AN INVESTIGATION OF THE ASSOCIATIONS AMONG RECOVERY, KEY ILLNESS CHARACTERISTICS AND BONE MINERAL DENSITY IN WOMEN WITH A HISTORY OF ANOREXIA NERVOSA

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Graduate Department of Health Policy, Management and Evaluation
University of Toronto

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Background: Reduced bone mineral density (BMD) is an established complication of anorexia nervosa (AN). There is inconclusive evidence as to whether this reduction in bone mass is permanent or can be reversed with recovery from AN. The objectives of this study were to: i. determine the extent of reversal of skeletal deficits with recovery from AN, and the duration of recovery required for complete reversal, if this occurred; and, ii. evaluate the effect of key illness characteristics on BMD.

Methods: Women (aged 17-40 years) who had previously received inpatient treatment for AN at one of two hospital-based programs were selected for this cross-sectional study; 514 healthy premenopausal women recruited from the community served as a control group. A detailed lifetime illness history was obtained by a Life History Calendar interview. BMD was measured by dual-energy X-ray absorptiometry (DXA) at the spine, hip and total body. Low BMD was defined as a weight and age-matched standard deviation (Z-score) of ≤ -1.5 at one or more skeletal sites. Participants were considered recovered if they had maintained a body mass index ≥ 18.5 kg/m² and resumed regular menstruation for ≥ 1 year.
Results: Of 190 AN participants, 77 were considered recovered and 113 were ill. The prevalence of low BMD was 11.7% in the recovered group, 47.3% in the ill group and 6.8% in the control group. The odds of low BMD in the recovered participants was significantly lower than in the ill participants (odds ratio [OR] = 0.17, 95% CI 0.07, 0.36, p<0.0001) and was not significantly different from the controls (OR = 1.81, 95% CI 0.79, 3.78, p=0.15). Duration of illness was associated with low BMD (OR = 1.16, 95% CI 1.08, 1.25, p<0.0001) and was negatively associated with the odds of AN recovery. Normal mean BMD values at each skeletal site were observed in women recovered ≥ 3 years.

Conclusion: The results emphasize the importance of early and sustained AN recovery for the prevention and treatment of low bone mass in this population and may offer motivation for AN patients to make positive behavioural changes leading to successful, long-term recovery.
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# TABLE OF CONTENTS

**ABSTRACT** ................................................................................................................................. ii
**ACKNOWLEDGEMENTS** .............................................................................................................. iv

## CHAPTER 1: Introduction .................................................................................................................. 1
  I. Study objectives .......................................................................................................................... 1
  II. Background ............................................................................................................................ 1
      A. Osteoporosis
          Epidemiology and burden of illness ................................................................................... 2
          Diagnostic classification of osteoporosis ............................................................................... 3
          Overview of bone metabolism .............................................................................................. 4
          Risk factors for low peak bone mass ................................................................................... 5
      B. Anorexia nervosa
          Epidemiology and burden of illness ................................................................................... 6
          Bone mineral density in women with anorexia nervosa ......................................................... 7
          Mechanisms of low BMD in anorexia nervosa ...................................................................... 8
          Fracture risk in women with anorexia nervosa .................................................................... 10
  III. Key determinants of bone mass in women with anorexia nervosa ......................................... 11
      1. Recovery of bone mass with recovery from anorexia nervosa ............................................ 12
      2. Effect of illness characteristics on bone mass .................................................................... 17
          i. Duration of illness ............................................................................................................. 17
          ii. Illness severity .................................................................................................................. 17
          iii. Age at onset ................................................................................................................... 18
          iv. Subtype .......................................................................................................................... 19
      3. Effect of exercise on bone .................................................................................................. 20
  IV. Overview of the present study ................................................................................................. 23
      1. Study design ....................................................................................................................... 24
      2. Life History Calendar interview method ............................................................................. 24
      3. Definition of recovery from anorexia nervosa ................................................................... 27
  V. Overview of the thesis .............................................................................................................. 28
  VI. Significance of the study ......................................................................................................... 30

## CHAPTER 2: (Paper 1) The effect of weight and menstrual recovery and other key illness characteristics on bone mineral density in young women with a history of anorexia nervosa ...31
  Introduction ................................................................................................................................. 31
  Methods ....................................................................................................................................... 33
  Results .......................................................................................................................................... 40
  Discussion ..................................................................................................................................... 46
  Tables 1-5 ....................................................................................................................................... 55
  Figures 1-2 ..................................................................................................................................... 61
<table>
<thead>
<tr>
<th>CHAPTER 3: (Paper 2) Characterization of changes in bone density associated with illness and recovery in young women with a history of anorexia nervosa</th>
<th>63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>63</td>
</tr>
<tr>
<td>Methods</td>
<td>64</td>
</tr>
<tr>
<td>Results</td>
<td>70</td>
</tr>
<tr>
<td>Discussion</td>
<td>73</td>
</tr>
<tr>
<td>Tables 1-4</td>
<td>79</td>
</tr>
<tr>
<td>Figures 1-3</td>
<td>83</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER 4: (Paper 3) The effect of exercise during illness and recovery on bone mineral density in young women with a history of anorexia nervosa</th>
<th>86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>86</td>
</tr>
<tr>
<td>Methods</td>
<td>88</td>
</tr>
<tr>
<td>Results</td>
<td>94</td>
</tr>
<tr>
<td>Discussion</td>
<td>97</td>
</tr>
<tr>
<td>Tables 1-6</td>
<td>103</td>
</tr>
<tr>
<td>Figure 1</td>
<td>109</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER 5: Discussion</th>
<th>110</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Contributions to the literature</td>
<td>110</td>
</tr>
<tr>
<td>II. Clinical implications</td>
<td>114</td>
</tr>
<tr>
<td>III. Study strengths and limitations</td>
<td>118</td>
</tr>
<tr>
<td>IV. Future research</td>
<td>124</td>
</tr>
<tr>
<td>V. Conclusions</td>
<td>126</td>
</tr>
</tbody>
</table>

| CANDIDATE’S ROLE                                                                                                               | 128|

| REFERENCES                                                                                                                     | 129|

<table>
<thead>
<tr>
<th>APPENDICES</th>
<th>129</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix A: Details of study recruitment</td>
<td>152</td>
</tr>
<tr>
<td>Appendix B: Table – comparison of characteristics of non-respondents vs. respondents.</td>
<td>157</td>
</tr>
<tr>
<td>Appendix C: Table – characteristics of prior studies investigating recovery of bone mass in women with anorexia nervosa</td>
<td>159</td>
</tr>
<tr>
<td>Appendix D: Initial letter of contact</td>
<td>169</td>
</tr>
<tr>
<td>Screening form</td>
<td>171</td>
</tr>
<tr>
<td>Appendix E: Data collection forms</td>
<td>174</td>
</tr>
<tr>
<td>Life History Calendar interview</td>
<td>175</td>
</tr>
<tr>
<td>Minnesota Leisure Time Physical Activity Survey</td>
<td>185</td>
</tr>
<tr>
<td>OP History and Treatment Questionnaire</td>
<td>188</td>
</tr>
<tr>
<td>Calcium Food Frequency Questionnaire</td>
<td>192</td>
</tr>
<tr>
<td>Non-respondents telephone interview</td>
<td>198</td>
</tr>
</tbody>
</table>
Chapter 1: INTRODUCTION

I. Study objectives

It is well-established that anorexia nervosa (AN) is associated with decreased bone mineral density (BMD).\textsuperscript{1-4} However, current evidence is inconclusive as to whether this reduction in bone mass is permanent or is reversible with sustained recovery from AN.\textsuperscript{5-10} This is important to clarify as low BMD associated with AN may not only increase contemporaneous fracture risk in this population, but if these deficits in bone density are sustained even in those who recover, there may also be increased susceptibility to fractures in later life as well. The primary objectives of this study were to determine the extent of reversal of skeletal deficits associated with recovery from AN, and to evaluate the effects of key illness characteristics on BMD, in a cohort of young women who had received inpatient treatment for AN. Secondary objectives were to determine the duration of AN recovery required for normalization of bone mass if complete reversal of skeletal deficits occurred, to examine whether there was a differential capacity for regeneration across skeletal sites, and to elucidate an optimal definition of AN recovery from a bone perspective.

II. Background

The first part of this chapter will provide an overview of the epidemiology of osteoporosis and of AN, the mechanisms of decreased bone mass in this clinical population and the significance of low BMD both in terms of the impact on the patient and the larger impact on the health care system.
A. Osteoporosis: epidemiology and burden of illness

Osteoporosis (OP) is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue resulting in reduced bone strength and increased fracture risk.\textsuperscript{11} The prevalence of OP in North America among women over the age of 50 is 19 – 30\%.\textsuperscript{12-14} It is estimated that 56\% of women will sustain a fragility fracture after the age of 60.\textsuperscript{15} A fragility fracture is one which is caused by injury that would be insufficient to fracture normal bone.\textsuperscript{16} The most common fracture sites are those of the wrist, vertebra and hip which can result in significant diminishment of quality of life, increased mortality rate and considerable health care costs.\textsuperscript{17-19}

This is particularly true for hip fractures which are associated with more deaths, disability and economic costs than all other OP-related fractures combined.\textsuperscript{14, 15, 20} The incidence of hip fracture increases after age 60 and is the most common fragility fracture site in those over 80 years of age.\textsuperscript{15} Up to 25\% of OP-related hip fracture cases die within the first year,\textsuperscript{21, 22} and at one year post-fracture, 40\% are unable to walk independently and 60\% have difficulty performing at least one essential activity of daily living.\textsuperscript{23} Moreover, 17-27\% of hip fracture patients are admitted to long-term care facilities for the first time as a direct consequence of the fracture.\textsuperscript{18, 19, 21-23} The estimated annual cost of hip fracture treatment in Canada is $650 million.\textsuperscript{22} Together, these statistics highlight the considerable costs of OP both to the health care system and to the patient.
Diagnostic classification of OP

OP is clinically defined by assessment of bone mineral density (BMD). Dual-energy X-ray absorptiometry (DXA) is accepted as the most accurate clinical method for measuring BMD. BMD is recognized as a continuous risk factor for fracture and thus, no specific fracture threshold exists. However, for diagnostic purposes, the World Health Organization (WHO) proposed two thresholds of BMD based on standard deviations (SD) below the healthy, young adult mean BMD value (ie. after peak bone mass has been achieved). The SDs are reported as T-scores. According to WHO classification criteria, OP is defined as a T-score ≤ -2.5, and low bone mass (or osteopenia) as a T-score between -1.0 and -2.5 at the lumbar spine (LSP) or femoral neck (FN). In general, it has been shown that for each SD decrease in BMD, fracture risk approximately doubles. There is also good evidence of high risk of fracture in patients with T-scores ≤ -2.5 and a significant reduction in fracture risk with treatment, making this threshold an ‘evidence-based’ criterion for the diagnosis OP and for treatment initiation.

The WHO diagnostic criteria, however, were intended to apply to postmenopausal Caucasian women only, and the applicability of these criteria to other populations is unclear. The use of T-scores, particularly in children who have not yet achieved peak bone mass is inappropriate and meaningless. It is recommended that Z-scores, which are SDs above or below the mean for age, weight, sex and ethnicity, be used for children as well as for women between the ages of 20-50 years. Z-scores are based on the DXA manufacturer’s reference population. At the commencement of the present study there was no recommended criterion for the diagnosis of low bone density in premenopausal women and we used the accepted cut-off value at the time, of a Z-score ≤ -1.5. Recently, the International Society for Clinical
Densitometry (ISCD) recommended that a Z-score of \( \leq -2.0 \) be considered abnormal. This threshold value is not based on evidence of associated fracture risk, as this has not been established in young women. Rather, it is based on the normal distribution of most biological variables in which a normal range is defined as the normal mean plus or minus 2.0 SDs.\(^{26}\)

**Overview of bone metabolism and pathogenesis of bone loss**

Bone is a dynamic connective tissue which undergoes a process called modeling to shape bones, and a lifelong, continuous process of bone resorption and formation termed remodeling, for bone renewal.\(^{27}\) Modeling occurs primarily during growth but can also occur in adults to change the shape of the bone in response to mechanical loads.\(^{28}\) The primary functions of bone remodeling are to maintain mechanical strength by continually replacing old, fatigued bone with new bone, and to maintain mineral homeostasis by providing access to calcium and phosphorus that are stored in the skeleton.\(^{28}\) Unlike the remodeling process, during bone modeling there is increased bone formation which is not closely linked to prior bone resorption. Conversely, remodeling involves the sequential action of a group of cells, the bone remodeling unit (BRU), including osteoclasts that are responsible for bone resorption and osteoblasts which replace bone that has been removed by the osteoclasts.\(^{27-29}\) In states of normal bone turnover there is a close coupling of resorption and formation which is essential to prevent bone loss. When this balance is disrupted due to hormonal alterations that occur during the menopause, or as a result of aging, medication use, or illness states such as AN, this can result in serious skeletal diseases, of which OP is the most common.\(^{28}\)

There are two types of bone in the human skeleton – cortical bone and trabecular (or cancellous) bone and the rate of remodeling differs by type, reflecting their different functional
roles. Approximately 80% of the adult skeleton is comprised of cortical bone, but the proportions of the two types of bone vary among different skeletal sites. The composition of human vertebrae is approximately 80% trabecular bone while the FN is composed of 65% cortical bone. Cortical bone has a much lower turnover rate than trabecular bone, reflecting its primary mechanical role of providing structural support and protection of vital organs. Trabecular bone with its high turnover rate is considered to play an important role in mineral metabolism. Because trabecular bone is more metabolically active than is cortical bone, it may be particularly susceptible to hormonal disturbances. Thus, bone loss at the LSP during the menopause is more marked than at the hip, at least in part due to the heightened response of trabecular bone to estrogen suppression. A greater rate of bone loss at the spine may also occur with illnesses such as AN as a result of hormonal disruptions. As well, regeneration of trabecular bone may occur at a faster rate than cortical bone with recovery from AN, but this remains uncertain.

Risk factors for low peak bone mass

Bone loss commences at the time of the menopause and continues until the end of life. Risk of OP and OP-related fractures depends not only on the rate of bone loss but on the amount of bone accrued earlier in life, as BMD at menopause is determined by peak bone mass acquired during adolescence. Factors negatively impacting the accumulation of bone mass during the critical period of rapid skeletal growth, therefore, may have serious consequences in later life. While hereditary factors are important determinants of peak bone mass, accounting for 60-80% of its variance, other factors affecting bone accrual have been identified. In a large Canadian cohort of healthy, premenopausal women, low body weight, older age at menarche,
low calcium intake and amenorrhea were negatively associated with BMD at the spine or hip.\textsuperscript{51, 52} Other lifestyle factors such as smoking and excessive alcohol consumption have also been evaluated in premenopausal women with conflicting results, but both may be associated with lower BMD.\textsuperscript{53, 54} Not only are these risk factors particularly prevalent among women with AN, but onset of AN typically occurs during adolescence, thus putting women with this illness at a significantly higher risk of low peak bone mass.

**B. Anorexia Nervosa: epidemiology and burden of illness**

AN is a psychiatric disorder, characterized by a distorted body image and an intense fear of becoming fat, that leads to substantial patient-induced weight loss, progressive malnutrition and primary or secondary amenorrhea.\textsuperscript{55} In Ontario, Canada, the prevalence of AN in women aged 15-65 years has been reported to be 0.56%.\textsuperscript{56} This is higher than that reported by a meta-analysis of studies conducted in Europe and the United States, where the average prevalence of AN was found to be 0.3% with an incidence of 8 cases per 100 000 population per year.\textsuperscript{57} Incidence rates are highest for females aged 15-19 years. In a population-based study in Rochester, Minnesota, USA the incidence rate in this age group was 74 per 100 000 person years between 1935-1989.\textsuperscript{58} Data on time trends are conflicting but there is some evidence to suggest that the incidence in the high risk age group (15-24 years) is rising while the incidence in older women has remained stable since 1970.\textsuperscript{57-59}

AN can cause significant complications in many organ systems including the cardiovascular, gastrointestinal, renal, reproductive, neurologic and skeletal systems.\textsuperscript{60} Profound endocrine and metabolic disturbances result from severe malnutrition and purging behaviours leading to amenorrhea, delayed puberty, hypercortisolism and decreased insulino-
like growth factor (IGF-1) and leptin levels.\textsuperscript{3, 61} The long-term consequences of these medical complications are unknown.\textsuperscript{61}

Numerous reports have been published on the course and outcome of AN. Although results from these studies are difficult to summarize due to wide variability in the outcome parameters used across studies, there is consistent evidence that AN often follows a variable and protracted course. Several reviews of these studies, in which follow-up periods ranged from 1-29 years, reported that approximately 50% of patients with AN achieve a good outcome (recovery from all essential clinical signs and symptoms of AN), 30% achieve an intermediate outcome (improvement with residual symptoms), and 20% develop a chronic course of illness.\textsuperscript{62-65} In general, studies with more stringent recovery criteria have documented lower rates of complete recovery (approximately 25%), finding that there are substantial continuing psychological features of the illness in many patients deemed to have a ‘good outcome’.\textsuperscript{66} The mortality rate associated with AN is reported to be 0.56% per year or 5.6% per decade (95% CI 3.3%-7.9%), more than 12 times higher than the annual death rate for females 15-24 years old in the general population and twice that associated with other psychiatric disorders.\textsuperscript{67} In studies specifying the cause of death, 54% died from complications of the eating disorder, 27% committed suicide and 19% died of unknown causes.\textsuperscript{67} These data emphasize that AN, although relatively rare, is a serious psychiatric disorder with significant morbidity and mortality risks.

**Bone mineral density in women with AN**

Since AN typically affects the adolescent female, thus occurring during a critical period of rapid bone accrual, one of the important consequences of AN is a failure to achieve peak bone mass; women with a later onset of AN may experience bone loss.\textsuperscript{41} Numerous cross-
Sectional studies have demonstrated that adolescents and young women with AN have lower BMD at the LSP, hip, whole body and radius than healthy age-matched controls.

Studies have provided wide-ranging estimates of the prevalence of low bone mass in this population. Differences in results are due primarily to variability in the criteria used to define low bone density: comparison of BMD values to small numbers of age-matched healthy controls; SDs below the young, healthy, adult mean BMD value (T-scores); or, SDs below the mean for weight, age and sex-matched normative data (Z-scores). The Z-score is considered the most appropriate way to report BMD in adolescents and young, premenopausal women. The largest study that used Z-scores included 170 adolescents with AN and reported that 44% and 13.5% had Z-score values < -1 and < -2, respectively, at the LSP, and 25% and 5.9% had Z-score values < -1 and < -2, respectively, at the FN. Smaller studies of adolescents (43 to 85 participants) reported a range in the prevalence of Z-scores of < -2 from 9.1% - 22% at the LSP and 3% - 6.8% at the FN. Only one small study of young adults (44 premenopausal women) reported Z-score values, finding that 50% of participants had Z-scores < -2 at either the LSP or FN. Although the estimates of the prevalence of low BMD varied across the studies, collectively they show reduced bone mass especially at the LSP, indicating preferential loss of trabecular bone which, as described earlier, may be particularly susceptible to hormonal disturbances.

Mechanisms of low BMD in AN

The underlying mechanisms responsible for low bone mass in AN patients are not fully understood but appear to involve multiple and interrelated endocrine disturbances that occur
in response to profound undernutrition. In postmenopausal OP the main precipitant of bone loss is increased bone resorption secondary to estrogen deficiency. In estrogen deficient states, osteoclasts are activated by cytokines, such as interleukin-6 and tumor necrosis factor (TNF) which are normally inhibited by estrogen, resulting in increased bone resorption. Estrogen deficiency and amenorrhea are hallmarks of AN: many studies have shown a negative correlation between duration of amenorrhea and BMD. However, estrogen therapy fails to improve bone density in these patients. Additionally, patients with AN have lower bone density than age-matched women with hypothalamic amenorrhea from other causes. Together, this suggests that hypoestrogenic status alone is insufficient to explain low BMD in this population. Studies using bone turnover markers have observed an uncoupling of bone turnover with decreased bone formation and increased bone resorption in adult, premenopausal women with AN. In adolescent girls, a decrease in both markers of formation and resorption have been observed, suggesting a state of low bone turnover rather than an uncoupling of the remodeling process. The effect of AN on bone metabolism, therefore, likely differs depending on the age of the patient.

A number of nutritionally-regulated hormones have been implicated in the disruption of bone turnover in AN; most of these studies have focused on the effects of insulin-like growth factor (IGF-1), leptin and cortisol. IGF-1, a bone trophic factor and a sensitive index of nutritional status, has consistently been shown to be reduced in AN and to increase rapidly with weight gain accompanied by an increase in bone formation markers. As well, the administration of recombinant human IGF-I to women with AN has been shown to significantly increase bone mass at the LSP. Similarly, low levels of leptin, a hormone involved in the regulation of food intake and energy expenditure, have been demonstrated in
AN patients with increased concentrations observed with weight gain, sometimes to excessive levels. Leptin’s effects on bone metabolism are not fully understood, but this hormone likely has indirect effects via its influence on the hypothalamic-pituitary-peripheral endocrine axes and may also directly stimulate bone formation. Hypercortisolemia has also been reported in women with AN due to increased frequency of secretory bursts and has been found to be associated with decreased markers of bone formation in this population. Investigators have recently identified numerous additional hormonal disturbances in AN with some evidence to suggest that they may be further contributing to the low bone density seen in these individuals. These include increased grehlin, osteoprotegerin, and peptide YY, and reductions in dehydroepiandrosterone sulfate (DHEAS), endogenous androgens, and tri-iodothyronine (T3).

**Fracture risk in women with AN**

The significance of low BMD is its association with increased fracture risk. In postmenopausal women, fracture risk is approximately doubled for each SD that BMD falls below young adult normal values. Although low BMD has been clearly associated with AN, an association with increased risk for fracture has not been clearly established in the AN population. Rigotti et al reported a relative risk (RR) for non-spine fractures of 7.1 compared with age-matched healthy women. This estimate was based on a sample of only 27 subjects (total follow up 59.8 person years). Lucas et al and Verstergaard et al both used historical data from administrative health registries and compared the occurrence of fractures in patients diagnosed with AN to age-and sex-specific population fracture rates. They reported a RR for all fracture types of 3.0 and 1.98, respectively, in AN patients, and noted that this increase in risk
persisted for more than 10 years after diagnosis. Vestergard et al\textsuperscript{124} pooled their results with those of Rigotti et al\textsuperscript{89} and Lucas et al\textsuperscript{122} to obtain a pooled RR of 2.6 for all fracture types, 4.7 for symptomatic spinal fractures and 5.3 for hip fractures. There are important issues, however, that were not addressed by the two studies that used health registries: they did not differentiate fractures as low-trauma fragility or traumatic fractures, and did not clarify whether the subjects had chronic AN or had recovered. Furthermore, none of the studies examined asymptomatic spine fractures using x-rays. As symptomatic spine fractures consist of only a small proportion of total spine fractures, the reported RR for spinal fractures may have been underestimated.

III. Literature review: key determinants of bone mass in women with AN

As previously described, the onset of AN typically occurs during adolescence, the time period of rapid growth when the majority of bone mineral is accrued. AN during this time period may critically impede the attainment of peak bone mass leading to permanent deficits and potentially increasing the risk for OP and fracture in later life, even in those who have recovered from this illness. This underscores the importance of determining the effect of recovery from AN on BMD and identifying key illness characteristics that may influence bone mass in women with a current and past history of AN: identification of risk factors for low BMD in this population will enable the implementation of optimal OP management strategies directed towards those individuals at greatest risk. The next section summarizes the current literature regarding the effect of AN recovery and other key illness characteristics on bone mass in the AN population.
1. Recovery of bone mass with recovery from AN

There have been a number of studies that have investigated whether BMD deficits are reversed with recovery from AN. (See Appendix C for details of studies). However, their results have been widely conflicting, demonstrating complete recovery of bone mass, partial recovery, no recovery, or recovery at some skeletal sites but not others. One of the earliest studies by Treasure et al\textsuperscript{9} reported that BMD values at the LSP, FN and radius (RD) of 25 recovered AN patients were not significantly different from a healthy comparison group. They concluded that bone density returns to normal with recovery from AN. However, a definition of recovery was not provided, duration of recovery was unclear and potential confounders such as duration and severity of the illness were not controlled for in the analysis. Since then, four small studies have reported similar results indicating complete reversal of bone deficits with AN recovery. Bachrach et al\textsuperscript{5} demonstrated that BMD values at the LSP and total body (TB) of 9 recovered AN patients were not significantly different from values observed in healthy controls. They defined recovery from AN as having attained a BMI within 1 SD of the mean for healthy, age-matched females. The duration of recovery was not specified. Hay et al\textsuperscript{125} found that 21 patients with a good outcome (defined as resumption of menstruation and weight rehabilitation to 85% of average weight for age and sex) had spinal BMD values similar to a control group, whereas patients classified as having an intermediate or poor outcome had significantly lower values. Wentz et al\textsuperscript{126} evaluated a sample of 36 patients assessed approximately 11 years after onset of AN and did not find significant differences in the prevalence of low BMD in AN participants compared to healthy controls. However, 42% of the participants had low BMD (defined by the authors as a T-score < -1.0) at the FN compared to 26% of controls. This difference may not have achieved statistical significance due to the small sample size. Moreover, the prevalence of low
BMD in the control group may be higher than would be expected in young, healthy women. A definition of recovery was not provided. The fourth study, by Bass et al,127 documented near normal values at the LSP (mean Z-score of -0.4) and normal values at the TB (mean Z-score of 0.2) in 13 patients recovered for 2.7 years. These patients were considered recovered if they had a body weight of 85% of that expected, and regular menses for at least three cycles.

Partial recovery of bone mass has been demonstrated in several studies, many of which were prospective studies that may have been of inadequate duration to detect complete normalization of bone density. The largest prospective study by Castro et al45 followed 108 ill adolescent patients for between 6 and 30 months after admission for inpatient treatment. Sixty-four patients were classified as having a good outcome at follow-up (BMI > 19kg/m² and resumption of menses at the follow-up visit). These patients experienced annual bone mass gains at both the LSP and FN, whereas those classified as having a poor outcome experienced a loss of bone mass at these sites. Despite gains in bone mass, only 17% of patients with a good outcome and low BMD at baseline achieved normal BMD values at follow-up; the authors suggest that in the longer term it may be possible for the majority to reach normal values. Viapiana et al128 followed 55 patients for 12 months after a treatment program and reported an increase equivalent to 1 SD at the LSP and FN. All patients maintained a BMI of > 17.5 kg/m² but it was unclear as to whether they had resumed menstruation. Dominguez et al129 noted an increase in BMD at the LSP and FN in 28 patients after only 2 months of inpatient treatment, but values remained lower than controls. In a recent 12 month prospective study of 34 AN patients, BMD at the LSP stabilized in 14 patients who experienced a 10% increase in BMI and resumed menstruation for three cycles, compared to those who either gained weight without menstrual recovery or experienced no recovery at all, who continued to experience bone loss.130 In their
cross-sectional study, Herzog et al. evaluated the long-term outcome of BMD in 51 AN patients approximately 11 years after admission to a treatment facility. They found that 28 patients with a good disease outcome (i.e. regular menstruation and a weight deviation <15% from the expected size-and age-averaged body weight) had significantly higher LSP and RD BMD values than those with a poor outcome, but their values were still lower than those of the healthy reference group. In summary, these studies generally show increases in BMD associated with improvements in weight and/or resumption of menstruation, but deficits were still observed. It is unclear if full recovery of bone mass is possible as no study followed sufficient numbers of recovered patients for a sufficient period of time.

In contrast, other studies found no evidence of regeneration of bone mass with AN recovery. Nine prospective studies, which together included only 78 recovered AN patients followed for 3 months to 2 years, found that change in bone density at the LSP and/or TB was not significantly different for recovered versus non-recovered patients. Recovery was variably defined across these studies; three studies defined recovery as weight restoration and resumption of menses, three studies defined recovery by a weight restoration criterion only, two studies by menstrual status only, and one did not specify a definition. Ward et al. reported that, in their cross-sectional study of 18 patients with a median duration of recovery of 6 years (recovery defined as a BMI > 18.5 kg/m² and resumption of menstruation for at least 6 months), 12 patients had BMD T-scores < -1.0. An additional cross-sectional study compared the lumbar spine BMD of 34 patients with active AN, 20 patients who were weight recovered and amenorrheic, and 19 patients who were both weight recovered and had regular menses for > 3 months (duration of recovery from 3-26 months). There were no significant differences in mean BMD values across the 3 groups; 26% of the weight and
menstrual recovered patients had BMD values more than 1 SD below the mean of an age-
matched reference population.97

Finally, several studies observed differential effects of AN recovery across skeletal sites. Bolton et al44 observed increases in BMD at the LSP and TB but not at the FN in 15 patients who achieved a normal body weight over the course of 1 year. Miller et al135 made the observation that patients who resumed menstruation had increased BMD at the LSP but not FN while those who had weight gain only (to > 85% of ideal weight) had significant increases in BMD at the hip but not LSP, over a mean follow-up period of 13 months. Morris et al136 examined BMD in a community-based sample of 51 non-recovered AN patients and 36 recovered AN patients (length of recovery ranged from 1 – 26 years; recovery was not defined) and observed that TB BMD was not significantly different between the recovered group and control group but BMD at the LSP remained significantly lower in the recovered group. Hartman et al46 reported that in 19 patients “recovered beyond clinical dispute” for a median of 21 years BMD was similar to controls at the LSP but was significantly lower at the FN.

There are many potential explanations for these inconsistent study results. First and foremost are the variable definitions used to define AN recovery across the studies. These included weight restoration only (defined as a > 10% increase in weight, weight to 85% of ideal weight, or a specific BMI cut-point) or weight restoration and resumption of menses, or resumption of menses without consideration of weight restoration. Recently, there has been growing evidence that weight recovery and menstrual recovery may have both combined and independent effects on regeneration of bone mass.97, 129, 130, 135 If so, the use of variable definitions of AN recovery would contribute to different conclusions regarding the effect of recovery on
BMD. Many prior studies were also limited by small sample sizes and significant loss to follow-up in longitudinal studies. This resulted in an inability to rigorously evaluate the effect of AN recovery on BMD while controlling for possible confounding factors such as illness duration and severity, calcium intake, and smoking and alcohol consumption, due to a limited distribution across key variables and inadequate statistical power. In particular, many of these studies did not include enough participants recovered for long periods of time in cross-sectional studies or follow-up participants in prospective studies for long enough to adequately examine the ability of bone mass to fully regenerate with sustained AN recovery. Variability in the durations of recovery or follow-up periods across studies may have also contributed to inconsistent results. Finally, small sample sizes and large drop-out rates also create the potential for selection bias. Overall, these methodological limitations may have contributed to the inconsistent findings reported by these studies and affected the internal validity and generalizability of their results.

