Novel Approaches in Adolescent Obesity Management

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I, William James White confirm that the work presented in this thesis is my own.

Where information has been derived from other sources, I confirm this has been

indicated in the thesis.

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Abstract

This PhD thesis on adolescent obesity focuses on the role of medical professionals and the interventions that they provide for obesity.

We undertook a feasibility and acceptability study to examine HELPclinic, a novel brief weight management intervention delivered by health professionals in a specialist obesity service. The intervention was shown to be feasible and acceptable. Four overlying themes were captured in participant interviews: HELPclinic relationships enabled discussions of a difficult topic; lack of novel medical approaches polarised participants' acceptance of HELPclinic; School vs HELPclinic – it's hard to do both; and ongoing support is crucial.

Qualitative interviews with young people and their families taking anti-obesity drugs (AOD) resulted in three theoretic models to explain their experiences of AOD, relating to commencement, relationship between dosing and side-effects, and drug cessation. Use of anti-obesity drugs is challenging for many adolescents. Multiple factors were identified that could be targeted to improve concordance and maximise efficacy.

A survey of GP AOD prescribing found low prescribing prevalence. Metformin was largely initiated by specialists for co-morbidities associated with obesity, and orlistat was largely initiated by GPs and outside NICE guidance. GPs reported lower confidence in AOD prescribing and wanted more support.

A systematic review of the psychological/social outcomes of bariatric surgery in adolescents found a small evidence base with few high quality studies and outcomes rare beyond 2 years post-surgery. Quality of life and depressive symptoms improved after surgery.

We present the first UK report of the outcomes of a bariatric surgery clinical pathway. Of fifty patients assessed, 12% were not eligible for surgery, 14% actively opted out,16% were lost to follow-up and 58% underwent surgery. Mean age at surgery was 18.3 years and mean BMI 53.1 kg/m^2. BMI outcomes and complications post-surgery were similar to those published in research cohorts. Follow-up was inconsistent and challenging.

Research Questions

1. Is it feasible and acceptable to deliver a HELPclinic, a brief lifestyle programme, in the outpatient (office) setting?

    a. Is it feasible for clinicians in the weight management service to deliver the intervention?

    b. Is it feasible to enrol young people and their families in HELPclinic and retain them for the whole programme?

    c. Is HELPclinic an acceptable intervention for participants and clinicians?

    d. What are the estimates for BMI change over the course of HELPclinic?

2. What are the experiences of young people taking an anti-obesity drug (AOD)?

3. What are the experiences of general practitioners prescribing anti-obesity drugs?

    a. What are the indications for drug initiation and reasons for cessation?

    b. Does their practice adhere to standards set by the National Institute of Health and Care Excellence?

    c. Do general practitioners have confidence in prescribing AOD, and what support do they need?

4. What psychological and quality of life factors are associated with outcomes of bariatric surgery?

5. What are the psychological and quality of life outcomes of surgery in adolescence?

6. What are the outcomes of an adolescent bariatric surgery pathway?

    a. What are the reasons for not undergoing surgery, and is there equal access to surgery?

    b. Are BMI and complication rates in an NHS service similar to published research cohorts?

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Outline

In this thesis I will summarise the research I have undertaken to gain a better understanding of obesity interventions delivered by secondary care clinicians to adolescents with obesity. There are currently few effective treatments available for obesity, and this research aims to guide the next generation of obesity interventions.

In chapter one I will describe the evidence base and current recommendations for clinicians in secondary care together with current guidelines. In chapter two I will outline some of the methodologies common across chapters.

In chapter three I will describe a feasibility and acceptability study undertaken to test a novel brief lifestyle intervention for young people delivered in the healthcare setting. This study aims to understand if a novel brief lifestyle intervention is acceptable and feasible, and gain feedback on the study prior to further evaluation (if deemed appropriate to continue).

In chapter four I will describe a qualitative study exploring young people's experiences of anti-obesity drugs.

