The growth and development of children with prepubertal and pubertal eating disorders
Cross sectional and longitudinal findings and their interpretation

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Abstract

Eating disorders are characterised by grossly disordered or chaotic eating behaviour. Nutritional compromise varies from extreme selectivity to severe malnourishment. During childhood, growth and development can be affected, some studies suggest permanently. Previously patient numbers have been limited, poor reference data used or growth parameters have not been taken into account when drawing conclusions about physical outcome for eating disorders in prepubertal and pubertal children.

We studied consecutive cases referred to a specialist eating disorders service for children aged 7 to 16 years. Cross sectional (n=206) and longitudinal (n=126) data included anthropometry, body composition, bone density, and onset or resumption of menses. Findings were compared to normal children through a database designed to calculate age and gender matched scores from reference tables.

The findings can be described in four categories. Firstly, in children who were malnourished, stature was significantly lower than age matched norms. Short stature was largely due to reduced spine length, and when adjusted for bone age was no longer evident, suggesting growth delay rather than stunting. Longitudinal data confirmed that ED subjects grew normally when adjusted for developmental stage, and those who had completed growth had a mean height on the 50th centile. Secondly, principal components analysis for anthropometry showed a specific deficit in fat mass in malnourished subjects, although an equivalent relative loss of lean mass was seen when growth parameters are taken into account. Thirdly, methods for adjusting bone density measurements for bone size were compared. Calculating volumetric bone density allows the impact of malnutrition to be evaluated. Finally, pre and postmenarcheal ED subjects were compared with control girls in terms of onset or resumption of menses. Both groups menstruated at weights normally distributed around 0 BMI SDS, but BMI at menses was age dependent.
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## Abbreviations

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<th>Description</th>
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<tbody>
<tr>
<td>AN</td>
<td>anorexia nervosa</td>
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<tr>
<td>BN</td>
<td>bulimia nervosa</td>
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<tr>
<td>EDNOS</td>
<td>eating disorder not otherwise specified</td>
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<tr>
<td>SE</td>
<td>selective eating</td>
</tr>
<tr>
<td>FAED</td>
<td>food avoidance emotional disorder</td>
</tr>
<tr>
<td>OCD</td>
<td>obsessive compulsive disorder</td>
</tr>
<tr>
<td>DSM IV</td>
<td>diagnostic and statistical manual of mental disorders - version IV</td>
</tr>
<tr>
<td>ED</td>
<td>eating disorder</td>
</tr>
<tr>
<td>EDT</td>
<td>eating disorders team</td>
</tr>
<tr>
<td>EDE</td>
<td>eating disorders examination</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>SDS</td>
<td>standard deviation score</td>
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<tr>
<td>SFT</td>
<td>skinfold thickness</td>
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<tr>
<td>MUAC</td>
<td>mid upper arm circumference</td>
</tr>
<tr>
<td>DXA</td>
<td>dual energy x-ray absorptiometry</td>
</tr>
<tr>
<td>QCT</td>
<td>quantitative computed tomography</td>
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<tr>
<td>BMD</td>
<td>bone mineral density</td>
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<tr>
<td>aBMD</td>
<td>areal bone mineral density</td>
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<tr>
<td>vBMD</td>
<td>volumetric bone mineral density</td>
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<tr>
<td>BMC</td>
<td>bone mineral content</td>
</tr>
<tr>
<td>BA</td>
<td>bone area</td>
</tr>
<tr>
<td>PBM</td>
<td>peak bone mass</td>
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<tr>
<td>FM</td>
<td>fat mass</td>
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<tr>
<td>FFM</td>
<td>fat free mass</td>
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<tr>
<td>HV</td>
<td>height velocity</td>
</tr>
<tr>
<td>PHV</td>
<td>peak height velocity</td>
</tr>
<tr>
<td>ROM</td>
<td>resumption of menses</td>
</tr>
<tr>
<td>GH</td>
<td>growth hormone</td>
</tr>
<tr>
<td>LH</td>
<td>luteinising hormone</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle stimulating hormone</td>
</tr>
<tr>
<td>IGF-1</td>
<td>insulin-like growth factor</td>
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1. Growth And Development In Early Onset Eating Disorders: a review of the literature

1.1. Introduction

The aim of this thesis is to examine the physical impact of early onset eating disorders, and through this explore the concept of middle childhood (ages 6 to 11) and the peripubertal years (ages 11 to 16) as critical periods for growth and development. The eating difficulties under consideration are all associated with significant abnormalities in nutritional intake or status, the most extreme in terms of physical complications being protein calorie malnutrition. However undernutrition is not the only means by which health may be compromised. Some of the complications of eating disorders are due to lack of energy, some to metabolic disturbance, and some to endocrine disturbance. Some are potentially life threatening, whilst others are associated with long term compromise of health. This study focuses on those medical aspects that are unique to younger patients, namely growth retardation, pubertal delay or arrest, alteration in body composition and reduction of peak bone mass. Previous studies and case reports have suggested that illness with onset in early puberty is likely to have a more profound impact on growth and development than illness with later onset (Bachrach 1993; Joughin et al. 1992; Pugliese et al. 1983; Russell 1983; Russell 1985). These observations are reviewed in detail below.

This review of the literature covers the following areas: the range of eating problems presenting in middle childhood and around puberty; theoretical concepts and findings from the literature on the impact of eating disorders on growth, pubertal development and menstrual function; and the impact of eating disorders on bone density and its measurement in childhood. The measurement of body composition in childhood and adolescence together with findings from body composition studies in adolescents and adult eating disorder patients are reviewed in chapter 2.
1.2. **Eating disorders in children and adolescents**

An overview of eating disorders and their defining characteristics is given, together with a consideration of these concepts to children and young adolescents. Descriptive terms used for the range of eating behaviours seen in the early onset population are introduced.

1.2.1. **Core concepts**

'Eating disorder' is perhaps a misnomer for the severe disturbances of mood, self esteem, cognition, social functioning and eating related behaviour encompassed by the term. Nevertheless it is the intense preoccupation with weight and shape, and the food related behaviours that distinguish the eating disorders from other mental disorders. The best defined and characterised are anorexia nervosa (AN) and bulimia nervosa (BN). The female gender is used to describe these disorders because of the overwhelming preponderance of female sufferers (8 to 10 times relative risk female to male).

Compared to knowledge of adult eating disorders, that of childhood and adolescent eating disorders is in its infancy. A developmental framework within which to integrate sociocultural, biogenetic, personality, family and behavioural studies remains lacking. Consequently, early onset patients must still be seen as a special group rather than part of a developmental continuum, with continuing uncertainty about whether they constitute a distinct population or 'more of the same' in terms of risk factors and predisposition. The available research suggests the latter (Arnow, Sanders, & Steiner 1999; Gowers et al. 1991; Jacobs & Isaacs 1986) i.e. that differences between premenarcheal and postmenarcheal AN are attributable to developmental differences in the expression rather than nature of the disorders. This supports the view from clinical experience.
Population studies in eating disorders are rare for a number of reasons, including poor prediction and low disclosure rates, and although a number of population based studies exist (e.g. Fairburn et al. 1997) by the far the majority of the eating disorders literature is based on clinical populations. Studies of premenarcheal cases remain limited in number and power and are mostly case series often studied retrospectively.

Knowledge in this area is further limited by the fact that AN is a disorder of low incidence but high prevalence, with chronicity leading to cumulating numbers with age. For example, the total population incidence of AN is near to 0.1%, while in very highest risk samples such as 13-18 year old female ballet dancers, AN has an incidence of around 1% (Crisp, Palmer, & Kalucy 1976). On the other hand one study found AN to be the 3rd commonest chronic illness of adolescence in terms of prevalence, after obesity and asthma (Lucas et al. 1991), and recent data show that AN is the commonest diagnosis in adolescent inpatient child and adolescent psychiatric inpatients units in the UK, accounting for 20.2% of the total inpatient population on census day (Department of Health 2001). Of these, 12 cases (9.8%) were under the age of 13: eight were age 12, two age 11, one age 10 and one age 5.

Most of the morbidity is therefore seen in late teens and early adulthood, despite a peak age of onset at around 14.5-15 years of age (Halmi 1985; Strober, Freeman, & Morrell 1997). Large cohorts of early onset patients are rare, and direct comparisons between studies can be difficult to make, in part as a result of differences in use of terminology. Early onset patients have been considered those with an onset at less than 16 years of age (Fosson et al. 1987); patients who are prepubertal (Jacobs & Isaacs 1986); and those who are premenarcheal (Gowers, Crisp, Joughin, & Bhat 1991; Treasure & Thompson 1988). The term, ‘prepubertal’ is even less useful, since puberty is a continuous process occurring anywhere from about age 8 up until age 16, or later if it is lengthened by the process of illness. ‘Premenarcheal’ has the disadvantage of being meaningless in boys. From a biological point of view however, it
does make sense to distinguish those issues specific to children and adolescents who have not yet completed growth and pubertal maturation from those who have. In the absence of an adequate terminology, the term premenarcheal will be used for this group, since menarche is a late pubertal event and the majority of our patients are girls. Where relevant boys are described in terms of their developmental stage.

Eating disorders/disturbance can be understood as the presence of disturbed, disordered or unusual eating behaviour associated with one or more of the following: specific psychological or developmental problems; negative effects on the child’s growth, development and/or physical health; negative effects on the child’s general development and/or family functioning. Presenting features causing concern can be thought of within the following domains:

- **Physical:**
  Concerns may be about significant changes in weight, either weight loss or weight gain; about single low or high weight measurements (e.g. lying outside the 3rd or 97th centile for age); failure to gain weight or height appropriately for age and stage of development; and delayed or disrupted puberty, especially failure of menarche to occur.

- **Behavioural:**
  Food intake may be limited, either in quantity (energy intake) or in range (nutrient intake); food intake may be excessive, irregular or chaotic; or eating difficulties may manifest as mealtime conflicts such as can result from inability to accommodate normal variations in eating patterns and dietary content.

- **Emotional:**
  Problem eating behaviours are commonly associated with emotional symptoms such as depression, mood swings and anxiety (including panic attacks).
Problem eating behaviours can go hand in hand with increasing social isolation and withdrawal, and a reluctance to engage in peer activities.

Once the eating difficulty is identified, the problem of applying current diagnostic criteria to children remains. A fairly consistent finding is that a significant number of those children presenting with severe eating problems do not fit diagnostic criteria (e.g. Nicholls, Chater, & Lask 2000). In fact this is not much different from the reported figures for adult specialist clinic samples (Clinton & Glant 1992). Recent study of the nosology of eating difficulties in middle childhood (Cooper et al. 2001), together with increasing sophistication of measures of childhood eating psychopathology (Bryant-Waugh et al. 1996a), have enabled specific psychological subgroups to be better identified and defined. The difficulties with applying the physical criteria are considered further below (section 1.2.2). Within the group of children who lose weight, having previously been normal weight, there a number of psychological mechanisms that are useful to distinguish for the purposes of assessing contributing factors and determining treatment needs. For the purposes of clarity, they are grouped them here on the basis of their related underlying psychopathology, as closely allied as possible to the classification of general mental disorders. It should be emphasised that, apart from AN and BN, these do not constitute validated diagnostic groups, but are merely descriptive terms that we have found useful in conceptualising and treating childhood eating difficulties.

I. Eating disorders.

True eating disorders do present in children as young as seven years old. True eating disorders in this context means disorders characterised by grossly disordered or chaotic eating behaviour associated with morbid preoccupation with body weight and shape.
AN is one of the most reliably diagnosed psychiatric disorders in adolescence (McCabe et al. 1996). Failure to recognise the disorder in younger patients is likely to be the result of failure to expect the disorder in younger subjects, rather than to complexity in the diagnosis (Bryant-Waugh et al. 1992). The same could be said of making the diagnosis in boys. For both it is of course necessary to bear in mind differences that are accounted for by age and gender. Overall, the clinical presentation is similar to presentation in adults. Nevertheless, important differences in presentation merit attention, reflecting these developmental differences.

Common weight control behaviours in children include restricted food intake, restraint around eating behaviour, excessive exercising and self-induced vomiting. Compensatory behaviours such as laxative or diuretic misuse are less common in this age group, as are those features characteristic of the binge-purge subtype of AN. Other common features of AN in children include preoccupation with food, eating and calories, a distorted view of 'normal' amount of food, guilt associated with eating, increased interest in food preparation and recipes, concern about eating in front of others and low self esteem. AN in boys may be characterised by concern around fitness and health, dietary restriction related to 'healthy' diet (e.g. re heart disease), and shape more important than weight. Excessive exercising is very common and there is a strong association with obsessive-compulsive disorder (Shafran et al. 1995).

I.i. Bulimia nervosa

BN tends to be very unusual indeed in children below 12, although premenarcheal BN has been reported in the literature (Kent, Lacey, & McCluskey 1992). As for AN, clinical presentation is similar to that in adults and weight control behaviours similar to those in AN, although with more laxative abuse (probably related to slightly older age). Most bulimic children engage in bingeing with compensatory vomiting. BN is often
associated with ‘teenage’ problems, such as underage drinking, smoking, sexual activity, etc. Depression and self-harm are often a feature.

II. Somatisation disorders

II.i. Food avoidance emotional disorder

In 1989 Higgs et al. (Higgs, Goodyer, & Birch 1989) conducted a case controlled study distinguishing childhood AN from other types of eating difficulties presenting to clinicians in an age matched population. They coined the term ‘food avoidance emotional disorder’ (FAED) to encompass a wide range of other eating difficulties in which the unifying feature was the avoidance of food for primarily psychological reasons. This included avoidance of quantity AND range of food, and no subdivision was made on the basis of reasons for avoidance. Over the years Lask and Bryant-Waugh (Lask & Bryant-Waugh 2000) have used and adapted the term FAED, restricting it to children who avoid food that results in weight loss (table 1.1). This use of the term thus excludes children who are chronically low in weight (restrictive eaters or failure to thrive), and those in whom the range of foods eaten is limited but weight is not generally compromised (see ‘selective eating’ below).

Children with FAED are, on average, younger than those with early onset AN at presentation, with less female:male bias. Psychologically the differences are more marked. Unlike AN patients, children with FAED know that they are underweight, would like to be heavier, and may not know why they find this difficult to achieve. They are more likely to have other medically unexplained symptoms, and their parents may attribute weight loss to an undiagnosed physical disorder. It is for this reason that we have linked FAED to somatisation, although think it unsatisfactory as a classification category. FAED sufferers are also more likely than AN sufferers to show generalised anxiety, unrelated to food. It is likely that children with FAED are a heterogeneous group of children, a minority of whom may later develop true eating disorders. Direct continuity has not been demonstrated.
It is important to differentiate this form of active food avoidance from the loss of appetite that occurs commonly in association with depression. Depression may be present in FAED, but often the food avoidance exists as an isolated symptom. We have come to use the term FAED when food avoidance is marked and merits treatment intervention in its own right.

II.i. Psychogenic vomiting

Psychogenic vomiting is a recognised diagnostic category in ICD 10 (section 1.2.2), although little clinical elaboration is provided other than to make the clear distinction between ‘vomiting associated with other psychological disturbances’ and vomiting as seen in bulimia nervosa. The diagnosis includes vomiting in association with dissociative disorders and in hypochondriacal disorder. In children the symptom may be anxiety related, in which case it might simply be seen as a symptom of food phobia or other anxiety disorder. Overt anxiety is not always present however, and it may be that the child has developed an extreme sensitivity to emetic triggers. A child who has a past history of gastro-oesophageal reflux or of vomiting associated with other illness may be more at risk. Occasionally the vomiting may be of sufficient severity to inhibit all food intake.

III. Anxiety disorders

III.i. Phobias associated with food avoidance

Phobias involving food may occur in isolation (i.e. as simple phobias), or as part of a more generalised anxiety disorder. The overlap with other eating problems is evident, since food avoidance is a feature of most of the problems described. There are children who develop specific circumscribed fears in relation to food however, which are associated with specific cognitions (unlike in FAED) and are not associated with obsessional rumination and checking/compulsive behaviours (see below). The nature of the specific fear will vary with, amongst other things, the child’s developmental stage, but it is probably the case that other severe food phobias are more common
than phobic fear of fatness in the 8 to 10 year old age group. The fears that are common are a fear of vomiting and a fear of contamination or poisoning. This may mean that only certain family members can be entrusted to prepare foods. One paper of interest in this area describes three boys, aged 6 to 8, consuming between 41 and 75% of their estimated daily needs for normal growth and development (Singer et al. 1992), representing the extreme end of the clinical spectrum.

III.i. Obsessive Compulsive Disorder

The coexistence of AN and obsessive compulsive disorder (OCD) is well recognised, as is the difficulty in separating some aspects of the disorders. AN is associated with OC symptoms, particularly in boys who may alternate between episodes of AN and OCD (Shafran, Bryant-Waugh, Lask, & Arscott 1995). In addition, OCD without AN can present as food related obsessions, where the primary behavioural symptom is unusual food related behaviours. For example, a child may develop obsessional fear about the cholesterol content of food, as one boy did following the death of his father from myocardial infarction; or about the freshness of food, such that food intake is limited to those sources which are of ‘known’ safety in terms of cleanliness. In children, factors determining the extent of elaboration of OCD rituals include contextual factors as well as responses to the symptoms. Presentation features may include rigid eating patterns and associated conflict (usually intrafamilial), restricted range of foods and in more extreme cases, restricted quantity of food leading to weight loss.

IV. Developmental disorders

IV.i. Selective eating

‘Selective eating' describes a highly selective pattern of food intake in terms of the range of foods eaten (Bryant-Waugh 2000). This phenomenon is also known as ‘few foods’, or ‘faddy eating’, both of which have the potential problem of confusion between limited quantity (calorie intake) and limited range (numbers of different foods) (table 1.2). ‘Faddy' implies that the eating pattern is temporary, a criterion specifically
excluded from this group. We have chosen ‘selective eating’ (SE) as a term that conveys the extreme selectivity in preferred foods.

A number of features differentiate SE from the other eating difficulties described so far. The first is the highly limited range of foods that is longstanding, often stemming from the time of weaning, but may also be secondary to some traumatic event. A range of less than 10 foods in total is usual in those presenting for help (Nicholls et al. 2001). The foods will typically be predominantly carbohydrate based, and may be brand specific e.g. only McDonald’s chips. The second feature is an extreme unwillingness to try new foods. In order to exclude other eating difficulties, the child should be in the normal range for weight and height, and not losing or gaining significant amounts of relative weight. In addition, in order to be considered outside the normal developmental range, SE should have persisted well into middle childhood and/or adolescence. In the majority of cases SE problems tend to resolve with age. Some will, however, persist in accepting only a very narrow range of foods, becoming adult selective eaters (Bryant-Waugh 2000).

The frequency of each of the eating subtypes described above in the general population is largely unknown. Estimates of relative frequency cannot be inferred from clinical samples as factors leading to help seeking are likely to be as significant as true incidence of the problem in determining presentation rates. The other eating difficulties outlined above are less well characterised than AN and BN, and both clinical and population studies are lacking. Very little information bar that cited in the text is available.

One factor influencing clinical presentation is developmental stage. In the age group under consideration in this thesis, the four commonest presentations are AN, FAED, SE and BN. Increasingly obesity is included in the eating disorder literature, in particularly when overeating is clearly emotionally cued or is associated with binge eating. Obesity is not considered in the present study.
Table 1.1: Description of food avoidance emotional disorder (FAED) as used in the study (based on Bryant-Waugh 2000)

<table>
<thead>
<tr>
<th>Food Avoidance Emotional Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>'an emotional disorder in which mood disturbance and food avoidance are prominent features; there is often a history of episodic food avoidance; the patient can be very low in weight; no abnormal cognitions about weight and shape are evident'.</td>
</tr>
</tbody>
</table>

Table 1.2: Description of selective eating as used in the study (based on Bryant-Waugh 2000)

<table>
<thead>
<tr>
<th>Selective eating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) A range of 10 foods or less are eaten</td>
</tr>
<tr>
<td>2) Unwillingness to try, avoidance or refusal of new foods</td>
</tr>
<tr>
<td>3) Persistence over the age of 7, or equivalent developmental stage</td>
</tr>
<tr>
<td>4) No physical illness sufficient to account for food avoidance</td>
</tr>
<tr>
<td>5) A normal range of foods for age may never have been eaten</td>
</tr>
</tbody>
</table>
In addition, food refusal associated with medical illness is a common clinical presentation. The co-occurrence of eating difficulties and medical illness is considered in the methodology. This study was designed to look at eating difficulties of primarily psychological origin.

1.2.2. Specific diagnostic issues in children and young adolescents

The two principle classification systems for mental disorders are the Diagnostic and Statistical Manual for the Classification of Mental Disorder, Version IV (DSM IV) and the World Health Organisation International Classification of Disease, Version 10 (ICD 10).

DSM IV includes only two specific eating disorder diagnoses - AN and BN (table 1.3 for criteria). Simple obesity is not included as it has not been associated with a consistent psychological or behavioural syndrome. ‘Feeding and Eating Disorders of Infancy or Early Childhood’ (including pica and rumination) are included in ‘Disorders Usually First Diagnosed in Infancy, Childhood or Adolescence’. These diagnostic criteria require that the child be under 6 years of age when the problem starts, and that there is concern about the child’s nutritional status. The final eating disorder diagnostic category in DSM IV is Eating Disorder Not Otherwise Specified (EDNOS), which approximates to a subclinical syndrome of AN or BN. The examples given all include abnormal cognitive preoccupation with weight, shape and food, with differences in the behavioural and somatic syndromes. The DSM IV definition of AN allows for the inclusion of children and premenarcheal adolescents in criterion A - ‘failure to make expected weight gain during period of growth’. Criterion D describes the impact of hypothalamic-pituitary- gonadal dysregulation for postmenarcheal women, but does not offer alternative signs for premenarcheal women or for males, be they adult or child.
### Table 1.3: DSM IV definitions of AN and BN

#### Anorexia Nervosa

| A. | Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g. weight loss leading to maintenance of body weight less that 85% of that expected; or failure to make the expected gain during period of growth leading to body weight less than that expected) |
| B. | Intense fear of gaining weight or becoming fat, even though underweight |
| C. | Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self evaluation, or denial of the seriousness of current low body weight |
| D. | In postmenarcheal females, amenorrhoea, i.e. the absence of at least three consecutive menstrual cycles |

**Subtypes:**

- Restricting type: during the current episode of AN the person has not regularly engaged in binge-eating or purging behaviours
- Binge eating/purging type: during the current episode of AN the person has regularly engaged in binge-eating or purging behaviour

#### Bulimia Nervosa

| A. | Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
1. eating, in a discrete period of time (e.g. within any 2 hour period) an amount of food that is definitely larger than most people would eat during similar period of time and under similar circumstances
2. a sense of lack of control over eating during the episode (e.g. feeling that one cannot stop eating or control what or how much is being eaten) |
| B. | Recurrent inappropriate compensatory behaviours in order to prevent weight gain, such as self induced vomiting, misuse of laxatives, diuretics, enemas or other medications; fasting or excessive exercise |
| C. | The binge-eating and inappropriate compensatory behaviours both occur, on average, at least twice a week for 3 months |
| D. | Self evaluation is unduly influenced by body shape and weight |
| E. | The disturbance does not exclusively occur during episodes of AN |

**Subtypes:**

- Purging type: during the episode of BN, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics or enemas
- Nonpurging type: during the current episode of BN the person has used other inappropriate compensatory behaviours such as fasting or excessive exercise but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics or enemas
In ICD 10 diagnostic criteria for AN, features relevant to children and adolescents include:

- 'Body weight is maintained at least 15% below that expected (either lost or never achieved) or Quetelet's body mass index is 17.5 or less. Prepubertal patients may show failure to make expected weight gain during the period of growth'.
- 'If onset is prepubertal, the sequence of pubertal events is delayed or even arrested (growth ceases; in girls the breasts do not develop and there is primary amenorrhoea; in boys the genitalia remain juvenile). With recovery, puberty is often completed normally but the menarche is late'.

Although both DSMIV and ICD10 make allowances for children in the somatic criteria, there are outstanding areas of difficulty. For example, DSM IV criterion A allows for failure of weight gain during the growth period, but requires a body weight less than 85% of expected. If growth arrest has occurred, weight would be interpreted in relation to the child’s actual (reduced) height, or in relation to the population norms for age, which may be inappropriate from parental or racial characteristics. The ideal would be to relate weight to predicted height for age from previous growth centile but this is often unknown.

There are also significant difficulties with the cognitive aspects of classification, although these are not considered further here. The unsatisfactory classification of eating problems in children has made comparison to their adult counterparts difficult. In addition atypical eating problems presenting in adulthood have not been sufficiently characterised for it to be clear how they relate to atypical eating problems of childhood.

Research has also tended to focus on those who fit diagnostic criteria, with atypical cases excluded. This means that little or no information is available about the substantial number of nutritionally compromised children who do not meet diagnostic criteria for AN, despite their poor prognosis (Higgs, Goodyer, & Birch1989).
Overall the mortality rate in early onset and adolescent eating disorders is lower than in adults (Steinhausen 1997) which may in part be due to a lower threshold for intervention and/or hospitalisation in children (up to 80% of adolescents receive some inpatient care (Kreipe, Churchill, & Strauss 1989; Nussbaum et al. 1985b; Steiner, Mazer, & Litt 1990)). More likely it is because the majority of complications are compounded by chronicity. The aim of this study is to provide accurate and information about aspects of growth and development and their interpretation in young people with severe eating difficulties. Quite apart from fully understanding the risks to physical health, the information obtained at physical assessments can be a powerful psycho-educational tool for both sufferers and parents/carers, improving motivation to change. Any study based on a clinical sample generalisability need careful consideration.

1.4. Growth at puberty in normal adolescents

1.4.1. Determinants of growth

The growth of an individual is subject to a complex network of regulation, the biological basis of which is subject to influence by environmental factors (Delemarre-van de Waal 1993). The ICP model of growth recognises three additive and partially superimposed components of the human growth curve to final height: infancy, childhood and puberty (Karlberg 1989), each representing a separate biological phase of the growth process\(^1\). The infant stage, rapidly decelerating growth rate, is thought to represent a continuation of foetal growth. These early years are critical in terms of environmental risk, including nutritional deprivation. The most convincing evidence of impaired growth arises as a consequence of nutritional deprivation during this period.

\(^1\) This is a simplified model compared, for example, to the bio-cultural model described by Bogin (2000), who distinguishes childhood, juvenile, pubertal and adolescent stages. Since neither model directly reflects stages of psychological development, nor transitions in feeding and eating behaviour, the ICP model is used here because of its focus only on linear growth.
For the first two years of life there is little or no correlation between height and parental height. The childhood phase corresponds basically to the effect of growth hormone (GH) and the correlation with parental height increases, so that parents account for 90% of the variance in a child’s height by about the age of 6 (Phillips 1990).

An interaction of growth velocity and the timing of puberty determine the final height of an individual, over which genetic and racial factors have by far the most powerful influence. Growth acceleration at puberty, stimulated by sex steroids, is intimately related to the stage of sexual maturation and the pubertal growth spurt is superimposed on the decelerating childhood component of growth. The mechanism is unclear, although both growth hormone and sex steroids are essential to the process and appear to be synergistic. Production of growth hormone (GH) and gonadotrophins (luteinising hormone, LH and follicular-stimulating hormone, FSH) is regulated from the pituitary gland. Sex steroids exert a direct effect upon growing cartilage and stimulate local production of insulin-like growth factor (IGF-1). Sex-steroids also stimulate an increase in amplitude of growth hormone production, which in turn stimulates IGF-1. An intact thyroid axis is also necessary for a successful pubertal growth.

Growth of an individual child is usually assessed by plotting the child’s height on a growth chart and thereby comparing to age and gender matched children. The chart shows the phases of growth in its curve, as well as the normal range of height for a child at any particular age by means of centiles. Based for many years on data obtained from the Harpenden growth studies of 1966 (Tanner & Whitehouse 1966; Tanner, Whitehouse, & Takaishi 1966), these growth charts, for both weight and height, have been revised to reflect secular changes in growth (Freeman et al. 1995).

During the childhood phase of growth, a child might be expected to grow roughly along a particular centile line, a process known as ‘canalisation’. Significant deviation from a centile for either height or weight for any particular child is often a cause for concern. During adolescence growth charts become more problematic to interpret. This is
because conventional cross sectional growth (height) charts smooth out the growth through adolescence, but do not take into account phase differences. In other words, the centiles (i.e. the age adjusted averages for height) do not take into account the impact of the pubertal growth spurt, the presence or absence of which at any particular stage may account for an apparent acceleration or deceleration in growth. This means that a child’s height may appear to be crossing centiles when in fact they are merely entering or failing to enter puberty.

The conventional method for studying growth around puberty is to look at height velocities with all the peak height velocities coinciding. This method, relies on peak height velocity (PHV) having been attained and passed (i.e. can only be ascertained retrospectively), and effectively adjusts growth for stage of pubertal development. From studies such as these, height and breadth of the pubertal growth spurt has been shown to be independent of age at maturation. Differences in growth pattern at puberty therefore depend on the point at which the pubertal spurt is superimposed on the decelerating childhood growth pattern.

1.4.2. Puberty and its relationship to growth

The control of pubertal development is also regulated from the pituitary gland, and mediated via the gonads and adrenal glands. The onset of puberty is more closely correlated with skeletal age than with chronological age (Marshall & de Limongy 1976) and again, genetic influence is prominent in determining timing; Monozygotic (MZ) twins onset puberty 1-2 months apart, while dizygotic (DZ) twins onset 1 year apart. The speed of puberty is unrelated to the age of onset (Marshall & Tanner 1969; Marshall & Tanner 1970), as for the related growth spurt noted above.

Tanner (1962) described what have become known as the Tanner stages of puberty, which divide puberty into 5 stages. Stage 1 is prepubertal i.e. everything from birth to the very first signs of puberty. The last stage is 5 i.e everything from the end of puberty
onwards. As with growth in height, puberty is a continuous developmental process, which can slow down or stop in adverse situations, but cannot fully reverse. Tanner staging has 3 components: breast development, pubic hair and axillary hair. The development of pubic hair usually occurs more or less in tandem with breast development, albeit under the influence of adrenal androgens for pubic hair and pituitary gonadotrophins for breast development. In 15% of girls the first sign of puberty is an increase in height velocity but the more commonly noted sign is the development of breast tissue, sometimes unilateral, under the influence of oestrogen secreted by the ovaries (Tanner 1962). Standard UK growth charts include centile bars for puberty ratings, indicating the normal range at which each pubertal stage is reached. These also show sequence of events in puberty which are remarkably consistent and largely irreversible, the exception being in the late stages of breast development where stage B5 can revert to stage B4.

The average age of menarche from the UK reference data is 13, and it is thus quite a late pubertal event. From the original Harpenden Growth studies, Marshall et al. (Marshall & Tanner1969) found that 51% of girls reached PHV in stage B3, and 62% reached menarche in stage 4. Menarche invariably followed attainment of PHV. Thus anyone who has already reached menarche (or has secondary amenorrhoea) is likely to be B4 or B5, or at the very earliest B3, and have completed much of their growth. The UK reference data for puberty are somewhat outdated (see section 4.4.2.5), and the issue of a secular trend for earlier puberty remains one of some controversy.

In boys, growth in penis and genitalia are both under androgen control. Growth of the testes is usually the first sign of puberty in boys, beginning on average 6 months after breast development commences in girls. Voice changes occur at a mean of 13.9 years, with adult voice appearing at 15 years. Facial hair on the upper lip occurs at approximately 15 years (quoted in Styne 1995). Changes in facial shape and body composition also occur, with a particular increase in lean body mass.
In girls the growth spurt commences with the onset of breast development and reaches a peak at B3. The growth of boys continues to decelerate until attainment of genital stage 3 to 4 or an average of 10ml testicular volume. Thus in girls the pubertal growth spurt is an early pubertal event, whilst in boys it is later. From the original Tanner data (1966) the age at PHV for boys was 14.1 ±0.13 years, and in girls was 12.1 ±0.18 years. PHV was 10.3±0.22 cm/yr for boys and 9.0±0.16 cm/yr for girls. The mechanism of timing of the pubertal growth spurt is unclear, but cannot be entirely sex steroid dependent since the rise in oestrogens seen in girls early in puberty is paralleled by a rise in testosterone without equivalent effects on growth.

1.4.3. Changes in weight during adolescence

Weight, unlike height, can decrease as well as increase. Tanner et al. (Tanner & Whitehouse1966; Tanner, Whitehouse, & Takaishi1966) produced the original cross sectional weight charts, and weight velocity charts, and noted that seasonal variations in weight were more marked than those for change in height, and weight loss occurred from time to time. This was particularly true of girls, whose fat content “varied with whim or weather” (Tanner, Whitehouse, & Takaishi1966) (p 463). The age at peak weight velocity (PWV) was 14.3±0.13 yrs for boys and 12.9±0.18 yrs for girls i.e. slightly later than PHV, and particularly so for girls. PWV was 9.8±0.3 kg/yr for boys and 8.8±0.25 kg/yr in girls. There was only a 0.29 correlation between PHV and PWV for boys and 0.18 correlation in girls. Furthermore there was no relationship between PWV and age of menarche. Thus for girls, increase in weight continued after growth in stature had slowed down, the poor correlation with height equating to actual changes in body size and shape.

Percentages of lean body mass, skeletal mass and body fat are roughly equal between prepubertal boys and girls. Changes in lean body mass precede changes in fat mass. By completion of puberty, boys have on average 1.5 times the skeletal mass
of girls, while women have roughly twice as much body fat as men (Grumbach & Styne 1992). Individual constituents of body composition are considered further in chapter 2.

### 1.5. Pubertal delay and growth failure

Pubertal delay is defined arbitrarily on the basis of statistical considerations, when no signs of puberty have occurred at 2 SD above the mean chronological age for the onset of puberty. In the UK this is at age 13.2 for girls and 14.2 for boys (Bridges & Brook 1995 p.262). The other common marker of delayed puberty is late onset of menses, or primary amenorrhoea. Menses are deemed to be delayed if there is failure of onset within 4.5 years of the start of puberty, or by a chronological or bone age of 14 years. The commonest reasons for delay in puberty are so called ‘constitutional delay of puberty’ (commoner in boys than in girls), chronic illness such as cystic fibrosis or renal disease, and combinations of low weight and high exercise levels, as seen in ballet dancers and athletes as well as in AN. Pubertal delay does not ordinarily interfere with the pattern of acquisition of stages of sexual maturation and the growth spurt.

The assessment of pubertal delay requires a careful history, physical examination, anthropometric measurements (standing height, sitting height, weight and pubertal rating) and bone age assessment. In addition to delayed acquisition of secondary sexual characteristics, pubertal delay can be ascertained from a discrepancy between bone age and chronological age, or by the assessment of uterine and ovarian morphology on pelvic ultrasound scan in girls (testicular scanning has not yet proven as useful). Endocrine assessment may be necessary to confirm the absence of other pathology.

Growth failure is more difficult to define than pubertal delay as it cannot simply be defined as fall in height relative to the normal population (or crossing centiles). The
difficulties in assessing growth failure are best illustrated by two cases from the study patient sample. Figure 1.1 shows the growth charts (in height SDS) of two girls who presented with weight loss. In chart a fall in height SDS is the equivalent of crossing from above the 93rd centile to nearer the 50th. She lost over 4 kg of weight at age 8, although her weight remained within the normal range (falling from 105% to 90% BMI). With progress through puberty she tended towards the mean height for her age. Thus her apparent 'growth failure' (negative change in height SDS) may be unrelated to her weight loss and simply be the growth pattern of an early maturing child who stopped growing in height at an early age. Her height SDS will move towards 0 SDS until growth is complete. Chart b looks similar in shape but values are below rather than above the mean. Following initial weight loss, she regained some but not sufficient weight to maintain progress through puberty. Her fall off in height SDS is therefore likely to be a result of weight loss and subsequent delay in puberty, and could constitute growth failure if sufficiently extreme.

These individual cases illustrate that growth failure cannot be evaluated from change in height SDS alone, since both examples show a significant fall in height SDS over time. This highlights the difficulty of measuring change without defining the starting point for the decline.

Another way of evaluating growth failure is in terms of height velocity (growth rate) and indeed what quantitative definitions there are for growth failure have been based on height velocity (HV) measurements. Brook et al. (Brook 1986) have defined normal height velocity as between -0.8 to 0.8 HV SDS. This represents the range of HV SDS of children growing along or parallel to the 3rd height centile. Although this definition is useful in prepubertal children, where a child may be expected to follow a growth centile, it does not take into consideration the 'phase effect' of puberty (see above).
Both cases described above would have met criteria for growth failure according to this definition.

A partial solution to problem of assessing growth failure in puberty has been offered by Rikken and Wit (Rikken & Wit 1992), who have extended the age references for prepubertal height velocity standards up to age 13.5 for girls and age 15.5 for boys. For children where pubertal delay has occurred, this removes the effect of comparing them to children who have entered puberty at the same age. An alternative would be to substitute bone age (section 1.5.1) for chronological age into HV SDS calculations. This assumes HV for bone age follows a similar pattern to that for chronological age. Direct substitution may not be valid however, because the appearance of a maturity indicator would change the bone age in a discontinuous way (Rikken & Wit 1992).

Whichever method for evaluating growth failure is chosen, correction for maturational stage is needed in order to be informative about true impact on growth.

1.5.1. Bone age

'Bone age' refers to the radiological assessment of skeletal maturity. An estimate of bone age defines the amount of growth that has taken place and how much is yet to come. Several methods have been devised. The most widely used method of determining bone age is the Greulich and Pyle (Greulich & Pyle 1959) atlas, based on the radiographs of the left hands of white children from Cleveland, USA. Adult height can be predicted using tables. Social, racial and economic factors are known to influence the rate of skeletal maturation, and the atlas when applied to British children will result in an under estimation of skeletal maturity. The advantage of the atlas is its acceptance throughout the world and the technique is accurate and reproducible when correctly used. Its misuse, by comparing a child’s whole hand to the x-ray standard, led Tanner et al. (Tanner et al. 1983) to develop a technique that requires evaluation of each bone individually. This method is preferred when maturation may have
Figure 1.1: Fall in height SDS in an early maturing girl [a] and as a result of weight loss [b] showing that fall in height SDS is not adequate for defining growth failure.

Note: Colours indicate changes of pubertal stage.

a] Pubertal stages 1 to 5.

b] Pubertal stages 2 and 3
occurred unevenly, as is likely in cases of extreme pubertal delay. A score is obtained which is then compared to a reference centile chart.

Metaphyseal growth arrest lines (Harris’s lines) may be seen on bone age x-rays and are a recognised feature of chronic illness. They have been described in conjunction with a number of disorders, including malnutrition, infections, Cushing syndrome, during chemotherapy and more recently in psychosocial dwarfism (Khadilkar et al. 1998). They do not appear as a feature of growth failure resulting from growth hormone insufficiency and/or panhypopituitarism. Growth arrest lines are thought to result from alteration in bone turnover at the growth plate, probably by affecting growth stimulating factors, and occur after a period of growth suppression followed by recovery. Cycles of growth suppression and recovery result in multiple lines. Growth arrest lines should not be present at acute presentation, nor during the acute phase of any illness. They will be present when growth has restored or will be indicative of chronicity if present at the time of presentation.

1.5.2. Impact of delayed puberty on adult height

For many years the belief prevailed that delayed puberty had no impact on final height, and that the reasons for treating otherwise uncomplicated (constitutional) delay in growth and puberty (CDGP) were principally to enable age appropriate psychological adjustment. A number of studies have raised doubts about this assumption. Albanese et al. (Albanese & Stanhope 1993; Albanese & Stanhope 1995) found that extreme delay of growth and puberty (with slowing of growth and short stature relative to parental centiles) was associated with impaired final adult height and a discrepancy in sitting height to leg length ratio, resulting in a relatively shorter spine, and longer legs. The criticism of possible attainment bias of subjects makes this finding questionable however, and Crowne et al. (Crowne et al. 1990), in a study of 43 boys with CDGP found no difference between final height and predicted adult height, although there
was a difference between final height and mid-parental height. Overall the issue of whether, if growth is significantly slowed or the growth period sufficiently prolonged, final height is compromised remains of enormous theoretical and clinical interest, and revolves around the central issue of adolescence as a time of nutritional programming, considered further below.

1.6. Critical periods and nutritional programming

The idea that nutrition during 'critical windows' in early life could influence or 'program' long term development and major disease in adulthood has important biological and health implications. Events in early life can influence long term development in one of three ways: a] direct damage (e.g. an accident resulting in injury), b] induction, deletion or impaired development of a somatic structure as a result of a stimulus or insult during a critical period, or c] alteration of physiological 'settings' during a critical period resulting in altered long term function (Lucas 1994). The term programming applies to the latter two, when it is clear that long term affects are only seen when the insult occurs during a critical period, but not at other times. General examples include the 'programming' of male gender as a result of hormonal signals during critical periods of fetal development. Nutritional programming refers to the findings, which are robust in animals but less so in humans, that even brief periods of dietary manipulation during early life can have lifelong effects on neurodevelopmental and health outcomes (Barker et al. 1993; Lucas1994).

1.6.1. Adolescence as a critical period for growth

Periods of accelerated growth may be particularly prone to nutritional influence although the nature of the nutritional insult, in terms of timing, duration and severity, required to confer permanent stunting remains unclear (Kulin et al. 1982). What evidence there is suggests that severe caloric deprivation in the first 5 years of life may be required. The question of altered long-term outcome remains as yet unanswered in
terms of nutritional deprivation during adolescence. Growth can undoubtedly be impaired as a result of malnutrition during adolescence, as has been demonstrated in many illnesses, eating disorders included (Root & Powers 1983; Russell 1985). However, puberty is also a time when growth may be accelerated and compensation or 'catch-up' can occur such that, in the long-term, outcomes such as final adult height are not influenced. For example, when chronically malnourished children in Kenya were compared to better nourished Kenyan adolescents, differences in height of more than 12 cm existed between the two populations at age 10 years, but this difference was eliminated by the time growth was complete (Kulin, Bwibo, Mutie, & Santner 1982). Further evidence of malnutrition was seen in the 2.1 year difference in age at menarche of the two groups. Although differences in nutritional status were apparent at all stages of development, including the onset of menses, height difference between the two groups was no longer significant by stage 3 of puberty for both the girls and boys. Mean BMI at 18 years old was 18 for girls and 18.9 for boys in the malnourished samples.

Similarly, Dreizen et al. (Dreizen, Spirakis, & Stone 1967), in the days before AN was a well recognised disorder in younger children, studied the growth patterns of 30 undernourished and 30 well nourished girls from childhood to early adulthood. The undernourished group were mainly deficient in ascorbic acid, vitamin A, calcium, iron and animal protein. Weight was not taken into account in the analysis. They found that chronic undernutrition slowed the rate of both skeletal growth and skeletal maturation, delayed menarche and prolonged the growth period. This effect was most pronounced in the premenarcheal period. However, no appreciable difference was found between the two groups in their final adult height, as the prolonged growth period seemed to have compensated for the slower skeletal growth.