Consequently, there remain many outstanding issues regarding the effect of recovery from AN on bone mass. It is still unknown whether full regeneration of bone mass occurs at each skeletal site, and, if so, the duration of recovery required. It is also unclear whether the potential for regeneration of bone is impacted by the age at which recovery occurs. Most of the studies were conducted on adolescents and these did not show an obvious difference in results compared to studies that included adult participants. The relative effect of weight restoration versus resumption of menses also requires further evaluation to help establish a definition of AN recovery for future investigations of AN and bone mass.
2. Effect of AN illness characteristics on bone mass

While recovery from AN may well be the strongest determinant of BMD, certain illness characteristics such as the duration and severity of the illness, age at onset of AN, AN subtype, and exercise may also have important effects on BMD.

i. Duration of illness

Many studies have demonstrated a negative association between either duration of illness or duration of amenorrhea and BMD in ill AN patients. However, the effect of illness duration on BMD among women who have recovered from AN is less clear. Three cross-sectional studies did not observe a relationship between duration of illness and bone mass in recovered patients, but small sample sizes may have precluded detection of a significant effect. One prospective study reported that illness duration was negatively correlated with change in BMD at the FN but not at the LSP in 19 patients who were followed for 2 years after an inpatient re-feeding program. A definition of recovery was not provided and it is unclear how many of these patients were weight restored and/or resumed menstruation over the 2 years.

ii. Illness severity

There have been inconsistent results regarding the effect of illness severity on BMD in both ill and recovered patients. This may be due in part to the different variables used to approximate severity of illness. Five studies found no association between BMD and lowest BMI, percentage decrease in body weight, and duration of time at 85% below normal weight. Other studies, however, reported a significant negative correlation between BMD and
lowest BMI,74, 79,125 duration of time at lowest BMI81, ‘degree’ of underweight below a BMI of 18.5 kg/m²,6 or having ever had a BMI < 15 kg/m².38 An issue that was not adequately addressed in these studies is the potential correlation between illness severity and other illness characteristics; in particular, duration of illness. In the studies that conducted a multivariable analysis including both severity and duration of illness,6, 38, 81, 125 only duration of illness remained significant, suggesting that illness severity may not be an important independent predictor of low bone mass. Rather, any observable effect of severity may, in fact, be due to a longer illness duration. Further investigation is required to determine the relative effects of chronicity and severity on BMD in both ill and recovered patients.

iii. Age at onset of illness

Almost half (46.5%) of bone mineral content (BMC) in adulthood is acquired during the 2-year period across peak height velocity, resulting from a combination of bone modeling and remodeling. Two years after menarche, BMC is 85% of the adult value, and 90% of peak bone mass is acquired by age 18.137, 138 Thus, it has been hypothesized that onset of AN during adolescence, because of the interruption during this critical period of rapid bone accrual, would result in a greater deficit in bone density than would adult onset AN.41, 127 While this makes biological sense, most studies have not demonstrated an association between age at onset of AN and BMD, although their findings were limited by small sample sizes and narrow ranges in onset ages.6, 10, 46, 68, 69, 71, 77, 82, 125, 139 Given the underlying hypothesis, it may be preferable to evaluate the effect of age at onset on bone mass in terms its relation to onset of puberty, and this has rarely been addressed. Two studies that compared bone density in patients with primary versus secondary amenorrhea did not find significant differences between the two groups, but
were limited by small numbers of patients in one or both groups. A third study reported that patients with primary amenorrhea had lower BMD at the spine and hip, but these differences were not significant after adjusting for duration of illness. More research, which specifically evaluates the effect of premenarcheal versus postmenarcheal onset of AN on BMD, is needed.

iv. Subtype of AN

The DSM-IV sub-divides AN into two types – restricting type (R) and binge-eating/purging type (BP). The R subtype describes presentations in which weight loss is achieved primarily through dieting or fasting whereas the BP subtype achieves weight loss by regularly engaging in purging behaviours, such as self-induced vomiting, misuse of laxatives, diuretics or enemas. It has been suggested that the BP type may be associated with lower BMD due to greater disturbances in the metabolic and endocrine systems. Yet, there is minimal evidence to support that AN subtype is an important determinant of bone density. One prospective study reported that, after adjusting for body weight, age at onset and duration of illness, subtype of AN was the best predictor of spinal BMD at follow-up, with the BP subtype associated with significantly lower BMD. However, only 7 and 8 patients of the R and BP subtypes, respectively, completed the study, raising the possibility that this may have been a spurious finding. Two cross-sectional studies also reported that patients with BP subtype had lower BMD, but the difference between the two groups was not statistically significant. Small subtype groups in these two studies may have precluded detection of significant differences. Conversely, several studies found that BP subtype was associated with higher BMD, although this may have been due to higher body weight in the BP participants.
Only one study appeared to adjust for weight and noted that, once weight was controlled for, the effect of subtype was no longer significant. Finally, one study reported that frequency of vomiting predicted spinal BMD, but it is unclear whether it was associated with higher or lower bone mass. Taken together, AN subtype seems unlikely to be a key predictor of bone mass and any effect may be due to differences in body weight or other illness characteristics. A study which controls for these factors is needed to confirm this.

In summary, the majority of these studies have been limited by small sample sizes and by inadequate consideration of important confounding factors, leading to inconsistent results. Many questions, therefore, remain regarding the effect of these illness characteristics on bone mass in women with a history of AN. Not only have the impact of these characteristics on BMD in ill patients not been clearly elucidated, but there is sparse evidence about the extent to which possible negative effects persist in women who have recovered from this eating disorder, or the extent to which prior illness history influences the rate of bone regeneration which may occur with AN recovery.

3. Effect of exercise on bone

Although exercise could be considered another key illness characteristic in women with AN, it is a factor that deserves particular consideration. Excessive or compulsive exercise is a salient feature of this disease and is believed to play a role not only in the progression and maintenance of AN but in its pathogenesis as well. Consequently, standard practice in the treatment of eating disorders is to proscribe exercise. Yet, very little is known about the effect of exercise on bone in ill patients and even less about the effect of exercise during recovery from AN.
Physical activity imparts mechanical loads on bone, initiating an adaptive structural response which involves increases in bone mass and changes in geometry that may ultimately enhance bone strength.\textsuperscript{147} Exercise in healthy women has consistently been shown to have a positive effect on bone density.\textsuperscript{148} Activities that impart both a high strain rate (rapid deformation of bone in response to mechanical load) resulting from dynamic and atypical movement directions, and a high force magnitude, have demonstrated the greatest osteogenic stimulus.\textsuperscript{149-151} Specifically, sports such as gymnastics, dance, volleyball, tennis and soccer have been found to have the most substantial effect on bone mass while minimal bone loading activities such as walking, swimming or cycling have no effect.\textsuperscript{149, 150, 152-157} The response of bone to physical activity in women with AN, however, has not been so clearly established. States of severe nutritional deficiency and subsequent disturbances of the endocrine environment may alter the anabolic response to mechanical loading on the skeleton such that greater loads may be required to trigger an adaptive response.\textsuperscript{158} Alternatively, excessive exercise during illness may attenuate any positive effects by contributing to further weight loss. In contrast to periods of malnutrition, during recovery an adaptive response may be stimulated by lower mechanical loads due to increases in estrogen and IGF-1\textsuperscript{100} and the possible rapid regeneration of bone mass that occurs during recovery from AN.

Prior studies of BMD and physical activity in women with AN have demonstrated marked inconsistency of results. Ten studies found no association between exercise and BMD.\textsuperscript{1, 6, 69, 70, 76, 80, 83, 89, 133, 159} These were small studies ranging from 18-69 participants (average of 37 participants). In contrast, three additional studies demonstrated moderate evidence of a positive effect of exercise on BMD.\textsuperscript{38, 41, 75} In a study of 170 adolescent AN patients, greater than 3 hours per week of exercise was associated with higher spinal BMD, but this association was not
significant after adjusting for duration of illness and body weight.\textsuperscript{38} Gordon et al\textsuperscript{75} observed, in their sample of 61 adolescent patients, that hours per week of current exercise participation was positively correlated with BMD at the LSP, FN and TB. Seeman et al,\textsuperscript{41} however, discovered significantly higher BMD at the FN, but not at the LSP, in participants who participated in sport at least 2-3 hours per week for 2-3 hours each time. Finally, two studies indicated that exercise may have a negative effect on bone mass.\textsuperscript{44, 139} Bolton et al\textsuperscript{44} stated that ‘high’ exercise was correlated with lower spinal BMD. The definition of ‘high’ exercise was unclear – that is, whether it was based on the amount of exercise or the type of bone-loading. The second study reported that 1-6 hours/week of exercise was positively associated with BMD at the hip and spine but that performing no exercise or exercising > 6 hours/week was negatively associated with both skeletal sites.\textsuperscript{139} However, these findings must be questioned as they were based on only 8 AN participants.

These conflicting results are undoubtedly due, at least in part, to the variability in the way exercise was assessed. Most of these studies had limited exercise data and evaluated the effect of current activity only. Many studies measured only intensity of exercise based on hours per week or estimates of caloric expenditure and did not take into consideration the osteogenic potential of specific activities. The type of exercise may be more relevant to the evaluation of bone response than is the amount and intensity of exercise. Furthermore, rather than considering only recent exercise, it may be important to determine the impact of exercise history throughout life, especially exercise performed during adolescence, which may confer a lifetime protective effect.\textsuperscript{160, 161}
Based on the current literature, it is still unknown whether exercise during AN illness is detrimental to, or protective of, bone mass, and whether exercise during recovery promotes bone accrual. Although caution must be taken with respect to recommendation of exercise in women with a history of AN, it may be beneficial for certain patients. A recent pilot study found that even short term bed rest in hospitalized adolescents with AN suppressed bone formation and resorption, 162 suggesting that the current practice of exercise prohibition may not be optimal for all individuals. More information is needed to inform appropriate recommendations regarding physical activity in this population.

IV. Overview of the present study to address important gaps in the literature

This literature review on the impact of AN on bone mass has revealed that few prior studies have investigated the long-term outcome of BMD in women with AN, and those have been limited by small sample sizes and lack of consideration of potential confounding factors that might influence this relationship. As a result, several key questions remain unanswered:

- To what extent are bone deficits that occur as a result of AN illness reversed with recovery?

- If full regeneration of bone mass following AN recovery is possible, what duration of recovery is required before it is apparent / measurable by DXA?

- What are the effects of AN illness characteristics on bone mass and do any effects persist in women who have recovered from the illness?

- What are the effects of exercise performed while ill, and exercise performed while recovered, on bone mass?
1. Study design and AN sample

The purpose of the study detailed in this thesis was to address these questions with a large cross-sectional study that dealt with fundamental limitations of prior investigations. While acknowledging that a prospective study would be the optimal design to determine factors that predict change in BMD over time in AN patients, the large sample size and length of follow-up time required to achieve this objective would result in prohibitive costs and challenging logistics. A particular strength of the present study included its large sample size (n=190) made possible through recruitment from the two largest eating disorder programs in Southern Ontario – Toronto General Hospital and Homewood Health Centre. (See Appendix A for recruitment details). Our large sample provided a broad distribution of responses on all key variables, including many participants with a long duration of recovery. This enabled the rigorous assessment of the effect of these variables on BMD and provided a good representation of different groups within AN, enhancing generalizability of the results.

2. The Life History Calendar interview method

Prior cross-sectional studies relied on chart review or traditional questionnaires to collect data on illness history. The present study sought to enhance recall and obtain comprehensive and sequential information on lifetime illness history of AN and related variables through the use of a cognitive interview technique, the Life History Calendar (LHC). The LHC interview uses a timeline-based semi-structured interview to aid in the recall of lifetime events. It was specifically designed to facilitate recall of variable life histories by incorporating the structure of autobiographical memory and encouraging the use of multiple retrieval pathways – top-down, sequential, and, parallel retrieval mechanisms. The calendar
grid used in this study (Appendix E) consisted of a horizontal axis that included the temporal
cues of age, school grade, admissions to hospital and personal landmark events (important
vacations, change in living arrangements, marriages etc). There were eight domains along the
vertical axis representing the inter-related variables of interest: weight, height, purging
behaviours, menstrual history, reproductive history, oral contraceptive use, smoking and
alcohol consumption. The order of these domains assisted in top-down retrieval mechanisms.
The first domain required recall of general events over longer time periods (the easiest to recall)
which were then used to provide contextual clues for recall in other domains. The chronological
retrieval of events with appropriate timing cues encouraged sequential retrieval mechanisms.165
At the end of the interview, cross-checks were conducted across each of the eight domains to
look for inconsistencies, thus improving accuracy. One interviewer conducted all interviews to
eliminate issues with inter-rater reliability.

The LHC method has been shown to be valid, but reliability has not been assessed.
Freedman et al164 compared historical data from an LHC interview to respondents’ reports from
previously collected concurrent data as part of a longitudinal study. These data had been
collected five years previously by face-to-face interview using a standard questionnaire and
included information regarding school attendance and employment status during the interview
month. They found that 87% and 72% of participants reported identical information about
school attendance and employment status, respectively. The authors suggested that the lower
consistency regarding employment status may be a result of increased variability of this factor
in this age group compared to school attendance which usually represents a long-term
commitment. A second study evaluated the accuracy of recall of social circumstances recorded
50 years earlier, using a similar method, the Life Grid.166 This study reported more than 80%
agreement with historical records for occupational and residential information but only 40% agreement for childhood illnesses and 15% agreement for information on childhood diet. A third study investigating lifecourse stress among adults found almost 100% agreement between historical reports on life events such as births, marriages, and divorces collected by the LHC method and reports collected 15 years earlier. Finally, Norell et al compared responses of lifetime oral contraceptive (OCP) use obtained by a life event calendar interview with pharmacy records and reported good levels of agreement (> 70%) for total duration of use and duration of use in different time windows but found a tendency to underreport specific types of OCP used in the past.

The LHC method has also been shown to have improved accuracy over traditional questionnaires. Two studies directly compared the LHC with standard questionnaire interview methods; both indicate that the LHC interview leads to better quality self-reported historical data. Belli et al compared responses from the two types of interviews to responses obtained two years previously from a standardized survey instrument regarding employment status, income, number of weeks absent from work and reasons for absenteeism. They reported significantly higher correlations between LHC and initial interview responses when compared to the questionnaire responses. The second study compared respondents’ responses regarding lifetime partner violence using a standardized interview and LHC interview. They found that the LHC interview elicited more reports of partner violence, particularly during earlier years, and that there were greater differences in distant-past recall than in past-year recall between the two methods. The authors concluded that this indicated the superiority of the LHC method, especially for distant-past recall.
3. Definition of AN recovery

A source of variation in the results of prior studies investigating the effect of AN recovery on bone mass was the variable criteria used to define AN recovery. Currently, there is no consensus on what constitutes recovery in AN. Some authors advocate comprehensive definitions that include physical, psychological and psychosocial measures. Others suggest defining recovery as simply no longer meeting the diagnostic criteria for AN for a specified time period. Some of the earliest work on outcome of AN by Morgan and Russell, which has since been incorporated into various conceptualizations of recovery, classified patients according to both a weight criterion and menstrual status. They categorized patients as having a ‘good’ outcome if they had achieved a body weight of >85% of their ideal weight and were menstruating regularly, an ‘intermediate’ outcome if they had either a pathologic menstrual status or a deviation in body weight > 15%, or a ‘poor’ outcome if they met neither criteria.

In the absence of a universally accepted definition, we also focused on these physical measures of recovery – weight restoration and resumption of menses – as both of these aspects of recovery appear to be important determinants of bone mass, while acknowledging that participants classified as recovered based on these criteria may have residual psychopathology. All prior studies of AN recovery and BMD that clearly defined recovery also did so based on one or both of weight and menstrual recovery criteria (see Section III and Appendix C). Specifically, our criteria for recovery was weight restoration to a BMI of \( \geq 18.5 \) kg/m\(^2\) and regular menstruation, each maintained for at least 12 months. The weight cut-off was based on Health Canada’s Guidelines for Body Weight Classification in Adults which classifies those with a BMI < 18.5 as being underweight. There is currently no agreement regarding the time
span of symptom resolution that constitutes AN recovery, and the duration of sustained AN recovery required for maximal regeneration of bone mass is not known. We chose a 12 month duration as there is some evidence that weight restoration maintained for 12 months is associated with long-term recovery,\textsuperscript{171, 172, 178} and would also be an adequate time period for measurable change in BMD to have occurred.

There is a need for a consistent definition of AN recovery. One of the objectives of the present study was to evaluate our recovery criteria with respect to BMD in order to advance the development of a standardized definition of recovery for use in future investigations of AN and bone mass.

\textbf{V. Overview of the thesis}

The remainder of the thesis presents the results of the study in the form of three separate papers (Chapters 2-4), as summarized below. The final chapter, Chapter 5, provides an in-depth discussion of the relevance of the findings to health care providers and the eating disorder community, limitations of the study, and recommendations for future research.

\textbf{Chapter 2. (Paper 1)}

\textbf{Title: The effect of weight and menstrual recovery and other key illness characteristics on bone mineral density in young women with a history of anorexia nervosa}

The primary objectives of this investigation were to determine the extent of reversal of skeletal deficits with recovery from AN and evaluate the effects of key illness characteristics on BMD in a cohort of young women who had received inpatient treatment for AN. Specifically, this paper answers the following questions: 1) What is the prevalence of low BMD in AN
recovered participants compared to ill participants and to healthy women who have never suffered from AN? 2) Controlling for recovery status, are other illness characteristics (duration, severity, subtype, age at onset of AN, age at onset of recovery) associated with low BMD among women with a history of AN? 3) Are the effects of illness characteristics on BMD different in recovered versus ill participants? And, 4) what are the relative effects of weight recovery and menstrual recovery on BMD?

Chapter 3. (Paper 2)

Title: Characterization of changes in bone density associated with illness and recovery in young women with a history of anorexia nervosa.

The purpose of this paper was to address our secondary objectives including determining the duration of recovery required for normalization of bone mass to occur and examining whether the capacity for regeneration of bone mass differs across skeletal sites. It provides additional important detail to the results reported in Paper 1 by describing the pattern and rate of bone loss and bone accrual associated with duration of AN illness and recovery at three skeletal sites (LSP, FN and TB), and re-examining the effect of key illness characteristics at each of these three sites in recovered participants. Specifically, the objectives were to: 1) examine the associations between BMD and duration of AN illness and duration of recovery; 2) determine whether these associations differed by skeletal site; and, 3) evaluate the effect of illness characteristics (duration and severity of illness, age at onset of AN, age at onset of recovery) on BMD at each of the three skeletal sites in women who have recovered from AN for a short versus longer time period.
Chapter 4. (Paper 3)

Title: The effect of exercise during illness and recovery on bone mineral density in young women with a history of anorexia nervosa.

This paper addresses the effect on BMD of another key AN illness characteristic – excessive exercise. The purpose of this paper was to describe habitual lifetime exercise in our cohort of young women and examine the effect of different types of bone-loading exercise performed during illness and during recovery on BMD at the LSP, FN and TB.

VI. Significance of the study

Osteoporosis is a serious health problem associated with both significant human costs in terms of mortality and decreased quality of life, and substantial economic costs.\textsuperscript{20-22, 179} Although osteoporosis primarily affects postmenopausal women, adolescents and young women with AN are also at risk of developing this disease. Approximately 20-50\% of women with AN have BMD more than two standard deviations below that expected for their age at one or more skeletal sites, indicating low bone mass.\textsuperscript{2, 38, 73} Not only may this increase their immediate fracture risk, but, if the AN-related deficits in bone density are permanent, this may also increase their susceptibility to fractures in later life. Much uncertainty exists as to the long-term outcome and management of BMD in these patients. It is important, therefore, to determine whether bone density recovers in women who experience sustained recovery from AN, and, if so, to what extent. It is also important to identify both modifiable and non-modifiable factors associated with low BMD. This will enable the development and implementation of optimal management strategies directed towards the prevention of low BMD, and ultimately fractures, in this population.
INTRODUCTION

Anorexia nervosa (AN) is a psychiatric disorder that is characterized by a distorted body image and an intense fear of becoming fat leading to substantial patient-induced weight loss, progressive malnutrition and amenorrhea.\textsuperscript{55} Since AN typically affects the adolescent female, thus coinciding with a critical period of rapid bone accrual, one of the important consequences of AN is a failure to achieve peak bone mass; women with a later onset of AN experience bone loss.\textsuperscript{41} Numerous studies have demonstrated that adolescents and young women with AN have lower bone mineral density (BMD) at the lumbar spine,\textsuperscript{1, 2, 4, 38, 41, 75, 77, 85} hip,\textsuperscript{38, 41, 69, 72, 75, 78, 79} total body\textsuperscript{1, 39, 82, 83} and radius\textsuperscript{6, 9, 71, 86} than healthy, age-matched peers. The underlying mechanisms responsible for low bone mass in AN patients are not fully understood but appear to involve multiple and interrelated endocrine disturbances that occur in response to profound undernutrition\textsuperscript{87} resulting in a state of low bone turnover\textsuperscript{4, 42} or an uncoupling of the remodeling process.\textsuperscript{94, 95}

Although decreased bone mass is a well-established consequence of AN, many questions remain regarding regeneration of BMD with recovery from AN. Both cross-sectional and prospective studies have yielded contradictory results demonstrating complete recovery of BMD,\textsuperscript{5, 9, 125, 127} partial recovery,\textsuperscript{6, 44, 45, 85, 97, 128, 129, 135} maintenance\textsuperscript{8, 82, 89, 130, 131, 133} and even loss.\textsuperscript{132, 134, 180} These inconsistent results may be due partly to variability in the criteria used to define recovery from AN (weight restoration, resumption of menses or both). As well, most studies had small
sample sizes, short follow-up periods and were conducted on adolescent girls. Hence, these prior investigations were limited in their ability to adequately examine and control for the effects of duration and severity of the disease and other potentially relevant illness-related characteristics such as subtype of AN and age at onset of AN on recovery of bone mass. Moreover, short durations of AN recovery may have been insufficient for normalization of BMD to have occurred.

It is, therefore, currently unclear to what extent deficits in BMD can be reversed in patients recovered from AN and the effect of key illness characteristics on bone mass in this population. Attention to this knowledge gap is important because not only may low BMD increase immediate fracture risk in AN patients, but if the observed deficits in bone density persist, low BMD may also increase their susceptibility to fractures in later life.

The purpose of the present study was to advance current knowledge with respect to recovery of BMD in young adult women who have recovered from AN. Specifically, we addressed the following questions: 1) What is the prevalence of low BMD in AN recovered participants compared to ill participants and to healthy women who have never suffered from AN? 2) After controlling for recovery status, are other illness characteristics (duration, severity, subtype, age at onset of AN, age at onset of recovery) associated with low BMD? 3) Are the effects of illness characteristics on BMD different in recovered versus ill participants? And, 4) what are the relative effects of weight recovery and menstrual recovery on BMD?
METHODS

AN participants

Female patients admitted between April 15, 1993 and May 31, 2006 to the University Health Network (Toronto General Hospital [TGH]) or between January 1, 1995 and May 31, 2006 to Homewood Health Centre, Guelph, Ontario for inpatient treatment of AN (defined by DSM-IIIR or IV criteria) were selected for this study. TGH is a large, urban tertiary health care centre and Homewood Health Centre is a specialized health centre providing mental health and addiction treatment. These centers operate the largest eating disorders programs for adults in Southern Ontario, Canada (population approximately 12 million). The two centers are demographically similar, although Homewood Health Centre does not admit severely ill patients (BMI < 15 kg/m²). Exclusion criteria for the study included a primary diagnosis of bulimia nervosa, age greater than 40 years at the time of the study, history of disease or use of medications known to affect bone metabolism, hysterectomy or bilateral oophorectomy, and, pregnancy or active breastfeeding at the time of the study or within the prior 12 months. Participants who had undergone prior BMD assessment(s), who had used oral contraceptives (OCP), or who had received bisphosphonates were not excluded. A wash-out period was not required for those on an OCP or bisphosphonate at the time of the study visit.

Five hundred and fifty age-eligible women were admitted for treatment of AN in the defined time period, of which 500 lived within travel distance of the study centre. Of these women, we were unable to contact 132 (26.4%) and 50 refused to be screened. Of 318 patients screened, 66 (20.7%) were ineligible (disease n=10; medications n=25; pregnant or breastfeeding n=28; hysterectomy n=3) and 62 refused. Including those who refused to be screened, there was
a total of 112 refusals (n = 13 too ill; n=33 too busy; n=31 not interested; n=16 unable to schedule study visit; n=8 uncomfortable with study requirements (recall of AN history, weight measurement); n=11 unstated). This provided a sample of 190 AN cases (125 participants from TGH and 65 participants from Homewood Health Centre). (Figure 1).

Control group

The control group consisted of a cohort of 514 healthy, premenopausal, Caucasian women recruited from the community through advertisements in local newspapers and flyers, for previous studies of determinants of peak bone mass. Details of recruitment methods have been previously reported. Women were excluded if they had a history of an eating disorder. Other exclusion criteria were the same as those for the AN participants.

Written informed consent was obtained from all participants. The study was approved by the ethics committees of Women’s College Hospital, the University Health Network, Homewood Health Centre and the University of Toronto.

Study design

This was a cross-sectional study. During a single visit, all participants completed bone density and body composition assessment and questionnaires to obtain demographic information and data on OP risk factors. The AN participants were interviewed to obtain a detailed illness history. A subgroup of 225 women in the control group participated in a 2-year prospective study; their baseline data were used in the present study.
**BMD assessment**

Participants with AN had BMD measured at the lumbar spine (LS) (L1-L4), femoral neck (FN) and total body (TB) by dual energy X-ray absorptiometry (DXA) using a Lunar Prodigy scanner (GE Healthcare, Madison, WI). Controls had BMD measurements at the same skeletal sites by DXA using a Lunar DPX-L absorptiometer. A cross-calibration study confirmed that differences between the two machines did not exceed the tolerance level of 0.02 g/cm². The coefficients of variation (%), determined by test-retest positioning for both densitometers were 1.18% at LSP, 1.56% at FN and 0.72% at TB. BMD was reported as g/cm² and expressed as Z-score values (standard deviations above or below the mean for body weight, age, sex and race). Low BMD was defined *a priori* as a Z-score value ≤ -1.5 at one or more of the LSP, FN and/or TB.

**Anthropometric measurements**

At the time of the study visit, body height (cm) was measured with a stadiometer and weight (kg) was measured with a balance beam scale, to calculate BMI (kg/m²). Body fat percentage, fat mass (kg) and lean mass (kg) were measured by DXA.181

**Life History Calendar Interview**

In AN participants, a Life History Calendar (LHC)163,164 interview was conducted to obtain a detailed history of the course of AN and associated variables. The LHC interview uses a timeline-based semi-structured interview to aid in the recall of lifetime events. It was specifically designed to facilitate recall of variable life histories by incorporating the structure of autobiographical memory and encouraging the use of multiple retrieval pathways165 and has been reported to improve the accuracy of historical data compared to traditional
The interview collected information on hospital admissions, body weight (annual ranges, admission and discharge weights), purging behaviours, menstrual history (pre-menarcheal, regular vs irregular cycles vs amenorrheic), reproductive history (pregnant or breastfeeding), oral contraceptive use, smoking and alcohol consumption. The participants were asked to recall each of these variables in yearly increments from age 10 or, in the case of weight, the age at which they first reported having a clear recollection of, or began documenting, their body weight (usually 1-2 years prior to onset of AN). Recall was enhanced by establishing a timeline based on age, school years, admission history and personal landmark events and by cross-checking inter-related variables (eg. weight and menstrual history). All interviews were conducted by a single interviewer. From this interview, the following variables were determined: age at menarche (years), age at onset of AN (adolescent < 18 years of age vs adult), sub-type of AN (restrictive [R] versus binge-purge [BP]), duration of illness and amenorrhea (years), duration of recovery (years), age at onset of recovery (years) (recovery defined below), lowest BMI (kg/m²) since AN onset, duration of pregnancy and breastfeeding (months), duration of oral contraceptive use (years), and smoking (never and past/current; total lifetime number of cigarettes) and alcohol consumption (lifetime average drinks/week).

**Questionnaires**

All participants completed a standardized pre-tested questionnaire to determine calcium and Vitamin D supplementation, personal osteoporosis (OP) history (prior BMD assessments, treatment of OP) and fracture history as well as family history of OP and fractures. The participants’ fracture history was documented by site, age and mechanism by which it had occurred and then classified as low trauma, high trauma or stress fracture. A participant was
considered to have a family history of OP if any first-degree (parent, sibling) or second-degree (grandparent, aunt, uncle) relative had been diagnosed with OP or had sustained a fracture of the wrist, hip or spine after the age of 50. Counts of first- and second-degree relatives were summed to create a categorical variable (< 3, or 3 or more relatives). Because we included first- and second-degree relatives, almost 50% of the participants had at least 2 relatives with a history of OP or fracture, and therefore, having at least 3 relatives was used to distinguish those with a strong family history of OP. Physical activity in the AN participants was assessed by an interviewer-administered Minnesota Leisure Time Physical Activity Questionnaire modified to obtain both past year and lifetime exercise history. Physical activity was measured by the Baecke scale in the controls. Finally, an interviewer-administered food frequency questionnaire (FFQ) was completed to measure past-year daily dietary intake of calcium from both dairy and non-dairy calcium sources. Food models and standardized portion sizes were used to aid participant recall.

Thirty-six women from the AN cohort who were eligible for the study but refused to participate consented to a telephone interview to obtain information about their key demographic and illness characteristics and enable comparison to the 190 AN participants who completed the study.

**Definition of AN recovery**

A priori, in the absence of a universally accepted definition of AN recovery, participants were considered to be recovered if they achieved a BMI $\geq 18.5$ kg/m² and spontaneously resumed regular menstruation (> 8 cycles/year), each maintained for $\geq 12$ months. Participants on an OCP at the time of weight recovery (n=19) were considered to be menstrually recovered; a
sensitivity analysis was conducted by excluding these individuals from the analysis. The 12-month duration was chosen to ensure an adequate time period for measurable change in BMD to have occurred. A participant who had ever met the definition of recovery and then had a BMI < 18.5 or stopped menstruating for at least 12 months was considered to have experienced a relapse. Participants who were classified as ill at the time of the study visit included those who had been previously recovered and were currently relapsed.

**Statistical Analysis**

All analyses were performed using SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC). The level of significance was established at $P \leq 0.05$ (two-tailed). All variables were assessed for normality. Associations among key variables and comparisons of characteristics between recovered and ill sub-groups and between recovered participants and controls were done by using parametric and non-parametric tests, as appropriate: $t$ tests or Wilcoxon rank-sum tests for continuous variables and chi-square tests or Fisher’s exact tests for categorical variables. Correlations between continuous variables were calculated using Pearson’s or Spearman’s correlation coefficients as appropriate.

The associations between recovery status (recovered/ill), key illness characteristics identified in the literature, and the outcome, low BMD (Z-score $\leq -1.5$ at one or more skeletal sites), were determined by logistic regression. The odds of low BMD in the recovered participants were compared to the odds in the control group, also by logistic regression. Maximum likelihood method was used for parameter estimation. Likelihood-ratio tests for individual coefficients were used and profile likelihood confidence intervals (CI) were generated.\(^{18}(p^{26,32})\) The illness characteristics being investigated were: duration of illness (years),
severity of illness (lowest BMI kg/m² since onset of AN), subtype of AN (R vs BP) and age at onset of AN (adolescent vs adult onset). Duration of illness was calculated three ways: total duration including all relapses, duration of the longest illness phase, and duration of the most recent illness phase. Duration of the longest illness phase and duration of the most recent illness phase generated similar c-statistics and were higher than total duration of illness; therefore, we chose to use duration of the most recent illness episode. Each independent predictor was examined bivariately and then together in a multivariable model. Unadjusted and adjusted OR estimates, 95% CIs and p-values were reported. Cross-product interaction terms between each illness variable and AN recovery status were evaluated to determine whether the effect of these illness characteristics on BMD were different in recovered versus ill participants. Interaction effects were considered to be important if the interaction term was statistically significant at p≤0.05 or improved the model fit by > 5%. Potential confounding effects of factors identified in the literature were determined; none of OCP use > 1 year (no/yes), smoking status (current / non- or past), lifetime alcohol intake (average drinks/week), current calcium intake (mg/day), lifetime exercise (average hours/week), or, family history of OP (< 3 / ≥ 3 relatives) changed the parameter estimates of the independent predictors being investigated by > 10% and were excluded from the model on the basis of parsimony. Bisphosphonate use was also considered as a potential confounding variable. However, only 12 participants had ever used a bisphosphonate for ≥ 6 months (median duration of 12 months), none were taking this medication at the time of the study visit, and it was associated with low BMD (ie. confounding by indication); therefore, this variable was not included in the model. BMD Z-scores are already adjusted for weight and age and were, therefore, not considered. Finally, in the sub-group of
recovered AN participants, the association between age at onset of recovery and low BMD was examined.

To evaluate the relative contribution of weight recovery versus resumption of menses and BMD, we created a variable with 4 categories: weight recovered only / menstrual recovered only / both weight and menstrual recovered / ill. The odds of low BMD in each of the three recovered groups were compared to the ill group by logistic regression. Duration of recovery was compared across the 3 recovered groups by one-way ANOVA.

RESULTS

One hundred and ninety women completed the study. Table 1 summarizes the demographic, physical and illness characteristics of the total AN sample, the ill versus recovered sub-groups and the control group. At the time of the study visit, 77 participants (40.5%) met our definition of recovery. Of the 113 participants who were ill, n=25 (22.1%) had been previously recovered and were relapsed. Compared to those ill, recovered participants were slightly older, had higher BMIs and body fat as would be expected, and were more likely to have used an OCP. Recovered participants also had significantly shorter duration of illness than their currently ill counterparts (median: 2.0 vs 5.0 years, in recovered and ill participants, respectively). Compared to the recovered participants, the controls were slightly older (median age: 31.0 vs 28.0 years), heavier (median BMI: 23.3 vs 20.9 kg/m²) and leaner (median lean mass: 40.0 vs 37.1 kg).

Among the 36 women with AN who refused to participate but completed a telephone interview, a greater percentage were recovered (61.1%) and fewer were nulliparous (69.5%)
compared to the 190 AN participants who completed the study. There were no other significant differences in key demographic and illness characteristics between the non-participants and participants. (See Appendix B).

Compared to participants recruited from the TGH eating disorder program (n=125), those recruited from the Homewood program (n=65) had a higher mean lowest BMI since AN onset (14.3 ± 1.7 vs 12.7 ± 1.7 kg/m², \( P < 0.0001 \)). The percentage of recovered participants was similar between the two recruitment sites (43.1% and 39.2% for Homewood and TGH, respectively). Among those recovered, Homewood participants had a longer mean duration of recovery (5.9 ± 2.9 vs 4.7 ± 4.2, \( P = 0.02 \)).

Sixteen AN participants (8.4%) reported a history of a low trauma fracture; only one of these participants was in the recovered group and had fractured 3 years after AN recovery. Three participants had experienced a hip fracture, 6 sustained a wrist fracture (1 of these participants sustained both hip and wrist fractures), 6 sustained fractures of the ribs or thoracic vertebrae and 2 had calcaneal fractures. Low BMD was associated with a higher risk of fracture: 17.2% of AN participants with low BMD reported fractures versus 4.5% of those with normal BMD (\( \chi^2 = 7.66, \) DF = 1, \( P = 0.006 \)).