In chapter five I will describe a survey undertaken to better understand prescribing of anti-obesity drugs by general practitioners. Lessons learnt from these studies and recommendations for future prescribing of anti-obesity drugs will be described in chapter eight.

In chapter six I will summarise a systematic review and meta-analysis of the psychological and social outcomes of bariatric surgery in adolescents, and the social and psychosocial predictors of surgery outcomes.

In chapter seven I will describe a bariatric surgery pathway and describe those undertaking an assessment for possible bariatric surgery. I will analyse the outcomes of the first 50 patients assessed in the NHS pathway. No previous NHS adolescent pathway has previously been assessed.

In chapter eight I will summarise this thesis and its implications for future research and policy.

1 Background

1.1 Overview

The last fifty years have seen a dramatic increase in both obesity and obesity-related research; however, effective interventions to prevent and treat obesity continue to be elusive. Advances in the understanding of obesity pathophysiology have highlighted the complexity of obesity which likely explains the limited successes of interventions to date.

The aim of this introduction is to summarise the current evidence base, focussing largely on what is relevant to the paediatric population. To fully understand paediatric obesity, it is important to summarise relevant research in both adults and animal models, where the majority of research has been conducted. Many questions remain in obesity management, and this review will inevitably raise more questions than answers.

Clinical obesity management is currently in its infancy, with many professionals and patients still believing that obesity can be cured simply by doing more activity and eating differently, a likely over-simplification of a complex problem. Whilst these factors undoubtedly influence weight status, they do not explain inter-individual variation in weight nor result in effective solutions to weight control.

A small minority of people have been able to overcome obesity by moderating their diet and increasing physical activity, (1) but many more have tried similar

approaches and failed. It is not understood why these outliers are able to achieve long term weight loss, while the majority who undergo similar strategies of calorie restriction and increased energy expenditure are not. What is clear though, is that there is a complex heterogeneous physiology underlying obesity that does not allow substantial long term weight loss for the majority. (2)

Obesity has yet to benefit from the advances of medicine seen in other fields, possibly because it has historically never been seen on such a scale or required such urgent public health intervention.

1.2 Adolescence

This thesis will focus on obesity in adolescents. The World Health Organization defines adolescence as the period in human growth and development that occurs after childhood and before adulthood, from the ages of 10 to 19 years. (3).

Adolescence is a time of rapid physical, psychological and social change. (4) These changes are largely driven by biological processes, most importantly puberty, which result in rapid growth, development of secondary sexual characteristics and changes in brain structure. (5) Whilst puberty is almost universally complete by 16-17 years of age, greater understanding of brain structure and function have led to the understanding that changes continue to occur into the third decade of life, with ongoing pruning of synapes and changes in brain volume. (6)

Unique challenges present during adolescence, including first presentations of new diseases, differing presentations of diseases, peak incidence of certain diseases and unique diseases only seen in this period. (2) First presentations include eating disorders, schizophrenia and acne. Increasing incidences of mood disorders, particularly anxiety and depression, make treating physical conditions more challenging. Furthermore, changes occur in psychological functioning from concrete to complex abstract thinking, and in social functioning from being largely parent-dependent to development of social autonomy. (4)

Global mortality in adolescence has changed little in the past few decades relative to large improvements in mortality seen in those under 5 years of age; by 2004, mortality in males aged 15-19 and 20-24 years was two and three times higher than in boys aged 1-4 years respectively and equal across those age groups in females. (7) Whilst absolute levels of global mortality in this age group have changed little, the causes have changed. Declines in communicable diseases have been seen across most regions, together with increases in injuries which have become the predominant cause of death in males aged 15-24 years.
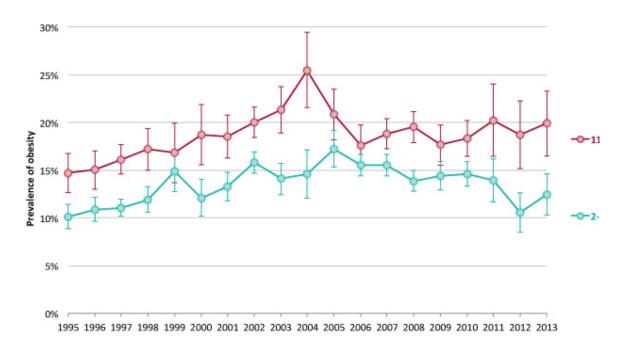
1.3 Obesity definition