In Western cultures, "nutritional dwarfing" is more commonly a result of self-imposed malnutrition (Lifshitz 1987), and by its nature quite different to the chronic malnutrition
of third world poverty. It may be that acute, self-imposed malnutrition in a previously healthy individual gives less of an opportunity for adaptation to low calorie intake. In addition, the intensity and timing, if not the duration, of the insult may be importantly different. Evidence is surprisingly limited, but AN provides a good model for studying this question since it is a disorder usually associated with previously normal growth, severe malnutrition and timing of the illness close to adolescence. At this point it is not clear whether the sort of malnutrition seen in AN and other eating disorders confers a different risk when it occurs during the critical period of adolescence from that of the chronic malnutrition described above.

### 1.6.2. Catch up growth

In 1986 Tanner wrote optimistically about the resilience of humans when it comes to growth - "deflect a child from its natural growth trajectory by acute malnutrition or a sudden lack of hormone, and a restoring force develops, so that as soon as the missing food or the absent hormone is supplied, the child hastens to catch-up towards its original growth curve" (Tanner 1986). Ordinarily a child's growth follows an extraordinarily regular path, such that a failure to do so is one of the best indices of a problem with the child's health (Tanner 1981). Following a period of impaired growth, for whatever reason, the invariable response is for the child to grow at a rate above that expected for either their chronological or bone age. This is known as catch-up growth. Clearly distinguishable from the adolescent growth spurt, early descriptions suggested that the catch-up period was twice as long as the period of illness (Bauer 1954). Catch-up growth may be complete (restoring the child to their original growth centile) or incomplete.

Tanner described three types of complete catch-up growth. 'True' catch-up, where growth accelerates from the time of intervention or resolution of the disorder impeding growth, such that the child returns to their previous growth centile for the duration of
the growth period; prolonged growth where growth is resumed at the average height velocity for chronological age; and prolonged growth where growth resumes at the average height velocity for bone age. The latter are not ‘true’ catch-up since the average growth rate for age is not exceeded.

Although the mechanisms underlying catch-up growth are not fully understood (Boersma & Wit 1997) there are some principles that apply. Firstly, the longer the growth retarding influence lasts and the earlier in life it occurs, the worse the ultimate outcome is likely to be. Secondly, the completeness and rate of catch-up may depend on the nature of the growth-retarding influence. Thus, growth retardation due to hypothyroidism is more easily caught up than when it is due to growth hormone deficiency. Thirdly those components of growth increasing fastest at the time of growth retardation may be the most influenced. Thus the strength of signal for growth is proportional to the mismatch between actual and expected signal production. The fact that over compensation does not occur has been cited as evidence for a mechanism of internal regulation of growth signals. The nature of these signals however is complex and may be open to external influence and possible ‘resetting’ (programming) such that incomplete growth occurs.

In order to assess which has occurred in terms of both growth failure and catch-up growth, accurate knowledge of the child’s previous growth and genetic growth potential are necessary. Genetic height represents the range of heights likely to be achieved by 95% of a couple's offspring, and either mid-parental height or target height are commonly used. Mid-parental height is simply the average of the parents’ height. Target height is calculated by adjusting the height of the opposite gender parent e.g. for a boy, 13 cm is added to maternal height and the average of this and fathers height taken. Target limit calculation includes the 95% confidence intervals either side of target height (±2SDS). An alternative is to take the mean of parental
height SDS. The correlation between mid-parental heights and final adult height of offspring is about 0.7 (Tanner1981).

During growth arrest or slowing, osteogenic activity at the epiphyses slows down. The process of growth in bone length is to some extent independent of maturation. If maturation has slowed less than growth in height, as is commonly the case, a rate of catch-up in height greater than the maturation rate will not result in ultimate stunting.

### 1.7. Growth in AN

Growth retardation and incomplete pubertal development are recognised serious potential complications of AN (Danziger et al. 1994; Lifshitz1987; Russell1985). A number of theories about growth in AN have been forwarded and the literature is mixed in its view about the potential for recovery of final stature (Gowers, Crisp, Joughin, & Bhat1991; Joughin, Varsou, Gowers, & Crisp1992; Pfeiffer, Lucas, & Ilstrup 1986). Suppression of gonadotrophins in AN is well documented (e.g. Boyar et al. 1974), as is delay in puberty associated with slowing of bone maturation (Lacey et al. 1979).

There is less clarity about what happens with growth hormone (GH). GH production is normally increased in protein malnutrition, presumably mobilising remaining fat tissue, and decreased in calorie malnutrition (Delemarre-van de Waal1993). Also of relevance is that GH production is increased in acute stress but decreased in chronic stress. About 50% of adult women with AN have normal or reduced GH production (Argente et al. 1997). This section reviews the findings of studies exploring growth and stature in AN.

#### 1.7.1. Short stature and AN

Height and its relationship to AN has been discussed within the framework of three hypotheses. Firstly, it has been suggested that AN can arrest growth and lead to
patients being chronically or temporarily short. Secondly, it has been suggested that either being short or tall is a risk factor for AN. Thirdly another underlying abnormality may contribute to both the development of AN and short or tall stature.

Is there evidence of an association between AN and short stature? Brinch and Manthorpe (Brinch & Manthorpe 1987), based on three cases, hypothesised that short stature may be a risk factor for AN. This theory has also been proffered as explanation for the association between Turner syndrome (gonadal dysgenesis) and AN, which has been repeatedly described (Muhs & Lieberz 1993). Short stature alone however is clearly not an adequate explanation for such severe psychopathology (Skuse 1987), and this association may be due to a combination of neurodevelopmental vulnerability and hormone treatment (Nicholls & Stanhope 1998).

Nussbaum et al. (Nussbaum et al. 1985a) observed that girls with AN were short in stature (76% were below the 50th centile), but found no significant differences between the pre and post menarcheal onset groups (n=85). The age range of the sample was 12 – 22 years, and since in 80% of their patients AN developed after menarche they assumed that malnutrition alone could not account for the height deficit i.e. that the majority of girls would have almost completed growth before AN onset. Only two girls in the sample were premenarcheal. Similarly, Crisp (1969) found 42 AN patients less than 17 years of age were shorter than controls but not significantly so. Clearly only associations about the relationship between AN and short stature and not causal hypotheses can be tested with this methodology.

A number of studies have addressed the question by looking at final height in AN sufferers whose illness onset during adolescence. Joughin et al. (Joughin, Varsou, Gowers, & Crisp1992) studied a sample of adult women who had past or present AN. In both those recruited from a specialist clinic (n=338) and those recruited from the community by advertisement for past AN sufferers (n=309), neither group was stunted when compared to the normal population. In fact those with a past history of AN were
relatively tall, despite correction for social class, raising the possibility that early
maturers or relative tallness were risk factors for AN, or even that AN may cause
tallness. The authors did note that in the few early onset cases in the sample, stunting
had occurred.

Nielsen (Nielsen 1985) measured longitudinal growth in 66 patients with AN (58
females, 8 males) by cross-sectional and longitudinal analysis. Although there was a
slight tendency for patients to be overweight before onset of AN, there was no
consistent pattern of premorbid growth. Mean age of PHV was 11.5 years, and PHV
was 8.03 cm/yr. Those with postmenarcheal onset had a mean age of menarche of
12.88 years. These are all comparable to norms for Scandinavia. Females had a
normal growth rate and a normal sequence and timing of pubertal events. The boys
however, had a significantly early PHV, at age 11.8 years, although the significance of
this on such a small sample is of question.

On the basis of these studies the evidence for predisposition to altered growth patterns
in AN sufferers is, at best, weak.

1.7.2. Growth retardation and catch-up growth

In order for height to be severely compromised AN must have onset before growth is
complete, and preferably before PHV. The close temporal association between PHV
and menarche makes menarche an obvious basis on which to differentiate risk. Is
premenarcheal onset AN therefore associated with compromised growth and what is
known of the potential for catch-up?

In one early report, Root and Powers (Root & Powers 1983) reported growth
retardation in 3 cases, 2 boys and a girl, who were originally referred for concerns
about short stature at ages 9 to 12. The diagnosis of AN was made after several years
of observation of falling height centiles, suggesting that AN without specific treatment
or recognition can lead to severe growth and pubertal retardation. Dreizen (Dreizen,
Spirakis, & Stone (1967) (cited above) showed that the retarding effect of malnutrition was maximal before menarche, and suggested that with increasing age, children become less prone to the forces that disrupt the normal skeletal maturation process. Since then a number of clinical case series have reported severe growth retardation in the context of premenarcheal onset AN. Danzinger et al. (Danziger, Mukamel, Zeharia, Dinari, & Mimouni 1994) studied the growth patterns of 15 patients (13 female, 2 male), all of whom had been suffering from AN for at least 6 months. Mean age at referral was 13.3 ± 1.3 years. All had growth arrest for 13 ±8.5 months prior to admission. Catch up growth occurred in 9 out of the 13 patients, all at Tanner stage 1-3. Catch up did not occur in 2 patients at Tanner stage 3 and 5, despite weight gain, and in two patients who did not complete treatment. The authors suggested that growth arrest is a common, if not universal, sign of AN during the pubertal and peripubertal period of 6 months duration or more, and that projected height should be included in the calculation of target outcomes. The final outcomes of these subjects are not known.

Pugliese et al. (Pugliese et al. 1987; Pugliese, Lifshitz, Grad, Fort, & Marks-Katz 1983) described a clinic sample of 14 out of 201 clinic attenders at an Pediatric Endocrinology, Metabolism and Nutrition Clinic who had presented with short stature, delayed puberty or both. The age range was 9 years 4 months to 17 years 11 months and 9 out of the 14 were boys. They were identified as having 'fear of obesity syndrome', which the authors argued differed from AN because of absence of compensatory behaviours. This distinction exemplifies the differences in childhood presentation of AN described above, including the gender bias in early onset cases, and would have been defined as AN within the framework described in section 1.2.1. All had weights below the 5th centile, and 11 had heights below the 5th centile; the mean weight for height 89.9% (± 6.6%). In the most severe case a final height of only 142cm was achieved in a girl who had grown along the 10th centile until the age of 8.
In all patients linear growth accelerated after normal nutrition was re-established. Growth hormone studies were not performed.

Lifshitz (Lifshitz 1987), writing on the subject of nutritional dwarfing, identifies three sub-syndromes: [1] fear of obesity syndrome, [2] failure to thrive because of specific parental health beliefs, [3] failure to grow because of malnutrition resulting from dietary restrictions that are based on a fear of the consequences of hypercholesterolaemia. He highlights that although the majority of his sample had presented with short stature below the 5th centile, a number had heights within the normal range. A fall off across centiles was documented with retrospective growth data. Follow-up data were not published.

Pfeiffer et al. (Pfeiffer, Lucas, & Ilstrup 1986) studied 71 patients in adulthood in whom AN had onset before the age of 16 (range 9-16). 13 of the sample were boys. The median height centile at diagnosis was 49; the median centile at follow-up in adulthood was 55. In 36.6% height centile decreased, but in only 4 patients did it decrease by more than 20 centiles. All four were boys. Unfortunately pubertal stage and menarcheal status were not recorded, and it is therefore not possible to know whether decreases in height centiles were a result of growth retardation or due to early maturing growth patterns. The mean age at presentation of the sample was 13.8 years (mean duration of illness 9 months) and is likely to have contained some premenarcheal patients. What struck the authors however, was that, despite weight loss of up to 45% of body weight, most patients with AN continue to grow according to expected norms, or at least return to their previous growth centile on weight restoration. They hypothesised that by early adolescence the growth mechanism may have already been set in motion and subjects were past the critical point at which nutrition can permanently curtail growth. They noted that to determine whether prepubertal onset of AN in either sex might interfere with ultimate stature would need prospective study with Tanner staging and bone age assessment.
The best evidence for a lasting impact of AN on growth comes from Russell's (Russell1985) study of 20 adult women in whom AN had onset before menarche. Follow-up was 4-27 years (mean 9.5) from the date of onset of illness. Only 2/20 reached the 50th centile or above. Evidence of catch up growth was seen in 7/20 but only if weight was regained before age 16 and if weight gain was sustained for at least 3 months. Some did not grow despite weight gain. 8 showed incomplete breast development and 9 had amenorrhoea beyond age 18. At that time the results of endocrine treatment had not been tested, although Russell (Russell1983) did demonstrate breast growth with oestrogen and progesterone given after weight gain. He suggested that as long as the patient recovers within 3 or 4 years, puberty is merely delayed. With more prolonged illness and associated malnutrition there was a risk that physical development would be incomplete. The findings refuted earlier studies which did not highlight disruption to physical development and contrasted with the growing body of work suggesting that, in the long term, catch up growth with adequate nutrition is possible, in so far as final height ascertainment can be demonstrated (Joughin, Varsou, Gowers, & Crisp1992; Pfeiffer, Lucas, & Ilstrup1986). One case study has described completion of puberty and attainment of normal adult height on weight restoration at the age of 27 in a male (Magner, Rogol, & Gorden 1984).

1.7.3. Summary

“Although malnourished children are stunted, their bone maturity is usually retarded to a comparable degree. This is seen in impoverished societies as well as in diseases such as coeliac disease, inflammatory bowel disease and hormonal deficiency. When these children are followed to adulthood they normally have some degree of spontaneous catch-up” (Golden 1994). If puberty is delayed and/or growth continues into the early or mid twenties, then a final adult height in the normal range can be
achieved. The most obvious reason why catch-up may not occur is if appropriate nutritional intake cannot be restored.

Whether AN in premenarcheal cases can have a lasting impact on final height when the illness occurs at a critical stage of growth and despite weight restoration remains unresolved in the literature at present. The different methodologies and failure to assess pubertal stage of the adult studies and the short duration of follow-up in the early onset studies make it hard to interpret the results conclusively. Several of the studies suggest that the very early onset cases had a worse outcome in terms of height, but it is not always clear whether this was final adult height or merely continuing delayed puberty. Stunting in adults in whom weight has not been restored since adolescence has been described, together with incomplete pubertal development. If it is possible for AN to have an irreversible effect on stature, the intensity and duration and timing of the nutritional compromise required are as yet unknown.

1.8. Nutritional status and menstruation

Loss of menses is a critical and cardinal sign of nutritional compromise, a loss of 10-15% of body weight for height being sufficient to result in amenorrhea (Knuth, Hull, & Jacobs 1977). Although it has been argued that menstruation is not predictive of future psychological and social well-being and adjustment in eating disorder outcome (Garfinkel et al. 1996), loss and resumption of menses remains a powerful marker of health status in this group of patients. Predicting and relating menstruation to outcome parameters has been the focus of many studies. The importance of adequate weight restoration, to what is termed 'target weight' has been highlighted by recent studies. Relating weight restoration to response to outcome, BMI (cut off 19) at discharge predicts later treatment response (and therefore risk of relapse) (Howard et al. 1999) and predicts long term outcome in terms of bone density and eating disorder pathology scores at 6 - 10 years (Gross et al. 2000). 'Target weight' in children and adolescents,
where menses may have not have started or development remains incomplete, is acknowledged as an area of continuing uncertainty (Parry-Jones & Parry-Jones 1994). This section reviews what is known about nutritional predictors of menstruation in normal adolescents, and studies of resumption of menses in eating disorder patients.

1.8.1. The Frisch hypothesis

In 1970, Rose Frisch and Roger Revelle of Harvard University Department of biostatistics, published their 'critical weight hypothesis' (Frisch et al. 1971; Frisch & Revelle 1971). Based on 3 longitudinal growth samples (n= 181 girls) their main, and unexpected, finding was that the mean absolute weight at menarche was no different between early and late maturing adolescents. The mean weight at menses throughout puberty was 47.7 kg. The same was not true of height, which was greater in those with later onset of menses. The hypothesis proposed was that the critical weight was a biological trigger of some kind for the onset of menstruation, independent of other aspects of developmental.

As a theory it was much criticised, primarily for over simplifying a complex issue involving relationships between age, weight, body fat and puberty. Frisch later changed her hypothesis to think about weight as a proxy for body fat. By 1974 she had published a set of criteria for the determination of the onset of menarche in primary and secondary amenorrhoea using estimations of total body water to determine body composition. She and colleagues argued that the reduced coefficient of variation in body fat by this method strengthened the threshold hypothesis. Using her method, Frisch found that a higher percentage of body fat was required for resumption of menses from secondary amenorrhoea than from primary amenorrhoea (Frisch & McArthur 1974). The study found that 22% body fat was necessary for resumption of menses (n=9), and only 17% for first onset menarche. Frisch attributed the difference to the fact that normal girls gain 4.5 kg fat between menarche and age 18 and the
higher figure reflect developmental changes in body fat. This runs counter to the observation that BMI SDS at menstruation would appear to go down with delayed onset menstruation, and the clinical experience that many patients onset menses at low weight if sufficient time passes.

Frisch's conclusions were criticised on statistical grounds (Billewicz, Fellowes, & Hytten 1976) and it has been suggested that the method used to estimate body fat is so imprecise as to render the evidence invalid (Trussell 1980). Cameron (Cameron 1976) analysed the weight and skinfold thickness of 36 girls from two years pre- to two years post-menarche, to assess the degree of variability of the parameters around the time of menarche, arguing that if the 'critical weight hypothesis' had a good basis, the variability should reduce around the onset of menses. No such reduction in variability was apparent.

Going back to the original data however, what Frisch and Revelle could have reported was 'BMI at the onset of menses was lower in late than in early maturing girls', since weight at menarche remained constant while height increased. In other words, girls of taller and slimmer build are more likely to menstruate later and at a lower BMI than relatively shorter and heavier girls who mature earlier. This not altogether surprising finding is consistent with that of Stark et al. (Stark, Peckham, & Moynihan 1989), who found a larger proportion of girls with early menarche were heavier for their height at all ages than those with late menarche. A number of population cohort studies have reported similar findings on nutritional status at menarche. A New Zealand cohort study found (n=415 girls) (St.George, Williams, & Silva 1994), found a mean BMI of 18.4 at menarche, at a mean age of 12.9 years. This is another circumstance in which BMI has been reported unadjusted for age, although it could be argued that the subjects will be roughly the same pubertal stage and therefore comparisons are appropriate. The mean weight at menarche for this sample, 41.1 kg, was lower than
that found by Frisch and colleagues but the trend for higher BMI at menarche in the early onset girls was consistent.

1.8.2. Resumption of menses following AN

In AN, and in other states of weight loss induced amenorrhoea, the pattern of gonadotrophin secretion reverts to that found in earlier stages of pubertal development (Boyar, Katz, Finkelstein, Kapen, Weiner, Weitzman, & Hellman 1974) and with it a regression to mid pubertal, multi-follicular, ovarian morphology (Treasure et al. 1988). These changes are reversible with weight gain, and allow weight restoration to be monitored in terms of its impact on endocrine function, since resting LH levels correlate with percentage fat, body weight, and percentage weight loss (Jeuniewic et al. 1978). Studies designed to explore the issue of nutritional status and amenorrhoea have usually used either endocrine markers or pelvic ultrasound scan appearances to predict resumption of menses.

Golden et al. (Golden et al. 1997), in 100 adolescents with AN (only those with secondary amenorrhoea were included) found that resumption of menses (ROM) occurred at a mean of 90% of standard body weight (SBW). 86% of patients who achieved weight had ROM within 6 months. This study found that ROM did not depend on body fat (estimated from 4 skinfold sites), and of all the endocrine and anthropometric measures, was best predicted by oestrogen levels. The findings from Golden et al. are comparable to those of Shometo and Kreipe (Shomento & Kreipe 1994), who found a mean SBW of 92.1%±7.4% at ROM.

Three studies have used pelvic ultrasound to predict ROM. Treasure et al. (Treasure et al. 1985) were one of the first groups to use pelvic ultrasound scans to determine ovarian maturity and ovulation. Five out of 11 subjects had developed a dominant follicle on ultrasound scan at BMI of 19. Sobanski et al. (Sobanski et al. 1997), found no clear cut off in terms of BMI and development of a dominant follicle (n=16),
although there was an increasing correlation between ovarian size and BMI with weight restoration. At BMI of 18, 53% of the sample had resumed menstruation, while at BMI 19.8, 82% had resumed menses. The only study to look at children using this method found a mean weight for height of 96.5% in those children who had resumed or started menstruation (Lai et al. 1994). These authors have argued that existing guidelines for target weight in adolescent onset AN are inappropriately low.

There are no studies to my knowledge that have looked at the relationship between age and BMI at menarche in AN patients.

1.8.3. Summary

Prediction of nutritional status at onset or resumption of menses remains one of the challenges for everyday clinical practice, and methods by which target weights are determined continue to vary significantly, with particular difficulty in subjects with primary amenorrhoea in whom premorbid menstrual weight cannot be used as a helpful guideline. Endocrine assessments and pelvic ultrasound scan are both useful adjuncts as target weight nears, but the overwhelming finding from the literature is the wide variation in menstrual weights found in both normal and AN recovering subjects. It remains unclear whether subjects recovering from AN behave the same as control subjects in terms of nutritional status required for the onset and maintenance of regular menstrual cycles.

1.9. Bone density

1.9.1. Definitions of osteopenia and osteoporosis

The term osteoporosis is synonymous with low bone mineral density (BMD). A WHO expert committee has divided the diagnostic categories into ‘normal’ BMD, ‘low’ BMD (osteopenia), ‘osteoporosis’, and ‘severe osteoporosis’. These criteria have practical utility but are synthetic, as BMD is a continuous variable; the lower the BMD the higher
the fracture risk. Values are expressed as a standard deviation scores (SDS) or T scores relative to the mean peak bone mass in young persons, i.e. relative to the mean BMD reached on completion of bone accretion at around the time of young adulthood. The mean BMD at peak bone mass is assigned a T score of zero; ± 1 SD around the mean includes 66% or the population; whilst ± 2 SD includes 95% of the population. T score cut offs are designated as follows:

1. 'Normal' BMD = T score between 0 and -1.
2. 'Low' BMD ('osteopenia') = T score between -2.5 and -1.
3. 'Osteoporosis' = T score more reduced than -2.5.
4. Severe osteoporosis = T score more reduced than -2.5 with fractures.

In children and adolescents who have not reached peak bone mass BMD is expressed as a z-score (or SDS). This allows comparison to age and sex matched children, but cannot be used to define osteoporosis since further bone accretion may still occur, and a low T-score may simply be a result of not yet having reached peak bone mass (PBM). No definition of osteoporosis therefore exists for children and young adolescents at present.

1.9.2. How is bone density measured?

Using dual energy x-ray absorptiometry (DXA) both bone and soft tissue composition can be measured in vivo, and this is by far the commonest method used to assess bone density. The total body radiation dose to the adult patient is <70 µSV which is equivalent to the amount of radiation exposure on a flight from London to New York, or 1/15th of a chest x-ray, although pencil beam scanners confer significantly lower radiation doses than fan beam scanners and are therefore preferred in children. Alternative methods of measuring bone mineral density include single and dual photon absorptiometry (SPA and DPA), single x-ray absorptiometry, and quantitative
computed tomography (QCT). Other methods of evaluating bone density in childhood are being evaluated, most notably calcaneal (heel) ultrasound. Bone ultrasound attenuation (BUA) is a non-invasive, rapid, relatively inexpensive procedure which provides valuable information on the structure of bone and hence its fragility and fracture risk, as well as an indirect measure of its density. Jaworski et al (1995) reported a good correlation (0.83) between BUA and DXA. Normative data for children using bone ultrasound has recently been published (Mughal et al. 1997) and studies are underway assessing the use of BUA in children with eating disorders (Mather et al. 1999). Since BUA tells us something about the structure of bone as well as its density it may be a useful tool, in combination with DXA, for assessing children.

1.9.3. Interpreting bone density measurements in childhood

Methods for the analysis of bone density have evolved significantly over the past ten years, with an increase in interest in child and adolescent bone health. With this has come realisation of the limitations of applying techniques and approaches used in adults to growing children.

In adults, bone density using two dimensional bone area (areal BMD or aBMD), as measured on standard postero-anterior dual x-ray absorptiometry (DXA) scan, is directly related to osteoporosis, and therefore an adequate measure of bone density (Kanis et al. 1994). True BMD however, is a function of BMC per volume of bone, or volumetric BMD (vBMD).

In children bone mineral density is closely related to age and growth (Katzman et al. 1991; Lu et al. 1996), particularly in the lumbar spine. Prentice et al. (Prentice, Parsons, & Cole 1994) were amongst the first to draw attention to the impact of size-related artefacts, and went so far as to advocate that the use of aBMD be discontinued in epidemiological research, for both adults and children. Unlike DXA, QCT measures
bone volume, but is rarely used on children in practice because of the relatively high radiation dose.

In normal child and adolescent populations, growing and reaching puberty within normal ranges, bone area may be an adequate estimate of bone volume and size when matched for age alone (correlation $r^2 = 0.4$ (Lu et al. 1994)). In patient populations this is less likely to be true, and correction will need to be made according to the nature of the patient population. Low bone mineral content (BMC) can be due to light bones, narrow bones or short bones (Molgaard, Thomsen, & Michaelsen 1998).

Since the mid 1990's authors have been warning against the use of aBMD in clinical populations because of the misleading results that can arise (Cowell et al. 1995; Prentice, Parsons, & Cole 1994; Seeman 1997).

A number of approaches have been proposed to correct for bone size, using data from reference children. One method is to use a correction for bone area to approximate bone volume, which assumes a cubical lumbar spine. Known as Kröger's (Kroger et al. 1992; Kroger et al. 1993) method, it uses the height and diameter of each lumbar vertebra from the two dimensional scan to calculate volume by:

$$\pi \times \left( \frac{d_L}{2} \right) \times \text{height} \quad \text{where } d_L = \text{diameter of lumbar vertebra}$$

BMD is then: $\text{BMC/bone volume}$

When applied to data from 209 reference children, Lu et al. (Lu, Briody, Ogle, Morley, Humphries, Allen, Howman Giles, Sillence, & Cowell 1994) found that vBMD is independent of age and less dependent than aBMD on growth variables throughout childhood and adolescence. Carter and Katzman have used the same method with reference children (Carter, Bouxsein, & Marcus 1992; Katzman, Bachrach, Carter, & Marcus 1991).

Prentice et al. (Prentice, Parsons, & Cole 1994) suggest that to express data as BMD implies that BMC is directly proportional to BA, related by a constant $k$ which varies
with age and stage of development. K is often assumed to be 1.5 for the lumbar spine (Carter, Bouxsein, & Marcus 1992; Katzman, Bachrach, Carter, & Marcus 1991), as if the spinal vertebrum were a perfect cube. This gives:

$$BMAD = \frac{BMC}{BA \times 1.5}$$

where BMAD = Bone mineral apparent density, equivalent to an estimated vBMD.

In fact, the spinal vertebrum is not a perfect cube, and the exact relationship between the BMC and BA can be derived from the regression coefficient of lnBMC on lnBA, which results in values often significantly higher than 1, depending on the region of interest (Prentice, Parsons, & Cole 1994). This suggests that BMD does not correct BMC entirely for differences in BA. In this case, Prentice et al. suggest that correction should be made for overall body size, which may be exerting an independent effect on BMC at these sites. In their view the 'ideal analysis' by this method uses BMC as the dependent variable and includes weight, height and bone area in all multiple regression models. If these variables are converted to natural logarithms (ln) the power relationships and proportional effects can be seen more easily. However, this method was devised to correct for size related artefacts in adult bone size, and therefore do not directly take age-related artefacts into account.

The other main method that has been used to correct for size is to use prediction equations based on regression models that adjust for the major growth related determinants of bone. Warner et al. (Warner et al. 1998) have calculated prediction equations for BMC for British reference children (n=58), based on bone area, height, weight, puberty and gender. Measured BMC can then be expressed as a % of the predicted value. Equations were derived by correcting BMD for BA until a linear association was achieved for BMC and BA, then entering height, weight, gender and puberty into regression models to obtain power coefficients.

For the lumbar spine the resulting derived prediction equation is:
\[
\ln (\text{BMC}) = (1.489 \times \ln (\text{BA})) + (0.172 \times \ln (\text{weight})) - \\
(0.977 \times \ln (\text{height})) + (0.058 \times \text{PS}) + 1.994
\]

where PS = pubertal stage

Predicted \%BMC mean and SD for lumbar spine were:

Mean 100.1 (SD 9.35) Range 79.96 – 160.73

\%BMC is then:

\%BMC = measured BMC x 100/predicted BMC

and

BMC SDS = (%BMC – 100.1)/ 9.35

Although the sample size used to calculate the prediction equations is relatively small for reference data, the advantage of this method is that it uses measures collected in clinical practice, and it does not assume a cylindrical shape for the lumbar spine. The model does not include gender. The authors compared their method to that used by Molgaard et al. (Molgaard, Thomsen, & Michaelsen 1998) for BMC SDS derived from 343 Danish children and found no significant difference between the two. Molgaard’s observations were from whole body bone density, and lumbar spine data from whole body scans reads lower than from dedicated lumbar scans (Molgaard – personal communication).

Hannan et al. (Hannan et al. 1995a), using similar methodology to that of Warner et al., have also produced prediction equations for BMC and BMD. Their model for the lumbar spine corrects for age, weight, height and shoulder width. In patients with early onset eating disorders, where significant delay in puberty is likely, the validity of using age instead of pubertal stage must be questioned. This model has not been used in the present study, although it may have value if bone age rather than chronological age were used.
1.9.4. Bone accretion in childhood and adolescence

Normal values for BMC and aBMD using DXA have been established for children from the age of 3 years onwards (De Schepper et al. 1991; Faulkner et al. 1996; Hannan, Cowen, Wrate, & Barton 1995a; Kroger, Kotaniemi, Kroger, & Alhava 1993) and are discussed further in chapter 4. Increases in bone mineralisation occur gradually in early childhood (Glastre et al. 1990; Ponder et al. 1990) and accelerate during adolescence (Gilsanz et al. 1991; McCormick et al. 1991). Between the ages of 10 and 15 years BMD of the lumbar spine is significantly greater in girls, boy's values equalling those of girls by age 16 (McCormick, Ponder, Fawcett, & Palmer 1991). Faulkner et al. (Faulkner, Bailey, Drinkwater, McKay, Arnold, & Wilkinson 1996) showed that growth during puberty contributed about 51% of peak bone mass in girls, while in boys the contribution was 15%.

In the normal population girls reach PBM between the ages of 14 and 15 and boys continue to accumulate bone up until age 18, following attainment of Tanner stage 5 in pubertal development. Bonjour et al. (Bonjour et al. 1991) found that in girls most total gain in BMD and BMC occurs between the ages of 11 and 15, and thereafter bone accretion reduces dramatically except at the femoral shaft, where weight bearing exercise continues to result in accretion of cortical bone up to 18 years of age. In their study bone mass accretion was not arrested by the onset of menarche however, and the linear rate of bone accumulation in postmenarcheal girls appeared to be more dependent on age-dependent stature than on pubertal stage alone. In boys the acceleration in bone mass accumulation is relatively delayed, but is most pronounced between age 13 and 17. Bonjour and colleagues proposed a critical height up to which BMC and BMD are correlated with age, but thereafter height and bone mass become dissociated. Boot et al. (Boot et al. 1997) in a study of 500 children and adolescents aged 2 to 20 years found that the major determinant of BMD was Tanner stage in girls.
and weight in boys. Calcium intake and physical activity were particularly significant for boys. Both these studies looked at aBMD, making the findings difficult to interpret. Both Kroger (Kroger, Kotaniemi, Kroger, & Alhava1993) and Katzman (Katzman, Bachrach, Carter, & Marcus1991), expressing their findings as vBMD (BMDvol. gm/cm$^3$), showed that the annual increases in BMD and vBMD in both spine and femur were most marked in girls at the time of menarche and in males later. The acquisition of bone mass and bone density stopped or was markedly diminished before the age of 20 years. Katzman (Katzman, Bachrach, Carter, & Marcus1991) showed BMC increased with age at all sites. These increases were most rapid in the early teens and plateau after 16 yr. of age. When bone mineral values at all sites were regressed against age, height, weight, or pubertal stage, consistent relationships emerged, in which BMC was most strongly correlated, BMD was correlated to an intermediate degree, and bone mineral apparent density (BMAD), which is BMC normalised to a derived bone reference volume, correlated less well. BMAD minimises the effect of bone geometry and allows comparisons of mineral status among bones of similar shape but different size. Dietary calcium and exercise level did not correlate significantly with bone mass. From these relationships, the authors considered 50% of the pubertal increase in spine mineral and 99% of the change in whole body mineral to bone expansion rather than to an increase in bone mineral per unit volume. In multiple regressions, pubertal stage most consistently predicted mineral status. This study emphasises the importance of pubertal development and body size as determinants of bone acquisition in girls.

1.9.5. Influences on bone accretion and loss

The principal factors that affect bone density are familial, race, nutrition and body weight, sex steroids and growth hormone, and exercise (Dhuper et al. 1990; Lloyd et al. 1992; Ott 1991). AN has an impact on all those factors over which it is possible to
have influence (i.e. all but genetic and racial influences). Although oestradiol plays an important role in the process of bone accretion in girls (Dhuper, Warren, Brooks Gunn, & Fox 1990). Oestrogen status, as measured by serum oestradiol concentrations, has not been shown to correlate with bone mineral density (Rigotti et al. 1984). In boys the relationship between sex hormone status and BMD is also not clearly characterised, but preliminary work has shown a correlation between bioavailable testosterone and BMD in older subjects (Diver MJ et al. 1996, oral communication).

The relationship between calcium intake and BMD in normal children has not been fully established (Katzman, Bachrach, Carter, & Marcus 1991; Kroger, Kotaniemi, Kroger, & Alhava 1993). In a prospective double blind trial, 45 pairs of identical twins (6-14 years) received a mean of either 908g (diet alone) or 1612mg (diet plus calcium supplements) (Johnston, Jr. et al. 1992). Supplements significantly enhanced the rate of BMD increase. Another study showed that by increasing daily calcium from 80% to 110% of the recommended intake resulted in a significant increase in total body and spinal bone density in adolescent girls (Lloyd et al. 1996). In a 24 month double blind randomised control trial of calcium supplementation versus placebo in healthy girls age 11.9±0.5 years, the gains made in the lumbar spine and pelvis in the supplemented group were 12-24% greater than the increases made by the control group.

In a recent 18 month randomised controlled trial of healthy adolescent girls given an average additional 300ml of milk per day, significant increases in BMD and BMC as measured on DXA were noted (Cadogan et al. 1997). There were no differences between the groups in anthropometric measurements, or in markers of bone turnover. However serum IGF-1 levels were increased in the milk group and the authors note that differences may be accounted for in part by protein mediated effect and stimulation of the growth hormone axis.
Weight bearing exercise is known to influence bone density. In ballet dancers who have low body weight and amenorrhoea, bone density at the femoral neck is higher than in population norms, but at the lumbar spine is significantly lower. Trabecular bone, particularly in the lumbar spine seems particularly susceptible to osteopenia. In AN, where patients are often keen to exercise, there is a need to balance the benefits of limited weight bearing exercise with the increase in calorie requirement needed to compensate.

Recent research has suggested that delay in the tempo of puberty can interfere with the accretion of bone during puberty, with a risk of osteoporosis in later life (Finkelstein et al. 1992). In a study of adult men with a history of delayed puberty BMD was measured in the radius by SXA and in the lumbar spine by DXA. Both were significantly lower than age matched population norms, with differences of over 1SD in almost half. The authors suggested that the timing of puberty was therefore an important determinant of peak bone density in these men.

There is evidence that BMD in black African girls is higher (Bell et al. 1995; Ettinger et al. 1997; Gilsanz, Roe, Mora, Costin, & Goodman1991; Nelson et al. 1995), and that standardisation for BMD as measured by Hologic DXA based on USA populations are not applicable to the UK population, especially in the younger age group where mean Z scores varied by as much as -0.79 (0.29) from the manufacturers normal data (Hannan, Cowen, Wrate, & Barton1995a).

1.10. Bone density in AN

1.10.1. Bone density in adult women and adolescents

In recent years the hidden toll of AN in terms of bone loss and fracture risk has become clearer, and with it considerable therapeutic strivings aimed at those at greatest risk. The lifetime relative risk for AN in terms of fracture rate is comparable to subjects taking long term steroid treatment (Lucas et al. 1999). In adolescents the
problem of bone loss in AN is compounded by failure of bone accretion. AN in adulthood increases the rate of bone loss. In adolescence that risk is thought to be increased by lowering peak bone mass and thereby increasing fracture risk even if recovery from AN is complete. The literature has suggested, but not yet provided evidence, that premenarcheal AN patients are at greatest risk.

Females who recover from AN at a young age (< 15 years of age) can have normal total body BMD, but regional (lumbar spine and femoral neck) BMD may remain low (Bachrach et al. 1991), the areas of high risk for fracture in later life. The longer the AN persists, the less likely it is that the BMD will return to normal. An episode of AN during adolescence may compromise potential peak skeletal mass and will increase future fracture risk. Golden has argued that the degree of osteopenia in patients with AN depends on the age of onset and duration of amenorrhoea. Other studies support this view. Biller et al. (Biller et al. 1989) found that adult patients with AN who developed amenorrhoea during adolescence had significantly lower bone mineral density BMD than those who developed amenorrhoea later. As in adults, the degree of osteoporosis is related to the length of history of AN and the length of time of amenorrhoea (Ward, Brown, & Treasure 1997).

The role of nutritional factors in the bone density of AN patients is unclear. No correlation is reported between bone density and daily calcium intake, serum calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and parathyroid hormone levels (Rigotti, Nussbaum, Herzog, & Neer 1984). In Hay’s study (1992) of 69 adult patients with AN, duration of inadequate calcium intake accounted for 7% of the variance in bone density, but adequate calcium intake during periods of low weight were not shown to prevent bone loss. Bachrach’s study of younger girls found no correlation between BMD and calcium intake (Bachrach et al. 1990).

In females aged 12-20 with AN BMD was reduced in the lumbar spine and whole body, but not the radial shaft (Bachrach, Guido, Katzman, Litt, & Marcus 1990). BMD
correlated with body mass index (BMI) in both AN and control patients. In the AN group, BMD correlated with age at onset and duration of AN but not with calcium intake, activity level, or duration of amenorrhoea. However, in those patients with primary amenorrhoea BMD was below -2SD, suggesting that in this younger age group the effect of AN on bone mass accretion may be more profound.

Preliminary studies have demonstrated that AN is associated with an uncoupling of the process of bone formation and resorption, i.e. at low weight there is an increase in markers of bone resorption, without a corresponding increase in bone formation markers. This formation/resorption discrepancy restores with weight gain, until the rate of both formation and resorption are raised relative to controls (Stefanis et al. 1998).

In an early review of the findings, Salisbury et al. (Salisbury & Mitchell 1991) suggested that the relative contributions of the factors involved in the low BMD of AN needed to be quantified, and that trials of oestrogen and calcium supplementation should be undertaken to determine appropriate treatment. In a high risk population for osteoporosis such as children with eating disorders, a small gain in bone accretion at this crucial age, if held to adult skeletal maturity, may provide protection against future fractures. Whether bone mass can be restored with recovery from the endocrine and nutritional abnormalities has yet to be determined. None of the studies to date to my knowledge have taken into account bone size when measuring bone density.

1.10.2. Reversibility of bone loss

The best studies in adolescent patients (n=18 in the cross sectional study; n= 15 in the longitudinal study) used a normal control group of adolescent girls, but did not correct for skeletal size (Bachrach, Guido, Katzman, Litt, & Marcus1990; Bachrach, Katzman, Litt, Guido, & Marcus1991). The majority of patients had, or were assumed to have reached adult maturity in terms of bone age. In the cross sectional study 8 patients had primary amenorrhoea, the remainder being post-menarcheal. By this method 2/3
of the sample had BMD of less than -2SDS. The authors concluded that marked
deficits were a frequent complication of adolescent onset AN, and that the
premenarcheal patients may be at the greatest risk. These conclusions may be
radically altered if results had been corrected for bone size.

Initial reports in adults suggest that, as for many other parameters in AN, bone loss
was reversible with weight gain in certain subgroups (Bachrach, Katzman, Litt, Guido,
& Marcus 1991; Hay et al. 1992; Klibanski et al. 1995; Treasure et al. 1987) However
the reversibility of the bone loss has also been questioned. In Bachrach's study
(Bachrach, Katzman, Litt, Guido, & Marcus 1991), of 9 patients who had recovered
from AN during adolescence, 3 had persistent osteopenia of the lumber spine. This
study also reported an increase in bone mass with weight gain before return of
menses (Bachrach, Katzman, Litt, Guido, & Marcus 1991). Ward and Treasure, in a
recent study of hip and spinal BMD found osteopenia in 14 of 18 women despite long
term weight recovery (Ward, Brown, & Treasure 1997). As before, duration of
amenorrhoea and an index of illness duration were the best predictors of bone density.
In the longest follow-up study to date, a mean of 11.7 years after onset, Herzog et al.
(Herzog et al. 1993) found marked differences between patients with a good disease
outcome (lumbar spine BMD -0.26 SDS; radial BMD -0.68 SDS) from those with poor
disease outcome (-1.73 and -2.18 respectively). They concluded that, in patients with
good disease outcome, trabecular bone loss may be mostly reversible, but that cortical
bone proceeds more slowly, if at all. Seeman et al. (Seeman et al. 1992) demonstrated
partial benefit on bone density for patients with AN who were taking the oral
contraceptive pill.

1.10.3. Summary

Patients with eating disorders are at very high risk for future osteoporosis, the
theoretical risk being greater in children and adolescents because of the impact on
attainment of peak bone mass as well as increased bone loss. Studies in children and adolescents are often flawed by failure to correct for bone size. This and the lack of good reference data for childhood bone density that takes into account stage of maturation, make findings to date difficult to interpret. There is an urgent need to better understand bone density in disorders such as early onset AN because of the implications for treatment and prevention.

