, 2010; Fairweather et al, 2011; McNaughton et al, 2011; Hardcastle et al, 2011; Whittle et al, 2012; Karamati et al, 2012;

Chen et al, 2015; Shin et al, 2015; Mangano et al, 2015; de Franca et al, 2016; Ward et al, 2016). However, little is known about the dietary patterns influencing bone health during adolescence (Noh et al, 2011; Shin et al, 2013; Monjardino et al, 2015; van den Hooven et al, 2015), and their potential long-term implications. Therefore, longitudinal studies that follow participants from adolescence to adulthood are of immense importance because they could bridge the current gap in knowledge.

The objectives of my study are: 1) to examine the association between adolescent dietary patterns and adolescent and adult bone measurements including total body (TB), femoral neck (FN) and lumbar spine (LS) BMC and aBMD, and 2) to evaluate the stability of dietary patterns from adolescence to adulthood. I hypothesized that a "healthy" dietary pattern, with an emphasize on a higher intake of fruits, vegetables, and dairy products would be beneficial for adolescence and early adulthood bone health; and dietary patterns remain relatively stable over time from adolescence to adulthood.

6.2. Methods

6.2.1. Participants

We recruited participants from the Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) (1991-2011). The mixed longitudinal design of the study has been described in detail elsewhere (Bailey et al, 1997; Baxter-Jones et al, 2003; Baxter-Jones et al, 2011). In brief, the PBMAS cohort consists of 251 individuals (133 girls and 118 boys; aged 8 to 15 years) recruited from two elementary schools in the city of Saskatoon between 1991 and 1993 who were subsequently followed with annual follow-ups until 2011. There were two four-year breaks in annual measurements: one between 1997 and 2002 and one between 2005 and 2010. The ages of the participants at the final follow-up were between 24 to 32 years. At each measurement occasion, participants underwent dual-energy X-ray absorptiometry (DXA) scans for bone and body composition. Anthropometry, dietary intake and physical activity (PA) were also assessed at each measurement point.

For the present study, the first measurement within the age of PHV±2 years was considered as the adolescent measurement. For most participants (n=105), the data collected during 1992 or 1993 were included in the analysis as adolescent data, because during 1991 no lumbar spine scans were obtained. The data collected during 2010 or 2011 were included in the

analysis as adult data. For participants who dropped out of the study before 2010, their last measurement was used in the analysis, if it was at least eight years after the age of PHV. I included data from 125 participants (fifty-three females) for adolescent analysis (cross-sectional) and 115 participants (fifty-one females) for adolescence to adult analysis (longitudinal).

All participants or their parents provided informed written consent. Ethics approval was obtained from the University of Saskatchewan and Royal Hospital advisory boards on ethics in human experimentation (Bailey et al, 1997).

6.2.2. Dietary Intake

The dietary intakes of participants were assessed using 24-hour recalls. To determine accurate estimates of portion sizes, participants had access to pictures of foods. Adolescent dietary intakes were assessed by two to four (mostly three) 24-hour recalls collected over a year and were analyzed using the Canadian compatible nutrition assessment software: NUTS Nutritional Assessment System, version 3.7 (Quilchena Consulting Ltd, Victoria, BC, 1988) to estimate the daily total energy and nutrient intakes. The yearly averages of the dietary intakes then were aligned with the other annual measurements during the same year. To include in dietary pattern analysis, first, I converted quantities of all consumed foods and beverages into grams per day; then, all items were assigned into twenty-five pre-defined non-overlapping food groups, manually, based on similar nutrient content or culinary usage of them (Table 6.1). Adult dietary intakes were assessed using one 24-hour recall and estimates of total energy and nutrient intakes were obtained using Food Processor version 8.0 and its revisions (ESHA Research Inc, Salem, Ore, 2003).

6.2.3. Bone Mineral Content and Areal Density

Adolescent and adult BMC and aBMD of total body, femoral neck and lumbar spine (L1–L4) were measured using DXA (Hologic QDR 2000, Hologic, Inc., Waltham, MA, USA) in the array mode; and analysis was conducted using enhanced global software version 7.1 (Bailey et al, 1999). To minimize operator-related variability in the scan analysis over the years, the same trained person analyzed all scans. The total body scans were analyzed using software version 5.67A and scans of the femoral neck and lumbar spine were analyzed using software version 4.66A. The in vivo coefficients of variations, which represent short-term precision, were comparable to the values from other studies employing the QDR 2000 in the array mode (0.60, 0.91 and 0.61 for total body, femoral neck, and lumbar spine BMC, respectively).

6.2.4. Physical Activity

Physical activity was defined as sports, games, or dance that makes you breathe hard, makes your legs feel tired or makes you sweat. The PAQ was used to assess adolescent physical activity during spare time in the previous 7 days by rating nine items in elementary schools or eight items in high schools (excluding the item regarding activity at recess) scored on a five-point scale (Bailey et al, 1999). Six of these questions were related to scaling the level of different activities in physical education classes, recess, lunch, right after school, in the evenings and on the weekend. Other three questions were asking about the frequency of physical activity during each day, the number of hours spent for watching TV and describing the whole week activity from low to very high activity levels (Kowalski et al, 1997). The average score derived from each PAQ ranged from one to five, with higher scores indicating higher levels of physical activity. To assess adult physical activity, PAQ was modified to a 7-item questionnaire including more age-relevant activities. The school-day structure of questions was replaced with a day section structure (i.e., morning, after lunch, before supper, evening) in the PAQ for adults (Copeland et al, 2005). The PAQ was administered three times a year during first 3 years of study and two times a year thereafter. The average physical activity scores derived from PAQs collected during each year were aligned with the other annual measurements (Bailey et al, 1999).

6.2.5. Anthropometry and Age of PHV

Weight and stature were measured following standard protocols for each participant while wearing lightweight clothing and no shoes (Bailey et al, 1997). To control for somatic maturity, the age of PHV for each participant was estimated. The process for determining PHV has been described elsewhere (Bailey et al, 1999). In brief, whole-year height increase velocity was computed using serial measurements of height for each participant by age. Using a cubic spline procedure, a growth curve was fitted to each individual's annual height velocities (GraphPad Prism Version 3.00) and the age of PHV was determined from the estimated growth curve (Bailey et al, 1999). Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

6.2.6. Statistical Analysis

Dietary patterns were identified using factor analysis via PCA. The PCA aggregates the food groups into a smaller number of the distinct factors (dietary patterns) based on inter-correlation between them (Newby & Tucker, 2004; Kant, 2004). To achieve a simpler structure

with higher interpretability, orthogonal rotation (Varimax option) was applied. To determine the number of dietary patterns that should be retained, I evaluated scree plot, eigenvalues, % of variance explained by and the combination of foods in each factor. Overall, 11 factors were extracted using PCA with an eigenvalue >1 accounting for 66% of the total variance in all food group intakes. Based on the breakpoint in scree plot, I retained 5 major factors (accounting for almost 40% of the total variance) for further evaluation and re-run the analysis with a five-factor solution. The percent of explained variance in my study was comparable to other studies (range from 14 % to 60%, mainly around 35%) (Tucker et al, 2002; Okubo et al, 2006; Kontogianni et al, 2009; Langestmo et al, 2010; Fairweather et al, 2011; McNaughton et al, 2011; Hardcastle et al, 2011; Noh et al, 2011; Whittle et al, 2012; Karamati et al, 2012; Shin et al, 2013; Chen et al, 2015; Shin et al, 2015; Mangano et al, 2015; Monjardino et al, 2015; van den Hooven et al, 2015; de Franca et al, 2016; Ward et al, 2016). Factor loadings represent the correlation between food groups and the factors (Table 6.2). The absolute value represents the strength of the correlation. A Positive loading shows a direct association and a negative loading shows an inverse association between the food group intake and dietary pattern score. Food groups with a factor loading ≥ 0.35 or ≤ -0.35 were considered informative for interpretation of dietary patterns in my study. Regression scores for each dietary pattern were calculated using the regression scores option in SPSS. Calculating regression scores enhances the validity of dietary pattern scores and reduces the probability of biased estimates of the true scores (DiStefano et al, 2009).

Descriptive statistics for all bone variables (total body BMC, total body aBMD, femoral neck BMC, femoral neck aBMD, lumbar spine BMC, lumbar spine aBMD), and covariate variables (age, the age of PHV, height, weight, physical activity score and total energy intake) were presented as mean ± SD in adolescence and adulthood. I used independent Student's t-test to compare variables of interest between females and males. Multiple linear regression using stepwise procedure were conducted to evaluate associations between adolescence dietary pattern and adolescence bone measurements. To assess the long-term impact of dietary patterns on the bone, I also ran the same modeling with adolescent dietary pattern scores as a predictor variable, and adulthood bone measurements as outcome variables. All models were adjusted for sex, the age of PHV, age, height, weight, physical activity score and total energy intake. Covariates measured during adolescence and adulthood were used in the adolescence and adulthood models, respectively.

Comparisons of the mean adolescence or adult bone variables across the quartile categories of adolescent dietary pattern score were conducted via a multivariate analysis of covariance (MANCOVA) (with a Bonferroni adjustment for multiple comparisons) while adjusting for scores of the other four dietary patterns (as continuous variables), sex, age of PHV, age, height, weight, physical activity score and total energy intake.

To evaluate the stability of dietary patterns from adolescence to adulthood, I calculated applied dietary pattern scores during adolescence and adulthood, based on the factor loadings for 25 food groups in five dietary patterns derived during adolescence. To control for the overall increase in consumption of food groups by age from adolescence to adulthood, I computed the consumed amount (g) per 1000 kcal of total energy intake for each food group. Then, these energy-adjusted intakes were multiplied by their corresponding factor loading in each dietary pattern and were summed up as the dietary pattern score. I standardized adolescence and adulthood dietary pattern scores for mean and standard deviation of adolescence dietary pattern scores in my sample. Then I calculated tracking coefficients using generalized estimating equations (GEE). This method allows measuring how participants maintained their position in a study population distribution, between two measurements (Twisk 2003). I regressed adolescence standardized dietary pattern scores (independent variable) against adulthood standardized dietary pattern scores (dependent variable) while adjusting for chronological age groups as a time-dependent variable, and sex and age at adolescence as time-independent variables. The ß coefficient of adolescence standardized dietary pattern scores takes values between 0 to 1, representing no tracking and strong tracking, respectively. The ß coefficient for chronological age indicates the change in dietary pattern score as z-score or SD for each year increase in age.

The dietary pattern analysis and all other statistical analyses were performed using SPSS software, version 24.0 (SPSS, Chicago, lL, USA). $P < 0.05$ was considered significant.

6.3. Results

The characteristics of the study population during adolescence and adulthood are shown in Table 6.3. My estimated mean follow-up period from adolescence to adulthood was 15.5±3.4 years. The first factor, labeled as “Vegetarian-style” dietary pattern, was rich in dark green vegetables, eggs, non-refined grains, 100% fruit juice, legumes, nuts and seeds, added fats, fruits and low-fat milk. The second factor, a “Western-like” dietary pattern was associated with higher

intakes of fruit drinks, refined grains, cream, poultry and processed meats. The most significant characteristic of the third factor, “high fat, high protein” dietary pattern, was high positive loadings for high-fat milk, tomato, red meat and legumes, nuts and seeds and a negative loading for low-fat milk. The fourth factor, a “Mixed” dietary pattern, was characterized by a high intake of yogurt, cheese, desserts and sweets, fish and seafood and 100% fruit juice. Dressings and sauces, vegetables (excluding dark green vegetables), chips and fries and poultry had high positive loadings and cheese had a negative loading in the fifth factor, labeled a “Snack” dietary pattern.

After controlling for covariates (sex, age of PHV and adolescent age, height, weight, physical activity score and total energy intake), multiple linear regression showed that the “Vegetarian-style” dietary pattern was a positive independent predictor of adolescent total body BMC (β =35.2, P = 0.025) and adult total body BMC (β=55.8, P = 0.021), total body aBMD (β = 0.016, P=0.041). No other adolescent dietary pattern was found to be an independent predictor for any of the adolescent or adult bone variables.

Comparison of adolescent or adult bone variables across adolescent dietary pattern score quartiles showed that, those in the third quartile of “Vegetarian-style” dietary pattern had higher adolescent total body aBMD (Table 6.4), and adult total body BMC, total body aBMD, femoral neck BMC and femoral neck aBMD (Table 6.5), compared to their peers in the lowest quartile, after adjusting for covariates and other four dietary pattern scores as continuous variables.

Tracking coefficients for standardized scores of five dietary pattern s and change in the score by age from adolescence to adulthood are presented in Table 6.6. The greater tracking coefficients show the higher stability of dietary patterns at the individual level. Since dietary pattern scores have been standardized for the baseline dietary pattern scores, ß coefficient for age variable was representing the amount of change in z-score. Overall, energy-adjusted scores increased for “Vegetarian-style” and decreased for “High-fat, high-protein” dietary pattern, from adolescence to adulthood (Table 6.6).

Table 6.1. Food groups and food items included in principal component analysis

Food groups	Food items
Dark green vegetables	Asparagus, green beans, broccoli, lettuce, green pepper, seaweed, spinach, mixed greens, snow peas
Eggs	Eggs
Non-refined grains	Whole grains and partially whole grains (60%) mostly cereals, mixed granola/grain bar, cracker, oat flakes, wheat germ, whole wheat bread, puffed wheat, brown and wild rice, popcorn, barley
Fruit juice 100%	Apple Cider, apple, lemon, orange juice canned or bottled, unsweetened cranberry, etc.
Legumes, nuts and seeds	Beans (black, kidney, lima, navy, small white, soy), chickpeas, hummus, tofu, Brazil nuts, coconut, almond, hazelnuts, walnuts, cashew, peanuts, mixed nuts, pecans, peanut butter, sunflower seeds
Added fats	Butter, margarine, vegetable oil, cooking oil, mayonnaise (salad dressing, miracle whip), coconut milk, dream whip, olive oil, pesto, meatless bacon bits
Fruits	All fresh and dried fruits, canned fruits (not sweetened), avocado, olives
Low-fat milk	1%, skim, rice beverage, soy beverage
Fruit drinks	Fruit juice (sweetened), fruit drinks, iced tea
Refined grains	Refined cereals, white bread, white rice, refined pasta, noodles, popcorns, ice cream cone, pie crust, pizza pop, pizza pocket
Cream	Sour cream, cream (10%, whipped or low fat)
Poultry	Chicken and turkey
Processed meats	Burger patties (beef, ham, chicken, etc.), sausages, bacon, canned meat (beef, ham, pork, chicken, turkey), dry ribs, fried chicken, Nugget
High-fat milk	2%, whole or almond milk
Tomato	Tomato and its products
Red meat	Beef, ham, pork, bison (ground, loin, rib, steak, stew, fried, pot roast, balls, loaf, chop)
Cheese	All kind of cheese
Yogurt	Yogurt (plain, vanilla or fruit)
Desserts and sweets	Sweet baked products, milk desserts, jelly, chocolate, sugar, jam, syrups, honey, and candies
Fish and seafood	Fish, shrimp, lobster, mussels, pickerel, prawns, scallops
Dressings, sauces, gravy	Gravy, dressings, Caesar, French, Ranch, Italian, 1000 island, Alfredo, blue cheese, chip dip, Greek, honey garlic, white sauce, sandwich spread, tartar, teen, sundried tomato
Vegetables, others	Carrots, snap beans, cabbage, cauliflower, celery, cucumber, garlic, mushroom, pepper, squash, bean sprouts, beets, onion, eggplant, radish, zucchini, potato, green peas, corn, sweet potato and soups
Chips & fries	Potato chips, fries, corn chips, nacho, hash brown

Soft drinks	Soft drinks (sugar-sweetened or diet
Others	Salt, spices, seasonings, additives, pickles (dill, beet), low-fat sauces (mustard, hot, soy, teriyaki), vinegar

Table 6.2. Food groups included in principal component analysis and their factor loading for the identified five dietary patterns during adolescence

	Factor loadings for dietary patterns				
	Vegetarian style	Western-like	High-fat, high protein	Mixed	Snack
Dark green vegetables	**0.64**	0.02	-0.00	0.07	-0.22
Eggs	**0.63**	-0.18	0.23	-0.05	-0.15
Non-refined grains	**0.54**	-0.13	-0.11	0.10	0.20
Added fats	**0.41**	**0.39**	-0.03	-0.04	-0.00
Fruits	**0.40**	0.24	-0.16	0.13	0.23
Others	-0.28	0.03	0.08	0.08	0.04
Fruit drinks	0.00	**0.73**	-0.04	-0.03	0.04
Refined grains	0.06	**0.66**	0.21	-0.10	-0.03
Cream	-0.06	**0.55**	-0.01	0.13	-0.02
Poultry	-0.27	**0.41**	-0.04	-0.10	**0.40**
Processed meats	-0.05	**0.35**	-0.12	0.01	-0.09
High-fat milk	-0.12	-0.17	**0.74**	-0.04	0.18
Tomato	0.22	0.30	**0.59**	-0.14	-0.34
Red meat	-0.07	-0.05	**0.52**	0.14	-0.07
Low-fat milk	**0.35**	0.03	**-0.48**	-0.01	-0.16
Legumes, nuts and seeds	**0.45**	0.11	**0.47**	-0.09	0.06
Cheese	0.03	0.12	0.06	**0.72**	**-0.36**
Yogurt	-0.11	0.04	-0.12	**0.61**	0.19
Desserts and sweets	-0.18	-0.05	0.23	**0.59**	0.08
Fish and seafood	0.24	-0.10	-0.08	**0.52**	-0.13
Fruit juice 100%	**0.46**	0.02	-0.04	**0.49**	0.18
Dressings, sauces, gravy	0.09	-0.30	0.24	0.08	**0.64**
Vegetables, others	-0.03	0.22	0.06	-0.03	**0.58**
Chips & fries	-0.03	-0.09	-0.02	0.00	**0.40**
pop	0.00	-0.02	-0.16	-0.20	0.20

Table 6.3. Descriptive characteristics during adolescence and adulthood by sex, in PBMAS participants[1]

	Females	Males	Total
Adolescence	n=53	n=72	n=125
Biologic age[2] (year)	0.2 ± 1.7	-0.1 ± 1.8	0.0 ± 1.7
Age (year)	12.0 ± 1.8	13.2 ± 1.8*	12.7 ± 1.9
Age of PHV (year)	11.8 ± 0.8	13.2 ± 0.9	12.6 ± 1.2
Physical activity (score)	2.9 ± 0.7	3.0 ± 0.6	3.0 ± 0.7
Total energy intake (kcal/d)	1714 ± 461	1978 ± 615*	1867 ± 569
Height (cm)	153 ± 11	162 ± 14**	158 ± 13
Weight (kg)	46.0±14	52.4±14*	49.8±14
TBBMC (g)	1402 ± 452	1751 ± 612**	1604 ± 575
TBaBMD (g/cm^2)	0.87 ± 0.10	0.94 ± 0.12*	0.91 ± 0.11
FNBMC (g)	3.3 ± 0.8	4.1 ± 1.0**	3.8 ± 1.0
FNaBMD (g/cm^2)	0.73 ± 0.13	0.81 ± 0.13*	0.77 ± 0.13
LSBMC (g)	35.8 ± 13.4	40.8 ± 16.0	38.7 ± 15.1
LAaBMD (g/cm^2)	0.76 ± 0.15	0.75 ± 0.14	0.76 ± 0.14
Adulthood	n=51	n=64	n=115
Biologic age[2] (year)	16.1 ± 3.5	15.0 ± 3.3	15.5 ± 3.4
Age (year)	27.9 ± 3.4	28.3 ± 3.4	28.2 ± 3.4
Physical activity (score)	2.3 ± 0.6	2.3 ± 0.7	2.3 ± 0.6
Total energy intake (kcal/d)	1823 ± 698	2823 ± 1235**	2401 ± 1151
Height (cm)	166 ± 7	179 ± 7**	174 ± 9
Weight (kg)	70.7±16	87.0±14**	80.3±16
TBBMC (g)	2286 ± 321	3020 ± 413**	2706 ± 523
TBaBMD (g/cm^2)	1.12 ± 0.09	1.22 ± 0.10**	1.18 ± 0.11
FNBMC (g)	4.3 ± 0.7	5.6 ± 0.8**	5.0 ± 0.9
FNaBMD (g/cm^2)	0.86 ± 0.10	0.95 ± 0.128**	0.91 ± 0.12
LSBMC (g)	62.0 ± 12.6	76.2 ± 12.8**	70.3 ± 14.5
LSaBMD (g/cm^2)	1.04 ± 0.12	1.06 ± 0.12	1.05 ± 0.12

[1]Values are Mean±SD. *P* values were obtained using independent samples Student's *t* test. [*]Different from females, $P < 0.01$. [**]Different from females, $P < 0.001$.