For the purpose of this thesis, I shall use the most commonly used definitions of obesity: adults with a body mass index (BMI) over 30 kg/m^2 and children with BMI > 98th centile, using UK 1990 data (2 standard deviations above the mean). (8) Whilst the use of BMI and these thresholds to categorise subjects by risk may not be the most appropriate given the data presented later, they are the only thresholds currently recommended in children and the most commonly used thresholds in adult.

1.4 Prevalence of childhood obesity in the UK

There are few historical obesity prevalence data for children in the UK prior to the 1970s. (9) Little change was seen in cross-sectional data for 4-11 year olds between 1974 and 1984, after which prevalence of overweight increased 5-6% to 9-10% in boys and 9-10% to 13-16% in girls from 1984 to 1994. (10) Cross-sectional data from the Health Survey for England (HSE) shows the overall prevalence of obesity in children aged 2 to 15 years further increased from 1995 to 2004/5. (11) Subsequent to this, prevalence in those aged 11-15 years has stabilised, with falling prevalence in those aged 2-10 years (figure 1.1 below).

Figure 1.1 Trends in obesity prevalence aged 2-15 years (source HSE)
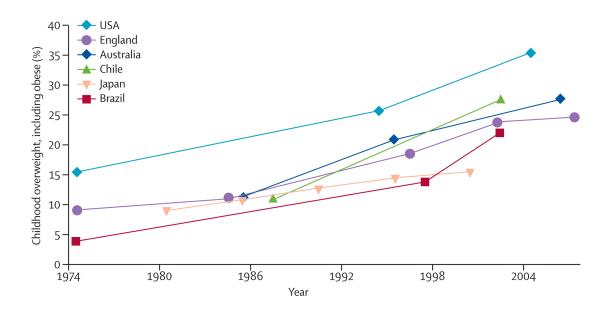
Severe obesity prevalence (defined as BMI >=99.6th centile of UK90 growth chart) in England in the latest available measurement year (2012/2013) was

1.9% (95% CI 1.8% to 1.9%) for girls and 2.3% (95% CI 2.3% to 2.4%) for boys

aged 4–5, and 2.9% (95% CI 2.8% to 3.0%) for girls and 3.9% (95% CI 3.9% to

4.0%) for boys aged 10–11 years. (12) The odds of being severely obese have

risen since 2006/7 in children aged 10-11 years and fallen in those aged 4-5

years.

This surge in obesity in the UK in the 1970s and 1980s occurred almost

concurrently in most high-income countries, with middle- and some lower-

income countries subsequently following suit (figure 1.2 below) (13)

Figure 1.2 Estimates of percentage of childhood population

overweight, including obese (with use of International Obesity Taskforce

cutoffs) in a selection of countries. (13)

Obesity trends in the US, where the majority of comparable research is located

are similar. Again, different thresholds are used. US data from National Health

and Nutrition Examination Survey (NHANES) recently published shows

improvement in obesity in younger children but not adolescents; prevalence in

children aged 2-5 years peaked in 2003/4 and subsequently decreased, in children aged 6-11 years increased until 2007-2008 and then levelled off, and in adolescents aged 12 to 19 year continued to increase. (14) Despite overall improvements in obesity prevalence in those aged 6-11 years, prevalence of severe obesity (BMI >=120% of 95th centile) has increased (4.3% in 2013/14). Increased rates of severe obesity were also observed in adolescents (9.1% in 2013/14)

A variation in obesity prevalence is seen by socio-economic status. (13) In low to middle income countries, it is those living with high socio-economic status that appear to have high prevalence first. The reverse is seen in high income countries. In the UK, with girls aged 10-11 years from the most deprived areas (lowest 10%) are 4.35 times more likely than those from the least deprived areas (highest 10%) to develop severe obesity.