1.11. Conclusions

Despite a wealth of knowledge about the endocrinology of the eating disorders, particularly AN, information relating to children remain obscure, particularly when the features are not absolutely typical. The contributions of weight loss and acute starvation to these endocrine abnormalities only account for part of the observed phenomena. Measures of childhood psychopathology in eating disorders are not yet sophisticated enough to use as quantitative measures, and therefore this element remains at the level of clinical description. Inter-individual and between group differences in anthropometric parameters may help in clarifying patterns of growth and pubertal development in the childhood onset eating disorders. The need for knowledge in this area is pressing, as our awareness increases of the potential irreversibility of physical parameters and the apparent rise in eating disorders in younger children.
2. The measurement of body composition in children and adolescents with eating disorders

2.1. Measuring body composition – why?

The term 'body composition' refers to a broad range of measurements and techniques that attempt, amongst other things, to quantify nutritional status, from the simplest anthropometrics to complex models differentiating fat, water, mineral and protein. Increasingly the distinction is being made between those methods that measure size and nutritional status from those that measure individual components of body composition. Individual components of body composition are important in a wide range of clinical situations, from calculating drug doses and rates of rehydration and nutrition to evaluating short and long term risk for particular diseases, including growth disorders. It is important therefore to clarify what each approach to measuring body composition is able to tell us, and what it cannot.

An index of nutritional status can be seen as a global index of health, at both ends of the nutritional spectrum. The first task is therefore to be able to distinguish, in a meaningful way, malnutrition and overnutrition. The second level of refinement is to determine the components of malnutrition or overnutrition once they occur i.e. what exactly is being lost or gained.

Body composition is divided into 'components', and different techniques measure different components. The simplest model is a two component model; fat mass (FM) and fat free mass (FFM). If body weight and either FM or FFM is known, the other can be calculated. FFM is composed of water, protein and minerals, in decreasing quantities. It is therefore not directly synonymous with lean mass, although the terms are often used interchangeably. Two component models assume a constant relationship between the relative contributions of the FFM components, an assumption that would not hold true in the majority of eating disorder patients. In general however,
if fat mass is the object of interest, this model is adequate provided the assumptions about the relationship of FM to FFM hold true. On the whole clinicians are interested in relative fatness and in the lean growth of their patients. Many measures used to assess nutritional status are not appropriate for the separate evaluation of body fatness and lean mass, although they are often used as if they were equivalent.

The problems of accuracy and precision with which body composition can be measured in disease states can be overcome to some extent by using multi-compartment models of body composition, which do not rely on assumed constant FFM properties such as hydration or density. Techniques have been developing that allow multi-component models to be evaluated (Dewit et al. 2000; Wells et al. 1999) and, although these remain cumbersome for clinical use, they have become more 'child friendly' and therefore of value for research purposes.

Using more sophisticated direct measures of individual body composition components allows a better understanding of the body composition of normal children, without which it would be difficult to interpret findings in disease states. The most detailed study is that of Fomon et al. (Fomon et al. 1982), who has analysed the 'reference child', based on data extrapolated from a small number of actual measurements and corrected for weight and height. Total body water and potassium and calcium data were also used. Although there were a number of assumptions necessary (e.g. that Na:K ratio are the same in children as in adults, and that glycogen accounts for 0.5% of body weight) some important observations were made. For example, Fomon noted that if adult constants were used, fat content would be over or under estimated in the child by as much as 47%. He concluded that age specific constants are needed if estimates of body composition are to be possible from indirect measurements. He also noted that a 'maturation' in chemical composition of FFM occurred: the percentage of water decreases with age and the proportion of protein and osseous mineral increase.
In other words, children are not simply small adults in terms of body composition, and techniques for measuring need to be adjusted accordingly.

Detailed techniques such as those applied by Fomon have not yet been used in children in disease states. In order to do so, reference data for children of all ages and pubertal stages would be required to adequately interpret findings from four component models, if FM and FFM were expressed in absolute terms i.e. kg. One convention that avoids this is to express FM as a ratio relative to weight, most usually % body fat. However, this assumes a normal amount of lean mass, in relation to which fat mass is either increased or decreased. If lean mass is also affected by a disease state this assumption is no longer valid (Wells 2001). These issues are discussed further below.

Whichever technique is used, all measures of body composition must be evaluated on the basis of their ability to address the issues of concern with adequate reliability and validity. This means not only ensuring that interpretation of the findings is appropriate, for example for the age of the child, but that the technique is measuring what it is purporting to measure. Van den Broek (Van den Broeck & Wit 1997) proposes considering measures of body composition at 3 levels of validity, outlined here.

2.1.1. Level 1: Estimates of body size.

Most of the anthropometric measures reflect some aspect of body size. Weight-for-height indices (including body mass index (BMI\(^1\))) are simply measures of weight corrected for height (± age and sex) and are used as surrogates for adiposity. One significant drawback in growing children is the lack of correction for other important aspects such as pubertal status, body size, and body shape. The second drawback is in the inability of weight for height indices to discriminate fat mass from lean tissue.

\(^1\) Body mass index = weight in kg/(height in m)^2
Over short intervals of time changes in body size can be primarily attributed to changes in fatness within individuals, particularly in the normal weight range, but this generalisation may be less applicable in very underweight or overweight children, or when weight change is significant over time. As an absolute measure of fatness accuracy is poor, and weight for height measures may have value as screening instruments but lack the sensitivity to detect subjects of clinical concern. For example, in obesity, children with high body fatness but low lean mass will appear in the normal range for the population.

Another widely used anthropometric measure is skinfold thickness (SFT). By directly measuring subcutaneous fat, SFT is also a proxy for adiposity but says little about FFM. Nor can much be said about regional distribution of fat from SFT, in particular in the lower body/legs.

The main problems at this level of validity are in technical and inter-observer reliability and in the interpretation of findings.

**2.1.2. Level 2: A ‘gold standard’ for body composition**

The validation of level 1 measures depends on their actual relationship to body components such as fat mass or lean mass. This requires a ‘gold standard’ measure against which other measures can be validated. The only truly direct measure of body composition is from the chemical analysis of cadavers. All other measures of body composition are derived or predicted rather than measured. Indirect measures usually assess a constituent of the body and then, assuming a constant relationship between that component and the rest of the body, other components are calculated.

Most techniques have been developed on adults, and are in their infancy in their application in children. Even in adults there is wide variation, and there is too little known about inter-individual variation. For example dual x-ray absorptiometry (DXA), is often upheld as the gold standard for body composition although many papers
specifically refute this e.g. (Roubenoff et al. 1993). It was designed for the measurement of BMD and its precision in the measurement of soft tissues is less compelling.

Applying these techniques in children causes further complications. Until recently, constants for constituents in children and adolescents have been derived from adult reference data. Moulton, in 1923, realising that children differed in their composition, proposed that 'chemical maturity' occurred at 4% of the adult lifespan, an assumption which was upheld for many years. It is now clear that components of body composition mature at different rates (Fomon, Haschke, Ziegler, & Nelson 1982). For example, bone accretion may continue into the third decade despite cessation of longitudinal growth.

A further problem at this level of validity is the lack of normal data in children to compare different techniques, necessary for the meaningful interpretation of findings in clinical populations. The reference child described by Fomon et al. (1982), whilst an invaluable model for changes in body composition during childhood, refers to children measured in the 60's and 70's, represents only the average and not the range for each sex, and was based on actual measures only in infancy and at 9 years, with other data points being smoothed onto the NCHS 50th centile. Reference data sets for predicted (not measured) body composition in children have been published subsequently, (Gerver & de Bruin 1996; Iwata et al. 1993; Schaefer et al. 1998), although none present data in a way that allows the separate adjustment of fatness and lean mass for body size. To date reference data for DXA evaluation of body composition through childhood have not been published.

2.1.3. Level 3: Defining abnormality

Assuming we are able to 'know' the true body composition of a normal child, Level 3 validity depends on being able to define a measure as abnormal, e.g. underweight or
overweight. This assumes a population standard, from which cut-off values can be derived. Ideally such a cut-off should be related to predicted increased morbidity, and would take into account, for example, inter-ethnic variability.

The validity of measures of body composition therefore depends on the component(s) being measured, the accuracy of that measurement, the nature of the assumption of relationships between body components, the validity of these assumptions in a particular disease state, and the applicability of that measurement to a reference child of the same age and gender. It also depends, fundamentally, on the research or clinical question being asked.

2.2. Measuring body composition – how?

2.2.1. Anthropometry

Several simple methods have been used to estimate elements of body composition, such as adiposity (or fat mass - FM), fat free mass (FFM), or interstitial water. The simplest include indices such as BMI, weight-for-height, SFT, arm fat area, mid-arm circumference – all standard anthropometric measures. Some indices combine these measurements, or involve the use of regression equations.

2.2.1.1. Weight for height

Van den Broek and Wit (Van den Broeck & Wit 1997) have summarised these measures, of which there are many variations. Ratio methods like the ponderal index (weight/height^3), Quetelet’s index (weight/height^0.5) or the Waterlow index (weight/expected weight for height) are extremely easy to use in routine clinical practice, screening and epidemiological studies and as such are popular. Nevertheless a recent study highlighted high interexaminer variability in calculating these ratio indices (Poustie et al. 2000). Generally indices derived from regression equations, such as the weight-for-height proposed by Tanner or Cole (see below), have greater
statistical validity than ratio methods. All of these indices can be expressed as a % of median reference values, as percentiles or as standard deviation scores (SDS) when applied to children. They require calculation in relation to suitable reference data. Despite their theoretical superiority, regression indices such as weight-for-height do carry their own inbuilt bias, and show consistent associations with each other even when they are not correlated. For example;

- higher mean weight-for-height values occur at extremes of height range for a given age (Freeman, Power, & Rodgers 1995)

- at a given age, the spread of weight-for-height is greater with increasing height. Therefore, amongst tall children a greater proportion would be classified as over or underweight.

- those reaching earlier maturity would tend to be heavier.

Whilst these caveats are true for the normal population, those with growth disorders are likely to present further complications. For example, indices for the measurement of adiposity may have greater validity if they are related to height rather than independent of it, or are disorder specific e.g. in Turner's syndrome.

Segmental proportions further confound the issue of measurement error or bias. During puberty there is considerable disproportion between sitting height and leg length, and for taller children (Brinkers et al. 1994) and those with pubertal delay (Albanese & Stanhope 1993), this discrepancy is most marked. For 10-30% of individuals BMI would alter by more than 1kg/m² if adjusted for sitting height (Norgan & Jones 1995).

In the UK literature % weight for height has been adopted by convention for expressing nutritional status in children and adolescents with eating disorders. There are several ways of expressing weight for height, none of which are ideal (Cole - personal communication):
1. Weight-for-(Height-for-Age): Given the child's height, the age where the child's height is equal to the median reference height is identified ('height-age'). Using the reference weight at this age as the denominator, the ratio of observed to reference weight can be calculated. This is known as the Waterlow method. This procedure gives similar answers to a formal weight for height curve. Its disadvantage is that after puberty, height stops but weight continues increasing, so if the child's height is above the median their height-age is undefined. This procedure also assumes that the weight-height relationship is independent of age, which is not true during infancy and puberty.

2. The child's height for age centile from the reference is identified. Taking the corresponding weight for age centile as the denominator, the ratio of observed to reference weight is calculated. This is the simplest procedure, but otherwise has little to commend it theoretically.

3. Using a power index weight/height to adjust weight for height at each age, the centiles of the index can be calculated at each age. This is the basis of the British BMI charts and is equivalent to the weight for height method proposed by Cole (Cole 1979). Thus %BMI = %weight for height by this method.

Appendix 2.1 outlines details of the basis of weight for height using this method, as this is the index used throughout the study.

For convenience, since the relationship cannot be represented in normal curves as for weight and height, Cole devised a slide rule (Cole1979), which is essentially a normogram. For a given age, weight and height of a child this generates a height-for-age, weight-for-age and weight-for-height as a percentage, based on the Tanner standard. The author indicates the presence of wasting as weight-for-height below 80%. Weight-for-height is likely to be replaced in the literature with the more accurately named but otherwise equivalent % BMI or alternatively BMI standard deviation score (BMI SDS). %BMI is the terminology used on the new version of the slide rule.
Alternatively reference charts for BMI may be used, although BMI charts only show nutritional status and are therefore of value only alongside height and weight charts.

Other methods of calculating weight-for-height differ only in their estimation of $n$. For example, if weight-for-height were judged by comparing weight-for-height of a child with weight:height of an age matched standard child, i.e. $n = 1$ (McLaren & Read 1975), the effect is to make tall children appear fat, and short children appear thinner than they really are. The McClaren and Waterlow methods can show disagreement by as much as 15%, particularly during the first year of life. Despite this, both are widely used.

In the USA the tradition has been to use percentage of ideal body weight (IBW).

\[
\text{Percentage of } = \left( \frac{\text{subject's weight}}{\text{ideal body weight}} \right) \times 100.
\]

IBW is obtained from U.S. Vital and Health Statistics Series 11 data, which provides reference data based on gender, in one year age bands, and at height intervals of 5 cm. For each height band centiles are provided. Although the sample size is good (e.g. 643 boys aged between 12 and 13, with 156 at the median height) this data collected between 1966-70, like the Tanner-Whitehouse standards in the UK, must now be out of date. Diagnostic criteria for AN include an ideal body weight of 85% or below. The normal range is considered to be 90-100% IBW.

The ability of any weight-for-height index to predict adiposity varies with age. Correlations of between 0.56 and 0.76 have been reported between these indices and prediction of %FM (Frischano & Flegel 1982). This is particularly true for infants, and in disorders where FM increases while lean body mass decreases, such as Prader-Willi syndrome. The opposite is true for AN, where exercising may increase lean body mass, whilst every attempt is being made to decrease subcutaneous fat. Thus a relatively normal weight-for-height index may be found in a child with a very low fat
mass. Alternatively, both lean mass and fat mass may be reduced, leading to a misleadingly high %FM as a proportion of the total, low, body mass.

2.2.1.2. Body mass index (BMI)

Body mass index (BMI) is discussed separately as it is the most widely used measure of nutritional status in the eating disorder literature. BMI or Quetelet’s index is also the most widely used measure of nutritional status in clinical practice generally and is a highly valuable screening tool for disorders influencing body composition. It is the recommended measure for population screening of obesity (Prentice 1998), for which it has high specificity but poor sensitivity (Reilly, Wilson, & Durnin 1995). It is also the basis for current definitions of chronic protein calorie malnutrition (James, Ferro, & Waterlow 1988) and eating disorders (WHO 1991), although its specificity and sensitivity for detecting undernutrition is less well studied. Like many useful screening tools, its value becomes less clear when looking at extremes and in severe disease states.

The rationale behind BMI as a nutritional index is that it is highly correlated with weight while being minimally correlated with height. Although, as previously discussed, it is not ideal to use height$^2$ for infancy and adolescence, this is the power coefficient that best adjusts weight for height whilst at the same time removing most of the trend of increasing weight with age. Both fat mass and lean mass are highly correlated with BMI, although it cannot distinguish them (Wells 2001).

BMI has other limitations. Its value as a measure of body composition in adult eating disorder patients has been questioned (Hannan et al. 1995b), as has the general validity of using BMI for clinical assessment of paediatric patients (Warner et al. 1997). Recent evaluation in children has demonstrated that BMI is a poor predictor of fatness in children (Ellis, Abrams, & Wong 1999; Wells 2000b). BMI is thus only an approximation of body fat in the normal population (although is better in obese conditions).
subjects). At any given value of BMI there is a wide range of body fat as a percentage of weight (Wells, Fuller, Dewit, Fewtrell, Elia, & Cole 1999).

The normal range for BMI in adults is 20 – 25 (Garrow & Webster 1985). This cut off relates only to slight increases in mortality risk and tells us nothing about other aspects of health and functioning. Furthermore little is known on a population basis about the relationship between low BMI and morbidity. Based on 1000 women and 5000 men, mostly between the ages of 17 and 34, a BMI of -2SDS for adult women would be 17.6 (Durnin & Rahaman 1967) and for men would be 18.5. This is based on fit and healthy adults. The lower level of acceptable BMI must depend in part on the level of physical activity or other energy expenditure. A BMI of 18.5 is the cut-off taken for definitions of chronic energy deficiency in adults (James, Ferro, & Waterlow 1988). Although women have a higher % body fat at any given BMI than a man, this seems to be necessary for biological (and particularly reproductive) functioning and there are no differences in definitions on the basis of gender.

BMI in growing children and adolescents is more complicated, since increases in weight, height and BMI are not linear during childhood, particularly in puberty. The average adiposity of children undergoes variation so that reference data are required to make meaningful interpretations of nutritional status. Also the total technical error of the BMI measurement is approximately 1kg/m² (Roubenoff, Dallal, & Wilson 1995). This is greater than the difference between the 5th and the 10th centiles for the general population. The distribution of BMI is skewed, so Z scores and centiles cannot be calculated from the mean and standard deviation assuming a normal distribution. Cole’s LMS method (Cole 1990) has made the process of smoothing and calculating centiles more user friendly. This method has been applied to British (Cole, Freeman, & Preece 1995) and French reference data (Rolland-Cachera et al. 1984). Curves such as these show that BMI increases shortly after birth, declines in middle childhood,
increasing steadily from the age of about 8. Thus BMI is about the same at age 12 as at age 1.

Without more detailed analysis it is not possible to know how much of the change in BMI is directly attributable to a change in body fat. Various factors apart from age and sex effect the BMI-fatness relationship in children, including ethnicity, segmental proportions, fat distribution and disease state (Daniels, Khoury, & Morrison 1997; Van den Broeck & Wit 1997; Warner, Cowan, Dunstan, & Gregory 1997). Therefore, whilst the use of BMI centiles or standard deviation scores have improved the validity of BMI in children, and has strengthened the position of BMI as the screening measure of choice for population based studies and the detection of overweight, their use in disease states requires further study. Cross-sectionally, the problem is defining the level of concern for underweight children, since studies comparable to those in adults are not available. Longitudinally, noting deviation from an individual’s centile position may be more sensitive to the identification of ill health than using cut off criteria. Interpretation will need to take into account regression to the mean, and can be corrected for by using conditional references, or correcting observed change for expected change.

2.2.1.3. Fat mass index (FMI) and fat free mass index (FFMI)

The limitations of BMI or equivalent ratio measures of body composition (e.g. weight-for-height or BMI standard deviation scores (SDS)) lie in their poor capacity to discriminate underweight from inadequate body fat. Recently, Wells (Wells 2000a) has argued that a more informative way to display and understand body composition in children and adolescents is to normalise both FM and FFM for height according to a method described by Van Itallie et al. (Van Itallie et al. 1990). This allows differentiation of energy store (fat) depletion from the more serious loss of lean muscle mass. Normalisation of FM and FFM also allows appropriate comparison between
paediatric patients and reference data where illness may have resulted in patients being shorter than age-matched controls.

Although it is theoretically possible to consider separate relationships between FM and height, and FFM and height, in practice it is more informative to base the normalisation on the general relationship between weight and height. As before, the question of the optimum power \( n \) by which height should be raised is an issue as yet unresolved for these indices (Wells2000a). Unpublished data suggest that the power by which height needs to be raised for FM is higher than that for FFM (Wells – personal communication). A value for \( n \) of 2 has been used on the basis of studies demonstrating that weight/height\(^2\) is successful in normalising weight for height for the majority of human childhood (Cole 1986; Gasser et al. 1994), and the belief there is little to be gained from using the Benn index (Benn 1971), where \( n \) varies with age. Thus both FM and FFM can be normalised for height by dividing by height squared (Hattori, Tatumi, & Tanaka 1997; Van Itallie, Yang, Heymsfield, Funk, & Boileau1990). These variables can be plotted against each other (Hattori, Tatumi, & Tanaka1997), with FMI on the x-axis and FFMI on the y-axis. Diagonal lines then represent BMI and percentage body fat. Figure 2.1 demonstrates the application of this method to a group of women from developing countries, women from Western countries and adult patients with AN, based on published studies of body composition (Wells and Nicholls 2002). It shows that adult women from industrialised countries with the same BMI have a higher FMI than women from developing countries, who have a greater lean mass (FFMI).
Figure 2.1: Hattori graph of fat mass index (FMI) against fat free mass index (FFMI) applied to women from developing countries, control women from Western countries and women with AN.

![Graph showing FMI against FFMI for different BMI levels and conditions.]

Figure 2.2: Hattori graph of reference girl and reference boy (reproduced with permission).

![Graph showing FMI against FFMI for different ages and BMI levels for boys and girls.]
Figure 2.2 shows data from children aged 1 to 10 and demonstrates the variation in FMI (or % fat) for a given BMI (Wells2000a). Although more cumbersome, this method of representing BMI, with its constituent FMI and FFMI, gives more useful information about body composition than BMI alone. For example, BMI can embrace a wide range of fatness across the sexes. At present there are no gender based distinctions in BMI cut-offs for obesity and disease states, including eating disorders.

Whilst this method is a good way to compare individuals of a single age, normalising for height² is only valid if the same stage of growth is being considered. In addition, children demonstrate natural age-related changes in relative FM and FFM deposition (Fomon, Haschke, Ziegler, & Nelson1982; Wells2000b). As such, FMI and FFMI are best considered separately in relation to age for data where a range of ages and stages of growth are under consideration. This method is used in the present study.

**2.2.1.4. Skinfold thickness**

Skinfolds thickness (SFT) only measures subcutaneous fat, and is thus a more direct measure of adiposity than weight-for-height indices. It is a simple technique, easy to use in children and therefore very popular with clinicians.

SFT is reputed to have high inter-measurer variation, although with training reliabilities of > 0.9 can be reached. Estimates of body fat from SFT may use one measure, or combine a SFT (e.g. triceps) with mid-arm circumference. In growth disorders dual sites are often used (usually triceps and subscapular) since treatments such as growth hormone lead to a redistribution of body fat. Regardless of sex and race, indices of weight and height have higher correlations to subscapular than to triceps SFT in normal adults (Frischano & Fiegl1982).

Standardly, prediction equations are used to predict % body fat from single or multiple SFTs. Prediction equations that combine multiple SFTs also combine their measurement errors. On the other hand, as predictors of body fat, multiple measures
have lower prediction errors than single measures. Standard error for these measures in children are 2.6-3.4% body weight (Heymsfield et al. 1997), a coefficient of variation of about 20%. Errors inherent in the measurement of SFT include both pathological changes and normal variation. Pathological changes might include oedema and dehydration. Normal variation may arise as a result of variations in compressibility. SFT tend to assume a constant thickness of the band of subcutaneous fat that surrounds the arm, which is not true in conditions of muscle wasting and obesity, where tissue may hang in folds.

The prediction equations that are used to convert raw measurements into values for % fat have been shown to be inaccurate in groups and in individuals (Reilly, Wilson, & Durnin1995; Wells, Fuller, Dewit, Fewtrell, Elia, & Cole1999). In addition, their validity has been questioned in very thin young women, because of the value of the reference data at the extremes of weight (Durnin & Rahaman1967). An alternative is to express SFT as SDS (Davies, Day, & Cole 1993), which are reasonably accurate at the extremes of the weight spectrum. However, the reference data are adapted from those collected by Tanner in 1966-7 and are unlikely to reflect the activity levels and dietary intakes of children today.

Despite theoretical and technical limitations, the commonest practice is to present SFT data in the form of percentage (%) body fat. Wells (Wells2001) has argued that the use of % body fat is flawed, especially in children, as it ignores between subject variation in lean mass. Two subjects will differ in percentage fat either if they have similar FFM but different FM, or if they have similar FM but different FFM. Percentage fat is therefore influenced by relative lean tissue mass, and is not an independent index of fatness (Van Itallie, Yang, Heymsfield, Funk, & Boileau1990). For example, if a child weighed 45 kg, height 165 cm and her fat mass was 6 kg, her % FM would be 13%. However, a girl were only 23 kg, height 165 cm and her fat mass 4 kg her %FM would be 17%, despite the fact that she is thinner and has lost a greater amount of
body fat than the first girl. This defect is less of an issue in the general population, where changes in weight are likely to reflect changes in body fat. However, many disease states, including eating disorders, influence lean and fat mass separately and this may be masked by the use of % body fat.

Finally, despite being widely used, little is known about SFT as a measure of health outcome. SFT may prove of value in evaluating intra-abdominal versus subcutaneous fat, which is known to have predictive validity for poor health outcome in adults.

2.2.1.5. Regional fat distribution

Waist circumference and waist circumference to height ratio have been proposed as better indicators of the need for weight management in obesity than BMI (Ashwell, LeJuene, & McPherson 1996). It is their relationship to abdominal fat that confers greater predictive value. The proportion of intra-abdominal fat increases steadily in males after puberty, while in females it remains constant, possibly even falling in late childhood (Ogle et al. 1995). Waist circumference:height has a higher correlation (0.83) to body fat as measured on CT scan in adults of normal or high weight, than does BMI, waist circumference alone, or waist:hip ratio (Ashwell, Cole, & Dixon 1996). Whether this holds true for children and at the extreme wasting end of the spectrum is not clear.

As predictors of long term morbidity, the focus has been on high waist:hip ratios. Whether the same is true at low weight, i.e. whether low waist hip ratios are as good as or better predictors of morbidity as total FM, is unclear. Given the discovery of leptin both as a marker of adipose tissue, particularly intra-abdominal adipose, and as endocrine modulator of the reproductive system, further exploration is warranted.
2.2.2. Other methods

A variety of techniques have now been used in research in children and adolescents to evaluate the two components of FM and FFM. Some examples of the most widely used are given. For a review, see Elia (1999).

2.2.2.1. Bioelectrical impedance

Bioelectrical impedance analysis (BIA), bioelectrical impedance spectroscopy (total BIS), and total-body electrical conductivity (TOBEC) are all non-invasive techniques based on differential electrical conductivity of body tissues. These methods tend to be used in conjunction with direct anthropometric measures, but only slightly increase the explained variance. They can be considered anthropometric measures that add a correction for electrical resistance. BIA measurements, the most widely used, are largely determined by impedance of the extremities.

Concern has been expressed about differences in results obtained from the application of different formulae to derive a prediction of body water, with widely varying results (Yanovski et al. 1996). One study comparing BIA, BIS, TOBEC and DXA found that fatness classification of an individual as normal, overweight, or obese on the basis of his/her %fat was significantly method dependent (Ellis, Abrams, & Wong 1999). BIA has been shown to overestimate % FM in underweight subjects and overestimate it in overweight subjects, compared to DXA (Okasora et al. 1999). Furthermore, the method suffers from the same limitations as SFT when it comes to normalising body fat for size and expression as a % FM.

Nevertheless, these methods are widely available, such that % FM calculated by one of these methods may be part of a routine medical check up, and are even available at many sports centres. Reference data are also now available for children (Iwata, Satou, Iwata, Hara, Fuchigami, Kin, & et al. 1993) and the technique is gaining credence rapidly. BIA has been used extensively for whole body measures of body composition,
but not for body parts, although it can be used for segmental purposes and should have greater accuracy there. Recent developments have made it possible to measure muscle and adipose in limbs, as well as skinfold thickness and blood volume. The best correlation between BIA and SFT has been found at the biceps (Elia and Ward 1999), but intra and inter observer variation was less with BIA, and may be of use in studies with multiple observers (Fuller et al. 1991).

2.2.2. Direct imaging (DXA/MRI/CT)

Dual x-ray absorptiometry (DXA), magnetic resonance imaging (MRI) and computerised tomography (CT) allow spatial anatomy to be measured directly, from which geometric reconstructions give a summary of ‘body composition by volumes’. Accurate mass measurements for organs can be determined using MRI and CT. These methods are being increasingly applied to a range of individuals and disease states, and look set to become the basis for a new criterion method of body composition measurement (Pierson, Wang, & Thornton 1997). For MRI and CT, high radiation, high costs or both mean that their use is limited to research and is entertained with caution in children.

DXA has, within the past 10 years, become one of the more reproducible ways of measuring body composition (Figueroa-Colon et al. 1998). Studies in normal children have been limited because of the small but significant radiation dose. Thus reference data for body composition by DXA in children have been hard to obtain. Nevertheless, increasingly DXA is being used in paediatric clinical practice to evaluate BMD and body composition.

DXA assumes a three compartment model for body composition, consisting of bone, lean tissue and fat mass. The strength of DXA lies in its measurement of bone and, as noted above, its accuracy with soft tissue is more questionable, although regional precision can be reasonably high. Errors in body composition measurement occur because soft tissue is not uniformly distributed. The DXA scanner assumes that the
soft tissue lying over bone is equivalent in thickness to soft tissue lying next to it. In one study (Ogle, Allen, Humphries, & et al 1995) DXA weight underestimated actual scale weight by a mean of 0.83kg. Thus, whilst it may be possible to determine %FM by DXA, the validity of this for clinical purposes is unclear. In addition, measurement error is intrinsic to the use of DXA in children, since the machine’s ability to determine size (area) is altered by the body size of the individual. The implications of adjusting for body size for the use of DXA across such a wide age range and body size has been discussed extensively in relation to BMD, but less so for body composition. Whilst DXA is fast becoming the ‘gold standard’ for measures of body composition in normal weight and obesity, it has its critics (Roubenoff, Kehayias, Dawson-Hughes, & Heymsfield 1993). In very underweight people and children the problems the machine has in estimating body size mean that results in patients with AN should be interpreted with caution.

2.2.2.3. **Water and air displacement methods**

Under water weighing (UWW) has been upheld as the most reliable method for determining body composition (Probst et al. 1996), with a test retest reliability of 0.95 and concurrent validity of >0.8, although other methods have now improved on this, particularly in middle childhood (Wells, Fuller, Dewit, Fewtrell, Elia, & Cole 1999). UWW uses Archimedes principle of water displacement to calculate body density. UWW density is calculated from the formula:

\[
D = \frac{W}{W-Ww/dw-(RV+GI)}
\]

W= weight in air; Ww=weight in water; RV= correction for lung vol.; GI= correction for gastrointestinal gas

Percentage body fat is then calculated from Siri’s equation (1900): \((4.95/D-4.50)\times100\)

The use of this method, which involves immersing the body entirely in a tank of water, is clearly impractical for clinical purposes, but is widely used to validate other measures.
New techniques in air-displacement plethysmography have overcome many of the problems of poor reproducibility and validity, as well as the discomfort of being submerged underwater. The BOD POD air-displacement system (BOD POD body composition system; Life Measurement Instruments, Concord, CA, USA) is more precise than hydrodensitometry, is simple and rapid to operate (approximately 1 minute measurements) and the results agree closely with those of hydrodensitometry (e.g. +/- 3.4% for estimation of body fat) (Elia & Ward 1999). Although still a research tool, the BOD-POD will allow more sophisticated, four component models of body composition to be applied to children.

2.2.2.4. Other techniques

Total body potassium (TBK) assumes that 98% of potassium lies in lean tissue and that the concentration is constant. Lean tissue (kg) is then TBK/potassium concentration per kg of lean tissue. TBK can be measured by administration of a radioisotope, or by using a whole-body scintillator to detect naturally emitted $^{40}$K.

Total body water (TBW) assumes that all body water is in fat free tissue in constant proportion. Using % water in FFM as 73.2%, derived from the analysis of cadavers, FFM (kg) can be calculated from TBW/0.732. Body fat (kg) is then Body weight – FFM. TBW is determined by using a tracer such as deuterium ($D^2O$), which is ingested and then enrichment measured 1-3 hours later. The technique is quick, easy, and minimally invasive and has been applied in children, but is expensive due to the cost of the analysis. Wells et al. (1999) found this technique to be the most accurate of the two component methods.

Finally, in-vivo neutron activation (IVNA) has been in use for over 25 years, although recent reference data for body minerals have improved the value of the technique. In conjunction with TBK, these techniques can provide high resolution for defining the biochemical composition of individual organs and body cell mass. The substantial radiation dose limits their use in children.
Although valuable in terms of research and validation of other methods, these techniques have little role in clinical practice.

2.3. **Body composition in eating disorders.**

Measures of body composition can be useful for diagnostic purposes, for guiding treatment, and for monitoring improvement. This section considers the application of body composition measures in eating disorder patients, particularly children and young adolescents. The majority of studies to date looking at body composition in eating disorders have been on adult patients or older adolescents.

2.3.1. **Nutritional definitions in eating disorders**

Current criteria for AN specify weight loss to a BMI of 17.5 or below in adults (WHO 1991), or to 85% of ideal body weight (American Psychiatric Association 1994). DSMIII-R described this weight criterion as “arbitrary but useful” (American Psychiatric Association 1987 p 65.), while DSMIV states that “it is unreasonable to specify a single standard for minimally normal weight that applies to all individuals of a given age and height” (American Psychiatric Association 1994 p. 540).

Until 1987 (before DSMIII-R), the weight loss criteria was to 75% of IBW or below. Revision of the weight criteria was based, in part, on attempts to make diagnostic criteria more applicable to children. Irwin (1981) argued that children differ from adults and from each other in their relative amount of body fat. Thus a child at 85% of ideal body weight could have the same degree of malnutrition as an adult at 75% IBW.

Taking this argument one step further Lask and Bryant-Waugh (Lask & Bryant-Waugh 2000) have argued that in children both rate of weight loss and weight loss relative to previous weight, not absolute body weight, are more relevant. Thus a child at 100% weight-for-height may show signs of starvation if she/he was previously 125% weight-for-height. The ‘Great Ormond Street checklist’ criteria for childhood onset AN
therefore do not include a weight threshold, but specify only significant weight loss. Empirical data supporting 85% of IBW as an appropriate cut off for children with AN have not been published to date, nor is it clear whether another, more direct measure of nutritional status could have greater value in the early onset population.

The need to determine some measure of body composition in eating disorder patients is without question. An extensive literature supports the value of body composition as a correlate of mortality and morbidity, including osteoporosis (Bachrach, Guido, Katzman, Litt, & Marcus 1990; Brooks, Ogden, & Cavalier 1998; Hotta et al. 1998; Treasure, Fogelman, & Russell 1986), infertility (Kohmura et al. 1986) and cardiac complications (Cooke et al. 1994; Swenne & Larsson 1999). What is lacking at present is an standard International notation for use across all ages of eating disorder patients. In adult patients absolute BMI is used fairly universally, but in adolescents and children BMI, BMI centiles, %IBW, or %weight for height (using various methods of calculation) are all used, making comparisons difficult across the literature.

2.3.1.1. The boundary between health and disease

As for the psychological characteristics and dieting behaviours in eating disorders, the boundary between 'normal' and unhealthy in terms of body composition is hard to define. That said, one of the first tasks in the management of eating disorders associated with malnutrition is to establish a weight goal, usually known as the 'target weight'. Target weight is recognised as a difficult concept, particularly in young patients (Parry-Jones & Parry-Jones 1994). In adult patients however, long term studies suggest that reaching a healthy weight during nutritional rehabilitation is related to prognosis. Patients who never reached adequate weight restoration had a worse response to treatment (Howard, Evans, Quintero-Howard, Bowers, & Andersen 1999) and a poorer outcome at 6 – 10 year follow-up (Gross, Russell, Beumont, Touyz, Roach, Aslani, Hansen, & Allen 2000). These studies found that a
BMI of 19 was the discriminant cut off value. This approximates to around 87% BMI on UK reference data.

One purpose of determining a target weight is to estimate the weight at which menses will return, since amenorrhoea is associated with so much of the long term morbidity of eating disorders. Even this categorical event has proved surprisingly hard to predict accurately. Treasure et al. (Treasure, Wheeler, King, Gordon, & Russell1988), in adult patients, found that premorbid BMI was better than current BMI at predicting the development of a dominant follicle seen on pelvic ultrasound scan. Golden et al. (Golden, Jacobson, Schebendach, Solanto, Hertz, & Shenker1997) found that BMI was a poor predictor of resumption of menses in adolescent patients, although sufficient had resumed menses at 90% weight for height for the authors to recommend this as a reasonable initial target for nutritional rehabilitation. Nevertheless, the study found no difference in BMI or % body fat, nor in initial eating disorder psychopathology, between those adolescents who had and those who had not resumed menses 1 year later.

This, and other evidence, suggests that the level of physiological functioning can vary amongst individuals of similar underweight by size, and size is therefore a poor reflection of nutritional status. At BMI’s of 16 – 17 some people are able to continue working, whereas others, as in Keys’ starvation experiments (Keys et al. 1950), are in a very poor state physically and psychologically. It has been suggested that a BMI of 12 is the lower limit compatible with life – around 50% of normal body weight. This would seem to be borne out by the mortality literature on AN (Herzog et al. 2000), although lower individual cases have been reported. In other words, at extremely low BMI the health risks are clearer, but there is wide individual variation in the ‘low normal’ range.

In early onset patients, as in male patients, there is no clear event such as resumption of menses to mark the boundary between illness and health. The markers of health vary with age and stage of development. For example, we might ask how likely it is
that a child's rate of growth will be normal given their current body composition? Will puberty onset or continue? Will the child's ovaries/uterus/testes grow? Is adequate bone accretion occurring? etc. Determining a healthy nutritional basis for these aspects of growth and development to occur normally is a complex task, and likely to require more sophisticated techniques than estimates of body size alone.

2.3.2. The validity of body composition measures in patients with eating disorders

Many of the problems of measuring body composition in eating disorder patients arise because most assessment methods were devised to assess overweight rather than underweight. Secondly, as previously discussed, single component models such as weight for height or %BMI are of limited value, particularly in childhood. They continue to be widely used, in part, precisely because they are widely used, and therefore a great deal is known about their performance in the normal range as well as a number of disease states. If the potentially more useful subdivision into FM and FFM is to be made, a similar degree of understanding of the meaning of these values in children is needed.

In addition to general factors about measuring body composition in underweight children, issues arise specific to eating disorders. The nature of eating disorders is such that the sufferer deliberately attempts to manipulate body composition, either to achieve an altered body shape or to deceive others. For example, restrictive AN is often characterised by an excess of exercise. Therefore, while muscle wasting is a feature of protein calorie malnutrition, some AN sufferers may be building up muscle mass, similar to athletes. Measures that do not differentiate lean and fat mass will not detect these changes, and the variation of body composition within a given BMI will be greater than expected. Secondly dieting, as well as resulting in an overall lowering of body fat, may specifically result in lowered calcium or protein intake. Albumin levels
may be low, and oedema present. Fluid balance will be altered by vomiting, laxative and diuretic use, or may be a result of fluid intake restriction or excess. This is well recognised in clinical practice, and simple tests such as urine specific gravity are used routinely to check for water loading or dehydration. Furthermore, the lower BMD in eating disorder patients results in lower overall weight and over estimation of lean muscle mass in two component models. Finally, there may be differences in body shape and fat distribution between different types of eating disorder, which at low weight are barely detectable, but may become evident on weight restoration.

Taken together, measures of body composition in growing children and adolescents with eating disorders merit careful appraisal if they are to be used for research and inform clinical practice.

2.3.2.1. **BMI and other ratio methods in eating disorders**

BMI has a well-established value in the assessment of eating disorders in adult and, as noted above, has a good correlation with morbidity and outcome. It is not without problems however, and on an individual and group basis is of questionable value when it comes to specificity and validity. This is perhaps not surprising in patients who have such profound disturbances of fluids, soft tissue and bone.

A BMI of 17.5, as in the ICD-10 definition of AN, represents a point at which the majority of women will have reached sufficient degree of emaciation for amenorrhoea to occur. Above this point the likelihood of menstruation increases with increasing BMI. Sobanski et al. (Sobanski, Hiltmann, Blanz, Klein, & Schmidt1997) observed a positive linear correlation between BMI and ovarian volume from a threshold BMI of 17.8 upward. Nevertheless, they could not find a clear cut-off BMI for definite prediction of recovered ovaries.

The greatest controversy lies in the BMI range between 17.5 and 20 (lower limit of the 'normal' range). Even at lower weights, where greater precision is needed, BMI may
be misrepresentative of nutritional status. Hannan et al. (Hannan, Wrate, Cowen, & Freeman 1995b) have argued that BMI is an inadequate measure of body composition in adult women with AN as it accounts for only 58% of the variance in measures of body fat by DXA imaging. This is lower than the correlation between BMI and %FM in normal weight and obese subjects. In Hannan's study the correlation was even worse when measuring change; only 32% of the variance in % FM could be accounted for by changes in BMI. The authors concluded that little confidence could be placed on BMI as a measure of body fat in eating disorder patients, despite a significant correlation between BMI and DXA % body fat (68% of the variance in eating disorder patients). Their main argument for dismissing the use of BMI as a measure of body fat is that wide inter-individual variation was seen within a BMI value (e.g. at a BMI of 20, % fat on DXA ranged between 18.1 - 32.5%).

The authors' conclusions from the findings can be questioned on a number of grounds. Firstly, there is as yet insufficient evidence for DXA measures to be taken as the gold standard in this population, and it could be that the study merely demonstrates that one poor proxy for body fat correlates poorly with another. Secondly, reference data for measures of body composition in underweight patients and children by DXA are limited. Thirdly, the adolescent girls span an age range (11-17.9 years) in which one would not expect BMI uncorrected for age to be useful, and where wide variation would be expected to be present on the basis of pubertal stage alone, independent of changes in weight. Finally, the explanation for the wide-inter-individual variation may lie on the expression of body fat as a percentage (thus failing to correct for size), rather than in BMI.

Nevertheless, the basic criticism that BMI is not really reflecting nutritional status may well be valid. In another study, Probst et al. (Probst, Goris, Vandereycken, & Van Coppenolle 1996) studied the relationship between BMI, % fat mass on UWW and % fat mass by skinfold thickness (SFT) in 200 patients with AN. All patients had
amenorrhoea, and were divided into two main groups - pure restrictive AN, and a mixed subtype, including binge-purge sub-type. Skinfolds were measured at 12 sites, but the % fat mass was calculated using the Durnin and Womersley equations on 4 sites. As previously, skinfolds and UWW showed high correlations in all measures. However, BMI only predicted 56.2 % (SFT) and 51.8 % (UWW) of the variance in body composition. Furthermore, the percentage of FM by SFT or UWW showed wide variation within a given BMI (7-27% FM). The purge subtype had significantly higher % FM than the restricting sub-type, except in the abdominal region. The adolescents (aged 14 and over) with AN were no different from young adults in this study, but older adults had higher % FM. This was not due to duration of illness. The authors conclude that BMI has limited value in the diagnosis of AN, as it poorly reflects % FM in this population. These conclusions are supported by Trocki and Shepherd (2000), who found that change in BMI could not predict change in either FM or FFM in adolescent girls with AN.

Together these studies suggest that BMI in severely malnourished patients performs poorly compared with other measures of nutritional status, or compared with in normal and overweight subjects. One possible explanation for this is that weight loss in eating disorder patients does not usually just mean loss of FM, but of all other tissue compartments, whereas changes in BMI in normal and overweight subjects are most likely to be due to changes in FM.

2.3.2.2. Differentiating FM and FFM.

When weight loss occurs in patients with eating disorders, interest for both the patient and clinician has traditionally been on loss of body fat. Their reasons for this differ. For the patient, fat represents undesired aspects of her body and is the target of her weight loss. From the clinician’s point of view, body fat reflects acute energy stores, and has a role in the maintenance of normal endocrine function. The relationship between body fat and adequate menstrual function has been recognised for over 25
years (Boyar, Katz, Finkelstein, Kapen, Weiner, Weitzman, & Hellman 1974; Frisch & Revelle 1971). Indirectly, reduced body fat may be responsible for much of the acute and chronic morbidity associated with eating disorders, such as osteoporosis (Rigotti, Nussbaum, Herzog, & Neer 1984); (Miller & Klibanski 1999).