[2] Biologic age is calculated as chronologic age minus age of PHV.

aBMD, areal bone mineral density; BMC, bone mineral accrual; FN, femoral neck; LS, lumber spine; PBMAS, pediatric bone mineral accrual study; PHV, peak height velocity; TB, total body

Table 6.4. Comparison of adjusted mean adolescence bone variables across the quartile groups of each dietary patterns derived during adolescence, in PBMAS participants[1]

	Dietary pattern score quartiles[2]				P value
	Quartile1 (n=31)	Quartile2 (n=31)	Quartile3 (n=31)	Quartile4 (n=32)	
Vegetarian-style					
TBBMC (g)	1555 ±33	1579 ±31	1649 ± 32	1634±32	0.18
TBaBMD (g/cm^2)	0.88±0.01[a]	0.90±0.01[a,b]	0.93±0.01[b]	0.91±0.01[a,b]	0.025
FNBMC (g)	3.7±0.0	3.7±0.0	3.9±0.0	3.8±0.0	0.31
FNaBMD (g/cm^2)	0.75±0.01	0.78±0.01	0.80±0.01	0.76±0.01	0.22
LSBMC (g)	37.1±1.2	39.7±1.2	39.0±1.2	38.9±1.2	0.52
LSaBMD (g/cm^2)	0.73±0.01	0.77±0.01	0.77±0.01	0.75±0.01	0.20
Western-like					
TBBMC (g)	1612±33	1623±31	1594±32	1588±33	0.86
TBaBMD (g/cm^2)	0.91±0.01	0.91±0.01	0.91±0.01	0.90±0.01	0.74
FNBMC (g)	3.8±0.1	3.7±0.1	3.8±0.1	3.8±0.1	0.92
FNaBMD (g/cm^2)	0.79±0.01	0.76±0.01	0.77±0.01	0.78±0.01	0.82
LSBMC (g)	39.2±1.2	39.5±1.1	38.2±1.2	37.8±1.2	0.73
LSaBMD (g/cm^2)	0.76±0.01	0.76±0.01	0.76±0.01	0.75±0.01	0.93
High fat, high protein					
TBBMC (g)	1630±32	1597±32	1586±32	1603±34	0.82
TBaBMD (g/cm^2)	0.91±0.01	0.90±0.01	0.90±0.01	0.91±0.01	0.92
FNBMC (g)	3.8±0.0	3.9±0.0	3.7±0.0	3.7±0.0	0.40
FNaBMD (g/cm^2)	0.77±0.01	0.79±0.01	0.77±0.01	0.77±0.01	0.74
LSBMC (g)	38.9±1.2	38.9±1.2	39.1±1.3	37.8±1.3	0.91
LSaBMD (g/cm^2)	0.74±0.01	0.76±0.01	0.77±0.01	0.76±0.01	0.77
Mixed					
TBBMC (g)	1580±32	1608±30	1657±30	1572±32	0.22
TBaBMD (g/cm^2)	0.89±0.01	0.91±0.01	0.92±0.01	0.90±0.01	0.24
FNBMC (g)	3.8±0.0	3.7±0.0	3.9±0.0	3.7±0.0	0.41

FNaBMD (g/cm^2)	0.77±0.01	0.77±0.01	0.80±0.01	0.76±0.01	0.50
LSBMC (g)	38.7±1.2	37.8±1.1	40.9±1.1	37.3±1.2	0.16
LSaBMD (g/cm^2)	0.75±0.01	0.75±0.01	0.78±0.01	0.75±0.01	0.37
Snack					
TBBMC (g)	1587±30	1639±30	1590±31	1601±32	0.59
TBaBMD (g/cm^2)	0.90±0.01	0.92±0.01	0.90±0.01	0.91±0.01	0.37
FNBMC (g)	3.8±0.0	3.8±0.0	3.6±0.0	3.8±0.0	0.43
FNaBMD (g/cm^2)	0.79±0.01	0.78±0.01	0.75±0.01	0.78±0.01	0.31
LSBMC (g)	38.0±1.1	41.0±1.1	37.3±1.1	38.4±1.2	0.12
LSaBMD (g/cm^2)	0.76±0.01	0.79±0.01	0.73±0.01	0.75±0.01	0.055

[1]Values are Mean±SE. Mean adolescence bone variables were adjusted for sex and adolescent age of peak height velocity, age, height, weight, physical activity score, total energy intake and other four dietary pattern scores as continuous variables and were compared across quartiles of adolescence dietary pattern scores using MANCOVA with Bonferroni adjustment for multiple comparisons. Labeled means in a row without a common superscript letter differ, $P < 0.05$

[2] Participants in Quartile 4 have the highest adherence to the dietary patterns in adolescence.

aBMD, areal bone mineral density; BMC, bone mineral accrual; FN, femoral neck; LS, lumber spine; TB, total body.

Table 6.5. Comparison of adjusted mean adulthood bone variables across the quartile groups of each dietary patterns derived during adolescence, in PBMAS participants[1]

	Dietary pattern score quartiles[2]				P value
	Quartile1 (n=29)	Quartile2 (n=29)	Quartile3 (n=29)	Quartile4 (n=28)	
Vegetarian-style					
TBBMC (g)	2592±46[a]	2693±46[a,b]	2813±47[b]	2709±49[a,b]	0.016
TBaBMD (g/cm^2)	1.14±0.01[a]	1.18±0.01 [a,b]	1.21±0.01[b]	1.18±0.01[a,b]	0.017
FNBMC (g)	4.7±0.1[a]	5.0±0.1[a,b]	5.2±0.1[b]	5.0±0.1[a,b]	0.042
FNaBMD (g/cm^2)	0.87±0.02[a]	0.92±0.02[a,b]	0.95±0.02[b]	0.89±0.02[a,b]	0.020
LSBMC (g)	66.2±1.9	71.7±1.9	72.1±2.0	68.9±2.0	0.14
LSaBMD (g/cm^2)	1.00±0.02	1.06±0.02	1.08±0.02	1.04±0.02	0.09
Western-like					
TBBMC (g)	2742±47	2688±47	2745±48	2629±48	0.28
TBaBMD (g/cm^2)	1.18±0.01	1.17±0.01	1.20±0.01	1.15±0.01	0.24
FNBMC (g)	5.0±0.1	4.9±0.1	5.1±0.1	4.9±0.1	0.39
FNaBMD (g/cm^2)	0.91±0.02	0.90±0.02	0.93±0.02	0.90±0.02	0.71
LSBMC (g)	70.1±2.0	71.3±1.9	71.3±2.0	66.1±2.0	0.25
LSaBMD (g/cm^2)	1.05±0.02	1.05±0.02	1.07±0.02	1.01±0.02	0.35
High fat, high protein					
TBBMC (g)	2715±48	2692±50	2684±48	2712±47	0.96
TBaBMD (g/cm^2)	1.18±0.01	1.18±0.01	1.17±0.01	1.18±0.01	0.98
FNBMC (g)	5.0±0.1	5.2±0.1	4.7±0.1	5.0±0.1	0.07
FNaBMD (g/cm^2)	0.90±0.02	0.93±0.02	0.88±0.02	0.92±0.02	0.27
LSBMC (g)	67.9±2.0	72.4±2.1	68.6±2.0	70.0±2.0	0.45
LSaBMD (g/cm^2)	1.02±0.02	1.07±0.02	1.04±0.02	1.06±0.02	0.41
Mixed					
TBBMC (g)	2713±48	2700±48	2721±48	2668±49	0.88
TBaBMD (g/cm^2)	1.17±0.01	1.19±0.01	1.18±0.01	1.17±0.01	0.78
FNBMC (g)	5.1±0.12	5.1±0.12	4.9±0.12	4.8±0.12	0.28

	FNaBMD (g/cm^2)	0.91±0.02	0.93±0.02	0.89±0.02	0.89±0.02	0.46
	LSBMC (g)	68.7±2.0	70.1±2.0	72.5±2.0	67.5±2.0	0.36
	LSaBMD (g/cm^2)	1.04±0.02	1.06±0.02	1.07±0.02	1.02±0.02	0.50
Snack						
	TBBMC (g)	2673±45	2780±47	2652±46	2699±47	0.24
	TBaBMD (g/cm^2)	1.17±0.01	1.20±0.01	1.17±0.01	1.17±0.01	0.58
	FNBMC (g)	5.0±0.1	5.0±0.1	4.8±0.1	5.0±0.1	0.64
	FNaBMD (g/cm^2)	0.92±0.02	0.90±0.02	0.88±0.02	0.92±0.02	0.41
	LSBMC (g)	68.2±1.9	72.0±2.0	68.1±2.0	70.5±2.0	0.45
	LSaBMD (g/cm^2)	1.05±0.02	1.07±0.02	1.03±0.02	1.04±0.02	0.58

[1]Values are Mean±SE. Mean adulthood bone variables were adjusted for sex and age of peak height velocity and adult age, height, weight, physical activity score, total energy intake and other four adolescence dietary pattern scores as continuous variables and were compared across quartiles of adolescence dietary pattern scores using MANCOVA with Bonferroni adjustment for multiple comparisons. Labeled means in a row without a common superscript letter differ, $P < 0.05$.

[2] Participants in Quartile 4 have the highest adherence to the dietary patterns in adolescence.

aBMD, areal bone mineral density; BMC, bone mineral accrual; FN, femoral neck; LS, lumber spine; TB, total body.

Table 6.6. Tracking coefficients and change in score by age for dietary patterns derived during adolescence, from adolescence to adulthood, in PBMAS participants[1]

	Tracking dietary patterns			Change in dietary pattern score		
	ß (adolescence score)	95% CI	P value	ß (age)	95% CI	P value
Vegetarian style	0.59	0.48, 0.71	<0.001	0.026	0.00, 0.04	0.008
Western-like	0.47	0.40, 0.53	<0.001	-0.008	-0.029, 0.012	0.42
High fat, high-protein	0.51	0.41, 0.60	<0.001	-0.019	-0.034, -0.005	0.009
Mixed	0.54	0.39, 0.69	<0.001	-0.003	-0.033, 0.028	0.85
Snack	0.63	0.55, 0.70	<0.001	-0.003	-0.023, 0.018	0.80

[1] Generalized estimating equations (GEE) was used for modeling association between adolescence and adulthood standardized and energy adjusted dietary pattern scores while controlling for sex, age and age at adolescence; $n = 125$. Tracking coefficient (ß coefficient for adolescent dietary pattern) shows how participants maintained their position in the study population distribution, between adolescence and adulthood. Tracking coefficient for age represents z score change in dietary pattern score from adolescence to adulthood.

CI, confidence intervals.

6.4. Discussion

In my prospective study, I found that a "Vegetarian-style" dietary pattern rich in dark green vegetables, eggs, non-refined grains, 100% fruit juice, legumes, nuts and seeds, added fats, fruits and low-fat milk during adolescence was positively associated with adolescent total body BMC; this positive association continued into adulthood, average 15 years later. I also found that participants in the third quartile of adherence to the "Vegetarian-style" dietary pattern during adolescence had higher total body BMC, total body aBMD during adolescence and higher total body BMC, total body aBMD, femoral neck BMC and femoral neck aBMD during adulthood, compared to those in the quartile one. Tracking dietary pattern scores showed that participants moderately maintained their position in the study population distribution from adolescence to adulthood, which means dietary patterns were relatively stable over time. However, the overall adherence to "Vegetarian-style" dietary pattern increased from adolescence to adulthood.

It seems that association between adolescent "Vegetarian-style" dietary pattern and bone measurements is stronger in adults compared to adolescents. This observation could be, in some part, explained by the moderate stability of "Vegetarian-style" dietary pattern and increased adherence to this dietary pattern over time and the cumulative impact of diet on bone, from adolescence to adulthood.

In the present study, I only observed a positive association between "Vegetarian-style" dietary pattern and adolescent and adult total body and adult femoral neck bone measurements, but no associations was observed in adolescent or adult L lumbar spine bone. Lack of significant association between "Vegetarian-style" dietary pattern bone measurements might be due to the small sample size within each category. It might also be explained by the different proportions of cortical and trabecular bone compartments in the different skeletal sites. The trabecular bone is the predominant bone compartment in lumbar spine, while total body and femoral neck mainly contain cortical bone (Eastell et al, 1999; Kuiper et al, 1997). Trabecular bone is metabolically more active than cortical bone and might be influenced by everyday changes in hormone or environmental factors. Hence adaptations in bone might last longer in cortical compared to trabecular bone (Dodds et al, 1989).

Our study is unique as it evaluated the long-term impact of adolescent dietary patterns on adult bone. To my knowledge, there are only four studies that evaluated the dietary patterns during adolescence in association with bone health (Noh et al, 2011; Shin et al, 2013;

Monjardino et al, 2015; van den Hooven et al, 2015). Even though three of these studies were similar to my study in their prospective design (follow-up period ranged from 22 months to 6 years) (Noh et al, 2011; Shin et al, 2013; Monjardino et al, 2015; van den Hooven et al, 2015), identified dietary patterns are not directly comparable, because of the differences in dietary pattern approaches, food groupings and dietary habits and other characteristics of the study population (Newby & Tucker, 2004; Kant 2004). However, my findings of a positive association between "Vegetarian-style" dietary pattern and bone measurements are in accordance with the results from two studies which used reduced-rank regression (RRR) to derive dietary patterns. The RRR has the advantage of deriving dietary patterns associated with bone variables such as BMD and BMC (Noh et al, 2011) or intermediate factors such as protein, calcium, and potassium (van den Hooven et al, 2015), as response variables. In Korean girls (aged 9-11 years, n=198), the RRR-derived "fruits, nuts, milk beverages, eggs and grains" dietary pattern was associated positively and "egg and rice" dietary pattern was associated negatively with BMC gain after 22 months (Noh et al, 2011). Also, a higher intake of low-fat dairy, whole grains, and vegetables, as components of a dietary pattern rich in protein, calcium and potassium in Australian adolescents (aged 14 years, n=1024) was associated with higher BMD and BMC at age 20 years (van den Hooven et al, 2015). Overall, higher intakes of fruit and vegetables, milk and alternatives, nuts and grains were the common components in all dietary patterns which determined to be beneficial for bone (Noh et al, 2011, van den Hooven et al, 2015).

Our results are in line with the findings from previous cross-sectional or longitudinal dietary pattern studies in adolescents, adults and elderly populations and suggest that a high intake of fruit and vegetables, whole grains, poultry and fish, nuts and legumes and low-fat dairy products labeled as "healthy" dietary pattern are beneficial for bone health (Tucker et al, 2002; Okubo et al, 2006; Kontogianni et al, 2009; Langestmo et al, 2010; McNaughton et al, 2011; Hardcastle et al, 2011; Noh et al, 2011; Whittle et al, 2012; Shin et al, 2013; Chen et al, 2015; Shin et al, 2015; van den Hooven et al, 2015; Ward et al, 2016). I found that a "Vegetarian-style" dietary pattern rich in dark green vegetables, eggs, non-refined grains, 100% fruit juice, legumes, nuts and seeds, added fats, fruits and low-fat milk is beneficial for aBMD and BMC. Vegetables, fruits, and 100% fruit juices are rich in potassium, magnesium, vitamins C, K and folate and carotenoids (New, 2003). Potassium and magnesium may contribute to acid-base balance (New, 2003) and calcium metabolism (Rafferty & Heaney, 2008; Allgrove, 2009) to prevent bone loss.