A. Bivariate results

Prevalence of low BMD in recovered versus ill participants and the healthy control group

BMD values are shown in Table 2. Low BMD (Z-score ≤ -1.5 at 1 or more skeletal sites) was observed in 11.7% (95% CI: 4.5, 18.9) of recovered participants compared to 43.4% (95% CI: 34.3, 52.5) of ill participants (27.3% of relapsed participants; 47.3% of ill patients who had never
recuperated) (Figure 2). The unadjusted odds ratio (OR) for low BMD in recovered versus ill participants was 0.17 (95% CI: 0.07, 0.36, \( P < 0.0001 \)). A sensitivity analysis excluding \( n=19 \) participants on OCP at the time of weight recovery yielded similar results (OR = 0.15, 95% CI: 0.05, 0.36, \( P < 0.0001 \)).

The prevalence of low BMD in the healthy control group was 6.8% (95% CI: 4.6, 9.0). The unadjusted OR for low BMD in recovered AN participants versus healthy controls was 1.81 (95% CI: 0.79, 3.78, \( P = 0.15 \)).

Associations between illness characteristics and low BMD (duration and severity of illness, subtype of AN, age at onset of AN, age at onset of recovery)

i) Duration of illness

A longer duration of illness (years) was positively associated with low BMD (unadjusted OR = 1.16 per year of illness, 95% CI: 1.08, 1.25, \( P < 0.0001 \)) and recovered AN participants had a significantly shorter duration of illness (Table 1). Therefore, the prevalence of low BMD in recovered and ill participants by duration of illness subgroups was examined (short duration: ill < 5 years vs long duration: ill \( \geq 5 \) years) (Table 3). Those with a short duration illness were more likely to be recovered than those with a long duration illness (OR = 4.24, 95% CI: 2.28, 8.14, \( P < 0.0001 \)). Among recovered participants, 8.8% (5/57) in the short duration group and 20% (4/20) in the long duration group had low BMD. Among ill participants, 35.6% (16/45) in the short duration group and 48.5% (33/68) in the long duration group had low BMD.
ii) Severity of illness

Severity of illness as measured by the lowest BMI since AN onset was not associated with low BMD (unadjusted OR = 1.09, 95% CI: 0.92, 1.29, \( P = 0.32 \)). However, greater illness severity was correlated with longer duration of illness (\( r = 0.34, P < 0.0001 \)) and with lower BMI at the study visit (\( r = 0.15, P = 0.04 \)). It was not associated with AN recovery status (\( P = 0.56 \)).

iii. Sub-type of AN

Subtype of AN (R vs BP) was not associated with low BMD (unadjusted OR = 1.13, 95% CI: 0.61, 2.10, \( P = 0.70 \)) or with AN recovery status (\( P = 0.53 \)). Participants with BP subtype were more likely to have experienced a relapse than participants with R subtype (35.3% vs 18.7%, \( P = 0.009 \)) and BP subtype was associated with a longer total duration of illness (4.7 y vs 3.6 y, \( P = 0.02 \)) but not with a longer duration of current illness episode (\( P = 0.21 \)). There was no difference in BMI between the two groups (\( P = 0.51 \)).

iv. Age at onset of AN

An adolescent onset of AN (before 18 years of age) versus adult onset was not associated with low BMD (unadjusted OR = 0.94, 95% CI: 0.51, 1.75, \( P = 0.85 \)) or with AN recovery status (\( P = 0.49 \)). We also examined the association between low BMD and age at onset categorized as pre/early pubertal onset (onset before menarche or within 2 years of menarche) versus late pubertal onset (after 2 years of menarche) and found no significant association (unadjusted OR = 1.02, 95% CI: 0.50, 2.0, \( P = 0.96 \)).
v. Age at onset of recovery

In the subgroup of 77 recovered participants, older age at onset of AN recovery was associated with a shorter duration of illness ($r = -0.20$, $P = 0.005$). Age at onset of AN recovery was not associated with low BMD either unadjusted (OR = 1.12, 95% CI: 0.97, 1.30, $P = 0.13$) or adjusted (OR = 1.09, 95% CI: 0.92, 1.28, $P = 0.30$) for duration of illness.

B. Multivariable logistic regression model

Table 4 shows the results of the multivariable logistic regression model. Controlling for all variables in the model, the odds ratio of low BMD in recovered versus ill participants was 0.25 (95% CI: 0.10, 0.55, $P = 0.0005$). Duration of illness was independently associated with low BMD (OR = 1.12, 95% CI: 1.03, 1.23, $P = 0.006$). No other illness characteristics were significant. There were no significant interactions between any illness characteristic variables and AN recovery status (data not shown).

C. Relative effects of weight recovery and menstrual recovery on low versus normal BMD

Eighteen participants were weight recovered only (had BMI ≥ 18.5 kg/m² for ≥ 1 year but were amenorrheic or had irregular cycles) while n=11 were menstrually recovered only (had regular cycles for ≥ 1 year but had not maintained BMI ≥ 18.5 kg/m² for ≥ 1 year) and n=77 were both weight and menstrually recovered. Participants who met none of these 3 definitions of recovery were categorized as ill (n=84). Those who were on an OCP and not weight recovered (i.e. had not spontaneously resumed menstruation) (n=14) were included in the ill group (Table 5). Compared to the ill group, the odds of low BMD in the weight recovered only group was 0.77 (95% CI: 0.26, 2.15, $P = 0.62$), in the menstrual recovered only group was 0.69 (95% CI: 0.17,
2.47, \( P = 0.58 \) and in the weight and menstrual recovered group was 0.17 (95% CI: 0.07, 0.35, \( P < 0.0001 \)).

Duration of weight recovery was associated with menstrual recovery status. Excluding the 19 participants who were using an OCP at the time of weight recovery, 60% of participants who were weight recovered for 1 year had resumed menses, 92.3% of those weight recovered for 2 years were menstrually recovered and 100% of those weight recovered \( \geq 3 \) years were menstrually recovered. Those in the weight only recovered group were recovered for a mean of 2.1 ± 1.5 years compared to 5.1 ± 3.8 years in the weight and menstrual recovered group (\( P = 0.007 \)). BMI was not significantly different between these 2 groups (\( P = 0.73 \)). Mean duration of recovery in the menstrual recovered only group was longer than both the weight only recovered (\( P = 0.006 \)) and weight and menstrual recovered groups (\( P = 0.05 \)). By definition, BMI was lower in the menstrual only recovered group compared to both the weight recovered groups. We compared the odds of low BMD in each of the weight only and menstrual only recovered groups versus the weight and menstrual recovered group and adjusted for duration of recovery to determine whether duration of recovery was mediating the differential effects on BMD across the groups. Duration of AN recovery had minimal effect on the OR estimate.

Compared to the weight and menstrual recovered group, the weight only recovered group had higher odds of low BMD both unadjusted (OR = 4.8, 95% CI: 1.5, 15.8, \( P = 0.009 \)) and adjusted (OR = 4.5, 95% CI 1.3, 15.5, \( P = 0.02 \)) for duration of recovery, and the menstrual only recovered group had higher odds of low BMD both unadjusted (OR = 4.3, 95% CI: 1.0, 17.5, \( P = 0.05 \)) and adjusted (OR = 4.6, 95% CI: 1.1, 19.4, \( P = 0.04 \)) for duration of recovery.
DISCUSSION

The purpose of the present study was to examine the prevalence of low BMD in adult women with a history of AN to determine the extent that low BMD persists in women recovered from AN and to elucidate the influence of illness characteristics and AN recovery criteria on BMD. We observed that the prevalence of low BMD in women who were both weight and menstrually recovered was not significantly different from their healthy age-matched peers but was significantly lower than in ill participants, suggesting that normalization of bone mass may occur with AN recovery. Our results also indicate that recovery of BMD may be negatively affected in those who experienced a long duration of illness (≥5 years) but that other illness characteristics do not appear to have a significant influence.

In our sample of 190 adult women who had been previously admitted for inpatient treatment of AN during a 12-year time period, those who, at the time of the study visit, were both weight and menstrually recovered for at least 1 year were 83% less likely to have low BMD compared to those who were ill; the prevalence of low BMD in these recovered participants, although slightly higher, was not statistically different from that in our control group. Moreover, the results of our analysis stratified by short versus long duration of illness showed that the majority of recovered participants were ill for <5 years and, in this group, the prevalence of low BMD in recovered AN participants was very similar to the control group (8.8% vs 6.8%). Among the 20 recovered participants who had been ill for ≥5 years, only 20% had low BMD compared to 48.5% with low BMD among participants ill for ≥5 years and not recovered. These data suggest that a considerable increase in BMD occurs with AN recovery even in those who had been chronically ill, but that a long duration of illness may have a slight
negative impact on bone mass in recovered patients. Indeed, duration of illness was an independent predictor of low BMD after controlling for recovery status.

Most prior studies have similarly demonstrated a negative association between either duration of illness or duration of amenorrhea and BMD in ill patients.\textsuperscript{1, 2, 38, 39, 41, 42, 75, 97} The effect of duration of illness in women who have recovered from AN had been less clear. Three studies did not observe a relationship between illness duration and bone mass in recovered participants,\textsuperscript{5, 46, 97} but small sample sizes may have precluded finding statistical significance. One prospective study reported that illness duration was negatively correlated with change in BMD at the FN but not at the LSP.\textsuperscript{8} In the present study, we did not find a significant interaction between recovery status and duration of illness indicating that the negative effect of illness duration on BMD was similar in recovered and ill patients. However, among the group of recovered participants with a long duration of illness, 2 of the 4 women with low BMD had been recovered for only 1 year and bone mass may continue to increase with a longer duration of recovery. Therefore, given the small subgroup of participants recovered after experiencing a long illness, it is not possible to conclusively determine the impact of chronic illness on BMD in recovered patients. We can conclude from our data that the majority of participants who recover from AN do so within 5 years of becoming ill, and among this group, the prevalence of low BMD is similar to their healthy, age-matched peers.

None of the other illness characteristics that we investigated (lowest BMI since AN onset, subtype of AN and age at onset of AN and at onset of recovery) were associated with low BMD. The results of most prior studies are consistent with our finding that severity of AN, as measured by lowest BMI since onset, is not a predictor of low BMD in either ill or recovered
patients. These studies measured severity by lowest ever BMI or weight (kg), percentage decrease in body weight or the degree of underweight (weight below BMI of 18). Three studies reported a correlation between lowest weight and BMD in ill patients but did not adjust for current weight or duration of illness, which may have influenced their results.

Only one prior study, to our knowledge, has reported that AN patients of the BP subtype were at an increased risk of low bone mass at the LSP compared to those of the R subtype. The authors noted, however, that those with BP subtype had a longer duration of amenorrhea and suggested that a lower estrogen exposure in this group may explain this result. Moreover, the analysis was conducted on a small subgroup of 15 patients. One other study reported that frequency of vomiting predicted spinal BMD, but it is unclear whether it was associated with higher or lower bone mass. Eight additional studies either did not detect a significant relationship between AN subtype BMD or found that the relationship was not significant after controlling for body weight. Taken together, AN subtype does not appear to be a key predictor of low bone mass and any observable effect of subtype of AN on BMD may be mediated by body weight and the duration of illness.

It has been postulated that adolescent onset of AN would result in a greater deficit in bone density than adult onset because of the interruption in rapid bone mineral accrual that occurs during growth. Yet, there is little evidence to date to support this hypothesis. Most studies have not demonstrated an association between age at onset and BMD and the findings of the present study, which included participants with a broad range in ages at onset (10 – 32 years), are consistent with these prior results. In two studies that found associations between age at onset and bone mass, one reported that women with age at onset
before 17 years had significantly lower cortical thickness at the radius as measured by 3D-pQCT but did not find an association between age at onset and BMD as measured by DXA, while the second study\textsuperscript{78} observed a negative association between age at onset and BMD at the LSP, which is inconsistent with the proposed rationale. The overall conclusion from these studies is that the age at which the disease presents itself does not appear to have a significant impact on the magnitude of bone deficits observed in this population. However, given the underlying hypothesis, it may be preferable to evaluate the effect of age at onset on bone mass in terms of its relation to onset of puberty, and this has rarely been addressed. Several studies\textsuperscript{39, 41, 126} compared bone density in patients with primary versus secondary amenorrhea and did not find any significant differences between the two groups, but they were limited by small numbers of patients in one or both groups. Similarly, in the present study, we had only 6 participants with primary amenorrhea. We combined these participants with those whose onset of AN was within 2 years of menarche but did not find that they were more likely to have low BMD than women with a late or post-pubertal onset. Future research, which specifically evaluates the effect of premenarcheal versus postmenarcheal onset of AN on bone loss and recovery, is needed to confirm these results.

The age at which recovery from AN occurs may also influence the ability of bone mass to regenerate. In their prospective study of 170 adolescent girls with AN, Castro et al\textsuperscript{45} observed annual gains in bone mass in those who recovered that was greater than the gains that have been documented in healthy adolescents. They inferred that there may be a ‘catch-up effect’ if recovery occurs in adolescence which may not be possible if recovery occurs at later age. Iketani et al\textsuperscript{189} also noted that in their sample of 17 females, adolescent patients had a greater increase in BMD at the LSP than adult patients over 0.3 – 3.3 years. This difference was not statistically
significant, possibly due to their small sample size. Given our sample of adult women, we could not compare adolescent versus adult onset of recovery. Nevertheless, we did not observe an association between age at recovery and low BMD and our main findings indicate that normalization of bone mass is possible in women who recover as adults.

In the absence of a universal definition of AN recovery, we defined recovery as being both weight restored and resuming regular menses. We examined the relative effects of weight restoration and resumption of menses on BMD to provide further clarity regarding this definition with respect to bone density. Our results indicate that being both weight and menstrually recovered is optimal for recovery of bone mass. Compared to ill participants, those who were weight restored but amenorrheic or oligomenorrheic were 23% less likely to have low BMD, those who had regular menses but were not weight restored were 31% less likely to have low BMD while women who were both weight restored and menstruating regularly were 83% less likely to have low BMD. This suggests that while recovery of body weight and resumption of menses may have independent effects on restoration of normal bone metabolism, both are essential for maximum regeneration of bone mass. This is consistent with the evidence regarding the underlying physiological mechanisms of OP in AN that both estrogen and nutritionally-regulated hormones such as insulin-like growth factor (IGF-1), leptin and cortisol are involved.87 Our results strengthen the observations of several recent studies which have documented a trend towards the additive effect of recovery of weight and menses on bone density. Miller et al135 followed 75 women with AN for 6-69 months and reported a differential effect of weight recovery versus menstrual recovery by skeletal site. They found that resumption of menstrual function predicted an increase in BMD at the LSP, independent of weight improvement, while weight improvement predicted an increase in BMD at the hip,
independent of menstrual function. They did not directly evaluate the effect on BMD of being both weight and menstrually recovered compared to being either one or the other. In a 1-year prospective study of 34 adolescent girls with AN, investigators found that girls with weight gain alone had a similar decrease in bone mineral content (BMC) at the LSP to girls who did not recover weight whereas girls with weight gain and menses recovery showed stabilization of bone parameters at this site. At the TB, weight gain alone was associated with an increase in BMC that was intermediate between those who did not recover weight and those who recovered weight and resumed menstruation. In their cross-sectional study, Audi et al. found that women who were weight recovered and had regular menses for at least 3 months had higher BMD than women who had achieved weight recovery only, although the difference was not statistically significant. Their hormonal data provide some rationale for the individual effects of weight and menstrual recovery on bone density. They found that IGF-1 levels were below normal limits in ill patients but were within normal ranges in patients who were weight recovered only. Serum estradiol levels, while higher in the weight only recovered group than in the ill patients, were within normal ranges only in the group that was both weight restored and had resumed normal menstrual function. Finally, in 28 adult women with AN undergoing nutritional rehabilitation over a 2-month time period, Domínguez et al. observed similar increases in BMD in those who were weight restored and resumed menstruation compared to those weight restored and amenorrheic. However, they reported that osteocalcin concentrations, a bone formation marker, increased with weight gain while elevated N-telopeptide (NTX) concentrations, a bone resorption marker, decreased only with resumption of menses. They proposed that recovery of bone metabolism is biphasic involving a primary nutritional mechanism that stimulates bone formation and a hormonal mechanism that
decreases bone resorption and postulated that over a longer period of follow-up larger increases in BMD would be observed in the weight and menstrual recovered group compared to the weight recovered only group. Although there is certainly further research needed to elucidate the physiological mechanisms of bone loss and regeneration associated with AN, the results of the present study and that of prior work strongly suggest that the definition of AN in future investigations regarding AN and bone mass should be one that includes both weight recovery and resumption of menses.

Finally, we observed that low BMD was associated with self-reported low trauma fractures. The association between BMD and fracture risk has not been established in young women, but our data imply that low BMD is indeed a risk factor for fracture in women with a history of AN.

The strengths of the present study include its large sample size and broad distribution of responses on all key variables thus enabling the assessment of the effect of these variables on BMD as well as providing a good representation of different groups within AN. However, there are several limitations. First, we only measured BMD at a single time point. Without baseline and follow-up BMD measurements, we can only speculate on the trajectory of changes in bone mass over time and on the effect of baseline BMD on the “follow-up” measurements. Second, AN illness history was obtained by retrospective recall. We sought to improve recall through the use of the LHC interview technique which has been found to enhance accuracy of historical data. Moreover, the accuracy of weight recall has been demonstrated in healthy women even up to a 30-year recall, and would be expected to be at least as accurate in women with AN who are preoccupied with weight. Although recall of menstrual history has not been shown to
be as reliable as weight recall, to periods of amenorrhea and resumption of menses are linked to weight and AN relapse and recovery, therefore women with AN may be expected to have a heightened recall of these events. Using the LHC we were also able to cross-check menstrual history with weight history to clarify inconsistent responses.

The recruitment of AN participants from two eating disorder programs provided a sample with a broad range of illness characteristics which enhances the generalizability of our results. However, the overall participation rate was 48%, which raises concern about a possible selection bias. Nonetheless, while the 36 non-participants who consented to a telephone interview were more likely to be recovered than the participants, there were no other discernable differences in demographic or illness characteristics that would affect the observed relationships between AN recovery and BMD.

In summary, our findings suggest that significant regeneration of BMD occurs in adult women with AN who are both weight and menstrually recovered. If recovered after being ill for less than five years, which represents the majority of recovered AN patients, they will be no more likely to have low BMD than healthy women who have never suffered from this disease. AN patients who recover after a long duration of illness may be at a slightly higher risk of having low BMD but further research which targets women with a chronic disease history is needed to clarify this. These results indicate that the best management of bone health in women with AN is nutritional rehabilitation with weight gain to the threshold of resumption of menses. Long-term management of bone health in the majority of recovered AN patients, particularly those with a short illness duration, may not be necessary. Rather, osteoporosis prevention efforts should be focused on chronically ill AN patients who not only are more likely to have
substantial deficits in BMD and consequently may have a greater risk of fracture, but are also less likely to recover from the illness.
**TABLE 1.** Demographic and illness characteristics of Anorexia Nervosa (AN) participants (ill versus recovered) and demographic characteristics of control group. Numbers are mean (median) (minimum-maximum values), or n (%).

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>WHOLE AN SAMPLE</th>
<th>ILL</th>
<th>RECOVERED1</th>
<th>CONTROL GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=190)</td>
<td>(n=113)</td>
<td>(n=77)</td>
<td>(n=514)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>27.2 (25.5) (17-40)</td>
<td>26.4 (24.0) (17-40)</td>
<td>28.3 (28.0) (18-40)</td>
<td>31.2 (31.0) (20-40)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>185 (97.4%)</td>
<td>109 (96.5%)</td>
<td>76 (98.7%)</td>
<td>514 (100%)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (2.6%)</td>
<td>4 (3.5%)</td>
<td>1 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school incomplete</td>
<td>12 (6.3%)</td>
<td>8 (7.1%)</td>
<td>4 (5.2%)</td>
<td>3 (0.58%)</td>
</tr>
<tr>
<td>High school diploma</td>
<td>63 (33.2%)</td>
<td>44 (38.9%)</td>
<td>19 (24.7%)</td>
<td>85 (16.5%)</td>
</tr>
<tr>
<td>Post-secondary degree</td>
<td>115 (60.5%)</td>
<td>61 (54%)</td>
<td>54 (70.1%)</td>
<td>426 (82.9%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>153 (80.5%)</td>
<td>100 (88.5%)</td>
<td>53 (68.8%)</td>
<td>310 (60.3%)</td>
</tr>
<tr>
<td>Married / common-law</td>
<td>33 (17.4%)</td>
<td>12 (6.3%)</td>
<td>21 (27.3%)</td>
<td>184 (35.8%)</td>
</tr>
<tr>
<td>Divorced / separated</td>
<td>4 (2.1%)</td>
<td>1 (0.9%)</td>
<td>3 (3.9%)</td>
<td>20 (3.9%)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>167 (87.9%)</td>
<td>103 (91.2%)</td>
<td>64 (83.1%)</td>
<td>414 (80.5%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.4 (19.3) (11-35.5)</td>
<td>17.9 (17.7) (11.1-30.5)</td>
<td>21.6 (20.9) (18.5-35.5)</td>
<td>24.3 (23.3) (16.2-43.7)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.1 (164.0) (145-181)</td>
<td>164.2 (164.0) (145-177)</td>
<td>163.8 (164.5) (148-181)</td>
<td>164.3 (164.0) (145-187)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>26.2 (27.3) (4.3-49.3)</td>
<td>22.2 (22.0) (4.3-48.2)</td>
<td>32.1 (31.7) (13.8-49.3)</td>
<td>33.7 (33.0) (10.1-57.4)</td>
</tr>
<tr>
<td>Lean tissue mass (kg)</td>
<td>36.0 (35.8) (24.9-55.4)</td>
<td>35.3 (35.1) (25.7-49.3)</td>
<td>37.1 (37.1) (24.9-55.4)</td>
<td>40.3 (40.0) (29.4-56.7)</td>
</tr>
<tr>
<td>Age at menarche (y)</td>
<td>12.9 (13.0) (9-17)</td>
<td>13.2 (13.0) (10-17)</td>
<td>12.6 (13.0) (9-16)</td>
<td>12.7 (13.0) (9-17)</td>
</tr>
<tr>
<td>Age at onset of AN (y)</td>
<td>18.2 (17.0) (10-32)</td>
<td>18.0 (17.0) (12-32)</td>
<td>18.5 (18.0) (10-31)</td>
<td>-</td>
</tr>
<tr>
<td>Before age 18</td>
<td>97 (51.0%)</td>
<td>60 (53.1%)</td>
<td>37 (48.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Type of amenorrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>6 (3.1%)</td>
<td>6 (7.8%)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Secondary</td>
<td>170 (89.5%)</td>
<td>102 (90.3%)</td>
<td>68 (88.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Never amenorrheic¹</td>
<td>14 (7.4%)</td>
<td>5 (4.4%)</td>
<td>9 (11.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Sub-type of AN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricting</td>
<td>91 (47.9%)</td>
<td>52 (46.0%)</td>
<td>39 (50.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Purging</td>
<td>99 (52.1%)</td>
<td>61 (54.0%)</td>
<td>38 (49.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Total duration of illness¹ (y)</td>
<td>6.2 (5.0) (0.5-25)</td>
<td>7.7 (7.0) (2-25)</td>
<td>4.0 (3.0) (0.5-15)</td>
<td>-</td>
</tr>
<tr>
<td>CHARACTERISTICS</td>
<td>WHOLE AN SAMPLE (n=190)</td>
<td>ILL (n=113) (59.5%)</td>
<td>RECOVERED^1 (n=77) (40.5%)</td>
<td>CONTROL GROUP (n=514)</td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>-------------------------</td>
<td>---------------------</td>
<td>-----------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Duration of most recent illness phase^1 (y)</td>
<td>5.2 (4.0) (0.5-25)</td>
<td>6.6 (5.0) (1-25)</td>
<td>3.0 (2.0) (0.5-13)^2</td>
<td>-</td>
</tr>
<tr>
<td>Lowest BMI since AN onset</td>
<td>13.2 (13.3) (7.2 -18)</td>
<td>13.1 (13.0) (7.2-18)</td>
<td>13.4 (13.6) (7.8-18)</td>
<td>-</td>
</tr>
<tr>
<td>Ever relapsed^1</td>
<td>44 (23.1%)</td>
<td>32 (28.3%)</td>
<td>20 (26%)</td>
<td>-</td>
</tr>
<tr>
<td>Duration of recovery (y)</td>
<td>N/A</td>
<td>N/A</td>
<td>5.1 (4.5) (1-26)</td>
<td>-</td>
</tr>
<tr>
<td>Age at recovery (y)</td>
<td>N/A</td>
<td>N/A</td>
<td>23 (22) (10-34)</td>
<td>-</td>
</tr>
<tr>
<td>Past year exercise (h/wk)</td>
<td>7.2 (4.7) (0-46.4)</td>
<td>8.2 (5.6) (0-46.4)</td>
<td>5.8 (3.8) (0-38.0)</td>
<td>-^4</td>
</tr>
<tr>
<td>Smoker – current</td>
<td>54 (28.4%)</td>
<td>35 (31.0%)</td>
<td>19 (24.7%)</td>
<td>51 (9.9%)^3</td>
</tr>
<tr>
<td>– past</td>
<td>19 (10%)</td>
<td>9 (8.0%)</td>
<td>10 (13.0%)</td>
<td>64 (12.5%)</td>
</tr>
<tr>
<td>Ever consumed alcohol</td>
<td>116 (61.1%)</td>
<td>65 (57.2%)</td>
<td>51 (66.2%)</td>
<td>436 (84.8%)^4</td>
</tr>
<tr>
<td>Lifetime average dr/wk</td>
<td>10.6 (5.5) (1-76)</td>
<td>12.7 (7.0) (1-76)</td>
<td>7.9 (5.0) (1-48.2)</td>
<td>3.1 (2.1) (0.1-17.2)^4</td>
</tr>
<tr>
<td>Calcium intake (mg/d)</td>
<td>1069 (880) (0-5461)</td>
<td>1031.1 (893.6) (0-4776)</td>
<td>1125 (858.3) (42-5461)</td>
<td>890.9 (834.4) (74-2911)</td>
</tr>
<tr>
<td>OCP use (ever used ≥ 1 y)</td>
<td>105 (55.3%)</td>
<td>53 (46.9%)</td>
<td>52 (67.5%)^2</td>
<td>354 (68.9%)</td>
</tr>
<tr>
<td>Duration of use (y)</td>
<td>5.7 (4.5) (1-21)</td>
<td>5.0 (4.0) (1-12)</td>
<td>6.3 (5.0) (1-21)</td>
<td>6.4 (6.0) (1-20)</td>
</tr>
<tr>
<td>Sustained fragility fracture</td>
<td>16 (8.4%)</td>
<td>15 (13.3%)</td>
<td>1 (1.3%)^2</td>
<td>49 (9.5%)^3</td>
</tr>
<tr>
<td>Had prior BMD test(s)</td>
<td>124 (65.3%)</td>
<td>82 (72.6%)</td>
<td>41 (53.2%)^2</td>
<td>0</td>
</tr>
<tr>
<td>Family history of osteoporosis (≥ 3 relatives)</td>
<td>18 (9.5%)</td>
<td>12 (10.6%)</td>
<td>6 (7.8%)</td>
<td>29 (5.6%)</td>
</tr>
</tbody>
</table>

^1 Definitions:

Recovered: participants who were both weight recovered (BMI ≥ 18.5) and resumed regular menstruation, each maintained for ≥ 1 year
Never amenorrheic: on oral contraceptives from onset of AN (n=12); never amenorrheic (n=2)
Total duration of illness: the total number of years ill including time periods between recovery phases (ie. relapses)
Duration of most recent illness phase: If recovered – duration of time since initial onset of illness or from last relapse until start of current recovery. If ill – duration of time of current illness episode, from initial onset of illness, or from start of most recent relapse if previously recovered
Relapse rate: of 102 ever recovered (77 currently recovered + 25 previously recovered and currently relapsed), n=44 experienced a relapse = 43.2% relapse rate

^2 Recovered AN participants significantly different from ill AN participants, at P ≤ 0.05
^3 Control group significantly different from recovered AN participants, all P <0.0001
^4 Control group: hours/week of exercise not documented; n (%) currently consuming alcohol and average drinks/week of current alcohol intake (lifetime alcohol intake not documented)
TABLE 2. Bone mineral density (BMD) values for Anorexia Nervosa (AN) participants and control group.
Numbers are mean (median)(minimum-maximum values), or n (%).

<table>
<thead>
<tr>
<th>BMD</th>
<th>WHOLE AN SAMPLE (n=190)</th>
<th>ILL (n=113)</th>
<th>RECOVERED(^1) (n=77)</th>
<th>CONTROL GROUP (n=514)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BMD at 1 or more sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ -1.5(^2)</td>
<td>58 (30.5%)</td>
<td>49 (43.4%)</td>
<td>9 (11.7%)</td>
<td>35 (6.8%)</td>
</tr>
<tr>
<td>≤ -2.0</td>
<td>22 (11.6%)</td>
<td>18 (15.9%)</td>
<td>4 (5.2%)</td>
<td>10 (2.0%)</td>
</tr>
<tr>
<td>≤ -2.5</td>
<td>12 (6.3%)</td>
<td>11 (9.7%)</td>
<td>1 (1.3%)</td>
<td>5 (1.0%)</td>
</tr>
<tr>
<td>Spine (L1-L4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g/cm(^2)</td>
<td>1.072 (1.074)</td>
<td>1.011 (0.999)</td>
<td>1.161 (1.159)</td>
<td>1.216 (1.215)</td>
</tr>
<tr>
<td>Z-score</td>
<td>-0.51 (-0.70)</td>
<td>-0.90 (-1.00)</td>
<td>0.07 (0.00)</td>
<td>0.13 (0.08)</td>
</tr>
<tr>
<td>≤ -1.5</td>
<td>43 (22.6%)</td>
<td>38 (33.6%)</td>
<td>5 (6.5%)</td>
<td>32 (6.2%)</td>
</tr>
<tr>
<td>≤ -2.0</td>
<td>18 (9.5%)</td>
<td>15 (13.3%)</td>
<td>3 (3.9%)</td>
<td>8 (1.6%)</td>
</tr>
<tr>
<td>≤ -2.5</td>
<td>10 (5.3%)</td>
<td>9 (8.0%)</td>
<td>1 (1.3%)</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g/cm(^2)</td>
<td>0.934 (0.918)</td>
<td>0.900 (0.895)</td>
<td>0.983 (0.958)</td>
<td>1.021 (1.010)</td>
</tr>
<tr>
<td>Z-score</td>
<td>-0.13 (-0.20)</td>
<td>-0.34 (-0.40)</td>
<td>0.17 (0.00)</td>
<td>0.35 (0.26)</td>
</tr>
<tr>
<td>≤ -1.5</td>
<td>25 (13.2%)</td>
<td>21 (18.6%)</td>
<td>4 (5.2%)</td>
<td>8 (1.6%)</td>
</tr>
<tr>
<td>≤ -2.0</td>
<td>10 (5.3%)</td>
<td>9 (8.0%)</td>
<td>1 (1.3%)</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>≤ -2.5</td>
<td>5 (2.6%)</td>
<td>5 (4.4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total body</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g/cm(^2)</td>
<td>1.092 (1.092)</td>
<td>1.065 (1.065)</td>
<td>1.133 (1.133)</td>
<td>1.183 (1.180)</td>
</tr>
<tr>
<td>Z-score</td>
<td>0.11 (0.10)</td>
<td>-0.08 (-0.10)</td>
<td>0.38 (0.30)</td>
<td>0.71 (0.72)</td>
</tr>
<tr>
<td>≤ -1.5</td>
<td>13 (6.8%)</td>
<td>11 (9.7%)</td>
<td>2 (2.6%)</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>≤ -2.0</td>
<td>8 (4.2%)</td>
<td>8 (7.1%)</td>
<td>0</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>≤ -2.5</td>
<td>4 (2.1%)</td>
<td>4 (3.5%)</td>
<td>0</td>
<td>3 (0.6%)</td>
</tr>
</tbody>
</table>

\(^1\)Definition: Recovered – BMI ≥ 18.5 kg/m\(^2\) and resumed regular menstruation, each for ≥ 1 year
\(^2\)Number of participants with low BMD at each cut-off includes those in the lower cut-off(s)
TABLE 3. Prevalence of low bone mineral density in recovered and ill Anorexia Nervosa participants, stratified by short versus long duration of illness. Numbers are n (%) and 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th></th>
<th>CONTROLS (n=514)</th>
<th>RECOVERED&lt;sup&gt;1&lt;/sup&gt; (n=77)</th>
<th>ILL (n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ill &lt; 5 years</td>
<td>Ill ≥ 5 years</td>
<td>Ill &lt; 5 years</td>
</tr>
<tr>
<td></td>
<td>(n=57)</td>
<td>(n=20)</td>
<td>(n=45)</td>
</tr>
<tr>
<td>35 (6.8%)</td>
<td>5 (8.8%)</td>
<td>4 (20%)</td>
<td>16 (35.6%)</td>
</tr>
<tr>
<td>(95% CI: 4.6, 9.0)</td>
<td>(95% CI: 1.4, 16.1)</td>
<td>(95% CI: 2.5, 37.5)</td>
<td>(95% CI: 21.6, 49.6)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Definition: Recovered – BMI ≥ 18.5 kg/m² and resumed regular menstruation, each for ≥ 1 year
TABLE 4. Evaluation of Anorexia Nervosa (AN) recovery status and illness characteristics as independent predictors of low bone mineral density (BMD) (Z-score ≤ -1.5 at lumbar spine, femoral neck and/or total body) by multivariable logistic regression\(^1\) in 190 AN participants.