Until now the role of lean mass in the long term morbidity of eating disorders has been relatively neglected, although the role of reduced lean mass in the development of osteoporosis in AN patients has been highlighted recently (Grinspoon et al. 1999). In children and adolescents, failure to acquire lean tissue during growth is as much, if not more of a concern than failure to gain FM. For this reason approaches to body composition measurement that do not allow for the separate evaluation of fat mass and lean mass are of limited value in patients where growth may be affected, or where FM and FFM are lost. A related issue is that patients may be smaller in lean mass size than age matched controls, and this needs to be taken in account when expressing measurements.

Applying the validity principles in section 2.1 to the evaluation of FM and FFM with eating disorder patients, definitions of the following are needed:

1. A normal range of FM and FFM across the age spectrum (adjusted for size as necessary), outside of which an individual may be said to be statistically abnormal.

2. The disease state, at which the probability of dysfunction is increased. This definition is necessary for diagnostic criteria, and may be based on reference ranges (statistical definition) or on other measures of disease state e.g. likely FM at which amenorrhoea occurs.

3. Measures of recovery, or target FM, which may or may not be the same as 2. This is important in considering treatment targets and monitoring chronic illness.
4. Measures of severity, including minimum safe FM and the FM at which death ensues.

Levels 2, 3 and 4 are highly dependent on developmental stage.

These parameters have been determined to some extent in adults. The mean %FM for the adult female population is 24-28% (Jackson & Pollock 1977). In Frisch's studies, about 17% FM was necessary for the onset of menarche (1974), and it was estimated that 22% FM is necessary for the maintenance of regular ovulatory cycles (Frisch 1984), although criticisms of these findings are reviewed in section 1.8.1. The minimum 'safe' FM in adults is said to be is 7-14%. A medically dangerous % FM is 5.

Such figures are all dependent on lean size, are not directly applicable to children, and comparable data are not available. Surprisingly, until recently there have been no published healthy ranges for % body fat. Gallagher and colleagues (2000) have now proposed ranges for % FM by linking healthy ranges of BMI to predicted % FM (from DXA and 4 component models). However, this itself is arbitrary as both BMI and %fat are influenced by lean size, and the correlation between the two therefore would be different for different size, as may be the case in ED patients. There is therefore a need for an improved understanding of the effect of early onset eating disorders on body composition and its clinical correlates before healthy ranges of FM can be applied to children.

Healthy values for FFM are more complex, and need to be considered in terms of sub-components. BMD, as a component of FFM is the subject of much study, the primary health outcome being associated fracture risk. Definitions of osteoporosis and osteopenia in adults are established (WHO 1994) and can be directly related to long term fracture risk. In children and adolescents these parameters cannot be determined so easily because developmental stage need to be taken into consideration when interpreting BMD measurements. Muscle mass is recognised as necessary for the development of healthy bones, but otherwise lean mass has not been directly...
associated with a particular morbid outcome and attempts have not been made to establish healthy ranges. This area may be of more importance in growing children than in adult populations, and the impact of loss of lean mass during puberty merits further study.

2.3.2.3. Other body composition measures in eating disorders

Studies in adults using two component model studies have largely focussed on the FM and its relationship to normal endocrine function (Birmingham et al. 1996); (Mazess, Barden, & Ohlrich 1990). Birmingham et al. (Birmingham, Jones, Orphanidou, Bakan, Cleator, Goldner, & Phang 1996) compared BIA to skinfold thickness as a measure of change in body fat, over a 3-month period in 20 adult women with AN. They found no significant correlation between the two measures. Furthermore, the inability of BIA to detect changes in hydration, and to assess the intracellular/extracellular distribution of water are serious limitations of the value of BIA in conditions of underweight, and where hydration states are altered as a result of disease or manipulation. Similarly Hannan et al. (1995b), despite developing prediction equations specifically for low weight AN sufferers, concluded that BIA provided no worthwhile improvement over simple height and weight related measures. Studies of BIA in premenarcheal AN have not been performed, perhaps because of the lack of encouraging resulting in adult patients. Given the problems of using standard measures such as BMI and DXA in children, this may be a worthwhile avenue for further research.

Increasingly in clinical practice with eating disorder patients, body composition is being measured at the same time as BMD, using DXA. Mazess et al. (Mazess, Barden, & Ohlrich 1990) assessed body composition using DXA in AN patients and controls (n=11, 18-46 yrs and n=22) and found very low % FM (7.7% in AN patients versus 26.4% in controls). The FM findings were significantly lower than those of Vaisman et al. (Vaisman et al. 1988), who found 17 %FM in his AN subjects measured from skinfold thickness (SFT). Vaisman’s patients were adolescents, but also had lower mean body
weights. A similar direction and magnitude of difference was found between DXA and skinfold thickness in Waller et al's (1996) study in AN. The differences were less marked after refeeding.

In very malnourished patients, SFT are bound to overestimate FM compared to the 'gold standard' of DXA, since the latter assumes a normal density of FFM, which is unlikely to apply in this population. However, estimates of FM from SFT have been shown to correlate well with TBK, total body nitrogen and isotope dilution methods (Russell et al. 1983; Vaisman, Corey, ossi, Goldberg, & Pencharz 1988). The alternative explanation is that DXA is under estimating FM. Problems with the interpretation of data from DXA in AN sufferers have been noted (Hannan, Wrate, Cowen, & Freeman 1995b; Waller et al. 1996), in addition to the significant inter-machine variation. There is a further complication in that adolescents may be scanned using adult settings for DXA or using paediatric settings, and the difference between the two within individual subjects can be substantial (Wang et al. 1999).

In addition to reduced FM, Mazess' study also found a 25% reduction in BMC and 5% reduction in lean tissue mass on DXA in AN patients (Mazess, Barden, & Ohlrich 1990). Indirect methods of body composition measurement such as dilution or underwater density methods, which do not take these effects into account, will result in an apparent increase in % FM of 4-6%.

### 2.4. Conclusions

The WHO Expert Committee, in their recent guidelines on the use and interpretation of anthropometry in infants and children, recommended the use of weight-for-height indices as screening instruments, with +2SDS as cut off for overweight (WHO 1995). The American Academy of Paediatrics and the American Medical Association recommend the use of BMI for screening for obesity in adolescence, with a BMI of over 30 being the recommended BMI for referral. Screening at the lower end of the
weight spectrum was not mentioned. And recently Cole et al. (2000) have called for a worldwide standard definition for child overweight and obesity based on centiles from adult definitions. Given the 'global epidemic' of obesity it is perhaps not surprising that overweight rather than underweight has been the focus of so much attention. But eating disorders are showing no signs of declining numbers, and while treatments may be improving, so is our understanding of the impact of untreated malnutrition in these adolescent girls (and boys). Age appropriate methods for assessing healthy nutritional status are necessary at both ends of the weight spectrum.

A major area of confusion is terminology. The majority of published work on adolescents with eating disorders continues to report BMI as the chosen measure of body composition (Bachrach, Katzman, Litt, Guido, & Marcus1991; Golden, Jacobson, Schebendach, Solanto, Hertz, & Shenker1997; Trocki & Shepherd 2000) despite the problems of using unadjusted BMI calculations in growing children and adolescents. The recent publication of BMI reference data has improved our ability to compare findings in children with those of adults, by the use of BMI centiles or standard deviation scores. It is to be hoped that % BMI will soon replace the various forms of weight for height and % IBW that have been used to date, and begin to establish an international definition of underweight in adolescents for screening purposes.

Although a step in the right direction, it is important to acknowledge the limitations that would remain. BMI does not take into account stunted growth and delayed puberty, nor the segmental disproportion of delayed puberty, nor can it discriminate loss of fat from loss of lean tissue. Similarly, reference data from which SDS or centiles are derived are purely matched for age and sex, and not for maturational stage.

The poor correlation between BMI and other measures of body fat begs questions about the usefulness of BMI centiles in clinical practice in those with established malnutrition. At this level, separate evaluation of FM and FFM are appropriate and account should be taken of the size and developmental stage of the patient.
Approaches such as using fat mass index (FM/height²) and fat free mass index (FFM/height²) merit further evaluation. However FM is derived, expression as % FM is misleading, nor can it be correlated directly with future morbidity.

Measurement techniques for assessing body composition in children are evolving rapidly, and technical and theoretical problems with measures such as BIA may soon be overcome, and could replace SFT as part of standard anthropometric screening. The increased use of DXA scanning in eating disorders for the assessment of BMD means that body composition measured by this method is also likely to increase. The major hurdles here are the quality of reference data and the interpretation of scan results at the lower limits of the weight range (Robinson, Bachrach, & Katzman 2000).

But the first and most obvious goal is the standardisation of definitions, and the recognition that chronic and acute malnutrition may need very different approaches. As with diagnostic criteria, unless like are compared with like, evidence from one sample cannot be compared with or generalised to another. Definitions need to remain context sensitive, for example by using appropriate reference data for a particular population. The introduction of BMI centiles in a number of countries (Cole & Roede 1999; Hosseini, Carpenter, & Mohammad 1999; Luciano, Bressan, & Zoppi 1997; Williams 2000), including the UK (Cole, Freeman, & Preece 1995), is a significant step towards this.
3. Design, subjects and methods

3.0. Aims

The study was undertaken to fill the gap in knowledge of the impact of eating disorders on growth and development in peripubertal children identified in Chapter 1, utilising anthropometric reference data and advances in statistical analysis for the expression of data to compare maturational patterns to those of typically developing children.

3.1. Design

The study was a prospective cohort study. The majority of data were collected between October 1996 and June 1999. Recruitment of new patients ceased one year before data collection was completed to allow at least one year’s growth data to be obtained on all patients. A small proportion of the data were obtained retrospectively.

The study had two components. The cross sectional component involved all patients at initial assessment. Subjects fell into a number of eating disorder categories, thereby allowing comparison between diagnostic subgroups; between patients at different ages and stages of development with the same disorders; and across genders.

The second component was longitudinal. Patients were recruited to return to the growth clinic until such time as growth and pubertal development were complete or until parameters had normalised to a degree that no further deviation from normal development was anticipated. The ‘catchment area’ for patients was National. There was general attrition from the time of initial assessment, and a bias towards longer term data being collected on the more serious and chronic patients.

Although all patients were within a narrow age range, the number of variables meant that each patient has unique characteristics. In many respects the study could be said to have a multiple single case study design, and some additional value of individual
case study at a descriptive level remains. Such data are of particular value in the rarer
types of eating problem, where information is limited.

The study was naturalistic and observational. In the growth clinic patients and parents
were provided with information about the impact of the disorder. No other systematic
intervention was included as part of the study protocol. Some patients were receiving
additional intervention, and others were not. The design of the study meant that some
preliminary observations were made about the outcome of those receiving growth
clinic intervention only, although caution should be exercised about generalising these
findings. For ethical reasons little is known about patients not receiving treatment.

3.2. Subjects

3.2.1. The study population

Subjects were a clinical population in a specialist centre. The Eating Disorders Team
(EDT) at Great Ormond Street Hospital is one of very few centres offering specialist
eating disorder services for children under 13 in the United Kingdom.

A number of factors make the study cohort uniquely suited for the study of growth and
development in eating disorders. Firstly the EDT provides a service for patients aged 7
to 16 years. The cohort therefore includes a higher number of early onset and
premenarcheal patients with AN than most eating disorders services would expect to
see. Secondly, as a tertiary service, referrals include large numbers of atypical
patients. These children, not currently classifiable in international taxonomies, may be
equally at risk of medical complications as a result of nutritional compromise. Thirdly
the specialist nature of the clinic means that severe cases will be seen for second
opinion and consultation. Thus the range of complications, as well as thresholds for
disorder and risk can be evaluated. Fourthly, boys are represented more frequently in atypical and early onset clinical populations (Fosson, Knibbs, Bryant-Waugh, & Lask 1987), an area where knowledge is limited. Finally, the growth service developed around this study attracted referrals of cases where there were concerns about growth and development.

Disadvantages of studying a specialist clinical population include whether results obtained will be generalisable to other sufferers of eating disorders. This concern can be addressed to some extent in the analysis, ensuring that risk factors or predictors are identified specifically for a particular outcome. Secondly, bias for the present sample occurred at the point of referral to the EDT. Thereafter the route of care depended on many factors, not least geographical ones. The only systematic bias in follow-up was ongoing concern about growth and development, sufficient to merit growth clinic attendance. Bias was therefore towards younger and iller patients.

### 3.2.2. Subjects

All patients referred to the EDT between 1995 and July 1998 under the care of Dr Bryan Lask, Consultant Psychiatrist were included in the study. A separate growth clinic was established for the assessment and follow-up of patients, under the supervision of Dr Richard Stanhope, Consultant Paediatric Endocrinologist. As an independent clinic, growth clinic attendance was not contingent on patients attending the EDT, although many did. A significant number went on to receive treatment elsewhere, refused treatment or did not require treatment.

Eating disorders, particularly AN, are characterised by denial and avoidance of intervention. During the study it became clear that patients were often willing to attend for medical follow-up appointments even when they (or their parents) were refusing psychiatric/psychological treatment. These patients represent ‘drop outs’ in many...
study samples. Outcome in patients not receiving regular psychological treatment is considered further in the discussion.

A strength of the study is therefore the prolonged nature of contact with the patients through the course of their illness, regardless of whether they were receiving one, multiple or no treatment, made possible through a collaborative care approach with a number of treatment services.

3.2.3. Criteria for inclusion

3.2.3.1. Inclusion criteria

All patients were assessed in the growth clinic as part of the initial assessment. Cross sectional data at presentation were obtained on all patients.

Longitudinal follow-up was based on clinical need. All patients presenting with underweight as a feature of their illness were invited for follow-up.

3.2.3.2. Exclusion criteria

Patients were excluded from the total sample for the following reasons.

- No significant eating abnormality
- Inadequate data collected
- Simple obesity and other disorders associated with significant overweight.
- Eating abnormality primarily accounted for by organic diagnosis. The most notable were patients who were subsequently found to have occult intracranial tumours (De Vile et al. 1995).
- Patients where there was a clear alternative explanation for growth abnormalities e.g. Turner’s syndrome.
Details of patients with significant medical problems are given in table 5.1. Some patients in whom a medical diagnosis became evident during the course of the study were included in the cohort, as discussed later in the methods.

### 3.2.4. Control subjects

Childhood and adolescence are complex in terms of growth and development. In considering appropriate control subjects for the study the number of variables for matching needed to be taken into consideration, and depended on the research question. For example for a question such as ‘is bone density lower in AN subjects than controls?’, the simplest method is to match for age. This may be far from adequate if, say, a 15-year-old patient is equivalent to a 12 year in terms of physical development. The alternatives are to match control subjects for bone age, for pubertal stage, for stature and so on. Other factors such as race, social class, geographic location would also need to be taken into account for a study of growth. Ideal control subjects may not be found if a large number of variables are under consideration.

One solution is to quantify the relationship between the patients measurement and age (and gender) matched control subjects, the principle of reference data centiles. Reference data rely on large enough numbers at each age for a spread of a particular measure at any one age to be derived. The issue of choosing the most appropriate reference data is discussed in chapter 4.

The main disadvantage of using this method over a selected control sample lies in the error associated with non-standardisation of data collection and measurement, including adjustment for secular trends, demographic mix etc. A strength of this study is the uniformity of data collection. On the whole however, for this study where a range of growth variables are affected, it was thought that comparing individual subject measurements to large reference samples was the preferable option.
Anthropometric measurements were therefore compared to reference children of the same sex and age, and expressed as standard deviation scores (SDS).

\[ SDS_x = \frac{x - \bar{x}}{\sigma} \]

where \( x \) is the measurement, \( \bar{x} \) is the mean measurement for an age and sex matched reference population and \( \sigma \) is the standard deviation of that reference mean. SDS are of particular value for data at the extreme ends of 'normal' (Davies, Day, & Cole 1993). Calculation of SDS for each variable are discussed in chapter four.

Two research question did benefit from a specific control group because raw data were needed for calculation (3.5.2, results chapter 6) or to allow graphical comparison with patient subjects (8.2.3).

**3.2.4.1. Control sample for body composition analysis**

Weight, height and skinfold data for reference children were obtained from two samples. The data were obtained for the investigation of body composition in the general population\(^2\). Children were recruited from schools in Cambridge, UK. The total reference population was 157 children (77 males and 80 females, age range 6 years to 16.75 years).

**3.2.4.2. Control sample for BMI at onset of menses analysis**

Control subjects for chapter 8 were normal British children attending a comprehensive school in Chard, Somerset\(^3\). The children were of mixed socio-economic status with a slight rural and white bias, but included children from a small town industrial

\(^2\) Thanks to Dr Jonathon Wells and Dr Atul Singh for their permission to use these data

\(^3\) Thanks to Professor Tim Cole and Professor Mike Preece for their permission to use these data
means of twice yearly visits at which anthropometry and venous sampling were performed. The measurer responsible for puberty ratings was always isosexual. Only data for the girls are used in the analysis, which was about onset of menses.

3.2.5. Consent procedure and ethical approval

All patients were given information prior to clinic attendance about the nature of research by the EDT, and informed that clinical data are routinely used for audit and research purposes. They were offered the opportunity to refuse involvement in clinical research at this stage. No patients refused information being used for research purposes. This was an observational study involving no intervention or additional investigations associated with patient risk. The study had the approval of the ethics committee of the Institute of Child Health and Great Ormond Street Hospital (Ref 96RP03).

At present there is a limited evidence base for clinical practice in the management of early onset eating disorders (especially premenarcheal patents) (Kreipe et al. 1995; Nicholls, de Bruyn, & Gordon2000; Palla & Litt 1988). The data obtained during the study were based on principles of best clinical practice, and in conjunction with clinicians treating the patient. For this study, only data indicated by clinical presentation were obtained.

No patients in the study were being treated for their eating disorder under the Mental Health Act 1983 or the Children Act 1989, nor were actively withholding consent to treatment. All patients and parents had a right to refuse measurements or investigations.
3.3. **Data**

3.3.1. **Summary of data collected**

- **Patient demographics**
  - Diagnosis
  - Eating behaviour
  - Intervention

- **Growth Data**
  - Auxology
  - Pubertal stage
  - Parental heights

- **Radiological Data**
  - Bone age x-ray
  - DXA lumbar spine

3.3.2. **Psychological data**

3.3.2.1. **Background history**

Background history was obtained by means of a questionnaire, given to all parents prior to the initial assessment. The questionnaire was devised by the EDT and data from it have been used in a number of studies published by the group (Bryant-Waugh et al. 1996b). Areas of questioning included:

1. **Medical**: birth history and perinatal difficulties; child’s past medical history; history of other psychosomatic symptomatology e.g. recurrent headaches, abdominal pain;

2. **Eating behaviour**: early feeding history; age of first eating difficulties and age of first concern about eating; parent’s view of the child’s reasons for not eating.

3. **Growth and development**: child’s sexual development and menstrual history; previous concerns about growth and development; weight and height prior to onset of eating concern if known.
4. Family risk factors: family life events occurring within 5 years of the onset of eating concerns; family history of eating difficulties or other psychiatric disorder.

A copy of the questionnaire is given in appendix 3.1.

3.3.2.2. Diagnosis

I. Assigning diagnosis

Diagnosis was reached by consensus of the assessing team. The assessment includes physical assessment, individual assessment of the child, and a parent or family interview.

From January 1996 onwards additional diagnostic information was obtained by administering the childhood version of the eating disorders examination (child EDE), a semi-structured interview designed to identify eating disorder psychopathology and generate diagnoses. The EDE was developed by Fairburn and Cooper (Fairburn & Cooper 1993) as a research and diagnostic interview and is considered the ‘gold standard’ of diagnostic interviewing for eating disorders. The childhood version has been adapted to elicit cognitions about eating disorder pathology in children (Bryant-Waugh, Cooper, Taylor, & Lask1996a). EDE interviews were administered by a clinician or research psychologist trained in the use and interpretation of both the adult and the child version. The child version of the EDE has not yet been validated on normal children. EDE scores were used to corroborate clinician diagnoses, or where there was disagreement between clinicians about the diagnosis, but were not the primary basis for diagnosis. The clinical and research basis for the diagnoses made in this study were the best available at this point in time for the age group under consideration.
II. Nosological considerations

The standard psychiatric taxonomies of DSMIV and ICD 10 were used for the axis one (primary illness) diagnosis for reasons of compatibility with other studies. Both DSM IV and ICD10 are multi-axial diagnostic systems. Given the complexity of the five axis diagnostic systems only axis one diagnoses were made in the present study according to DSMIV and ICD 10. Patients may have more than one axis one diagnosis (comorbid disorder), e.g. obsessive compulsive disorder in addition to AN. Two further variables were created: secondary axis one disorders present at the time of assessment and comorbid medical illness (e.g. asthma).

In addition to the standard taxonomies, all patients were also given a diagnosis according to the schema known as the Great Ormond Street Hospital criteria for early onset eating disorders, as described in section 1.2.1. In view of the lack of empirical data supporting these diagnostic categories, an independent inter-rater reliability study of clinician based diagnosis was undertaken to assess the value and reproducibility of the diagnoses according to the three schema in common clinical practice, DSMIV, ICD 10 and Great Ormond Street Hospital criteria. Details of the study can be found in Nicholls et al (Nicholls, Chater, & Lask2000).

III. Diagnostic categories

On the basis of the inter-rater reliability study, it was concluded that ICD 10 diagnoses were not useful for the classification of eating disorders in this age group. Eating disorder diagnoses were made according to Great Ormond Street Hospital and DSM IV criteria. These categories are shown in table 3.1. The second issue was that of comorbid (non-eating disorder) diagnoses. In reality, the number of comorbid diagnoses was limited. All patients were therefore assigned the comorbid diagnoses within the categories shown in table 3.2.
Table 3.1: Eating Disorder diagnoses

<table>
<thead>
<tr>
<th>Great Ormond Street Diagnoses</th>
<th>DSM IV Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Code</strong></td>
<td><strong>Diagnostic category</strong></td>
</tr>
<tr>
<td>1</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>2</td>
<td>Bulimia nervosa</td>
</tr>
<tr>
<td>3</td>
<td>Food Avoidance Emotional Disorder (FAED)</td>
</tr>
<tr>
<td>4</td>
<td>Selective Eating</td>
</tr>
<tr>
<td>5</td>
<td>Other (low weight)</td>
</tr>
</tbody>
</table>

Table 3.2: Comorbid diagnoses

<table>
<thead>
<tr>
<th>Great Ormond Street Diagnoses</th>
<th>DSM IV Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Code</strong></td>
<td><strong>Diagnostic category</strong></td>
</tr>
<tr>
<td>6</td>
<td>Chronic Fatigue Syndrome/M.E.</td>
</tr>
<tr>
<td>7</td>
<td>Psychogenic Vomiting</td>
</tr>
<tr>
<td>8</td>
<td>PTSD</td>
</tr>
<tr>
<td>9</td>
<td>Conversion Disorder</td>
</tr>
<tr>
<td>10</td>
<td>Depression</td>
</tr>
<tr>
<td>11</td>
<td>Brain Tumour</td>
</tr>
<tr>
<td>12</td>
<td>Obsessive compulsive disorder</td>
</tr>
<tr>
<td>13</td>
<td>Not Known</td>
</tr>
<tr>
<td>14</td>
<td>Other</td>
</tr>
<tr>
<td>15</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>16</td>
<td>No eating disorder</td>
</tr>
</tbody>
</table>
Finally there was the issue of evolving diagnoses. For example BN is known to be preceded by a period of AN in a large number of patients. The continuities between the other eating disorders is less well documented, but clinical experience suggests that SE can be precipitated into weight loss, and that some patients with FAED may eventually show the classical features of AN. Diagnoses were therefore reviewed on a regular basis where known.

IV. A single ‘diagnosis’ variable

For the study the eating disorder diagnoses were merged into a single diagnostic variable, based on cross groupings for the two sets of criteria, making seven diagnostic groups in total.

i. Diagnosis variables AN and EDNOS/AN

The diagnosis AN was given to patients who met DSM IV and GOS criteria for AN. Patients who have sub-threshold AN criteria would be classified EDNOS (Eating Disorders Not Otherwise Specified) in DSM IV, but may meet childhood (GOS) criteria. These were classified EDNOS/AN. This grouping was also used for patients who had previously met full criteria for AN but were partially weight restored at the time of recruitment into the study. All patients assigned this diagnosis therefore had an AN-like illness associated with weight loss.

ii. Diagnosis variables BN and EDNOS/BN

DSM IV requires bingeing to have occurred twice a week for at least three months, for binges to take place over 2 hours and for the sufferer to experience (and be able to describe) lack of control. GOS criteria are less stringent in terms of the frequency of these behaviours, based on the belief that dependent children and adolescents have greater external constraints on these behaviours than adults do. BN patients met full DSM IV criteria. EDNOS/BN was used to classify those who show binge/purge
behaviours, are not underweight but who do not meet frequency criteria. In some analyses the two BN categories, in which numbers were small, have been combined. When this is so, it is clearly stated in the results.

iii. Diagnosis variable FAED

Patients in this category presented with eating difficulties, weight loss or failure to gain weight, and emotional disorder not sufficient to meet criteria for AN, BN or other emotional disorder (e.g. depression). DSM IV has no suitable diagnostic category and would be included under the rubric of EDNOS. The DSM IV category ‘Feeding Disorder of Infancy or Early Childhood' may be appropriate for a few but not all of these children (see section 1.2.1). FAED rather than EDNOS/FAED has been used for the purposes of simplicity.

iv. Diagnosis variable SE

This category is used for children whose eating difficulty is the range of foods, not the quantity. Weight loss is not a feature. As before, SE rather than EDNOS/SE was used.

v. Diagnosis variable Other

A number of patients with significant malnutrition were referred, where food avoidance was a feature of another primary psychiatric diagnosis. The types of food phobia or other food avoidance are described in section 1.2.1. As these were relatively few in number they have been grouped together under 'other'. For consistency, the same low weight criteria were applied as for anorexia i.e. only those with wt/ht of 85% or less were included.

V. Medical disorder as a selector variable

In the cross sectional analysis the problem of recognising the contribution of medical disorder to the weight, growth and eating difficulties was managed by creating a separate variable for medical disorder yes/no. This was a patient linked variable,
rather than visit linked, such that if a medical disorder became evident at anytime during contact the patient would be marked as a 'yes'. For the purposes of analysis, results were calculated excluding those who had medical disorder, and repeated including the subgroup, such that a true 'cross sectional' picture of the presenting population can be described.

VI. Summary

GOS and DSM IV have been combined into a single variable, making seven diagnoses in total (table 3.3). Some of these eating patterns are associated with underweight, others are not (table 3.4). Medical diagnosis not evident at initial presentation has been included as a separate variable, allowing inclusion or exclusion of the small number of subjects to whom this applies.
Table 3.3: a single diagnosis based on DSM IV and GOS criteria

<table>
<thead>
<tr>
<th>DSMIV</th>
<th>GOS</th>
<th>Diagnosis variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia nervosa</td>
<td>Anorexia nervosa</td>
<td>AN</td>
</tr>
<tr>
<td>EDNOS</td>
<td>Anorexia nervosa</td>
<td>EDNOS/AN</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>Bulimia nervosa</td>
<td>BN</td>
</tr>
<tr>
<td>EDNOS</td>
<td>Bulimia nervosa</td>
<td>EDNOS/BN</td>
</tr>
<tr>
<td>EDNOS</td>
<td>Food avoidance emotional disorder</td>
<td>FAED</td>
</tr>
<tr>
<td>EDNOS</td>
<td>Selective Eating</td>
<td>SE</td>
</tr>
<tr>
<td>Other low weight (&lt;85% wt/ht)</td>
<td>Other low weight</td>
<td>Oth</td>
</tr>
</tbody>
</table>

Table 3.4: Weight status within single diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Underweight? (&lt;85% wt/ht)</th>
<th>Intermediate (low end of normal or previously underweight)</th>
<th>Normal weight range</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDNOS/AN</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>BN</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>EDNOS/BN</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>FAED</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
### 3.3.2.3. Intervention

Therapy is notoriously hard to quantify, in terms of measuring dose response. As this was an observational study, the details of therapy were not the subject of systematic inquiry. However, if a significant change in status of the child is observed, the question of whether such a change was associated with intervention or not becomes relevant. For this reason, a measure of intervention was designed as a grouping variable for the intensity of therapeutic intervention the patient and family received.

The four categories were defined as:

1. No intervention beyond initial assessment and growth clinic follow-up.

2. Minimal intervention – assessment, followed by regular review and monitoring within an eating disorder or other Child and Adolescent Mental Health Team (CAHMS), or brief therapy interventions.

3. Outpatient intensive treatment – more than six months of outpatient individual or family therapy within an eating disorder or CAHMS team.

4. Inpatient treatment. No distinction was made between those treated in generic inpatient psychiatric units and those treated within specialist eating disorder inpatient units. This is because there is no evidence as yet that there is a difference in outcome between the two types of unit.

As data were obtained from inquiry and patient report, the reliability of this variable is limited. As such, it was not used as a dependent variable in analyses.
3.3.3. Physical data

3.3.3.1. Auxology

After the initial assessment, follow-up appointments were offered at 3, 4 or 6 monthly or yearly intervals. Three months was taken as the minimum time between visits that would give meaningful height velocity data.

A standard auxology assessment (Brook 1982) was performed for each visit. This includes height, weight, sitting height, triceps and subscapular skinfold thickness, arm circumference, head circumference and pubertal stage. Height was measured using a Harpenden stadiometer, and skinfold thickness using a Harpenden calliper. All measurements were performed by two trained growth nurses. Inter-measurer reliability was assessed on a sample of consecutive patients. Inter-measurer technical error of measurement for height was 0.24; triceps skinfold 1.26; subscapular skinfold 0.88. This degree of measurement error would be classified good or fair, with overall coefficient of reliability >0.95 (Ulijaszek & Lourie 1997). Differences between measurers were not consistently biased in either direction.

The few refused weights were recorded as missing, since interpolation of weight data is less meaningful and less accurate than interpolation of height data, particularly in patients with eating disorders where wide fluctuations in weight are common.

VII. Parental heights

Parental heights represent a way of evaluating the contribution of a genetic disposition to short stature as a reason for referral bias. There are several methods for estimating a child’s growth pattern, although some methods rely on the availability of longitudinal growth data, or data prior to the onset of illness. Since previous growth data were very rarely available in the present study, the 'mid parental height' method was used, using parental height SDS.
VIII. Puberty

Pubertal stage was rated by the author (trained by RGS) or by RGS, according to the Tanner method of pubertal staging (Tanner 1962). Testicular volume was assessed using a Prader orchidometer. When possible the examiner was isosexual with the patient. Missing data were usually as a result of refusal to be examined.

Puberty as a variable in the analysis is considered in some depth as the impact of pubertal status is crucial in this age group when looking at physical parameters. The various ways of evaluating the data on the basis of pubertal stage are:

i. Tanner’s 5 stages of puberty.

Usually this is based on the rating of breast stage (girls) or genital stage (boys) or pubic hair. This would mean 10 groups, subdividing on the basis of gender and Tanner stage. For 7 diagnostic categories this would reduce the sample size of each group to very small numbers.

ii. Early puberty/late puberty.

This method is used particularly when growth is an issue. For girls, this also roughly equates to ‘before growth spurt/after growth spurt’. Conventionally breast stage 1 would be prepubertal, stages 2 and 3 early puberty, and stages 4 and 5 late puberty. Criteria are slightly different in boys, where the growth spurt is later in puberty.

Both Tanner stages and the early/late methods have pros and cons. The first is the issue of different criteria for different genders. Secondly, within breast stage (B)1 will be some that are appropriately B1 (e.g. at age 8) and some who have delayed pubertal onset (e.g. B1 at age 13) as a result of their illness. Data are available on the mean age of puberty and the standard deviation score for age, based on the original Tanner data of 1966. Cross sectional reference data for pubertal stage is useful in the mid-pubertal range, and a puberty centile or standard deviation score derived for
stages 2, 3 and 4. However, a measure of spread cannot be derived from an unbounded distribution. Both ends of the pubertal spectrum are unbounded. In other words the girl at stage B1 at age 13 may be on the 90\textsuperscript{th} centile, but no centile can be assigned to the 8 year old girl in stage B1, who may be just about to enter puberty or be 5 years away from it. The same applies in stage 5 puberty. A girl who reaches stage 5 at age 17 will be late, and may be on the 3rd centile or below, whilst another girl of 17 may have reached stage 5 five years earlier. A cumulative number of girls will reach stage 5 from about age 10 onwards. Simply grouping patients by pubertal stage does not solve the problem of puberty's normal distribution, although analyses which include age as a covariate can be adjusted for pubertal stage.

In an eating disorders population the problem is one ended, since a centile for late pubertal stage 5 can be defined from its boundary with stage 4. The problem is in younger girls who are stage 1. A centile cannot be assigned to a 10 year old girl in stage 1 puberty when the age of transition to stage 2 puberty is unknown. This is a big problem when looking at patients with pubertal delay.

iii. Change in pubertal stage

One option for longitudinal data is to calculate a new variable, 'change in pubertal stage'\textsuperscript{4}; thus marking limits of pubertal stage and/or to denote pubertal progress. Questions such as 'is the change in bone density attributable to a change in pubertal stage?' can be addressed in this way. The second option is to interpolate on the basis of previous or later record to derive a presumed date of pubertal change, and from that a centile for the cross sectional data point.

iv. Premenarcheal/postmenarcheal

\textsuperscript{4} Change in puberty = within the same patient, pubertal stage is not equal to the previous pubertal stage
Grouping the prepubertal and early puberty groups into a premenarcheal group has been used in a number of other studies of early onset AN. It has two main drawbacks. The first is the 'appropriately or true premenarcheal' versus 'delayed premenarcheal' distinction. The second is how to classify boys. Nevertheless, for questions regarding the impact of illness on growth and development, the pre/post menarche distinction is a relatively reliable (easy to ascertain) and meaningful distinction.

This study principally used the premenarcheal/postmenarcheal distinction for grouping, and the 5 Tanner stages in regression models were the entire sample (including boys) are included.

### 3.3.3.2. Bone age x-ray

Bone age x-ray of left hand and wrist was performed on patients where there was evidence of growth retardation, pubertal delay or significant weight loss. Growth retardation was suggested from previous growth data, by a significant discrepancy between the patient's predicted height and target height according to parental heights, or by height below the 3rd centile. In practice previous growth data were rarely available. Puberty thresholds for bone age x-ray were taken as no signs of pubertal development in a girl by the age of 11 and in a boy by the age of 12 (50th centile for breast stage or genital stage 2 in UK reference data (Marshall & Tanner 1969) (Marshall & Tanner 1970). Significant weight loss was taken as a weight below 85% weight for height (% BMI).

Bone age x-rays were performed at approximately yearly intervals. All bone ages were determined by one person (RGS) using the Tanner and Whitehouse (TW-2) method (Tanner, Whitehouse, Cameron, Marshall, Healy, & Goldstein 1983) and calculated using a computerised bone age calculator (KGS 4). Consistency of bone age assessment by this author has previously been reported (Albanese et al 1995).
3.3.3. Bone densitometry

Bone density was measured using a dual x-ray absorptiometry (DXA) scanner (Hologic 4500 QDR; Waltham; MA). The coefficient of variation for replicate measurements for our scanner is 1% at the lumbar spine. The Hologic 45000 is a fan beam scanner. The fan beams give a significantly higher dose of radiation than the pencil beams, and as such are only used in children when clinical need justifies the radiation exposure. Reference data on children for this scanner are limited. What normal data are available for children tend to be for the newer, pencil beam scanners with a smaller radiation load (see section 4.4.2.6).

DXA scans were only obtained on the lumbar spine, in order to minimise exposure of the children to radiation whilst maximising the possibility of finding compromised bone density. The literature on patients with AN suggests that the lumbar spine is the most vulnerable site (Bachrach, Guido, Katzman, Litt, & Marcus1990; Bachrach, Katzman, Litt, Guido, & Marcus1991; Golden 1992), and also the one in which most change is seen, as it has a high proportion of trabecular bone.

DXA scans of the lumbar spine measure areal bone size of each of the four lumbar vertebrae, and a total area size (sum of L1 – L4 ); bone mineral content (BMC) for each lumbar vertebra and a total BMC; and bone mineral density (BMD) for each lumbar spine and a total BMD.

\[
\text{BMD} = \frac{\text{BMC}}{\text{Area}}
\]

These values were expressed as SDS or Z score, as for anthropometric data.
3.4. Methods

3.4.1. Statistical considerations

All auxology data were transformed to SDS (3.2.4) to correct for age and gender. Data transformations were performed in Microsoft Access database (chapter 4) and exported to DataDesk 6.1.1 for analysis.

A combination of descriptive, univariate and multivariate analyses was used. Pearson’s bivariate correlations were used to examine relationships between normally distributed continuous variables; normally distributed mean scores were compared using t-tests; cross diagnosis comparisons were performed by ANOVA for continuous variables, with log transformation where necessary to make near normal distributions within each diagnostic group. Residuals were plotted for each variable to assess the normal distribution and a scatterplot of predicted versus residuals plotted to ensure that data points were centred around 0.

Multivariate analyses were conducted using multiple regression for continuous outcome variables and multiple logistic regression for binary outcome variables. Adjusted regression models were performed using the General Linear Modelling method in DataDesk.

A principal components analysis (PCA) was performed on cross sectional data to determine whether auxology data measured on many variables can be described more concisely in fewer dimensions. Principal components in Data Desk 6.1.1 are standardised from the matrix of correlations of the X variables. Eigen values are the variances of the projections of the points along each of the principal axes. The largest eigen value is the variance of the projection into the first principal axis.

---

5 Thanks to Professor Mike Preece and Professor Tim Cole for their statistical guidance
A particular strength of DataDesk is the visual display of data, facilitating recognition of patterns and outliers. Results are therefore presented graphically wherever possible.

### 3.4.2. Body composition analysis

Body composition data (BMI and skinfold thickness) from the eating disorders cohort (n= 172) were transformed to give values for fat mass index (FMI) and fat free mass index (FFMI) and superimposed on normal curves derived on the basis of body composition data from a control sample (3.2.4.1).

BMI for the control group was calculated from weight (kg)/height (m)$^2$, and BMI SDS calculated using the 1990 UK reference data (Cole, Freeman, & Preece1995).

Individuals who lay outside the range ± 2 SD scores were omitted, and the extent to which the remaining subjects were representative of the UK population was assessed. The mean SDS value for the total sample was 0.13 (SD 0.85), with a non-significant trend of increasing SDS with age. Thus at each age, mean BMI of the control data was within 0.5 kg/m2 of the UK 1990 reference data, equivalent to 8% in centile terms.

Percentage fat for patient and control subjects was derived using Slaughter’s equations using triceps and subscapular skinfold data (Slaughter et al. 1988), which vary with Tanner pubertal stage.

\[
\text{SKK} = \text{the sum of triceps and subscapular skinfolds.}
\]

For boys, (Tanner 1 & 2): \(\% \text{ fat} = (1.21 \times \text{SKK}) - (0.008 \times (\text{SKK}^2)) - 1.7\)

For boys, Tanner 3 the equation is the same, except subtract 3.4, not 1.7

For boys, Tanner 4+ the equation is the same, except subtract 5.5 not 1.7

For girls, (all Tanner stages); \(\% \text{ fat} = (1.33 \times \text{SKK}) - (0.013 \times (\text{SKK}^2)) - 2.5\)

FM was calculated from \((\% \text{ FM} / 100) \times \text{weight}\). FFM was calculated from weight – FM.

Fat mass index (FMI) and fat-free mass index (FFMI) were calculated from \(\text{FM}/\text{height}^2\)
and FFM/height^2 respectively (Van Itallie, Yang, Heymsfield, Funk, & Boileau 1990), for all patients and controls. The use of FMI and FFMI for the expression of childhood body composition is discussed in section 2.2.1.3.

Curves for means and SDs of FFMI and FMI in the healthy children were then produced using Lowess smoothing in Data Desk Version 6.1.1 and values computed along the age continuum. These data were used to construct graphs of smoothed FFMI or FMI reference values, ±1SD, against age (Wells, 2001). Results for the patient groups were superimposed on these reference data.

In order to confirm the results obtained with the Slaughter skinfold equations, all calculations were repeated using Deurenberg’s equations for predicting body composition (Deurenberg, Pieters, & Hautvast 1990; Weststrate & Deurenberg 1989), which use the same raw skinfold data and are suitable for use across the sample age range.

For boys aged 2-18 yrs: 
\[
\text{fat} = \left( \frac{562 - 4.2(\text{age}-2)}{D} \right) - \left[ 525 - 4.7(\text{age}-2) \right]
\]

For girls aged 2-10 yrs: 
\[
\text{fat} = \left( \frac{562 - 1.1(\text{age}-2)}{D} \right) - \left[ 525 - 1.4(\text{age}-2) \right]
\]

For girls aged 10-18 yrs: 
\[
\text{fat} = \left( \frac{553 - 7.3(\text{age}-10)}{D} \right) - \left[ 514 - 8(\text{age}-10) \right]
\]

where D is the body density = pubertal stage dependent constant – (mean skinfold coefficient *LogSKK) + (mean age coefficient *age-3).

The nine prediction equations can be found in Deurenberg (1990). Using these equations, prediction error is only slightly lower for two skinfold measurements than for four.

**3.4.3. Bone density: methodology**

DXA scans were performed in a clinical context and therefore could not be performed routinely on the day of assessment. The delay between growth visit assessment and
DXA was usually between 1 and 3 months. Within this period it was anticipated that significant change in weight would have occurred, and possibly also in stature. All cases where lag between DXA and growth visit was greater than 3 months were excluded (n=16). Anthropometric variables were then interpolated between the previous growth visit and the next growth visit, to produce measures 'as if' the child had been measured on the day of the DXA scan. This method is well recognised for the interpolation of height, since growth is relatively slow and always increases. The validity of interpolation for weight and other indices of body mass however is of less certainty, since the interpolated value may bear no or little relation to actual weight at the time of the DXA scan. However, figure 3.1 shows the values for weight SDS at the growth visit before (Prev Wt SDS) and after (Next Visit SDS) the DXA scan, with the interpolated values between (DXA Wt SDS). This shows that the change in weight SDS was minimal for the majority of the group, and that the direction of change was almost always upwards. Weight SDS is therefore taken as a proxy for weight around the time of the DXA scan. The same interpolation was applied to other anthropometric indices.

3.4.3.1. **Correction of bone data for growth variables.**

Four of the methods discussed in section 1.9.3 were used to express bone density findings for the sample, and results compared across methods.