Vitamin C acts as a cofactor for osteoblast differentiation and collagen formation which are active processes during adolescent growth (Gabby et al, 2010; Finck et al, 2014). Vitamin K also plays a role in bone matrix formation where mineralization happens (Gundberg et al, 2012). Low-fat milk and its alternatives are the main contributors of calcium and magnesium in the diet (Heaney, 2009), which have a structural role in bone health (Peters & Martini, 2010). They are also a source of protein, vitamin D, vitamin B_{12}, zinc and riboflavin (Heaney, 2009). An adequate protein intake is essential for bone matrix formation and maintenance. Eggs, legumes, nuts and seeds, as meat alternatives, are good sources of protein (Bonjour, 2011). Dietary fiber from non-refined grains and other plant sources might also have a beneficial impact on bone through decreasing glycemic load and inhibiting hyperinsulinemia which in turn prevents urinary calcium loss induced by insulin (Rosen, 2008). Added fats including mainly butter, margarine and mayonnaise seem to be the only unhealthy component of the "Vegetarian-style" dietary pattern. However, they might play a role in providing adequate dietary energy for adolescents during their growth spurt, when they are consumed along with other components of "Vegetarian-style" dietary pattern. Taken together, the "Vegetarian-style" dietary pattern represents a combination of beneficial nutrients and dietary components with potential synergic or interacting effects, therefore no single nutrient or dietary components could be pointed out as the one responsible for the beneficial impact of the dietary pattern on bone.

Our study has several strengths. This is the first study that evaluated dietary patterns during adolescence (aged 12.7±1.9 years) in association with adult (aged 28.2±3.4 years) bone health. In my sample, all participants during adulthood had their PBM confirmed by a plateau in bone mineral accrual curve, representing a steady status of bone (Baxter-Jones et al, 2011). I also controlled for somatic maturity by including the age of PHV as a covariate in my models. Adolescent dietary intake data were collected using multiple, mostly three, 24-h recalls over a year for each participant, which is preferred to food frequency questionnaires (Bingham et al, 1994), the method used by the majority of previous studies. In addition, I analyzed the impact of the whole diet, instead of a single food or nutrient, on bone.

The main limitation of my study was the small sample size (n=125 for adolescent analysis, and n=115 for adult analysis), which did not allow us to run the separate analysis for females and males or run other dietary pattern approaches such reduced-rank regression method. Small sample size also limited us from adding more covariates in the model such as adult dietary

patterns, smoking status, oral contraceptive use or reproductive history (in females). Even though I did not control the models for adult dietary patterns, I assessed change in dietary patterns from adolescence to adulthood to overcome this limitation. Two further limitations of my study are reliance on only one 24-hour recall in adulthood and using two different nutrient assessment systems from adolescence to adulthood. However, my focus was food group intake and these two systems were only used to measure total energy intake.

In conclusion, my results suggest that a diverse and well-balanced dietary pattern, rich in dark green vegetables, eggs, non-refined grains, 100% fruit juice, legumes, nuts and seeds, added fats, fruits and low-fat milk during adolescence has a beneficial impact on bone health during adolescence and this positive impact on bone accrual can be carried into adulthood. Further population-based studies are needed to confirm my findings and generalize these results in other populations.

To confirm the positive impact of single food groups on bone health, we also evaluated the impact of fruit and vegetables or milk and alternatives intake during adolescence on bone structure and strength during adulthood. Next Chapter represents the study results.

CHAPTER 7

STUDY 2

Published Paper:

Movassagh EZ, Kontulainen S, Baxter-Jones ADG, Whiting S, Szafron M, Papadimitropoulos M, Vatanparast H. **Are milk and alternatives and fruit and vegetable intakes during adolescence associated with cortical and trabecular bone structure, density and strength in adulthood?** Osteoporosis International 2017;28(2):609-619

7.1. Introduction

During the adolescent growth spurt, height velocity, and bone length increase substantially and bone mineral deposition is accelerated (Baxter-Jones et al, 2003; Bailey et al, 1999). More than 40% of the adult total bone mass is acquired during the 5-year period around the adolescent growth spurt (Baxter-Jones et al, 2011). Concurrently, adaptation in size and structure of long bones preserves bone stability and shape in growing skeleton (Rauch 2005; Kontulainen et al, 2005). Bone strength is determined by bone size, bone mineral mass and its spatial distribution within cortical and trabecular envelop, and bone material properties (Bouxsein & Seeman 2009; Kontulainen et al, 2007). Long bones are the most common site for fractures during the adolescent growth spurt and later in life (Bala et al, 2015; Bergstrom et al, 2008). Optimizing bone structural properties and strength during adolescence could lead to a long-term adaptation in bone and reduce the risk of fractures (Kontulainen et al, 2007; Bala et al, 2015). Therefore, it is important to determine modifiable factors that could influence the bone development and maintenance from adolescent to adulthood.

There is evidence from prospective and cross-sectional studies that milk and alternatives (M&A) intake (Du et al, 2002; Esterle et al, 2009; Mouratidou et al, 2013) and fruit and vegetable (F&V) intake (McGartland et al, 2004; Tylavsky et al, 2004; Vatanparast et al, 2005; Prynne et al, 2006; Li et al, 2013) are associated with greater bone mineral accrual in childhood and adolescence, as assessed by DXA. However, DXA as a two-dimensional method does not provide volumetric information of bone structure. Hence it is not clear if the increased bone mass was due to increase in bone size, density or both (Genant et al 2008). Peripheral QCT (pQCT) enables the assessment of bone structure from both cortical and trabecular bone in three

dimensions from the appendicular skeleton (Petit et al 2005). The evidence of the association between food group intake and pQCT bone measurements during the adolescent growth spurt is limited. In a 2-year randomized controlled trial, Cheng et al. (2005) reported that M&A intake (mainly cheese) was more effective in enhancing tibia cortical thickness in girls aged 10-12 years compared to the groups with calcium or calcium and vitamin D supplementation with the same amount of calcium (1000 mg/d) or placebo. Since the importance of potential benefits of M&A and/or F&V depends on their long-term persistence, prospective studies are needed to evaluate if the potential bone benefits from M&A and/or F&V intake during the adolescent growth spurt could be maintained into adulthood.

Thus, I aimed to determine whether consumptions of M&A or F&V during the adolescent growth spurt is associated with tibia and radius bone size, content, volumetric density and estimated strength in adulthood, after controlling for potential confounders. I hypothesized that adult males and females who had consumed a high intake level of M&A or F&V during their adolescent growth spurt have greater bone parameters compared to those with a low intake level of M&A or F&V while controlling for potential confounders.

7.2. Methods

7.2.1. Study Design and Participants

We recruited participants from the Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) (1991-2011). The mixed longitudinal design of the study has been described in detail elsewhere (Bailey et al, 1997; Baxter-Jones et al, 2011). In brief, the PBMAS cohort consists of 251 individuals (133 girls; aged 8 to 15 years) recruited from two elementary schools in the city of Saskatoon between 1991 and 1993. The PBMAS began with eight chronological age clusters (8 to 15 years) in 1991 (n=228), with the additional recruitment of 8- and 9-year-olds in 1992 and 1993. In the initial study phase, data were collected annually between 1991 and 1997; after a five-year break, annual data collection resumed between 2002 and 2005 during which data were obtained from 163 participants (90 females). Further annual data were collected between years 2010 and 2011 from 123 participants (74 females). At each measurement occasion, anthropometrics, physical activity (PA) and dietary intakes were recorded using the same instruments. Between 2010 and 2011, one pQCT scan was obtained from 122 participants (73 females, aged 24 to 34 years).

To control for somatic maturity, I defined adulthood and the adolescent growth spurt by the age of peak height velocity (PHV), which has been estimated for each participant previously and is explained elsewhere (Bailey et al, 1999; Baxter-Jones et al, 2011). For the present study, I included 116 of participants with available data for pQCT scans (69 females and 47 males, aged 29.2 ± 2.3 y at the time of pQCT scan) who had at least one available annual data for physical activity and dietary intake during adulthood (the period after the age at PHV+8 years) and at least one available annual data for physical activity and dietary intake around their adolescent growth spurt (5 years around PHV). Ethics approval was obtained from the University of Saskatchewan and Royal Hospital advisory boards on ethics in human experimentation (Bailey et al, 1997).

7.2.2. Dietary Intake

The dietary intakes of participants were assessed using 24-hour recalls. During the first six years of the study (1991-1996), 2-4 recalls per participant per year (in a school or research setting) were obtained. During 1997, 2002 to 2005, and 2010 to 2011 only one recall per participant was completed per year. For accurate estimations, participants had access to pictures of foods for portion size determination. We used the Canadian compatible nutrition assessment software: NUTS Nutritional Assessment System, version 3.7 (Quilchena Consulting Ltd, Victoria, BC, 1988) for the first phase of the study, and Food Processor version 8.0 and its revisions (ESHA Research Inc, Salem, Ore, 2003) for the follow-up studies, to analyze recall data and calculate total energy (kcal/d) and calcium (mg/d) intake. The M&A and F&V consumptions (servings/d) were determined directly from recalls using the definition of food groups and serving sizes in Canada's Food Guide to Healthy Eating 2014 (2007). Mean dietary intake estimated by all recalls collected over the one year represented the usual annual dietary intake. Most participants had more than three (maximum five) annual measurements during the growth spurt (81% of males and 64% of females) or adulthood (80% of males and 84% of females). The mean energy, calcium, M&A and F&V intake from all available annual data during the adolescent growth spurt or adulthood were averaged to represent mean usual intake during each period for each participant.

7.2.3. pQCT Bone Measurements

The pQCT scans were obtained on the non-dominant wrist, forearm, ankle and lower leg (Stratec XCT 2000; Stratec Medical, Pforzheim, Germany) according to our standard protocols

described in detail elsewhere (Duckham et al, 2014). For the shaft sites of radius and tibia (65% of the forearm and 66% of lower leg length), I report total area (ToA, mm^2) and cortical bone area (CoA, mm^2), density (CoD, mg/cm^3) and content (CoC, mg/mm). The density-weighted polar section modulus (SSI_p, mm^3) was also derived as the estimate of bone's resistance to torsion. For the distal sites of radius and tibia (4% of the forearm and lower leg length), I report trabecular area (TrA, mm^2), density (TrD, mg/cm^3) and content (TrC, mg/mm). The bone strength index (BSI_c, $mg^2/ mm^4=ToA\times ToD^2$) was calculated to estimate bone strength in compression (Kontulainen et al, 2008). In our laboratory, the short-term precision error (coefficient of variation, CV_{rms}) for the reported bone outcomes ranged from 1.4% to 6.1% at the radius and 0.7% to 2.1% at the tibia (Duckham et al, 2014). I assessed muscle area (mm^2) from the forearm and lower leg shafts. The precision error (CV_{rms}) for muscle area was 2.1% in the forearm and 3.5% in the lower leg (Frank-Wilson et al, 2015).

7.2.4. Physical Activity (PA)

PA was defined as sports, games, or dance that makes you breathe hard, make your legs feel tired or make you sweat. The PAQ administered, at least, three times per year during first three years and two times per year thereafter during the first phase of the study (1991-1997) and one time per year during follow-up. The PAQ was assessing physical activity during spare time in the previous 7 days by rating nine items in the questionnaire, scored on a five-point scale (Bailey et al, 1997). The average score derived from each questionnaire ranged from one to five, with higher scores indicating higher levels of physical activity. The PAQ administered in high school excluded the item regarding activity at recess in elementary school. A modified version of PAQ (7-item) was used during follow-up study. The physical activity scores from all PAQs collected during the adolescent growth spurt and adulthood were averaged to represent mean physical activity score during each period for each participant.

7.2.5. Statistical Analysis

We performed analysis in 47 males and 69 females separately. Based on the average intake of M&A or F&V (servings/d) during the adolescent growth spurt, participants were clustered into three intake levels (low intake= bottom quartile, moderate intake=middle quartiles, high intake= top quartile). I compared descriptive characteristics, including chronologic age, height, weight, BMI, physical activity score, M&A intake, F&V intake and total energy and calcium intake during adulthood or adolescence and lower leg and forearm muscle area during

adulthood, across the three M&A or F&V intake levels using ANOVA with Tukey HSD pairwise comparisons. I reported mean and SD for descriptive characteristics. To address the study objective, I compared adult site-specific (distal radius, radius shaft, distal tibia, tibia shaft) bone parameters (ToA, ToD, CoA, CoC, CoD, TrA, TrC and TrD) and strength indicators (SSIp and BSIc) across the three M&A or F&V intake levels using multivariate analysis of covariance (MANCOVA) with Bonferroni adjustment for multiple comparisons. The covariates were adult measures of height, muscle area, physical activity score, energy and calcium intake and adolescent physical activity score and energy intake. Selection of covariates was based on their linear correlation with adult bone parameters in our data and previous knowledge from the literature, and absence of multicollinearity between covariates. The normality of standardized residuals was tested using Shapiro-Wilk test. In the case of unequal variances of bone parameters (violation of homogeneity of variances), I transformed adult bone parameters (i.e. $x \rightarrow 1/x$) and p-value was reported for the transformed data. If MANCOVA revealed a significant between-group difference, I performed pairwise comparisons. I reported adjusted mean, SE and percent difference in bone variables across three intake levels. The Statistical Package of Social Science software (SPSS Inc, Version 22, Chicago, IL, USA) was used for all statistical analysis. An alpha level of $p < 0.05$ was considered significant.

7.3. Results

Mean descriptive characteristics across three intake levels are shown in Table 7.1 for adolescent M&A intake and Table 7.2 for adolescent F&V intake. The adult bone characteristics across adolescent M&A intake levels are shown in Table 7.3 for females and Table 7.4 for males. In females, no significant between-group differences were found at distal radius bone parameters ($p > 0.05$) (Table 7.3). At radius shaft, females who had consumed a high level of M&A had greater adjusted mean ToA (14%, $p < 0.05$), CoA (15%, $p < 0.01$) and CoC (16%, $p < 0.01$) compared to those with low levels of M&A intake during adolescence (Table 7.3). I found no significant between-group differences at distal tibia and tibia shaft bone parameters in females ($p > 0.05$) (Table 7.3). I found no significant between-group differences at distal radius, radius shaft, distal tibia or tibia shaft bone parameters in males ($p > 0.05$) (Table 7.4).

The adult bone characteristics across adolescent F&V intake levels are shown in Table 7.5 for females and Table 7.6 for males. In females, no significant between-group differences were found at distal radius, radius shaft and tibia shaft bone parameters ($p > 0.05$) (Table 7.5).

Females who consumed a moderate level of F&V had greater adjusted mean ToA (8.5%, $p < 0.05$) compared to those with low levels of F&V intake (Table 7.5). In males, I found no significant between-group differences across F&V intake levels ($p > 0.05$) (Table 7.6).

Table 7.1. Adult descriptive characteristics based on sex and adolescent levels of M&A intakes[1]

Females	Low intake (n =17)	Moderate intake (n =34)	High intake (n =18)
Age (years)	29±2	28±2	29±2
Height (cm)	164±6	165±5	168±8
Weight (kg)	77.4±22.9	66.5±13.8	72.3±16.3
BMI (kg/m^2)	28.1±6.8	24.0±4.8	25.4±5.7
Muscle area lower leg (mm^2)	6973±1221	6564±1053	6641±1451
Muscle area forearm (mm^2)	2937±447	2753±506	2690±685
M&A (serving/d)	1.7±1.0	1.9±0.9	1.6±0.8
F&V (serving/d)	4.1±1.9	4.3±2.4	4.6±1.9
Energy intake (kcal/d)	1724±465^{a,b}	1916±563^{a}	1519±429^{b}
Calcium intake (mg/d)	760±300	861±314	843±221
PA (score)	2.0±0.3	2.2±0.6	2.3±0.6
Adolescent age (years)	12±1	12±1	12±1
Adolescent height (cm)	155±9	155±7	158±9
Adolescent weight (kg)	50.5±13.9	46.9±10.4	50.0±11.3
Adolescent BMI (kg/m^2)	20.4±4.0	19.2±3.3	19.7±3.3
Adolescent M&A (serving/d)	1.3±0.4^{a}	2.3±0.3^{b}	3.8±0.7^{c}
Adolescent F&V (serving/d)	4.1±1.2	3.9±1.8	3.8±1.2
Adolescent energy intake (kcal/d)	1458±329^{a}	1672±309^{a}	2006±382^{b}
Adolescent calcium (mg/d)	665±195^{a}	986±209^{b}	1445±256^{c}
Adolescent PA (score)	2.8±0.6	2.9±0.6	2.7±0.5
Males	**Low intake (n =12)**	**Moderate intake (n =23)**	**High intake (n =12)**
Age (years)	29±2	29±2	30±1
Height (cm)	180±6	179±6	180±8
Weight (kg)	87.7±13.3	82.7±13.6	86.9±10.8
BMI (kg/m^2)	26.9±3.0	25.6±4.1	26.8±4.0
Muscle area lower leg (mm^2)	8715±1409^{a,b}	8176±1172^{a}	9325±905^{b}
Muscle area forearm (mm^2)	4982±1114	4570±661	5072±734
M&A (serving/d)	1.6±1.1	2.4±2.0	2.1±1.1
F&V (serving/d)	5.1±3.0	5.3±2.5	5.4±3.7
Energy intake (kcal/d)	2594±961	2565±664	2733±784
Calcium intake (mg/d)	968±437	1245±515	1099±394
PA (score)	2.5±0.5	2.2±0.5	2.3±0.3
Adolescent age (years)	13±1	13±1	14±0
Adolescent height (cm)	163±10	165±8	168±9
Adolescent weight (kg)	54.2±14.0	55.3±10.4	57.3±9.6
Adolescent BMI (kg/m^2)	20.0±2.9	20.2±3.0	20.0±2.5
Adolescent M&A (serving/d)	1.4±0.7^{a}	3.0±0.4^{b}	4.8±0.8^{c}
Adolescent F&V (serving/d)	3.7±1.3	4.4±1.2	3.8±1.6
Adolescent energy intake (kcal/d)	1941 ±365^{a}	2096±317^{a}	2538±513^{b}
Adolescent calcium (mg/d)	752±133^{a}	1173±168^{b}	1811±346^{c}
Adolescent PA (score)	3.3±0.4	2.9±0.6	3.0±0.5

[1]Values are mean ± SD, ANOVA, Tukey HSD post hoc pairwise comparisons. Labeled means in a row without a common superscript letter differ, $P < 0.05$.