<table>
<thead>
<tr>
<th>Dependent variable: low BMD</th>
<th>Unadjusted odds ratio (95% confidence interval)</th>
<th>P-value</th>
<th>Adjusted odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AN recovered (yes vs no)</td>
<td>0.17 (0.07, 0.36)</td>
<td>&lt;0.0001</td>
<td>0.25 (0.10, 0.55)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>1.16 (1.08, 1.25)</td>
<td>&lt;0.0001</td>
<td>1.12 (1.03, 1.23)</td>
<td>0.006</td>
</tr>
<tr>
<td>Lowest BMI since AN onset</td>
<td>1.09 (0.92, 1.29)</td>
<td>0.32</td>
<td>0.98 (0.81, 1.19)</td>
<td>0.85</td>
</tr>
<tr>
<td>Age at AN onset (adolescent vs adult onset)(^2)</td>
<td>0.94 (0.51, 1.75)</td>
<td>0.85</td>
<td>0.71 (0.35, 1.44)</td>
<td>0.34</td>
</tr>
<tr>
<td>Subtype of AN (restrictive vs binge-purge)</td>
<td>1.13 (0.61, 2.10)</td>
<td>0.70</td>
<td>1.37 (0.68, 2.77)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Adjusted (multivariable) model: Hosmer and Lemeshow goodness-of-fit test: chi square 6.2, \(P = 0.63\)

\(^{1}\)Notes: i) unadjusted odds ratio estimates – not adjusted for other illness variables; adjusted odds ratio estimates – adjusted for all other illness variables

\(^{2}\)Adolescent vs adult onset: younger than 18 years of age vs 18 years of age or older

Abbreviations: BMI = body mass index (kg/m\(^2\))
**TABLE 5.** Comparison of body mass index (BMI) at time of the study visit, duration of recovery and prevalence of low bone mineral density (BMD) in participants categorized by three recovery criteria for Anorexia Nervosa.1

Numbers are mean ± standard deviation, or n (%).

<table>
<thead>
<tr>
<th></th>
<th>Weight only recovered (n=18)</th>
<th>Menstrual only recovered (n=11)</th>
<th>Both weight and menstrual recovered (n=77)</th>
<th>III (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI kg/m²</td>
<td>21.8 ± 3.8</td>
<td>16.9 ± 1.3²</td>
<td>21.7 ± 2.8</td>
<td>17.2 ± 2.2</td>
</tr>
<tr>
<td>Duration of recovery (y)</td>
<td>2.1 ± 1.5</td>
<td>7.8 ± 8.8²</td>
<td>5.1 ± 3.8²</td>
<td>N/A</td>
</tr>
<tr>
<td>Low BMD</td>
<td>7 (38.9%)</td>
<td>4 (36.4%)</td>
<td>9 (11.7%)³</td>
<td>38 (45.2%)</td>
</tr>
</tbody>
</table>

1 Definitions:

- **Low BMD:** Z-score ≤ -1.5 at lumbar spine, femoral neck and/or total body
- **Weight only recovered:** maintained BMI ≥ 18.5 kg/m² for at least one year but not menstruating regularly for at least one year
- **Menstrual only recovered:** resumed spontaneous regular menses for at least one year but did not maintain BMI ≥ 18.5 kg/m² for at least one year
- **Both weight and menstrually recovered:** BMI ≥ 18.5 kg/m² and regular menses, both maintained for at least one year
- **III:** does not meet any of the three recovery definitions

² Significantly different from weight only recovered group, by ANOVA, at \( P \leq 0.05 \)

³ Significantly different from the other three groups, by logistic regression analysis, at \( P \leq 0.05 \)
FIGURE 1. Recruitment flow-chart

Toronto General Hospital

New admissions (Apr 15/93-May 21/06)  
\( n = 427 \)

- Excluded:  \( n = 143 \)
  - > 40 yoa: 99
  - male: 6
  - not AN: 8
  - deceased: 17
  - out of province/country: 13

- Total cohort targeted for recruitment:  \( n = 284 \)

- Not screened:  \( n = 83 \)
  - unable to locate/contact: 52
  - refused: 31
  - too ill: 2
  - busy/uninterested: 21
  - uncomfortable with study: 2
  - other: 6

- Total screened for eligibility:  \( n = 201 \)

- Ineligible:  \( n = 40 \)
  - disease: 8
  - medications: 17
  - pregnant: 14
  - hysterectomy: 1

- Refused:  \( n = 36 \)
  - too ill: 5
  - busy/uninterested: 16
  - uncomfortable with study: 5
  - unable to schedule: 10

- Completed study:  \( n = 125 \)

Homewood Health Centre

New admissions (Jan 1/95-May 31/06)  
\( n = 380 \)

- Excluded:  \( n = 164 \)
  - > 40 yoa: 77
  - male: 12
  - not AN: 1
  - deceased: 1
  - out of province/country: 37
  - duplicate with TGH: 36

- Total cohort targeted for recruitment:  \( n = 216 \)

- Not screened:  \( n = 99 \)
  - unable to locate/contact: 80
  - refused: 19
  - too ill: 2
  - busy/uninterested: 13
  - other: 4

- Total screened for eligibility:  \( n = 117 \)

- Ineligible:  \( n = 26 \)
  - disease: 2
  - medications: 8
  - pregnant: 14
  - hysterectomy: 2

- Refused:  \( n = 26 \)
  - too ill: 4
  - busy/uninterested: 14
  - uncomfortable with study: 1
  - unable to schedule: 1
  - other: 1

- Completed study:  \( n = 65 \)

TOTAL ANOREXIA NERVOSA PARTICIPANTS: 190

\(^1\) Participation rate: 190 / ([284 + 216 total cohort] – 20.75% ineligibility rate) = 48.0%
FIGURE 2. Percentage of Anorexia Nervosa participants with low bone mineral density (BMD) (Z-score ≤ -1.5 at one or more skeletal sites) by illness status (ill, relapsed, recovered)\textsuperscript{1} compared to the control group.

\begin{itemize}
\item ILL (never recovered) (n=88)
\item ILL (relapsed) (n=25)
\item Recovered (n=77)
\item Controls (n=514)
\end{itemize}

\textsuperscript{1} Recovered: BMI \geq 18.5 kg/m\textsuperscript{2} and resumed regular menstruation, each for \geq 1 year
Relapsed: previously met definition of recovery; at time of study visit, did not meet 1 or both recovery criteria
Chapter 3: PAPER 2

Title: Characterization of changes in bone mineral density associated with illness and recovery in young women with a history of anorexia nervosa

INTRODUCTION

Decreased bone mineral density (BMD) is a well-established consequence of anorexia nervosa (AN).\(^1,2,41,97\) Less well-substantiated is the extent to which deficits in BMD can be reversed with recovery from AN. Prior studies investigating the relationship between BMD and recovery from AN have reported inconsistent results, from complete reversal of AN-induced deficits in BMD\(^9,125,127\) to partial or no reversal.\(^4,8,44,85,97,129,130,134\) Still others have reported differential results by skeletal site.\(^6,45,46,82,128\) These conflicting findings may be a consequence of small sample sizes precluding adequate power to detect differences in BMD and to control for heterogeneity in illness characteristics, short durations of recovery that may have been insufficient to allow for normalization of BMD, as well as variability in the criteria used to define AN recovery.

Many important questions, therefore, remain regarding the effect of recovery from AN on bone mass. Paper 1 compared the prevalence of low BMD in recovered participants to ill participants and to a control group to examine the extent of reversal of skeletal deficits associated with AN recovery and evaluated the effect of additional key illness characteristics on BMD. The duration of recovery required for maximal regeneration of bone mass, however, is uncertain. As well, trabecular and cortical bone may have a differential capacity to regenerate following AN recovery and this requires further investigation. Finally, further evaluation of the effects of illness characteristics on BMD in recovered participants is needed to determine
whether potential effects differ across skeletal sites and whether these effects are moderated in those recovered for a long period of time.

The purpose of the present study was to address these outstanding issues and extend current knowledge regarding the impact of AN recovery on BMD. Specifically, our objectives were to: 1) examine the associations between BMD and duration of AN illness and duration of recovery; 2) determine whether these associations differed by skeletal site; and, 3) evaluate the effect of illness characteristics (duration and severity of illness, age at onset of AN, age at onset of recovery) on BMD at each of the three skeletal sites in women who have recovered from AN for a short versus longer time period.

METHODS

Participants

The AN cohort consisted of female patients admitted between April 14, 1993 and May 31, 2006 to the University Health Network (Toronto General Hospital [TGH]) or between January 1, 1995 and May 31, 2006 to the Homewood Health Centre, Guelph, Ontario for inpatient treatment of AN (defined by DSM-III-R or IV criteria). TGH is a large, urban tertiary health care centre and Homewood Health Centre is a specialized health centre providing mental health and addiction treatment. Exclusion criteria included a primary diagnosis of bulimia nervosa, age greater than 40 years at the time of the study visit, a history of disease or use of medications known to affect bone metabolism, hysterectomy or bilateral oophorectomy, and, pregnancy or active breastfeeding at the time of the study or within the prior 12 months.
Participants who had used oral contraceptives (OCP), who had undergone prior BMD assessment(s), or who had received bisphosphonates were not excluded.

Five hundred and fifty age-eligible women were admitted for treatment of AN during the defined time period. Of these women, we were unable to contact 132 (26.4%), 50 lived out of province/country and 50 refused to be screened. Of 318 patients screened, 66 (20.7%) were ineligible (disease n=10; medications n=25; pregnant or breastfeeding n=28; hysterectomy n=3), 9 were too ill due to AN to participate and 53 subsequently refused to participate (n=24 too busy; n=16 unable to schedule study visit; n=6 not interested; n=6 uncomfortable with study requirements; n=1 other), providing a sample of 190 women (n=125 from TGH; n=65 from Homewood Health Centre). (Figure 1).

Written informed consent was obtained from all participants. The study was approved by the ethics committees of Women’s College Hospital, the University Health Network, Homewood Health Centre and the University of Toronto.

Study design

This was a cross-sectional study. During a single visit, AN participants completed an interview and questionnaires to obtain illness history and key correlates of BMD and underwent bone density and body composition assessment.

BMD assessment

BMD was measured at the lumbar spine (LSP) (L1-L4), femoral neck (FN) and total body (TB) by dual energy X-ray absorptiometry (DXA) using a Lunar Prodigy scanner (GE Healthcare, Madison, WI). The CV’s, determined by test-retest positioning, were 1.18% at LSP,
1.56% at FN and 0.72% at TB. BMD was reported as g/cm² and expressed as Z-score values (standard deviations above or below the mean for body weight, age, sex and ethnicity). Low BMD was defined \( a \ priori \) as a Z-score value \( \leq -1.5 \).

**Anthropometric measurements**

At the study visit, body height (cm) was measured with a stadiometer and weight (kg) was measured with a balance beam scale to calculate body mass index (BMI) (kg/m²). Body fat percentage, fat mass (kg) and lean mass (kg) were measured by DXA.\(^{181}\)

**Questionnaires**

Participants completed a standardized pre-tested questionnaire to gather demographic information and determine calcium and Vitamin D supplementation, personal osteoporosis (OP) history (prior BMD assessments, treatment of OP) and fracture history, as well as family history of OP and fractures. An interviewer-administered Minnesota Leisure Time Physical Activity Questionnaire was modified to collect past year and lifetime exercise history.\(^{182-184}\) Finally, a food frequency questionnaire (FFQ) was completed to measure past-year daily dietary intake of calcium. Food models and standardized portion sizes were used to aid participant recall.

**Life History Calendar Interview**

A Life History Calendar (LHC)\(^{163,164}\) interview was conducted to obtain a detailed history of the course of AN and associated variables. A single interviewer conducted all interviews. The LHC interview uses a timeline-based semi-structured interview to aid in the recall of lifetime events. It was specifically designed to facilitate recall of variable life histories.
by incorporating the structure of autobiographical memory and encouraging the use of multiple retrieval pathways\textsuperscript{165} and has been reported to improve the accuracy of historical data compared to traditional questionnaires.\textsuperscript{169, 170} The interview was used to collect data on 8 variables including body weight (annual ranges, admission and discharge weights), purging behaviours, menstrual history (age at menarche, regular, irregular, or absent cycles), reproductive history (pregnant or breastfeeding), oral contraceptive use, smoking and alcohol consumption. Participants were asked to recall each of these variables in yearly increments from age 10. To enhance recall, a timeline was established at the start of the interview based on age, school years, admission history and personal landmark events. Before the completion of the interview inter-related variables (eg. weight and menstrual history) were cross-referenced to identify inconsistent responses. From this interview, the following variables were determined: age at menarche (years), age at onset of AN (before age 18 versus 18 or older), sub-type of AN (restrictive versus binge-purge), duration of illness (years), duration of AN recovery (years), age at onset of recovery (years), illness severity (lowest BMI [kg/m\textsuperscript{2}] since onset of AN), duration of pregnancy and breastfeeding (months), duration of oral contraceptive use (years) and smoking (never/past/current) and alcohol consumption (lifetime average drinks per week).

**Non-participants**

Thirty-six women who were eligible for the study but refused to participate, consented to a telephone interview to obtain their key demographic and illness characteristics and enable comparison to the 190 AN participants who completed the study.
**Definition of AN recovery**

For the purposes of this analysis, and in the absence of a universally accepted definition of AN recovery, participants were considered to be recovered at the time of the study visit if they had both a BMI $\geq 18.5$ kg/m$^2$ and had spontaneously resumed menstruation. (Note in Paper 1, participants were considered recovered if they had sustained recovery for $\geq 1$ year. In this paper, in order to more precisely estimate the effect of duration of recovery on BMD, participants recovered < 1 year were included in the recovered group). All other participants were categorized as being ill at the time of the study visit, including those who had a history of being previously recovered and were currently relapsed and those who were ill and had never recovered. Participants on an OCP at the time of weight recovery ($n=20$) were considered to be menstrually recovered; a sensitivity analysis was conducted by excluding these individuals from the analysis.

**Statistical analysis**

All analyses were performed using SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC). The level of significance was established at $P \leq 0.05$ (two-tailed). All variables were assessed for normality. Comparisons of characteristics between ill and recovered subgroups were done by using $t$ tests or Wilcoxon rank-sum tests for continuous variables and chi-square or Fisher’s exact tests for categorical variables. All analysis were stratified by ill versus recovered groups. In the ill group, duration of illness (years) was determined based on the duration of the current illness episode (i.e. if never recovered, from the initial onset of the illness; if previously recovered, then from the onset of the most recent relapse). In the recovered group, duration of illness was determined based on their most recent illness episode (i.e. if
never previously recovered, from the initial onset of illness until current recovery; if previously
recovered, then from onset of last relapse until current recovery). Duration of recovery (years)
was determined based on the onset of the current recovery period. One outlier in the ill group
was removed from the analysis. This participant had been ill for 25 years and had abnormally
high BMD values possibly due to high dosage estrogen therapy for 3 years.

Scatterplots were created to visually examine the pattern of the relationships between
BMD Z-scores at each skeletal site and each of duration of illness and duration of recovery.
Average trend lines were overlayed on each scatterplot; a smooth line was fitted to the data
using a spline routine with a smoothing parameter of 70.254. Estimates of the association
between BMD Z-scores and duration of illness and recovery were determined by linear
regression analysis. In the ill group, a simple model with duration of illness as the independent
variable and BMD Z-scores as the dependent variable was generated. As well, the ill group was
stratified according to their duration of illness into two groups, short versus long duration of
illness (< 5 versus ≥ 5 years ill), and Z-score values and the prevalence of low BMD (Z-score ≤ -
1.5) were compared between the two illness duration groups by Wilcoxon rank sum tests and
Fisher’s exact tests, respectively.

In the recovered group, based on visual examination of the scatterplots depicting the
relationship between duration of AN recovery and BMD, a binary variable was created
identifying those recovered for a short versus long time period, using ≤ 3 versus > 3 years as the
cut-point. Participants recovered for > 3 years may have less bone mass to regenerate and,
therefore, in this group duration of recovery might be expected to have a different association
with BMD than in those recovered ≤ 3 years. To determine whether the association between
duration of recovery and BMD is significantly different in those recovered ≤ 3 years compared to those recovered > 3 years, an interaction term between the duration of recovery variable and short versus long recovered binary variable was included in the regression model.

Since our data suggested that the association between duration of recovery and BMD may be different in those recovered for a short (<3 years) versus long (>3 years) time period, we subsequently conducted a stratified analysis to examine whether the effects of illness characteristics on BMD were also different in those recovered for a short versus long time period. The illness characteristics investigated were: duration of illness (years), illness severity (lowest BMI kg/m² since AN onset), age at onset of AN (before age 18 vs 18 years or older) and age at onset of recovery from AN (years). The association between the illness characteristics and BMD Z-scores at each skeletal site was evaluated by linear regression analysis. Each variable was assessed one at a time and then all variables were considered simultaneously in a multivariable model. Unadjusted and adjusted beta estimates, 95% CI and p-values were reported.

RESULTS

One hundred and ninety women completed the study. Table 1 summarizes the demographic, physical and illness characteristics of the total sample and of the ill versus recovered patient groups. At the time of the study visit, 83 (43.7%) participants met our definition of recovery. Of the 107 participants who were ill, n=25 (23.4%) had been previously recovered and were relapsed at the time of the study visit. Compared to ill participants, recovered participants, as expected, were heavier and had a higher body fat percentage and were more likely to have used an oral contraceptive. Recovered participants also had
experienced a significantly shorter duration of illness compared to participants who were currently ill (median: 3.0 versus 5.8 years, for recovered and ill participants, respectively).

Among the 36 women with AN who refused to participate but completed a telephone interview, a greater percentage were recovered (61.1%) and fewer were nulliparous (69.5%) compared to the 190 AN participants who completed the study. There were no other significant differences in key demographic and illness characteristics between the non-participants and participants. (See Appendix B).

Participants recruited from the Homewood program (n=65) had a higher mean lowest BMI since AN onset compared to TGH participants (n=125) (14.3 ± 1.7 vs 12.7 ± 1.7 kg/m², \( P < 0.0001 \)). The percentage of recovered participants was similar between the two recruitment sites (46.2% vs 42.4% for Homewood and TGH, respectively). Among those recovered, Homewood participants had a longer mean duration of recovery (5.6 ± 3.2 vs 4.4 ± 4.2 y, \( P = 0.04 \)).

**Association between duration of illness and BMD**

*Figure 2* depicts the relationship between the duration of current illness episode and BMD Z-scores at each skeletal site in 106 participants who were ill at the time of the study visit (one outlier removed from analysis). None of these participants had been ill for < 1 year (median duration: 5.3, range 1-20 years). Each year of illness was associated with lower BMD Z-scores at the LSP (beta: -0.04; 95% CI: -0.10, 0.003, \( P = 0.06 \)), the FN (beta: -0.10; 95% CI: -0.15, -0.05, \( P < 0.0001 \)) and the TB (beta: -0.09; 95% CI: -0.13, -0.04, \( P = 0.0001 \)). *Table 2* summarizes the Z-score values at each skeletal site stratified by short versus long duration of illness (< 5 versus ≥ 5 years ill). Among participants ill for < 5 years, 26.8% had low BMD (Z-score ≤ -1.5) at the LSP.
compared to 2.4% and 0% at the FN and TB, respectively. Among participants who were ill ≥ 5 years, low BMD was observed in 35.4% at the LSP, 30.8% at the FN and 16.9% at the TB. The percentage of participants with low BMD was significantly different between the two illness duration groups at the FN and TB but not at the LSP.

**Association between duration of recovery from AN and BMD**

**Figure 3** illustrates the relationship between duration of AN recovery and BMD Z-scores at each skeletal site in 83 participants who were both weight restored (BMI ≥ 18.5 kg/m²) and had resumed menstruation. The graphs depict a rapid increase in BMD at each skeletal site during the first 3-4 years of AN recovery followed by stabilization of BMD. **Table 3** summarizes the association between duration of recovery and BMD Z-scores obtained by linear regression analysis. This model includes an interaction term to determine whether the association between duration of recovery and BMD is different in those recovered ≤ 3 years compared to those recovered > 3 years. The interaction term was significant at the LSP but not at the FN or TB; however, parameter estimates in all three models indicate the same pattern of a greater increase in Z-scores per year of recovery for the first 3 years versus > 3 years of AN recovery. Based on this model, among women recovered ≤ 3 years, each year of recovery was associated with a higher mean Z-score of 0.57 (95% CI: 0.07, 1.08) at the LSP, 0.28 (95% CI: -0.25, 0.82) at the FN and 0.25 (95% CI: -0.20, 0.70) at the TB. In women recovered > 3 years, each year of recovery was associated with a minimal increase in Z-scores of 0.02 (95% CI: -0.06, 0.11) at the LSP, 0.02 (95% CI: -0.07, 0.12) at the FN and 0.01 (95% CI: -0.07, 0.09) at the TB. A sensitivity analysis excluding the 20 participants using an OCP at the time of weight recovery yielded a slightly greater predicted increase in Z-scores at each skeletal site associated with each year of recovery in those
recovered ≤ 3 years, but similar parameter estimates for those recovered > 3 years (data not shown). The mean Z-scores in those recovered ≤ 3 years were -0.27 ± 1.06 at the LSP, -0.13 ± 1.18 at the FN and 0.01 ± 0.85 at the TB and in those recovered > 3 years were 0.15 ± 1.17 at the LSP, 0.33 ± 1.11 at the FN and 0.60 ± 1.01 at the TB.

Effect of illness characteristics (duration and severity of illness, age at onset of illness and age at recovery) on BMD in recovered participants

To determine whether the associations between illness characteristics and BMD were different in participants recovered ≤ 3 years versus those recovered > 3 years, we conducted a stratified analysis of these two groups (Table 4). Among those recovered for ≤ 3 years (n=36), a longer duration of illness was bivariately associated with lower BMD at the LSP ($P = 0.02$), and TB ($P = 0.04$) but not at the FN. Greater illness severity (lowest BMI since AN onset) was associated with lower BMD at the LSP ($P = 0.02$); the association was borderline significant at the FN and TB ($P = 0.06$, both sites). Neither age at onset of AN nor age at recovery were significantly associated with BMD at any skeletal site. In the multivariable model, no illness characteristics were significantly associated with BMD at any skeletal site. In those recovered > 3 years (n=47), illness characteristics were not associated with BMD at any skeletal site either in bivariate or multivariable analysis.

DISCUSSION

In this large cohort of young women who had received inpatient treatment for AN, we found that the association between duration of illness and BMD differed by skeletal site while the association between duration of AN recovery and BMD was similar across sites.
Furthermore, we observed that among women recovered < 3 years, each year of recovery was associated with substantially greater increases in BMD than in women recovered for 3 or more years. Women recovered for at least 3 years were found to have normal mean BMD values regardless of prior illness history. Taken together, these cross-sectional data suggest that while there may be differential patterns of trabecular and cortical bone loss due to AN, normalization of bone mass appears to occur at each skeletal site within 3-4 years of sustained weight and menstrual recovery.

The observed relationship between BMD Z-scores at the different skeletal sites and duration of AN suggests that rapid loss of bone mass (or decrease in bone accrual) occurs at the LSP initially, within the first year of illness, followed by a decline in the rate of bone loss. We did not have any participants ill < 1 year to enable us to describe the pattern of bone loss during the first year of illness. However, our data imply that BMD at the LSP was reduced early in the course of AN; among participants ill for 1 year the median BMD Z-score at the LSP was already approaching -1.0 (ie. below normal for age) and ¼ of participants ill < 5 years were classified as having low BMD (Z-score ≤ -1.5). In contrast, BMD at the FN and TB appears to decline more gradually. Only one participant who had been ill for < 5 years had low BMD at these sites. Our results are supported by prior studies of AN patients which have reported lower BMD at the LSP than at the FN or TB. These findings are consistent with current knowledge about the differential effects of hormonal alterations, particularly estrogen deficiency, on trabecular versus cortical bone. The composition of bone at the LSP is approximately 80% trabecular while the total adult skeleton is composed of approximately 80% cortical bone, and the FN specifically, of 65% cortical bone; consequently, the LSP is particularly susceptible to the multiple endocrine disturbances that occur with AN. It has also been speculated that BMD loss
at the FN observed in perimenopausal women may be partly due to loss of muscle mass, rather than purely a function of estrogen deficiency.\textsuperscript{35} Lean mass has been found to be positively associated with BMD at the FN and TB but not at the LSP in healthy premenopausal women.\textsuperscript{161, 198} Therefore, we would also speculate that the loss of muscle mass that accompanies severe weight loss in AN patients may contribute to lower BMD at the FN and TB in this patient group. Not only, then, do these skeletal sites respond more slowly to hormonal alterations due to their greater composition of cortical bone, but any negative impact on BMD due to the diminished mechanical stimulus from deteriorating muscle mass might also be expected to be a gradual rather than a rapid process.

Another potential explanation for the observed differences across skeletal sites that must be considered is that it may be a spurious finding due to BMD measurement error. Measurement of BMD at the FN is less precise than at the LSP due to positioning requirements as well as the greater impact of the soft tissue/bone interface on BMD estimates at this site. Decreased soft tissue (both muscle and fat mass), as in women with AN, will affect the precision of FN BMD estimates, thus decreasing the power to detect significant changes in BMD associated with duration of the illness.

In contrast to the differential pattern of BMD loss associated with duration of illness that was observed at the three skeletal sites, our data suggest that the pattern of increase in BMD associated with recovery from AN is similar across sites. Furthermore, our findings indicate that regeneration of bone mass occurs over the first 3-4 years of sustained weight and menstrual recovery such that normal values of BMD for age are attained at each site. Among women recovered > 3 years, none of age at onset of AN, the age at which recovery occurred, or the
duration or severity of the illness, appeared to negatively impact the ability of bone to recover. Only in women recovered ≤ 3 years were illness characteristics related to BMD. This implies that there may be a ‘catch-up effect’, such that the lower the BMD, perhaps due to a longer illness duration, the greater the improvement in bone mass that occurs with recovery from AN. Although duration of illness was not associated with lower BMD among participants recovered > 3 years, few individuals who had achieved recovery had been ill > 5 years. Therefore, the potential impact of chronic illness on restoration of BMD cannot be conclusively determined, particularly at the FN and TB, where significantly decreased values were associated with longer disease durations.

Previous studies have inferred a greater capacity for reversibility of decreased BMD in trabecular bone than in cortical bone.6, 45, 89, 199 This was not borne out by our data; on average, BMD at all skeletal sites was normal in women who had experienced sustained recovery. However, as noted above, the majority of recovered women in our study were ill for a short duration and therefore may not have suffered as great a loss of bone at the FN and TB as compared to the LSP. Consequently, there may not have been as much bone mass to recover at these two sites. A limitation of our cross-sectional study design is that ‘baseline’ BMD values (i.e. at onset of recovery) are unknown and we can only hypothesize that this may be the case. Based on our study, it would seem that the likelihood of recovery from AN decreases with increasing duration of the illness. Research is needed to confirm this finding and specifically evaluate recovery of cortical bone in women who recover after a prolonged illness.

The strengths of our study include the large sample size with a broad representation across the spectrum of key illness characteristics including wide ranges in both durations of
illness and of recovery. However, there are some limitations. First, we made an assumption from our cross-sectional data that BMD had been affected by the time elapsed since the onset of AN and by the onset of recovery from AN. While we would contend that this is a reasonable assumption, because BMD was measured at a single time point, this allows only speculation about the longitudinal progression and exact timing of bone loss and gain over the course of AN illness. Second, the illness history was obtained by self-reported recall. Good to moderate recall of weight has been reported in healthy women\textsuperscript{190, 191, 193, 194} and would be expected to be at least as accurate in AN patients due to their weight preoccupation. It has also been demonstrated that, while recall of age at menarche is reliable, recall of cycle length and occurrence of irregularity may be less reliable.\textsuperscript{195, 196} In this study, we did not require participants to recall minor disruptions such as variations in cycle length, but rather, periods of menstrual cessation and resumption. Research on memory formation indicates that recall ability is directly related to the salience of the event for the respondent. As periods of amenorrhea and resumption of menses are linked to weight and AN onset and recovery, AN participants may have a heightened recall of these events. As well, we sought to improve recall through the use of the LHC interview technique which enables cross-checking of weight and menstrual history to identify inconsistent responses. The LHC has been found to enhance the accuracy of historical data.\textsuperscript{169} Nevertheless, given these limitations, prospective studies of adequate duration are needed to confirm our findings.

In summary, our cross-sectional study suggests that, in adult women with a history of AN, sustained recovery of weight and menses for 3-4 years is associated with normal BMD values at all skeletal sites. Lower bone mass at the LSP, as a consequence of AN, appears to occur in patients who have been ill for even a very short period of time, while reduced BMD at
the FN and TB is associated with longer disease durations. These findings emphasize the importance of early intervention in the form of nutritional rehabilitation and appropriate support to ensure sustained AN recovery for optimal management of bone health in this clinical population.
TABLE 1.  Key demographic and illness characteristics of 190 Anorexia Nervosa (AN) participants.

Numbers are mean (median) (minimum-maximum), or n (%).

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>WHOLE SAMPLE (n=190)</th>
<th>ILL (n=107)</th>
<th>RECOVERED(^1) (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>27.2 (25.5) (17-40)</td>
<td>26.7 (25.0) (17-40)</td>
<td>27.7 (28.0) (18-40)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>185 (97.4%)</td>
<td>103 (96.3%)</td>
<td>82 (98.8%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.4 (19.3) (11.1-35.5)</td>
<td>17.8 (17.7) (11.1-30.5)</td>
<td>21.5 (20.7) (18.5-35.5)(^2)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>26.2 (27.3) (4.3-49.3)</td>
<td>21.8 (21.8) (4.3-48.2)</td>
<td>31.9 (31.3) (13.8-49.3)(^2)</td>
</tr>
<tr>
<td>Age at menarche (y)</td>
<td>12.9 (13.0) (9-17)</td>
<td>13.2 (13.0) (10-17)</td>
<td>12.6 (13.0) (9-16)(^2)</td>
</tr>
<tr>
<td>Age at onset of AN (y)</td>
<td>18.2 (17.0) (10-32)</td>
<td>18.0 (17.0) (12-32)</td>
<td>18.4 (18.0) (10-31)</td>
</tr>
<tr>
<td>Before age 18</td>
<td>97 (51.0%)</td>
<td>58 (54.2%)</td>
<td>39 (47.0%)</td>
</tr>
<tr>
<td>Sub-type of AN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>restricting</td>
<td>91 (47.9%)</td>
<td>48 (44.9%)</td>
<td>43 (51.8%)</td>
</tr>
<tr>
<td>purging</td>
<td>99 (52.1%)</td>
<td>59 (55.1%)</td>
<td>40 (48.2%)</td>
</tr>
<tr>
<td>Lowest BMI since AN onset</td>
<td>13.2 (13.3) (7.2-18.0)</td>
<td>13.1 (13.0) (7.2-18.0)</td>
<td>13.4 (13.6) (7.8-18.0)</td>
</tr>
<tr>
<td>Total duration of illness(^1) (y)</td>
<td>6.2 (5.0) (0.5-25)</td>
<td>8.0 (7.0) (2-25)</td>
<td>3.9 (3.0) (0.5-15)(^2)</td>
</tr>
<tr>
<td>Duration of current or most recent illness episode(^1) (y)</td>
<td>5.2 (4.0) (0.5-25)</td>
<td>6.8 (5.8) (1-25)</td>
<td>3.0 (2.0) (0.5-13)(^2)</td>
</tr>
<tr>
<td>Duration of recovery (y)</td>
<td></td>
<td></td>
<td>4.8 (4.0) (0.5-26)</td>
</tr>
<tr>
<td>Age at recovery (y)</td>
<td></td>
<td></td>
<td>22.9 (21.5) (10-34)</td>
</tr>
<tr>
<td>Past year exercise (hr/wk)</td>
<td>7.2 (4.7) (0-46.4)</td>
<td>8.3 (5.7) (0-46.4)</td>
<td>5.3 (3.6) (0-29.5)</td>
</tr>
<tr>
<td>Daily calcium intake (mg)</td>
<td>1069 (880) (0-5461)</td>
<td>1026 (896) (0-4776)</td>
<td>1125 (858) (0-5461)</td>
</tr>
<tr>
<td>Alcohol (drinks/week)</td>
<td>6.5 (2.0) (0-76)</td>
<td>7.4 (1.5) (0-76)</td>
<td>5.2 (2.9) (0-48.2)</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>current</td>
<td>54 (28.4%)</td>
<td>33 (30.8%)</td>
<td>21 (25.3%)</td>
</tr>
<tr>
<td>past</td>
<td>19 (10%)</td>
<td>9 (8.4%)</td>
<td>10 (12.0%)</td>
</tr>
<tr>
<td>OCP use (ever used ≥ 1 y)</td>
<td>105 (55.3%)</td>
<td>51 (47.7%)</td>
<td>54 (65.1%)(^2)</td>
</tr>
</tbody>
</table>

\(^1\)Definitions:

- **Recovered**: participants who were both at a BMI ≥ 18.5 kg/m² and had spontaneously resumed menstruation at the time of the study visit
- **Duration of illness**: total duration of illness refers to total duration of illness including time periods in between recovery periods (ie. relapses); duration of current illness episode refers to the duration of time ill since onset of last relapse or since onset of the illness if never previously recovered or duration of most recent illness episode, if currently recovered

\(^2\)Recovered participants significantly different from ill participants, \(P \leq 0.05\)
Table 2. Bone mineral density (BMD) Z-score values and percentage of Anorexia Nervosa participants with low BMD\(^1\) at the lumbar spine (LSP), femoral neck (FN) and total body (TB) in those ill at the time of the study visit, for a short duration (< 5 years) versus a long duration (≥ 5 years).