1.4.1 Obesity tracking

Studies of different birth cohorts born since 1958 show a consistent increased risk of adult obesity if the child is obese, with overweight children having at least twice the risk of becoming overweight adults compared to children who are not overweight, and older obese children having higher risk than younger obese children. (15) Overall, 64-85% of obese adolescent boys and 55-90% of adolescent girls continued to be obese as adults in 3 different longitudinal cohorts. Presence of parental obesity increased the risk of obesity in adult life, but it did not confer additional risk if the child or adolescent was already obese. (16)

1.5 Obesity & health

The term obesity has been used widely with multiple different definitions. They largely all relate to a phenomena which the World Health Organization defines as "abnormal or excessive fat accumulation that may impair health". (17)

The term has also been used for individuals with a body mass above certain thresholds; however, this has led to unhelpful dichotomisation and incorrect inferences that individuals with body mass below the threshold are not at risk from poor health related to abnormal or excessive fat accumulation.

Obesity in adulthood is associated with an increased risk of death and illness from cardiovascular disease (relative risk 2-3), type 2 diabetes (RR>3) and certain cancers (RR1-2, including oesophageal and colon in men, endometrial, gall bladder and post-menopausal breast cancer in women). (18) (19) These risks are also associated with obesity in childhood with hazard ratios of 1.1-5.1; (20) this increased risk persists when adult obesity status is accounted for. (21)

Furthermore, obesity is linked to osteoarthritis, sleep apnoea, and asthma. In addition to physical co-morbidities, obesity is related to high levels of psychopathology, especially in those with severe obesity. (22)

1.5.1 Adiposity and risk: body mass index

The association between body mass and health was identified as far back as Egyptian and Roman times by Herodotus, Hippocrates, Galen and Plutarch. (23) Plutarch observed: "…thin people are generally the most healthy; we

should therefore not indulge our appetites with delicacies or high living, for fear of growing corpulent." (24)

Advances in the quantification of risk associated with obesity were made by insurance companies from 1912 onwards. Louis Dublin, a statistician at the Metropolitan Life Insurance company,(25) was responsible for identifying clients who were at increased risk of early death, primarily so that the insurance company could charge them higher premiums. He identified a correlation between risk of premature death and different habitus; those who maintained weight similar to the average 25-year old lived the longest. In 1942 Metropolitan Life Insurance Company introduced charts which stratified health risk by body proportion.

Subsequent work to stratify health risk largely used the Body Mass Index (BMI; weight/height^2), a measure initially developed by Adolf Quetelet in the 1800s and previously known as the Quetelet Index.(26) The index is calculated by dividing weight in meters by the square of the height in meters and was originally devised as a tool for finding the values of the "average man" (figure 1.3) (27)

Figure 1.3 (next page) Weight chart devised by Adolf Quetlet showing range of weights and Quetlet Indices at different ages.

Table of the Size and Weight of Man at Different Ages.