ANOVA, analysis of variance; BMI, body mass index; F&V, fruit and vegetables; M&A, milk and alternatives; PA, physical activity

Table 7.2. Adult descriptive characteristics based on sex and adolescent levels of F&V intakes[1]

Females	Low intake (n =17)	Moderate intake (n =35)	High intake (n =17)
Age (years)	29±2	29±2	28±2
Height (cm)	165±4[a,b]	165±7[a]	169±6[b]
Weight (kg)	68.9±20.0	72.6±18.5	69.2±12.3
BMI (kg/m^2)	25.2±7.2	26.3±5.7	23.9±3.7
Muscle area lower leg (mm^2)	6818±1703	6660±923	6616±1225
Muscle area forearm (mm^2)	2818±575	2802±583	2704±448
M&A (serving/d)	1.7±0.8	1.7±1.0	1.9±0.8
F&V (serving/d)	3.4±1.6	4.3±2.0	5.2±2.4
Energy intake (kcal/d)	1939±596	1694±527	1737±441
Calcium intake (mg/d)	822±331	803±287	902±246
PA (score)	2.0±0.4	2.2±0.6	2.2±0.5
Adolescent age (years)	12±1	12±1	12±1
Adolescent height (cm)	156±6	155±9	159±7
Adolescent weight (kg)	49.8±14.7	48.2±11.5	48.2±7.9
Adolescent BMI (kg/m^2)	20.0±4.8	19.8±3.2	18.9±2.2
Adolescent M&A (serving/d)	2.5±0.8	2.3±1.0	2.6±1.0
Adolescent F&V (serving/d)	2.1±0.4[a]	3.7±0.5[b]	6.0±1.0[c]
Adolescent energy intake (kcal/d)	1547±227[a]	1665±386[a]	1967±407[b]
Adolescent calcium (mg/d)	1006±276	957±351	1204±404
Adolescent PA (score)	2.8±0.5	2.7±0.6	3.0±0.6
Males	**Low intake (n =12)**	**Moderate intake (n =22)**	**High intake (n =11)**
Age (years)	29±2	30 ±2	28±1
Height (cm)	180±6	178±7	181±7
Weight (kg)	82.7±13.6	82.8±12.8	91.4±12.1
BMI (kg/m^2)	25.5±4.3	25.9±3.6	27.7±4.0
Muscle area lower leg (mm^2)	8304±1172	8386±1175	9339±1328
Muscle area forearm (mm^2)	4697±1019	4785±794	4966±696
M&A (serving/d)	1.5±0.9	2.2±2.0	2.7±1.3
F&V (serving/d)	3.3±2.0[a]	5.7±2.1[b]	7.00±3.8[b,c]
Energy intake (kcal/d)	2575±916	2553±767	2724±690
Calcium intake (mg/d)	837±346	1191±543	1324±381
PA (score)	2.2±0.4	2.3±0.4	2.4±0.6
Adolescent age (years)	13±1	13±1	13±1
Adolescent height (cm)	164±8	165±9	165±10
Adolescent weight (kg)	53.8±12.9	54.4±10.8	58.4±10.3
Adolescent BMI (kg/m^2)	19.7±3.2	19.6±2.5	21.4±3.1
Adolescent M&A (serving/d)	3.00±1.6	3.00±1.3	3.00±1.3
Adolescent F&V (serving/d)	2.4±0.5[a]	4.1±0.6[b]	6.0±0.6[c]
Adolescent energy intake (kcal/d)	2000±270	2116±350	2307±562
Adolescent calcium (mg/d)	1151±491	1225±409	1244±469
Adolescent PA (score)	2.9±0.3	3.0±0.7	3.2±0.3

[1]Values are mean ± SD, ANOVA, Tukey HSD post hoc pairwise comparisons. Labeled means in a row without a common superscript letter differ, $P < 0.05$.

ANOVA, analysis of variance; BMI, body mass index; F&V, fruit and vegetables; M&A, milk and alternatives; PA, physical activity

Table 7.3. Adult females' adjusted bone parameters by adolescent level of M&A intakes[1]

		M&A intake	
Distal radius[2]	Low intake (*n* =17)	Moderate intake (*n* =33)	High intake (*n* =18)
ToA (mm^2)	355±9	358±6	343±9
ToD (mg/cm^3)	284±11	299±7	302±11
TrA (mm^2)	307±12	305±8	287±12
TrC (mg/mm)	67±3	68±2	62±3
TrD (mg/cm^3)	218±6	225±4	217±6
BSIc (mg^2/mm^4)	28±2	32±1	32±2
Radius shaft[2]	Low intake (*n* =17)	Moderate intake (*n* =33)	High intake (*n* =18)
ToA (mm^2)	112±3[a]	117±2[a,b]	128±3[b]
CoA (mm^2)	78±2[a]	83±1[a,b]	90±2[b]
CoC (mg/mm)	87±2[a]	94±2[a,b]	102±3[b]
CoD (mg/cm^3)	1117±8	1129±5	1132±8
SSIp (mm^3)	235±11	251±8	286±12
Distal tibia[3]	Low intake (*n* =16)	Moderate intake (*n* =31)	High intake (*n* =17)
ToA (mm^2)	1039±29	1051±19	1066±29
ToD (mg/cm^3)	284±10	289±6	301±10
TrA (mm^2)	949±34	953±23	957±34
TrC (mg/mm)	233±9	233±5	243±9
TrD (mg/cm^3)	246±7	246±4	254±7
BSIc (mg^2/mm^4)	84±5	89±3	97±5
Tibia shaft[3]	Low intake (*n* =16)	Moderate intake (*n* =31)	High intake (*n* =17)
ToA (mm^2)	524±14	537±9	575±13
CoA (mm^2)	310±7	315±5	330±7
CoC (mg/mm)	341±8	349±5	361±8
CoD (mg/cm^3)	1100±6	1108±4	1095±6
SSIp (mm^3)	2126±73	2237±46	2362±70

[1]Values are mean ± SE: MANCOVA, pairwise comparisons with Bonferroni adjustment. Labeled means in a row without a common superscript letter differ, $P < 0.05$.

[2]Adjusted for adult height 166.2 cm, forearm muscle area 2790 mm^2, physical activity 2.2, energy intake 1761 kcal and calcium intake 834 mg, and adolescent energy intake 1707 kcal and physical activity 2.8.

[3]Adjusted for adult height 166.3 cm, lower leg muscle area 6701 mm^2, physical activity 2.2, energy intake 1739 kcal and calcium intake 836 mg, and adolescent energy intake 1712 kcal and physical activity 2.8.

BSIc, bone strength index in compression; CoA, cortical area; CoC, cortical content; CoD, cortical density; MANCOVA, multivariate analysis of covariance; M&A, milk and alternatives; SSIp, bone strength in torsion; ToA, total area; ToD, total density; TrA, trabecular area; TrC, trabecular content; TrD, trabecular density.

Table 7.4. Adult males' adjusted bone parameters by adolescent level of M&A intakes[1]

		M&A intake	
Distal radius[2]	Low intake (*n* =12)	Moderate intake (*n* =23)	High intake (*n* =12)
ToA (mm^2)	455±22	474±15	476±23
ToD (mg/cm^3)	401±17	355±11	373±17
TrA (mm^2)	357±25	388±17	384±25
TrC (mg/mm)	104±6	105±4	101±7
TrD (mg/cm^3)	293±8	270±6	267±9
BSIc (mg^2/mm^4)	71±4	60±3	64±4
Radius shaft[2]	Low intake (*n* =12)	Moderate intake (*n* =23)	High intake (*n* =12)
ToA (mm^2)	168±6	165±4	165±6
CoA (mm^2)	116±3	115±2	113±3
CoC (mg/mm)	129±4	127±3	127±4
CoD (mg/cm^3)	1117±8	1104±5	1119±8
SSIp (mm^3)	440±22	414±15	411±22
Distal tibia[3]	Low intake (*n* =12)	Moderate intake (*n* =23)	High intake (*n* =12)
ToA (mm^2)	1324±57	1324±40	1341±60
ToD (mg/cm^3)	361±12	340±8	349±13
TrA (mm^2)	1153±61	1164±43	1150±64
TrC (mg/mm)	354±18	336±12	331±19
TrD (mg/cm^3)	308±9	289±6	292±9
BSIc (mg^2/mm^4)	173±11	154±8	163±12
Tibia shaft[3]	Low intake (*n* =12)	Moderate intake (*n* =23)	High intake (*n* =12)
ToA (mm^2)	726±18	724±12	716±18
CoA (mm^2)	418±12	437±8	420±12
CoC (mg/mm)	450±13	477±9	458±13
CoD (mg/cm^3)	1077±7	1093±5	1090±7
SSIp (mm^3)	3398±120	3502±81	3369±120

[1]Values are mean ± SE: MANCOVA, pairwise comparisons with Bonferroni adjustment. Labeled means in a row without a common superscript letter differ, $P < 0.05$.

[2]Adjusted for height 179.6 cm, forearm muscle area 4803 mm^2, physical activity 2.3, energy intake 2615 kcal and calcium intake 1137 mg, and adolescent energy intake 2169 kcal and physical activity 3.0.

[3]Adjusted for adult height 179 cm, lower leg muscle area 8607 mm^2, physical activity 2.3, energy intake 2615 kcal and calcium intake 1137 mg, and adolescent energy intake 2169 kcal and physical activity 3.0.

BSIc, bone strength index in compression; CoA, cortical area; CoC, cortical content; CoD, cortical density; MANCOVA, multivariate analysis of covariance; M&A, milk and alternatives; SSIp, bone strength in torsion; ToA, total area; ToD, total density; TrA, trabecular area; TrC, trabecular content; TrD, trabecular density.

Table 7.5. Adult females' adjusted bone parameters by adolescent level of F&V intakes[1]

	F&V intake		
Distal radius[2]	Low intake (*n* =17)	Moderate intake (*n* =35)	High intake (*n* =17)
ToA (mm^2)	338±8	357±6	361±10
ToD (mg/cm^3)	298±10	292±7	301±12
TrA (mm^2)	285±11	305±7	307±12
TrC (mg/mm)	62±3	68±2	68±3
TrD (mg/cm^3)	218±6	223±4	222±7
BSIc (mg^2/mm^4)	30±2	31±1	32±2
Radius shaft[2]	Low intake (*n* =17)	Moderate intake (*n* =35)	High intake (*n* =16)
ToA (mm^2)	118±3	119±2	118±4
CoA (mm^2)	85±2	83±1	84±2
CoC (mg/mm)	97±3	93±2	94±3
CoD (mg/cm^3)	1140±7	1124±5	1119±8
SSIp (mm^3)	260±11	257±8	248±13
Distal tibia[3]	Low intake (*n* =15)	Moderate intake (*n* =33)	High intake (*n* =16)
ToA (mm^2)	998±26[a]	1082±18[b]	1040±28[a,b]
ToD (mg/cm^3)	300±9	290±6	285±10
TrA (mm^2)	887±31	985±21	949±33
TrC (mg/mm)	222±8	245±5	228±8
TrD (mg/cm^3)	249±7	249±4	244±7
BSIc (mg^2/mm^4)	92±5	91±3	85±5
Tibia shaft[3]	Low intake (*n* =15)	Moderate intake (*n* =33)	High intake (*n* =16)
ToA (mm^2)	529±13	555±9	536±14
CoA (mm^2)	314±7	321±5	313±7
CoC (mg/mm)	350±7	353±5	346±8
CoD (mg/cm^3)	1112±5	1097±4	1104±6
SSIp (mm^3)	2234±69	2275±49	2188±75

[1]Values are mean ± SE: MANCOVA, pairwise comparisons with Bonferroni adjustment. Labeled means in a row without a common superscript letter differ, $P < 0.05$.

[2]Adjusted for height 166.2 cm, forearm muscle area 2790 mm^2, physical activity 2.2, energy intake 1761 kcal and calcium intake 834 mg, and adolescent energy intake 1707 kcal and physical activity 2.8.

[3]Adjusted for height 166.3 cm, lower leg muscle area 6701 mm^2, physical activity 2.2, energy intake 1739 kcal and calcium intake 836 mg, and adolescent energy intake 1712 kcal and physical activity 2.8.

BSIc, bone strength index in compression; CoA, cortical area; CoC, cortical content; CoD, cortical density; MANCOVA, multivariate analysis of covariance; M&A, milk and alternatives; SSIp, bone strength in torsion; ToA, total area; ToD, total density; TrA, trabecular area; TrC, trabecular content; TrD, trabecular density.

Table 7.6. Adult males' adjusted bone parameters by adolescent level of F&V intakes[1]

		F&V intake	
Distal radius[2]	Low intake (*n*=12)	Moderate intake (*n*=22)	High intake (*n* =11)
ToA (mm^2)	451±22	472±15	481±22
ToD (mg/cm^3)	381±18	373±12	358±18
TrA (mm^2)	358±25	381±17	393±17
TrC (mg/mm)	97±6	105±4	107±6
TrD (mg/cm^3)	271±9	277±6	275±9
BSIc (mg^2/mm^4)	65±4	65±3	62±4
Radius shaft[2]	Low intake (*n* =12)	Moderate intake (*n* =22)	High intake (*n* =11)
ToA (mm^2)	165±6	168±4	163±6
CoA (mm^2)	114±3	114±2	115±3
CoC (mg/mm)	127±4	126±3	128±4
CoD (mg/cm^3)	1118±7	1105±5	1109±7
SSIp (mm^3)	408±21	432±15	408±22
Distal tibia[3]	Low intake (*n* =12)	Moderate intake (*n* =22)	High intake (*n* =11)
ToA (mm^2)	1345±57	1334±39	1313±60
ToD (mg/cm^3)	347±12	351±8	338±13
TrA (mm^2)	1153±60	1163±42	1172±64
TrC (mg/mm)	331±18	347±12	340±19
TrD (mg/cm^3)	287±9	299±6	292±10
BSIc (mg^2/mm^4)	165±11	164±8	149±12
Tibia shaft[3]	Low intake (*n* =12)	Moderate intake (*n* =22)	High intake (*n* =11)
ToA (mm^2)	737±17	727±11	694±17
CoA (mm^2)	424±12	434±8	418±12
CoC (mg/mm)	461±13	471±9	456±13
CoD (mg/cm^3)	1088±7	1087±5	1092±7
SSIp (mm^3)	3472±113	3500±75	3253±115

[1]Values are mean ± SE: MANCOVA, pairwise comparisons with Bonferroni adjustment. Labeled means in a row without a common superscript letter differ, $P < 0.05$.

[2]Adjusted for height 179.5 cm, forearm muscle area 4806 mm^2, physical activity 2.3, energy intake 2601 kcal and calcium intake 1138 mg and adolescent energy intake 2131 kcal and physical activity 3.0.

[3]Adjusted for height 179.5 cm, lower leg muscle area 8597 mm^2, physical activity 2.3, energy intake 2601 kcal and calcium intake 1138 mg and adolescent energy intake 2131 kcal and physical activity 3.0.

BSIc, bone strength index in compression; CoA, cortical area; CoC, cortical content; CoD, cortical density; MANCOVA, multivariate analysis of covariance; M&A, milk and alternatives; SSIp, bone strength in torsion; ToA, total area; ToD, total density; TrA, trabecular area; TrC, trabecular content; TrD, trabecular density.

7.4. Discussion

Comparing adjusted bone parameters in adults aged 24 to 34 years old across adolescent M&A or F&V intake levels suggests a beneficial effect of greater adolescent M&A or F&V consumption on cortical and trabecular bone size and content in females but not in males. To our knowledge, this is the first study evaluating the longer-term effect of M&A or F&V intake through adolescence on the adult bone properties in a healthy cohort of females and males. These findings complement previous DXA reports of positive associations between M&A (Du et al, 2002; Esterle et al, 2009; Mouratidou et al, 2013) or F&V intakes (McGartland et al, 2004; Tylavsky et al, 2004; Vatanparast et al, 2005; Prynne et al, 2006; Li et al, 2013) and bone mineral accrual in children and adolescents.

In the current study, I found that females who had consumed high levels of M&A (3.8 ± 0.7 servings/d) compared to those who consumed low levels of M&A (1.3 ± 0.3 servings/d) during adolescence had greater ToA, CoA and CoC at radius shaft during adulthood. This finding suggests that increase in M&A intake might lead to a greater bone accrual in the periosteal surface in the radius shaft during the adolescent growth spurt, which could be carried over into adulthood. Although estimated bone strength (SSIp) did not differ between the high and low levels of M&A intake, greater CoA and CoC improve bone's resistance to both bending and axial forces (Kontulainen et al, 2008). On the other hand, I did not reveal any differences in the adult tibia shaft structure and strength parameters across adolescent M&A intake levels in females or males. We previously showed that adults who were physically active during adolescence had greater tibia shaft CoA and CoC in females and ToA in males compared to those who were physically inactive (Duckham et al, 2014). Adjusting for physical activity in my analysis might have attenuated the possible association between M&A intake and tibia shaft parameters. Results of the study did not reveal any positive association between M&A intake and trabecular bone measurements in females and males. In the cross-sectional study by Radavelli-Bagatini et al., higher intake of dairy during older years was associated with a greater tibia (at 15% lower leg) ToC, CoC, ToD and TrD in elderly women (aged 80-92 y) (Radavelli-Bagatini et al, 2014).

Our results suggest a long-term beneficial effect of adolescent F&V intake on adult distal tibia ToA as a weight-bearing site when I compared moderate intake (3.7 ± 0.5 servings/d) and low intake levels (2.1 ± 0.4 servings/d), in females. In a previous study, we showed that adult

females who were physically active during adolescence had greater TrC in distal tibia compared to those who were physically inactive during adolescence (Duckham et al 2014). Current finding is important because even after adjusting for PA, the positive impact of adolescent F&V intake on long-term bone adaptation persisted in distal tibia. When I aggregated moderate and high intake levels (4.5 ± 1.3 servings/d) (n=49) to increase the cell size, participants in this group had, respectively, 7% (p=0.022) and 10% (p=0.018) greater adjusted mean ToA and TrA compared to those in the low intake (2.1 ± 0.4 servings/d) group (n=15). In the study by New et al. (2000), F&V intake during adolescence or early adulthood was not associated with ultra-distal radius cortical and trabecular properties during late adulthood (aged 44-55 y) in women (New et al 2000). In the current study, I did not identify any beneficial associations of adolescent F&V intake on adult bone pQCT measurements in males.