<table>
<thead>
<tr>
<th>BMD Z-score</th>
<th>ILL &lt; 5 years (n=41)</th>
<th>ILL ≥ 5 years (n=65)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z-score, mean (median) (min-max)</td>
<td></td>
</tr>
<tr>
<td>LSP Z-score, ≤ -1.5, n (%)</td>
<td>-0.63 (-0.80) (-2.4 to 3.3)</td>
<td>-1.04 (-1.20) (-4.7 to 1.9)</td>
</tr>
<tr>
<td>FN Z-score, ≤ -1.5, n (%)</td>
<td>0.18 (0.0) (-1.8 to 3.5)</td>
<td>-0.68 (-0.60) (-3.1 to 2.8)(^3)</td>
</tr>
<tr>
<td>TB Z-score, ≤ -1.5, n (%)</td>
<td>0.39 (0.20) (-1.1 to 3.7)</td>
<td>-0.40 (-0.30) (-3.0 to 2.1)(^3)</td>
</tr>
</tbody>
</table>

1 Low BMD defined as a Z-score ≤ -1.5
2 One outlier in ill group removed from analysis (ill for 25 years with normal BMD)
3 Participants ill ≥ 5 years significantly different from participants ill < 5 years, \(P \leq 0.05\), by Wilcoxon rank sum tests and \(^4\)Fisher’s exact tests
**TABLE 3.** Linear regression model\(^1\) estimating the association between duration of recovery from Anorexia Nervosa (AN) and bone mineral density (BMD) Z-scores at the lumbar spine (LSP), femoral neck (FN) and total body (TB) in 83 recovered participants. The interaction term is included to evaluate whether the association between duration of AN recovery and BMD Z-scores is different in those recovered for ≤ 3 years (short recovery) versus > 3 years (long recovery).

<table>
<thead>
<tr>
<th></th>
<th>Parameter estimate (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LSP BMD Z-scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.03 (-0.74, 0.71)</td>
<td>0.94</td>
</tr>
<tr>
<td>Short (≤ 3 y) vs long (&gt; 3 y) recovery</td>
<td>-1.20 (-2.26, -0.15)</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of recovery (y)</td>
<td>0.02 (-0.06, 0.11)</td>
<td>0.58</td>
</tr>
<tr>
<td>Short vs long recovery x Duration of recovery (y)</td>
<td>0.55 (0.13, 0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>FN BMD Z-scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.17 (-0.58, 0.92)</td>
<td>0.64</td>
</tr>
<tr>
<td>Short (≤ 3 y) vs long (&gt; 3 y) recovery</td>
<td>-0.78 (-1.90, 0.34)</td>
<td>0.16</td>
</tr>
<tr>
<td>Duration of recovery (y)</td>
<td>0.02 (-0.07, 0.12)</td>
<td>0.64</td>
</tr>
<tr>
<td>Short vs long recovery x Duration of recovery (y)</td>
<td>0.26 (-0.18, 0.70)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>TB BMD Z-scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.52 (-0.10, 1.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>Short (≤ 3 y) vs long (&gt; 3 y) recovery</td>
<td>-0.93 (-1.85, -0.01)</td>
<td>0.05</td>
</tr>
<tr>
<td>Duration of recovery (y)</td>
<td>0.01 (-0.07, 0.09)</td>
<td>0.79</td>
</tr>
<tr>
<td>Short vs long recovery x Duration of recovery (y)</td>
<td>0.24 (-0.13, 0.61)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

\(^1\)The model is:  
\[ Z\text{-score} = \text{intercept} + \beta_1 \times \text{short vs long recovery binary variable} + \beta_2 \times \text{duration of recovery} + \beta_3 \times \text{duration of recovery} \times \text{short vs long recovery binary variable} \]

where: \(\beta_1\) is the estimate of the mean difference in BMD Z-scores in those recovered ≤ 3 y versus > 3 y  
\(\beta_2\) is the estimate of the change in Z-scores associated with each year of recovery  
\(\beta_3\) is the estimate of the additional change in Z-scores associated with each year of recovery in those recovered ≤ 3 y (the p-value indicates whether the slope quantifying the change in Z-score per year of recovery is significantly different for those recovered ≤ 3 y versus > 3 y  

Definition: AN recovery = BMI ≥ 18.5 kg/m\(^2\) and menstruating at the time of the study visit
TABLE 4. Association between illness characteristics and bone mineral density (BMD) Z-scores at the lumbar spine (LSP), femoral neck (FN) and total body (TB), stratified by short (≤ 3 years) versus long (> 3 years) Anorexia Nervosa (AN) recovery duration groups, in 83 participants recovered from AN. Estimates determined by linear regression analysis.

<table>
<thead>
<tr>
<th></th>
<th>Recovered ≤ 3 years (n=36)</th>
<th>Recovered &gt; 3 years (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted parameter estimate¹ (95% confidence interval)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>LSP Z-scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>-0.18 (-0.33, -0.03)</td>
<td>0.02</td>
</tr>
<tr>
<td>Illness severity³</td>
<td>-0.21 (-0.38, 0.03)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age at AN onset³</td>
<td>0.16 (-0.58, 0.89)</td>
<td>0.68</td>
</tr>
<tr>
<td>Age at recovery (y)</td>
<td>0.03 (-0.07, 0.13)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>FN Z-scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>-0.15 (-0.32, 0.03)</td>
<td>0.10</td>
</tr>
<tr>
<td>Illness severity³</td>
<td>-0.19 (-0.39, 0.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Age at AN onset³</td>
<td>0.00 (-0.82, 0.82)</td>
<td>0.99</td>
</tr>
<tr>
<td>Age at recovery (y)</td>
<td>-0.07 (-0.17, 0.04)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>TB Z-scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>-0.13 (-0.25, -0.01)</td>
<td>0.04</td>
</tr>
<tr>
<td>Illness severity³</td>
<td>-0.14 (-0.28, 0.004)</td>
<td>0.06</td>
</tr>
<tr>
<td>Age at AN onset³</td>
<td>0.42 (-0.16, 0.99)</td>
<td>0.16</td>
</tr>
<tr>
<td>Age at recovery (y)</td>
<td>-0.02 (-0.10, 0.06)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

¹ Unadjusted estimate: not adjusted for other illness variables (bivariate analysis)
² Adjusted estimate: adjusted for all other illness variables (multivariable analysis)
³ Definitions: i) Recovered: BMI ≥ 18.5 kg/m² and menstruating at the time of the study visit ii) Illness severity: lowest BMI (kg/m²) since onset of AN; iii) Age at AN onset: before age 18 vs 18 years or older
FIGURE 1. Recruitment flow-chart

TOTAL COHORT\(^1\): n=550

Not screened: n=232
- out of province: 50
- unable to locate: 132
- immediate refusal: 50

Screened: n=318

Ineligible: n=66
- disease: 10
- medications: 25
- hysterectomy: 3
- pregnant / breastfeeding: 28

 Eligible for study: n=252

Completed study: n=190
- TGH: n=125
- HHC: n=65

Did not complete study: n=62
- too ill: n=9
- subsequent refusal: n=53
  - too busy (school/work): 40
  - not interested: 6
  - not comfortable with study requirements: 6
  - trying to conceive: 1

\(^1\)Total cohort: number of women < 41 years of age admitted to either Toronto General Hospital (TGH) or Homewood Health Centre (HHC) for treatment of anorexia nervosa between April 15, 1993 and May 31, 2006
FIGURE 2. Scatterplots\(^1\) of the relationship between duration of illness of Anorexia Nervosa and bone mineral density Z-scores at the lumbar spine, femoral neck and total body in 106 ill participants.

\(^1\) A smoothed trend line was fitted to the data using a spline routine and smoothing parameter of 70. (SAS Course Notes 2005. *Longitudinal Data Analysis*, Cary, NC, SAS Institute. Pg 1-32).
FIGURE 3. Scatterplots\(^1\) of the relationship between duration of recovery from AN and BMD Z-scores at lumbar spine, femoral neck and total body in 82 recovered participants.\(^2\)

\(^{1}\) A smoothed trend line was fitted to the data using a spline routine and smoothing parameter of 70. (SAS Course Notes 2005. *Longitudinal Data Analysis*, Cary, NC, SAS Institute. Pg 1-32).

\(^{2}\) 1 participant recovered for 26 years was excluded from the scatterplots to improve visual clarity.
INTRODUCTION

Physical activity imparts mechanical loads on bone, initiating an adaptive structural response which involves increases in bone mass and changes in geometry that may ultimately enhance bone strength. Results from observational studies of athletes have demonstrated that high-impact and odd-impact weight-bearing sports such as gymnastics, dance, volleyball, tennis and soccer have the most substantial effect on bone mass while low- or non-impact activities such as walking, swimming or cycling have no effect. These studies, as well as findings from animal studies, indicate that activities which provoke the greatest osteogenic stimulus have both a high strain rate (rapid deformation of bone in response to load) resulting from dynamic and atypical movement directions, and a high force magnitude. The optimal amount of physical activity to improve bone strength and to maintain this improvement is unclear.

The response of bone to physical activity in women with anorexia nervosa has not been established; specifically, it is uncertain whether the beneficial effect of physical activity on bone mass observed in healthy women is also manifested in this clinical group. States of severe nutritional deficiency and consequent disturbances of the endocrine environment may alter the anabolic effect of mechanical loading on the skeleton such that a greater load may be required to trigger an adaptive response. Alternatively, excessive exercise, a common behaviour among women with this illness, may be detrimental to bone by contributing to further weight...
loss and amenorrhea. It is also unknown whether exercise during recovery from AN promotes bone accrual. In contrast to periods of malnutrition, during recovery an adaptive response may be stimulated by lower mechanical loads due to the increases in estrogen and IGF-1 and the regeneration of bone mass that occurs during recovery from AN, rendering the skeleton particularly sensitive to mechanical loading such as has been demonstrated in adolescents during a period of rapid skeletal growth. Prior studies of BMD and physical activity in women with AN have demonstrated marked inconsistency of results, from a positive effect of physical activity on BMD at all skeletal sites measured or at weightbearing sites only, to no significant effect. Most of these studies had limited exercise data and evaluated only the effect of recent activity on bone density. The type of exercise may be more relevant than the amount of exercise, but many of these studies were conducted before current knowledge of optimal osteogenic activities. Furthermore, rather than considering only recent exercise, it may be important to determine the impact of exercise history throughout life, especially activity during adolescence, which may confer a lifetime protective effect.

Because very little is known or understood about the effect of exercise on bone in women with AN, the purpose of this paper was to describe habitual lifetime exercise in a cohort of young women with a history of AN recruited to investigate recovery of BMD and key correlates of BMD, and to investigate whether any associations exist between BMD and exercise performed while ill and while recovered, after controlling for the effect of exercise performed prior to illness.
METHODS

Participants

Participants selected for this study were female patients admitted to the University Health Network (Toronto General Hospital [TGH]) and/or Homewood Health Centre, Guelph, Ontario for inpatient treatment of AN (defined by DSM-III-R or IV criteria) between April 15, 1993 and May 31, 2006. TGH is a large, urban tertiary health care centre and Homewood Health Centre is a specialized health centre providing mental health and addiction treatment. Exclusion criteria included a primary diagnosis of bulimia nervosa, age greater than 40 years at the time of the study, history of disease or use of medications known to affect bone metabolism, hysterectomy or bilateral oophorectomy, and, pregnancy or active breastfeeding at the time of the study or within the prior 12 months. Participants who had used oral contraceptives (OCP), who had undergone prior BMD assessment(s), or who had received bisphosphonates were not excluded.

Five hundred and fifty age-eligible women were admitted for treatment of AN in the defined time period, of whom 500 lived within travel distance of the study centre. Of these women, 132 (26.4%) could not be contacted and 50 refused to be screened. Of 318 patients screened, 66 (20.7%) were ineligible (disease n=10; medications n=25; pregnant or breastfeeding n=28; hysterectomy n=3), 9 were too ill due to AN to participate and 53 subsequently refused or were unable to participate, providing a sample of 190 women. (Figure 1).
Written informed consent was obtained from all participants. The study was approved by the ethics committees of Women’s College Hospital, the University Health Network, Homewood Health Centre and the University of Toronto.

Study design

This was a cross-sectional study. During a single visit, participants underwent bone density and body composition testing and completed an interview and questionnaires to obtain illness and exercise histories.

BMD assessment

BMD was measured at the lumbar spine (LS) (L1-L4), femoral neck (FN) and total body (TB) by dual energy X-ray absorptiometry (DXA) using a Lunar Prodigy scanner (GE Healthcare, Madison, WI). Test-retest CV’s were 1.18% at LSP, 1.56% at FN and 0.72% at TB. BMD was reported as g/cm² and expressed as Z-score values (standard deviations above or below the mean for body weight, age, sex and race, based on Prodigy reference database).

Anthropometric measurements

At the time of the study visit, body height (cm) was measured with a stadiometer and weight (kg) was measured with a balance beam scale, to calculate body mass index (BMI) (kg/m²). Body fat percentage, fat mass (kg) and lean mass (kg) were measured by DXA.181

Life History Calendar Interview

A Life History Calendar (LHC)163,164 interview was conducted to obtain a detailed history of the course of AN. All interviews were done by one interviewer. The LHC interview
uses a timeline-based semi-structured interview to assist in the recall of lifetime events. It was
developed to facilitate recall of variable life histories by incorporating the structure of
autobiographical memory and promoting the use of multiple retrieval pathways\textsuperscript{165} and has been
reported to improve the accuracy of historical data compared to traditional questionnaires.\textsuperscript{169, 170}
Participants were asked to recall in yearly increments from the age of 10 their body weight,
menstrual history, purging behaviours, reproductive history, oral contraceptive use, and
smoking and alcohol consumption. Recall was enhanced by establishing a timeline based on
age, school years, treatment admission history and personal landmark events and by cross-
checking inter-related variables such as weight and menstrual history. Key illness
characteristics were determined from these data including age at onset of AN, subtype of AN
(restricting vs binge-purging), duration of illness (years), duration of recovery (years), and
severity of illness (lowest BMI since AN onset).

**Measurement of exercise**

We collected data on exercise only, defined as specific planned physical activity;
household, occupational and other non-planned physical activity was excluded.

The Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ), an
interviewer-administered questionnaire was adapted to gather both past year and lifetime
exercise history. The MLTPAQ was designed to measure habitual leisure time physical activity
over the previous year\textsuperscript{184} It has been widely used in epidemiological studies to investigate
associations between physical activity and various diseases including OP.\textsuperscript{202-204} The
psychometric properties of this measurement have been extensively evaluated in various
populations and age groups. These studies have reported excellent short-term reliability for the
MLTPAQ and several adapted versions (Spearman correlations from 0.79-0.92) and moderate long-term reliability (Spearman correlations from 0.69-0.72).\textsuperscript{182, 205, 206} Construct validity has been demonstrated through direct measures of physical activity (diaries, accelerometers, doubly-labeled water techniques)\textsuperscript{183, 205, 207} and through indirect measures (physical fitness parameters).\textsuperscript{183, 184, 208, 209} The MLTPAQ has not been specifically evaluated in an AN population nor has a lifetime version been assessed.

To assist in recall, the detailed time-line and landmark events developed in the LHC interview (described above) were linked to the MLTPAQ interview. Specifically, individualized reference periods were created based on school and illness time periods: elementary school, junior high school, high school, post-secondary school, work history and periods of AN illness and recovery. As well, questions probed specific seasonal activities. Participants were asked to identify with the aid of an activity list, all the activities that they had participated in at least 10 times during each reference period. Annual frequency (the number of months/year, days/week and minutes/day, converted to average hours/week per year) and duration (number years performing an activity with the same frequency) were recorded for each activity. Each reference period was then categorized by the phase of illness: ‘before ill’/ ‘while ill’ / ‘while recovered’. To quantify skeletal loading, the final step was to assign each activity a bone loading unit (BLU) score developed by Dolan et al,\textsuperscript{210} which is calculated based on both load magnitude ratings (ground reaction forces and forces applied by muscle attachments) and strain rate (the rate at which force is applied). BLU’s for the hip were used in the present study. BLUs for activities not included in the list by Dolan et al, were estimated based on similar activities. Each activity was categorized as none-or-low (BLU < 5), moderate (BLU ≥ 5 and < 8) and high (BLU ≥ 8) bone loading exercise. (Table 1 summarizes categorization of specific activities). For each individual,
weighted average hours/week of each category of bone-loading exercise were calculated for
total lifetime exercise and for each of the three illness phases. This was done by multiplying the
average hours per week for each exercise category by the duration and dividing by the number
of years spent in each phase. The length of the before ill phase was the age at onset minus age
10.

Definition of AN recovery

In the absence of an established definition of AN recovery, participants were considered
to be recovered at the time of the study visit if they had a BMI $\geq 18.5$ kg/m$^2$ and had
spontaneously resumed menstruation, both sustained for at least one year. Participants on an
OCP at the time of weight recovery (n=19) were considered to be menstrually recovered. All
other participants were categorized as being ill at the time of the study visit. A participant who
had ever met the definition of recovery and then no longer met one or both criteria for at least
one year was considered to have experienced a relapse.

Statistical analysis

Participants with a history of relapse were excluded from this analysis due to the
complexity of considering the effect of exercise on BMD during intermittent phases of illness
and recovery.

All analyses were performed using SAS statistical software (version 9.1; SAS Institute
Inc, Cary, NC). The level of significance was established at $P \leq 0.05$ (two-tailed). All variables
were assessed for normality. Characteristics of ill versus recovered participants were
determined by t-test, Wilcoxon rank sum test or chi-square test, as appropriate. Descriptive
statistics (medians, minimum-maximum values) were used to describe the amount (average hours/week) of each bone-loading type of exercise in ill and recovered participants during each illness phase.

The association between exercise and BMD was then analyzed in two ways. None-or-low bone loading exercise was included for descriptive purposes but excluded from this part of the analysis to preserve statistical power, as there is good evidence that there is no adaptive bone response to minimal loads. Thus, the focus was on the effect of moderate and high loading exercise on BMD. Analyses were conducted separately in ill and recovered subgroups. First, linear regression was used to examine the bivariate association between i. total lifetime moderate loading exercise, and ii. high loading exercise (lifetime average hours/week) and Z-scores at the LSP, FN and TB. This association was then adjusted for duration of illness (years) and severity of illness (lowest BMI since AN onset) to control for possible confounding. Average hours/week of exercise were log transformed (lg10) for this analysis. Second, in order to determine the effect of types of bone-loading exercise done in combination and the effects of exercise during specific illness phases, participants were divided into 4 exercise groups based on tertiles of average hours/week of each of moderate and high loading exercise types: i. MOD-ONLY: in highest tertile of moderate loading exercise and lowest two tertiles of high; ii. HI-ONLY: in highest tertile of high loading exercise and lowest two tertiles of moderate; iii. BOTH: in highest tertiles of both moderate and high exercise; iv. NEITHER: in bottom two tertiles of both moderate and high loading exercise. A variable with these 4 categories was created for each phase of illness: ‘before ill’ / ‘while ill’ / ‘while recovered’. Linear regression was used to compare BMD Z-scores at each skeletal site in each exercise group with the NEITHER group (the reference group). The models included this categorical exercise variable for each phase of
illness (‘before ill’ and ‘while ill’, and in recovered participants, ‘while recovered’) to adjust for residual effects of prior bone-loading on BMD. An initial model was generated without adjusting for duration and severity of illness and then a second model was generated including these possible confounding variables.

RESULTS

One hundred and ninety women completed the study. At the time of the study visit, 77 participants met our definition of recovery, of which 19 had a history of a prior relapse. Of the 113 participants who were ill, 25 had been previously recovered and were relapsed. A total of 146 participants who had no history of relapse (88 ill and 58 recovered) were used in this analysis. Demographic and illness characteristics of these 146 participants are summarized in Table 2.

Description of amounts of exercise during each phase of illness

Table 3 summarizes the percentage of participants who engaged in each bone-loading type of exercise, and the average hours per week of exercise, during each illness phase. Overall, exercise amount and type were similar between the ill and recovered participants during the ‘before ill’ time period. Both ill and recovered participants did greater amounts of exercise during the ‘while ill’ phase than ‘before ill’, particularly of the moderate loading type. Fewer recovered participants exercised ‘while ill’ compared to the ill participants; recovered participants who did exercise, engaged in greater amounts, although the difference was not statistically significant (median 10.9 versus 6.2, in recovered and ill, respectively, $P = 0.58$). A
large majority (88%) of recovered participants exercised during the recovery phase but did a lesser amount than during the ‘while ill’ phase.

**Table 4** describes the typical activities performed by participants categorized in each of the exercise groups (MOD-ONLY, HI-ONLY and BOTH). Activities were similar in the ill and recovered groups during each illness phase. Typical activities ‘before ill’ differed from those performed ‘while ill’ and ‘while recovered’. Activities performed ‘while ill’ and ‘while recovered’ were similar. Participants in the MOD-ONLY group ‘before ill’, were either generally active in recreational level sports such as baseball, volleyball and skating or were walking for exercise. Most of the ‘before ill’ HI-ONLY group participated in competitive dance, gymnastics or figure skating, while those in the BOTH group were active in a variety of organized and school sports such as baseball, soccer, basketball and track-and-field. ‘While ill’, all participants in the MOD-ONLY group engaged in excessive walking, pacing and stair-climbing as well as none-or-low loading activities such as sit-ups and leg lifts. The primary activity in the ‘while ill’ HI-ONLY group was jogging/running. Participants in the BOTH group both ran and walked, or ran during part of their illness and then walked as they became too ill to run. Activities ‘while recovered’ were similar except that walking was the only activity in the MOD-ONLY group.

*Association between exercise and BMD Z-scores at the LSP, FN and TB*

i) **What is the effect of exercise during illness on BMD in women currently ill with AN?**

In the 88 ill participants, there was a significant negative association between total lifetime moderate loading exercise and BMD at the TB (beta: -0.79, 95% CI: -1.56, -0.02). This association was not significant at the LSP (beta: -0.63, 95% CI: -1.45, 0.18) or FN (beta: -0.61, 95%...
There was a significant positive association between total lifetime high loading exercise and BMD at the FN (beta: 1.13, 95% CI: 0.18, 2.08) and TB (beta: 0.93, 95% CI: 0.06, 1.80). This association was not significant at the LSP (beta: 0.72; 95% CI: -0.21, 1.65). Adjusting for duration of illness (years) and severity (lowest BMI since AN onset) slightly attenuated the relationships between both moderate and high loading exercise and BMD but did not change overall results (data not shown).

Table 5 shows the results of the linear regression analysis comparing BMD Z-scores in the three exercise groups (MOD-ONLY, HIGH-ONLY and BOTH) to the NEITHER reference group, in ill participants. After controlling for the effect of exercise 'before ill' on BMD, participants in the ‘while ill’ MOD-ONLY group had lower BMD at each skeletal site compared to the ‘while ill’ NEITHER group. BMD in the ‘while ill’ MOD-ONLY group was significantly lower than the NEITHER group at the TB and was borderline lower at the LSP ($P = 0.06$). The ‘while ill’ HI-ONLY group had the highest BMD at each skeletal site, but was not statistically higher than the NEITHER group. Adjusting for duration and severity of illness slightly attenuated the effect of ‘while ill’ MOD-ONLY and HI-ONLY exercise on BMD, but the negative effect of MOD-ONLY exercise remained significant at the TB.

ii) What is the effect of exercise during recovery in women with a past history of AN?

In the 58 recovered participants, total lifetime moderate loading exercise was not associated with BMD Z-scores at any skeletal site: LSP (beta: -0.03, 95%CI: -1.09, 1.03), FN (beta: 0.36, 95% CI: -0.71, 1.43), TB (beta: 0.12, 95% CI: -0.79, 1.03). Total lifetime high loading exercise had the greatest positive effect at the FN (beta: 2.78, 95% CI: 1.80, 3.76) but was also significantly associated with higher BMD at the LSP (beta: 1.31, 95% CI: 0.23, 2.39) and TB (beta: 1.21, 95% CI:
0.29, 2.13). Adjusting for duration and severity of illness did not change these parameter estimates.

Table 6 shows the results of the linear regression analysis comparing BMD Z-scores in the three exercise groups (MOD-ONLY, HIGH-ONLY and BOTH) to the NEITHER reference group, in recovered participants. After controlling for the effects of ‘before ill’ and ‘while ill’ exercise on BMD, the ‘while recovered’ HI-ONLY exercise group had significantly higher BMD at the FN and TB compared to the NEITHER group. This group also had the highest BMD at the LSP, but was not significantly higher than the NEITHER group. Adjusting for duration and severity of illness did not alter the parameter estimates of the ‘while recovered’ HI-ONLY group.

DISCUSSION

We investigated the association between lifetime exercise and BMD in young women with a history of AN and found that, similar to observations in healthy women, lifetime high bone-loading exercise was positively associated with BMD, particularly at the FN. This effect was greater in the recovered participants. Considering only total lifetime exercise, however, may lead to an overly simplistic representation of the mechanical loading-bone relationship in the AN population. Our examination of the association between exercise and BMD during each illness phase, suggests that this relationship in women with AN is especially complex, such that the bone response to loads may be dependent on both the type of exercise and when it was performed. We found that, in ill participants, high amounts of moderate loading exercise while ill was negatively associated with BMD. High loading exercise in these ill participants had no
association or perhaps at best, a modest positive effect, while high loading exercise performed while recovered had a significant positive association.

To our knowledge, the negative effect of moderate loading exercise during periods of AN illness on BMD has not been previously documented. The potential consequences of this adverse relationship could be significant for the bone health of women with AN. Excessive or compulsive exercise is common in these individuals and is typically of the moderate exercise variety, mostly in the form of walking and pacing as was observed in our study. The underlying mechanism by which moderate loading exercise stimulates loss of bone mass can only be hypothesized. It would be reasonable to assume that excessive exercise might generate further weight reduction and be associated with greater illness severity, thus inducing bone loss. However, BMD Z-scores control for body weight and the negative relationship persisted after adjusting for duration and severity of illness. Still, this does not rule out the possibility that considerable amounts of daily moderate loading exercise might cause subtle changes in energy status, further lowering levels of energy availability (defined as dietary energy intake minus exercise expenditure). It has been shown that energy deficient states in exercising women are associated with significant disruptions in metabolic hormones such as leptin and IGF-1, in addition to reduction in estrogen, and that these endocrine disturbances, in the presence of energy deficiency, are associated with both an increase in bone resorption markers and suppression of bone formation markers, leading to bone loss.

Excessive exercise may also be reflective of heightened anxiety in individuals with AN, particularly during the acute phase of the illness, and this may provide an alternative hypothesis regarding the observed negative association between moderate loading exercise and
BMD. Several studies have reported higher levels of depression and anxiety in AN patients who reported excessive exercise.\textsuperscript{213-215} Stress is well known to provoke hyperactivity of the hypothalamic-pituitary-adrenal axis resulting in increased cortisol secretion. Hypercortisolemia has been documented in AN patients generally,\textsuperscript{70, 106, 115} and in one small study, higher urinary cortisol was specifically reported to be associated with greater activity levels.\textsuperscript{216} Similarly, elevated physical activity in AN patients has been linked to suppression of leptin.\textsuperscript{217, 218} It is unclear whether excessive exercise directly generates alterations in cortisol and leptin secretion or whether these neuroendocrine abnormalities are solely adaptations to semistarvation and energy deficiency and are, in fact, ‘driving’ hyperactivity.\textsuperscript{216, 219} Nevertheless, cortisol and leptin have direct and indirect influences on bone metabolism and therefore may contribute to bone loss associated with excessive exercise.\textsuperscript{3, 108, 110, 112, 113}

We also observed that moderate loading exercise while ill was not associated with lower BMD in the recovered participants even though they engaged in similar activities, such as walking and pacing, in even greater amounts than did participants who were currently ill. This might suggest that any adverse effect on BMD attributable to exercise during illness is attenuated by AN recovery and is consistent with our findings (paper 1 and paper 2) that regeneration of bone mass occurs to within normal levels with recovery from AN regardless of prior illness history.

Our data also suggest that in the ill participants, high loading exercise while ill does not have similar detrimental effects on bone density as does moderate exercise and, although the findings were not statistically significant, may have a slight positive effect. This may be because the participants who did primarily high loading exercise participated in substantially fewer
hours of exercise than their counterparts who did primarily moderate loading exercise, resulting in less caloric expenditure and reduced energy-deficiency related disruptions in metabolic hormones which impact bone turnover. Alternatively, high loading exercise, unlike moderate, may have provided an osteogenic stimulus that was sufficient to negate at least some of the adverse neuroendocrinological consequences of exercise-related energy deficiency.

High loading exercise performed ‘while recovered’ was strongly associated with higher BMD particularly at the FN, unlike high loading exercise performed during the illness phase which had modest effects at most. This is despite the fact that the type of high loading exercise was similar in both the ‘while ill’ and ‘while recovered’ phases, consisting primarily of running, and that the hours/week spent running were less during the recovery phase. These findings are congruent with the perspectives presented by Skerry and by Bass et al. that an altered nutritional status affects the sensitivity by which bone adapts to an identical mechanical load both directly through its effect on lean mass and body mass and indirectly through associated changes in the endocrine environment.

The results of the present study must be considered in light of inherent limitations in the study design. First, cross-sectional data limit causal inferences regarding the observed associations between exercise and BMD. As well, reliability and validity of recalled lifetime physical activity has not been well established. Studies have reported moderate correlations between recalled activity and activity documented 1-30 years previously. Overall, most studies have shown a decrease in accuracy of recall with increasing recall interval, but this may be partly mitigated through the use of cognitive interview techniques such as were used in the present study. Given the large age range of our participants, the reliability of recall of
‘before ill’ activity in particular may vary widely among these individuals. As well, recovered participants may recall ‘while ill’ exercise differently from currently ill participants. Vigorous intensity activity also tends to be recalled more accurately than light or moderate intensity activities.\textsuperscript{221, 226, 227} However, it may be reasonable to assume that walking may be recalled with greater accuracy in individuals with AN as it is a salient feature during illness periods. Classification of some activities by BLUs may also have been incorrect as these units have not been validated against objective measures but were determined by Dolan et al\textsuperscript{210} based on published literature, reported ground reaction forces for specific activities and consensus from biomechanical experts. Another limitation is that the amount of exercise was summarized as average hours/week over each time period which does not take into account the adaptive response of bone to intra-individual patterns of exercise. Finally, the small numbers of participants in each exercise subgroup may have limited statistical power to detect small but significant differences among the groups.

Given these limitations, definitive conclusions cannot be derived from the present study, but rather the results must be interpreted with a view to generate hypotheses for future research. Further investigation at both the basic science and clinical levels is needed. A better understanding of excessive exercise during illness and its potential adverse effects on bone density may lead to more effective management of this behaviour and of bone health in patients with AN. Furthermore, although exercise recommendation in women with a history of AN must be provided with caution, if exercise during recovery is shown to enhance bone strength, it may be beneficial in certain individuals, and therefore further research to determine the optimal type, frequency and intensity of exercise is warranted.
In conclusion, the results of the present study suggest that the effect of exercise in women with a history of AN may be dependent not only on the type of exercise but also on the stage of illness during which it was performed. These findings demonstrate the complexity of the relationship between mechanical loading and bone and the interaction with nutritional status and the endocrine environment. It is hoped that this study will inform future research of exercise and bone health in the eating disorder population.
TABLE 1. Categorization of activities according to bone loading units (BLU)\(^1\) into none/low, moderate and high bone loading exercise types.