Method 1: Bone mineral density (BMD) results were obtained for cross sectional measurements according to diagnosis and adjusted for age and gender by z score calculation, using reference data within the Hologic software. Reference data for this software are taken from a sample of Canadian children (Faulkner, Bailey, Drinkwater, McKay, Arnold, & Wilkinson 1996) – section 4.4.2.6.
Figure 3.1: Interpolation of weight measurements from previous and next clinic visits to derive a DXA weight SDS

![Diagram showing interpolation of weight measurements from previous and next clinic visits to derive a DXA weight SDS.]

Figure 3.2: Length of follow-up for longitudinal sample (n=106)

![Histogram showing the number of patients over years since first visit.]

Number of patients
Stepwise linear regression was performed to identify anthropometric and illness variables that were significant predictors of z score for BMD by this method.

Method 2 used Warner et al’s (1998) prediction equation method, correcting BMC for height, weight and Tanner stage to produce a standard deviation score for BMC. Results were then compared within diagnostic groups to the z score obtained from method 1.

Method 3 used a linear regression model according to Prentice (1994), where lnBMC was corrected for lnHeight and lnWeight. Since this model does not include any age-related variable this analysis was repeated with lnAge, and then lnHeight and lnWeight as SDS in the model. Natural log (Ln) transformation of negative numbers is not possible, so height SDS and weight SDS were adjusted to ensure all values were positive.

Method 4 used the regression coefficient obtained from method 3 to calculate volumetric or apparent bone mineral density (BMAD).

Finally, data were compared longitudinally to identify predictors of rise and fall in bone density over 1 and 2 year periods. This part of the analysis examined trends in bone density over time, and considered factors that might predict poor outcome. Specifically, the following hypotheses were tested:

- Low weight premenarcheal patients are at greater risk of relative bone loss than postmenarcheal patients
- Change in bone density is not entirely accounted for by changes in size. Other predictors include duration of illness and stage of development
- ‘Catch-up' bone density occurs with restoration of weight
Changes in bone density measures were analysed using paired t-test or repeated measures MANOVA. All analyses were performed using Data Desk version 6.1.1 (1999).

3.4.4. Longitudinal follow-up

142 of the original study sample of 206 patients made more than one growth visit.

752 growth visits in total were made by the 142 patients (mean 5.3 visits (SD 3), min 2, max 17). The mean time between visits reflected the clinical status of the patient. Therefore visits were more frequent during acute concern about weight loss and nutritional status, and less frequent for longitudinal monitoring of growth, pubertal development and bone density.

Mean length of follow-up for the total sample was 1.9 years (SD 1.27, range 0.1 – 6.6 years).

3.4.4.1. Excluded data

IX. Refusal to be weighed

No weight was recorded at a total of 9 visits on 6 girls, all with severe AN who refused to be weighed. No corresponding data on BMI SDS, weight for height or weight SDS were available.

X. Medical conditions

Patients with a medical problem that was clearly primary to the eating pathology, albeit diagnosed later (e.g. intracranial tumour), were excluded from the analysis of long term growth data (n= 11). All had severe eating difficulties and malnutrition where the relative physical and psychological contributions were unclear at presentation. Two girls had true AN. Details of their case histories can be found in appendix 8.1.

XI. Short duration of follow-up
Changes in height are not usually considered significant at less than 3 monthly intervals. Patients with follow-up of less than 3 months were excluded (n=5; Details shown in table 3.5).

At presentation those excluded from the analysis on the basis of short duration of follow-up did not differ significantly from the rest of the cohort in terms of height SDS (-0.14 vs. -0.61 SDS; p 0.425); % weight for height (84.64 vs. 84.56 %; p 0.99); duration of illness (1.27 vs. 2.32 years; p 0.44); or age at assessment (13.14 vs. 12.48 years; p 0.52), using ANOVA to compare means.

3.4.4.2. Relationship between height and weight change

To explore the relationship between change in height and change in weight, measures were standardised within each subject by calculating the 'residual' value for each data point. The residual is the difference between the predicted value and the observed value for a given data point. Predicted values are the midpoint of each individual’s values. For example, if a subject’s height SDS ranged between -2 and -1 SDS, the midpoint would be -1.5 SDS, with values ranging ± 0.5 SDS either side of the midpoint. The midpoint becomes 0 SDS (no deviation from predicted). Calculating the residuals enables identification of influential data points and allows growth plots to be superimposed on one another, centred around 0 SDS. Cases far from the center of the data have a greater potential to harm a regression. Results are shown as scatterplots of residuals of height and weight SDS.

The relationship between change in height SDS and height velocity SDS is not self-evident. Height velocity SDS is effectively correcting for where the child lies in the growth centiles, such that all are centred around 0 on the basis of peak height velocity. Height SDS residuals basically does the same, but instead of centering around peak
Table 3.5: Patients excluded due to short duration of follow-up (<3 months)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Assess Age (Years)</th>
<th>Diagnosis</th>
<th>Duration Illness (Yrs)</th>
<th>Wt4Ht (%)</th>
<th>BMI SDS</th>
<th>Height SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>10.4</td>
<td>EDNOS/AN</td>
<td>0.61</td>
<td>98.07</td>
<td>-0.18</td>
<td>-0.34</td>
</tr>
<tr>
<td>F</td>
<td>13.7</td>
<td>BN</td>
<td>0.34</td>
<td>89.0</td>
<td>-0.97</td>
<td>1.30</td>
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<td>F</td>
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<td>4.22</td>
<td>83.39</td>
<td>-1.58</td>
<td>0.88</td>
</tr>
<tr>
<td>F</td>
<td>14.3</td>
<td>AN</td>
<td>0.73</td>
<td>78.11</td>
<td>-2.25</td>
<td>-2.18</td>
</tr>
<tr>
<td>F</td>
<td>14.3</td>
<td>BN</td>
<td>1.47</td>
<td>95.90</td>
<td>-0.33</td>
<td>-0.44</td>
</tr>
</tbody>
</table>

Figure 3.3: Residuals plots of height SDS against weight SDS - interpreting the gradient

[Diagram showing the relationship between Height SDS residual and Weight SDS residual with categories for increasing height centile or catch-up growth, no change in height centile i.e. normal growth, decreasing height centile or growth failure.]
height velocity, height is centred around the available data, which is not necessarily
the child’s channel. Ideally one would centre around premorbid height SDS.

3.5. Summary

This was a four year, prospective, cross sectional and longitudinal study of growth and
development in a specialist clinical sample of children and young adolescents with
eating disorders. Young people were assessed at presentation with a range of eating
problems, including AN. Follow-up was determined by low weight at presentation.
Comparisons were made between eating disorder diagnostic groups and with control
children on a range of variables, with illness features such as age of onset and
duration of onset as covariates. The main outcome measures were height, weight,
BMI, body fat, pubertal status and bone density, expressed as standard deviation
scores compared to age and gender matched children. Particular consideration was
given to the expression of anthropometric findings, including correction for
developmental stage and physical size of the patient sample.
4. Database development and reference data

4.1. Why develop a new database?

Data storage, cleansing, manipulation and analysis are crucial where large numbers of variables are collected on a substantial cohort of patients. The sophistication of software for this purpose has increased rapidly over recent years. During the present study, for example, there have been 4 versions of Windows, 4 of Microsoft Office, 4 of SPSS (Statistical Package for Social Sciences) and 4 of Reference Manager. In addition new software has been introduced that may be more helpful in the analysis of particular data types. On this basis, decisions made about data entry and analysis have required repeated updating and revision during the course of the study.

It was apparent that a simple data spreadsheet would not meet the needs of the present study for a number of reasons. Firstly, variable numbers of observations were performed on subjects, and data were collected in a number of distinct domains. In a simple spreadsheet form data may appear as if 'missing' when in reality it was never intended that the data be collected (e.g. breast development in boys). The database therefore needed to be able to manage multiple numbers of data types collected on multiple occasions.

Secondly, the majority of data needed to be transformed to make the raw data meaningful for cross group comparisons. Although most statistical packages and spreadsheets allow these functions to be performed, Microsoft Access performs the transformations in a stepwise fashion, such that each calculation is saved as a separate query. In a multi-relational database reference tables can all be stored within the same data set, and complex relationships and transformations can be managed
within one database. The most complex transformations in the current data set require
the use of reference tables (see section 3.4).

4.2. Database design

4.2.1. Summary of database relations

The tables and their relationships are shown in appendix 4.1. The data types can be
seen as being at three levels.

Level one: Background data.

These data only existed once per patient, were unchanging and did not depend on
transformation or calculation. The data were separated into 3 tables:

1. Basic patient data.

This table contained the minimum data set per patient, and its main function was to
serve as a link between other tables, ensuring that all relevant data related to the
same patient. Microsoft Access uses a primary key method to achieve the link, but
names provide confirmation. This minimum set was used for most calculated functions,
where the smaller the data set the quicker the function is performed. At its most
complex, the database was required to calculate SDS on 25 variables from 816 growth
visits i.e. 20,400 calculations in a single query.

2. Background variables.

This included data on the patients' birth, known medical illness at the time of
presentation, and information on parents' height and, sometimes, weight. This
information was obtained in the growth clinic at first visit.

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7 My thanks to John Douglas for his invaluable help in the design of this database
3. Preliminary information.

Obtained by questionnaire from parents (usually mother), this information was collected at the first visit. It contained background information relevant to the context of the child and the onset of the eating difficulties, as described in section 3.3.2.1. Apart from the clinician diagnosis, this was the only information in the present study that related to the type of eating difficulty and its onset.

**Level two: Diagnosis**

Diagnosis was obtained as described in section 3.3.2.2. Diagnosis could not be in the same relation as background data as patients may have more than one diagnosis at assessment and where longitudinal data were obtained diagnoses may change over time. The Diagnosis table therefore related to the Patient table in a one-to-many relationship.

**Level three: Growth visit and bone density data**

These two sets of data form the core of the total data set. They were separated from patient and diagnostic information because each of these data sets could be single or multiple for each patient, and bore no relationship to the number of diagnostic assessments made. They were separated from each other because each data set represented a discrete set of observations on a particular patient, not necessarily related in either time or frequency to each other. Each data set at this level was therefore related directly to Patient table, with a one-to-many relationship, rather than to the growth visit data (Visit table).

4.2.2. Key features of the database relations

In order to maintain organisation within the system between the three levels of data, the database uses a number of features.
4.2.2.1. **Referential integrity.**

Referential integrity is a system of rules that the database uses to ensure that relationships between records in related tables are valid, and that related data cannot be accidentally deleted or changed.

4.2.2.2. **Cascade update and delete**

Selecting the Cascade Update Related Fields check box when defining a relationship, means that any time the primary key of a record is changed in the primary table, the database automatically updates the primary key to the new value in all related records.

4.2.2.3. **Join types**

There are three types of table join, one-to-one, one-to-many or many-to-many:

In a one-to-one relationship, each record in Table A can have only one matching record in Table B, and vice versa. If this were applied to all joins the result would be the equivalent of a single spreadsheet.

A one-to-many relationship is the most common type of relationship, in which a record in Table A can have many matching records in Table B, but a record in Table B has only one matching record in Table A.

A many-to-many relationship is really two one-to-many relationships with a third table and has not been used in this study.

There are three types of field join, those where the joined fields from both tables are equal (default), and those where all the records from a particular table are selected whether or not they have matching records in the other table. So type 2 selects all the records from table A and only those records from table B where the joined fields are equal, and vice versa for type 3 joins.
4.3. **Calculated variables**

4.3.1. **Queries**

Queries within the database were used, amongst other things, to:

- Relate data between tables into a single spreadsheet.
- Calculate new variables, using function keys and commands.

Appendix 4.1 details the main types of calculated variables used in the database, with examples. The development of a database that could calculate standard deviation scores for a wide variety of anthropometric data was a unique feature of the study.

4.4. **Reference data**

4.4.1. **The use of reference data**

The chosen method for comparison to ‘normal children’ in this study was to calculate standard deviation scores (SDS) for each measured variable in the anthropometric measures. The arguments for using this method over using case controls are discussed in section 3.2.4.

However, the standard way of calculating SDS is flawed at times during development when the measurement in question is not normally distributed. For example, BMI is skewed during puberty. To overcome this, Cole (1990) developed a method that takes skew into account when calculating a SDS, and where the median rather than the mean is taken as the central point of the data. This has become known as the LMS method, and it relies on the assumption that the data in question become normally distributed after a Box-Cox power transformation. L represents the degree of age dependent skew, M the median, and S the coefficient of variation at each age. LMS data can be tabulated for a series of ages, and z scores calculated using the formula:
The LMS data have been applied to the updated UK reference data for weight, height and body mass index, and these data are available in a tabulated form for use in Microsoft Excel through a specifically adapted function. The principle is transferable to other software, but up to the time of the study, no such modules for running with a Microsoft Access, or similar database had been developed. In addition, there were other sources of reference data to which the LMS principle could and should be applied, but which had not been appropriately adapted for the function. In data where the skew at a particular age was, or could be assumed to be 1, the value of L is 1.

4.4.2. Reference data sources

4.4.2.1. New UK data: height, weight, and BMI

Tanner and colleagues in 1966 (Tanner, Whitehouse, & Takaishi1966) in the Harpenden Growth Study collected the original UK reference data. This has been the basis of growth charts in the UK, until Freeman et al. (Freeman, Cole, Chinn, Jones, White, & Preece1995) updated the records. The New UK reference data, as they are known, were based on growth measurements that were cross-sectional, recent, high quality, and representative of British children. Data came from 12 sources in all, described in Cole et al. (Cole, Freeman, & Preece 1998) comprising a total of 40,999 weight measurements and 32,334 height measurements on boys and girls ranging from 23 weeks gestation to 22.98 years. Regional data sets were adjusted to a common baseline derived from the 1990 National Study of Growth and Health data, which were the most recent, and most nationally representative. Reference centiles were then derived using the LMS method (Cole1990) by means of a 2 stage fitting procedure to model age trends and estimate confidence intervals for the reference
curves (Cole, Freeman, & Preece 1998). Data from ethnic minorities were specifically excluded.

The main advantages of the New UK reference data over the original Tanner data are twofold. Firstly the samples are more nationally representative (including Wales and Scotland) than the Tanner data, which were all collected within the South East of England. Secondly, secular changes in rates of maturity and greater adult height made the Tanner data out of date. The resulting curves show greater values for stature and, to a lesser extent weight, and a change in shape of the distribution with age.

The main, as yet not fully addressed, limitation of this reference data is the issue of racial groups. Is it valid to use a single growth standard for all populations or do different populations need different standards? There is no easy solution to this problem, since intermarriage and changes between first and second generation populations confound the issue (Chinn et al. 1996). The best solution depends on the question being asked. In relation to this study, for following growth in height, the standards are fairly adequate. However, for cross sectional measures, particularly relating to body proportions rather than height alone, different standards may apply. This is particularly so at adolescence, when, for example, the Asian growth pattern, with early menarche, early height spurt and short legs, differs too much for a European standard to be adequate. Adjustment for individual populations have been suggested (Chinn, Cole, Preece, & Rona 1996), although the authors conclude that secular changes as well as generational change make the UK reference data the preferred option for growth monitoring. No specific adjustments other than for parental height were made in the present study on the basis of ethnicity.

National reference data for BMI for children were derived from the same studies as the UK height and weight data, using datasets for 15,636 girls and 14,899 boys, aged birth to 23 years (Cole, Freeman, & Preece 1995). Constructed similarly using the LMS method, they allow BMI SDS to be calculated in relation to UK children.
4.4.2.2. *Height velocity*

Growth standards based only on cross sectional data are different in form from those that represent individual longitudinal curves of growth (Cole 1994; Tanner & Whitehouse 1976), and this is particularly relevant over the period of the adolescent growth spurt. One solution in clinical practice is to use longitudinal or 'distance' charts for growth monitoring. An alternative measure, which can be quantified, is to use height velocity standards, either on charts or as SDS. Height velocity standards are centred around the peak height velocity, with more extreme centiles representing the growth rate for early and late maturers.

Height velocity reference data on which these standards are based have not been updated in the UK since 1966. The Harpenden growth study, from which the standards are derived, are based on measures from 49 boys and 41 girls followed throughout their adolescence (Tanner, Whitehouse, & Takaishi1966). Measurements were taken at 3 monthly intervals during the growth spurt and at 6 monthly intervals before and after this time. Each individual's growth data was smoothed to remove measuring error and to take into account seasonal and other variation. The resulting curves were then read off at 3 monthly intervals and velocity curves derived. SDS for peak height velocity were then obtained by arranging the curves over one another, so that the peak coincide, thus giving a spread of growth velocity around the central peak. The average age at which the peak was achieved was obtained from averaging the growth velocity curves. From these, centiles for height velocity were obtained (Tanner & Whitehouse1966), and SDS calculated as in appendix 4.2: section II.2.

4.4.2.3. *Skinfold thickness*

Skinfold thickness reference data were taken from the Tanner-Whitehouse standards (1975) from birth to 19 years, converted to SDS using the LMS method (Davies, Day, & Cole1993). The advantage of this conversion is that SDS using the LMS method
takes into account both the skewness of the normative skinfold data, and the fact that
the degree of skewness varies with age. Tables for L, M, and S values for triceps and
subscapular measurements are given in Davies et al. (Davies, Day, & Cole 1993), and
SDS calculated as described in appendix 4.2; II.1.

Skinfold thickness, as with other indices of nutritional status, are undergoing secular
change (Chinn & Rona 1994), particularly for girls. However, as yet there is no rival to
the Tanner-Whitehouse standard with reference to skinfold thickness, last revised 30
years ago, although revision has been called for (Paul et al. 1998). In addition,
discrepancies within ethnic groups of skinfold thickness have been noted, but as yet
no racially diverse reference standards exist (Rona & Chinn 1987).

4.4.2.4. Arm circumference

The most widely quoted reference for mid arm circumference is from Jelliffe (Jelliffe &
However, the more recent study of 2,555 Dutch children from birth to 19 years of age
in the town of Osterwolde between 1979 and 1980, provide detailed percentiles of mid
upper arm circumference (Voorhoeve 1990). The values from the Dutch data are
approximately 0.5 cm above the figures for Jelliffe’s national standard. Although not
ideal, in view of the increasing trend towards overweight (Reilly, Dorosty, & Emmett
1999), they are likely to be an improvement on 1964 data from Polish children. In
addition, what bias there is will tend to under-represent the degree of relative
malnutrition in underweight patients to today’s child and adolescent population.

The second source of reference data available for the relevant age group for this study
is from a Spanish cohort (Hernandez et al. 1998). Although more up to date, the
numbers in the study are smaller. Comparisons between the Dutch and Spanish data
(males and females) are shown in figures 4.1. Overall similarity between the data sets
can be seen. For the purposes of the present study the Dutch reference data were
chosen on the basis of slightly higher values (mimicking secular trends) and smoother
fit of data over the age distribution. SDS were calculated from the 50th centile figures and SD entered into a reference table, using the SD function described in appendix 4.2; section II.2.

4.4.2.5. Puberty

Standards for pubertal development and derived puberty centiles (Tanner & Whitehouse1976) are based on the data from the original 1966 Harpenden cohort, and were assessed using the method described by Tanner (1962). These standards are undoubtedly out of date, although as yet no better reference dataset has been developed. Tanner et al. advise that pubic hair and penis size or breast size be rated separately, since the two often develop with different timings.

Unfortunately for the purposes of the present study, in which delay of puberty would be an anticipated finding, 'puberty SDS' are harder to derive. Therefore, whilst a cross over between stage 1 and stage 2 of puberty can be defined, there is no median or mean for stage 1 puberty (prepubertal) and for stage 5 (adult maturity). Pubertal stage has therefore been used in the analyses as a grouping variable where appropriate.

4.4.2.6. Bone Density

Reference data for DXA scans in children are inadequate. The main obstacle is the ethics of exposing large numbers of normal children to radiation, albeit low quantities. This was particularly true for the older, pencil beam scanners, and efforts to collect good quality reference data for children are now being made. It was beyond the scope of this study to produce reference data on normal populations. In addition, the number of different scanners makes comparison across machines problematic, and reference data obtained on one machine is not directly transferable to another machine. The two main manufacturers of DXA scanners are Hologic, who make the Q1000 and the
Figure 4.1: Comparison of mid-arm circumference reference data from two sources by gender


**Series 2:** Dutch Mid-upper Arm Circumference (Voorhoeve, H.W.A. Journal of Tropical Paediatrics Vol 36 October 1990)
Table 4.1: Sources of normative data for children by DXA machine and age range

<table>
<thead>
<tr>
<th>Machine</th>
<th>Age range</th>
<th>Age Interval</th>
<th>No. of children</th>
<th>Source</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hologic QDR4500</td>
<td>8-17 yrs</td>
<td>3 years</td>
<td>666</td>
<td>Hologic (adapted from Faulkner et al. (1996) Calcif. Tissue Int. 59:5:344)</td>
<td>No difference between male and female values. Age bands too wide.</td>
</tr>
<tr>
<td>Hologic QDR1000/W</td>
<td>4-14 yrs</td>
<td>1 year</td>
<td>83F</td>
<td>Cambridge schoolchildren 1994-1997 Personal communication</td>
<td>Only up to 14 years. No. of children in higher age groups limited.</td>
</tr>
<tr>
<td>Lunar DPX software version 3.6</td>
<td>4-25 yrs 0.25 Years</td>
<td>138 F 139 M</td>
<td>Lu et al. (1994) J Bone Miner. Res. 9: 1451</td>
<td>Best available data, except toward end of puberty</td>
<td></td>
</tr>
<tr>
<td>Hologic QDR-1000/W</td>
<td></td>
<td></td>
<td>180 children and young adults</td>
<td>Nysom et al. (1998) Acta Radiologica 39 632-636</td>
<td>Lumbar data from whole body scan lower than from a dedicated lumbar scan</td>
</tr>
</tbody>
</table>

Figure 4.2: Comparison of bone density data using different DXA scanners.
Q4500 models; and Lunar. The reference data summarised in table 4.1 were available at the time of the study: all have their limitations for the present study cohort.

The scan data collected during the study included z scores calculated from the reference data used by the Hologic QDR4500 software. In order to improve the interpretation of the results obtained for subjects, the options were:

- recalculate z scores from better data but collected on different machines
- examine the relationship between reference data from various machines, looking for sources of systematic error.

The latter was performed, on the basis that if there was a significant non-linear relationship between the data sources, that z scores could be recalculated. Figure 4.2 show the relationship between the four sets of reference data at stepped time points from age 7 to 17 (the age of range of the study cohort) for girls. Findings were comparable for boys. Hologic 4500 readings were comparable to those from other samples and machines in a consistent way. The slight bias towards lower readings was not thought significant enough to merit reanalysis of the data.

4.5. **Summary**

The database was designed to collate and present data in a flexible format that allowed it to be transformed to compare with reference data. Using queries, results were drawn from subsets of the data. Microsoft Access is not a statistical package, and data needed to be analysed in appropriate statistical packages. Any alteration or transfer of data from one source to another introduced the risk of error, with the added effect that once outside the main database, delete and alteration functions need to be systematically backdated to include the entire dataset. Methods used by the database to minimise such errors are described.
5. Results: Cross sectional – population characteristics and anthropometric findings

5.1. Population characteristics

5.1.1. Age at presentation

The range of age at presentation (table 5.1) reflects a sample bias towards early onset eating disorders. The mode age of 14.5 years was compatible with the eating disorder literature about peak age of onset for AN, which comprised the majority of the sample. Figure 5.1 shows the age distribution for the total sample, with males differentiated. An excess of females starts to become evident in peripubertal age group.

When subcategorised by gender, the girls were on average older than boys (table 5.1).

5.1.2. Diagnosis by gender

Table 5.2 shows the breakdown of the sample by eating difficulty type and gender. Numbers for AN and EDNOS/AN are in line with previous literature, showing a gender bias of almost 9:1. In this sample, no boys had a diagnosis of bulimia nervosa or EDNOS/BN.

For the ‘atypical eating behaviours’, selective eating showed significant bias towards males; ratio M:F of 3.2:1. FAED had slight female excess at 1.8 to 1. The female/male ratio for FAED did not vary over the age range.

In summary, different types of eating difficulty were strongly associated with gender, with FAED showing the least gender bias. It is also the least specific diagnosis.
Figure 5.1: Age at initial assessment for the total patient sample.

Key: Black shading = males

Table 5.1: Median and range of age at presentation according to gender.

<table>
<thead>
<tr>
<th>Group</th>
<th>Count</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>149</td>
<td>13.22</td>
<td>6.3</td>
<td>16.6</td>
<td>10.25</td>
</tr>
<tr>
<td>M</td>
<td>57</td>
<td>10.58</td>
<td>7.2</td>
<td>14.8</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Table 5.2: Total sample by diagnosis and gender

Rows are Sex, Columns are Diagnosis (DSMIV/GOS), Numbers represent counts (%) of patients

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>BN</th>
<th>EDNOS/AN</th>
<th>FAED</th>
<th>Other</th>
<th>SE</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>49</td>
<td>14</td>
<td>37</td>
<td>35</td>
<td>7</td>
<td>7</td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>32.9</td>
<td>9.4</td>
<td>24.8</td>
<td>23.5</td>
<td>4.7</td>
<td>4.7</td>
<td>100</td>
</tr>
<tr>
<td>M</td>
<td>4</td>
<td>0</td>
<td>6</td>
<td>19</td>
<td>5</td>
<td>23</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>7.02</td>
<td>0</td>
<td>10.5</td>
<td>33.3</td>
<td>8.77</td>
<td>40.4</td>
<td>100</td>
</tr>
<tr>
<td>total</td>
<td>53</td>
<td>14</td>
<td>43</td>
<td>54</td>
<td>12</td>
<td>30</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>25.7</td>
<td>6.8</td>
<td>20.9</td>
<td>26.2</td>
<td>5.83</td>
<td>14.6</td>
<td>100</td>
</tr>
</tbody>
</table>
5.1.3. Pubertal status and menarche

Results are shown for menstrual status at time of presentation (table 5.3) and for menstrual status by diagnosis (table 5.4). In total 44 premenarcheal girls met Great Ormond Street Hospital criteria for AN (and DSMIV present or past AN). 42 postmenarcheal girls with Great Ormond Street Hospital AN allowed comparison between the two groups in further analyses. Of the total sample 84% of the girls had primary or secondary amenorrhoea. The distinction between normal and abnormal primary amenorrhoea was not identifiable from these data.

Figure 5.2 shows the sample by Tanner stage. The sample represented all pubertal stages, with a bias towards stage 1, which is an unbounded category at the lower end.

5.1.4. Duration of eating difficulties

Data on age of onset of eating difficulties were available for 179 patients by parent report. Duration of eating difficulties was taken as:

\[ \text{Age at presentation} - \text{Age of onset of concern} \] (in years)

Figure 5.3 shows the duration of illness for each diagnostic group. For the majority of the sample, eating difficulties had been present for less than a year at the time of presentation. There was no overall correlation between age at assessment and duration of eating difficulties (\( r = -0.2 \)).

Using ANOVA models, duration of illness was examined between diagnostic groups. Duration of eating difficulties was log transformed to make near normal distributions within each diagnostic group. There was a significant difference in log(duration of illness) between selective eating and all other diagnostic groups (\( F \) 13.04; \( p < 0.0001 \)). With selective eaters removed from the analysis, FAED had a significantly longer duration of illness at the time of assessment than AN (\( F \) 6.94; \( p = 0.01 \)) or EDNOS/AN (\( F \) 9.56; \( p = 0.002 \)) groups.
Table 5.3: Sample by menstrual status at the time of presentation.

<table>
<thead>
<tr>
<th>Menstrual status</th>
<th>Count (n=206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>57</td>
</tr>
<tr>
<td>Primary amenorrhoea</td>
<td>87</td>
</tr>
<tr>
<td>Post menarcheal</td>
<td>60</td>
</tr>
<tr>
<td>Secondary amenorrhoea</td>
<td>38</td>
</tr>
<tr>
<td>Regular ongoing periods</td>
<td>9</td>
</tr>
<tr>
<td>Irregular periods</td>
<td>13</td>
</tr>
<tr>
<td>Uncertain (includes one possible bleed)</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 5.4: Sample by menstrual status and diagnosis

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>BN</th>
<th>EDNOS/AN</th>
<th>EDNOS/BN</th>
<th>FAED</th>
<th>SE</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmen</td>
<td>18</td>
<td>5</td>
<td>24</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>61</td>
</tr>
<tr>
<td>Premen</td>
<td>31</td>
<td>2</td>
<td>13</td>
<td>2</td>
<td>31</td>
<td>5</td>
<td>4</td>
<td>88</td>
</tr>
<tr>
<td>Female total</td>
<td>49</td>
<td>7</td>
<td>37</td>
<td>7</td>
<td>35</td>
<td>7</td>
<td>7</td>
<td>149</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>7</td>
<td>43</td>
<td>7</td>
<td>54</td>
<td>30</td>
<td>12</td>
<td>206</td>
</tr>
</tbody>
</table>

Figure 5.2: The sample according to Tanner pubertal stage

Key: Tanner stage = breast stage (girls) or genital stage (boys – shaded black)
5.1.5. Medical diagnosis

Ten patients had a medical diagnosis in addition to their eating difficulties. The diagnoses are listed below (table 5.5), together with the eating disorder diagnosis, age and weight for height at presentation.

For the six whose medical diagnosis was known at assessment, the severity of weight loss and the suspected contribution of psychological factors to the eating difficulties were the reason for referral. All required extensive psychological intervention in addition to their medical care.

Of the four whose diagnosis was not known at presentation, features of note are that all presented with atypical eating difficulties and the course of their illness was characterised by failure to respond to psychological intervention. Case reports have been published for those with intracranial tumours (De Vile, Sufraz, Lask, & Stanhope 1995).

The majority of analyses were completed excluding those children who had a medical diagnosis that may have had an impact on their growth and development, independent of eating difficulties. However, since this study aims to look at a cohort of children presenting with eating difficulties analyses were repeated including patients with comorbid organic illness. Results are reported if inclusion of the group altered the result.
Table 5.5: Patients excluded because of medical diagnoses, in addition to their eating difficulties, that might influence their growth and development

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Medical problem known at presentation?</th>
<th>Medical diagnosis</th>
<th>%Wt/ht at presentation</th>
<th>Eating disorder diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.7</td>
<td>F</td>
<td>Yes</td>
<td>Asthma</td>
<td>72.1</td>
<td>AN</td>
</tr>
<tr>
<td>16.6</td>
<td>F</td>
<td>Yes</td>
<td>Turner's syndrome</td>
<td>75</td>
<td>AN</td>
</tr>
<tr>
<td>13.6</td>
<td>M</td>
<td>Yes</td>
<td>Immunoglobulin deficiency</td>
<td>64.4</td>
<td>FAED</td>
</tr>
<tr>
<td>14.4</td>
<td>M</td>
<td>Yes</td>
<td>Crohn's disease</td>
<td>78.1</td>
<td>FAED</td>
</tr>
<tr>
<td>13.6</td>
<td>F</td>
<td>Yes</td>
<td>Chronic lung disease</td>
<td>51.6</td>
<td>FAED</td>
</tr>
<tr>
<td>11.6</td>
<td>F</td>
<td>Yes</td>
<td>Learning disability/autism</td>
<td>71.6</td>
<td>FAED</td>
</tr>
<tr>
<td>7.9</td>
<td>M</td>
<td>No</td>
<td>Occult intracranial tumour</td>
<td>75.5</td>
<td>FAED</td>
</tr>
<tr>
<td>10.4</td>
<td>M</td>
<td>No</td>
<td>Occult intracranial tumour</td>
<td>82.7</td>
<td>FAED</td>
</tr>
<tr>
<td>13.7</td>
<td>M</td>
<td>No</td>
<td>Occult intracranial tumour</td>
<td>82.8</td>
<td>FAED</td>
</tr>
<tr>
<td>8.1</td>
<td>F</td>
<td>No</td>
<td>Mitochondrial disorder</td>
<td>84.4</td>
<td>FAED</td>
</tr>
</tbody>
</table>
5.1.6. Intervention

The four levels of intervention described in section 3.4.2.3. can be summarised as:

1. Assessment and medical review only
2. Assessment, mental health team monitoring and/or brief intervention
3. Outpatient treatment – more than 6 months
4. Inpatient treatment

Data for treatment level were not available for 3 patients treated elsewhere. Roughly equal numbers received each level of intervention (level 1 n=51; level 2 n= 54; level 3 n= 47; level 4 n= 51). Figure 5.4 shows the breakdown of intervention level by diagnosis. As might be expected, inpatient treatment was confined almost exclusively to those diagnostic groups where malnutrition was a feature. The majority had AN or EDNOS/AN, recalling that most patients diagnosed EDNOS/AN had met full criteria for AN at some time. Weight for height at assessment did not differentiate the intervention levels, perhaps because it is merely a 'snap shot' in the time course of a chronic illness. A significant number of FAED patients required inpatient treatment. 35% of those with AN or EDNOS/AN received level 1 or 2 intervention.
Figure 5.4: Percentage of patients at each level of treatment intensity according to diagnosis. Numbers at each treatment level were approximately equivalent.
5.1.7. Parental Heights and mid-parental Heights

103 fathers (50%) were measured, 73 were reported i.e. father not present, 30 cases were missing data i.e. unknown or not asked. For mother's height, 156 mothers were measured, 28 reported and 22 missing.

There were no significant differences between the diagnostic groups for mother or fathers height SDS. Any slight trends between diagnostic groups were attributable to outliers: one father in the FAED group (height –5.45 SDS); and one father in the ‘Other’ group (height +2.99 SDS).

Mid parental height SDS (an approximation to the child’s ‘genetic’ height potential) were approximately normally distributed within each diagnostic subgroup. No differences were found between the mean mid parental height SDS, either for the seven diagnostic groups together or on individual between group differences. (F ratio 1.5, p> 0.1). No group mean was significantly different from the population mean of 0 SDS. This means that differences between the diagnostic groups for subjects measured height were unlikely to be attributable to differences in parental heights.

The two options for dealing statistically with extreme cases were to exclude cases outside ± 2SDS (n= 4) for all growth related measures, or to include mid-parental height as a covariate in the analyses. The latter option was chosen, as there was no bias for parental height towards a single diagnostic group.

The resulting variable, mid parental height SDS, had a mean value of –0.17, with minimal skew (-0.07) and kurtosis of 0.29, suggesting slight bunching toward the mean.
Figure 5.5: The distribution of height SDS for subjects’ fathers (FHtSDS) and mothers (MHtSDS).

![Graph showing the distribution of height SDS for subjects' fathers and mothers.]

Table 5.6: BMI SDS and % weight for height at presentation for 206 total cases of which 11 are missing (10 with medical problems; 1 refused to be weighed).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Mean (BMI)</th>
<th>Std</th>
<th>Min (BMI)</th>
<th>Max (BMI)</th>
<th>Mean (SDS)</th>
<th>Std</th>
<th>Min (SDS)</th>
<th>Max (SDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN</td>
<td>50</td>
<td>-2.86</td>
<td>1.07</td>
<td>-5.31</td>
<td>-1.51</td>
<td>74.88</td>
<td>6.85</td>
<td>61.07</td>
<td>84.42</td>
</tr>
<tr>
<td>BN</td>
<td>7</td>
<td>0.85</td>
<td>1.63</td>
<td>-1.24</td>
<td>3.89</td>
<td>122.05</td>
<td>43.06</td>
<td>86.42</td>
<td>215.51</td>
</tr>
<tr>
<td>EDNOS/AN</td>
<td>43</td>
<td>-0.91</td>
<td>0.77</td>
<td>-2.17</td>
<td>0.63</td>
<td>90.77</td>
<td>7.87</td>
<td>78.77</td>
<td>108.93</td>
</tr>
<tr>
<td>EDNOS/BN</td>
<td>7</td>
<td>0.71</td>
<td>1.09</td>
<td>-0.58</td>
<td>2.50</td>
<td>113.28</td>
<td>20.42</td>
<td>93.21</td>
<td>151.80</td>
</tr>
<tr>
<td>FAED</td>
<td>47</td>
<td>-1.84</td>
<td>1.47</td>
<td>-7.80</td>
<td>1.15</td>
<td>84.05</td>
<td>10.71</td>
<td>57.31</td>
<td>117.63</td>
</tr>
<tr>
<td>SE</td>
<td>30</td>
<td>-0.11</td>
<td>1.11</td>
<td>-2.59</td>
<td>2.17</td>
<td>100.95</td>
<td>13.24</td>
<td>79.46</td>
<td>141.56</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>-2.37</td>
<td>1.13</td>
<td>-5.45</td>
<td>-1.31</td>
<td>79.3</td>
<td>6.14</td>
<td>64.8</td>
<td>88.7</td>
</tr>
</tbody>
</table>

Although equivalent, both measures are given for the purposes of comparison, together with minimum and maximum within each diagnostic group.

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5.2. Anthropometry: cross sectional results

5.2.1. Summary of weight for height/BMI SDS

Table 5.6 shows the average and distribution of underweight in the total sample and by diagnostic subgroups.

Four groups were underweight. AN (AN) and 'other underweight' (Other) have a threshold for degree of underweight and patients were, by definition, less than 85% weight/height. Children in the FAED category had all lost weight, but not to a specified threshold. Patients with BN and EDNOS/BN were, by definition, over 85% weight for height. Selective eating has no weight criteria.

ANOVA revealed significant differences between the groups in terms of BMI SDS at presentation (F ratio 31.4, p<0.0001). Within the underweight groups, AN and Other were more underweight than FAED and EDNOS/AN. However, the difference between FAED was removed when a single highly significant outlier was added into the model (F ratio 7.06, p 0.008).

There was a trend for EDNOS/AN to have lower BMI SDS than the EDNOS/BN group, but this difference was not significant (p<0.06), probably due to low numbers in the EDNOS/BN group. For further analyses, the groups of BN and EDNOS/BN were combined.

5.2.2. Summary of height data

As a group the total sample had a height SDS distribution with a normal distribution around 0 with a tail of short to extreme short stature, in which the underweight patients were strongly represented (figure 5.6 – cases with medical illness excluded).
Mean height for the total group was -0.2 SDS (comparable to their mid-parental heights), but for the underweight group the mean HtSDS was -0.62, significantly below the expected mean of 0.

8.7% of the variance in height SDS was accounted for BMISDS, and 11.6% by mid parental height.

5.2.2.1. Height as a function of pubertal stage

When grouped by Tanner stage, height SDS was significantly different between the stages. Most of the difference was between early (stages 1 and 2) and late puberty (stages 4 and 5). With the addition of diagnosis as a factor in the model, the effect was less marked between the groups. In other words, subjects in early puberty were particularly likely to have a height SDS below the reference mean, and this was strongly associated with particular eating disorder diagnoses. If weight SDS, BMI SDS and subscapular skinfold SDS are entered into the model, they have decreasing influence on the effect of Tanner stage on height SDS. In other words, there may be a greater influence of 'size' than fatness on the low height SDS of early puberty in eating disorders.

5.2.2.2. Height Adjusted for bone age

When height SDS was calculated based on the patient's bone age not chronological age there were no differences between the diagnostic groups on height (BA) SDS. The difference across Tanner stage remained, with relative tallness being a feature of early puberty. Table 5.7 shows the results of the one way ANOVA.

When a two-way interaction between diagnosis and Tanner stage was entered, there ceased to be any significant difference in height (BA) SDS between the diagnostic groups or Tanner stages. In other words, most of the impact on height of a particular diagnosis can be explained by its impact on bone age and pubertal delay. The overall correlation between height SDS and bone age height SDS was 0.4.
Figure 5.6: Histogram of Height SDS at presentation for total patient sample

Key: Black shading = underweight (<85% weight for height)

Table 5.7: One-way ANOVA results for Height(bone age)SDS. Differences in height between the diagnostic groups were no longer significant when adjusted for bone age.

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>Sums of Squares</th>
<th>Mean Square</th>
<th>F-ratio</th>
<th>Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>Const</td>
<td>1</td>
<td>9.39925</td>
<td>9.39925</td>
<td>6.7396</td>
<td>0.0114</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>4</td>
<td>2.95255</td>
<td>0.738137</td>
<td>0.52927</td>
<td>0.7146</td>
</tr>
</tbody>
</table>
5.2.2.3. Segmental proportions

For the total sample, mean sitting height SDS (SHSDS) and subischial leg length SDS (SLLSDS) and proportions (SHSDS/SLLSDS) were within 0.5 SDS, although mean SHSDS was 0.47 SDS, thus almost reaching significance.

Across diagnoses, there was not much difference or deviation in SLLSDS from 0 SDS in all groups except FAED, where mean SLLSDS was –0.69 SDS i.e. leg length was particularly short for this group relative to spine. SHSDS however, showed marked between diagnosis difference (F 3.88, p 0.002), with AN and FAED having mean SHSDS significantly below 0 SDS.

When SHSDS and SLLSDS were expressed as a ratio (SHSDS/SLLSDS = proportionsSDS), the discrepancy between leg length and sitting height for FAED disappeared, whereas for AN it remained. The mean proportionsSDS for AN was –0.56 SDS i.e. short spine relative to leg length (n=50). This trend was even more marked when restricted to boys and premenarcheal AN girls. In other words, almost the entire deficit in height was accounted for by reduced spinal length. This finding is particularly important when considering the measurement of bone density in the spine (see Chapter 7). Figure 5.7 shows segmental proportionsSDS for the prepubertal girls and the boys by diagnostic category, showing the negative skew for AN and FAED.
Figure 5.7: Segmental proportions (sitting height SDS – subischial leg length SDS) by diagnosis and gender at presentation

Key: Pink circles = premenarcheal girls. Blue crosses = boys
5.2.3. Pubertal stage at presentation - relationship to weight loss.

For this analysis, selective eaters (n=30) were excluded on the basis that:

- For the majority, selective eating is a primary eating difficulty (at least 23/30). The age and stage at presentation therefore may be attributable to the clinic profile and age limits more than to the disorder.

- Most selective eaters were boys (23/30) in stage 1 puberty (18/21 (2 missing data)), and inclusion would bias results towards finding significant differences between stage 1 and other stages.

The remaining data were then analysed exploring the question of when eating difficulties present in relation to stage of puberty. Low BMISDS at presentation was strongly correlated with Tanner stage (F 6.07, P<0.001). The main effect was seen between stages 2/3 and stage 5. In other words, in this sample low weight subjects were most likely to present in stage 2 or stage 5 puberty. Given hypotheses that AN represents a phobic stance towards pubertal development, the attainment of stage 2 puberty and stage 5 (adult maturity) may represent particular biological triggers for subjects with maturational fears.

5.2.4. The relationship between anthropometric measures

All cases (including and excluding those with a medical diagnosis) were examined by means of a correlation matrix to quantify the relationship between measures of size and measures of fatness, in recognition that BMI is, at best, a crude measure of body fatness. Table 5.8 shows the correlations between measures of nutritional status for the total sample and the underweight sample.