Several theoretical mechanisms have been suggested for the beneficial effects of F&V on bone. One of the main mechanisms is the role of F&V in the acid-base balance. During metabolic acidosis, bone tissue releases components with alkalinity effects to buffer the acid load that results in higher urinary calcium excretion (Welch et al, 2008). It is believed that higher content of potassium and magnesium in F&V can spare bone tissue and retain calcium (Welch et al, 2008). However, in a recent study adjustment for dietary acid load did not change the association between F&V and bone mass, suggesting a different possible mechanism for F&V (Aghajanian et al, 2015). The vitamin C (Aghajanian et al, 2015) and K (Weber et al, 2001), which are necessary for bone matrix formation, are also abundant in F&V. After adjustment for vitamin C intake, positive association between F&V and bone mass attenuated (Liu et al, 2015) or remained significant (McGartland et al, 2004; Prynne et al, 2006; Li et al, 2013). Phytochemicals and phytoestrogen may also induce beneficial effects on bone by imitating the estrogen effects through its receptors on the bone tissue (Weaver et al, 2012). In general, findings from existing studies suggest that mechanism of positive association between higher intake of F&V and bone might be multifactorial, therefore further research is required.

The present study has some limitations. Dietary intake and physical activity were assessed using self-reported methods, which are prone to recall and reporting biases. Only a small proportion of adolescents met the recommendations by Canada's food guide (2007) for an adequate intake of M&A (25% of females and 40 % of males) or F&V (less than 30% of females and males) restricting my analysis to intakes less than recommended levels. Hence, to obtain an

appropriate distribution, I had to classify participants into three groups of low, moderate and high intake levels based on quartiles of food group intake, not adequate and inadequate intake. My analysis did not account for dietary intake for late adolescence and early adulthood because of limited data collection during these periods. Although dietary intake during adolescence might have a critical impact on bone growth and development, the long-term adaptation might also be influenced or confounded by dietary intakes during years preceding or following the adolescent growth spurt (Kant 2004). Despite sequential measurements of dietary intake and physical activity from childhood to adulthood, only one pQCT bone scan was obtained during adulthood, making it difficult to control for the adolescent pQCT bone measurements. The absence of any association between M&A or F&V intake during the adolescent growth spurt and adult bone properties in males might be due to the small sample size (n=47) and smaller proportion of them in low and high intake levels (n=12).

Our study has several strengths, including its longitudinal nature, which allowed us to evaluate the long-term effect of M&A or F&V intake during the adolescent growth spurt (as the critical period during bone growth and development) on early adulthood bone. Aligning participants based on their age of PHV provided the opportunity to control for somatic maturity and puberty stage. Using the pQCT bone measurements enabled us to investigate the impact of M&A or F&V intake on cortical and trabecular bone properties and bone strength. This information could not be obtained using the DXA method.

In conclusion, this is the first study evaluating the long-term effects of M&A or F&V intake during the adolescent growth spurt on bone structural properties in adulthood in a prospectively followed cohort. I found that milk and alternatives and fruit and vegetable intakes during adolescence in females were positively associated with the adult total area, cortical area and cortical content at the radius shaft, and total area at the distal tibia, respectively. This association was independent of adult height, muscle area, physical activity and energy and calcium intake and adolescent energy intake and physical activity.

In Chapter 6 and 7 we addressed our research Objective One. We found that those participants who have had higher adherence to a “Vegetarian Style” dietary pattern during adolescence had higher BMC or BMD during adulthood. However, it is not clear whether the established dietary patterns during adolescence has maintained until adulthood or not. To address this question (Objective two) we conducted the following study in Chapter 8.

CHAPTER 8

STUDY 3

Movassagh EZ, Whiting S, Baxter-Jones ADG, Kontulainen S, Vatanparast H. **Tracking dietary patterns over 20 years from childhood and adolescence to adulthood.**

8.1. Introduction

Nutrition is a lifestyle factor that is associated with etiology of numerous chronic conditions (Kant et al, 2004). The complex mixture of nutrients and dietary components from a variety of foods, with synergistic or confounding effects on each other, might influence a health outcome (Tapsell et al, 2016). In nutritional epidemiology, dietary pattern approach has gained a growing attention as an alternative to the conventional method of assessing single nutrient or food intakes (Tucket, 2016). Dietary patterns provide a comprehensive image and allow for assessing the contributions from various dietary aspects on the health outcomes, simultaneously (Newby 2004).

There is a belief that dietary habits established during childhood and adolescence might persist into adulthood. Accordingly, early modification in eating habits and behaviors might promote health, and decrease the risk of developing certain health conditions during later in life (Bennet et al, 2015). However, there are limited studies evaluating the stability of dietary patterns over time from childhood to adolescence (Dekker et al, 2013) or from childhood to adulthood (Mikkila et al, 2005). The majority of studies in children and adolescents followed participants over a short period ranging from 3 to 6 years (Northstone et al. 2008, Ambrosini et al. 2014, Lioret et al. 2015, Scheneider et al. 2016). Findings from these studies were inconclusive due to variations in age at baseline, longer or shorter follow-up periods and different dietary pattern approaches or statistical analysis.

None of these studies examined the consistency of dietary patterns at individual level over the entire time. In 2003, Twisk suggested an approach to measure how individuals maintained their position in the study population distribution in the subsequent measurements (Twisk 2003). Based on this method, tracking coefficients can be calculated for dietary pattern scores in a longitudinal study with repeated measurements. Mixed longitudinal data from Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS, 1991-2011) (Bailey, et al, 1997;

Baxter-Jones et al, 2011) provided a unique opportunity for tracking dietary patterns from childhood to adulthood and change in dietary pattern scores by age.

We previously identified five dietary patterns in 125 PBMAS participants (53 females and 72 males) during age 12.7±2 years using the dietary intake data collected in 1992/1993, to evaluate the impact of adolescent dietary patterns on the adult bone (aged 28.2±3.4 years). In this study, my objective is to evaluate 1) stability of these dietary patterns from childhood and adolescence to adulthood and 2) change in dietary pattern scores by age from age 8 to 34 years.

8.2. Methods

8.2.1. Participants

Longitudinal data from the PBMAS participants were analyzed in this study. The details about the mixed longitudinal design of the study have been described elsewhere (Bailey, et al, 1997; Baxter-Jones et al, 2011). In brief, 251 children (133 girls and 118 boys; aged 8 to 15 years) were recruited from two elementary schools in the city of Saskatoon between 1991 and 1993. Participants then were followed with annual measurements until 2011 except two gaps between 1997 and 2002 and between 2005 and 2010. During study years, anthropometrics, dietary intake, physical activity (PA) and body composition were assessed.

For the present study, only 130 participants (53 females and 77 males), who had at least one available annual dietary intake assessment, comprise my data set. The maximum number of observations for each participant was thirteen, corresponding to the total number of annual measurements conducted during the study years: 1991, 1992, 1993, 1994, 1995, 1996, 1997, 2002, 2003, 2004, 2005, 2010, 2011. Decimal chronological age of participants was calculated using their date of birth. I created chronological age groups using one-year intervals, for instance, I included observations between 8.50 and 9.49 years in the 9 years old age group. Because of the various number of subsequent measurements for each participant and overlapping in ages, there were a different number of observations at each age group. Overall, there was a consecutive 27-year developmental pattern (8 to 34 years) over the 20-year period of the study from 1991 to 2011. Ethics approval was obtained from the University of Saskatchewan and Royal Hospital advisory boards on ethics in human experimentation (Bailey et al, 1997).

8.2.2. Dietary Intake

The dietary intakes of participants were assessed using 24-hour recalls. For all participants, 24-hour recalls were self-administered, except for the younger children from grades 2 and 3 for which the interviewer wrote down the verbally provided information. A training session on food portion sizes conducted for children at the beginning of the study. In addition, to determine accurate estimates of portion sizes, participants had access to pictures of foods. Dietary intake information was collected 3-4 times per year during the first four years of study from 1991 to 1994 and 2-3 times per year during 1995 and 1996. Dietary intake data from multiple 24-hour recalls per year were used to estimate average intake during the year. Only one 24-hour recall per year was completed for each participant, thereafter. To have a consistent unit of measure, quantities of consumed foods reported in the 24-hour recalls were converted to gram weight. Then, I assigned all food and beverage items into 25 non-overlapping food groups based on their similarity in nutrient content or culinary usage. These food group intake data then were aligned with other measurements for each year, as annual measurements. I used the dietary intake data of 25 food groups in dietary pattern analysis. Table 6.1 (Chapter 6) represents the 25 food groups and food items assigned to each group.

To estimate total energy intake per day, dietary intake data collected from 1991 to 1997 was analyzed using Canadian compatible nutrition assessment software: NUTS Nutritional Assessment System, version 3.7 (Quilchena Consulting Ltd, Victoria, BC, 1988). Estimates of total energy for the other follow-up years was obtained using Food Processor version 8.0 and its revisions (ESHA Research Inc, Salem, Ore, 2003).

8.2.3. Statistical Analysis

We calculated the applied dietary pattern scores for all study years from 1991 to 2011, based on the factor loadings for 25 food groups in five dietary patterns (Table 6.2, Chapter 6). To control for the increase in overall intake over the time, first, I adjusted intakes of 25 food groups for total energy intake (g/1000 kcal). Then, energy-adjusted food group intakes (g/1000 kcal) were multiplied by their factor loadings for each dietary pattern and were summed up, or subtracted for negative loadings, to generate a dietary pattern score for each participant during each study year. This method of computing the dietary pattern scores allows food groups with higher factor loadings to have a higher contribution to the total dietary pattern score (DiStefano et al, 2009).

To evaluate tracking (stability) of the five dietary patterns over time (addressing the first

objective), applied dietary pattern scores from 1991 to 2011 were used. For each participant, the first available measurement was considered as baseline dietary pattern score. Dietary pattern scores for all repeated measurements were standardized for mean and standard deviation of baseline dietary pattern scores, using this formula*:

$$Z - score\ (\text{DP score}) = \frac{X(\text{DP score}) - \bar{X}(\text{baseline DP score})}{SD(\text{baseline DP score})}$$

*DP = dietary pattern

Tracking coefficients for each dietary pattern were calculated using generalized estimating equations (GEE). I regressed baseline standardized dietary pattern scores (independent variable) against all other standardized dietary pattern scores (dependent variable) during entire follow-up time, simultaneously, while adjusting for chronological age groups (age 8 to 34 years) as the time-dependent variable, and sex and age at baseline as time-independent variables. As sex and its interaction with age were significant, I evaluated tracking for males and females separately. The tracking coefficient represents the correlation between baseline dietary pattern scores and all other follow-up dietary pattern scores. In other words, it shows how participants maintained their position in the total sample distribution from baseline to the last follow-up measurement. As I used the standardized values, the tracking coefficient only takes values between 0 and 1, indicating no tracking and strong tracking, respectively. However, there are no standard cutoffs indicating the classification of tracking strength within this spectrum. Some investigators categorized coefficients between 0.30 and 0.60 as moderate tracking (Northstone 2012). The beta coefficient for chronological age represents the change in dietary pattern score for each year increase in age (addressing the second objective).

To assess the stability of dietary patterns I also evaluated the transition between dietary pattern score quartiles from childhood to adolescence and adulthood (addressing the first objective). To do this, I averaged all the measurements collected during age 8-13 years, 14-18 years and >18 years as childhood, adolescence and adulthood measurements for each participant, respectively. The number of participants who had one average measurement during childhood, adolescence or adulthood was 100, 119 and 124, respectively. Participants were assigned into quartiles of dietary pattern scores during childhood, adolescence, and adulthood. Participants in the quartile four had the highest adherence and those in quartile one had the lowest adherence to the dietary pattern. Proportion of participants (%) who remained in the same quartile from

childhood to adolescence or adulthood and from adolescence to adulthood was determined and the level of agreement was estimated using the Cohen's kappa coefficient. The kappa agreement represents the proportion of participants who remained in the same quartile after accounting for the possibility of chance. Standard cut-offs for kappa coefficient are as follows: <0.2 poor; 0.2–0.4 fair; 0.41–0.6 moderate; 0.61– 0.8 good and >0.81 very good (Landis & Koch, 1979).

All statistical analysis was performed using SPSS software, version 24.0 (SPSS, Chicago, lL, USA). A P-value of <0.05 was considered significant.

8.3. Results

Table 8.1 represents tracking coefficients for standardized scores of five dietary patterns and change in the score by age from age 8 to 34. The greater tracking coefficients show the higher stability of dietary patterns. Tracking coefficient, ordered from more stable to less stable dietary patterns, were 0.44 "Vegetarian-style", 0.39 for "High-fat, high-protein", 0.26 for "Snack" and 0.22 for "Mixed" dietary pattern, in females; and were 0.30 for "Vegetarian-style", 0.28 for "High-fat, high-protein" and "Snack", 0.25 for "Mixed" and 0.19 for "Western-like" dietary pattern, in males. Tracking coefficient for "Western-like" dietary pattern in females was not significant.

For each year increase in age, "Vegetarian-style" dietary pattern score increased by 0.017 SD and "High-fat, high-protein" dietary pattern score decreased by 0.019 SD in females. For each year increase in age, "Vegetarian-style" dietary pattern score increased by 0.032 SD, "Western-like" dietary pattern score increased by 0.028 SD, "High-fat, high-protein" dietary pattern score decreased by 0.014 SD and "Mixed" dietary pattern score increased by 0.019 SD, in males. The "Western-like" and "Mixed" dietary patterns in females and "Snack" dietary pattern in females and males did not reveal any significant change by age (Table 8.1).

Mean age of participants during childhood (aged 8-13 years), adolescence (aged 14 to 18 years) and adulthood (aged >18 years) were 12.2±0.7 years, 15.6±1.1 years, and 25.1±2.6 years, respectively. Table 8.2 shows the proportion (%) of participants who remained in the same quartile of dietary pattern score from childhood to adolescence or adulthood and from adolescence to adulthood. In females, the proportion ranged between 34% to 44% for "Vegetarian-style", 22% to 34% for "Western-like", 43% to 48% for "High-fat, high-protein", 25% to 44% for "Mixed" and 33% to 41% for "Snack" dietary patterns. There was a significant

level of agreement in quartile assignment for “High-fat, high-protein” (κ 0.24) or “Snack” dietary patterns (κ 0.21) from childhood to adolescence; for “Vegetarian-style” (κ 0.22), “High-fat, high-protein” (κ 0.30), “Mixed” (κ 0.25) and “Snack” (κ 0.16) dietary pattern from adolescence to adulthood, and for “Vegetarian-style” (κ 0.26) or “High-fat, high-protein” (κ 0.26) from childhood to adulthood, in females.

In males, proportion of participants who remained in the same quartile varied from 31% to 51% for “Vegetarian-style”, 21% to 34% for “Western-like”, 18% to 49% for “High-fat, high-protein”, 25 to 35% for “Mixed” and 25% to 35% for “Snack” dietary patterns. There was a significant level of agreement in quartile assignment for “Vegetarian-style” (κ 0.34) or “High-fat, high-protein” (κ 0.32) from childhood to adolescence; for “Mixed” (κ 0.13) and “Snack” (κ 0.13) dietary pattern from adolescence to adulthood, in males. No significant level of agreement was detected from childhood to adulthood in males.

Table 8.1. Tracking coefficients of standardized dietary pattern score and change of standardized dietary pattern score by age in PBMAS participants[1]

	Tracking dietary patterns			Change in dietary patterns		
	ß (baseline score)	95% CI	P value	ß (age)	95% CI	P value
Females (*n=53*)						
Vegetarian style	0.44	0.32, 0.56	<0.001	0.017	0.003, 0.031	0.020
Western-like	0.11	-0.08, 0.31	0.264	-0.009	-0.026, 0.008	0.321
High fat, high-protein	0.39	0.27, 0.51	<0.001	-0.019	-0.031, -0.007	0.002
Mixed	0.22	0.07, 0.37	0.004	-0.014	-0.031, 0.004	0.127
Snack	0.26	0.17, 0.36	<0.001	0.009	-0.002, 0.020	0.124
Males (*n=77*)						
Vegetarian style	0.30	0.13, 0.46	<0.001	0.032	0.015, 0.048	<0.001
Western-like	0.19	0.07, 0.31	0.001	0.028	0.011, 0.045	0.001
High fat, high-protein	0.28	0.15, 0.40	<0.001	-0.014	-0.027, -0.001	0.042
Mixed	0.25	0.13, 0.38	<0.001	0.019	0.003, 0.035	0.018
Snack	0.28	0.20, 0.36	<0.001	-0.013	-0.028, 0.002	0.096

[1] Generalized estimating equations (GEE) was used to estimate tracking coefficient. Tracking coefficient was adjusted for chronologic age and age at baseline. In each category, z-scores calculated for just the corresponding category. Beta coefficient for age represents z score change in dietary pattern score from baseline to adulthood. CI, confidence intervals.

CI, confidence intervals.

Table 8.2. Proportion (%) of participants remaining in the same quartile for dietary pattern score from childhood to adulthood in total sample[1]

		Childhood vs. adolescence			Adolescence vs. adulthood			Childhood vs. adulthood		
		%	Kappa agreement	P value	%	Kappa agreement	P value	%	Kappa agreement	P value
Females		*n=44*			*n =48*			*n=45*		
	Vegetarian style	34.1	0.121	0.164	41.7	0.222	0.008	44.4	0.259	0.003
	Western-like	34.1	0.121	0.164	33.3	0.111	0.182	22.2	-0.038	0.663
	High fat, high-protein	43.2	0.242	0.005	47.9	0.306	<0.001	44.4	0.259	0.003
	Mixed	25.0	0.000	1.000	43.8	0.250	0.003	28.9	0.051	0.551
	Snack	40.9	0.212	0.015	37.5	0.167	0.046	33.3	0.111	0.199
Males		*n=47*			*n=65*			*n=50*		
	Vegetarian style	51.1	0.347	<0.001	30.8	0.077	0.284	32.0	0.093	0.256
	Western-like	34.0	0.120	0.154	21.5	-0.046	0.517	28.0	0.039	0.629
	High fat, high-protein	48.9	0.319	<0.001	24.6	-0.005	0.940	18.0	-0.094	0.250
	Mixed	25.5	0.007	0.937	35.4	0.138	0.054	32.0	0.093	0.256
	Snack	25.5	0.007	0.937	35.4	0.138	0.054	32.0	0.093	0.256

[1]Childhood: 9-13 years; adolescence: 14-18 years; adulthood: >18 years

8.4. Discussion

We found a moderate tracking for the "Vegetarian-style" and "High-fat, high-protein" dietary patterns in females and "Vegetarian-style" dietary pattern in males. Except for no tracking for the "Western-like" dietary pattern in females, remaining dietary patterns showed a poor-to-fair tracking in females and males. Assessing transition between dietary pattern score quartiles from childhood to adolescence or adulthood or adolescence to adulthood revealed no consistent trend in males and females for different dietary patterns. I found a significant increase in "Vegetarian-style" dietary pattern score and a significant decrease in "High-fat, high-protein" dietary pattern scores, by age, in both sexes. The "Western-like" and "Mixed" dietary patterns scores increased significantly by age, only in males. These changes were independent of increase in energy intake from adolescence to adulthood.