<table>
<thead>
<tr>
<th><strong>NONE or LOW</strong> (BLU &lt; 5)</th>
<th><strong>MODERATE</strong> (BLU ≥ 5 ≤ 8)</th>
<th><strong>HIGH</strong> (BLU &gt; 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>swimming</td>
<td>walking</td>
<td>running</td>
</tr>
<tr>
<td>cycling</td>
<td>hiking</td>
<td>dance (competitive)</td>
</tr>
<tr>
<td>canoe/kayaking</td>
<td>elliptical trainer</td>
<td>gymnastics</td>
</tr>
<tr>
<td>badminton</td>
<td>baseball/softball</td>
<td>figure skating (with jumps)</td>
</tr>
<tr>
<td>yoga</td>
<td>ice hockey</td>
<td>high impact aerobics class</td>
</tr>
<tr>
<td>pilates</td>
<td>skating (without jumps)</td>
<td>basketball</td>
</tr>
<tr>
<td>leg lifts</td>
<td>inline skating</td>
<td>soccer</td>
</tr>
<tr>
<td>sit-ups</td>
<td>boxing</td>
<td>tennis/squash</td>
</tr>
<tr>
<td></td>
<td>skiing (alpine, x-country, water)</td>
<td>volleyball (competitive)</td>
</tr>
<tr>
<td></td>
<td>snowboarding (without jumps)</td>
<td>ultimate frisbee</td>
</tr>
<tr>
<td></td>
<td>horseback riding</td>
<td>jump rope/jumping jacks</td>
</tr>
<tr>
<td></td>
<td>stairclimbing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>volleyball (recreational)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dance (recreational)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2. Demographic and illness characteristics of 146 Anorexia Nervosa (AN) participants.
Numbers are mean (median) (minimum-maximum), or n (%)

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>WHOLE SAMPLE¹ (n=146)</th>
<th>ILL (n=88)</th>
<th>RECOVERED (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>26.5 (25.0) (17-40)</td>
<td>26.1 (24.0) (17-40)</td>
<td>27.2 (27.0) (18-40)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.4 (19.2) (11.1-35.5)</td>
<td>17.7 (17.7) (11.1-28.9)</td>
<td>21.8 (21.1) (18.5-35.5)²</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.9 (164.0) (145-181)</td>
<td>164.3 (164.0) (145-177)</td>
<td>163.2 (162.8) (148-181)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>26.6 (27.8) (4.3-49.3)</td>
<td>22.2 (22.1) (4.3-48.2)</td>
<td>33.1 (32.6) (21.9-49.3)²</td>
</tr>
<tr>
<td>Age at onset of AN (y)</td>
<td>18.6 (18.0) (10-32)</td>
<td>18.4 (18.0) (12-32)</td>
<td>19.0 (18.5) (10-31)</td>
</tr>
<tr>
<td>Subtype of AN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricting</td>
<td>77 (52.7%)</td>
<td>42 (47.7%)</td>
<td>35 (60.3%)</td>
</tr>
<tr>
<td>Purging</td>
<td>69 (47.3%)</td>
<td>46 (52.3%)</td>
<td>23 (39.7%)</td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>5.8 (4.0) (0.5-25)</td>
<td>7.5 (6.0) (1-25)</td>
<td>3.3 (2.3) (0.5-13)²</td>
</tr>
<tr>
<td>Lowest BMI since AN onset</td>
<td>13.1 (13.3) (7.2-17.5)</td>
<td>13.0 (12.8) (7.2-17.5)</td>
<td>13.4 (13.7) (7.8-16.5)</td>
</tr>
<tr>
<td>Duration of recovery (y)</td>
<td>N/A</td>
<td>N/A</td>
<td>5.1 (4.3) (1-26)</td>
</tr>
</tbody>
</table>

¹excludes n=44 with a history of relapse (n=25 were ill and n=19 were recovered at time of the study visit)
²recovered participants significantly different from ill participants, at P ≤ 0.05

Definitions: AN recovery: BMI ≥ 18.5 kg/m² and resumption of regular menstruation, each maintained for ≥ 1 year
TABLE 3. Descriptive statistics of exercise by bone-loading type during each phase of illness in 146 Anorexia Nervosa (AN) participants who were ill versus recovered at the time of study visit.

Numbers are n (%), median (minimum-maximum) of average hours /week.

1 excluded n=46 participants with a history of relapse (n=25 were ill and n=19 were recovered at time of the study visit)

2 average hours/week among those who exercised

3 many participants did more than one type of exercise, therefore % > 100

Definitions: AN recovery: BMI ≥ 18.5 kg/m² and resumption of regular menstruation, each maintained for ≥ 1 year

<table>
<thead>
<tr>
<th></th>
<th>ALL PARTICIPANTS (n=146)</th>
<th>ILL PARTICIPANTS (n=88)</th>
<th>RECOVERED PARTICIPANTS (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. BEFORE ILL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercised (yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NONE or LOW</td>
<td>102 (69.9%)</td>
<td>62 (70.4%)</td>
<td>40 (69.0%)</td>
</tr>
<tr>
<td></td>
<td>2.2 (0.12 – 22.2)</td>
<td>2.2 (0.12 – 17.0)</td>
<td>2.3 (0.19 – 22.2)</td>
</tr>
<tr>
<td>MODERATE</td>
<td>56 (38.4%)</td>
<td>34 (38.6%)</td>
<td>22 (37.9%)</td>
</tr>
<tr>
<td></td>
<td>0.6 (0.07 – 9.7)</td>
<td>0.5 (0.07 – 9.7)</td>
<td>0.6 (0.07 – 6.0)</td>
</tr>
<tr>
<td>HIGH</td>
<td>63 (43.1%)</td>
<td>37 (42.1%)</td>
<td>26 (44.8%)</td>
</tr>
<tr>
<td></td>
<td>0.7 (0.07 – 3.0)</td>
<td>0.8 (0.07 – 2.9)</td>
<td>0.7 (0.12 – 3.0)</td>
</tr>
<tr>
<td></td>
<td>86 (58.9%)</td>
<td>50 (56.8%)</td>
<td>36 (62.1%)</td>
</tr>
<tr>
<td></td>
<td>1.1 (0.05 – 21.6)</td>
<td>1.3 (0.12 – 16.4)</td>
<td>1.0 (0.05 – 21.6)</td>
</tr>
<tr>
<td><strong>2. WHILE ILL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercised (yes)</td>
<td>127 (87.0%)</td>
<td>84 (95.4%)</td>
<td>43 (74.1%)</td>
</tr>
<tr>
<td></td>
<td>6.8 (0.09 – 57.4)</td>
<td>6.2 (0.09 – 40.4)</td>
<td>10.9 (0.3 – 57.4)</td>
</tr>
<tr>
<td>NONE or LOW</td>
<td>79 (54.1%)</td>
<td>56 (63.6%)</td>
<td>23 (39.7%)</td>
</tr>
<tr>
<td></td>
<td>1.5 (0.03 – 15.3)</td>
<td>1.3 (0.03 – 15.3)</td>
<td>1.6 (0.24 – 14.2)</td>
</tr>
<tr>
<td>MODERATE</td>
<td>105 (71.9%)</td>
<td>73 (83.0%)</td>
<td>32 (55.2%)</td>
</tr>
<tr>
<td></td>
<td>4.1 (0.13 – 41.0)</td>
<td>3.1 (0.13 – 27.1)</td>
<td>10.2 (0.19 – 41.0)</td>
</tr>
<tr>
<td>HIGH</td>
<td>89 (61%)</td>
<td>56 (63.6%)</td>
<td>33 (56.9%)</td>
</tr>
<tr>
<td></td>
<td>2.3 (0.02 – 33.9)</td>
<td>1.3 (0.02 – 10.2)</td>
<td>4.8 (0.23 – 33.9)</td>
</tr>
<tr>
<td><strong>3. WHILE RECOVERED</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercised (yes)</td>
<td></td>
<td></td>
<td>51 (87.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.2 (0.28 – 20.0)</td>
</tr>
<tr>
<td>NONE or LOW</td>
<td>N/A</td>
<td>N/A</td>
<td>29 (50.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4 (0.08 – 4.1)</td>
</tr>
<tr>
<td>MODERATE</td>
<td></td>
<td></td>
<td>39 (67.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0 (0.26 – 15.8)</td>
</tr>
<tr>
<td>HIGH</td>
<td></td>
<td></td>
<td>29 (50.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0 (0.05 – 20.0)</td>
</tr>
<tr>
<td>EXERCISE GROUPS</td>
<td>Description of specific activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1. Before Ill</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOD-ONLY</td>
<td>recreational sport: baseball, volleyball, skating, skiing, walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI-ONLY</td>
<td>competitive dance, gymnastics, figure skating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOTH</td>
<td>wide variety of organized and school sports (recreational and/or competitive): basketball, soccer, baseball, volleyball, track and field</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2. While Ill</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOD-ONLY</td>
<td>walking, pacing, stairclimbing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI-ONLY</td>
<td>running, aerobics classes or videos, jumping jacks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOTH</td>
<td>running, walking$^2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. While Recovered</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOD-ONLY</td>
<td>walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI-ONLY</td>
<td>running</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOTH</td>
<td>walking and running and/or aerobics classes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$(Based on average hours/week of each type of bone-loading exercise):
MOD-ONLY: in upper tertile of moderate loading exercise and lower two tertiles of high loading exercise
HI-ONLY: in upper tertile of high loading exercise and lower two tertiles of moderate loading exercise
BOTH: in upper tertile of both moderate and high loading exercise

$^2$Running and walking done in combination, or running during early part of illness followed by switch to walking when became too ill to run.
TABLE 5.  Unadjusted and adjusted results\(^1\) in 88 ill Anorexia Nervosa participants, comparing bone mineral density (BMD) Z-scores in exercise groups\(^2\), by linear regression analysis.

<table>
<thead>
<tr>
<th></th>
<th>Lumbar spine BMD (Z-scores)</th>
<th>Femoral neck BMD (Z-scores)</th>
<th>Total body BMD (Z-scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
</tr>
<tr>
<td><strong>BEFORE ILL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOD-ONLY</td>
<td>0.07 (-0.63, 0.77)</td>
<td>0.08 (-0.62, 0.78)</td>
<td>0.24 (-0.52, 1.0)</td>
</tr>
<tr>
<td>HI-ONLY</td>
<td>-0.50 (-1.19, 0.19)</td>
<td>-0.48 (-1.18, 0.22)</td>
<td>0.24 (-0.51, 0.99)</td>
</tr>
<tr>
<td>BOTH</td>
<td>0.42 (-0.28, 1.12)</td>
<td>0.37 (-0.35, 1.09)</td>
<td>0.48 (-0.28, 1.24)</td>
</tr>
<tr>
<td>NEITHER</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>WHILE ILL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOD-ONLY</td>
<td>-0.61 (-1.25, 0.03)</td>
<td>-0.57 (-1.22, 0.06)</td>
<td>-0.41 (-1.11, 0.29)</td>
</tr>
<tr>
<td>HI-ONLY</td>
<td>0.43 (-0.20, 1.06)</td>
<td>0.43 (-0.21, 1.07)</td>
<td>0.36 (-0.33, 1.05)</td>
</tr>
<tr>
<td>BOTH</td>
<td>0.24 (-0.62, 1.10)</td>
<td>0.28 (-0.59, 1.15)</td>
<td>0.16 (-0.78, 1.10)</td>
</tr>
<tr>
<td>NEITHER</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted results are adjusted for duration of illness (years) and illness severity (lowest BMI since onset of AN). Both unadjusted and adjusted models include the exercise variable for both time periods. The NEITHER group is the reference group.

\(^2\)Exercise groups: (categorized by tertiles of average hours/week of each bone-loading type of exercise): MOD-ONLY: in upper tertile of moderate loading exercise and bottom two tertiles of high loading exercise and bottom two tertiles of moderate loading; HI-ONLY: in upper tertile of high loading exercise and bottom two tertiles of moderate loading; BOTH: in upper tertile of both moderate and high loading exercise; NEITHER: in bottom two tertiles of both moderate and high loading exercise

Bold-faced type = significant at \( p \leq 0.05 \) vs NEITHER group
TABLE 6. Unadjusted and adjusted results\(^1\) in 58 recovered Anorexia Nervosa participants, comparing bone mineral density (BMD) Z-scores in exercise groups\(^2\), by linear regression analysis.

<table>
<thead>
<tr>
<th></th>
<th>Lumbar spine BMD (Z-scores)</th>
<th>Femoral neck BMD (Z-scores)</th>
<th>Total body BMD (Z-scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>BEFORE ILL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOD-ONLY</td>
<td>0.50 (-0.44, 1.44)</td>
<td>0.49 (-0.42, 1.40)</td>
<td>0.30 (-0.54, 1.14)</td>
</tr>
<tr>
<td>HI-ONLY</td>
<td>0.02 (-0.88, 0.92)</td>
<td>0.05 (-0.83, 0.93)</td>
<td>0.14 (-0.70, 0.98)</td>
</tr>
<tr>
<td>BOTH</td>
<td><strong>1.04 (0.08, 2.0)</strong></td>
<td><strong>0.78 (-0.18, 1.74)</strong></td>
<td><strong>1.50 (0.64, 2.36)</strong></td>
</tr>
<tr>
<td>NEITHER</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WHILE ILL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOD-ONLY</td>
<td>-0.20 (-1.14, 0.80)</td>
<td>-0.17 (-1.08, 0.74)</td>
<td>0.15 (-0.69, 0.99)</td>
</tr>
<tr>
<td>HI-ONLY</td>
<td>-0.14 (-1.0, 0.71)</td>
<td>-0.17 (-1.0, 0.67)</td>
<td>-0.14 (-0.90, 0.62)</td>
</tr>
<tr>
<td>BOTH</td>
<td>0.50 (-0.60, 1.60)</td>
<td>0.55 (-0.51, 1.61)</td>
<td>0.80 (-0.18, 1.78)</td>
</tr>
<tr>
<td>NEITHER</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WHILE RECOVERED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOD-ONLY</td>
<td>-0.08 (-0.95, 0.78)</td>
<td>-0.05 (-0.89, 0.79)</td>
<td>0.35 (-0.42, 1.12)</td>
</tr>
<tr>
<td>HI-ONLY</td>
<td>0.61 (-0.22, 1.45)</td>
<td>0.61 (-0.22, 1.44)</td>
<td><strong>0.90 (0.15, 1.65)</strong></td>
</tr>
<tr>
<td>BOTH</td>
<td>-0.30 (-1.75, 1.15)</td>
<td>-0.20 (-1.61, 1.21)</td>
<td>0.12 (-1.18, 1.42)</td>
</tr>
<tr>
<td>NEITHER</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted results are adjusted for duration of illness (years) and illness severity (lowest BMI since onset of AN). Both unadjusted and adjusted models include the exercise variable for each time period. The NEITHER group is the reference group.

\(^2\)Exercise groups: (categorized by tertiles of average hours/week of each bone-loading type of exercise): MOD-ONLY: in upper tertile of moderate loading exercise and bottom two tertiles of high loading; HI-ONLY: in upper tertile of high loading exercise and bottom two tertiles of moderate loading; BOTH: in upper tertile of both moderate and high loading exercise; NEITHER: in bottom two tertiles of both moderate and high loading exercise

**Bold-faced type** = significant at \( p \leq 0.05 \) vs NEITHER group
FIGURE 1. Recruitment flow-chart

TOTAL COHORT\(^1\): n=550

- Not screened: n=232
  - out of province: 50
  - unable to locate: 132
  - immediate refusal: 50

Screened: n=318

- Ineligible: n=66
  - disease: 10
  - medications: 25
  - hysterectomy: 3
  - pregnant / breastfeeding: 28

Eligible for study: n=252

- Did not complete study: n=62
  - too ill: n=9
  - subsequent refusal: n=53

Completed study: n=190

- TGH: n=125
- HHC: n=65

- Had illness history of recovery and relapse: n=44

Used in this analysis: n=146

\(^1\)Total cohort: number of women < 41 years of age admitted to either Toronto General Hospital (TGH) or Homewood Health Centre (HHC) for treatment of anorexia nervosa between April 15, 1993 and May 31, 2006.
Chapter 5: DISCUSSION

This chapter will summarize the results of the thesis in terms of its contribution to the current literature and implications for AN patients and the clinicians involved in their care. The limitations and strengths of the study will be discussed and suggestions for key areas of future research will be presented.

I. Contributions to the literature

The main objectives of the present study were to determine the association between recovery from AN and reversal of skeletal deficits and the effect of key illness characteristics on BMD in both ill and recovered patients. Secondary objectives were to determine the duration of AN recovery required for normalization of bone mass, if complete reversal of skeletal deficits occurred, to examine whether there was a differential capacity for regeneration across skeletal sites, and to elucidate an optimal definition of AN recovery from a bone perspective. The results were presented in the thesis in the form of three papers. The contributions to the literature of each the three papers are described below.

PAPER 1: THE EFFECT OF WEIGHT AND MENSTRUAL RECOVERY AND OTHER KEY ILLNESS CHARACTERISTICS ON BONE MINERAL DENSITY IN YOUNG WOMEN WITH A HISTORY OF ANOREXIA NERVOSA

This paper reported that recovered participants, particularly those who recovered after being ill for less than five years, which represented the majority of the recovered group, had a similar prevalence of low BMD compared to a healthy control group, and were 83% less likely to have low BMD than their ill counterparts. We believe that these results provide the strongest
evidence to date that recovery from AN confers the establishment of normal BMD in premenopausal women who experience both weight restoration and resumption of regular menstruation.

This study also showed that many of the illness characteristics previously presumed to have a detrimental effect on BMD do not appear to be important determinants of low bone mass in this population. Despite a broad range in values across the illness variables in our AN cohort and therefore a robustness to detect significant effects, we did not find that illness severity (lowest BMI since AN onset), age at onset of AN, or subtype of AN were associated with low BMD. Once recovery status was accounted for, only duration of illness was correlated with bone mass. Our findings indicate that duration of illness is particularly important; not only is longer duration associated with greater reduction in bone mass, but a protracted course of illness also appears to reduce the likelihood of recovery. We had few participants who recovered after an illness of greater than five years and, consequently, the impact of chronic illness following recovery remains uncertain.

It has also been purported that age at recovery may affect the ability of bone to regenerate, such that there may be a complete ‘catch-up effect’ if recovery occurs during adolescence that may not be possible if recovery occurs at a later age.\textsuperscript{45, 189} All but two of our participants recovered as adults (age 18 or older) and, therefore, we were not able to determine whether there was a difference in the duration of recovery required to achieve normalization of bone mass, which would reflect a difference in the rate of regeneration in adolescents compared to adults. However, the fact that we demonstrated normal BMD in most recovered participants suggests that normalization is possible when recovery occurs as an adult.
Our results also demonstrated a clear combined effect of weight restoration and resumption of regular menstrual cycles on BMD, strengthening the growing evidence that both are necessary for optimal bone accrual. These findings strongly suggest that the definition of AN recovery in future investigations regarding AN and bone mass should be one that includes both weight recovery and resumption of menses. Standardization of the definition of recovery in AN will also serve to enable comparison of results across studies.

Finally, although fractures were not a focus of this investigation due to a relatively low prevalence, we found that self-reported minimal trauma fractures were associated with low BMD and that they were much more prevalent in the ill participants. In fact, only one recovered participant reported sustaining a low trauma fracture. The association between BMD and fracture risk is not well-established in young women, but these findings indicate that low BMD in AN patients may increase susceptibility to fractures and that recovery may afford protection.

PAPER 2: CHARACTERIZATION OF CHANGES IN BONE DENSITY ASSOCIATED WITH ILLNESS AND RECOVERY IN YOUNG WOMEN WITH A HISTORY OF ANOREXIA NERVOSA

We conducted additional analysis to investigate the pattern and rate of bone loss and bone accrual in AN illness and recovery at three skeletal sites. To do so with our cross-sectional data, the association between each of duration of illness and duration of recovery and BMD Z-scores was visually examined by scatterplots and quantitatively evaluated by linear regression analysis. In effect, groups of participants were assembled according to the number of years that they were ill or recovered. The change in BMD values were then deduced from the pattern of successive values in each illness/recovery duration group. Using this approach, we
observed that regeneration of bone mass appears to occur rapidly over the first two years of AN recovery with normalization achieved after three years. This pattern of bone accrual was present at trabecular and cortical bone-dominated sites – the LSP, and FN and TB, respectively. However, consistent with prior investigators whose findings implied differential responses to AN recovery across skeletal sites, our data also indicated that ‘change’ in BMD at the LSP was greater than at the other two sites. Our data also suggested that bone loss (or decrease in bone accrual) during AN illness may proceed at different rates, with greater deficits in BMD observed at the LSP than at the FN or TB in those ill for a short period of time. The reported differences in bone regeneration, then, may be reflective of the fact that there is more bone to “recover” at trabecular versus cortical sites (ie. important baseline differences across sites). This reinforces the need for prospective studies and consideration of the effect of baseline BMD on follow-up measurements in order to accurately document the precise timing and rate of bone loss and bone gain over the course of illness.

PAPER 3: THE EFFECT OF EXERCISE DURING ILLNESS AND RECOVERY ON BONE MINERAL DENSITY IN YOUNG WOMEN WITH A HISTORY OF ANOREXIA NERVOSA

Very little is known about the effect of exercise in women with AN. Our results provide preliminary evidence that the relationship between exercise and BMD may, in fact, be very complex in this clinical group. We found that excessive walking while ill may negatively affect BMD, while exercise that supplies a greater osteogenic stimulus, such as running, may be beneficial to bone, particularly when performed during recovery. These results indicate that the impact on BMD may be dependent on both the type of exercise and on the stage of illness when it was performed.
II. Clinical implications

The main findings of the study are that the key determinants of bone mass in women with AN are two strongly linked variables – recovery and illness duration. These findings reinforce what is already well recognized: that early identification and intervention of AN is crucial, not only for the best outcome with respect to AN itself, but also for the management of OP and prevention of OP-related fractures. As current evidence does not support the use of oral contraceptives for the prevention or treatment of bone loss in AN patients, and there is limited evidence regarding the efficacy and safety of bisphosphonates in young women with AN, nutritional rehabilitation with weight gain to the threshold of resumption of menses remains the key strategy for managing bone health in this clinical population. Nevertheless, pharmacological intervention may be appropriate, particularly in the subset of chronically ill patients who are not only at an increased risk of low BMD and fractures, but who are also less likely to recover. More clinical trials are needed to evaluate the use of bisphosphonates and other pharmacological interventions that have shown early promise, such as recombinant human IGF-1 and dehydroepiandrosterone (DHEA), in patients who are resistant to nutritional rehabilitation.

We also found that several years of sustained recovery are necessary for normalization of bone mass. This highlights the need for maintenance treatment to be an essential component of the overall management strategy of AN to prevent relapse following completion of inpatient programs. Not only is adequate funding required to ensure that this is provided, but there is a need for research to determine the most effective maintenance program.
Our results infer that long-term management of bone health in women who have recovered from AN may not be necessary, particularly in those who were ill for a short duration and have maintained a healthy body weight and regular menstrual cycles. However, additional large studies which confirm our results are required before recommending change in practice with respect to the assessment and treatment of bone in women who present with a past history of AN. As in a normal, healthy population, there were recovered participants in our sample with low BMD values. This variability may reflect an AN disease characteristic that was not measured, or alternatively, risk factors unrelated to AN. Regardless, our results suggest that, if a woman with a prior history of AN presents with low BMD, it should not be assumed that her decreased BMD values are due to AN, and other secondary causes of OP should be sought.

As expressed by numerous study participants, OP is of great concern to many AN patients. The study results may, therefore, offer reassurance that one of the serious consequences of their illness can be reversed. Whether this knowledge might facilitate recovery by provoking behavioural change is uncertain. According to the Health Belief Model, there are four components that are necessary to motivate individuals to seek preventive care, or as applied in this case, to change harmful behaviours: i. a perception that a disease or condition is threatening; ii. a belief that change in behaviour is efficacious; iii. that they find barriers to change to be minimal; and, iv. that cues to action are provided. The study results may aid in the second component of this model. Most AN patients undergo BMD testing, at least in part, to convince them of the negative effects that AN has on the skeleton. Stoffman et al qualitatively explored the impact of providing AN patients with BMD results on their motivation to recover. They reported that 50% of the patients took some action after receiving the results of their BMD test, including increased efforts to gain weight and increased compliance with calcium intake.
They also noted that the reaction to the BMD results varied according to the participants’ perceptions of their stage of illness at the time of the test, such that those who felt they were at an early or mid stage of their illness were less concerned about the results or less inclined to change behaviour. However, later in their illness, these same patients became more concerned about their BMD results and felt that it influenced their motivation to make healthy changes. Given these results by Stoffman et al, it is not expected that the knowledge that skeletal deficits are reversible will prompt recovery in patients who are not ready for change. Nonetheless, it is hoped that this knowledge may be a motivational influence for those who are at a stage of increased ‘readiness for change’, as well as an ongoing source of motivation for those who have recovered to persevere with the recovery process.

Although our results as to the effect of exercise on BMD must be considered preliminary, they raise important questions regarding the best approach to managing exercise in AN patients from a bone health perspective. The study identified a subgroup of patients who were excessive walkers who may be at increased risk for low bone mass. Although preliminary, this indicates that these patients should be targeted for assessment and management of OP. There is also a need to further advance the understanding of the mechanisms of hyperactivity in AN and its negative impact on bone in order to determine the best way to modify this detrimental behaviour. It is currently unclear if excessive exercise is planned activity for the specific purpose of losing weight, or a means of controlling anxiety, which then stimulates bone loss through resultant weight reduction, caloric deficits and alterations in the endocrine environment. Alternatively, hyperactivity may be induced by endocrine adaptations to semistarvation, such as decreased leptin, which influence bone metabolism. This knowledge could have important therapeutic implications: reduction in excessive activity may
be achieved through anti-anxiety medication or leptin administration rather than through attempts at behavioural modification.

Current practice in the management of AN typically involves the proscription of exercise because it is thought to play a role in the maintenance of the illness. However, our results imply that, while excessive walking may promote bone loss, exercise that provides a stronger osteogenic stimulus, such as running, may not. High bone loading exercise during recovery may be particularly beneficial. A recent pilot study also reported that short term bed rest in hospitalized adolescents with AN suppressed bone formation and resorption. Taken together, these results suggest that the current practice of exercise restriction may not be optimal, or warranted, for all individuals from a bone perspective. Moreover, almost 90% of our study participants reported exercising both while they were ill and while they were recovered, providing clear evidence that advice to stop exercising is not being heeded. These findings support the idea of incorporating a supervised exercise component into the controlled treatment environment to facilitate self-responsibility for this aspect of the disorder and to assist in returning the patient to a normal lifestyle outside of the hospital where exercise is widely promoted. Others have proposed this idea in the past. Several small studies have investigated the impact of a structured exercise intervention as part of a treatment program for hospitalized AN patients and have reported that such programs increased quality of life and exercise capacity and improved body composition without adversely affecting weight gain or recovery of menstruation. This remains controversial, but deserves further consideration as exercise may confer many benefits including positive effects on bone mass, and may be appropriate for certain individuals. Much more research on exercise in women with AN is required to inform clinical practice in this regard.
III. Strengths and limitations

The main strengths of the study are its comprehensiveness and generalizability of results. The main study limitations are the cross-sectional design, reliance on self-reported historical data, and moderate participation rate.

A. Strengths:

i. Comprehensiveness

As described in Chapter 1 of this thesis, we used a Life History Calendar interview technique to obtain detailed chronological lifetime information on all variables of interest and potential confounding factors. Prior studies have relied either on chart review, which limited their ability to measure all necessary variables and to do so in a consistent manner, or on traditional questionnaires which may not yield as accurate data as that obtained by LHC, particularly for variables that fluctuate over time. This is also the first study to obtain detailed lifetime exercise history in AN patients. Furthermore, the large sample size provided good variability across all key variables as well as adequate statistical power to rigorously evaluate the effects of these key variables on the outcome while adjusting for confounding factors.

ii. Generalizability

The results of this study should be generalizable. The two recruitment sites, Toronto General Hospital (TGH) and Homewood Health Center, operate the largest eating disorder programs in Southern Ontario and together are believed to provide care to the majority of AN patients requiring inpatient treatment in this densely populated region. The programs at the
two sites are slightly different in that the TGH program is publicly funded while Homewood Health Centre is a private institution. Homewood Health Centre also does not accept severely ill patients. We feel that these differences enhance the generalizability of the results by providing a broader range of demographic and illness characteristics and treatment environments. Despite this, it cannot be completely ruled out that there may be something unique about the treatment programs at TGH and Homewood that contributed to our results. As well, our focus on patients hospitalized for treatment of AN might have hampered generalizability to individuals with less severe AN as our cohort likely represented those at highest risk for low BMD. However, since we observed normal BMD values in the recovered participants, it is reasonable to assume that recovery in those with less severe disease would also confer the establishment of normal bone mass.

B. Limitations

i. Cross-sectional design

The cross-sectional design makes it difficult to establish causal relationships as it cannot be determined with certainty that the outcome (ie. normal BMD) occurred after, and as a result of, the exposure (i.e. recovery from AN). Nevertheless, there is strong, consistent evidence in the literature that AN is associated with low BMD, which was confirmed in our ill participants. As the recovered participants did not differ from the ill participants on any key prognostic factors other than duration of illness, which was controlled for, we feel it is a solid assumption that the higher prevalence of normal BMD observed in the recovered participants compared to their ill counterparts was a direct consequence of having experienced weight and menstrual recovery.
Still, it is possible that there may have been something different about the recovered individuals that was not measured, that prevented bone loss to the same extent as in the ill participants.

ii. Self-reported data

The accuracy of self-reported data is dependent on numerous factors. These include respondent characteristics such as age, gender, personality traits (e.g. need for approval), physical condition (e.g. fatigue), affective stage (e.g. depression, anxiety) and innate recall ability. It is also dependent on the task attributes which includes the mode of administration (e.g. paper-and-pencil questionnaire, in-person interview), the duration of the task, and the instrument design (e.g. question sequencing, response format). These factors combine to affect the respondents’ ability and willingness to provide accurate information and can lead to invalid study results due to unreliable data (i.e. ‘garbage in-garbage out’ scenario) or to response bias.

The existing epidemiological literature provides evidence for moderate to good reliability and validity of the key variables included in the present study. As has been described previously in the thesis (Papers 1 and 2) accuracy of historical weight recall has been demonstrated in healthy individuals for recall periods of up to 30 years. While this has not been investigated in AN patients, there is no reason to assume that weight recall would be less accurate in a clinical group that is focused on weight. Recall of age at menarche has also been shown to be reliable but self-report of menstrual cycle irregularities less so. However, in AN patients, periods of amenorrhea tend to be of lengthy duration and linked to illness and recovery and, therefore, we contend that women with a history of AN may have heightened recall of their menstrual histories. Similarly, the reliability and validity of self-reported lifetime exercise has not been well-established. Studies have reported moderate correlations between
recalled activity and activity documented 1-30 years previously\textsuperscript{221-223} with vigorous intensity activities being recalled with better reliability than moderate ones, such as walking. Yet, as walking is a salient feature during illness periods, recall of this activity may be enhanced in AN patients.

We also considered several potential confounding factors, obtained by self-report, including alcohol consumption, smoking, OCP usage, and calcium intake. The reliability and validity of alcohol consumption derived from calendar based formats, similar to the LHC used in the present study, has been established and estimates from calendar procedures shown to produce more valid estimates than those from standard questionnaires.\textsuperscript{243-245} Studies comparing the accuracy of self-reported smoking and cotinine-assessed smoking status have shown trends of underestimation of tobacco consumption,\textsuperscript{246-248} but this would not lead to misclassification of smoking status (current versus past versus non) as analyzed in the present study. The validity of self-reported OCP usage has been reported in one study,\textsuperscript{168} in which lifetime OCP use obtained by a life event calendar interview was compared with pharmacy records and found to have good levels of agreement (> 70\%) for total duration of use and duration of use in different time windows. Finally, dietary calcium intake was obtained by a food frequency questionnaire. While the reliability and validity of this method has been demonstrated,\textsuperscript{249-252} it is acknowledged that there are unique issues with respect to measurement of dietary intake in women with AN. Many study participants were reticent to describe their food intake, and may have been susceptible to over-reporting. Furthermore, calcium intake was likely highly variable over the course of the illness, dependent on stage of illness and nutritional requirements during inpatient treatment.
Self-report data may also result in bias if the error is not random. In the present study, internal validity could be threatened if there was a systematic difference in the way the ill versus recovered participants recalled or reported information. However, other than reported exercise performed while ill, there were no differences in the distribution of variables between the two groups except for duration of illness and OCP usage, which were plausible differences. This would indicate that there was no significant self-report response bias. It is unclear whether recovered participants tended to over-report the amount of exercise performed while ill, perhaps due to exaggerated perceptions of activity levels during illness, or whether ill patients under-reported in response to perceived desirability of the behaviour (i.e. “they are not supposed to be exercising”). If the latter case is true, then the observed negative effect of exercise while ill on BMD would be underestimated.