Ages	Size	Weight	Ratio of Weight to Size	Size Observed Max.	Size Observed Min.	Weight Observed Max.	Weight Observed Min.
	met.	kilog.		met.	met.	kilog.	kilog.
Birth,	0·496	3·20	6·19	0·532	0·438	4·50	2·34
1 year,	0·696	10·00	14·20	0·750	0·682	11·00	9·00
2 ..	0·797	12·00	15·00	0·824	0·730	13·50	10·50
3 ..	0·860	13·21	15·36	0·875	0·840	13·60	12·10
4 ..	0·932	15·07	16·32	0·965	0·840	18·20	12·50
5 ..	0·990	16·70	16·98	1·080	0·915	18·50	14·00
6 ..	1·046	18·04	17·44	1·115	0·960	20·40	15·80
7 ..	1·112	20·16	18·31	1·162	1·109	24·50	17·20
8 ..	1·170	22·26	18·92	1·260	1·120	28·50	19·00
9 ..	1·227	24·09	19·68	1·325	1·150	29·00	22·20
10 ..	1·282	26·12	20·37	1·325*	1·163	32·00	22·70
11 ..	1·327	27·85	21·58	1·405	1·215	33·80	25·00
12 ..	1·359	31·00	22·80	1·450	1·270	36·30	25·00
13 ..	1·403	35·32	25·30	1·490	1·300	39·50	34·60
14 ..	1·487	40·50	27·49	1·630	1·330	45·00	37·00
15 ..	1·559	46·41	29·88	1·658	1·380	61·50	37·00
16 ..	1·610	53·39	33·00	1·730	1·430	61·50	40·00
17 ..	1·670	57·40	34·25	1·790	1·467	65·50	45·00
18 ..	1·700	61·26	35·67	1·790	..	67·00	45·00
19 ..	1·706	63·32	37·00	1·800	..	70·00	48·20
20 ..	1·711	65·00	37·99	1·838	..	72·70	..
25 ..	1·722	68·29	39·66	1·890	..	98·50	..
30 ..	1·722	68·90	40·02	..	..	..	..
40 ..	1·713	68·81	40·03	..	..	..	..
50 ..	1·674	67·45	40·14	..	..	..	..
60 ..	1·639	65·50	40·01	..	..	..	..
70 ..	1·623	63·03	38·83	..	..	..	49·1
80 ..	1·613	61·22	37·96	1·820	1·467	83·00	49·7

Table of the Size and Weight of Woman at Different Ages.

Ages	Size	Weight	Ratio of Weight to Size	Size Observed Max.	Size Observed Min.	Weight Observed Max.	Weight Observed Min.
	met.	kilog.		met.	met.	kilog.	kilog.
Birth,	0·483	2·91	6·15	0·555	0·438	4·25	1·12
1 year,	0·690	9·30	13·50	0·704	0·660	10·5	8·3
2 ..	0·780	11·40	14·50	0·798	0·720	12·0	8·3
3 ..	0·850	12·45	14·70	0·895	0·795	15·8	10·5
4 ..	0·910	14·18	15·10	0·950	0·810	15·8	11·5
5 ..	0·974	15·50	15·70	1·085	0·876	17·5	13·3
6 ..	1·032	16·74	16·24	1·085	0·956	20·3	13·3
7 ..	1·096	18·45	16·85	1·177	1·050	23·4	16·0
8 ..	1·139	19·82	17·45	1·330	1·050	23·4	16·0
9 ..	1·200	22·44	18·65	1·330	1·110	25·7	18·3
10 ..	1·248	24·24	19·45	1·390	1·160	28·3	20·3
11 ..	1·275	26·25	20·60	1·385	1·160	39·8	21·6
12 ..	1·327	30·54	23·00	1·476	1·160	42·3	21·6
13 ..	1·336	34·65	24·50	1·580	1·160	42·8	21·6
14 ...	1·447	38·10	25·35	1·580	1·160	51·0	32·0
15 ..	1·475	41·30	28·10	1·638	1·160	55·2	32·0
16 ..	1·500	44·44	29·62	1·638	1·160	57·6	32·0
17 ..	1·544	49·08	31·75	1·688	1·284	61·6	..
18 ...	1·562	53·10	34·05	1·740	..	79·9	..
20 ..	1·570	54·46	34·70	..	..	..	..
25 ..	1·577	55·08	35·26	..	..	..	..
30 ..	1·579	55·14	35·90	..	..	..	..
40 ..	1·555	56·65	36·50	..	..	..	..
50 ..	1·536	58·45	38·15	..	1·444	90·5	39·8
60 ..	1·516	56·73	37·28	..	1·436	..	..
70 ..	1·514	53·72	35·49	..	1·431	93·8	..
80 ..	1·506	51·52	34·21	1·701	1·408	72·5	38·0