To my knowledge, only two studies in adults (Batis et al, 2014; Johns et al. 2014) and one study in children (Ambrosini et al 2014) used GEE for tracking dietary pattern scores over time. In the China health and nutrition survey, applied scores for "traditional southern" and "modern high-wheat" dietary patterns, derived using PCA, were tracked in 9253 participants aged ≥18 years from 1991 to 2009. Dietary intake data were collected using 3-day 24-hour recalls at 7 time-points over 18 years. Both dietary patterns were remarkably stable over time, with stronger tracking for traditional southern compared to modern high-wheat dietary patterns (0.71 vs. 0.55) (Batis et al 2014). In Swedish obese subjects (SOS) study, the "energy-dense, high saturated fat and low fiber density" dietary pattern derived using reduced-rank regression (RRR) method, were tracked in 2037 severely obese subjects aged 47±6 years at baseline. A semi-quantitative diet questionnaire was used to assess dietary intake at 10 time-points over ten years. They found a moderate tracking, 0.40 in women and 0.38 in men (John et al. 2014). Even though I used a similar approach in tracking dietary pattern scores over time, my findings are not directly comparable to these results since these studies only evaluated the change in dietary pattern during adulthood. In the Avon Longitudinal Study of Parents and Children (ALSPAC) in UK, a "high energy, high fat, low fiber" dietary pattern identified by RRR method in 7027 children aged 7 years at baseline were tracked 3 years and 6 years later. They reported a moderate tracking, 0.38 in girls and 0.48 in boys, from 7 to 13 years of age (Ambrosini et al, 2014). Despite shorter follow-up time in this study, the tracking coefficients were comparable to those estimated in my study for "high-protein, high fat" dietary pattern.

Another popular method of evaluating the change in dietary patterns over time is assessing the proportion of participants who remained in the same class of dietary pattern score or same cluster over time. In Doetinchem cohort study in Netherlands, the stability of two dietary patterns, "low-fiber bread" and "high-fiber bread", derived using cluster analysis was investigated in children from age 6 (n=6113) to age 11 (n=4916) and 16 (n=4520) years. Results of the study showed that there was a good reproducibility for food groups at each cluster and almost 42% of participants remained in the same cluster of dietary patterns after 10 years (Dekker et al, 2013). In another study, change in dietary patterns of 3823 adolescents in Brazil was investigated from age 15 to 18 years. Using latent class analysis, participants were categorized into four dietary pattern classes including "varied", "traditional" and "dieting" at both time points, and "processed meats" at age 15 years or "fish, fast food, and alcohol" at age 18 years. The most frequent change was a transition of participants from "processed meat" to "dieting" class (38%). However, 36% of participants in "dieting" class at age 15 remained in the same class at age 18 years (Schneider et al 2016). These studies were different from my study due to a shorter period of follow-up time, different dietary pattern approaches and a smaller number of repeated measurements.

Only one study has evaluated the change in dietary patterns from childhood to adulthood (Mikkila et al, 2005). Mikkila et al have investigated the longitudinal change of dietary patterns in participants of Cardiovascular Risk in Young Finns Study (aged 3-18 years at baseline, n=1768) after 6 and 21 years using a 48-hour recall at each time point. The two "traditional Finnish" and "health-conscious" dietary patterns, derived using PCA, showed a moderate correlation (0.32 and 0.38, respectively) between baseline and 21-year follow-up, with higher tracking in adolescents (aged 15-18 years) compared to children (aged 3-14 years). Assessing the transition between quintiles of dietary pattern scores showed that 41% and 38%of participants remained in the top quintile of "traditional Finnish" and "health-conscious", respectively, after 21 years (Mikkila et al, 2005). In my study, the overall proportion of participants remained in the same quartile of "Vegetarian-style" dietary pattern, from childhood (mean age of 12.2±0.7 years) to adulthood (mean age of 25.1±2.6 years), was 44% in females and 32% in males. However, my findings are not directly comparable to this study because of different analytical approaches and age at baseline. A larger number of repeated measurements and mixed longitudinal design in my study allowed for tracking dietary patterns from age 8 to 34 with a maximum number of thirteen

measurements for each participant over the entire period from childhood to adulthood.

Our findings of higher tracking for the "Vegetarian-style" dietary pattern, representing a healthy diet, and lower tracking for "Western-like" dietary pattern, representing an unhealthy diet, are in line with other studies implying that healthy dietary habits are more stable over time (Mishra et al, 2006; Borland et al, 2008; Milkkila et al, 2005; Weismayer et al, 2006; Harrington et al, 2014; Lioret et al, 2015). However, some investigators reported a higher stability for Western/unhealthy dietary pattern compared to the healthy dietary pattern (Northstone et al, 2009; Van Dam et al, 2002). All components of "Vegetarian-style" dietary pattern seems to be healthy, except added fats (butter, margarine, vegetable oils and mayonnaise). Stronger tracking or more stability means that higher or lower adherence to "Vegetarian-style" dietary pattern which is established during childhood or adolescence could persist into adulthood. However, it seems that adherence to "Western-like" dietary pattern could be inconstant over time. Therefore, it seems that childhood or adolescence is the best time for any modification diet in terms of enhancing health-conscious dietary habits.

In my study, I computed applied dietary pattern scores for all observations based on the factor loadings of the initial dietary patterns, as an alternative approach of deriving dietary patterns at each time point. Several previous studies used applied dietary pattern scores similar to my study (Mishra et al 2006, Borland et al 2009, Ambrosini et al 2014, Jankovic et al 2014, Batis et al 2014, Johns et al 2014). This method has the advantage of assessing change in a specific baseline dietary pattern over time. However, it could not identify any new dietary pattern that might have arisen during later years. Assessing the stability of dietary patterns over time by deriving dietary patterns at each of multiple time points, especially when derived dietary patterns have altered food composition and factor loadings, is challenging.

The present study has some strengths. This is the first study tracking the change in PCA-derived dietary patterns from childhood to adulthood over the entire time using GEE modeling. Stability of dietary patterns was assessed as participants grew from their age at the elementary school to early adulthood, incorporating the critical periods during growth. Owing to the mixed longitudinal design of the study, it was possible to assess change in dietary patterns from age 8 to 34 years over a 20-year period of the study. The number of available repeated measurements for each participant was more than any similar studies. I used multiple 24-hour recalls to represent usual intake. Compared to FFQ, the commonly used method in other studies, this method does

not depend on long-term memory and has the advantage of being more flexible and open-ended to collect the more detailed food consumption data (Bingham 1994). The limitations of my study were the smaller sample size compared to other studies and using a single 24-hour recall to assess dietary intake during each study year after 1997.

In conclusion, overall, the "Western-like" dietary pattern had the poorest tracking and "Vegetarian-style" dietary pattern had the strongest tracking over entire time. Tracking was stronger in females than males and there was a fair-to-moderate tracking for "Vegetarian-style" and "High-fat, high-protein" dietary patterns. Adherence to the "Vegetarian-style" dietary pattern increased and "High-fat, high-protein" dietary pattern decreased by age, in females and males. There was also an increase in adherence to "Western-like" and "Mixed" dietary patterns, only in males. This increase was independent of the increase in total energy intake by age. My findings suggest that healthy dietary habits established during childhood and adolescence could continue into adulthood. Therefore, it is necessary to implement policies for dietary intake modifications in children and adolescents to increase intake of fruit and vegetables, non-refined grains and low-fat milk and milk alternatives, as the key components of a healthy dietary pattern, which could continue into adulthood.

In Chapter 9, a general discussion is provided based on the results from all of three studies in Chapters 6 to 8.

CHAPTER 9
GENERAL DISCUSSION

There is evidence that peak bone mass achieved during late adolescence is the key determinant of risk of osteoporosis later in life (Bonjour et al, 2009). Assessing modifiable factors influencing bone growth during its highest velocity, and maintenance of their impact from adolescence to adulthood has an immense importance. The Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) provided mixed longitudinal data allowing to evaluate the long-term impact of nutrition and physical activity on bone accrual. In my thesis, I mainly focused on the association of dietary patterns on bone DXA and pQCT measurements (Objective One) and change in dietary patterns over time (Objective Two). I designed the Study One (Chapter 6) to address my main objective which includes determining dietary patterns during adolescence and examining the association between adherence to those dietary patterns and BMC and aBMD in total body, femoral neck, and lumbar spine, during adulthood. Study Two was designed as an extension to Study One analysis, in which I assessed the association between consumption of two main food groups (M&A and F&V) and bone structure and strength properties measured by pQCT during adulthood (Chapter 7). To assess how participants changed their dietary patterns from childhood and adolescence to adulthood, I designed Study Three (Chapter 8).

9.1. Scientific Contributions of the Study One

This is the first study that evaluated dietary patterns during adolescence (aged 12.7±1.9 years) in association with adult (aged 28.2±3.4 years) bone health. I derived five dietary patterns in PBMAS participants during adolescence using PCA. I labeled them as “Vegetarian-style”, “Western-like”, “High-fat, high-protein”, “Mixed” and “Snack” dietary patterns. I found that the “Vegetarian-style” dietary pattern, rich in dark green vegetables, eggs, non-refined grains, 100% fruit juice, legumes, nuts and seeds, added fats, fruits and low-fat milk during adolescence was positively associated with adolescent total body BMC, total body aBMD. I also found that participants who had higher adherence to the “Vegetarian style” dietary pattern during adolescence had higher total body BMC, total body aBMD, femoral neck BMC and femoral neck aBMD during adulthood, an average of 15 years later. In this sample, all participants during

adulthood had attained their PBM confirmed by a plateau in bone mineral accrual curve, representing a steady status of bone (Baxter-Jones et al, 2011). This study has the advantage of controlling for somatic maturity by including the age of PHV as a covariate in my models. Physical activity was also an important predictor of bone variables during adolescence and adulthood. The sex-specific analysis did not reveal any association between adolescent dietary patterns and adolescent bone mineral status in males or females (Appendix A, Table A.2 and Table A.3). However, I revealed a direct association of adolescent "Vegetarian-style" and an inverse association of "Western-like" dietary patterns with adult total body aBMD, only in females (Appendix A, Table A.5 and Table A.6). It is also important to understand that, one might have a high score for more than one dietary pattern. For example, the participants who fell into the highest quartile of "Vegetarian-style" dietary pattern, might also be in the highest quartile of "Western-like" dietary pattern at the same time. Therefore, I performed all analysis while adjusting for the scores from other dietary patterns to determine the exclusive impact of each dietary pattern.

Evaluating the association between dietary patterns and pQCT-measured bone properties in radius and tibia (Appendix B) showed that higher adherence to the "Vegetarian-style" dietary pattern during adolescence had a positive impact on the trabecular and cortical structure of distal radius, distal tibia and tibia shaft (Appendix B, Table B.1). We previously showed that adults who were physically active during adolescence had improved bone properties in tibia shaft compared to those who were physically inactive (Duckham et al, 2014). Current findings are important because even after adjusting for physical activity, the impact of "Vegetarian-style" dietary pattern on long-term bone adaptation persisted in tibia shaft. In contrast, "High-fat, high-protein" and "Mixed" dietary patterns showed detrimental impacts on adult tibia shaft and distal tibia bone properties, respectively.

Factor analysis via PCA is the most common dietary pattern approach used in the studies. Different dietary pattern approaches have their advantages and disadvantages. There has been an increasing interest in using RRR method for deriving dietary patterns associated with health outcomes in the recent studies. The dietary patterns derived using RRR represent a group of foods associated with a specific health outcome or intermediate factors leading to a health outcome. Compared to RRR, factor analysis has the advantage of defining actual dietary patterns of study population using the correlation between consumed food items and explaining the intake

variation. Whereas, foods in each dietary pattern derived by RRR method are not necessarily associated with each other. Instead, they are associated with pre-known intermediate factors as response variables. Therefore it seems that factor analysis has more public health implications compared to RRR method (Kant 2004; Newby et al. 2004). Two studies in adolescents (Noh et al, 2011; van den Hooven et al, 2015) and one study in adults (Ward et al. 2016) used reduced-rank regression (RRR) to derive dietary patterns in association with bone measurements. To compare the results, I also conducted RRR approach using total or site-specific BMC or BMD as response variables. No dietary pattern was derived using RRR approach in my study, probably because of small sample size. However, the "Vegetarian-style" dietary pattern, which I derived using factor analysis, had a set of components, which were shown to be associated positively with bone health, in the studies that used RRR approach. Higher intake of fruit and vegetables, low-fat milk and dairy, and non-refined grains were the common components of the dietary patterns associated positively with bone health (Noh et al, 2011; van den Hooven et al, 2015; Ward et al. 2016).

9.2. Scientific Contributions of the Study Two

As the main components of "Vegetarian-style" dietary pattern, I evaluated the impact of fruit and vegetables and milk and alternatives, as individual food groups, on pQCT-measured bone properties in radius and tibia, as well (Study Two). I found that adolescent milk and alternatives intake was associated with greater ToA, CoA, and CoC at radius shaft during adulthood, and adolescent fruit and vegetable intake was associated with greater ToA and TrA at distal tibia, in females.

When we interpret the results from dietary pattern analysis versus food group intake analysis, we should keep in mind that dietary pattern approaches are to describe and quantify the whole diet and consider contributions from various foods and dietary aspects in association with bone health (Kant et al, 2004; Newby et al, 2004; Hoffmann et al, 2004). The five dietary patterns derived using factor analysis (PCA) in my study reflect the habitual intake of the combination of different foods. For instance, the "Mixed" dietary pattern revealed a combination of healthy (yogurt, cheese, fish and seafood and %100 fruit juice) and unhealthy (desserts and sweets) food groups. Yogurt and cheese are sources of calcium and magnesium (Heaney et al, 2009), which have a structural role in bone health (Peters & Martini, 2010). Higher factor

loadings for yogurt and cheese allow these food groups to have a higher contribution to the total dietary pattern score (DiStefano et al, 2009). However, it does not necessarily mean that participants with higher scores had a higher intake of yogurt and cheese, where the dietary pattern score might be simply increased due to increase in intake of other components of the pattern such as desserts and sweets. Therefore, the negative association observed between "Mixed" dietary pattern and distal tibia bone properties resulted from the overall impact of the dietary pattern components on bone. Even though "Mixed" dietary pattern was rich in yogurt and cheese, in the separate analysis for food groups, adolescent milk and alternatives intake, as an individual food group, did not show any negative impact on bone properties at distal tibia, instead it was associated with greater ToA, CoA, and CoC at radius shaft during adulthood in females. Therefore, complementary food group analyses were needed to confirm these associations.

9.3. Potential Mechanisms: Study One and Study Two

Our findings of positive association between "Vegetarian-style" dietary pattern and bone health, or the association between fruit & vegetables or milk and alternatives as food groups and bone structural properties are in line with other studies in different populations to our study population (Okubo et al., 2006; Kontogianni et al., 2009; McNaughton et al. 2011; Hardcastle et al. 2011; Whittle et al. 2012; Chen et al. 2015; Shin et al 2015; Langstemo et al. 2010; Langestemo et al 2016; Shin and Joung 2013; Mu et al. 2014; Park et al 2012; Zeng et al 2013; Langstemo et al. 2011; Dai et al 2014; Tucker et al. 2002; Ward et al 2016; van den Hooven et al, 2015; Noh et al, 2011). Findings from these studies suggest that dietary patterns dominated by intakes of fruit and vegetables, low-fat dairy products, whole grains, poultry and fish, and nuts and legumes are beneficial for bone health.

The benefits of the healthy dietary pattern can be related to bone-beneficial properties of the foods within this pattern. Fruit and vegetables are rich in nutrients necessary for bone growth and mineralization, including potassium and magnesium, vitamin C, vitamin K, folate, carotenoids and flavonoids (New et al, 2003). Potassium and magnesium may contribute to acid-base balance in the body and prevent bone loss (New et al, 2003). Potassium could also increase the retention of calcium in kidney, independent of its role in the alkaline state of the body (Rafferty et al, 2008). Magnesium takes part in different enzyme reactions including synthesis of

proteins and nucleic acid. Therefore, it is necessary for bone growth and development (Allgrove et al, 2009). Vitamin C may affect bone growth through its cofactor activity for osteoblast differentiation and collagen formation (Gabby et al, 2010; Fink et al, 2014). Carotenoids, flavonoids and other antioxidants also affect bone health by reducing oxidative stress (Sheweita et al, 2007). Vitamin K is involved in bone matrix formation where mineralization happens (Gundberg et al, 2012).

Dairy products are the main contributors of calcium and magnesium in the diet (Heaney et al, 2009), which have a structural role in bone health (Peters et al, 2010). They are also a source of vitamin D, protein, vitamin B-12, zinc and riboflavin (Heaney et al, 2009). Fish, poultry, dairy products, legumes, nuts and seeds are the sources of protein in a healthy diet. Adequate protein intake is essential for bone matrix formation and maintenance. However, it is believed that excessively high protein intake might induce a negative calcium balance (Isaia et al, 2007). Recently it has been suggested that the positive or negative association between protein intake and bone health depends on the amount of consumed calcium (Isaia et al, 2007; Vatanparast et al, 2007).

In my study, "Western-like", "High-fat, high-protein" and "Mixed" dietary pattern revealed a negative impact on bone. My finding confirm the results from previous studies that suggest Western dietary pattern, which is characterized by intake of soft drinks, fried foods, meat and processed products, sweets and desserts and refined grains, was associated negatively with bone health (McNaughton et al. 2011; Hardcastle et al. 2011; Whittle et al. 2012; Karamati et al. 2012; Franca et al 2016; Langstemo et al. 2010; Langestemo et al 2016; Park et al 2012; Zeng et al 2013; Tucker et al. 2002; Mangano et al. 2015). All the "Western-like", "High-fat, high-protein" and "Mixed" dietary patterns derived in my study, represented some aspects of Western dietary patterns such as higher intake of red meat, processed meats, and sugar-sweetened drinks. High adherence to Western diet is associated with high intake of fat, protein, refined carbohydrates, sodium, and phosphorus (Calvo et al, 2014). High fat intake can directly interfere with intestinal calcium absorption. Sodium is associated with calciuria, which leads to an increased bone remodeling and bone loss (Heaney et al, 2006). Disruption of calcium: phosphorus ratio due to excessive intake of inorganic phosphorus from food additives may affect endocrine regulation of calcium balance. This could be detrimental to bone health (Calvo et al, 2014). The negative association between Western dietary pattern and bone health is in part

accounted for by high net endogenous acid production. During an acidity state, bones provide alkali to maintain acid-alkali balance, which results in a gradual bone loss (Nicoll et al, 2014). Even though the separate role of key nutrients or foods in bone health has been clarified previously, these associations might be confounded by any change in the other dietary components.