There may also have been the possibility that misclassification of the illness status groups (ill versus recovered) occurred if there was biased reporting of the variables used for categorization: body weight and regular menstruation. Although self-reported weight history was used to determine if they had met the weight criterion for recovery for at least one year, body weight was measured at the time of the study visit in conjunction with BMD assessment. Thus, there was minimal reliance on weight recall in the determination of illness status. It is possible, however, that participants who were borderline weight recovered or previously recovered and were relapsing may not have wanted to admit that they were not menstruating regularly and, consequently, would have been incorrectly classified as recovered rather than ill. However, this misclassification would have resulted in a higher estimate of the prevalence of low BMD in the recovered group and biased the results towards the null hypothesis.
iii. Participation rate and possible selection bias

Our participation rate was approximately 50%, creating the potential for selection bias in our cohort. Non-respondents consisted of those who could not be located (26.4% of non-respondents) and those who refused (22.4%). While we had a broad range of responses on all key variables, it does not eliminate the possibility that non-respondents could have very different responses. We were able to gather information on key demographic and illness variables from 36 non-participants and found no significant differences compared to the AN study participants, except that they were more likely to be recovered and have children. Therefore, there may be a difference in the prevalence of AN recovery in respondents versus non-respondents, but there is no evidence of a major selection bias that would impact our observed associations between AN recovery and other illness variables and BMD.

There is also the potential for volunteer bias in our healthy, control group. These women were recruited from the community through newspaper advertisements and posted flyers and may represent women who are particularly concerned about OP. This could lead to either over- or under-estimation of the prevalence of low BMD in the normal population. If the control group was especially concerned about their bone health due to a family history of OP, the prevalence of low BMD in this group may have been higher than in the average population. However, only 5.6% reported a family history of OP and this was lower than that reported by the AN participants. Alternatively, the control group, in response to heightened concern about OP, may engage in healthier lifestyles and be more inclined to take preventive measures such as increased calcium intake, Vitamin D supplementation and physical activity. This might have
lead to an overestimation of the prevalence of normal BMD in the general population, which would have biased our study results towards the null hypothesis.

Overall, the study was primarily limited by its cross-sectional design and reliance on self-reported data. However, these limitations are minimized by several strengths including its comprehensiveness and generalizability, thus enabling the study to provide significant contributions to the literature.

IV. Future research

This study highlighted key areas for future investigations. These are outlined here.

1. Prospective studies are required to confirm patterns of bone loss and bone gain with illness and recovery observed in this cross-sectional study. In particular, participants need to be followed for at least 3-4 years after weight and menstrual recovery to confirm whether normalization of bone mass occurs in this time frame.

2. Although the likelihood of AN recovery is limited after a protracted illness, regeneration of bone mass needs to be investigated specifically in women who have recovered after being ill for at least 5 years to determine whether normalization of bone mass is possible in this subgroup, and, if so, the duration of recovery required.

3. Investigations are needed to determine whether the rate of bone regeneration following recovery can be escalated through specific interventions, thereby decreasing the duration of time required for normalization of bone mass and narrowing the window of susceptibility for fractures. These interventions may include pharmacologic therapy or
dietary and lifestyle measures such as calcium and Vitamin D supplementation or exercise.

4. Much more research is required to elucidate the effects of exercise on bone mass in women who are in the acute phase of the illness as well as those who are in the recovery phase. The mechanisms by which excessive, moderate bone loading exercise negatively impacts bone mass need to be established and the optimal type, amount and frequency of exercise that promotes an adaptive bone response in recovered patients needs to be determined. As well, it may be important to ascertain the time period during recovery when exercise has the greatest positive effect on bone. As described above (# 3), exercise during the early part of the recovery phase may provoke a more rapid bone response. However, if physical activity also stimulates bone accrual at later stages, it may be preferable to recommend exercise when recovery has been maintained for several years and the likelihood of relapse is lower.

5. The outcome in this study was BMD as measured by conventional DXA. Fracture risk is related to bone strength, which is determined by both the quantity and quality of bone, but DXA does not provide information about bone structure. Changes in trabecular micro-architecture have been documented in AN patients. AN recovery may stimulate increases in bone density, as evidenced by our study, but there may be permanent structural changes that lower the fracture threshold. An evaluation using quantitative computer tomography (QCT), which differentiates trabecular and cortical bone and provides detail on bone architecture, could provide important information regarding the structural response to recovery and the potential for ongoing increased susceptibility for
fractures. This is also important with respect to exercise. DXA does not capture all the adaptive changes to the geometry and structure of bone that occurs with mechanical loading. QCT could provide additional information about the structural changes that may occur with excessive exercise during illness or exercise during recovery, to better understand the impact of physical activity on bone strength and fracture risk in this population.

6. Research is required to determine safe and effective therapies for low bone mass in women with AN who, if they do not recover, are at a substantial risk for low BMD and possibly fracture.

V. Conclusions

This study provides good evidence that normalization of bone mass is possible in adult women with AN with weight and menstrual recovery. Both weight restoration and resumption of menses were shown to be necessary for optimal bone density, and approximately three years of sustained recovery appears to be required for full reversal of skeletal deficits. In addition to disease state, duration of illness was the only illness characteristic identified as a key determinant of BMD. Illness duration may be a particularly important factor as not only are greater skeletal deficits associated with longer disease durations, but AN recovery is less likely after a protracted illness. Excessive walking while ill may also put patients at higher risk of low bone mass, but high bone loading activities may be protective during illness and provoke bone accrual during recovery. Much more research is required to enhance knowledge of the complex relationship between mechanical loading and bone in AN patients to enable appropriate recommendations regarding this potentially modifiable factor.
The results of this thesis highlight the significant skeletal risks associated with prolonged AN and reinforce the importance of early and sustained recovery for the prevention and treatment of OP in this population. It is hoped that these results will not only be of benefit to the clinicians involved in the care of AN patients but offer reassurance to the patients themselves and provide motivation to make positive behavioural changes which ultimately lead to successful, long-term recovery.
CANDIDATE’S ROLE

The candidate (EJW) conceived the research questions addressed in this thesis, developed the study protocol with input from thesis committee members (Dr. G. Hawker, Dr. B. Woodside, Dr. D. Beaton, Dr. P. Coté), supervised the recruitment of the anorexia nervosa (AN) participants, conducted all interviews with the AN participants, performed all data analyses and wrote the thesis manuscript.
REFERENCES


APPENDIX A

Recruitment Details

Toronto General Hospital, Toronto, and Homewood Health Centre, Guelph
APPENDIX A.  RECRUITMENT DETAILS

DETAILED REPORT

This report describes recruitment from the two sites: Toronto General Hospital (TGH) and Homewood Health Centre (HHC).

1. TGH COHORT (admissions between April 15, 1993 – May 31, 2006)

Total TGH cohort: 427 new admissions
Less:
  > 40 yoa: 99
  Males: 6
  Not AN: 8
  Deceased: 17
  Out of country/province: 13
TOTAL: 284 age-eligible females with AN within travel distance of study site

2. HHC COHORT (admissions between January 1, 1995 – May 31, 2006)

Total HHC cohort: 380 new admissions
Less:
  > 40 yoa: 77
  Males: 12
  Not AN: 1
  Deceased: 1
  Out of country/province: 37
Duplicate admissions to TGH: 36
TOTAL: 216 age-eligible females with AN within travel distance of study site

TOTAL COHORT AVAILABLE FOR RECRUITMENT: 284 + 216 = 500

Notes:
• Age and sex exclusion criteria confirmed by chart review or screening
• Diagnosis: list of patients admitted for treatment of AN were reviewed by the Directors of the TGH and HHC programs to identify any who were not AN; during screening or during the study interview if an incorrect diagnosis was suspected, chart review was used to confirm
• Deceased identified by ED program directors or upon contact
• Out of province/country confirmed by contact or if unable to contact, by last recorded address
I. UNABLE TO CONTACT: 132 (132/500 total cohort = 26.4%)
   TGH: 52 (52/284 = 18.3%)
   HHC: 80 (80/216 = 37.0%)

   Reasons for inability to contact:
   • Unable to locate: 112 (112/500 = 22.4%)
     TGH: 45 (45/284 = 15.8%)
     HHC: 67 (67/216 = 31.0%)
   • Contact not completed: 20 (20/388 located = 5.2%)
     TGH: 7 (7/239 = 2.9%)
     HHC: 13 (13/149 = 8.7%)
     o Reached parent – not allowed to contact patient: 8
     o Reached patient once – unable to contact again: 6
     o Never able to reach patient (correct contact info confirmed): 6

II. CONTACT COMPLETED: 368 (368/500 total cohort = 73.6%)
   TGH: 232 (232/284 = 81.7%)
   HHC: 136 (136/216 = 63.0%)

   A. TOTAL NOT SCREENED (immediate refusal): 50 (50/368 contacted = 13.6%)
      TGH: 31 (31/232 = 13.4%)
      HHC: 19 (19/136 = 14.0%)

   Reasons for refusal:
   • too ill: 4
   • not interested: 14 (TGH) + 11 (HHC) = 25
   • too busy: 7 (TGH) + 2 (HHC) = 9
   • other: 16
     o dispute with TGH: 5
     o dispute with HHC: 4
     o wants to be paid: 1
     o uncomfortable with study requirements: 2
B. TOTAL SCREENED: 318 \( \left( \frac{318}{368} \text{ contacted} = 86.4\% \right) \)
   - TGH: 201 \( \left( \frac{201}{232} = 86.6\% \right) \)
   - HHC: 117 \( \left( \frac{117}{136} = 86.0\% \right) \)

i. INELIGIBLE: 66 \( \left( \frac{66}{318} \text{ total screened} = 20.75\% \right) \)
   - TGH: 40 \( \left( \frac{40}{201} = 19.9\% \right) \)
   - HHC: 26 \( \left( \frac{26}{117} = 22.2\% \right) \)

Reasons for ineligibility:
- Disease: 8 (TGH) + 2 (HHC) = 10
- Medication: 17 (TGH) + 8 (HHC) = 25
- Pregnant / breastfeeding: 14 (TGH) + 14 (HHC) = 28
- Hysterectomy / oophorectomy: 1 (TGH) + 2 (HHC) = 3

ii. ELIGIBLE: 252 \( \left( \frac{252}{318} \text{ total screened} = 79.2\% \right) \)
   - TGH: 161 \( \left( \frac{161}{201} = 80.1\% \right) \)
   - HHC: 91 \( \left( \frac{91}{136} = 77.8\% \right) \)

Subsequent refusal: 62 \( \left( \frac{62}{252} \text{ eligible} = 24.6\% \right) \)
   - TGH: 36 \( \left( \frac{36}{161} = 22.4\% \right) \)
   - HHC: 26 \( \left( \frac{26}{91} = 28.6\% \right) \)

Reasons for refusal:
- Too ill: 5 (TGH) + 4 (HHC) = 9
- Not interested: 5 (TGH) + 1 (HHC) = 6
- Too busy: 11 (TGH) + 13 (HHC) = 24
- Uncomfortable with study requirements: 5 (TGH) + 1 (HHC) = 6
- Unable to schedule: 10 (TGH) + 6 (HHC) = 16
- Other: 1

TOTAL: COMPLETED STUDY: 190
   - TGH: 125
   - HHC: 65

PARTICIPATION RATE: \( \frac{190}{500 - 66 \text{ ineligible}} = \frac{190}{434} = 43.8\% \)
RECRUITMENT SUMMARY

**Participation rate:** Actual rate: $190/(500-66\text{ ineligible}) = 43.8\%$

TGH: $125/(284-40\text{ ineligible}) = 51.2\%$

HHC: $65/(216-26\text{ ineligible}) = 34.2\%$

(Assuming similar ineligibility rate in those not located/contacted: $190/(500-20.75\%) = 48.0\%$)

**Refusal rate:** $112/368\text{ total contacted} = 30.4\%$

TGH: $67/232 = 28.9\%$

HHC: $45/136 = 33.1\%$

**Ineligibility rate:** $66/318\text{ total screened} = 20.7\%$

TGH: $40/201 = 19.9\%$

HHC: $26/117 = 22.2\%$

**Completion rate:** $190/252\text{ total screened and eligible} = 75.4\%$

TGH: $125/161 = 77.6\%$

HHC: $65/91 = 71.4\%$

**Unable to locate/contact:** $132/500\text{ total cohort} = 26.4\%$

TGH: $52/284 = 18.3\%$

HHC: $80/216 = 37.0\%$
APPENDIX B

Table comparing demographic and illness characteristics of respondents versus non-respondents
Comparison of key characteristics in 190 AN participants to 36 women who were eligible and refused to participate but consented to a telephone interview to gather demographic and illness information. Numbers are mean (median) (minimum-maximum), or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>190 AN study participants</th>
<th>36 non-participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>27.2 (25.5) (17-40)</td>
<td>28.1 (27.0) (19-40)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>167 (87.9%)</td>
<td>25 (69.5%)²</td>
</tr>
<tr>
<td>Age at menarche (y)</td>
<td>12.9 (13.0) (9-17)</td>
<td>13.2 (13.0) (11-19)</td>
</tr>
<tr>
<td>BMI (kg/m²)¹</td>
<td>19.4 (19.3) (11-35.5)</td>
<td>19.7 (20.2) (12.1-24.2)</td>
</tr>
<tr>
<td>Illness status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently ill</td>
<td>113 (59.5%)</td>
<td>14 (38.9%)²</td>
</tr>
<tr>
<td>Currently recovered¹</td>
<td>77 (40.5%)</td>
<td>22 (61.1%)</td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>18.2 (17.0) (10-32)</td>
<td>18.0 (16.6) (11-29)</td>
</tr>
<tr>
<td>Sub-type of AN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>restricting</td>
<td>91 (47.9%)</td>
<td>16 (44.4%)</td>
</tr>
<tr>
<td>purging</td>
<td>99 (52.1%)</td>
<td>20 (55.6%)</td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>5.0 (3.5) (0.5-25)</td>
<td>4.8 (3.0) (1-14)</td>
</tr>
<tr>
<td>Duration of recovery (y)</td>
<td>5.1 (4.5) (1-26)</td>
<td>5.3 (5.0) (1-15)</td>
</tr>
<tr>
<td>Lowest weight since AN onset (lbs)</td>
<td>79.1 (80.0) (42-120)</td>
<td>78.9 (78.0) (56-107)</td>
</tr>
<tr>
<td>OCP use (ever used ≥ 1 y)</td>
<td>105 (55.3%)</td>
<td>20 (55.6%)</td>
</tr>
</tbody>
</table>

¹Notes: i. BMI was measured at the time of the study visit in the 190 study participants; in the 36 non-participants, BMI was calculated based on self-report of current weight (lbs) and height (ft/in).

ii. Definition of recovery: at a BMI of ≥ 18.5 kg/m² and resumed menstruation for at least 12 months.

²36 non-participants significantly different than the 190 study participants, at P ≤ 0.05.
APPENDIX C

Table summarizing characteristics of prior studies investigating recovery of bone mass in anorexia nervosa
# Appendix C. Summary of characteristics and results of studies investigating recovery of bone mass in women with anorexia nervosa (AN)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>N</th>
<th>Study participants</th>
<th>Outcome (bone measurement)</th>
<th>Definition of AN recovery</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misra(^{130}) (2008)</td>
<td>prospective (with control group) F/U: 0, 6, 12 mos</td>
<td>n=14 recovered over course of study n=20 ill n=33 controls</td>
<td>recruited from referrals to ED treatment centers age: 12-18 y ill durn: 11.2±12.4 mos rec durn: median 9 mos</td>
<td>BMD and Z-scores: LSP and TB</td>
<td>Weight gain: 10% increase in BMI AND menstruation x 3 mos</td>
<td>stabilization of BMD in recovered participants; ill continued to lose bone</td>
</tr>
<tr>
<td>Mika(^{8}) (2007)</td>
<td>prospective F/U: 0, 24 mos</td>
<td>n=11 recovered over course of study n=8 ill</td>
<td>consecutive sample from inpt ED program age: 14.4±1.6 y ill durn: 10.6±6.7 mos rec durn: not specified</td>
<td>BMD and Z-scores at LSP, FN</td>
<td>not specified (noted that n=11 resumed menses)</td>
<td>no change in BMD (but normalization of bone turnover markers)</td>
</tr>
<tr>
<td>Viapiana(^{128}) (2007)</td>
<td>prospective (with control group) F/U: 0, 3, 15 mos</td>
<td>n=55 at 0, 3 month F/U n=25 at 15 month F/U all increased wt at 3 months (unclear if still 'recovered' at 15 mos)</td>
<td>consecutive sample from inpt ED program age: 16-42 y ill durn: 8.1±5.7 y rec durn: not specified (? 3-12 mos)</td>
<td>BMD at LSP, FN</td>
<td>BMI &gt; 17.5 kg/m(^2) (none resumed menses)</td>
<td>at 3 month F/U: 1.2% increase at LSP; 3.5% increase at FN at 15 month F/U: additional increase at LSP of 4.8%, at FN 7.1% &quot;in those who did not lose weight&quot;</td>
</tr>
<tr>
<td>Dominguez(^{129}) (2007)</td>
<td>prospective (before/after 2 month inpt treatment)</td>
<td>n=28 (all weight recovered; n=9 also menstrual recovered) (note: n=37 at baseline)</td>
<td>consecutive sample from inpt ED program age: 18-35 y ill durn: 98±59.5 mos rec durn: not specified (&lt; 2 mos)</td>
<td>BMD at LSP, FN, TB</td>
<td>body weight: 90% of ideal body weight</td>
<td>4.4% increase at LSP; 3.8% at FN BMD lower than controls no difference in increase in menstruating vs non-menstruating</td>
</tr>
<tr>
<td>Reference</td>
<td>Study design</td>
<td>N</td>
<td>Study participants</td>
<td>Outcome (bone measurement)</td>
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<tr>
<td>Oswiecimska (2007) [134]</td>
<td>prospective F/U: 0, 7.8 ± 2.4, 19.4 ± 5.6 mos</td>
<td>n=9 recovered over course of study n=9 ill</td>
<td>consecutive sample from inpt ED program age: 11.5 -18.1 y ill durn: 3-56 mos rec durn: not specified</td>
<td>BMD and Z-scores at LSP, TB</td>
<td>BMI ≥ 18.5 AND menstruation ≥ 6 mos</td>
<td>no significant difference in change in BMD in those who recovered and those who did not</td>
</tr>
<tr>
<td>Compston (2006)  [132]</td>
<td>prospective F/U: 0, 3, 12 mos</td>
<td>n=12 recovered over course of study n=9 ill</td>
<td>consecutive sample from inpt ED program age: 13-20 y ill durn: 2-36 mos rec durn: not specified (&lt; 12 mos)</td>
<td>BMD at LSP, FN, TB</td>
<td>resumption of menses (BMI increased from mean 14.2 to 17.6 over course of study)</td>
<td>no significant difference in change in BMD in those who resumed menses and those who did not (also reported no difference in BMI change in recovered vs non-recovered)</td>
</tr>
<tr>
<td>Miller (2006) [135]</td>
<td>prospective F/U: 6-60 mos (mean: 13.5 mos)</td>
<td>n=7 wt and menstrual recovered n=11 menstrual recovered n=22 wt recovered n=19 ill</td>
<td>recruited from research centre (? all ill at baseline) age: 18-40 y durn ill: u/k durn rec: not specified</td>
<td>BMD at T-scores at LSP, hip</td>
<td>menstrual recovery: 1 cycle in previous 3 months weight recovery: increased by 10% or to &gt; 85% of ideal wt</td>
<td>Menstrual recovered (included 4 wt recovered): significant increase at LSP but not hip compared to not menstrual recovered Wt recovered (included 7 menstrual recovered): significant increase at hip but not LSP compared to not wt recovered</td>
</tr>
<tr>
<td>Reference</td>
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<tr>
<td>Bolton44 (2005)</td>
<td>prospective F/U 0, 12 mos</td>
<td>n=15 at F/U (all wt recovered; n=8 also menstrual recov) (note: n=55 at baseline)</td>
<td>consecutive sample from inpt ED program</td>
<td>BMD at LSP, FN, radius</td>
<td>“achieving and maintaining normal weight based on mean matched popn weight”</td>
<td>LSP increased by 4.3% no change at FN, radius, no difference in change b/w those menstrual recovered and those not</td>
</tr>
<tr>
<td>Bass127 (2005)</td>
<td>mixed</td>
<td>n=18 disease cohort n=13 recovery cohort</td>
<td>participants previously or currently being treated in combination inpt/outpt ED program</td>
<td>BMD, Z-scores at LSP, TB</td>
<td>body weight within 15% of that expected for age and height AND regular menses x 3 cycles</td>
<td>recovery cohort: at baseline Z-score at LSP : -1.9; TB - 1.0 recovery cohort: at follow-up: Z-score -0.4 at LSP; TB 0.2</td>
</tr>
<tr>
<td>Morris136 (2004)</td>
<td>cross-sectional (with control group)</td>
<td>n=36 recovered n=51 ill (plus 56 BN or EDNOS)</td>
<td>recruited from community: advertisements, flyers, self-help groups</td>
<td>BMD, T-scores at LSP, TB OP: T-score &lt;=-2.5</td>
<td>not specified</td>
<td>recovered pts had significantly lower BMD at LSP but not TB vs controls (and significantly higher than ill pts) n=10 ill pts had OP n=0 recovered had OP</td>
</tr>
<tr>
<td>Reference</td>
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</tr>
<tr>
<td>Bertoli131 (2004)</td>
<td>prospective F/U: 3, 24 mos</td>
<td>n=8 completed final F/U</td>
<td>consecutive sample from inpt ED program</td>
<td>BMD at TB</td>
<td>&gt; 15% weight gain maintained until F/U</td>
<td>no increase in BMD over time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>age: 23.9±5.6 y ill durn: 1.9±2.7 y rec durn: not specified (&lt; 24 mos)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Wentz126 (2003)</td>
<td>cross-sectional (with control group)</td>
<td>n=36  (unclear how many recovered)</td>
<td>&quot;recruited from population-based sample of individuals with teenage onset of AN&quot; age: 24.6-26 y ill durn: u/k rec durn: u/k (pts were assessed approx 10 years post AN onset)</td>
<td>BMD, T-scores at LSP, hip osteopenia and osteoporosis defined according to WHO norms</td>
<td>not specified</td>
<td>n=15 had osteopenia (n=11 controls also had osteopenia) n=6 had osteoporosis</td>
</tr>
<tr>
<td>Soyka4 (2002)</td>
<td>prospective (with control group) F/U: 0, 6, 12 mos</td>
<td>n=11 recovered n=6 ill</td>
<td>recruited through mass mailings to health care providers age: 12.9-17.8 y ill durn: 1-48 mos rec durn: not specified</td>
<td>BMD at LSP</td>
<td>&gt; 10% increase in BMI from baseline</td>
<td>BMD significantly lower than controls at all time points change in LSP no different between recovered and non-recovered groups</td>
</tr>
<tr>
<td>Audi97 (2002)</td>
<td>cross-sectional</td>
<td>n=19 recovered n=20 wt recovered only n=34 ill</td>
<td>recruitment: not specified age: 17.2±1.7 y ill durn: rec: 25±12 mos wt only rec: 19±12 mos ill: 15±9 mos rec durn: not specified</td>
<td>BMD at LSP expressed as SD matched on age, sex to normative data</td>
<td>BMI higher than -1 SD AND regular menses for &gt; 3 months</td>
<td>BMD not significantly different across 3 groups 26% of recovered group were osteopenic (≤ - 1 SD)</td>
</tr>
<tr>
<td>Reference</td>
<td>Study design</td>
<td>N</td>
<td>Study participants</td>
<td>Outcome (bone measurement)</td>
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</tr>
<tr>
<td>Zipfel85</td>
<td>prospective F/U: 3.6 ± 1.5 y</td>
<td>n=9 recovered n=15 ill (plus 14 BN)</td>
<td>consecutive sample from inpt and outpt hospital ED program age: rec: 24.4±4.8 y ill: 24.6 ±4.7 y ill durn: rec 3.8±3.7 y ill: 7.0±3.8 y rec durn: not specified</td>
<td>BMD at LSP</td>
<td>BMI &gt; 18.5 AND resumption of menses ≥ 6 mos</td>
<td>annual loss at LSP of 3.7% in ill AN vs insignificant gain of 0.7% in recovered; significant difference in BMD at LSP b/w 2 groups</td>
</tr>
<tr>
<td>Castro45</td>
<td>prospective F/U: mean 15.4 mos (6-30 mos)</td>
<td>n=64 recovered n=44 ill (n=62 did not complete study)</td>
<td>consecutive sample from inpt ED program age: 15.2±1.5 y ill durn: 14.4±13.2 mos rec durn: not specified (? approx 7 mos)</td>
<td>BMD, Z-scores at LSP, FN</td>
<td>BMI &gt; 19 AND resumption of menstruation at F/U</td>
<td>recovered and normal BMD at baseline: increase of 3% at LSP, 1.3% at FN recovered and low BMD at baseline: increase 9.1% at LSP, 4.5% FN; 17.2% had normal BMD (Z-score &gt; -1) at LSP ill: loss of 2.1% at LSP, 1.3% at FN</td>
</tr>
<tr>
<td>Hartman46</td>
<td>cross-sectional (with control group)</td>
<td>n=19 recovered</td>
<td>part of group of patients followed for 20 years after treatment program age: median 40.2 y ill durn: unclear rec durn: median 21 y</td>
<td>BMD at LSP, FN</td>
<td>“beyond clinical dispute”</td>
<td>BMD at FN significantly lower than controls; LSP not significantly different from controls but “trend towards lower”</td>
</tr>
</tbody>
</table>
## APPENDIX C. (cont).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>N</th>
<th>Study participants</th>
<th>Outcome (bone measurement)</th>
<th>Definition of AN recovery</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hotta77 (1998)</td>
<td>prospective</td>
<td>n=10 recovered over course of study n=19 ill (n=51 at baseline)</td>
<td>patients of lead author, in outpt treatment program age: 19-42 y ill durn: 7-270 mos rec durn: not specified</td>
<td>BMD at LSP</td>
<td>resumption of menses</td>
<td>in the 10 recovered patients, the change in LSP BMD ranged from -0.5 to 7.5% per year</td>
</tr>
<tr>
<td>Ward10 (1997)</td>
<td>cross-sectional</td>
<td>n=18 recovered</td>
<td>recruitment: unclear (participants part of another study) age: 20-46 (median: 30.5) y ill durn:0.3-16 (median: 1.5)y rec durn: 1-31 (median: 6) y</td>
<td>BMD, Z-scores, T-scores at spine, hip BMI &gt; 18.5 AND resumption of menses ≥ 6 mos</td>
<td>BMI &gt; 20 AND menstruating</td>
<td>spine: median z-score: -1.4 hip: median z-score: -1.2 12 participants had t-scores &lt; -1.0</td>
</tr>
<tr>
<td>Kooh133 (1996)</td>
<td>prospective</td>
<td>n=4 recovered at F/U n=8 ill at F/U</td>
<td>recruited from Adolescent Medicine Clinic at hospital age: 16.9±1.7 y ill durn: 19.7± 13.1 mos rec durn: not specified</td>
<td>BMD at LSP, FN BMI &gt; 20 AND menstruating</td>
<td>no increase in LSP BMD in n=4 recovered (did not report on change in BMD in n=8 ill)</td>
<td></td>
</tr>
</tbody>
</table>
## APPENDIX C. (cont.)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
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<th>Outcome (bone measurement)</th>
<th>Definition of AN recovery</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herzog</strong>(^6) (1993)</td>
<td>cross-sectional (with control group)</td>
<td>n=28 recovered n=23 ill</td>
<td>consecutive patients treated previously at inpt ED program</td>
<td>BMD at LSP, radius (SDs from age-matched control group)</td>
<td>weight &lt; 15% deviation from expected AND menstruation</td>
<td>mean LSP SD: -0.26 in recovered group; -0.54 in group who were either menstrual or wt recovered but not both: -2.2 in ill group; mean radius SD: -0.68 in recovered; -1.7 in ill</td>
</tr>
<tr>
<td><strong>Rigotti</strong>(^8,9) (1991)</td>
<td>prospective F/U: 9-53 mos (median: 25 mos)</td>
<td>n=11 recovered n=16 ill</td>
<td>patients receiving treatment at outpt ED program</td>
<td>BMD at radius</td>
<td>attained weight ≥ 80% of ideal weight</td>
<td>no difference in change in BMD in those recovered vs ill; also no difference in subset of 6 who resumed menses and those who only regained weight</td>
</tr>
<tr>
<td><strong>Bachrach</strong>(^5) (1991)</td>
<td>cross-sectional (with control group)</td>
<td>n=9 recovered</td>
<td>recruitment: unclear</td>
<td>BMD at LSP, TB</td>
<td>BMI within 1 SD of of mean for healthy age-matched girls, and/or resumption of menses</td>
<td>mean LSP BMD not significantly different from control group; 3 of 9 patients had LSP BMD &gt; 2SD below normal for age</td>
</tr>
<tr>
<td><strong>Hay</strong>(^1,2,5) (1992)</td>
<td>cross-sectional (with control group)</td>
<td>n=21 recovered n=48 ill</td>
<td>participants were “selected from 110 consecutive outpatients”</td>
<td>single QCT of LSP</td>
<td>weight ≥ 85% of expected AND menstruation ≥ 6 mos</td>
<td>LSP lower than, but not significantly different from, controls</td>
</tr>
</tbody>
</table>
APPENDIX C. (cont).

<table>
<thead>
<tr>
<th>Reference</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treasure³ (1987)</td>
<td>cross-sectional (with control group)</td>
<td>n=25 recovered n=45 ill</td>
<td>recruitment: not described age: rec AN: 23-52 y ill AN: 14-53 y ill durn: not specified rec durn: not specified</td>
<td>BMD at LSP, FN, radius</td>
<td>not defined</td>
<td>BMD in recovered pts not significantly different from control group, at each skeletal site BMD in ill pts significantly lower than controls at each site</td>
</tr>
</tbody>
</table>

Abbreviations: F/U = follow-up; ED = eating disorder; AN = anorexia nervosa; BN = bulimia nervosa; EDNOS = eating disorder not otherwise specified; BMD = bone mineral density; OP = osteoporosis; LSP = lumbar spine; FN = femoral neck; TB = total body; BMI = body mass index; wt = weight; mos = months; y = years; durn = duration; inpt / outpt = inpatient / outpatient; pts = patients; u/k = unknown; SD = standard deviation; QCT = quantitative computer tomography
APPENDIX D

. Initial contact letter
. Screening form
Date

Dear

Re: A study of osteoporosis in young women

I am writing to you to let you know about an important research study that is being conducted to examine osteoporosis in women who may be at high risk of low bone mass due to their current or past medical history. This study is being done through the Osteoporosis Research Program at Women’s College Hospital, in collaboration with the Toronto General Hospital.

Certain medical illnesses can cause low bone mass, or osteoporosis. It is not known whether this decreased bone mass improves over time or whether the bone loss is permanent. Osteoporosis is associated with an increased risk of sustaining fractures, typically of the wrist, spine or hip. If bone loss is permanent, then the risk of fractures may increase even further in later life when bone density decreases after menopause.

The good news is that osteoporosis can be prevented and treated, but more research is needed to determine the best way to manage bone loss in young women with previous medical illnesses. The purpose of this research study is to identify key risk factors for osteoporosis in women who have suffered from medical illnesses and to determine whether the loss of bone is permanent. The results of this study will help determine whether long-term treatment of osteoporosis is required, and will also help identify those who are most at risk for low bone density so that treatment and preventative measures can be started at a stage in their illness when they may be the most beneficial.

In brief, this study will involve one visit to the Osteoporosis Research Program at the Women’s College Ambulatory Care Centre, where you will undergo bone density and body composition tests and complete an interview and questionnaires regarding your medical history, general risk factors for osteoporosis, physical activity level and calcium intake. This visit will take approximately 1.5 hours to complete.
We are contacting all women who have received medical treatment under my care at Toronto General Hospital between January 1, 1994 and December 31, 2003, to invite them to participate in this very important research. You will receive a telephone call from my research assistant in the next few weeks to discuss the project with you in more detail.

You are under no obligation to participate in this study. This study may benefit others with similar medical histories and provide you with personal information that you may find helpful. If you wish, you will be given educational information about osteoporosis and your family doctor will be sent your bone density results.

If you would like to contact the study coordinator at the Osteoporosis Research Program directly, please do not hesitate to do so. (Esther Waugh, XXX-XXX-XXXX), Email: _____. Also, please feel free to contact me if you have any questions or concerns. My contact information is provided below.

Thank you for taking the time to read this letter.