Early studies showed an increased mortality risk in those with BMI over 25 kg/m^2 and subsequently the term "overweight" has been used to define adults with BMI over 25 and "obesity" in those with BMI greater than 30 kg/m^2. (28) Health risk associated with weight status has subsequently been shown to vary by ethnic groups, leading to population-specific BMI threshold, particularly for those of South Asian origin.(29) Studies in children confirmed that those with raised BMI for their age also had increased morbidity and mortality in later life compared to those with normal BMI. (30, 31)

More recent systematic reviews of the association between mortality and BMI have challenged these thresholds, with one showing that only those with grades 2 and 3 obesity (35-39.9 kg/m^2 and 40-44.9 kg/m^2, respectively) had increased all-cause mortality risk compared to subjects with normal BMI (18.5-24.9 kg/m^2). (32) Furthermore, those with a BMI of 25-29.9 kg/m^2 (defined as overweight) had a lower risk of mortality than normal BMI subjects.

1.5.2 Adiposity and health risk: better makers of poor health?

At an individual level, BMI alone has been shown to be a poor differentiator of individual risk. This is due in part to BMI being a poor differentiator between muscle and fat, meaning that those with tall or muscular physiques have a higher BMI. (33) There are ongoing attempts to better correlate the health risks associated with excess or abnormal adiposity. A better understanding of what is "abnormal or excessive fat accumulation", developing mechanisms to measure it, and understanding the pathways that cause impaired health are key in understanding how we define obesity, and monitor outcomes of treatment.

Adipose deposits are scattered throughout the body; in addition to the main visceral and subcutaneous deposits, they are also found in bone marrow, pericardium, lung parenchyma and peri-renal and peri-adventitial areas. (34) Differing health risk has been demonstrated by distributions of adipose tissue. Adipose deposits around the hips appear to be protective against obesity-related poor health(35) whereas deposits in the abdomen confer a higher risk, with abdominal obesity being a better predictor of myocardial infarction than BMI in large epidemiological studies. (36, 37) These fat distribution are known as gynoid and android, or colloquially as 'pear' and 'apple' distributions, respectively.

Furthermore, location of adipose deposits within the abdomen influences risk; increased adipose tissue in the liver and around abdominal organs is associated with higher risk than subcutaneous deposits. (33) These visceral fat deposits are associated with increased risk independent of abdominal girth,

implying that those who are slim and therefore not classified as obese using traditional definitions can be at increased risk of obesity-related disease if they have increased visceral fat.

The reason for these differing risks has been explained by better understanding of adipose tissue (AT) physiology, most notably due to differences in adipokine (adipose tissue-derived hormones), inflammation and lipid activity. (34) Adipose tissue was initially thought to be an inert organ whose role was largely to store energy in the form of lipids. It is now appreciated that it has a key role in the integration of systemic metabolism with secretion of multiple proteins called adipokines. AT has been shown to be highly metabolically active, with complex hormonal pathways that communicate with all body systems particularly the gut and hypothalamus. These pathways are integrally involved in energy regulation and digestion.