9.4. Scientific Contributions of Study Three

This is the first study that assessed the stability of dietary patterns as participants grew from their age at the elementary school to early adulthood, incorporating the critical periods during growth. Owing to the mixed longitudinal design of the study, it was possible to assess change in dietary patterns from age 8 to 34 years over a 20-year period of the study. In my analysis for association between adolescent dietary patterns and adult bone measurements, the mean follow-up period was 15 years. My findings suggested that adolescence is a crucial period during which any modification in dietary patterns might have an influence on bone health that could persist into adulthood. However, because of the cumulative nature of diet throughout one's life (Kant, 2004; Wakimoto & Block, 2001), the effects of adolescent dietary patterns on bone might be influenced or confounded by the change in dietary intakes over 15 years. Even though I controlled for adult total energy intake in my analysis, it was not clear whether dietary patterns established during adolescence were continued throughout the entire follow-up period until adulthood or not.

To address this question, I assessed tracking in adolescent dietary patterns over the entire period from adolescence to adulthood. I found that "Vegetarian-style" dietary pattern, as the one with a long-term positive influence on the bone, had a higher stability over time compared to other dietary patterns in both sexes. This might suggest that healthy dietary habits established during childhood and adolescence could continue into adulthood. Therefore, their extended impacts on adult bone health might be due to the moderate consistency in adherence to these dietary patterns from adolescence to adulthood. I also found a moderate tracking for "High-fat, high-protein" dietary pattern in females, which was associated negatively with adult bone health. Remaining dietary patterns showed a poor-to-fair tracking in females and males. The "Western-like" dietary pattern showed no tracking in females. However, it was associated with a long-term negative impact on bone in females (Appendix A, Table A.6). In other words, although higher

adherence to “Western-like” dietary pattern might have been discontinued or altered over time, it is noteworthy that the negative impact of “Western-like” dietary pattern on bone persisted from adolescence into adulthood. Similar to my study, higher tracking for “healthy” dietary patterns and lower tracking for “unhealthy” dietary patterns were frequently reported in previous studies (Mishra et al, 2006; Borland et al, 2008; Milkkila et al, 2005; Weismayer et al, 2006; Harrington et al, 2014; Lioret et al, 2015), implying that healthy dietary habits are more stable over time. However, some investigators reported a higher stability for Western/unhealthy dietary pattern compared to the healthy dietary pattern (Northstone et al, 2009; Van Dam et al, 2002). Overall, tracking was stronger in females than males. Children and adolescents increased their adherence to the “Vegetarian-style” dietary pattern and decreased their adherence to the “High-fat, high-protein” dietary pattern as they grew older, independent of an increase in total energy intake, in females and males. Males increased their adherence to the “Western-like” and “Mixed” dietary patterns from adolescence to adulthood.

9.5. Strengths

My study has several strengths. This is the first study that evaluated dietary patterns during adolescence in association with adult bone DXA and pQCT measurements and evaluated stability of PCA-derived dietary patterns from childhood to adulthood over the entire time using GEE modeling. Using the pQCT bone measurements enabled us to investigate the impact of diet on cortical and trabecular bone properties and bone strength. This information could not be obtained using the DXA method. Owing to the mixed longitudinal design of the study, it was possible to assess change in dietary patterns from age 8 to 34 years over a 20-year period of the study. Therefore, this study has the longest follow-up period among the similar studies in other populations. Another advantage of this study is including male participants, while most of other studies only focused on females. I controlled for somatic maturity by including the age of PHV as a covariate in my models to align males and females based on their adolescent growth spurt. Even after controlling for different factors, such as physical activity, which are known to be associated with bone health, I revealed several significant associations between diet and bone measurements. I used multiple 24-hour recalls representing usual intake. Compared to FFQ, the commonly used method in other studies, this method does not depend on long-term memory and

has the advantage of being more flexible and open-ended to collect the more detailed food consumption data (Bingham 1994).

9.6. Limitations

The main limitation of my study was the small sample size, which did not allow us to run separate dietary pattern analysis for females and males or run other methods of dietary pattern approaches such RRR method in the total sample. I assumed that dietary habits are established during adulthood. Therefore, during the study years after 1997, only one 24-hour recall was collected annually for each participant. Since a single 24-hour recall might misrepresent the usual intake of the participant during that study year; this is important in the analysis for tracking dietary patterns over time. The five-year gap in data collection between original study and first follow-up resulted in missing data during the crucial period of peak bone mass achievement in most participants. Even if I adjusted models for sex, age, the age of PHV, weight, height, physical activity score and total energy intake, there might be other confounding factors that have not been controlled in my study. For example, the long-term adaptation might also be influenced or confounded by dietary intakes during years preceding or following the adolescent growth spurt (Kant 2004). Finally, participants were a convenience sample of Caucasian people. Hence the results of my study could not be generalized to the whole population.

9.7. Future Research

Even though the beneficial impact of a healthy dietary pattern on bone mineral status or structural properties have been studied in several cross-sectional and longitudinal studies, only one randomized controlled trial (RCT) have investigated the impact of a Mediterranean-based dietary pattern in adolescents (Seiquer et al. 2008). A higher number of RCTs in diverse age, sex and race groups would confirm the findings and reduce controversies from different studies.

The small number of PBMAS participants at the beginning and the high number of drop-outs over the entire period of the study left us with a small sample size for dietary pattern analysis. Despite the evidence on differences in bone growth and mineral accrual pattern in girls and boys, I was not able to conduct separate analysis in females and males to derive sex-specific results. Future research should consider a sample size of at least 92 participants of each sex, for a power of 80% in such analysis.

To identify target populations for nutrition modification, a quick scoring tool, which assesses intake of specific food groups associated with bone health, would be helpful. Several dietary indices have been developed aiming to improve overall health but not exclusively for bone health. Recently the "BMD diet-score" was developed to reflect the beneficial diet for BMD in the Rotterdam Study in Netherlands (de Jonge et al. 2015). Scoring method was based on ascending values for quartiles for "high-BMD" components (vegetables, fruits, dairy products, whole grain products, fish and legumes & beans) and descending values for quartiles of "low-BMD" components (red meat, processed and organ meat and confectionary). Therefore, the next step in research could be examining and confirming the newly developed BMD diet-score in my study population.

The mixed-longitudinal set of data from PBMAS provides the opportunity for further investigations. In PBMAS, two sets of data on bone health were collected over the years. Bone DXA measurements, representing bone mineral status in total body, femoral neck, and lumbar spine bones, were obtained annually during all study years. Whereas, bone pQCT measurements, representing bone structural and strength properties in peripheral bones (forearm and lower leg), were obtained only during 2010/2011. Measuring bone structure and strength by HR-pQCT could be considered in the future data collection on the PBMAS participants. As the PBMAS participants get older, osteoporosis and osteoporotic fractures incidence can also be evaluated. Further, the retrospective associations with early modifications in diet and physical activity and bone measures could be examined. A combination of different measurement methods would provide a better indicator of bone quality compared to any single method.

As participants of PBMAS are getting older, they might develop multiple health conditions, such as cardiovascular disease, diabetes, and osteoporosis. In this situation, dietary recommendations should target the overall health rather than a single health outcome. Using specific analysis might help to create a scoring system to examine overall health as a single score. This would warrant further analysis to identify dietary patterns associated with overall health score. In addition, the longitudinal design of the study would help us to study the concurrence of different health conditions and their possible cause and effect associations.

9.8. Conclusion

In conclusion, my results suggest that a "Vegetarian-style" dietary pattern, rich in dark green vegetables, eggs, non-refined grains, 100% fruit juice, legumes, nuts and seeds, added fats, fruits and low-fat milk during adolescence has a beneficial impact on bone health during adolescence and this positive impact on bone accrual can be carried into adulthood. Assessing the impact of individual food groups revealed a positive association between milk and alternatives or fruit and vegetable intakes during adolescence and adult peripheral bone structure, in females. In contrast, dietary patterns which were representing some characteristics of Western dietary patterns with higher intakes of fast foods, high red meat and high intake of sweetened beverages had a negative impact on the bone during adolescence and adulthood. Overall, the "Western-like" dietary pattern had the poorest tracking and "Vegetarian-style" dietary pattern had the strongest tracking over entire time. This finding suggests that healthy dietary habits established during childhood and adolescence could continue into adulthood. Therefore, it is necessary to implement policies for dietary intake modifications in children and adolescents to increase intake of fruit and vegetables, non-refined grains and low-fat milk and milk alternatives, as the key components of a healthy dietary pattern, which could continue into adulthood.

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APPENDICES

Appendix A

Appendix B

Appendix A

Table A.1. Multiple linear regression coefficients for independent variables predicting bone mineral content and density in BMAS adolescents (n=124)[1]

Independent variables	Unstandardized β	95% CI for β	P value
TBBMC			
Intercept	-2404	-2888, -1920	<0.001
Weight	20.0	16.2, 23.9	<0.001
Height	15.5	10.9, 20.0	<0.001
Age	43.6	15.2, 72.14	0.003
"Vegetarian style" DP score	35.2	4.5, 65.9	0.025
Model significance			<0.001
Adjusted R square=0.91			
TBBMD			
Intercept	0.275	0.081, 0.468	0.006
Weight	0.003	0.002, 0.005	<0.001
Age	0.023	0.012, 0.034	<0.001
Height	0.002	0.000, 0.003	0.033
PA score	0.018	0.002, 0.034	0.027
Age of PHV	-0.011	-0.021, -0.001	0.032
Model significance			<0.001
Adjusted R square=0.75			
FNBMC			
Intercept	-2.9	-4.34, -1.48	<0.001
Weight	0.033	0.022, 0.043	<0.001
Height	0.022	0.009, 0.034	0.001
Sex	-0.188	-0.364, -0.013	0.036
Age	0.100	0.023, 0.176	0.011
PA score	0.152	0.027, 0.277	0.017
Model significance			<0.001
Adjusted R square= 0.80			
FNBMD			

Intercept	0.133	-0.007, 0.274	0.063
Weight	0.005	0.003, 0.007	<0.001
Age	0.023	0.011, 0.036	<0.001
PA score	0.031	0.007, 0.054	0.010
Model significance			<0.001
Adjusted R square=0.61			
LSBMC			
Intercept	-53.9	-74.8, -33.0	<0.001
Height	0.55	0.38, 0.71	<0.001
Weight	0.17	0.02, 0.03	0.022
Age of PHV	-3.04	-4.16, -1.92	<0.001
Age	2.7	1.5, 3.9	<0.001
Model significance			<0.001
Adjusted R square= 0.82			
LSBMD			
Intercept	0.21	-0.115, .535	0.203
Weight	0.004	0.002, 0.005	<0.001
Sex	0.038	0.001, 0.076	0.045
Height	0.002	0.000, 0.004	0.044
Age	0.034	0.018, 0.018	<0.001
Age of PHV	-0.033	-0.050, -0.016	<0.001
Model significance			<0.001
Adjusted R square=0.74			

[1] Independent variables included in the model were sex, age, and age of PHV, height, weight, physical activity score, total energy intake and five adolescence dietary patterns scores ("Vegetarian style", "Western-like", "High-fat, high-protein", "Mixed" and "Snack") by stepwise regression analysis.
CI, confidence interval; BMAS, bone mineral accrual study; BMC, bone mineral content; BMD, bone mineral density; DP, dietary pattern; FN, femoral neck; LS, lumber spine, PA, physical activity; PHV, peak height velocity; TB, total body

Table A.2. Multiple linear regression coefficients for independent variables predicting bone mineral content and density in BMAS male adolescents (n=72)

Independent variables	Unstandardized β	95% CI for β	P value
TBBMC			
Intercept	-2532	-3345, -1719	<0.001
Weight	25.0	18.3, 31.7	<0.001
Height	18.2	11.4, 25.0	<0.001
Model significance			<0.001
Adjusted R square=0.89			
TBBMD			
Intercept	0.668	0.451, 0.886	<0.001
Weight	0.004	0.002, 0.006	0.001
Age	0.031	0.015, 0.047	<0.001
Age of PHV	-0.025	-0.044, -0.007	0.008
Model significance			<0.001
Adjusted R square=0.71			
FNBMC			
Intercept	-2.26	-4.47, -0.05	0.045
Weight	0.039	0.021, 0.058	<0.001
Height	0.027	0.008, 0.045	0.005
Model significance			<0.001
Adjusted R square= 0.72			
FNBMD			
Intercept	0.473	0.382, 0.564	<0.001
Weight	0.006	0.005, 0.008	<0.001
Model significance			<0.001
Adjusted R square= 0.44			
LSBMC			
Intercept	-34.66	-73.83, 4.49	0.082
Height	0.52	0.27, 0.76	<0.001
Age of PHV	-4.93	-6.97, -2.89	<0.001
Age	4.2	2.35, 6.21	<0.001
Model significance			<0.001

Adjusted R square= 0.797			
LSBMD			
Intercept	0.672	0.433, 0.910	<0.001
Weight	0.004	0.001, 0.006	<0.001
Age of PHV	-0.050	-0.071, -0.030	0.002
Age	0.043	0.025, 0.060	<0.001
Model significance			<0.001
Adjusted R square=0.74			

[1] Independent variables included in the model were sex, age, and age of PHV, height, weight, physical activity score, total energy intake and five adolescence dietary patterns scores ("Vegetarian style", "Western-like", "High-fat, high-protein", "Mixed" and "Snack") by stepwise regression analysis.
CI, confidence interval; BMAS, bone mineral accrual study; BMC, bone mineral content; BMD, bone mineral density; DP, dietary pattern; FN, femoral neck; LS, lumber spine, PA, physical activity; PHV, peak height velocity; TB, total body

Table A.3. Multiple linear regression coefficients for independent variables predicting bone mineral content and density in BMAS female adolescents (n=52)

Independent variables	Unstandardized β	95% CI for β	P value
TBBMC			
Intercept	-2090	-2633, -1547	<0.001
Weight	17.7	14.1, 21.4	<0.001
Height	14.5	9.7, 19.3	<0.001
Age	36.6	8.0, 65.2	0.013
Model significance			<0.001
Adjusted R square=0.93			
TBBMD			
Intercept	0.422	0.329, 0.515	<0.001
Weight	0.004	0.002, 0.005	<0.001
Age	0.023	0.013, 0.033	<0.001
Model significance			<0.001
Adjusted R square=0.76			
FNBMC			
Intercept	-2.80	-4.40, -1.21	0.001
Weight	0.032	0.022, 0.043	<0.001
Height	0.031	0.018, 0.043	<0.001
Model significance			<0.001
Adjusted R square= 0.82			
FNBMD			
Intercept	0.184	0.045, 0.324	0.011
Weight	0.006	0.004, 0.008	<0.001
Age	0.024	0.009, 0.040	0.003
Model significance			<0.001
Adjusted R square=0.70			
LSBMC			
Intercept	-87.48	-112.52, -62.45	<0.001
Height	0.606	0.385, 0.827	<0.001
Age of PHV	0.290	0.122, 0.458	0.001
Age	1.411	0.092, 2.729	0.037

Model significance			<0.001
Adjusted R square=0.83			
LSBMD			
Intercept	0.443	-0.788, -0.099	0.013
Height	0.005	0.002, 0.008	0.003
weight	0.004	0.002, 0.007	<0.001
Age	0.023	0.004, 0.041	0.016
Model significance			<0.001
Adjusted R square=0.77			

[1] Independent variables included in the model were sex, age, and age of PHV, height, weight, physical activity score, total energy intake and five adolescence dietary patterns scores ("Vegetarian style", "Western-like", "High-fat, high-protein", "Mixed" and "Snack") by stepwise regression analysis.
CI, confidence interval; BMAS, bone mineral accrual study; BMC, bone mineral content; BMD, bone mineral density; DP, dietary pattern; FN, femoral neck; LS, lumber spine, PA, physical activity; PHV, peak height velocity; TB, total body

Table A.4. Multiple linear regression coefficients for independent variables predicting bone mineral content and density in BMAS participants during adulthood (n=115)

Independent variables	Unstandardized β	95% CI for β	P value
TBBMC			
Intercept	-2276	-3479, -1073	<0.001
Height	22.20	15.27, 29.12	<0.001
Weight	12.4	9.28, 15.66	<0.001
Sex	-214.2	-345.63, -82.84	0.002
PA score	91.02	16.14, 165.89	0.018
"Vegetarian style" DP score	55.84	8.77, 102.91	0.021
Model significance			<0.001
Adjusted R square=0.77			
TBBMD			
Intercept	0.688	0.526, 0.851	<0.001
Weight	0.002	0.001, 0.003	0.001
Age	0.010	0.006, 0.015	<0.001
Sex	-0.057	-0.092, -0.021	0.002
PA score	0.033	0.009, 0.053	0.008
"Vegetarian style" DP score	0.016	0.001, 0.031	0.041
Model significance			<0.001
Adjusted R square=0.42			
FNBMC			
Intercept	-2.58	-5.69, 0.52	0.103
Height	0.038	0.020, 0.056	<0.001
Weight	0.015	0.006, 0.023	0.001
Sex	-0.450	-0.792, -0.109	0.010
Model significance			
Adjusted R square= 0.53			
FNBMD			
Intercept	0.536	0.413, 0.659	<0.001
Weight	0.003	0.002, 0.004	<0.001
PA score	0.047	0.014, 0.079	0.005
Model significance			<0.001

Adjusted R square=0.24			
LSBMC			
Intercept	-101.6	-137.86, -65.35	
Height	0.986	0.778, 1.194	<0.001
Model significance			<0.001
Adjusted R square= 0.43			<0.001
LSBMD			
Intercept	0.883	0.777, 0.989	<0.001
Weight	0.002	0.001, 0.003	0.002
Model significance			0.002
Adjusted R square=0.07			