The strongest correlation for the total sample was between BMI SDS and Arm circumference SDS. All correlations between measures were weaker in the
Table 5.8 (a): Correlation between height, BMI, arm circumference and skinfold thickness of all diagnostic groups across the whole weight spectrum within the sample.

<table>
<thead>
<tr>
<th>Cases selected according to No Medical Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Product-Moment Correlation</td>
</tr>
<tr>
<td>WiSDS  BMISDS  ArmSDS  TriSDS  SubScapSDS</td>
</tr>
<tr>
<td>WiSDS  1.00</td>
</tr>
<tr>
<td>BMISDS 0.87  1.00</td>
</tr>
<tr>
<td>ArmSDS 0.84  0.90  1.00</td>
</tr>
<tr>
<td>TriSDS 0.59  0.73  0.77  1.00</td>
</tr>
<tr>
<td>SubScapSDS 0.70  0.79  0.78  0.79  1.00</td>
</tr>
</tbody>
</table>

Table 5.8 (b) within the underweight group

<table>
<thead>
<tr>
<th>Cases selected according to Underweight (+ no medical problem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Product-Moment Correlation</td>
</tr>
<tr>
<td>WiSDS  BMISDS  ArmSDS  TriSDS  SubScapSDS</td>
</tr>
<tr>
<td>WiSDS  1.00</td>
</tr>
<tr>
<td>BMISDS 0.72  1.00</td>
</tr>
<tr>
<td>ArmSDS 0.72  0.81  1.00</td>
</tr>
<tr>
<td>TriSDS 0.35  0.55  0.67  1.00</td>
</tr>
<tr>
<td>SubScapSDS 0.51  0.60  0.61  0.62  1.00</td>
</tr>
</tbody>
</table>
underweight population, including a correlation of only 0.6 between triceps and subscapular skinfold thickness. Nevertheless, the strongest correlation \((r=0.81)\) remained between BMI SDS and arm circumference, a finding that may be of use in patients who refuse to be weighed.

### 5.2.4.1. Principal components analysis of anthropometric data

Several of the anthropometric measures may be measuring the same, or a similar thing e.g. BMI and mid arm circumference are both measures of nutritional status. A principal components analysis (PCA) was performed to determine whether data measured on many variables can be described more concisely in fewer dimensions.

Principal components in Data Desk 6.1.1 are standardised from the matrix of correlations of X variables. Eigen values are the variances of the projections of the points along each of the principal axes. The largest eigen value is the variance of the projection into the first principal axis. Eigen values of less than 1 are not usually considered of significance.

Analyses were performed for the group as a whole (including those with a medical problem) and then repeated for the underweight group (excluding those with a medical problem). Finally PCA was performed for each individual diagnosis. Results are only reported where the findings were different from the results of the whole group.

Table 5.9 shows Principal Component Analysis for total sample and underweight groups (with casewise exclusion for missing data).

Results show that the first principal component \((V1)\) includes all variables, and might be thought of as 'size'. This accounts for 62% of the variance in the total sample and 55% of the variance in the underweight sample \((n=91)\).

The second component \((V2)\) is one of length and proportionality i.e. that children have small size and then a change of body proportions (sitting height to subischial leg length ratio) because of their reduced stature and pubertal delay. This was so for the
total sample and when restricted to the underweight sample, and is in keeping with the findings of section 5.2.2.3.

From V3 onwards the eigen vectors differed between the total and the underweight groups, with no other components carrying significant eigen values in the total sample.

In the underweight group, the third factor (V3) had triceps and subscapular skinfolds (i.e. fatness) in a different vector to other body size components. V4 and V5 were not significant.

Within diagnostic groups, notable features were:

- Selective eating: V1 did not include proportions along with other measures. Most of the selective eating group were boys in Stage 1 puberty. Proportions would be expected to reflect pubertal delay and be more marked in underweight children, with which this finding is consistent.

- In most diagnostic groups, including bulimia nervosa, a vector for BMI, arm circumference and triceps accounted for a significant amount of the variance.

- Height, weight ± arm circumference was also a separate vector of note, of greater importance in normal weight groups than the underweight groups.

Skinfold thicknesses were only a separate vector in AN and EDNOS/AN cases. In other underweight groups (FAED, Other) nutritional status measures e.g. not purely fat, were prominent.
### Table 5.9(a): Principal components analysis for total and underweight samples

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
<th>Underweight sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eigen Values</td>
<td>Variance Proportion</td>
</tr>
<tr>
<td>e1</td>
<td>4.372</td>
<td>62.5</td>
</tr>
<tr>
<td>e2</td>
<td>1.198</td>
<td>17.1</td>
</tr>
<tr>
<td>e3</td>
<td>0.882</td>
<td>12.6</td>
</tr>
<tr>
<td>e4</td>
<td>0.229</td>
<td>3.3</td>
</tr>
<tr>
<td>e5</td>
<td>0.201</td>
<td>2.9</td>
</tr>
<tr>
<td>e6</td>
<td>0.101</td>
<td>1.4</td>
</tr>
<tr>
<td>e7</td>
<td>0.017</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### Table 5.9(b)

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eigen Vectors (n=173)</td>
</tr>
<tr>
<td>HtSDS</td>
<td>-0.208</td>
</tr>
<tr>
<td>WtSDS</td>
<td>-0.445</td>
</tr>
<tr>
<td>BMISDS</td>
<td>-0.454</td>
</tr>
<tr>
<td>Proportions</td>
<td>-0.147</td>
</tr>
<tr>
<td>ArmSDS</td>
<td>-0.451</td>
</tr>
<tr>
<td>TriSDS</td>
<td>-0.386</td>
</tr>
<tr>
<td>SubScapSDS</td>
<td>-0.423</td>
</tr>
</tbody>
</table>

### Table 5.9(c)

<table>
<thead>
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<th>Underweight subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eigen Vectors (n=91)</td>
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</tr>
<tr>
<td>WtSDS</td>
<td>-0.452</td>
</tr>
<tr>
<td>BMISDS</td>
<td>-0.452</td>
</tr>
<tr>
<td>Proportions</td>
<td>0.015</td>
</tr>
<tr>
<td>ArmSDS</td>
<td>-0.460</td>
</tr>
<tr>
<td>TriSDS</td>
<td>-0.342</td>
</tr>
<tr>
<td>SubScapSDS</td>
<td>-0.397</td>
</tr>
</tbody>
</table>
5.3. Summary of cross sectional results

Chapter five explored the cross sectional growth and nutritional data for a heterogeneous group of eating difficulties across middle childhood and early adolescent. The main findings were:

- Types of eating difficulty were not only gender, but also age and pubertal stage biased in their onset.

- The courses of eating difficulties differed significantly in terms of duration and likely level of intervention.

- In premenarcheal onset eating disorders associated with weight loss height was on average < - 0.5 SDS (a centile equivalent). Deficits in height were unlikely to be accounted for by parental short stature. Measuring of parental height may therefore be helpful in considering differential diagnosis. The majority of height difference was accounted for by pubertal and bone age delay.

- Reduced sitting height to subischial leg length ratio was a feature of AN associated with pubertal delay and short stature.

- Measures of nutritional status had poorer inter-measure correlation in underweight children than in the total sample. The best correlation was seen between BMI SDS and arm circumference SDS.

Principal components analysis of anthropometry identified that, for the total sample, 2 vectors added significantly to the variance:

- All measures - size

- Height and skeletal proportions – a measure of reduced stature and altered spine to leg length, reflecting the impact of delayed puberty on growth

For the underweight sample the principal components influencing variance were:
- All measures - size
- Height and skeletal proportions as above
- Triceps and subscapular skinfolds – direct measures of fat
6. Results II: Cross sectional - body composition

6.1. Introduction

Clinicians use BMI or % BMI as a determinant of target weight and resumption of menses (chapter 2). The relationships between %BMI and %body fat at underweight and normal weight range thresholds were determined for the patient sample since one is often taken as a proxy for the other. Body composition findings are reported for the total cross sectional ED patient sample (n=206). Where a control group is identified, data were from the Cambridge school children sample described in section 3.2.4.1. Calculations for body composition parameters are described in section 3.4.2.

6.2. Relationship between BMI SDS and % body fat in eating disorders patients compared to controls

6.2.1. Girls

For the entire female sample, patients plus controls, the correlation between % fat (Slaughter's method) and BMI SDS was 0.8 (adjusted $R^2$ 63.7%; t ratio 18.8). Very similar figures were found using the Deurenberg equations (section 3.5.2). Residuals were normally distributed around 0, with no difference in slope for the patients and control groups i.e. the correlation was largely independent of weight status. One girl, highlighted in figure 6.1, accounted for 8% of the variance.

6.2.2. Boys

The correlation between BMISDS and %fat for boys was lower than for girls (0.61) although still significant (adjusted $R^2$ 36.8%; p < 0.0001; t ratio 8.25) (figure 6.2). This was largely due to subjects at the lower end of the weight range. Discontinuity between the patient and the control group was more apparent than for girls (figure 6.3).
Figure 6.1: Scatterplot of BMI SDS versus %body fat for girls, with regression line

Key: patients in red; controls subjects in blue

Figure 6.2: Scatterplot of BMI SDS versus %body fat for boys, with regression line
Figure 6.3: residuals plot for boys, patient and control samples, showing difference in slope for the two groups.

Figure 6.4: Scatterplot of %BMI versus %body fat for the female patient sample only.

Key: Blue = <85% BMI; green >85% BMI
6.2.3. % Body fat in relation to definitions of underweight

Figure 6.4 shows the relationship, with regression line, between % BMI and % body fat. The correlation of % BMI and % body fat for the female patients (cross sectional findings) was 0.73. Despite this strong correlation, figure 6.4 shows the degree of variation within underweight subjects. At 85% BMI and below the range of body fat is from 5.2% to 24.2%.

For the total sample (patients + controls, both sexes), 0 SDS or 100 % BMI corresponded to 20-21% body fat using both Slaughter and Deurenberg's regression equations.

The relationship between % body fat, %BMI and onset or resumption of menses is further explored in section 8.2.

6.3. Fat free mass index (FFMI) and fat mass index (FMI) in eating disorder patients compared to controls

Figure 6.5 shows individual values (females only) for FMI and FFMI against age for the three ‘typical’ eating disorder sub-groups (AN, EDNOS, BN), overlying reference curves of mean FFMI or FMI ±1SD.

With weight loss both FM and FFM were lost, across the weight and age spectrum, and consistency between the two compartments remained. For example, in AN patients, when two SDs of weight were lost, one SD was FM and one was FFM. All BN patients lay within 1 SD for both FM and FFM. Continuity between the three diagnostic categories in terms of body composition can be seen, with the overlap between AN and EDNOS occurring at around -1SD of FM. EDNOS patients above the mean line on the FMI chart are in the normal range for BMI, but do have relatively higher FM than FFM.
Figure 6.5 (a): FMI for eating disorder subgroups (females)

Figure 6.5 (b): FFMI for eating disorders subgroups (females)
Figure 6.6: FMI and FFMI against age in girls with FAED compared with AN with reference curves.

Figure 6.7: FMI and FFMI against age in boys with FAED compared with AN with reference curves.

Figure 6.8: FMI and FFMI against age for boys with SE with reference curves.
FAED patients, restricted to those less than 85% weight for height, were compared to AN patients (figures 6.6 and 6.7). For both genders FAED patients are similar to younger AN patients in terms of their body composition, having similar patterns of FM and FFM loss.

Patients with selective eating (SE) (figure 6.8 - boys only shown) had normal FMI and FFMI, especially the younger ones. Towards adolescence there was a tendency towards a relative reduction in FM i.e. they became leaner relative to the normal population of teenage boys.

6.4. Summary

This chapter of results explored body composition across the range of eating difficulties in the early onset population. The strengths and weaknesses of % BMI as a measure of % body fat were identified for the sample.

Using a two component model, values were calculated for FM and FFM normalised for height, and looked at across diagnostic groups. Almost 1 SD of both FM and FFM were lost in AN and other eating disorders associated with extreme weight loss. This does not mean equal fat mass and fat free mass were lost pound for pound, but that loss relative to the norm was equivalent in both compartments. Secondly, in the area that borders on weight criteria for AN there was quite a wide range of body fat, with a number of patients who met AN criteria falling within 1SD of the normal range for body fat. This was particularly so during mid-adolescence. The numbers of subjects was too limited to make definitive statements about boys although when AN and FAED cases were looked at together, the similar proportional loss of FM and FFM was seen clearly. As age increased the differential between FM and FFM loss was evident, with a trend towards relatively greater loss of FM than FFM.
7. Results III: Bone density in early onset eating disorders - a comparison of methods adjusting for size

7.1. Introduction

The results in this chapter are both cross sectional and longitudinal. Details of the sample are given at each stage of follow-up. The methods used to correct for bone size and body size are described in section 3.4.3.

7.2. Cross sectional results

7.2.1. Method 1: Z-scores

Clinical characteristics of the diagnostic subgroups are shown in table 7.1, together with mean (±SD) areal bone mineral density (aBMD) z scores for each group.

Using ANOVA, differences between the diagnostic groups for BMD z score did not quite reach statistical significance (F ratio 2.3; p = 0.055). Given the degree of overlap and amount of variance within the groups this is perhaps not surprising (see figure 7.1). The three underweight groups all had median values less than –1 SDS BMD z scores.

Further analyses were performed on the subgroup of patients with AN or AN/EDNOS on the basis of menarcheal status. There were 22 in the premenarcheal and 21 in the postmenarcheal groups. For BMD z score, a difference in BMD z score was found at the 0.01 level (S.E. 0.14) between the pre and post menarcheal patients for the two AN diagnoses. Taken on face value, this would suggest that premenarcheal patients do indeed have lower bone densities than postmenarcheal patients, and supports the findings of the literature so far. (Bachrach, Katzman, Litt, Guido, & Marcus 1991)
Table 7.1: Number of subjects for each diagnostic group, age at assessment and duration of eating disorders.

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>AN/EDNOS</th>
<th>BN</th>
<th>FAED</th>
<th>Other</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>25</td>
<td>18</td>
<td>3</td>
<td>23</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>%</td>
<td>31.7</td>
<td>22.8</td>
<td>3.8</td>
<td>29.1</td>
<td>7.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Mean age (SD) at DXA</td>
<td>14.5 (1.7)</td>
<td>14.3 (1.5)</td>
<td>15.7 (0.8)</td>
<td>12.9 (1.8)</td>
<td>12.9 (2.5)</td>
<td>9.8 (2.0)</td>
</tr>
<tr>
<td>Mean duration of illness (SD) (years)</td>
<td>1.8 (1.6)</td>
<td>2.0 (1.3)</td>
<td>3.4 (3.3)</td>
<td>3.7 (3.6)</td>
<td>1.9 (1.5)</td>
<td>5.2 (3.5)</td>
</tr>
<tr>
<td>Mean Ht SDS (SD)</td>
<td>-0.4 (1.4)</td>
<td>-0.4 (1.2)</td>
<td>-0.6 (0.1)</td>
<td>-1.0 (1.1)</td>
<td>-1.0 (0.7)</td>
<td>-0.1 (0.9)</td>
</tr>
<tr>
<td>Mean BMI SDS (SD)</td>
<td>-1.3 (0.9)</td>
<td>-0.5 (0.7)</td>
<td>0.6 (0.9)</td>
<td>-1.7 (1.3)</td>
<td>-1.1 (1.2)</td>
<td>-0.9 (0.7)</td>
</tr>
<tr>
<td>Mean BMD Z score (SD)</td>
<td>-1.3 (0.9)</td>
<td>-0.9 (1.1)</td>
<td>0.3 (0.5)</td>
<td>-1.5 (0.8)</td>
<td>-1.3 (1.3)</td>
<td>-0.9 (0.7)</td>
</tr>
<tr>
<td>Min: Max</td>
<td>-3.28:1.42</td>
<td>-3.1:1.1</td>
<td>-0.2:0.8</td>
<td>-3.7:0.6</td>
<td>-2.9:0.2</td>
<td>-1.3:0.1</td>
</tr>
</tbody>
</table>

Figure 7.1: Median, range and interquartile range for aBMD by diagnostic group.
7.2.2. Method 2: Regression model

Figure 7.2 shows the BMC SDS for the three underweight diagnostic groups, adjusted for height, weight and pubertal stage using the Warner et al. regression model (1998). Mean values no longer fell in the osteopenic range. BMC SDS were compared to aBMD SDS (z scores) (figure 7.3). BMC SDS was significantly closer to 0 than BMD z score (p<0.0001). Within these 3 diagnostic groups, there was no significant difference between BMC SDS, using ANOVA.

Although scores using this correction were nearer to those expected for the normal population, there were 26 patients with a BMC SDS of < -1, a level that would indicate osteopenia if it were found in adults. BMC SDS was correlated with measures of weight and development, with the strongest correlations being with weight SDS at time of DXA, and with sitting height SDS (more so than full stature). Together these predicted 51.1% of the variance of BMC SDS (adjusted R²). Duration of illness and age showed no relationship with low BMC SDS, a finding confirmed using logistic regression, with low BMC status as a categorical variable.

Analysis on the AN subgroups, dividing into pre and post menarcheal patients, was performed as in method 1, and this time no significant differences were found between the two groups (p 0.48). In other words, the apparent differences between pre and postmenarcheal AN patients in their BMD z scores became insignificant when adjustments for height, weight and Tanner stage were made.
Figure 7.2: BMC SDS for the three underweight groups as calculated using the Warner et al. (1998) regression model.

Figure 7.3: Z score compared to BMC SDS for the total sample
7.2.3. Method 3: Adjustment for size

Using Prentice et al.'s method (Prentice, Parsons, & Cole 1994), there were no significant differences between diagnostic groups in terms of BMC corrected for bone area, weight and height. Together bone area, weight and height account for 98.2% of the variance (adjusted $R^2$) in lnBMC (Table 7.2). Log (ln) BA alone accounts for 97.4% of the variance (adjusted $R^2$) ($t_{52.9}$; p<0.0001).

None of these variables adjust for age, which is likely to account for the majority of variation in growing children. lnAge alone accounts for 47.7% (adjusted $R^2$) of the variance in lnBMC. If bone area is then entered into the regression model, 97.5% of the variance is accounted for, and weight and height variables then add little to the model. In other words, age and size account for almost all of the variation in BMC, leaving little room for analysis of the influence of other illness related variables.

One option was to use variables in the model which have already been adjusted for age. For example, 'weight for height' takes into account weight and height adjusted for age. Once lnBA and ln Weight for height are entered into the regression model, there is no significant main effect of duration of illness, even when restricted to those patients most theoretically at risk i.e. patients who have not yet reached menarche [n=43].

Alternatively, age can be taken into account with weight and height variables in the usual way, by using SDS. Since negative values cannot be log transformed, weight and height SDS were first adjusted by adding 5 to the SDS value and then taking the natural log. Using this adjustment, lnBA was first entered, followed stepwise by adjusted HtSDS, then adjusted WtSDS. All 3 variables were significant at the $<0.001$ level, with a total adjusted $R^2$ of 98% (see table 7.3). The coefficient for lnBA following the regression was 1.71. Neither further anthropometric indices, nor duration of illness improved the model.
Table 7.2: Regression of lnBMC on lnBA, lnHt and lnWt, as suggested by Prentice et al. (1994). Body size related variables account for 98.2% of the variance in lnBMC.

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F-ratio</th>
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</thead>
<tbody>
<tr>
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<td>3</td>
<td>3.51699</td>
<td>1.42e3</td>
</tr>
<tr>
<td>Residual</td>
<td>0.180516</td>
<td>73</td>
<td>0.00247283</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Variable</th>
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<th>s.e. of Coeff</th>
<th>t-ratio</th>
<th>prob</th>
</tr>
</thead>
<tbody>
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<td>0.785</td>
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<td>&lt; 0.0001</td>
</tr>
<tr>
<td>lnHt</td>
<td>-0.839283</td>
<td>0.1583</td>
<td>-5.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>lnWt</td>
<td>0.275924</td>
<td>0.04568</td>
<td>6.04</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Table 7.3: Regression of lnBMC on lnBA and height and weight, adjusted for age then log transformed.

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F-ratio</th>
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</thead>
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<td>Residual</td>
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</table>

<table>
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<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>s.e. of Coeff</th>
<th>t-ratio</th>
<th>prob</th>
</tr>
</thead>
<tbody>
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<td>0.107</td>
<td>-26.4</td>
<td>&lt; 0.0001</td>
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<tr>
<td>lnBA</td>
<td>1.70842</td>
<td>0.03135</td>
<td>54.5</td>
<td>&lt; 0.0001</td>
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<tr>
<td>lnHtAdj</td>
<td>-0.157807</td>
<td>0.0303</td>
<td>-5.21</td>
<td>&lt; 0.0001</td>
</tr>
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<td>lnWtAdj</td>
<td>0.089383</td>
<td>0.02554</td>
<td>3.5</td>
<td>0.0008</td>
</tr>
</tbody>
</table>
In summary, measured bone mineral content in early onset eating disorders is highly dependent on patient size i.e. bone area, weight, height. It is probable that the greatest amount of this effect is due to age, which can easily be adjusted for. Nevertheless, these factors together still account for so much of the main effect that the impact of other illness related variables are hard to differentiate.

7.2.4. Method 4: Volumetric bone density

Method 4 adjusts for bone size only, allowing body size variables to be addressed separately.

Volumetric bone density was calculated using the regression coefficient for the group derived from lnBMC regressed on lnBA, which produced a value of 1.65 (see table 7.2). The bone mineral apparent density is then:

\[ \text{BMAD} = \frac{\text{BMC}}{\text{BA}^{1.65}} \text{ in g/cm}^3 \]

Once this adjustment has been made, the role of illness variables relating to degree of emaciation and illness severity was examined using linear modelling. Only weight related variables were then significant independent predictors of BMAD, i.e. weight SDS (p 0.0003), weight for height or BMI SDS (p 0.0001), and triceps skinfolds (p 0.004), but not subscapular skinfolds. Tanner stage, height SDS, and skeletal proportions (sitting height/leg length ratio), age and duration of illness did not show significant main effects.

Within the whole group, BMAD was associated with menarcheal status (p 0.017), but when restricted to the AN patients this effect became less marked and was no longer significant. In fact, for the AN subgroup, the BMAD was on average lower for the postmenarcheal than for the premenarcheal patients (figure 7.4). This is not fully accounted for by the adjustment for weight-related measures such as BMI SDS, but may be related to severity of illness.
Figure 7.4: Volumetric bone density in premenarcheal versus postmenarcheal AN

Key: 0 = no menarche, 1 = postmenarcheal

Table 7.4: Number of subjects and BMD Z scores by years of follow-up

<table>
<thead>
<tr>
<th>Years</th>
<th>Cases</th>
<th>Mean Z score</th>
<th>StdDev</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0 Z Score</td>
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<td>1.04</td>
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<tr>
<td>T1 Z Score</td>
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<td>-1.36</td>
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<tr>
<td>T2 Z Score</td>
<td>14</td>
<td>-1.71</td>
<td>0.81</td>
</tr>
<tr>
<td>T3 Z Score</td>
<td>4</td>
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<td>0.57</td>
</tr>
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</table>

Table 7.5: Change in mean BMD Z score over one year (n=37)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Count</th>
<th>Mean</th>
<th>StdDev</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0 Z Score</td>
<td>37</td>
<td>-1.26</td>
<td>1.04</td>
</tr>
<tr>
<td>T1 Z Score</td>
<td>37</td>
<td>-1.35</td>
<td>0.83</td>
</tr>
</tbody>
</table>
7.3. Longitudinal data

7.3.1. Total cohort results

Table 7.4 shows the total longitudinal data DXA results, reported as unadjusted z scores.

The figures show mean z scores below the normal range, a fall off in numbers of cases over time, and a fall in mean z-score over time. These observations are explicable by a] the duration of the study, b] bone density being measured in clinically vulnerable patients, c] follow-up continuing for longest on the most compromised patients.

7.3.2. Bone density at one year

1 year follow-up data were obtained for 37 patients (table 7.5).

When longitudinal data were expressed as z-scores, there was an apparent decrease in age adjusted bone density (figure 7.5), on average, over the first year, although there was no significant difference between the means (p 0.29) using paired t-test. The same data, if bone density is expressed as BMAD rather than z scores, difference between years 1 and 2 reduced significantly for the majority of cases (figure 7.6). Over the same time period there was a significant increase in BMI SDS (figure 7.7).

Paired t-test showed no significant difference between the mean BMAD at T0 and T1 (0.0620 vs 0.0622, p>0.4 ns.). Note that BMAD only corrects for bone volume, and not for height, weight and stage of puberty. The analysis was repeated only for patients with past or present AN (AN + EDNOS/AN) (n=21). Change in z score and BMAD was compared between premenarcheal and postmenarcheal patients.

Change in z score was significantly different between the pre and postmenarcheal patients (0.1 vs. −0.44: F ratio 12.85, p <0.002). This difference was less marked but
still significant for changes in BMAD (0.002 vs. -0.0003: F ratio 5.64; p 0.029). In both cases, postmenarcheal patients showed the least rise in bone density over the year.

Using linear modelling, differences between the premenarcheal and postmenarcheal patients change in z score over 1 year was not accounted for by mean weight SDS, BMI SDS, minimum BMI SDS reached during illness, change in pubertal (Tanner) stage over 1 year, nor by duration of illness. Change in z score between pre and postmenarcheal patients was significantly associated with change in height SDS (F ratio 56; p <0.0001). This was accounted for by change in both sitting height (F ratio 28.5; p <0.0001) and sitting leg length (F ratio 30.4; p<0.0001). This relationship between change in z score and menarcheal status remained when the sequence of the regression was changed i.e. if height SDS was entered, change in z score continued to be predicted by pre/post menarcheal status, but not by changes in weight related variables.

When the analysis was repeated for change in BMAD, change in height SDS was no longer significant in predicting difference at the 0.05 level between pre and postmenarcheal patients (F ratio 4; p 0.06). Menarcheal status and change in height SDS together predicted 33% of the variance in BMAD, but the best predictor of BMAD at 1 year was BMI SDS at the time of initial scan (t ratio−2.94; p<0.009) together with menarcheal status.

To increase power all patients who had significant weight loss at presentation were included (n=34). Of these, 10 were postmenarcheal and 24 premenarcheal. The premenarcheal group contained 10 patients with AN or EDNOS/AN, and 14 patients with FAED.

Using the same model, change in z score at 1 year continued to be significantly different between the premenarcheal patients and the post menarcheal ( F ratio 5.5; p < 0.025). However, once adjusted for bone volume using BMAD this difference was no longer evident (F 0.002; p 0.96 n.s.).
Figure 7.5: Change in BMD Z score over one year (n=37)

Figure 7.6: Change in volumetric bone density over one year (n=37)

Figure 7.7: Change in BMI SDS for the sample over the same time period
Significant predictors of BMAD for the total group of 34 patients were; minimum weight for height achieved during illness, and growth in sitting height SDS (adjusted R² 25.4%). Progress in puberty and total linear growth would all appear to have been taken into account by adjusting for bone size.

7.3.3. Bone density at two years

Figure 7.8 shows the trend in bone density z scores over 2 years (n=12).

For the girl who’s z-score fell most dramatically (top point at T0 on both graphs), her BMAD had in fact increased over the first year. Overall the trend at two years was similar.

The same data presented as BMAD, shows that there is relatively little change in volumetric bone density (figure 7.9: key as before) over two years.

Minimum weight for height reached during illness was the only significant predictor of change in BMAD over 2 years (F ratio 21.26; p<0.0006), and this was inversely correlated. In other words, the greater the initial weight loss, the greater the potential for increase in bone density (or 'catch-up' bone accretion). Predictably, this potential would appear to be greater in premenarcheal than post menarcheal patients, although numbers were too small for formal analyses.

7.3.4. 3 year follow-up: case studies

Figure 7.10 shows the BMAD change for 3 cases. These illustrate more explicitly the points made above. Two patients had not completed pubertal development: 1 boy in mid puberty who presented with an ankle fracture, and 1 girl, age 10, who showed no external signs of puberty. Both had AN. The third is an adolescent girl also with AN and continuing secondary amenorrhoea. Their bone density findings are shown in z scores and then as BMAD.
Figure 7.8: Change in BMD z score over 2 years (n=12)

Key: O = AN; X = EDNOS/AN; -- = FAED. red: post menarcheal; blue: premenarcheal

Figure 7.9: Change in volumetric BMAD over 2 years for the same subjects

Figure 7.10: Change in z score and change in BMAD over 3 years (n=3).
Firstly, apparent fall in age adjusted bone density (z score) may not represent a true fall in bone density. Secondly, bone accretion would appear to increase rapidly following a period of cessation (rather than loss) of bone growth during illness.

7.4. Summary

Mean BMD z scores were below –1 SDS for the three underweight diagnostic groups, AN, EDNOS and FAED. Mean BMD z score was lower for premenarcheal than for postmenarcheal AN patients.

BMC SDS (i.e. BMC was adjusted for age, bone area, height, weight and pubertal stage) was significantly closer to 0 than BMD z score (p<0.0001). 26 patients had a BMC SDS lower than –1 SDS. Weight SDS and sitting height SDS had the strongest correlations with low BMC SDS. There was no difference between premenarcheal and postmenarcheal mean BMC SDS.

Adjusting for bone area, height and weight using the Prentice et al. method accounted for over 98% of the variance in lnBMC.

Expressing bone density as volumetric bone density (BMAD), weight related variables i.e. weight SDS (p 0.0003), BMI SDS (p 0.0001), and triceps skinfolds (p 0.004) were significantly associated with BMAD. Tanner stage, height SDS, sitting height SDS, age and duration of illness did not show significant main effects.

When bone density was expressed as BMAD rather than z scores, the apparent fall in bone density over 1 year for the total sample almost disappeared.

Postmenarcheal patients showed less change in bone density over one year than premenarcheal patients. Change in z score was almost entirely accounted for by change in height, but change in BMAD reflected BMI SDS and menarcheal status.

Minimum weight for height reached during illness was the only significant predictor of change in BMAD over 2 years (F ratio 21.26; p0.0006), and this was an inverse
relationship i.e. greater initial weight loss was associated with greater 'catch-up' bone accretion over 2 years.
8. Results IV: Longitudinal - onset and resumption of menstruation

8.1. The samples

The methods and samples for longitudinal results are described in full in Chapter 3. Where a control group is identified, data were from the CHARD school children sample described in section 3.2.4.2.

The sample on whom longitudinal data were obtained is shown in table 8.1. Of the total sample (n=126) 29 were male and 97 female (3.6:1 F:M). In view of the small numbers, and the fact that BN/BN and EDNOS/BN are differentiated on the basis of psychological but not physical criteria, these two diagnostic groups were combined into one BN group for analyses.

8.1.1. Follow-up growth visits

The total number of growth visits for the sample was 642, a median of 4 (range 2 to 17) visits per patient. The mean time between visits was 5.6 months (SD 3 months). The majority of visits were at 3 to 4 months spacing, with wider spaced visits during times of little growth and change. Two girls were seen on only 2 occasions approximately 2 years apart.

8.1.2. Menarcheal status

Of 97 girls, the majority were premenarcheal at the time of initial presentation. Table 8.2 shows the number of girls, by diagnosis and menarcheal status.
Table 8.1: follow-up sample in terms of diagnosis and gender.

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<thead>
<tr>
<th></th>
<th>AN</th>
<th>BN</th>
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<th>FAED</th>
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<td>30.2</td>
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</table>

Figure 8.1: Time between growth visits (years)

![Time between growth visits (years)](image)

Table 8.2: Girls by menarcheal status and diagnosis

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
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<td>24</td>
<td>25</td>
<td>6</td>
<td>5</td>
<td>97</td>
</tr>
</tbody>
</table>
8.2. Results

8.2.1. Weight, height and BMI at menarche in control sample

Weight at menarche was taken as the weight measurement after menses had been reached. Two extreme outliers were removed from the sample, both over 82kg at onset of menses. The data in figure 8.2 are presented in a way comparable to that of Frisch and Revelle (1971), and show that mean weight at menarche was indeed almost constant across early and late maturers, and that height at menarche increased (n= 51). Mean weight at menarche for our sample was 49.6 kg, comparable to the 47.7 kg found by Frisch et al.

Expressed as BMI (unadjusted for age) at menarche was lower in taller and/or slimmer and/or late maturing girls than in shorter, heavier, early maturing girls. This trend became even more marked when results are expressed as BMI SDS (figure 8.3), with age accounting for 15.3% of the variance (adjusted R²) in BMI SDS (p<0.003).

Figure 8.4 shows the longitudinal change in BMI SDS for individual girls, with green marking the transition period between primary amenorrhoea and onset of menses, and red marking menses. The majority of the sample began menses within ±2 BMI SDS, with a concentration within the ±1 BMI SDS band (as would be expected for a normal distribution). The four cases at the lower end of the BMI spectrum had lost weight prior to the onset of menses. There is very little fluctuation of BMI SDS within individuals. The overall trend was for a constant or slight gain relative weight gain during the course of puberty (regression of BMI SDS on age = 0.05 units/yr). These findings suggest that relative weight at menarche is normally distributed between + and −2 BMI SDS for normal girls but dependent on age (fig. 8.3).
Figure 8.2: Weight and height at menarche in control sample (n=51)

Figure 8.3: BMI SDS at onset of menses in control sample (n=51)
Figure 8.4: Onset of menses according to BMI SDS in control girls (longitudinal data)

Note: Transition to red indicates onset of menses
8.2.2. BMI SDS at onset of menses in ED subjects on weight recovery - premenarcheal cases

Figure 8.5 shows BMI SDS plotted against age for all cases who were premenarcheal at presentation, regardless of diagnosis. Onset of menses occurred within a fairly narrow BMI SDS band with a lower bound of -1.5 SDS (85% weight for height). This is compatible with the weight threshold in the definition of AN. One girl with AN below this threshold had previously reached a weight of > -1 BMI SDS. She was lost to follow-up and it is therefore unclear whether menses ceased again with weight loss.

There was one girl (A) who fell significantly below -2 BMI SDS at menarche. She was from Eritrea and causing concern to her school about her weight, but not to her parents. No accurate records were available to ascertain her weight prior to assessment. She varied between 68% and 70% weight for height between age 12 and 15, but despite this entered puberty normally and started menses. Her weight SDS fell to almost -3 SDS, as she grew through puberty. The likeliest explanation for this exception is her racial and cultural origin. Her family fled famine conditions in their country and her development probably represents adaptation to chronic poor nutrition.

8.2.3. BMI SDS at resumption of menses in ED subjects – postmenarcheal cases

The same spread of BMI SDS was seen for resumption of menses as for first menstruation. With one exception (figure 8.6) the lower limit was -1.4 BMI SDS. It is notable that a number of patients were well within the normal range for BMI SDS who had not resumed menstruation. This may reflect altered body composition, or it may be that within a normal distribution for BMI SDS at onset of menses, not all patients with AN fall within the lower end of this range, despite their wish to do so. One girl (B) who fell outside of this range at first recorded menstruation (-1.94 BMI SDS) had previously gained weight to well within the normal range (-0.15 SDS).
8.2.4. Comparison of BMI SDS in normal, primary amenorrhoea and secondary amenorrhoea girls.

Figure 8.7 shows the distribution of BMI SDS at resumption of menses for the control sample and the total ED sample. For control subjects BMI SDS was a normal distribution (mean 0, SD 1). For ED subjects there were some outliers around the normal curve, and there was a trend for secondary amenorrhoea subjects to menstruate at lower BMI SDS than primary amenorrhoea subjects. However, there were no differences between BMI SDS (or %BMI) (table 8.2) at menstruation for the normal, premenarcheal and postmenarcheal groups by ANOVA (F ratio 1.46; p 0.24). As in control subjects, BMI SDS at onset or resumption of menses in ED subjects was age dependent (regression coefficient -0.25). Mean age at onset of menses in the primary amenorrhoea ED sample (n=19) was 14.6 yrs (SD 1.0 yrs), compared to 13.4 yrs (SD 0.9) mean age at menarche for the control sample.
Figure 8.5: BMI SDS at onset of menarche in premenarcheal ED subjects

Figure 8.6: Resumption of menses by BMI SDS following secondary amenorrhoea in ED subjects

Key: Secondary amenorrhoea = blue: Irregular or regular ongoing periods = red
Figure 8.5: BMI SDS at onset of menses in control sample [a] and ED subjects (secondary amenorrhoea cases highlighted) [b]

Table 8.2: Comparison of BMI SDS at menstruation for control (N), premenarcheal/primary amenorrhoea (P) and postmenarcheal/secondary amenorrhoea (S) girls.

Note: Results are given as both BMI SDS and %BMI

<table>
<thead>
<tr>
<th>Group</th>
<th>Count</th>
<th>Mean BMI SDS at menstruation</th>
<th>StdDev</th>
<th>Mean % BMI at menstruation</th>
<th>StdDev</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>50</td>
<td>-0.03</td>
<td>1.00</td>
<td>100</td>
<td>19.0</td>
</tr>
<tr>
<td>P</td>
<td>19</td>
<td>-0.40</td>
<td>1.13</td>
<td>96.9</td>
<td>12.0</td>
</tr>
<tr>
<td>S</td>
<td>19</td>
<td>-0.42</td>
<td>0.98</td>
<td>96.5</td>
<td>13.3</td>
</tr>
</tbody>
</table>
8.2.5. Is there a more specific anthropometric predictor of menstruation than BMI SDS?

8.2.5.1. Skinfold thickness

There was a wider range of subscapular skinfold thickness SDS than for BMI SDS in the secondary amenorrhoea subjects (figure 8.8 – compare to figure 8.6 for the same subjects). For subscapular skinfolds the lower limit was –2.7 SDS. The figure also shows the fluctuation in skinfold thickness over the period of weight recovery. The findings for the premenarcheal group were comparable. Together these results suggest that subscapular skinfold centiles are not particularly informative when it comes to predicting resumption of menses, probably as a result of measurement error in very underweight subjects.

By contrast, for triceps skinfold SDS the range was comparable to BMI SDS, with a lower bound of –1.5 SDS in the secondary amenorrhoea group and an even higher threshold for the primary amenorrhoea group (-1.15 SDS). It could be that triceps skinfold SDS is an alternative predictor of target weight in AN sufferers.

Although it had the highest correlation with BMI SDS among anthropometric measures in the cross sectional sample (section 5.2.5), mid arm circumference (MUAC), had a broader range for resumption of menses than either BMI SDS or triceps skinfold SDS and no threshold effect.

Skinfold and MUAC data were not available for the control sample.
Figure 8.8: Resumption of menses by subscapular skinfold SDS
8.2.5.2. Percentage body fat

Despite theoretical criticisms in children (section 2.2.1.4), % body fat is used in many specialist centres to determine target weight for nutritional rehabilitation in AN. The analysis was therefore repeated for the eating disorder sample using Slaughter’s equations (section 3.5.2) to derive % body fat from combined triceps and subscapular skinfold measurements.

In figure 8.9 a threshold of onset of or resumption of menses is seen at around 15% body fat for the total sample (n=38), with the majority of girls menstruating by 22% body fat. This is equivalent to 100% BMI according to these data. The correlation between %body fat and % BMI was 0.66. There were no appreciable differences between the primary and secondary amenorrhoea subjects in terms of the threshold and range of %body fat at menstruation. Interestingly the mean % body fat at menstruation was constant across age (19.85 (SD 4.6) figure 8.10), although the range was quite large (12.5 to 29 %).
Figure 8.9: Relationship between % BMI and %body fat for the total ED sample.

Key: red = resumption of menses; ○ = menses occurring; • = no menstruation

Figure 8.10: %body fat at onset or resumption of menses by age.

Primary amenorrhoea = blue; secondary amenorrhoea = red.
8.3. **Summary**

In the control sample our findings confirm those of Frisch and Revelle, i.e. mean weight at onset at menarche was fairly constant across early and late maturing girls, although there is nothing about the distribution that suggests a threshold or 'critical' weight. Expressed as BMI or BMI SDS, nutritional status at menarche decreased with age. In other words, late maturing girls tend to be relatively slimmer than early maturing girls at the time of menarche in the control sample.

The ED subjects were no different to the control sample in terms of the range of BMI SDS (or % BMI) at onset or resumption of menses i.e. ±2 BMI SDS. There was a non-significant trend for patients to menstruate at lower BMI SDS than control subjects. As for control subjects, BMI SDS in ED subjects was age dependent, and this alone would account for differences between primary and secondary amenorrhoea subjects in terms of expected nutritional status at onset or resumption of menses.

Skinfold thickness SDS showed wide fluctuations over time and were poor for defining a threshold for menses. % Body fat showed a threshold effect at 15% body fat for onset or resumption of menses, with a mean % body fat of 19.85%. Most girls had resumed menstruation by 22% body fat (≈ 100% BMI from these data).
9. Results V: Longitudinal - relationship between change in weight and change in height

9.1. Correlation of weight SDS and height SDS

9.1.1. Controls

The expected correlation of height and weight in the normal, growing, child and adolescent population is about 0.7 i.e. on a height SDS/weight SDS plot constant BMI SDS would be a slope of 0.7 based on the UK reference data (Cole1986). For our control group it was 0.64. This difference was more evident for girls (correlation 0.6) than for boys (correlation 0.71) and remained even when the most extreme case (case 1 below) was taken out. The lower correlation for the total is largely accounted by the low correlation between weight and height in the overweight, mainly female subjects.

9.1.2. Eating disorders population

Subject data were divided into underweight and normal weight, on the basis of 85% BMI. Correlations were also calculated with groupings based on -2 SDS. 85% BMI approximates to the weight definition for AN.

For ED subjects as a whole, the correlation between height and weight SDS was 0.72 (table 9.1). When restricted to those under 85% BMI, the correlation was much higher, at 0.88.
Table 9.1: correlation of height SDS and weight SDS for eating disorder sample
banded by weight category using two different cut off criteria.

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All weights</td>
<td>0.72</td>
<td>0.79</td>
<td>0.73</td>
</tr>
<tr>
<td>Underweight &lt; -2 BMI SDS</td>
<td>0.87</td>
<td>0.9</td>
<td>0.85</td>
</tr>
<tr>
<td>Normal weight ±2 BMI SDS</td>
<td>0.79</td>
<td>0.75</td>
<td>0.79</td>
</tr>
<tr>
<td>Underweight &lt;85% BMI</td>
<td>0.89</td>
<td>0.88</td>
<td>0.88</td>
</tr>
<tr>
<td>Normal weight -85 to 115% BMI</td>
<td>0.89</td>
<td>0.76</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Table 9.2: Case 1, female from control sample

Case 1: Gained weight steadily from the start of data collection, with a corresponding steady gain in height. The extraordinary feature is the extent of weight gain, from 29.3 to 87 kg during adolescence. She remained in stage 1 puberty until almost 13 years of age.