Adipose tissue has been shown to be composed of different subtypes, with brown adipose tissue (BAT) largely producing heat, white adipose tissue (WAT) storing fat, and beige adipose tissue that appears to show plasticity in its form. (38)

Inflammation and macrophage infiltration in adipose tissue, with release of pro-inflammatory cytokines such as TNF-α, is seen with increasing adiposity, especially in visceral deposits. This excess of pro-inflammatory adipokines counteracts anti-inflammatory adipokines, such as adiponectin and SFPR5, to result in a pro-inflammatory state. This qualitative aspect of adipose tissue has been shown to an important effect on the systemic metabolic phenotype and

associated mortality and morbidity. (34) Furthermore, the production of extracellular matrix components by fibroblasts may interfere with adipose tissue expansion and contribute to metabolic dysregulation. (39)

1.5.3 Adipose tissue: alternative risk stratification tools

Given the role of adipose tissue activity and distribution, attempts have been made to quantify obesity-related risk using markers other than adipose mass. (40) An analysis of 58 prospective studies and 221,934 participants found that addition of weight status (BMI, waist to hip ratio, or waist circumference) into a cardiovascular disease risk prediction tool that already included known cardiovascular risk factors did not improve its accuracy. (41)

The term "metabolically healthy obesity" (MHO) has been used to define those with obesity and without cardiovascular (CV) risk factors of hypertension, diabetes, abnormal lipids and inflammation. (42) This term has been developed because of epidemiological studies suggesting that those without CV risk factors have similar incidence of mortality or CV events, regardless of BMI status. (43) Meta-analyses of studies have shown conflicting results, and these data were challenged in a meta-analysis using only studies with >10 year follow-up; patients with MHO had 24% increased risk of a major CV event compared to metabolically healthy lean subjects. (44)

Either way, Kramer showed that patients with MHO had a markedly lower risk of CV events compared to metabolically unhealthy lean subjects, a finding known as the "obesity paradox". (44) Although those with obesity are less likely to be

metabolically healthy than those without, these studies show that obesity status *per se* should not be used to define future risk.

Cardiorespiratory fitness is likely to be another major factor that propagates the risk associated with obesity; one meta-analysis showed that those who were classified as 'fit' had a similar mortality risk, regardless of BMI group. (45)
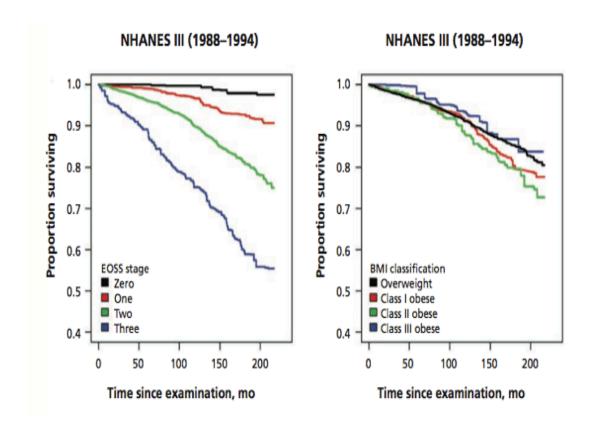
Similar risk factors for ischaemic heart disease are seen in children with obesity as in adults.(46) These risk factors have been shown to track into adulthood and closely correlate with adult risk factors and morbidity. (47) (48). Fewer studies have been performed examining the prevalence of metabolically health obesity in children than in adults; one showed that the strongest independent predictor of MHO was moderate to vigorous physical activity (OR 1.8, 95%CI 2.14 – 2.62). (49)

1.5.4 Obesity co-morbidities and mortality

Co-morbidities have been shown to better predict mortality risk than BMI, even when non-cardiovascular co-morbidities are included in the model. The Edmonton Obesity Staging System (EOSS) uses a 5-stage clinical staging tool across 3 domains (medical and psychological and functional impairment). (50) Modelling using the NHANES 1988-1994 dataset showed the EOSS score more accurately predicted 15-year mortality risk than BMI. Those with highest EOS score of 3 (score of 4 or more not used due to missing data) had a relative risk of 2.69 (95% CI 1.98-3.67) of dying compared to those with scores of 0 or 1, even when adjusted for BMI. (51) Figure 1.4 below shows survival curves when

classified by EOSS stage (left) and by BMI classification, with clear

demonstration that EOSS is superior at predicting survival. EOSS has also

been adapted for use in children, (52) but its risk stratification has not been

evaluated to date.