Warm regards,

D. Blake Woodside, MD, FRCP
Email: __________
Ph: XXX-XXX-XXXX
THE TORONTO ANOREXIA BONE STUDY

Screening Interview

Study ID# __________

Date of Interview: _____ / ____/ ____ (dd/mm/yy)

Screener: __________

AGE

1. How old are you? _____ yrs ≥ 40 years of age? ____ NO ____ YES

DISEASES

2. Have you ever been diagnosed with the following diseases?
   
   . Cancer that required chemotherapy ____ NO ____ YES
   
   . Rheumatoid arthritis ____ NO ____ YES
   
   . Bowel Disease (Crohn’s, ulcerative colitis, Celiac disease) ____ NO ____ YES
   
   . Hyperthyroidism (Grave’s disease) If yes, - ? untreated ____ NO ____ YES
      - if treated, are blood tests normal? ____ NO ____ YES
   
   . Cushing’s Disease ____ NO ____ YES
   
   . Addison’s Disease ____ NO ____ YES
   
   . Pituitary tumours ____ NO ____ YES

3. Have you ever been diagnosed with any other major illness? If yes, what? __________________________
   ____ NO ____ YES
MEDICATIONS

4. Have you ever taken steroids (orally or by IV) for at least 3 months? (e.g. prednisone, cortisone)  ____ NO  ____ YES

5. Have you ever used a puffer daily for at least 1 year?  ____ NO  ____ YES

6. Have you ever taken anti-convulsant medication for at least 3 months? (Dilantin, Tegretol)  ____ NO  ____ YES

7. Have you ever had heparin therapy for at least 1 year?  ____ NO  ____ YES

8. Have you ever had DepoProvera injections?  ____ NO  ____ YES
   . if yes, for how long?  _________ months

9. Have you ever taken hormones to treat endometriosis?  ____ NO  ____ YES
   . if yes, what type of hormones were you given?
   . oral contraceptive ........................................
   . DepoProvera..............................................
   . Other (Lupron, Danazol, Nafarelin, clomid, perganol, progesterone, HCG, Metrodin)
   . if other, were you given estrogen therapy within 3 months of starting treatment?  ____ NO  ____ YES

10. Have you ever taken hormones to treat infertility?  ____ NO  ____ YES
    . if yes, how long did you take them?  _____ months
    . List names, if known: ________________________
        ________________________

REPRODUCTIVE HISTORY

11. Are you currently pregnant, or have you been pregnant in the past 12 months?  ____ NO  ____ YES

12. Are you currently breastfeeding, or have you breastfed in the past 12 months?  ____ NO  ____ YES

13. Are you presently trying to conceive?  ____ NO  ____ YES

14. Have you had a hysterectomy (uterus removed?)  ____ NO  ____ YES

15. Have you had an oophorectomy (ovaries removed)?  ____ NO  ____ YES
    . if yes, were both ovaries removed?  ____ NO  ____ YES  ____ Don’t know

16. Have you experienced premature menopause? (either naturally or due to surgery?)  ____ NO  ____ YES
IS ELIGIBLE TO PARTICIPATE: _____ YES _____ NO _____ Unsure

COMMENTS:
______________________________________________________________________
______________________________________________________________________
______________________________________________________________________
______________________________________________________________________
______________________________________________________________________
______________________________________________________________________

NOTE:
1. Shaded answers indicate that participant is NOT eligible for the study
2. Other major illnesses that are ineligible: chronic liver disease, renal failure, Lupus
3. Oral contraceptive therapy IS permitted (oral, patch, or DepoProvera injection)
4. Hormone therapy for fertility treatment IS permitted
5. Medication to treat low bone mass IS permitted (eg. bisphosphonates)
6. If unsure if both ovaries removed, ask permission to check with surgeon. If unable to
   find out this information, then participant is NOT eligible for the study.
7. If trying to conceive, need to do BMD tests while participants have their periods or
   shortly thereafter to ensure they are not pregnant.
8. If UNSURE about eligibility, check with study coordinator or Dr. Gillian Hawker
APPENDIX E

Data Collection Forms/Interview

. Life History Calendar (LHC) Interview
  . calendar
  . interview: standardized prompts
  . summary form (LHC Adjunct Data Collection Form)

.Minnesota Leisure Time Physical Activity Survey

.Osteoporosis History and Treatment Questionnaire

.Calcium Food Frequency Questionnaire

.Telephone Interview Questionnaire (for non-participants)
## APPENDIX E.  Life History Calendar (LHC)

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APPENDIX E. Life History Calendar Interview

Standardized prompts and questions

Introduction
The purpose of this interview is to gather information about your eating disorder history as well as several lifestyle risk factors for osteoporosis.

To help you recall your past history, we are going to base the interview on a timeline/calendar.

Landmarks
We will start by identifying some important events in your life which will help you remember the history of your eating disorder.
- school grades
- graduation from high school or university / commencement of high school or university
- important birthdays, anniversaries
- employment (start new job)
- dating history
- wedding
- birth of child
- admissions to hospital for eating disorder (may include in next section)
  - when were you admitted and for how many weeks

A. History of eating disorder
The specific aspects of your eating disorder that we are interested in are your weight history and menstrual history. We would also like to know a little bit about any purging behaviours you may have engaged in.

Weight history (and onset of AN)
1) When did you first start having difficulties with eating?
2) Can you recall your weight at that time?
3) How old were you when you first severely restricted your food intake for at least 3 consecutive months because of an intense fear of becoming fat, and to influence your weight and shape?
   - did you have significant weight loss due to refusal to maintain weight?
   - how old were you when this happened? How much weight did you lose?
   - did you have feelings of fatness at this low weight / OR was your self-esteem dependent on thinness?
4) How old were you when you were first formally diagnosed with anorexia nervosa by a psychiatrist?
5) Now, let’s review your weight history since you first started having difficulties with eating until now. (can link this with admissions to hospital)
   Additional prompts:
   - what was your lowest weight since onset of your eating disorder?
   - how old were you at this time?
- what was your highest weight? How old were you at this time?
- (lowest / highest weight as adolescent and adult)
- weights at hospital admissions

* if they have not weighed themselves since recovery, ask:
  Do you think your weight has changed much since ____________ (eg. since released from the hospital / last known weight)
  Do your clothes fit the same. Are you the same size now?

**Height** (we also need to ask about height so we can calculate your BMI)
6) What is your current height?
7) What age were you when you first reached your current height?
8) Can you recall your height as an adolescent?

**Purging behaviours**
9) Have you ever made yourself vomit, or used laxitives or diuretics at least 1x/week for at least 3 consecutive months to control your weight or shape? How old were you when you first engaged in these behaviours?
10) If yes, which of these behaviours did you engage in?
11) If yes, also ask if had episodes of overeating (defined as loss of control and consuming a large amount of food)
   - did you have a sense of loss of control at the time?
   - could you have stopped eating once you started?
   - have them describe the amount of food and length of time to consume
12) Let’s review your use of these behaviours.
   - for each time period: ask if engaged in them at least 1x/week for at least 3 consecutive months
   * even if ‘recovered’, ask if continues to engage in purging behaviours (and ask about binging/episodes of overeating)

**Menstrual history** (link with reproductive hx and OCP use)
13) When did you first get your period? (age)
14) If secondary amenorrhea:
   - when did you first stop menstruating for 3 consecutive months?
   - did you have regular or irregular periods before then (irregular = < 8 periods in the previous year)
15) Have you ever resumed menstruation?
   - review time periods of menstruation and ask if regular / irregular

**Reproductive history** (link with menstrual hx and OCP use)
16) Have you ever been pregnant (including any miscarriages and abortions)?
17) If yes, review time periods when pregnant
18) Review time periods when breastfeeding
Use of oral contraceptives (link with menstrual and reproductive hx)
19) Have you ever used birth control (pill or patch)?
20) If yes, review time periods when using OCP.
21) If possible, can you remember the name of the birth control pill you were on? (for each time period)

B. Other Lifestyle factors

Now we are going to ask you about your smoking history and alcohol use as they may be associated with osteoporosis.

Smoking history
22) Have you ever smoked for >6 months?
23) If yes, at what age did you start smoking?
24) Review all time periods. During this time, how many cigarettes did you smoke per day, on average? (for each time period)

Alcohol use
25) Do you consume any alcoholic beverages?
26) If yes, how many drinks do you consume per week, on average? (includes wine, beer, cocktails)
27) How long has this been a typical pattern for you?
28) If this is not a typical pattern, let’s review your past history of alcohol use:
   - when did you start consuming alcohol?
   - how many drinks consumed per week, for each time period

REVIEW QUESTIONS ON ADJUNCT LHC DATA COLLECTION FORM TO ENSURE COMPLETENESS

Specifically:

- duration of time at lowest adolescent weight, lowest and highest adult weight
- duration of time pregnant and breastfeeding
- names of OCPs
- TGH and Homewood admissions: admission and discharge weights

- Is there any other information that you think might be relevant?

- Do you have any comments about this study?
APPENDIX E.

**TABS: Life History Calendar Interview**

**Adjunct Data Collection Form**

### WEIGHT HISTORY

1. **Age at onset of AN:** __________ yrs
   (age at which met the criteria for AN: 1. 3 consecutive months of severely restricting food intake +/- binge/purging so that weight fell below 85% of ideal 2. significant weight loss due to refusal to maintain weight 3. feelings of fatness at low weight OR self-esteem dependent on thinness 4. amenorrheic x 3 months – see menstrual history)

2. **Age at formal diagnosis of AN:** _______ yrs

3. **Sub-type of AN:** _____ restricting
   _____ restricting + binge/purge

4a. **Lowest adolescent weight:** __________ lbs _______ BMI

4b. **Age at lowest adolescent weight:** __________ yrs

4c. **Duration of time at lowest adolescent weight:** _______ weeks

5a. **Lowest adult weight:** __________ lbs _______ BMI

5b. **Age at lowest adult weight:** _______ yrs

5c. **Duration of time at lowest adult weight:** _______ weeks

6a. **Highest adult weight:** __________ lbs _______ BMI

6b. **Age at highest adult weight:** _______ yrs

6c. **Duration of time at highest adult weight:** _______ weeks

### PURGING BEHAVIOURS

7a. _____ 0. never engaged in purging behaviours (go to MENSTRUAL HISTORY)

7b. ____ 1. engaged in purging behaviours only (at least 1x/week for 3 mos)

7c. _____ 2. engaged in binging behaviours only 

7d. _____ 3. both binging + purge
7b. Type of purging: 
- vomiting  
- laxitives  
- diuretics  

7c. Duration of time engaged in purging behaviours: 
- vomiting _______ months  
- laxitives _______ months  
- diuretics _______ months  

7d. Total duration of time used purging behaviours: _______ months  

MENSTRUAL HISTORY

8. _______ 1. primary amenorrhea  
_______ 2. secondary amenorrhea  

9. Age at menarche: _________ yrs  (N/A: 88)  

10. Age at first amenorrhea x 3 months: _______ yrs  (N/A: 88)  

11. Duration of time amenorrheic (excl pregnancy): _________ yrs  (N/A: 88)  

12a. Duration of time regular menstruation: _______ yrs  
12b. Duration of time irregular menstruation: ______ yrs  
12c. Duration of time regular + irregular: _______ yrs  

HISTORY OF RECOVERY / RELAPSE

13a. Ever BMI recovered: ___ 0. No ___ 1. Yes (BMI ≥ 18.5 for 1+ years) If no: go to 14a.  
13b. Duration of time weight recovered _______ years  
13c. Age when first achieved BMI ≥ 18.5 for 1+ years: ______ years  
13d. Number of relapses: _________  
13e. Total duration of relapses: _______ years  

14a. _____ 0. never resumed spontaneous menstruation  
_____ 1. resumed spontaneous menstruation  
_____ 2. on OCP / never amenorrheic (if yes, then 14b, 15a, 16b, 17b, 17c N/A)  

14b. Ever Menstruation recovered: _____ 0. No _____ 1. Yes ____ N/A (mens ≥ 1 yr)  
14c. Duration of time menstruation recovered: _______ years  
14d. Age at first resumption of spontaneous menstruation for 1+ year: _____ yrs  

15a. Ever BMI-Menstruation recovered: _____ 0. No _____ 1. Yes ____ N/A (13a PLUS 14b)  
15b. Duration of time BMI-Menstruation recovered: _______ years  
15c. Age when first achieved BMI ≥ 18.5 PLUS menstruation for 1+ years: _____ yrs
16a. Duration of illness (weight only): ______ years  
(current age – age at onset – duration of time at BMI ≥ 18.5)

16b. Duration of illness (weight + menstruation): ______ years  (N/A: 88)  
(current age – age at onset – duration of time at BMI ≥ 18.5 PLUS menstruation)

17a. Current recovery status (weight only): _____ 0. never recovered  
_____ 1. currently relapsed  
_____ 2. recovered (BMI ≥ 18.5 for ≥ 1 yr)

17b. Current recovery status (menstruation only): _____ 0. never recovered  
_____ 1. currently relapsed  
_____ 2. recovered (mens ≥ 1 yr)  
_____ N/A

17c. Current recovery status (weight + mens): _____ 0. never recovered  
_____ 1. currently relapsed  
_____ 2. recovered (BMI ≥ 18.5+mens)  
_____ N/A

18a. Binge-purge recovery status (weight only): _____ 0. never recovered  
_____ 1. currently relapsed  
_____ 2. recovered with no B/P  
_____ 3. recovered with B/P

18b. _____ 0. BMI never ≥ 18.5 for ≥ 1 yr  
_____ 1. engaged in purging behaviours when BMI ≥ 18.5 for ≥ 1 yr  
_____ 2. NEVER engaged in purging behaviours when BMI ≥ 18.5 for ≥ 1 yr

REPRODUCTIVE HISTORY

19. Number of natural children: _______

20. Total # months pregnant: ____________ months

21. Total # months breastfeeding: ________ months

ORAL CONTRACEPTIVE USE

22a. Ever used OCP: _____ 0. No  (go to RELATIVE ESTROGEN EXPOSURE)  
_____ 1. Yes

22b. Used OCP before 18 yoa: _____ 0. No  
_____ 1. Yes
22c. Total # months on OCP: __________ months

22d. List names of OCPs: __________________          duration _______ months
__________________          duration _______ months
__________________          duration _______ months
__________________          duration _______ months

RELATIVE ESTROGEN EXPOSURE

23. Relative estrogen exposure ________ %

Formula:

\[
\text{Relative Estrogen Exposure} = \left( \frac{\# \text{ months menstruation incl. OCP use} + \# \text{ months pregnant} + \# \text{ months breastfeeding}}{12} \right) \times 100
\]

TGH and Homewood ADMISSION HISTORY

24. _______ 1. inpatient
     _______ 2. outpatient (ambulatory care) (go to QUESTION 26)
     _______ 3. both

25. Inpatient program: number of admissions: ____________

   Admission #1 weight: ___ lbs  Discharge #1 weight: _____ lbs  TGH/HHC
   Admission #2 weight: ___ lbs  Discharge #2 weight: _____ lbs  TGH/HHC
   Admission #3 weight: ___ lbs  Discharge #3 weight: _____ lbs  TGH/HHC
   Admission #4 weight: ___ lbs  Discharge #4 weight: _____ lbs  TGH/HHC
   Admission #5 weight: ___ lbs  Discharge #5 weight: _____ lbs  TGH/HHC
   Admission #6 weight: ___ lbs  Discharge #6 weight: _____ lbs  TGH/HHC

26. Outpatient program: number of admissions: ____________
SMOKING HISTORY

27a. _____ 0. never smoked (go to ALCOHOL USE)
      _____ 1. past smoker
      _____ 2. current smoker

27b.  Total # years smoked: __________ years

27c.  Total # of cigarettes over lifetime / 1000: ________

ALCOHOL USE

28a. _____ 0. NO, never consumed alcohol (questionnaire is completed)
      _____ 1. YES, has consumed alcohol

28b.  Total # years consumed alcohol: __________ years

28c.  Average total # of drinks per week: ________ / week

28d.  Total # drinks over lifetime / 1000: ________

Any other information that you think might be relevant?
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________

Any comments regarding this study?
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
**APPENDIX E**

**MINNESOTA LEISURE TIME PHYSICAL ACTIVITY SURVEY**

<table>
<thead>
<tr>
<th>Past Year</th>
<th>_______ # years</th>
<th>(of similar physical activity)</th>
<th>Stage of illness: ill / recovered / stable / before ill</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical year 1</td>
<td>_______ # years</td>
<td>(of similar physical activity)</td>
<td></td>
</tr>
<tr>
<td>Typical year 2</td>
<td>_______ # years</td>
<td>(of similar physical activity)</td>
<td></td>
</tr>
<tr>
<td>Typical year 3</td>
<td>_______ # years</td>
<td>(of similar physical activity)</td>
<td></td>
</tr>
<tr>
<td>Typical year 4</td>
<td>_______ # years</td>
<td>(of similar physical activity)</td>
<td></td>
</tr>
<tr>
<td>Typical year 5</td>
<td>_______ # years</td>
<td>(of similar physical activity)</td>
<td></td>
</tr>
</tbody>
</table>

**LIST OF ACTIVITIES**

<table>
<thead>
<tr>
<th>_______</th>
<th>_______</th>
<th>_______</th>
<th>_______</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hi-impact aerobics class</td>
<td>Golf</td>
<td>Squash</td>
<td>Swimming</td>
</tr>
<tr>
<td>Lo-impact aerobics class</td>
<td>Gymnastics</td>
<td>Tennis</td>
<td>Volleyball (regular / beach)</td>
</tr>
<tr>
<td>Baseball / softball</td>
<td>Hiking</td>
<td>Waterskiing</td>
<td></td>
</tr>
<tr>
<td>Basketball</td>
<td>Hockey (ice / field)</td>
<td>Weight training</td>
<td></td>
</tr>
<tr>
<td>Boxing / Kickboxing</td>
<td>Inline or ice skating</td>
<td>Walking</td>
<td></td>
</tr>
<tr>
<td>Climbing (indoor / outdoor)</td>
<td>Figure skating</td>
<td>Yoga</td>
<td></td>
</tr>
<tr>
<td>Canoeing / Kayaking</td>
<td>Pilates</td>
<td>Dance class</td>
<td></td>
</tr>
<tr>
<td>Cross-country skiing</td>
<td>Running</td>
<td>Specify types:</td>
<td></td>
</tr>
<tr>
<td>Cycling (outdoor / spinning / stationary)</td>
<td>Snowboarding / downhill skiing</td>
<td>Dance class</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soccer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other (specify):

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

185
List each activity that was checked off, in the box below. Check the months each activity was performed and determine the amount of time spent participating in each activity (days per week and minutes per day).

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>Jun</th>
<th>Jul</th>
<th>Aug</th>
<th>Sep</th>
<th>Oct</th>
<th>Nov</th>
<th>Dec</th>
<th>Days per week</th>
<th>Minutes per day</th>
<th>MET code</th>
<th>Bone loading code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>
CALCULATIONS:

A) Number of hours / week for each bone loading category:

0. Non or low-impact exercise: ________ hrs / week
1. Moderate impact exercise: ________ hrs / week
2. High impact exercise: ________ hrs / week
3. Weight training exercise: ________ hrs / week

Total hours of exercise: ________ hrs / week

**Formula:** \[
\frac{[(# \text{ months/year}) \times (4.2) \times (# \text{ days/week}) \times (# \text{ minutes/day})]}{60} \times \frac{1}{52} \text{ weeks} = \text{ hours / week}
\]

B) Number of Activity Metabolic Index (AMI) units / week, for each intensity category:

Light AMI (METs ≤ 4.0): ________ AMI / week
Moderate AMI (METs 4.5 – 5.5): ________ AMI / week
Heavy AMI (METs ≥ 6.0): ________ AMI / week

Total AMI: ________ AMI / week

**Formula:** \[
\frac{[(\text{MET intensity code}) \times (# \text{ months/year}) \times (4.2) \times (# \text{ days/week}) \times (# \text{ minutes/day})]}{52} \text{ weeks} = \text{ AMI units /week}
\]
Osteoporosis: History and Treatment Questionnaire

INTERVIEWER: ________________________________

BACKGROUND INFORMATION

1. Study ID: ____________
2. Visit Date: _______/_____/_____ (dd/mm/yy)
3. Date of Birth: _____/_____/_______ (dd/mm/yyyy) Age: ______ years
4. Current marital status:
   ___ 1. Single
   ___ 2. Married
   ___ 3. Widowed
   ___ 4. Separated
   ___ 5. Divorced
   ___ 6. Common-law
   ___ 7. Other

5. Highest level of education
   ___ 1. High-school diploma
   ___ 2. College or university undergraduate degree
   ___ 3. Post-graduate degree
   ___ 4. Other: (state) ________________________________

6. Ethnic background:
   ___ 1. Caucasian (includes East Indian, East Asian, Arabic)
   ___ 2. Asian (includes Chinese, Korean, Japanese, Malaysian, Filipino)
   ___ 3. African-American
   ___ 4. Hispanic
   ___ 5. Multi-racial (Mother _____________ Father _____________)
   ___ 6. Other: (state) ________________________________

OSTEOPOROSIS HISTORY

7a. Have you ever had a bone density test?   ___ 0. NO   ___ 1. YES

  If NO, go to Question 8.
  If YES, please continue.
7b. i) How many bone density tests have you had? _______

ii) What was the date of your last bone density test? ___ /___/____ (dd/mm/yy)

iii) Were you diagnosed with having low bone density?       ___ 0. NO
                                                    ___ 1. YES
                                                    ___ 2. Unsure

iv) Who referred you for your first bone density test?
     _____ 1. family doctor
     _____ 2. specialist    Please state: (eg. rheumatologist, psychiatrist)

v) Have you received treatment specifically for osteoporosis? ___0. NO ___ 1.YES

If YES, what treatment(s) did you receive? Check all that apply. Indicate type and duration of medication use where indicated.

   ___ 1. medications

   If yes, did you take these medications before age 18? _____ 0. No _____ 1. Yes

<table>
<thead>
<tr>
<th>Name of medication</th>
<th>Type of medication (circle one)</th>
<th>Duration of time on each medication (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Bisphosphonate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Oral contraceptive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Hormone therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>_______ months</td>
</tr>
</tbody>
</table>

|                    | 1. Bisphosphonate               |                                            |
|                    | 2. Oral contraceptive          |                                            |
|                    | 3. Hormone therapy             |                                            |
|                    | 4. Other                        |                                            |
|                    |                                 |    _______ months                         |

|                    | 1. Bisphosphonate               |                                            |
|                    | 2. Oral contraceptive          |                                            |
|                    | 3. Hormone therapy             |                                            |
|                    | 4. Other                        |                                            |
|                    |                                 |    _______ months                         |

   ___ 2. calcium supplementation

   ___ 3. Vitamin D supplementation

   ___ 4. Exercises (general instruction or specific prescription)

   ___ 5. Other: (state) ____________________________________________

______________________________________________________________________
7c. In general, as a result of having a bone density test, would you say that you have made specific lifestyle changes?
   ___ 0. NO
   ___ 1. YES. Please describe
   ____________________________________________________________________
   ____________________________________________________________________
   ____________________________________________________________________
   ____________________________________________________________________

8. Have you ever had any fractures / broken bones?
   ___ 0. NO
   ___ 1. YES
   If YES, please complete the following table:

<table>
<thead>
<tr>
<th>Age when fracture occurred</th>
<th>Site of fracture</th>
<th>How it occurred:</th>
<th>Office use only (LT, HT, SF) do not complete</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

9a. To your knowledge, have any of your family members ever been diagnosed with osteoporosis?
   ___ 0. I am adopted. **Go to question 10.**
   ___ 1. NO
   ___ 2. YES If YES, whom? Check all that apply.
   ___ 1. Mother
   ___ 2. Father
   ___ 3. Sister(s): # diagnosed ________
   ___ 4. Brother(s): # diagnosed ________
   ___ 5. Maternal relatives (grandparents, aunts, uncles, first cousins)
       # diagnosed ________
   ___ 6. Paternal relatives (grandparents, aunts, uncles, first cousins)
       # diagnosed ________
9b. Have any of your family members (NOT already checked off in the previous question) ever had a wrist fracture, hip fracture or spinal fracture after the age of 50?

___ 0. NO
___ 1. YES If YES, please complete the following table:

<table>
<thead>
<tr>
<th>Relative</th>
<th>Age</th>
<th>Site of fracture</th>
<th>How it occurred:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
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<td></td>
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<tr>
<td>3.</td>
<td></td>
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<td></td>
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<tr>
<td>4.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CALCIUM and VITAMIN D SUPPLEMENTATION**

10. Are you currently taking Calcium and/or Vitamin D supplements? (This includes those taken as part of a multivitamin tablet). Indicate duration of use and usual brand.

___ NO – you have completed the questionnaire

___ Yes, Calcium supplements duration of use: ________ months

___ Yes, Vitamin D supplements duration of use: ________ months

If YES, which brand of supplements do you usually take, and much do you take per day

Usual brand of calcium supplement / multivitamin: __________________________
__________________________ mg calcium per day

Usual brand of Vitamin D supplement / multivitamin: _________________________
___________________________ IU Vit D per day
THE TORONTO ANOREXIA BONE STUDY
DIET QUESTIONNAIRE for CALCIUM INTAKE

STUDY ID#: _____________________                INTERVIEWER: ____________________

INSTRUCTIONS:

1. The following table includes food items which may or may not be a regular part of your diet.

2. Please circle YES or NO in the left column to indicate if you consume the specified food item approximately once a month or more.

3. Remember to consider your complete diet, including ready-made, take-out, and restaurant meals.

4. Remember to include canned and frozen products.

5. If you are not sure how to answer, please leave the item blank. The interviewer will review this with you.

6. Only refer to the food item and complete the YES or NO column of the questionnaire. The serving sizes and other shaded sections will be completed during your interview. Please see the examples below.

LEFT COLUMN

<table>
<thead>
<tr>
<th>Circle Yes or No</th>
<th>Food Item</th>
<th>Serving Size</th>
<th>Office Space</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day</td>
<td>Week</td>
</tr>
<tr>
<td>Yes No</td>
<td>potato chips</td>
<td>LEAVE BLANK</td>
<td>LEAVE BLANK</td>
</tr>
<tr>
<td>Yes No</td>
<td>grapefruit</td>
<td>LEAVE BLANK</td>
<td>LEAVE BLANK</td>
</tr>
</tbody>
</table>

ie. If you eat potato chips approximately once a month or more, circle yes in the left column.

ie. If you do not eat grapefruit approximately once a month or more, circle no in the left column.
Do you eat the following food items approximately once a month or more? Circle yes or no in the left column.

<table>
<thead>
<tr>
<th>Circle Yes or No</th>
<th>Food Item</th>
<th>Serving Size</th>
<th>Day (30.4)</th>
<th>Week (4.3)</th>
<th>Month (1.0)</th>
<th>Total per month</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILK as beverage, in coffee/tea, and in cereal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes No</td>
<td>skim, 1%, 2%, homo, buttermilk, goat, chocolate milk, lactose reduced, cream (half-half; full)</td>
<td>1 cup</td>
<td>193</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes No</td>
<td>evaporated</td>
<td>½ cup</td>
<td>360</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes No</td>
<td>condensed</td>
<td>½ cup</td>
<td>435</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes No</td>
<td>powdered</td>
<td>1 tbsp</td>
<td>60</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>MILK in products</td>
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</tr>
<tr>
<td>Yes No</td>
<td>custard</td>
<td>½ cup</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes No</td>
<td>pudding (rice, instant, ready to eat)</td>
<td>½ cup</td>
<td>Rice – 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes No</td>
<td>soup (not broth)</td>
<td>1 cup</td>
<td>Oth - 150</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes No</td>
<td>milkshake</td>
<td>1.5 cups/12 oz</td>
<td>180</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes No</td>
<td>other: please specify</td>
<td></td>
<td>450</td>
<td></td>
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<tr>
<td>CHEESE</td>
<td></td>
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<tr>
<td>Yes No</td>
<td>FIRM CHEESE: brick, cheddar, swiss, mozzarella, etc.</td>
<td>1 oz</td>
<td>210</td>
<td></td>
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</tr>
<tr>
<td>Yes No</td>
<td>SOFT CHEESE: blue, camembert, feta</td>
<td>1 oz</td>
<td>145</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes No</td>
<td>cottage cheese</td>
<td>½ cup</td>
<td>275</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/No</td>
<td>Description</td>
<td>Amount</td>
<td>Calories</td>
<td></td>
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<td></td>
<td>ricotta cheese</td>
<td>½ cup</td>
<td>330</td>
<td></td>
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<tr>
<td></td>
<td>PROCESSED CHEESE SLICES</td>
<td>1 slice</td>
<td>125</td>
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<tr>
<td></td>
<td>GOAT CHEESE: (soft, semi-soft, firm)</td>
<td>1 oz</td>
<td>40 / 85 / 254</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>GRATED CHEESE: parmesan, romano</td>
<td>1 tbsp</td>
<td>55</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>CREAM CHEESE: (regular, light)</td>
<td>1 tbsp</td>
<td>Reg – 12 Light - 29</td>
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<td></td>
<td>CREAM CHEESE: (regular, light)</td>
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<td></td>
<td>MACARONI &amp; CHEESE (from mix, homemade)</td>
<td>½ cup</td>
<td>92</td>
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<tr>
<td></td>
<td>PIZZA, CHEESE TOPPING</td>
<td>1 slice</td>
<td>Chz - 120 Other - 65</td>
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<tr>
<td></td>
<td>CHEESE-FILLED RAVIOLI/TORTELLINI</td>
<td>½ cup</td>
<td>75</td>
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<td>OTHER: (Please specify)</td>
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<tr>
<td></td>
<td>YOGURT plain/ flavoured (regular, reduced fat)</td>
<td>1 container</td>
<td>Reg 264 Light 320</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FROZEN fruit-bottom (regular, reduced fat)</td>
<td>1 container</td>
<td>Reg 214 Light 281</td>
<td></td>
<td></td>
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<td></td>
<td>FROZEN (regular, non-fat)</td>
<td>½ cup</td>
<td>Reg 104 Light 150</td>
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<td>92</td>
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<td></td>
<td>ICE CREAM reduced fat</td>
<td>½ cup</td>
<td>115</td>
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<td>Yes</td>
<td>No</td>
<td>Kellogg's All Bran</td>
<td>General Mills Cheerios</td>
<td>Quaker Harvest Crunch, regular</td>
<td>Bread, bagel (any type)</td>
<td>English muffin (regular, whole wheat)</td>
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<td>Yes</td>
<td>No</td>
<td>1 bowl / ½ cup</td>
<td>1 bowl / ½ cup</td>
<td>1 bowl / ½ cup</td>
<td>1 slice / 4” bagel</td>
<td>1 muffin</td>
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<td>30</td>
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<td>1/3 cup cooked</td>
<td>1/3 c. cooked</td>
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<td>45</td>
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<th>No</th>
<th>turnip, beet greens</th>
<th>dandelion greens</th>
<th>bok choy, swiss chard, okra</th>
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<td>1/2 cup cooked</td>
<td>1/2 cup cooked</td>
<td>½ cup cooked</td>
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<th>Tomato sauce</th>
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<td></td>
<td></td>
<td></td>
<td>½ cup</td>
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</tr>
<tr>
<td>FRUIT</td>
<td></td>
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<td>Yes</td>
<td>No</td>
<td>Figs (Fig Newtons)</td>
<td>2 dried</td>
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<td>Yes</td>
<td>No</td>
<td>oranges / tangerines</td>
<td>1 medium</td>
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<th>JUICES / BEVERAGES</th>
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<td>Yes</td>
<td>No</td>
<td>Orange juice (calcium fortified; not fortified)</td>
<td>1 cup</td>
<td>Fort 300 Reg 20</td>
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<tr>
<td>Yes</td>
<td>No</td>
<td>Rice beverage (calcium fortified) Name: ____________</td>
<td>1 cup</td>
<td>300</td>
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TOTAL CALCIUM (mg): _______ month (divided by 30.4) _______ day

FOR OFFICE USE ONLY - DO NOT COMPLETE
ADDITIONAL COMMENTS from the QUESTIONNAIRE

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APPENDIX E.

TABS: Telephone Interview
Data Collection Form

_____________________________________________________________________

Study ID#: _______
Date of interview: ______ / _____/ _____  (dd/mm/yy)
Interviewer: _______________________

_____________________________________________________________________

A. DIAGNOSIS
1. At what age were you diagnosed with AN? _______ years old

2. In addition to restricting your diet, did you ever purge regularly? ____NO ____ YES (3x/week for at least 3 months)

B. ADMISSION HISTORY
3. How many admissions have you had to TGH/Homewood programs?
   TGH Inpatient: ________ admissions
   TGH Outpatient: ________ admissions
   Homewood: ________ admissions

   When was your last admission? _____ year

C. WEIGHT HISTORY
4. What was your lowest weight since diagnosis? ______ lbs

5. What was your highest weight since diagnosis? ______ lbs (excluding pregnancy weight)

6. What is your current weight? ______ lbs For how long? ______ months

7. What is your current height? ______ ft ______ inches
D. MENSTRUAL HISTORY

8. At what age did you start menstruating? ______ years old

9. Have you ever stopped menstruating for more than 3 months? ____ NO ____ YES
   . If yes:
      . At what age? _____ years old
      . For how long in total? ______ years

10. Are you currently menstruating? _____ NO _____ YES
    . If yes:
      . For how long? _____ years

E. REPRODUCTIVE HISTORY

11. Have you ever used oral contraceptive pills? _____ NO _____ YES
    (for at least 1 year)

    Are you currently on an OCP? _____ NO ____ YES

12. Do you have any children? _____ NO _____ YES
    . If yes: how many? _____

F. EXERCISE

13. Do you currently exercise: _____ NO _____ YES
    . If yes: How many hours per week? ______ hours

14. Approximately how many hours per week did you exercise as a teenager?
    _____ not at all
    _____ 1-3 hrs/week
    _____ 4-6 hrs/week
    _____ 6-9 hrs/week
    _____ 10+ hrs/week

15. Approximately how many hours per week did you exercise as a child?
    _____ not at all
    _____ 1-3 hrs/week
    _____ 4-6 hrs/week
    _____ 6-9 hrs/week
    _____ 10+ hrs/week