In SDS terms, she went from the low normal range for weight to well above the normal range. Having been in the normal range for height, she ended up at the top end of the normal range following her growth spurt. This degree of variation within a single individual is unusual and is seen in the residual plot as significant deviation from around 0 SDS.
9.2. *Longitudinal height and weight change in control adolescents*

The methods are discussed in section 3.5.4.2. Plots show the relationship between weight and height SDS centred around 0 for each individual subject, by taking the residuals for height and weight SDS. If there were little change in height SDS and weight SDS within an individual over time (i.e. they grew exactly along a centile curve for both weight and height) there would be a central cluster of points around 0. As discussed in section 3.5.4.2, a negative slope for height SDS indicates slower than expected growth, a positive slope faster than expected growth and a horizontal slope normal growth along a centile.

Figure 9.1 (girls) and 9.2 (boys) show the residuals plots for height and weight for the control children. In girls, the majority (in blue) of the sample varied within 1 SDS for both weight and height around their own axis. Case 1, highlighted in orange, illustrates how unusual growth patterns (equivalent to centile crossing) are easily identified by this methodology. Case 1 is exceptional in her weight SDS range around 0 SDS (from −1 SDS to + 2SDS residual weight SDS). Case 1 is described in detail in table 9.2.

Variation within boys was much less marked (figure 9.2 – same scale), the majority varying only within ±0.4 SDS, apart from one boy (highlighted in orange). For him, the most likely explanation for the variation in weight SDS seen is data error in the lowest weight measurement, or an episode of acute illness that did not impair growth in height.
Figure 9.1: Height and weight SDS residuals for control girls

Figure 9.2: Height and weight SDS residuals for control boys
9.3. Longitudinal height and weight change in eating disorder patients

The same methods as for the control children were used to display the relationship between weight SDS change and height SDS change within individual ED patients.

Note that horizontal (or vertical) straight lines denote change in height (or weight) without corresponding change in weight (or height) centile.

9.3.1. Premenarcheal girls

Figure 9.3 shows the results for premenarcheal girls. They would be expected to grow at a fairly steady rate but with little variation of height SDS with weight SDS, as for the control sample above. Figure 9.3 shows a number of time periods during which height SDS did not change much, whilst weight changed significantly. Below -1 weight SDS as a residual, change in height SDS was mainly negative, and positive slopes tend to be to the right of the graph, where weight SDS are relatively higher. The regression in figure 9.4 shows that this relationship is curvilinear. In other words, weight loss of more than 1 SDS for a given individual, from wherever they start off in relation to the population, may be sufficient to inhibit growth.

The majority of variation in height SDS was concentrated within ±0.3 SDS. Those girls who lay outside this range illustrate the other main finding for this group, periods of accelerated or decelerated height change with little change in weight centile. These are seen as horizontal lines on the graph. A single case is highlighted to illustrate this.
Figure 9.3: Height and weight residuals for premenarcheal ED girls. Height SDS and weight SDS are centred around 0 for each individual.

Note: Case 2 is highlighted in red, starting from point C.

Table 9.3: Case 2 - premenarcheal AN

Case 2 presented with restricting AN (AN-R) at 9.8 yrs old weighing 74% BMI, height -1.75 SDS, with 1.3 years bone age delay. She rapidly gained weight (starting point C on figure) with no appreciable change in height. Her weight then remained static for some time, while her height SDS dropped (i.e. growth slowed). After some time her weight also began to fall. At her lowest point she had lost over 1 SDS in height and was almost 1 SDS below her maximum weight SDS. Her stature became such a concern that she was started on daily growth hormone, in the hope of limiting some of the damage from her chronic AN. The subsequent growth spurt is seen in the horizontal lines to the left of her growth trajectory. So far she has gained 11 cm (4 inches) in height over 1.5 years.
Figure 9.4: Regression of weight on height and height² showing that the relationship is curvilinear.

Dependent variable is: WtSDS

R squared = 54.2%  R squared (adjusted) = 54.0%
s = 0.8851 with 633 - 3 = 630 degrees of freedom

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>s.e. of Coeff</th>
<th>t-ratio</th>
<th>prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-0.622187</td>
<td>0.04236</td>
<td>-14.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HtSDS</td>
<td>0.529641</td>
<td>0.04335</td>
<td>12.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HtSDS Sq</td>
<td>-0.071687</td>
<td>0.01586</td>
<td>-4.52</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Figure 9.4: Height and weight residuals for post menarcheal ED girls

Note: case 3 highlighted
9.3.2. Postmenarcheal girls

Figure 9.4 shows the change in height and weight for girls with postmenarcheal onset of their eating disorder. As expected, the variation in weight is much greater than in height and a large number of horizontal lines (change in weight SDS without change in height SDS) are seen. These girls would be expected to be within 1-2 cm of their final height.

Albeit more limited, there is quite wide variation in within patient height SDS (+0.76 to −0.45). The direction of change is invariably from higher to lower height SDS. As discussed in section 1.5, decrease in height SDS can occur as a result of early maturation. Case 3 (highlighted) is used to illustrate this point.

9.3.3. Boys

Residuals for height and weight SDS are shown in figure 9.6 for all boys who were underweight at the time of presentation. The degree of variation is greater than that for the control boys. A single individual (case 4) accounts for a great deal of this variation.
Case 3 illustrates postmenarcheal onset AN in a girl with relatively advanced puberty prior to illness. Table 9.4 gives her height and weight from the age of 12 to 16 years. From above the 50th centile at age 12, she fell to the 25th centile by age 16 whilst competing her last 2.6 cm of growth in stature. Her profound weight loss may have had some limited impact on her growth pattern simply because of her stage of development at the time of onset.

<table>
<thead>
<tr>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>Tanner</th>
<th>Height SDS</th>
<th>Weight SDS</th>
<th>BMI SDS</th>
<th>BMI %</th>
<th>Menstrual status</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.9</td>
<td>156.8</td>
<td>31.1</td>
<td>4</td>
<td>0.29</td>
<td>-2.18</td>
<td>-3.93</td>
<td>67.6</td>
<td>2° amenorrhoea</td>
</tr>
<tr>
<td>13.2</td>
<td>157.8</td>
<td>44.9</td>
<td>4</td>
<td>0.21</td>
<td>-0.20</td>
<td>-0.38</td>
<td>95.3</td>
<td>2° amenorrhoea</td>
</tr>
<tr>
<td>13.4</td>
<td>158.0</td>
<td>43.9</td>
<td>4</td>
<td>0.09</td>
<td>-0.48</td>
<td>-0.65</td>
<td>92.3</td>
<td>Irregular</td>
</tr>
<tr>
<td>13.8</td>
<td>158.4</td>
<td>39.7</td>
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<td>-0.05</td>
<td>-1.32</td>
<td>-1.73</td>
<td>82.2</td>
<td>2° amenorrhoea</td>
</tr>
<tr>
<td>14.1</td>
<td>158.9</td>
<td>48.4</td>
<td>5</td>
<td>-0.17</td>
<td>-0.27</td>
<td>-0.12</td>
<td>98.5</td>
<td>2° amenorrhoea</td>
</tr>
<tr>
<td>14.4</td>
<td>159.0</td>
<td>47.8</td>
<td>5</td>
<td>-0.29</td>
<td>-0.49</td>
<td>-0.30</td>
<td>96.4</td>
<td>2° amenorrhoea</td>
</tr>
<tr>
<td>14.8</td>
<td>159.0</td>
<td>45.7</td>
<td>5</td>
<td>-0.45</td>
<td>-0.98</td>
<td>-0.77</td>
<td>91.1</td>
<td>Irregular</td>
</tr>
<tr>
<td>15.3</td>
<td>159.4</td>
<td>47.7</td>
<td>5</td>
<td>-0.52</td>
<td>-0.88</td>
<td>-0.56</td>
<td>93.4</td>
<td>Regular periods</td>
</tr>
<tr>
<td>16.3</td>
<td>159.4</td>
<td>43.8</td>
<td>5</td>
<td>-0.65</td>
<td>-1.82</td>
<td>-1.55</td>
<td>83.8</td>
<td>Irregular</td>
</tr>
</tbody>
</table>
Case 4 presented with obsessional food avoidance at the age of 10, by which time he was severely underweight (-4.4 SDS) and short in stature (-2.4 SDS). His illness was hard to treat, and persisted through adolescence. The resulting pubertal delay was managed as for constitutional delay of growth and puberty, with Sustanon (testosterone) injections. Once puberty was completed he lost weight again, but had gained stature to within the normal range.
9.4. Is deficit in height simply an effect of pubertal delay?

9.4.1. Height adjusted for bone age

The following analyses addressed the issue of whether deficits in height SDS were a result of delayed maturation or whether they represented true stunting of growth. Height SDS was adjusted for bone age for ED subjects. A total of 106 bone age measurements were obtained for the total sample over the follow-up period, at approximately yearly intervals. Figure 9.7 shows the histogram and normal probability plot for height SDS (bone age). The distribution is centred around 0, for both initial assessment data and for the total follow-up measures, but with a greater than normal spread. This suggests that the observed deficit in height is accounted for by delay in skeletal maturation in most cases, but the large SD indicates that a number are shorter or taller than might be expected for their stage of development.

9.4.2. Height adjusted for pubertal stage

To confirm these findings, growth data were adjusted for pubertal stage. Figure 9.8 shows height SDS (chronological age) against pubertal stage. This figure shows the following:

- For the sample as a whole, height SDS corrected for pubertal stage did not decrease over time, if anything it increased.
- Menstruation occurred at stage 3 to 4, as in control subjects.
- Subjects were generally consistent in their growth centile (i.e. lines within individuals are horizontal).
- By stage 5, mean height SDS was 0 (almost exactly), although this is in part accounted for by attrition of subjects at stage 4 or below in the lower range for height SDS.
Figure 9.7 (a): Distribution of heightSDS adjusted for bone age for the total follow-up sample (n= 106 measures).

Note: The dark area indicates measurements at first assessment.

Figure 9.7 (b): Normal probability plot for heightSDS (bone age).
Figure 9.8: plot of height SDS by pubertal stage for all cases.

Note: Onset of menstruation is indicated in red.

Figure 9.9: plot of height SDS by pubertal stage for all control girls.
Those cases where height SDS did decline over development tended to be less than -3 SDS, and may represent the most extreme cases of malnutrition.

The same plot for the control sample is shown in figure 9.9 and shows a similar pattern to the ED cases, suggesting that the pubertal stage is all important in the interpretation of height SDS within individuals.

### 9.4.3. Growth arrest lines

32 patients had single or multiple growth arrest lines (section 1.5.1) identified on bone age x-ray (e.g. figure 9.10), suggesting that temporary cessation of growth occurred. In 15 patients the lines were evident at presentation. In 17 patients they became apparent during treatment and follow-up.

Of those with growth arrest lines at presentation, the mean age at presentation was 12.1 years. Table 9.5 shows the age, diagnosis, duration of illness and pubertal status of these children. The mean weight was -2.6 SDS, BMI was -2.8 SDS (equivalent to 78% BMI). Height at presentation was -1.4 SDS i.e. within the normal range though significantly below the population mean.

Comparative data are shown for those whose growth arrest lines became evident during treatment. There were no differences on continuous variables (age, delay and auxology) between those with growth arrest lines at presentation and those who developed them later, using independent sample t-tests, although the sample size was small.
Table 9.5: Patients with growth arrest lines (GAL) on bone age x-ray, comparing those with GAL at presentation to those with later GAL development.

<table>
<thead>
<tr>
<th>Age at presentation (years)</th>
<th>Growth arrest lines at presentation (n=15)</th>
<th>Growth arrest lines developed during follow-up (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>10</td>
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<td>Male</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AN</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Atypical AN</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Duration of eating concern (years)</td>
<td>Mean (SD) 1.8 (2.3)</td>
<td>3.1 (4.3)</td>
</tr>
<tr>
<td>Pubertal stage/no. of patients</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Bone Age delay (years)</td>
<td>Mean (SD) 2.1 (1.4)</td>
<td>2.1 (1.9)</td>
</tr>
<tr>
<td>Menstrual status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary amenorrhoea</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Secondary amenorrhoea</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Height SDS</td>
<td>Mean (SD) -1.4 (1.1)</td>
<td>-0.5 (2.6)</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>Mean (SD) -2.6 (1.5)</td>
<td>-1.8 (1.9)</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>Mean (SD) -2.8 (2.4)</td>
<td>-2.3 (1.4)</td>
</tr>
<tr>
<td>% BMI (%weight for age)</td>
<td>Mean (SD) 78.2 (13.1)</td>
<td>80.9 (10.6)</td>
</tr>
<tr>
<td>Lowest height velocity SDS (~1 year after presentation)</td>
<td>Mean (SD) -1.4 (1.8)</td>
<td>-2.7 (1.9)</td>
</tr>
<tr>
<td>Maximum height velocity SDS (~2 years after presentation)</td>
<td>Mean (SD) 2.4 (3.2)</td>
<td>3.1 (2.4)</td>
</tr>
</tbody>
</table>
Figure 9.10: Wrist x-ray of a 13 year old girl who had AN from age 8 years, showing multiple growth arrest lines at the distal radius.
9.5. **Risk factors for growth failure**

To test the hypothesis that height SDS within individuals did not fall significantly during pubertal development, general linear modelling was performed of height SDS on pubertal stage, with patient ID as a second independent variable. Results are shown in table 9.6. If the null hypothesis were true i.e. no fall in height SDS within an individual during development, an insignificant result would be expected. Table 9.7 shows that, contrary to the hypothesis, a small but significant increase in height SDS occurred over the course of pubertal development (coefficient +0.37). This is the equivalent of an increase of over 1SDS during the course of puberty, and suggests that catch-up growth occurred in a significant number of patients. Periods of accelerated growth in this sample were largely occurring at stages 3 and 4 of development, whilst rate of growth at stage 2 was slower than expected. Subgroup analyses were performed to ascertain predictors of rise or fall in height SDS.

Grouping first by diagnosis, BN and SE patients were excluded from further analyses on the basis of absence of malnutrition in these diagnostic groups and no significant change in height SDS with puberty. Simple and then multiple regression was performed on the remaining subjects, who had all experienced significant malnutrition at some point during development. Factors entered into the regression as being likely to influence growth failure are listed in table 9.8, together with coefficients and significance values.

In the model, Tanner stage at presentation was no longer significant when lowest BMI SDS and duration of illness were entered. Together these two variables accounted for 29.8% (adjusted $R^2$) of the variance in HtSDS adjusted for puberty within patients. 'Age at assessment' was not significant as an individual factor, but did slightly improve the model (adjusted $R^2$ 30.5%; coefficient for factor 'age at assessment' -0.08; p <0.02). In summary growth failure was predicted by length of illness and severity of weight loss,
Table 9.7: General linear modelling of height SDS on pubertal stage within individuals.

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>Sums of Squares</th>
<th>Mean Square</th>
<th>F-ratio</th>
<th>Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>Const</td>
<td>1</td>
<td>412.104</td>
<td>412.104</td>
<td>6373.3</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Breast stage</td>
<td>4</td>
<td>1.493</td>
<td>0.37</td>
<td>5.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>PtD</td>
<td>125</td>
<td>1019.02</td>
<td>8.15</td>
<td>126.1</td>
<td>≤0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of Breast stage</th>
<th>Coefficient</th>
<th>std. err.</th>
<th>t Ratio</th>
<th>prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.017</td>
<td>0.036</td>
<td>-0.48</td>
<td>0.6291</td>
</tr>
<tr>
<td>2</td>
<td>-0.10</td>
<td>0.029</td>
<td>-3.39</td>
<td>0.0007</td>
</tr>
<tr>
<td>3</td>
<td>0.076</td>
<td>0.029</td>
<td>2.63</td>
<td>0.0087</td>
</tr>
<tr>
<td>4</td>
<td>0.077</td>
<td>0.026</td>
<td>2.89</td>
<td>0.0040</td>
</tr>
<tr>
<td>5</td>
<td>-0.035</td>
<td>0.039</td>
<td>-0.90</td>
<td>0.3667</td>
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</tbody>
</table>

Table 9.8: Factors entered into regression model, with coefficients and significance values

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation</td>
<td>-0.02</td>
<td>p = 0.46</td>
</tr>
<tr>
<td>Age at onset of illness</td>
<td>0.08</td>
<td>p = 0.1</td>
</tr>
<tr>
<td>Duration of illness at presentation</td>
<td>-0.2</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Duration of illness at time of measurement</td>
<td>-0.18</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Lowest BMI SDS achieved during illness</td>
<td>0.32</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Tanner (pubertal) stage at first assessment</td>
<td>0.2</td>
<td>p &lt; 0.003</td>
</tr>
</tbody>
</table>
and mediated by delay in puberty. The stage of development at onset of the illness in patients who have not yet reached final height is of some importance in determining height outcome.

Finally, Russell’s hypothesis that age at onset of illness and duration of illness in premenarcheal onset AN of more than 3 to 4 years results in stunting was addressed. Since stunting can only be ascertained at final height, only those subjects who had reached Tanner stage 5 were included (n= 43). Of these, 25 were postmenarcheal and 18 premenarcheal girls or early pubertal boys. HtSDS were adjusted for mid parental height SDS, to exclude any bias due to inherent short stature that may have been operating at referral or follow-up. Neither age at onset of eating difficulties (coefficient 0.08; p 0.2), nor duration of illness (coefficient −0.065; p = 0.25) were significant in relation to final HtSDS, but there was a trend for menarcheal status to be significant at the 0.05 level (F 4.1; p =0.05). Overall however, the extent to which final height differed from expected height (final height SDS − mid parental height SDS), was not predicted by menarcheal status or Tanner stage at presentation.

9.6. Summary

This chapter explored the relationship between weight and height change in control and eating disorder subjects. Taking residuals for height and weight SDS centres data around 0, and allows differences between individual to be seen. For control subjects weight and height SDS varied within individuals more for girls than for boys, but individual cases with wide variation were the exception rather than the rule.

Using the same technique for ED subjects, large variations in weights SDS were seen, with very little change in height. When change in height did occur it was usually after and independent of weight change i.e. after weight restoration.

The issue of whether observed height deficits simply reflect delayed maturation was addressed in a number of ways. Firstly, height SDS was calculated on the basis of
bone age rather than chronological age. The resulting histogram was centred round 0 SDS, although the SD was larger than would be expected for a normal distribution. This suggests that the majority of short stature observed in eating disorders is a consequence of delayed maturation. Secondly height SDS was adjusted for pubertal stage. Individuals showed little change in height SDS over puberty suggesting that pubertal delay rather than growth failure is the usual pattern. For those who had reached stage 5 puberty the mean height SDS was 0, as for controls. Finally, final height was examined on the basis of stage of development at the onset of the illness and duration of illness. There was a non-significant trend for premenarcheal onset patients to be shorter in stature at final height, adjusted for mid-parental height. Change in HtSDS (centile crossing) within individuals was predicted by duration of illness, lowest weight reached during illness and pubertal stage at first assessment. Growth arrest lines were observed on bone age x-rays in 32 of the ED sample. Almost all had primary amenorrhoea and a mean %BMI at presentation of 75%.
10. Summary, discussion and conclusions

This chapter summarises the study, and discusses the findings with reference to the hypotheses. The limitations and strengths of the study are identified and suggestions made for future research. The conclusions and implications of the study will be outlined.

10.1. Summary of literature

10.1.1. Characteristics of eating disorders in early onset populations

Eating problems in children less than age 6 are usually termed feeding disorders, and the continuity between feeding and eating problems is poorly understood. In the mid childhood and peripubertal age range eating and feeding disorders as currently defined describe less than half of children presenting to specialist eating disorders service (Nicholls, Chater, & Lask2000), even if children with obesity are excluded. In adolescent populations the incidence of AN increases and becomes the predominant eating disorder diagnosis, certainly at the level of specialist services. The recent National Inpatient Child and Adolescent Survey undertaken by the Royal College of Psychiatrists (Department of Health2001) found that 130 (20.2%) of the total population resident in inpatient child and adolescent mental health services (CAMHS) on the NICAPS census day had an eating disorder diagnosis. Of these, 9.2% were under the age of 13 years. These figures are higher than for any other single diagnosis, including psychotic and mood disorders.

Developmental differences need to be taken into account when applying both physical and psychological diagnostic criteria. If eating disorders are defined in a broader sense as “disorders of childhood in which there is an excessive preoccupation with weight or
shape, and/or food intake, and accompanied by grossly inadequate, irregular or chaotic food intake” (Bryant-Waugh & Lask 1995) that have an impact on physical, social or emotional development, a need for additional terminology becomes necessary. These terms are far from adequate at present. For the present study, looking at the impact of eating disorders on physical parameters, the terms used needed to identify those subjects who had significant malnourishment (protein calorie malnutrition (PCM)) as part of the presenting illness. The terms food avoidance emotional disorder (FAED) and selective eating (SE) were be used to describe other eating problems common in the study cohort. For the ‘true’ eating disorders AN (AN), and bulimia nervosa (BN), a combination of the widely used DSM IV criteria and the Great Ormond Street Hospital (GOS) criteria developed for children have been used. Children meeting both sets of criteria were termed AN, and those meeting GOS but not DSM IV, AN/EDNOS (eating disorder not otherwise specified).

10.1.2. The impact of eating disorders on growth

The impact of PCM in children can be seen in a variety of diseases as well as in the context of famine and poverty. Stunting and delay in pubertal development is seen, although is usually accompanied by a comparable degree of delay in bone maturation, such that by adulthood spontaneous catch-up has usually occurred (Golden1994) and a final adult height in the normal range can be achieved. In extreme circumstance, growth and pubertal development can continue into the mid to late 20s (Magner, Rogol, & Gorden1984). The degree to which nutritional intake (and its anthropometric correlates) need to have normalised for this to occur is not yet clear.

To date, studies of AN with premenarcheal onset have been unable to resolve three principal questions. Firstly, can AN (or other acute and severe malnourishment) have an impact on final height when it occurs at a critical stage of growth, despite weight restoration? Secondly, if adequate weight is not restored, is continuing growth and pubertal development possible? Thirdly, what is the timing, severity or duration of
illness necessary for irreversible effects to occur? In 1983 Russell put forward the hypothesis that when AN commences at a critical period during the pubertal sequence and before menarche, the complex hypothalamic control of puberty becomes arrested, at least temporarily (Russell1983). He suggested that as long as the patient recovers within 3 or 4 years, puberty is merely delayed. Based on the retrospective study of adults with premenarcheal onset, this study has not been replicated prospectively.

10.1.3. Resumption of menses and the critical weight hypothesis

Loss of menses is one of the principal defining characteristics of AN, and resumption of menses a main goal of treatment and measure of outcome. The concept of 'target weight' is notoriously difficult and many attempts made to reach acceptable criteria for weight restoration, with very little consensus. In premenarcheal subjects, the notion of 'target weight', or the weight at which pubertal development may continue for menarche to occur is even more complex. Endocrine evaluation and pelvic ultrasound scans can both be useful ways of identifying restoration of normal hypothalamic-pituitary-gonadal function during recovery, but are of little value for predicting the 'target weight' of a specific individual. The overwhelming finding from the literature is the wide variation in menstrual weights found in both normal and AN recovering subjects. It remains unclear whether subjects recovering from AN behave the same as control subjects in terms of nutritional status required for the onset and maintenance of regular menstrual cycles.

10.1.4. Bone density

Measurement of bone density is usually performed by dual x-ray absorptiometry (DXA). However, there are problems with the interpretation of bone density results in young patients with AN. Firstly, the normal reference data for children are poor. Secondly, measurement in very underweight and osteoporotic patients can lead to
spurious readings in children. Thirdly, and most importantly, the bone density of a child is being compared to age matched children and does not take into account variation in bone size, height, or pubertal stage. Thus the only statement that can be made about a bone density result is whether it is significantly below that for a child of the same age. It is not possible to say that a child has osteoporosis or even osteopenia, since these are defined in relation to peak bone mass (t-score) and not to developing bone mass (z-score). These problems with interpretation of bone density results makes it difficult to test hypotheses relating to whether premenarcheal onset patients are at greater risk of osteoporosis than postmenarcheal patients, as theoretical arguments suggest. The potential for catch-up in bone density is not yet clear (Bachrach, Katzman, Litt, Guido, & Marcus1991; Ward, Brown, & Treasure1997), but it is likely that in a child who has not completed growth and puberty that bone loss can be at least partially compensated for.

10.1.5. Body composition and definitions of underweight

The measurement of body composition can be considered at many levels of complexity, with ratio methods being those most commonly used in practice for screening. The recent publication of BMI centiles for children in a number of countries, including the UK, means that measures in children with eating disorders can be more in keeping with practice for adult patients. Limitations for use in underweight children remain however. BMI and related ratio methods do not take into account stunted growth and delayed puberty, nor can they discriminate loss of fat from loss of lean tissue. In addition, reference data for SDS or centiles are matched for age and sex, but not for maturational stage. The study of eating disorders merits a degree of sophistication in measures of body composition beyond that used for screening.

Technical issues of measurement aside, BMI SDS in underweight children needs to be of predictive value if it is to be useful in screening for clinical cases. The principle used
to obtain cut off points for overweight and obesity in children (Cole et al. 2000) could also provide a cut off point for underweight in children, based on the World Health Organisation's cut off point of a body mass index of 18.5 kg/m² for adult underweight. However, a BMI of 18.5 kg/m² in a young adult is equivalent to the British 12th centile (Cole, Freeman, & Preece 1995), an unacceptably high prevalence of childhood underweight. A possible alternative would be a cut off point of a BMI of 17 kg/m², on the British second centile at age 18 (Cole, Freeman, & Preece 1995). At the upper end of the weight spectrum, substantial data link cut off points of 25 and 30 kg/m² to morbidity in adults (National Institutes of Health 1998) and the corresponding centile cut off points are associated with morbidity in children (Freedman et al. 1999). For underweight, the health effects of cut off points corresponding to a BMI below 17 or 18.5 kg/m² have not been studied. These cut off points for underweight need validating as markers of disease risk.

10.2. Study design

The study was a four year prospective cohort study of consecutive cases referred to a specialist clinic for the assessment and treatment of eating difficulties and eating disorders. Cross sectional analyses were performed on all cases on the basis of initial assessment and were grouped in relation to psychiatric diagnosis (n = 206). Longitudinal analyses were performed on all cases seen for a period of greater than 3 months (n = 127). Principal outcome measures were height, weight, pubertal and menstrual status, skinfold thickness, mid-arm circumference, and bone density. From these additional body composition measures were calculated using prediction equations. Anthropometric measurements were converted to standard deviation scores (SDS) to enable comparison to age and gender matched children within a specially constructed database using appropriate reference data. Analyses were performed in Data Desk 6.1.1 using a combination of univariate, multivariate and linear modelling techniques. Control groups were used for two analyses: cross-sectional
body composition measures and longitudinal growth analyses and anthropometric correlates of menstruation.

10.3. Aims

The aims of the study were to examine principles used for understanding physical parameters in patients with eating disorders in terms of their application to children and young adolescents with eating difficulties across a broader range of age and eating pathology than current diagnostic criteria for eating disorders encompass.

10.4. Discussion of findings

10.4.1. Eating disorders within middle childhood/early adolescence

Distinct patterns were found in relation to specific types of eating difficulty. Types of eating difficulty were not only gender biased, but also related to age and pubertal stage in their onset. The preponderance of girls with AN and BN is a consistent finding in the literature. This study confirms previous findings suggesting that males presenting with clinically significant eating difficulties are less likely than girls to fit into current eating disorder diagnostic criteria. Of the two categories used in the present study, selective eating showed a definite male bias (3.2:1; n= 30), while FAED showed a slight female excess (1.8:1 ; n=54). For FAED the gender ratio is similar to other emotional disorders such as depression and anxiety (female: male in the region of 1-1.2:1 (Meltzer et al. 2000)) than to true eating disorders (9:1). The male:female ratio for selective eating is lower than might be expected for a neurodevelopmental disorder (typically 7-10:1 male:female), and emphasises the uncertainty of whether selective eating is best of thought of primarily as a developmental or emotional difficulty (Nicholls, Christie, Randall, & Lask2001).
The four main types of eating difficulty also differed in terms of duration and likely level of intervention. AN had the shortest duration of illness at time of presentation, with a mean of less than 1 year. Most AN subjects received more than 6 months outpatient treatment or inpatient treatment, although 20% received little or no intervention. Weight for height at assessment did not predict treatment level. This perhaps unexpected finding is in keeping with results from a recent and controversial 5 year study from Australia, which found that many subjects from their unselected sample received either no or minimum treatment and that the level of treatment received was not directly related to outcome (Ben-Tovim et al. 2001). Ben-Tovim's study found that body weight, duration of illness and age were not predictive of outcome, whereas extent and intensity of ED symptoms were, in particular psychosocial functioning and body-related attitudes.

BN patients had been symptomatic for slightly longer than the AN group, and most were treated as outpatients or not at all. FAED patients and other low weight psychiatric disorder patients had had eating difficulties of significantly longer duration than AN or BN subjects (mean 2.66 years (FAED) vs. 1.03 (AN) and 1.68 years (BN) respectively). Over 25% of those requiring inpatient treatment had a diagnosis of FAED. Selective eating had by far the longest duration of difficult eating behaviours, in many cases since the introduction of solid foods at weaning. This group was more likely than any other to receive little or no intervention.

It was not the primary aim of the present study to characterise the different psychological subtypes. The findings do suggest however, that it is valid to separate out FAED from AN and BN, and that SE also merits separate consideration, since both have different profiles in terms of age of onset, gender distribution and level of intervention required. These observed differences in characteristics between types of eating difficulty were taken into account during subsequent analyses.
The physical characteristics of the ED subtypes were considered within this diagnostic framework. Cross sectional height measurements were on average the equivalent of a centile lower in subjects with premenarcheal onset EDs associated with weight loss. Deficits in height were not accounted for by parental short stature, and the measurement of parental height may therefore be helpful in considering differential diagnosis. The majority of height difference was accounted for by pubertal stage and bone age delay, and was largely seen as a reduction in sitting height relative to leg length. These findings confirm previous observations that short stature is a consistent feature in premenarcheal onset eating disorders associated with malnutrition and suggest that the mechanism operates through delay in growth and maturation.

In terms of interpreting anthropometric measures of nutritional status, the study found that the correlation between anthropometric measures was not as good in the underweight children as in the total sample, suggesting a reduction in measurement accuracy in thinner subjects leading to increased variance. This finding has clinical implications, since the need for measurement accuracy increases rather than decreases at lower weights, particularly since important clinical decisions often rest on measures such as these. The most commonly used measure of nutritional status, % BMI was highly correlated with % body fat overall, but there was wide variation in % body fat in underweight subjects. The best correlation was between BMI SDS and arm circumference. Principal components analysis of anthropometry suggested that composite anthropometric assessments may be of differing value in underweight versus normal weight subjects. For example, in normal weight subjects weight, BMI and arm circumference may usefully classify subjects according to relative fatness, but in underweight subjects direct measures of body fat such as skinfold thickness are necessary to determine nutritional status.

Overall, the findings support the view that BMI SDS or equivalent ratio measures are of some but limited value for assessing fatness in underweight subjects, and over
reliance on their use in clinical practice may account for the inability to make accurate predictions regarding target weights, refeeding status etc.

10.4.2. Body composition

Our findings confirm those of previous studies outlining the high correlation but poor specificity of BMI as a measure of % body fat. Using a two component model, we calculated values for FM and FFM normalised for height to evaluate body composition in an early onset population presenting with severe eating difficulties. Two component models of body composition have significantly more value than traditional BMI/BMI SDS/weight-for-height indices alone. For the majority of complications of AN and other eating disorders, interest has focused on measures of percentage body fat or absolute FM, since FM reflects energy reserves and is closely linked to endocrine dysfunction. A relationship has been shown between gonadotrophin levels and percentage fat, body weight and percentage of weight loss in AN (Jeuniewic, Brown, Garfinkel, & Moldofsky 1978), and with resumption of menses (Beumont et al. 1976). It is clear however, that estimates such as 22% FM is necessary for the maintenance of regular ovulatory cycles (Frisch 1984) are over simplistic. More recently leptin, a marker of body fat, has been the focus of much interest (Audi et al. 1998; Grinspoon et al. 1996; Miller et al. 1998).

Individual constituents of FFM are also of relevance however, whether that be loss of muscle, bone or water. Reduced FFM has been implicated as a major risk factor in the development of osteoporosis (Grinspoon, Miller, Coyle, Krempin, Armstrong, Pitts, Herzog, & Klibanski 1999). Moreover, the loss of FFM in eating disorders is likely to confound assessments of fatness based on percentage fat, while assessments based on FM ignore the possible effect of reduced height and size. Appropriate normalisation

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9 This study was performed in conjunction with Dr Jonathon Wells and has been accepted for publication to the European Journal of Clinical Nutrition
for size of both components of weight is essential if the effects of eating disorders on health and body composition are to be understood.

Our findings identify a number of specific issues in relation to body composition in patients with early onset eating problems. Firstly, whilst it may not be surprising to find that FFM as well as FM is lost in AN, our results suggest almost 1 SD of both FM and FFM are lost. This does not mean equal fat mass and fat free mass are lost pound for pound, but that loss relative to the norm is equivalent in both compartments. This finding is consistent across the weight and age range, and applies to patients with atypical eating patterns (e.g. food phobias), classified here as FAED, as much as to typical AN patients. It is of note that FAED patients, unlike AN patients, rarely attempt to actively alter their body composition or shape by exercising or altering their hydration state. The implication of FFM loss has perhaps been under-emphasised in the literature to date, and has certainly received little attention in the early onset population when its impact may be greatest. Although we have used prediction equations rather than more direct estimates of body composition, our findings highlight the importance of addressing both aspects of body composition in future studies. The implications of altered FM and FFM on growth and development in early onset patients are not clear.

Secondly, the continuity between AN, EDNOS and BN is evident in both FM and FFM. In the area that borders on weight criteria for AN there is quite a wide range of body fat, with a number of patients who meet AN criteria falling within 1SD of the normal range for body fat. This is particularly so during adolescence, and suggests that the 85% weight-for-height criteria for AN may not have equivalent biological significance at all stages of development.

The numbers of subjects is too limited to make definitive statements about boys with AN, although if boys with FAED are included (as the female data suggest is valid), some preliminary observations can be made. The similar proportional loss of FM and
FFM can be seen. As age increases a differential between FM and FFM loss occurs in males, with a trend towards relatively greater loss of FM than FFM.

These are the first data to our knowledge looking at the body composition of SE children. Typically SE children will eat 10 foods or less, have a heavy bias toward carbohydrate intake, and often have little or no protein in their diet (Nicholls, Christie, Randall, & Lask2001). Despite severe dietary limitation, these (mainly) boys are within the normal range for FM and FFM and, if anything, have a tendency to build up FFM more than FM as they reach adolescence.

The one methodological drawback to this part of the study is that we have used skinfold thickness data to predict total FM, and hence FFM by difference with weight, using equations which have been shown to produce consistent bias (Reilly, Wilson, & Durnin1995; Wells2000b). Our findings require confirmation using other measures predicting FM for both the control and the patient samples. However, use of the same equations in the control and patient groups allows relative rather than absolute differences to be seen. Also, we have used two different sets of equations, and the results were similar.

The basic approach of normalising body composition for height rather than weight for evaluating and displaying FM and FFM in a paediatric cohort has not previously been applied to clinical populations. Body composition data of patients are generally expressed in terms of percentage fat, which ignores possible deviations in FFM. In the present study, the expression of fatness as a percentage of weight would disguise the extent to which the patients have lower fatness compared to controls. Our approach addresses two common problems (Wells 2001) simultaneously: 1) assessment of fatness is unconfounded by relative FFM deposition, and 2) adjustment is made for potential differences in size between patients and controls. We believe that the independent normalisation of FM and FFM for height has important implications in other fields of paediatric research.
10.4.3. Weight, body fat and resumption of menses

The concept of target weight is difficult and much criticised, especially in children. Nevertheless, in ED patients BMI (cut off 19) at discharge predicts later treatment response (and therefore risk of relapse) (Howard, Evans, Quintero-Howard, Bowers, & Andersen 1999) and BMI predicts long term outcome in terms of bone density and EDI scores at 6-10 years (Gross, Russell, Beumont, Touyz, Roach, Aslani, Hansen, & Allen 2000). Menstruation is used clinically and in research as a marker of having achieved a healthy target weight. Predicting resumption of menses has been the basis of many studies (Golden, Jacobson, Schebendach, Solanto, Hertz, & Shenker 1997; Knuth, Hull, & Jacobs 1977; Sobanski, Hiltmann, Blanz, Klein, & Schmidt 1997; Treasure, Wheeler, King, Gordon, & Russell 1988). The amenorrhoea of AN is of hypothalamic origin (Boyar, Katz, Finkelstein, Kapen, Weiner, Weitzman, & Hellman 1974; Golden & Shenker 1994; Halmi & Falk 1981; Vigersky et al. 1977), and a relationship has been shown between gonadotrophin levels and percentage fat, body weight and percentage of weight loss in AN (Jeuniewic, Brown, Garfinkel, & Moldofsky 1978), and with resumption of menses (Beumont, George, Pimstone, & Vinik 1976). Although percentage body fat, percentage weight loss, and absolute body weight are all significant correlates of gonadotrophin reactivity, no one in particular has been found to be superior (Jeuniewic, Brown, Garfinkel, & Moldofsky 1978). In other words there seems to be a specific targeted effect of weight loss on hypothalamo-pituitary-gonadal functioning, mediated through gonadotrophins and predicted by body weight or body fat. Attempts to specify the measure of body weight or body fat required to menstruate have proved relatively unfruitful.

The mechanisms linking body fat to endocrine function are not straightforward. It is known that a significant proportion of patients cease menstruating before weight loss has occurred (Sherman, Halmi, & Zamudio 1975), that at the same weight and amount of body fat some females will menstruate and others will not (Golden, Jacobson,
Schebendach, Solanto, Hertz, & Shenker1997; Kohmura, Miyake, Aono, & Tanizawa1986; Weltman et al. 1990). The identification of leptin (Barinaga 1995) in 1995 promised much in explaining the relationship between body fat and endocrine function, and there were over 3000 publications about leptin in the 5 years following its identification. Leptin assays were not widely available at the conception of this study and data therefore not available to explore the role of leptin in the present cohort.

Leptin is a protein encoded by the ob gene and expressed in adipocytes and is thought to act as a signal informing the hypothalamus (and thereby the pituitary-gonadal system) that the body has sufficient fat stores to sustain reproduction (Barash et al. 1996). Patients with AN have low leptin levels (Argente, Caballo, Barrios, Munoz, Pozo, Chowen, Morande, & Hernandez1997; Hebebrand et al. 1995) while in BN they are comparable to controls or possibly below normal (Brewerton et al. 2000). Although leptin levels may be useful in assessing adipose tissue stores, it is not yet clear what their role is in the diagnosis or prognosis of severe eating disorders (Lifshitz1987).

In practice, the commonest methods used to predict resumption of menses are measures of nutritional status (BMI, weight for height), % body fat, and pelvic ultrasound appearances. There remain a paucity of data on which to base predictions, both from normal adolescents and ED subjects. Our findings are the first to compare ED subjects with normal adolescents using the same methodology. In addition, these are the first data to compare subjects with primary and secondary amenorrhoea.

In the control girls (n=51) we found that the mean weight at menarche was 49.6kg and the regression of weight on age was only 0.14. This finding is comparable to that of Frisch and Revelle (Frisch & Revelle1971) who found that mean weight at menarche was the same (47.7kg for their sample) whether puberty was early or late. Also in keeping with Frisch's findings, our control subjects had a greater mean height in late maturers, i.e. BMI and BMI SDS at menarche was lower in late than early maturing girls. This finding is congruous with results from other cohort studies, although the
results are often been presented in a way that is inappropriate for growing children (e.g. unadjusted BMI) or in a way that makes it difficult to discern the implications for practice. For example, St. George et al. (1994), in a New Zealand cohort study (n=415) found that heavier, taller, high BMI girls reached menarche earlier, and that the mean BMI at menarche was 18.4 (41.1 kg), at a mean age of 12.9 years. Our study found that BMI SDS at menarche was a normal distribution around 0 SDS for control girls, and that BMI SDS at menarche is dependent on age. These findings together allow the likelihood of BMI at menarche to be predicted for each child at a particular BMI SDS and age.

The second question related to whether ED patients behave similarly to, or different from control subjects in terms of weight at menstruation. Frisch suggested in a later paper that secondary amenorrhoea subjects needed to be heavier for resumption of menses than for menarche (Frisch & McArthur1974). This observation was based on 11 AN subjects and used a widely criticised method for predicting body fat from weight and total body water (Trussell1980). Nevertheless, the idea that weight for resumption of menses in ED subjects may be different from that for normal adolescent girls has persisted, and good evidence to refute the idea not available. Our study found that BMI SDS at menarche in ED sample is a normal distribution (n=38) around 0 SDS. There was a slight trend for secondary amenorrhoea subjects to menstruate at lower weights than primary amenorrhoea subjects, but this finding is best accounted for by the observation that for ED patients, as for controls, BMI SDS at menstruation is age dependent. In summary our data found that ED patients did not different significantly from control subjects. The range of BMI SDS at which menstruation occurs was similar for the 1° amenorrhoea and 2° amenorrhoea ED patients, and not all ED patients fell within the lower end of this range, despite their wish to do so. The lower bound for BMI SDS at menstruation was -1.5 BMI SDS (85% BMI), compatible with current diagnostic
criteria, with the exception of one girl from Eritrea. This highlights the need to consider racial differences and in acculturation when it comes to setting target weights.

Frisch went on to develop her 'critical weight hypothesis', arguing that weight was a proxy for body fat. Importantly, her data did not suggest a threshold in terms of a narrow and critical band but rather, as for our data, a wide range. Our data showed that a number of more direct measures of body fat, including adjusted triceps and subscapular skinfold thicknesses, and upper arm circumference did not show a threshold effect and in fact appeared more random in their relationship to menses than %BMI. Despite our theoretical criticisms of % body fat in this age group, we did find that mean % body fat on menarche or resumption of menses was constant with age, although the range was large. Reservations about the use of prediction equations to derive %body fat in this population have been discussed above.