[1] Independent variables included in the model were sex, age, and age of PHV, height, weight, physical activity score, total energy intake and five adolescence dietary patterns scores ("Vegetarian style", "Western-like", "High-fat, high-protein", "Mixed" and "Snack") by stepwise regression analysis.
CI, confidence interval; BMAS, bone mineral accrual study; BMC, bone mineral content; BMD, bone mineral density; DP, dietary pattern; FN, femoral neck; LS, lumber spine, PA, physical activity; PHV, peak height velocity; TB, total body

Table A.5. Multiple linear regression coefficients for independent variables predicting bone mineral content and density in BMAS male during adulthood (n=64)

Independent variables	Unstandardized β	95% CI for β	P value
TBBMC			
Intercept	-2556	-4418, -695	0.008
Weight	15.95	10.59, 21.32	<0.001
Height	21.56	10.59, 32.53	<0.001
PA score	132.44	22.08, 242.80	0.019
Model significance			<0.001
Adjusted R square=0.59			
TBBMD			
Intercept	0.594	0.339, 0.849	<0.001
Weight	0.003	0.001, 0.004	0.001
Age	0.011	0.004, 0.018	0.002
PA score	0.036	0.001, 0.071	0.041
Model significance			<0.001
Adjusted R square=0.172			
FNBMC			
Intercept	2.34	0.954, 3.731	0.001
Weight	0.025	0.013, 0.038	<0.001
PA score	0.411	0.129, 0.694	0.005
Model significance			<0.001
Adjusted R square= 0.24			
FNBMD			
Intercept	0.501	0.271, 0.732	0.016
Weight	0.003	0.001, 0.005	<0.001
PA score	0.070	0.023, 0.116	0.003
Model significance			0.004
Adjusted R square= 0.18			
LSBMC			
Intercept	-67.98	-143.37, 7.40	0.076
Height	0.800	0.381, 1.22	<0.001
Model significance			<0.001

Adjusted R square= 0.18			
LSBMD			
Intercept	0.824	0.638, 1.011	<0.001
Weight	0.003	0.001, 0.005	0.014
Model significance			0.014
Adjusted R square= 0.08			

[1] Independent variables included in the model were sex, age, and age of PHV, height, weight, physical activity score, total energy intake and five adolescence dietary patterns scores ("vegetarian style", "Western-like", "High-fat, high-protein", "Mixed" and "Snack") by stepwise regression analysis.
CI, confidence interval; BMAS, bone mineral accrual study; BMC, bone mineral content; BMD, bone mineral density; DP, dietary pattern; FN, femoral neck; LS, lumber spine, PA, physical activity; PHV, peak height velocity; TB, total body

Table A.6. Multiple linear regression coefficients for independent variables predicting bone mineral content and density in BMAS female during adulthood (n=50)

Independent variables	Unstandardized β	95% CI for β	P value
TBBMC			
Intercept	-2426	-3829, -1023	0.001
Height	15.95	15.88, 32.76	<0.001
Weight	21.56	5.64, 13.22	<0.001
Model significance			<0.001
Adjusted R square=0.56			
TBBMD			
Intercept	0.541	0.343, 0.739	<0.001
Age	0.015	0.009, 0.021	<0.001
PA score	0.045	0.012, 0.077	0.008
"Vegetarian style" DP score	0.046	0.017, 0.074	0.002
"Western-like" DP score	-0.028	-0.048, -0.008	0.008
Total energy intake	36.62E-5	0.000, 0.000	0.013
Model significance			<0.001
Adjusted R square=0.44			
FNBMC			
Intercept	-4.59	-8.14, -1.04	0.012
Height	0.048	0.027, 0.067	<0.001
Weight	0.014	0.004, 0.023	0.006
Model significance			<0.001
Adjusted R square=0.37			
FNBMD			
Intercept	0.668	0.549, 0.787	<0.001
Weight	0.003	0.001, 0.004	0.002
Model significance			0.002
Adjusted R square=0.17			
LSBMC			
Intercept	-125.06	-189.11, -61.01	<0.001
Height	1.125	0.74, 1.51	<0.001
Model significance			<0.001

Adjusted R square=0.09			
LSBMD			
Intercept	0.089	-0.675, 0.854	0.815
Height	0.006	0.001, 0.010	0.016
Model significance			0.016
Adjusted R square=0.09			

[1] Independent variables included in the model were sex, age, and age of PHV, height, weight, physical activity score, total energy intake and five adolescence dietary patterns scores ("Vegetarian style", "Western-like", "High-fat, high-protein", "Mixed" and "Snack") by stepwise regression analysis.
CI, confidence interval; BMAS, bone mineral accrual study; BMC, bone mineral content; BMD, bone mineral density; DP, dietary pattern; FN, femoral neck; LS, lumber spine, PA, physical activity; PHV, peak height velocity; TB, total body

Appendix B

Table B.1. Adult adjusted pQCT bone parameters by adolescent "Vegetarian style" dietary pattern quartiles[1]

	Quartile one (*n* =19)	Quartile two (*n* =19)	Quartile three (*n* =19)	Quartile four (n=20)
Distal radius				
ToA (mm^2)	329±15	427±15	445±15	420±15
ToD (mg/cm^3)	345±13	355±13	330±12	330±12
TrA (mm^2)	318±17	344±17	375±16	347±16
TrC (mg/mm)	78±4[a]	89±4[a,b]	98±4[b]	86±4[a,b]
TrD (mg/cm^3)	244±6	258±6	259±6	245±6
BSIc (mg^2/mm^4)	47±3	55±3	50±3	48±3
Radius shaft				
ToA (mm^2)	141±5	146±5	147±5	147±5
CoA (mm^2)	96±3	104±3	103±3	102±3
CoC (mg/mm)	108±4	117±4	115±4	113±3
CoD (mg/cm^3)	1119±6	1130±6	1120±6	1117±6
SSIp (mm^3)	327±17	359±17	359±17	356±16
Distal tibia				
ToA (mm^2)	1181±36	1212±35	1216±34	1243±34
ToD (mg/cm^3)	309±9	341±8	331±8	312±8
TrA (mm^2)	1055±38	1040±38	1083±37	1114±36
TrC (mg/mm)	275±10	296±10	310±10	302±10
TrD (mg/cm^3)	262±6	282±6	286±6	268±6
BSIc (mg^2/mm^4)	115±7[a]	146±7[b]	136±6[a,b]	125±6[a,b]
Tibia shaft				
ToA (mm^2)	634±13	636±12	646±12	670±12
CoA (mm^2)	360±7[a]	392±7[b]	389±7[b]	383±7[a,b]
CoC (mg/mm)	394±9[a]	430±8[b]	424±8[a,b]	421±8[a,b]
CoD (mg/cm^3)	1094±5	1099±5	1089±5	1098±5
SSIp (mm^3)	2764±74[a]	2962±72[a,b]	2953±71[a,b]	3052±70[b]

[1]Values are mean ± SE: MANCOVA, pairwise comparisons with Bonferroni adjustment. Adjusted for age of sex=0.4, age=30, PHV=12.7, height=173, weight=79.0, physical activity score=2.3, total energy intake=2393, "Western-like" dietary pattern score=0.06, "High-fat, high-protein" dietary pattern score =-0.08, "Mixed" dietary pattern score =0.14, "Snack" dietary pattern score =-0.04. Labeled means in a row without a common superscript letter differ, $P < 0.05$.

BSIc, bone strength index in compression; CoA, cortical area; CoC, cortical content; CoD, cortical density; MANCOVA, multivariate analysis of covariance; pQCT, peripheral quantitative computed tomography; SSIp, bone strength in torsion; ToA, total area; ToD, total density; TrA, trabecular area; TrC, trabecular content; TrD, trabecular density.

Table B.2. Adult adjusted pQCT bone parameters by adolescent "Western-like" dietary pattern quartiles[1]

	Quartile one (*n* =19)	Quartile two (*n* =19)	Quartile three (*n* =19)	Quartile four (n=20)
Distal radius				
ToA (mm^2)	411±15	443±15	406±15	422±14
ToD (mg/cm^3)	336±13	330±12	351±12	342±12
TrA (mm^2)	336±17	369±16	331±17	347±16
TrC (mg/mm)	82±5	93±5	85±5	89±5
TrD (mg/cm^3)	240±6	250±6	261±6	255±6
BSIc (mg^2/mm^4)	48±3	50±3	52±3	51±3
Radius shaft				
ToA (mm^2)	141±5	147±5	150±7	144±5
CoA (mm^2)	100±3	103±3	102±3	100±3
CoC (mg/mm)	113±4	115±4	114±4	111±3
CoD (mg/cm^3)	1130±6	1118±6	1123±6	1115±6
SSIp (mm^3)	331±17	352±17	369±17	349±16
Distal tibia				
ToA (mm^2)	1204±36	1241±35	1232±36	1177±34
ToD (mg/cm^3)	323±9	321±9	327±9	322±8
TrA (mm^2)	1069±39	1089±38	1088±39	1048±36
TrC (mg/mm)	294±11	296±10	303±11	289±10
TrD (mg/cm^3)	275±7	270±6	280±6	274±6
BSIc (mg^2/mm^4)	128±7	132±7	136±7	125±7
Tibia shaft				
ToA (mm^2)	635±12	645±12	661±12	646±12
CoA (mm^2)	379±8	381±7	381±8	383±7
CoC (mg/mm)	414±9	420±9	414±9	419±8
CoD (mg/cm^3)	1093±6	1102±5	1088±5	1096±5
SSIp (mm^3)	2859±74	2975±71	2972±73	2922±68

[1]Values are mean ± SE: MANCOVA, pairwise comparisons with Bonferroni adjustment. Adjusted for age of sex=0.4, age=30, PHV=12.7, height=173, weight=79.0, physical activity score=2.3, total energy intake=2393, "Vegetarian-style" dietary pattern score=0.02, "High-fat, high-protein" dietary pattern score =-0.08, "Mixed" dietary pattern score =0.14, "Snack" dietary pattern score =-0.04. Labeled means in a row without a common superscript letter differ, $P < 0.05$. BSIc, bone strength index in compression; CoA, cortical area; CoC, cortical content; CoD, cortical density; MANCOVA, multivariate analysis of covariance; pQCT, peripheral quantitative computed tomography; SSIp, bone strength in torsion; ToA, total area; ToD, total density; TrA, trabecular area; TrC, trabecular content; TrD, trabecular density.

Table B.3. Adult adjusted pQCT bone parameters by adolescent "High-fat, high-protein" dietary pattern quartiles[1]

	Quartile one (*n* =19)	Quartile two (*n* =19)	Quartile three (*n* =19)	Quartile four (n=20)
Distal radius				
ToA (mm^2)	439±15	409±15	425±15	411±14
ToD (mg/cm^3)	327±12	348±12	343±12	342±11
TrA (mm^2)	367±16	330±17	347±17	340±16
TrC (mg/mm)	92±5	86±5	87±5	85±4
TrD (mg/cm^3)	248±6	259±5	246±6	253±6
BSIc (mg^2/mm^4)	49±3	52±3	51±3	48±3
Radius shaft				
ToA (mm^2)	152±5	141±5	150±5	139±5
CoA (mm^2)	105±3	100±3	104±3	97±3
CoC (mg/mm)	117±3	112±3	116±3	109±3
CoD (mg/cm^3)	1116±6	1125±6	1123±6	1121±6
SSIp (mm^3)	370±17	341±17	358±17	333±16
Distal tibia				
ToA (mm^2)	1223±35	1186±35	1257±35	1188±33
ToD (mg/cm^3)	323±9	337±9	313±9	319±8
TrA (mm^2)	1089±37	1031±37	1118±38	1055±35
TrC (mg/mm)	303±10	292±11	304±11	285±10
TrD (mg/cm^3)	278±6	281±6	269±7	271±6
BSIc (mg^2/mm^4)	130±7	137±7	131±7	123±7
Tibia shaft				
ToA (mm^2)	$678±12^{a}$	$649±12^{a,b}$	$646±12^{a,b}$	$615±11^{b}$
CoA (mm^2)	388±7	385±7	373±8	378±7
CoC (mg/mm)	424±9	419±9	410±9	415±8
CoD (mg/cm^3)	1091±5	1087±5	1100±5	1100±5
SSIp (mm^3)	$3068±72^{a}$	$2969±72^{a,b}$	$2912±73^{a,b}$	$2789±68^{b}$

[1]Values are mean ± SE: MANCOVA, pairwise comparisons with Bonferroni adjustment. Adjusted for age of sex=0.4, age=30, PHV=12.7, height=173, weight=79.0, physical activity score=2.3, total energy intake=2393, "vegetarian-style" dietary pattern score =0.01, "Western-like" dietary pattern score=0.06, "Mixed" dietary pattern score =0.14, "Snack" dietary pattern score =-0.04. Labeled means in a row without a common superscript letter differ, $P < 0.05$
BSIc, bone strength index in compression; CoA, cortical area; CoC, cortical content; CoD, cortical density; MANCOVA, multivariate analysis of covariance; pQCT, peripheral quantitative computed tomography; SSIp, bone strength in torsion; ToA, total area; ToD, total density; TrA, trabecular area; TrC, trabecular content; TrD, trabecular density.

Table B.4. Adult adjusted pQCT bone parameters by adolescent "Mixed" dietary pattern quartiles[1]

	Quartile one (*n* =19)	Quartile two (*n* =19)	Quartile three (*n* =19)	Quartile four (n=20)
Distal radius				
ToA (mm^2)	408±15	423±15	448±14	405±15
ToD (mg/cm^3)	349±12	348±12	320±12	343±12
TrA (mm^2)	329±16	348±16	378±16	330±16
TrC (mg/mm)	82±4	89±4	94±4	84±4
TrD (mg/cm^3)	251±7	256±7	247±6	252±7
BSIc (mg^2/mm^4)	51±3	52±3	47±3	50±3
Radius shaft				
ToA (mm^2)	144±5	151±5	148±5	139±5
CoA (mm^2)	103±3	103±3	102±3	98±3
CoC (mg/mm)	116±4	115±4	115±4	109±4
CoD (mg/cm^3)	1134±6	1120±6	1119±6	1112±6
SSIp (mm^3)	349±16	373±16	356±16	324±16
Distal tibia				
ToA (mm^2)	1201±34[a,b]	1232±33[a,b]	1287±33[a]	1133±33[b]
ToD (mg/cm^3)	332±9	327±9	306±9	328±9
TrA (mm^2)	1044±36[a,b]	1099±36[a,b]	1163±35[a]	988±35[b]
TrC (mg/mm)	291±10	310±10	309±10	273±10
TrD (mg/cm^3)	277±6	282±7	265±6	275±6
BSIc (mg^2/mm^4)	137±7	134±7	123±7	127±7
Tibia shaft				
ToA (mm^2)	646±12	658±12	658±12	625±12
CoA (mm^2)	379±8	382±8	381±7	382±8
CoC (mg/mm)	417±9	416±9	417±9	418±9
CoD (mg/cm^3)	1101±5	1089±5	1095±5	1094±5
SSIp (mm^3)	2937±71	2950±71	3000±69	2843±71

[1]Values are mean ± SE: MANCOVA, pairwise comparisons with Bonferroni adjustment. Adjusted for age of sex=0.4, age=30, PHV=12.7, height=173, weight=79.0, physical activity score=2.3, total energy intake=2393, "vegetarian-style" dietary pattern score =0.01, "Western-like" dietary pattern score=0.06, "High-fat, high-protein" dietary pattern score =-0.08, "Snack" dietary pattern score =-0.04. Labeled means in a row without a common superscript letter differ, $P < 0.05$. BSIc, bone strength index in compression; CoA, cortical area; CoC, cortical content; CoD, cortical density; MANCOVA, multivariate analysis of covariance; pQCT, peripheral quantitative computed tomography; SSIp, bone strength in torsion; ToA, total area; ToD, total density; TrA, trabecular area; TrC, trabecular content; TrD, trabecular density.

Table B.5. Adult adjusted pQCT bone parameters by adolescent "Snack" dietary pattern quartiles[1]

	Quartile one (*n* =19)	Quartile two (*n* =19)	Quartile three (*n* =19)	Quartile four (n=20)
Distal radius				
ToA (mm^2)	403±14	442±15	414±14	425±14
ToD (mg/cm^3)	349±12	336±12	342±12	332±12
TrA (mm^2)	326±16	366±16	338±16	355±16
TrC (mg/mm)	83±4	93±4	85±4	90±4
TrD (mg/cm^3)	252±6	252±6	250±6	252±6
BSIc (mg^2/mm^4)	51±3	52±3	50±3	48±3
Radius shaft				
ToA (mm^2)	148±5	144±5	147±5	141±5
CoA (mm^2)	103±3	102±3	100±3	99±3
CoC (mg/mm)	116±3	115±4	112±4	111±3
CoD (mg/cm^3)	1122±6	1121±6	1121±6	1121±6
SSIp (mm^3)	361±16	349±17	361±16	329±16
Distal tibia				
ToA (mm^2)	1182±32	1271±34	1200±33	1201±33
ToD (mg/cm^3)	325±9	324±9	319±9	323±9
TrA (mm^2)	1040±35	1116±37	1074±36	1065±36
TrC (mg/mm)	284±10	308±10	297±10	295±10
TrD (mg/cm^3)	272±6	275±6	274±6	276±6
BSIc (mg^2/mm^4)	128±7	139±7	126±7	129±7
Tibia shaft				
ToA (mm^2)	655±11	659±12	655±12	619±12
CoA (mm^2)	385±7	387±7	378±7	374±7
CoC (mg/mm)	420±8	422±8	414±8	411±8
CoD (mg/cm^3)	1091±5	1095±5	1093±5	1101±5
SSIp (mm^3)	2994±68	3021±71	2953±69	2767±69

[1]Values are mean ± SE: MANCOVA, pairwise comparisons with Bonferroni adjustment. Adjusted for age of sex=0.4, age=30, PHV=12.7, height=173, weight=79.0, physical activity score=2.3, total energy intake=2393, "vegetarian-style" dietary pattern score =0.01, "Western-like" dietary pattern score=0.06, "High-fat, high-protein" dietary pattern score =-0.08, "Mixed" dietary pattern score =0.14 Labeled means in a row without a common superscript letter differ, $P < 0.05$. BSIc, bone strength index in compression; CoA, cortical area; CoC, cortical content; CoD, cortical density; MANCOVA, multivariate analysis of covariance; pQCT, peripheral quantitative computed tomography; SSIp, bone strength in torsion; ToA, total area; ToD, total density; TrA, trabecular area; TrC, trabecular content; TrD, trabecular density.