10.4.1.4. Bone density

Eating disorders are recognised as high-risk disorders for osteoporosis, and low bone density has been consistently demonstrated over short and long term illness in adult patients (Brooks, Ogden, & Cavalier1998; Herzog., Minne., Deter., Leidig., Scellberg., Wuster., Gronwald., Sarembe., Kroger., Bergmann., Petzold., Hahn., Schepank., & Ziegler.1993; Poet et al. 1993; Rigotti et al. 1991; Siemers, Chakmakjian, & Gench 1996; Treasure, Fogelman, & Russell1986; Ward, Brown, & Treasure1997). Ours is the first study to look specifically at differences between premenarcheal and postmenarcheal onset AN in their impact on bone density. The best previous studies that have looked at bone density in adolescent onset AN (Bachrach, Guido, Katzman, Litt, & Marcus1990; Bachrach, Katzman, Litt, Guido, & Marcus1991) included only 8 patients with primary amenorrhoea in the cross sectional study and 4 in the follow-up study. On the basis of these studies it had been suggested that premenarcheal patients may be at greater risk of osteoporosis than later onset patients are. There are no previous studies to our knowledge that have directly addressed this question.
We have analysed bone density data in a cohort of pre, peri and postpubertal patients with eating disorders, using a number of previously published methods to interpret and compare results. In routine clinical practice, bone density in children is reported as z scores of areal BMD. Our results show that using this method of reporting will identify a majority of early onset eating disorder patients as having low or very low bone density for age. 46 patients (59% of the cohort) had a BMD z score of less than –1SDS, and 15 patients (19%) less than -2SDS. Z score adjusts for age and gender, and does not take into account the delay in growth and development associated with AN, and which renders comparison to age matched reference children spurious.

The regression method for adjustment (method 2) takes into account weight, height and stage of puberty. It has many advantages in terms of ease of application, and would seem to adjust for development related artefacts. However, clearly weight is a significant contributor to BMC, and when weights are normally distributed within the sample population adjustment for weight is entirely appropriate. But, when weight is one of the main variables that differentiates the patient population, as is the case here, and where weight is covertly present in independent variables such as diagnostic group, the validity of this method must be questioned in this clinical population.

The main criticism of the Prentice method (method 3), which uses height, weight and bone area in regression models, is that it does not allow separation of bone size (reflected in bone area) from person size (reflected in height and weight variables), since the model adjusts for both. Bone size has been shown to have independent effects on fracture risk in post menopausal women (Michelotti & Clark 1999). A method that allows the independent contributions of each to be analysed may be of greater value with certain kinds of problem particularly when the body size values are a particular focus of interest, as in eating disorders.

Volumetric bone density (method 4) has the value of adjusting for bone size, allowing more detailed analysis of the impact of body size (including weight). Weight in patients
who are in a state of acute or chronic starvation will be a poor estimate of body size, and is of most value as a covariate once adjustment for bone size has occurred. This method would seem to have the greatest value in the early onset eating disorder population and adequate reference data for vBMD in children and adolescents are urgently needed.

Longitudinal data from this early onset population show that bone density does not, on average, recover at one year, despite significant increases in body mass measures. By the second year trends in bone accretion or loss become evident, largely accounted for by weight change and growth in sitting height as opposed to leg length (which is more growth hormone dependent). In terms of identifying at risk patients therefore, a baseline and a two year scan may be sufficient in routine practice.

Our study is the first to compare bone density in pre and postmenarcheal onset AN. Contrary to current ideas, there was no significant difference between the two groups once size related effects have been taken into account. Furthermore, there was a suggestion that the early onset patients had time to compensate for bone loss, in a way that postmenarcheal onset patients may not.

There are a number of limitations to the study. Firstly, the cross sectional measurements, made at or shortly after the initial assessment, are extremely heterogeneous by nature of the sample both in terms of duration of illness and type of eating difficulty. However, to study question of BMD accretion and loss in young ED patients it makes little sense to restrict analyses only to subjects with typical DSM IV AN, given the problems with this diagnosis in this age group (Bryant-Waugh2000; Nicholls, Chater, & Lask2000) and the lack of distinction on physical (but not psychological) grounds between the typical and the atypical cases. Secondly, numbers were limited (10 in each group) in the longitudinal follow-up, although the findings did
not alter significantly when FAED patients were added to the cohort. Thirdly, bone density measurement was restricted, for ethical reasons, to lumbar spine measurements, and it is not clear how representative this is of total bone mineral content. Fourthly, the technicalities of measurement of bone density in children and underweight subjects give rise to concerns about the validity of the measurements. To date however, DXA remains the ‘gold standard’ for bone measurement, is widely used in clinical practice, and therefore merits evaluation of its usefulness in this patient population.

Our data support the notion of resilience - that the body responds to the threat of starvation by conservation and damage limitation. From the present study we cannot determine how long the threat can persist before recovery is no longer possible. Long term outcome studies of recovered patients are needed to determine the capacity for new bone to regenerate following severe depletion and loss.

10.4.5. Growth and the relationship between weight and height

One of the main difficulties of analysing growth during puberty is the difficulty of adjusting for the ‘phase effect’ of the pubertal growth spurt. These effects become more marked when studying disease states associated with pubertal delay. Whilst individual growth patterns can be interpreted, and periods of increased and decreased growth velocity identified, group characteristics are harder to describe accurately. Many authors who have looked at ‘catch-up growth’ avoid the problem altogether by including only prepubertal children (Boersma & Wit1997). We have chosen to address the issue in the present study by adjusting growth parameters around 0 SDS within individuals, such that periods of accelerated and decelerated growth are identified in relation to the individuals own growth pattern. There are advantages and disadvantages to this method of displaying longitudinal growth patterns. The main advantage of this method is that deviations from expected growth trajectories are
much easier to identify. The disadvantage is that time is not adequately conveyed, other than by the sequence of data points. Spacing visits equally and adding directional arrows or pubertal stages to the charts could rectify this.

As our data from control subjects show, the usual pattern is for very limited deviation within individuals from their own growth trajectory, within ±1SDS at most for both weight and height, with variation within boys being much less marked than for girls. With only a few exceptions, deviation in height SDS was as marked as for weight SDS. For the ED subjects, anticipated periods of weight loss and gain can be clearly seen together with periods of increased and decreased growth. Our data showed that very little positive change in height occurs below a residual weight of +0.5 SDS. Also evident from these data is the fact that substantial changes in weight can occur without corresponding change in height.

The study addressed the question of whether decelerations in height SDS represented 'true' growth failure or simply reflected delay in puberty. The significance of this issue lies in the potential for catch-up growth. If deficits in height SDS reflect delay in maturation then nutritional rehabilitation, at whatever point it occurs, should enable the normal development path to be regained. If however, true growth failure is occurring then stunting would be a final outcome, as suggested by Russell's study of 20 adult women who had premenarcheal onset AN. Our data support the hypothesis that deficits in height seen in ED subjects reflect pubertal delay. For the ED sample as a whole, height SDS corrected for pubertal stage did not decrease over time, if anything it increased. In addition, once adjusted for puberty, subjects were generally consistent in their growth centile (i.e. lines within individuals are horizontal). Thirdly, by Tanner stage 5, mean height SDS was 0 (almost exactly) i.e. those subjects in the study who had achieved final height did not show height deficits relative to reference norms. This is in part accounted for by attrition of subjects at stage 4 or below, who had not reached final height by the end of the study. The duration of our study was not
sufficient to see whether these cases, who may represent the most extreme cases of malnutrition, were able to attain stage 5 of development and a final height in the normal adult range. Those cases where height SDS did decline over development tended to be in the lower quartile for height SDS. In order to answer the question of whether nutritional deficits during adolescence impact on final height, a prospective study would need to follow subjects until completion of bone maturation, which the literature suggests may be until they are well into their twenties. A number of subjects in the present study were continuing to show signs of pubertal development in their late teens.

10.5. Limitations of study

Limitations to specific aspects of the study and findings have been discussed above. There were a number of limitations of the study in terms of generalisability of the findings and ability to fully address some of the research questions. Subject ascertainment bias has been considered in section 3.2.1. For the premenarcheal onset patients the principle bias operating relates to age of onset of illness. Findings from the study might be expected to generalise to children at the same developmental stage provided a comparable level of nutritional compromise is apparent. Less clear is the bias in relation to postmenarcheal patients, for whom services are more widely available and whose referral to the EDT depended on factors other than age of onset. This bias is more likely to operate in the cross sectional analyses than the longitudinal, since the patient operates to some extent as their own control over time, with normalisation of growth parameters allowing before and after comparisons. Secondly there is the issue that data were collected in a clinical context and therefore represent subjects who present with, rather than suffer from, eating disorders. Subclinical eating difficulties are common, and even with full blown syndromes intensity and duration of symptoms are not the only factors influencing help seeking. Finally, but perhaps most importantly in relation to understanding the findings,
the decision to include subjects who do not meet diagnostic criteria for eating
disorders according to DSM IV means that these results are difficult to compare to
those of previous studies. However, since the focus is on interpretation of findings in
this age group, it is hoped that these findings will be of value in the planning of future
studies addressing specific questions that include premenarcheal cases.

In terms of the capacity of the study to answer the research questions there are some
limitations evident. Firstly, three to four years of observation is insufficient to answer
questions about long term growth patterns, where outcome can only be determined
when final height has been achieved. This has been taken into account as far as is
possible within the parameters of the study, and to address it fully may require many
more years of follow-up for treatment resistant cases. In Russell's study, from which
one hypothesis arose, bone age was not determined and therefore it is not clear
whether those subjects in which stunting was observed had reached final height or, as
suggested by subsequent menstruation in one subject, further development was still
possible.

Questions about how height changes with weight are difficult to address in full and this
study has highlighted some of the issues, the most apparent being the 'phase effect' of
puberty. For example, one research question related to the weight gain required for
catch-up growth to occur. This could not be answered using the current methodology,
and would require the addition of a mechanism by which growth could be corrected for
development, such as a measure of pubertal deviation. Bone age assessments are
limited in their capacity to address this issue due to their reliability in this context and
the frequency of x-rays that would be required to adjust each growth measurement.

Finally, the study did not have the duration or power necessary to fully address the
hypothesis relating to bone density that premenarcheal subjects were at greatest risk
for future osteoporosis.
10.6. Strengths

This is the largest and most comprehensive study of physical aspects of prepubertal and pubertal eating disorders subjects and is a significant contribution to the literature in this area of growing concern.

The recruitment and more specifically retention of subjects to the study was a strength attributed in part to the independence of data collection from other aspects of psychological treatment.

The database designed and developed for the study incorporated the latest in terms of technical function and reference data and enabled raw data to be transformed into meaningful data comparable to norms.

The setting of the study in both clinical and academic terms was essential in the execution of the study, not least in terms of availability of expertise. As a result the study was able to address issues that might otherwise have required a multi-centre collaborative study.

10.7. Suggestions for future research

In addition to clarifying some differences between types of problem eating, there are many areas of overlap between the subtypes and the literature to date is limited in its understanding of the continuity of eating disorder subtypes. The duration of this study was insufficient to raise more than speculative theories about the risk each type of eating difficulty confers for future disorder. It is an area that merits further research however, given that feeding difficulties, particularly picky eating and digestive problems, have been identified as risk factors for AN and problem eating shows stability over time (Marchi & Cohen 1990). Developmental continuity is an issue that has been neglected in research to date.
Better, more reliable, methods for the measurement of body composition in underweight children and adolescents for use in clinical practice are needed so that there is less need to rely on the gross measures of nutritional status best used as screening measures. The methods would need to take into account aspects of growth and development and differentiate lean from fat mass. This will enable further research to address specific questions relating to body composition, including its relationship to menstruation, bone density and other aspects of endocrine function.

The finding that onset of menses follows a normal distribution for BMI SDS but is somewhat age dependent is important and needs replication. In particular, previous literature has suggested that a strictly normal distribution for nutritional status eating disorders subjects may not be expected, based on both what is known of premorbid nutritional status (Fairburn, Welch, Doll, Davies, & O'Connor1997) and outcome (Gillberg, Rastam, & Gillberg 1994). BN (and possibly AN-binge purge subtype) is associated with premorbid overweight, while AN-restrictive subtype is associated with relatively low premorbid weight. These subtypes are often not apparent on initial presentation in younger patients but may be significant in relation to expected menstrual weight. This issue requires further research.

The results on stature and longitudinal growth patterns, together with what is known from the literature, raise questions about possible phased effects of malnutrition on endocrine functioning, analogous to a sequential shut down and subsequent 'reawakening' with weight restoration. They suggest that gonadotrophic function is quickly affected by weight loss, resulting in amenorrhoea, slower growth of the lumbar spine and loss of lumbar spine BMD, and that growth hormone requires more profound levels of malnutrition or greater duration of illness before it is affected. Growth hormone and bone turnover studies in prepubertal and pubertal subjects with AN are needed.
Bone density measurement in this group of subjects is still in the early stages of refinement, and problems relating to measurement, interpretation and reference data need to be addressed before findings in children with eating disorders can be reliably studied. The preliminary finding that, once adjusted for growth parameters, there was no difference between the premenarcheal and postmenarcheal subjects requires further investigation, since this is at variance with current hypotheses. Bone density questions relating to capacity for recovery need to be addressed through longitudinal studies through to peak bone mass ascertainment or by retrospective studies of women at peak bone mass (i.e. late 20s to early 30s), comparing premenarcheal and postmenarcheal onset subjects. Large numbers would be required to achieve sufficient power to detect differences in BMD.

10.8. Conclusions

AN and related eating disorders, when onset occurs before the completion of growth and pubertal maturation and prior to attaining peak bone mass, could theoretically have serious long term repercussions on adult outcome in terms of physical development. This study attempts to quantify the risk relative to later onset subjects and normal children, and addresses issues of measurement and interpretation bias applicable to children in a variety of measures including body composition and bone density. The findings suggest that significant malnutrition during the critical period of adolescence results in severe delay of growth and puberty and that growth parameters need to take the degree of delay into account to be meaningful. In the majority of cases delay alone was sufficient to account for discrepancies between pre and postmenarcheal subjects and controls. After adjusting for delay in all but a few cases ED subjects outcomes were not significantly different from controls, including weight at onset or resumption of menses and in bone mineral density. Follow-up at final height would be necessary to ascertain the duration and severity of malnutrition necessary for
permanent deviation of development to occur and whether complete catch-up were possible.

10.9. Implications

- Assessment of stage of pubertal maturation is essential for the interpretation of anthropometric indices, particularly height and bone density.
- Height needs to be taken into consideration in the assessment of early onset eating disorder patients, and in the interpretation of weight–for-height indices.
- Measurement accuracy and cross-correlation of anthropometric indices decreases with increasing malnourishment. BMI SDS together with arm circumference SDS may classify degree of underweight better than BMI SDS alone.
- Normalising FM and FFM independently for height allows the independent contribution of each to the effects of eating disorders on growth and development to be identified.
- Adolescent girls meeting full diagnostic criteria for AN fell within 1SD of the normal rage for FM, suggesting that caution needs to be exercised when applying the 85% weight for height criteria in the adolescent group.
- Bone density measurements in children must be corrected for growth parameters, and expressed in volumetric rather than areal terms.
- BMI SDS at onset or resumption of menses is a normal distribution around 0 SDS (100% BMI) for ED subjects as for controls. Earlier developers can be expected to menstruate at higher BMI SDS (%BMI) than late developers.
- Growth arrest lines on bone age x-ray are an indicator of periods of malnutrition during growth.
- Until final height has been reached there remains the possibility of continuing growth and development, regardless of age.
References


Ashwell, M. A., LeJuene, S. R. E., & McPherson, K. 1996, "Ratio of waist circumference to height may be a better indicator of need for weight management."

*British Medical Journal*, vol. 312, p. 377.


255


Clinton, D. N. & Glant, R. 1992, "The eating disorders spectrum of DMSR-III-R: Clinical features and psychosocial concomitants of 86 consecutive cases from a Swedish urban catchment area.", *Journal of Nervous and Mental Disease*, vol. 180, pp. 244-250.


centiles for weight, height, body mass index and head circumference fitted by

0-20 years in 1980--a baseline to assess recent trends in obesity", *Annals of Human
Biology*, vol. 26, no. 4, pp. 303-308.

Treasure, T. 1994, "QT interval in anorexia nervosa", *British Heart Journal*, vol. 72, no.
1, pp. 69-73.

Cooper, P., Watkins, B., Bryant-Waugh, R., & Lask, B. The nosological status of early
onset anorexia nervosa. 2001.

Ref Type: Unpublished Work

R., Reed, E., Knight, J., Howman Giles, R., & Gaskin, K. 1995, "Volumetric bone
mineral density--a potential role in paediatrics", *Acta Paediatrica Supplement*, vol. 411,
pp. 12-6,discussion.

Crisp, A. 1969, "Some skeletal measurements in patients with primary anorexia

Crisp, A. H., Palmer, R. L., & Kalucy, R. S. 1976, "How common is anorexia nervosa?

"Final height in boys with untreated constitutional delay in growth and puberty.",
*Archives of Disease in Childhood*, vol. 65, pp. 1109-1112.


Dewit, O., Fuller, N. J., Fewtrell, M. S., Elia, M., & Wells, J. C. 2000, "Whole body air displacement plethysmography compared with hydrodensitometry for body composition analysis", *Archives of Disease in Childhood*, vol. 82, no. 2, pp. 159-164.


Frisch, R. E. & Revelle, R. 1971, "Height and weight at menarche and a hypothesis of menarche", *Archives of Disease in Childhood*, vol. 46, pp. 695-701.


Hannan, W. J., Cowen, S. J., Wrate, R. M., & Barton, J. 1995a, "Improved prediction of bone mineral content and density.", *Archives of Disease in Childhood*, vol. 72, pp. 147-149.


270


and total body bone density in premenarchal females", *Journal of Clinical Endocrinology & Metabolism*, vol. 75, no. 2, pp. 383-387.


Mather, S. J., de Bruyn, R., Pokropek, T., & Lask, B. Ultrasound Bone Analysis in 53 Children and Adolescents with Eating Disorders and 100 Healthy Children and Adolescents. 1st International Conference on Children’s Bone Health Maastricht. 1999. Ref Type: Abstract


*Lancet*, vol. 2, no. 7927, pp. 219-221.

Children and Adolescents in Great Britain*, HMSO, London.

Michelotti, J. & Clark, J. 1999, "Femoral neck length and hip fracture risk", *Journal of 

Clin.Endocrinol.Metab.*, vol. 84, no. 6, pp. 1775-1783.

Miller, K. K., Parulekar, M. S., Schoenfeld, E., Anderson, E., Hubbard, J., Klibanski, A., 
& Grinspoon, S. K. 1998, "Decreased leptin levels in normal weight women with 
hypothalamic amenorrhea: the effects of body composition and nutritional intake", 
*Journal of Clinical Endocrinology & Metabolism*, vol. 83, no. 7, pp. 2309-2312.

Molgaard, C., Thomsen, B. L., & Michaelsen, K. F. 1998, "Influence of weight, age and 
puberty on bone size and bone mineral content in healthy children and adolescents", 


identification, evaluation, and treatment of overweight and obesity in adults; the 
evidence report.", *Obesity Research*, vol. 6, no. suppl 2, pp. 51S-209S.

differences in regional bone density, hip axis length, and lifestyle variables among 
healthy black and white men", *Journal of Bone and Mineral Research.*, vol. 10, no. 5, 
pp. 782-787.


Rikken, B. & Wit, J. M. 1992, "Prepubertal height velocity references over a wide age range [see comments]", *Archives of Disease in Childhood*, vol. 67, no. 10, pp. 1277-1280.


Salisbury, J. J. & Mitchell, J. E. 1991, "Bone mineral density and anorexia nervosa in

curves and percentage fat mass in healthy German schoolchildren and adolescents.",

Seeman, E. 1997, "From density to structure: Growing up and growing old on the

Seeman, E., Szmukler, G. I., Formica, C., Tsalamandris, C., & Mestrovic, R. 1992,
"Osteoporosis in anorexia nervosa: the influence of peak bone density, bone loss, oral
12, pp. 1467-1474.

symptoms in children with eating disorders: A preliminary investigation", *Eating
Disorders: The Journal of Treatment and Prevention.*, vol 3, no. 4, pp. 304-310.

Sherman, B. M., Halmi, K. A., & Zamudio, R. 1975, "LH and FSH response to
gonadotropin-releasing hormone in anorexia nervosa: Effect of nutritional
rehabilitation", *Journal of Clinical Endocrinology & Metabolism*, vol. 41, no. 1, pp. 135-
142.

Shomento, S. H. & Kreipe, R. E. 1994, "Menstruation and fertility following anorexia
nervosa", *Adolescent Pediatric Gynecology*, vol. 7, pp. 142-146.

Siemers, B., Chakmakjian, Z., & Gench, B. 1996, "Bone density patterns in women
179-186.


Additional reference:
Appendices
Appendix 1.1: Theoretical basis of weight for height calculated by Cole’s method

Cole’s method calculates the regression curve for weight on height and age, which is equivalent to age-standardised- weight on age-standardised-height. Weight for height shows most dependence on age in the first year of life, and then again at puberty (Waterlow 1973). At other ages, authors have made the assumption that the relationship between weight and height holds constant, an assumption that is not strictly accurate.

Age standardised weight (or height), at its simplest, is given by

\[(\text{weight/median weight for age})\]

Variance around the median varies with age, reaching a peak during puberty up to peak height velocity and then falling sharply. In addition, weight and, to a lesser extent height, are skewed distributions, particularly around puberty. These can be taken into account by using

\[(\text{weight/median weight for age})^{-1}\]

or

\[\log (\text{weight/ median weight for age})\]

These methods derive a weight-for-age or height-for-age. These may be more satisfactory than the usual method of calculating age standardised heights and weights which, although widely used, take neither skew nor variance into account:

\[
\text{Child’s height-for-age = } \frac{\text{Child’s actual height}}{\text{Expected height for age and the same for weight.}}
\]

Using Waterlow’s method, weight for height has been taken to mean (1973):

\[
\text{Child’s actual weight} = \frac{\text{Expected weight for child’s height}}{\text{Weight for height}}
\]

However this equation takes no account of age. More accurately, bearing in mind the above, weight for height could, and arguably should, be
Child's actual weight for-age

Expected weight-for-age for child's height-for-age

Thus for a child who is relatively stunted for age, this equation takes this into account in terms of the expected weight. In other words, NOT the % of ideal body weight for height, but % of weight for individual child's height.

The relationship between weight-for-age and height-for-age, a regression through 0 for the whole population, is shown by

\[ \text{weight-for-age} = (\text{height-for-age})^n \]

When weight-for-age is plotted against height-for-age for large populations, the slope of the line approximates to 2 (range 1.7 - 2.5) up to the age of 7 in girls and 10 in boys. Thereafter, the relationship is nearer to 3 at the peak of pubertal development. This holds true for a wide range of populations, resulting in the proposal that a single value for the regression line of 2 would hold relatively true for children irrespective of sex, age, ethnic group or growth status.

Thus \[ \text{weight-for-height} = \frac{\text{weight-for-age}}{\text{height-for-age}^2} \]

In puberty the issue becomes more complicated, since there is a wide variation in stage of development, at the time of maximal change in height. For example, in populations where there was relative obesity, the mean weight-for-height at puberty will be greater than 3, and the extra weight will be correlated with fat deposits unrelated to height.

Thus, weight for height calculated by Cole’s method during puberty is, at best, a weak approximation for body composition. However, weight-for-age/ (height-for-age)2 can be thought of as the child’s BMI /BMI of a child of the same age, thus making this the analogous expression to BMI in adults. In both cases, the height2 standardises for body size.
Appendix 3.1: Parents Preliminary Questionnaire
PARENT'S PRELIMINARY QUESTIONNAIRE

Please answer the following questions as carefully as possible. You are free to talk to whoever you want in order to obtain the information required. “Your child” refers throughout the questionnaire to the child referred to this hospital for eating problems. Please either return questionnaire in return envelope or bring with you to your first appointment.

FAMILY STRUCTURE

1) Your Child’s name: ___________________________

2) Your Child’s date of birth: ____________________

3) Please list all your family members and:
   their ages
   their relationship to your child
   whether or not they live at home
(Please include cohabiting partners and step-family members)

4) Occupations

If unemployed for longer than six months, please state previous employment. If homemaker, please state.

Father’s occupation: _____________________________

Mother’s occupation: _____________________________

5) Please indicate where your child lives at the moment:
   a - At home
   b - With other relatives (Please state relationship to child) __________
   c - Fostered / Adopted (please state from what age) __________
   d - Boarding School
   e - Children’s home
   f - Other (please specify) ________________________________
INFORMATION ABOUT YOUR CHILD

IF YOUR CHILD IS FEMALE, PLEASE ANSWER QUESTION 6

IF YOUR CHILD IS MALE, PLEASE ANSWER QUESTION 7

6) Please indicate stage of puberty that your daughter is at, at the moment:

NB: secondary sexual characteristics in girls include the start of breast development, and growth of body hair in the genital region and under the arms.

   a - Periods have not started and there are no secondary sexual characteristics
   b - Periods have not started, but some secondary sexual characteristics are present
   c - Periods have begun, but have now stopped
       Age at which periods started: _______________
       Age at which periods stopped: _______________
   d - Periods are regular and ongoing
       Age at which periods started: _______________
   e - Don't know

Are there any other details of pubertal development that you feel are relevant? ________________________________

7) Please indicate the stage of puberty that your son is at, at the moment:

NB: secondary sexual characteristics in boys include the enlargement of genitals (testes, scrotum, penis), and development of body hair in the genital region and under the arms.

   A - No development of secondary sexual characteristics
   b - Development of secondary sexual characteristics
   c - Don't know

Are there any other details of pubertal development that you feel are relevant? ________________________________

8) How old was your child when the present eating problems first started? _______________________________

9) How old was your child when these problems first caused you concern? If you can't remember the specific date, please give the date when you first consult your GP about the problem. _______________________________
10) MEDICAL HISTORY

Is your child currently on any medication? if yes ..... 
Name of medication: ______________________________
Dosage: __________________________________________
How long has he/she been taking this medication: ____________

Did mother experience either:

a - Ill health during pregnancy 
   If yes, please give details: __________________________

b - Difficulties during labour (e.g. Caesarian birth, Forceps delivery) YES / NO

c - Post-natal difficulties (e.g. Post-natal depression) YES / NO
   If yes, please give details: __________________________

d - Was your child breast-fed or bottle-fed? ________________

   For how long was your child:
   breast fed? ________________
bottle fed? ________________

f - Did your child grow normally in infancy and early childhood? YES / NO
   If not, please give details:
   __________________________________________________

g - Has your child suffered from any regular / serious medical illness NOT connected with
   the stomach? YES / NO
   If yes, please give details:
   __________________________________________________

h - Has your child suffered from any regular / serious medical illness connected with the
   stomach? YES / NO
   If yes please give details:
   __________________________________________________

I - Has your child suffered from regular stomach pains for which the doctor can find no
   physical cause? YES / NO
J - Has your child suffered from regular headaches / coughs / back pain or any other
   symptom for which the doctor can find no physical cause? YES / NO
k - Has your child seen a Mental Health professional before? YES / NO If yes, please give reason for visit(s):
________________________________________________________________________

I - Has your child ever been in hospital for anything other than eating and/or weight problems? YES / NO
If yes please give details: __________________________________________

m - Has your child suffered from regular bouts of vomiting in the past? YES / NO
If yes, please give details: __________________________________________

n - Is there any other medical information about your child which you consider relevant?
________________________________________________________________________

11) BEHAVIOURAL HISTORY

Has your child experienced any Emotional or Behavioural difficulties (e.g. sleep disturbance, excess crying, distress at being away from parents, school refusal, toileting problems, temper tantrums, head banging, rocking etc.) during the following periods?

a - Infancy YES / NO
If yes, please give details: __________________________________________

b - Pre-school period (1 - 5 years) YES / NO
If yes, please give details: __________________________________________

c - Primary school-age period (5 - 11 years) YES / NO
If yes, please give details: __________________________________________

d - Secondary school age (11+ years) YES / NO
If yes, please give details: __________________________________________

12) FOOD DIFFICULTIES

Has your child suffered from feeding difficulties during the following periods?

a - Infancy (0 - 1 year) YES / NO
If yes, please give details: __________________________________________

b - Pre-school period (1 - 5 years) YES / NO
If yes, please give details: __________________________________________

c - Primary school-age period (5 - 11 years) YES / NO
If yes, please give details: ________________________________

d - Secondary school age (11+ years)  YES / NO
If yes, please give details: ________________________________

13) Has your child received previous treatment for eating and/or weight problems?

If so, please give:
Name and Professional of person seen ________________________________
Name of hospital/clinic _____________________________________________
Type of treatment received __________________________________________
Age at which your child received treatment ____________________________
Duration of treatment _______________________________________________
Any other relevant information _________________________________________

14) If known, please give details of:

Maximum weight reached in the past - __________
Age when reached maximum weight - __________
Height when reached maximum weight - __________

If underweight now, has your child been overweight in the past? YES/NO/
NOT APPLICABLE

15) Please tick which of the following applies to your child now, in the past or never.

<table>
<thead>
<tr>
<th>NOW</th>
<th>PAST</th>
<th>NEVER</th>
</tr>
</thead>
<tbody>
<tr>
<td>a - Regular vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b - Regular use of laxatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c - Bingeing (excessive food intake within short space of time)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d - Excessive exercising</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e - Thinks looks fat even though is not overweight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f - Has considered suicide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>g - Has attempted suicide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>h - Has cut / hurt self deliberately</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
16) If currently restricting food intake, please tick the main reason given by your child for food refusal. If no single main reason is given, please tick all those that are expressed commonly.

- a - Denies food refusal
- b - Frightened of becoming fat
- c - Wants to lose weight
- d - Not hungry
- e - Physical symptoms (e.g. feels full, hurts to swallow etc.)
- f - Feels guilty
- g - Unhappiness
- h - Other (please specify): ________________________________

17) Sometimes particular stresses may precede or exacerbate problems. Please indicate if any of the events below have happened to your child in the past, and if possible, the year in which the event(s) occurred.

<table>
<thead>
<tr>
<th>EVENT</th>
<th>YES</th>
<th>NO</th>
<th>YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>a - death of relative or friend</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If yes, please specify: ______</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b - Parental separation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c - Family member leaving home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d - Family move</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e - Family illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f - Starting new school</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g - Academic pressures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h - Marital / family tensions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i - Teasing about size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>j - Family member or friend dieting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k - Recent illness or operation (of the child)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>l - Birth of a sibling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m - Pubertal development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n - Sexual experience</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o - Other e.g. loss or death of a pet, accidents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If yes, please specify: ________________________________</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

18) RELATED ILLNESSES IN FAMILY

a - Has there been a history of psychological or nervous illness in a close relative, severe enough to require the services of a mental health professional?

- YES / NO

- If yes, please specify which illness and which relative: ________________________________
b - Has any of your child's close relatives had an eating disorder?  
   YES / NO  
   If yes, please specify which relative and approximate date:

   _____________________________________________________________

   c - Has there been a history of weight problems in the family?  
   YES / NO  
   If yes, please give any relevant details:-

   _____________________________________________________________

   d - Does any member of your family have a history of dieting?  
   YES / NO  
   If yes, please give details:

   _____________________________________________________________

   e - Does any member of your family have a special diet, e.g. vegetarian?  
   YES / NO  
   If yes, please state kind of diet: _______________________________

19) FAMILY EATING PATTERNS

Please tick the most appropriate answer to each question, i.e. “always”, “sometimes” or “never”.

Always    Sometimes    Never

a - Do you usually eat together as family?  
b - Do you all eat the same foods at family meals?  
c - Do you usually watch TV during family meals?  
d - Does your family snack between meals?  
e - Is there any conflict over the content of family meals?  
f - Do family members regularly diet?

At a later date, we may wish to contact your child's GP and school. Please could you give name, address and, if possible, telephone number's, if you have no objections to us contacting them.

GP:  

SCHOOL:  

Do you wish to add any other information not covered in the previous questions which you feel is relevant to your child's present difficulties? If so, please do so below.

Thank you very much for your help.
Appendix 3.2: Growth data collection (ANGRO) form
ANGRO FORM

APPOINTMENT DATE: ____________________

PATIENT NAME: _______________________  HOSPITAL NO. __________

CHRONOLOGICAL AGE (yrs/months): ______  BIRTH DATE: ____________

HEIGHT(cm): ___________________________  WEIGHT(kgs) _____________

HT / AGE: __________  WT/Age: ______  HT / WT: _____________________

PULSE: __________  BP: __________  CIRCULATION: ________________

HYDRATION: ___________________________  LANUGO HAIR: __________

PUBERTAL STAGE:

Breast/Genital Pubic Hair Axillary Hair Menstrual Status Testes L R

__________ __________ __________ __________ __________

Periods: __________ Regular / Irregular LMP: __________

ADDITIONAL INFORMATION

FOLLOW UP APPOINTMENT:

INVESTIGATIONS

1. Bone Densitometry (Dexa): □ ____________
2. Bone Age Requested: □ ____________
3. Bone Ultrasound: □ ____________
4. Pelvic Ultrasound: □ ____________
5. MRI Scan: □ ____________
6. Other: □ ____________
7. Bloods Taken: Yes / No

SH: __________  TRICH(skinfold) __________

SLL: __________  SUBSCAP (skinfold) __________

HEAD CIRC: __________  ARM CIRC: __________

MOTHER HT(cm): __________  WT(kgs): __________

FATHER HT(cm): __________  WT(kgs): __________
ANGRO FORM

APPOINTMENT DATE: __________________________
PATIENT NAME: ____________________________  HOSPITAL NO. __________

CHRONOLOGICAL AGE (yrs/months): ______  BIRTH DATE: __________

HEIGHT(cms): ____________________________  WEIGHT(kgs) __________

HT/AGE: _______  WT/Age: _______  HT/WT: __________
PULSE: _______  BP: __________  CIRCULATION: __________

HYDRATION: ____________________________  LANUGO HAIR: __________

PUBERTAL STAGE:
Breast/Genital  Pubic Hair  Axillary Hair  Menstrual Status  Testes L  R

__________  _______  _______  __________  _______

Periods: __________  Regular / Irregular  LMP: __________

ADDITIONAL INFORMATION

FOLLOW UP APPOINTMENT:

INVESTIGATIONS
1. Bone Densitometry (Dexa): □ __________
2. Bone Age Requested: □ __________
3. Bone Ultrasound: □ __________
4. Pelvic Ultrasound: □ __________
5. MRI Scan: □ __________
6. Other: □ __________
7. Bloods Taken: Yes / No

SH: __________  TRICH(skinfold) __________
SLL: __________  SUBSCAP (skinfold) __________
HEAD CIRC: __________  ARM CIRC: __________

MOTHER HT(cms): __________  WT(kgs): __________
FATHER HT(cms): __________  WT(kgs): __________
ANGRO FORM

APPOINTMENT DATE: ______________________

PATIENT NAME: ________________________ HOSPITAL NO. ____________

CHRONOLOGICAL AGE (yrs/months): ______ BIRTH DATE: _______________

HEIGHT(cm): ________________________ WEIGHT(kgs) ________________

HT / AGE: ___________ WT/Age: ___________ HT / WT: ________________

PULSE: ___________ BP: ___________ CIRCULATION: ________________

HYDRATION: _______________ LANUGO HAIR: ________________

PUBERTAL STAGE:
Breast/Genital Pubic Hair Axillary Hair Menstrual Status Testes L R

__________ __________ __________ _______________ __________

Periods: ___________ Regular / Irregular LMP: _______________

ADDITIONAL INFORMATION

FOLLOW UP APPOINTMENT:

INVESTIGATIONS
1. Bone Densitometry (Dexa): ☐ ______________
2. Bone Age Requested: ☐ ______________
3. Bone Ultrasound: ☐ ______________
4. Pelvic Ultrasound: ☐ ______________
5. MRI Scan: ☐ ______________
6. Other: ☐ ______________
7. Bloods Taken: Yes / No

SH: ___________ TRICH(skinfold) ______________
SLL: ___________ SUBSCAP (skinfold) ______________
HEAD CIRC: ___________ ARM CIRC: ______________

MOTHER HT(cm): ___________ WT(kgs): ___________

FATHER HT(cm): ___________ WT(kgs): ___________
Appendix 4.1: Relationship between tables in Access database

<table>
<thead>
<tr>
<th>Table</th>
<th>Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>PatientID, HospNo, Surname, FirstName, Sex, DOB, DOAssess</td>
</tr>
<tr>
<td>PatientBackground</td>
<td>PatientID, HospNo, MRC, MedicalProblem, MedicalProblemType, BirthWt, GestAge, BirthProb</td>
</tr>
<tr>
<td>tblresponse_code</td>
<td>response_code_id, response_code_desc</td>
</tr>
<tr>
<td>Visit</td>
<td>VolID, PatientID, VisitDate, Height, Weight, SH, Tri, Subscap, Arm, Head, BoneAgeReq, BoneAge</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>PatientID, ScanDate, VolUterus, LengthUterus, APFundus, APCervix, Transverse, Endo, RightOvaryVolume, LeftOvaryVolume</td>
</tr>
<tr>
<td>DEXA</td>
<td>PatientID, DexaDate, LI Area, L2Area, L3Area, L4Area, TotArea, L1BMC, L2BMC</td>
</tr>
</tbody>
</table>

Diagram illustrating the relationship between tables.
Appendix 4.2: Calculated functions in the Microsoft Access database

Date difference’ function

This can be used to calculate time between two dates. For example, used to calculate age (in years) at assessment:

Assessment Age = (DateDiff("y",[DOB],[DOAssess]))/365.25

or alternatively:

Assessment Age = DecimalYears(DateDiff("d",[DOB],[DOAssess]))

A more complex form of this function is used to extract date relating to two different dates. For example, height velocity:

HeightVel: (T0).[Height]-T1.[Height])

(DateDiff('y',[T1].[VisitDate],[T0].[VisitDate])\365.25)

'Immediate if' function

The ‘immediate if’ (IIf) function is used when the value (or absence of a value) in one field to determines which one of two possible results is returned. For example, used to calculate the nearest growth visit to the date of a DEXA scan:

NearestDate:IIf([PrevDateLag]>[NextDateLag],[NextDate],[PrevDate])

In other words, if the time to the previous visit is longer than the time to the next growth visit, then the value for the next date is given, and if not then the previous date is given.
**SDS for anthropometric measures**

The LMS functions developed for use on Microsoft Excel was adapted for the purposes of this study to be recognised by Microsoft Access as a function⁹.

**LMS SDS**

SDS were calculated according to the LMS method if skew (L), median (M) and coefficient of variation (S) were available from the reference data. This applied to height, weight, BMI, triceps skinfold thickness, and subscapular skinfold thickness.

For example, using LMS method for height:

\[
\text{HtSDS: CSng(LMSScore([Sex],[ChrAge],[Height]),"Ht")}
\]

**Standard SDS**

The standard SDS calculation was used where reference data were expressed in the form of mean and standard deviation. This applied to height velocity, sitting height, leg length, and mid arm circumference.

For example, using standard SDS calculation:

\[
\text{HeightVelSDS: SDScore([Sex],[ChrAge],[HeightVel],"HtVel")}
\]

**Weight for height/%BMI**

Weight for height (or % BMI) was calculated by obtaining the median BMI for the age of the child:

\[
\text{BMIMed: invLMSScore([Sex],[ChrAge],0,"BMI")}
\]

and then expressing the child’s BMI as a percentage of the median for age:

\[
\text{Wt4Ht: } ([\text{BMI}]/[\text{BMIMed}]) \times 100
\]

⁹ Many thanks to John Douglas for his skill and patience with this. Details of the SQL functions for this growth module can be obtained by writing to the author.
Interpolated height for DXA results

Interpolated height was obtained from identification of the previous and subsequent heights and dividing the difference in height by the time interval.

E.g. InterHeight:

\[
\text{If}([\text{Dexa}].[\text{DexaDate}]=[\text{PrevDate}], [\text{PrevHeight}], ((([\text{NextHeight}]-[\text{PrevHeight}])/\text{DateDiff}("y", [\text{NextDate}], [\text{PrevDate}]))*(\text{DateDiff}("y", [\text{Dexa}].[\text{DexaDate}], [\text{PrevDate}]))+[\text{PrevHeight}]))
\]
Appendix 8.1: Case histories of girls with AN excluded from longitudinal data as a result of confounding medical conditions.

EC

E was 12 years old when she presented to the Eating Disorders Team, at 72% BMI (-3.14 BMI SDS), with a height of -1.2 SDS. She was in stage 1 puberty, and with 3.5 years of bone age delay, and her bone age x-ray showed growth arrest (Harris’) lines. On presentation she was avoiding food, was tearful and sullen, refusing to communicate, but was passive in her resistance. The diagnosis of AN was questioned at first as she did not clearly endorse determined weight loss. Once hospitalised for nutritional rehabilitation, her weight loss behaviours became more marked. Vomiting however was associated with anxiety rather than self induced.

E had a lifelong history of asthma, and had been hospitalised on numerous occasions. She regularly took inhaled steroids, and 3 to four times a year needed oral steroids (Prednisolone) in addition. Previous growth data obtained from her respiratory physician showed that, despite chronic illness, she had grown normally long the 10th centile for both weight and height until weight loss at the age of 11. During the 3-4 years that AN was prominent her growth rate slowed down and she failed to progress in puberty. She was also hospitalised on three occasions with severe asthma and treated with intravenous and oral steroids. Her weight stabilised when she was around fourteen years of age, by which time her height regained its pervious normal centile. Although the growth pattern was compatible with AN the coexistence of severe asthma, which could have produced a similar growth pattern of severe enough, necessitated her exclusion from the sample.
Almost complete growth arrest is seen between the ages of 11.5 and 13 years, with subsequent catch-up growth to her premorbid centile following weight gain.
RH

Turner syndrome (45X0) was diagnosed at birth and at age 9.8 years she was started on low dose ethinyl oestradiol, 1μg daily. The dose of ethinyl oestradiol was increased gradually up to 20μg per day over the following 6 years. One year after starting oestrogen, oxandrolone treatment was commenced at a dose of 1.25 mg /day, increasing to 2.5 mg/day after 4 years. The relationship between weight, pubertal stage and dose of exogenous hormone is shown in figure XIII.i.

Some slight moodiness and irritability were noted in the first few months of low dose oestrogen treatment, but the onset of AN was not until 16 years of age, prior to stopping anabolic steroid therapy. Her previous maximum weight for height had been 109% (74th centile for BMI). The presentation was that of typical AN, characterised by desire for weight loss, fear of weight gain and body image distortion. Her body image dissatisfaction was not solely related to her stature. Severity warranted a 10 week admission to a specialist inpatient unit, with a loss of body weight to 75% weight/height (0.37th BMI centile).

Apart from reports of moodiness by her mother, there was little psychological distress noted prior to the onset of dieting behaviour. On restoration of weight she continued to report teasing, social isolation and self consciousness about her height.
Figure XIII.ii: Weight, pubertal stage and treatment data for a girl with Turner syndrome who developed anorexia nervosa at age 16. Duration and dose of Oxandrolone is indicated by the dark bars and for oestrogen by the shaded bars.