Figure 1.4 EOSS risk prediction tool. Left figure shows survival based
on EOSS staging. Right figure shows survival based on BMI category**.**

1.6 Causes of obesity

1.6.1 Physiology
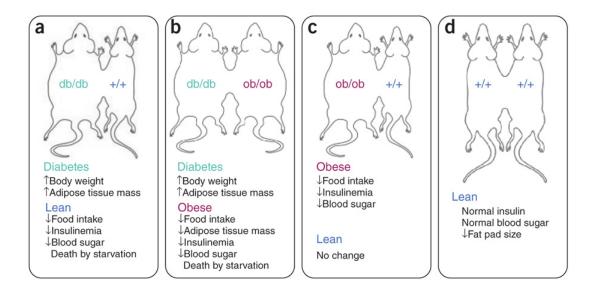
1.6.1.1 Genetic contribution

Children have an increased likelihood of being obese as an adult if one parent is obese, with further increased likelihood if both parents are obese.(16) Twin and adoption studies have offered insights into the relative roles of nature and nurture in obesity. There is good evidence that body weight is highly heritable, with BMI and waist circumference in monozygotic twin pairs more closely correlated than in dizygotic twins, resulting in estimates of heritability of BMI of 40-70%. (53) In clinical practice, this implies that between 40% and 70% of inter-individual differences have been attributed to genetic factors. Furthermore, whilst there is some correlation between adopted children and their adoptive parents to support the role of nurture, the correlation between the adopted children and their biological parents is stronger, further supporting a strong genetic contribution to obesity.(53) These estimates of heritability have not changed over time as the environment has become more obesogenic and overall obesity rates have increased, suggesting that the main explanatory factor to explain the variance of childhood weight is heritability. (54)

Although obesity appears to be highly heritable, the underlying genetic mechanisms are still poorly understood. Candidate gene (monogenic) studies have uncovered some rare, but important, causes of extreme obesity, such as leptin deficiency and Melacortin 4 receptor (MC4R) gene mutations.

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One of the earliest and most widely used animal models of obesity is the ob/ob mouse. (55, 56) This genotype arose by chance in a colony of c57bl/skf mice in 1949. The ob/ob mouse was phenotypically similar to its siblings at birth but was hyperphagic, undertook lower levels of physical activity and grew to three times the size of its siblings.(57) It developed insulin resistance, hyperglycaemia and compensatory pancreatic enlargement. Parabiosis experiments, in which the circulatory blood flow of mice from two different genotypes are connected, demonstrated that the ob/ob mice lacked a circulating factor that acts on the brain to reduce food intake, whereas the db/db mouse produced the circulating factor but could not respond to it. Figure 1.5 summarises the effect of parabiosis experiments with differing combinations of wild type, db/db and ob/ob mice.

Figure 1.5 Four different parabiotic combinations and impact on each of the phenotypes in each mouse pair. (58)

This circulating factor was subsequently found to be the protein leptin, made predominantly in adipose tissue and encoded by the leptin gene which acts on

the hypothalamus to reduce appetite. Leptin has now been demonstrated to be a key hormone in energy regulation and changes in energy balance alter leptin gene expression; a 10% reduction in body weight (mostly fat mass) results in a 53% increase in serum leptin. (59) Substantial weight loss was seen after leptin therapy in children with congenital leptin deficiency, offering early hope that leptin could be used as a mainstream treatment for obesity. However very few subjects were found to have absolute leptin deficiency.(60) (61)

Leptin has been shown to regulate the production of α-melanocyte stimulating hormone (α-MSH). α-MSH acts on the melanocortin 4 receptor (MC4R) which is widely expressed in the central nervous system; up-regulation of MC4R results in decreased food intake. Mutations in MC4R result in increased appetite and food intake, increases in fat and lean mass, and hyperinsulinaemia;(62) one study showed defects in MC4R in up to 40% of children who become obese before the age of 10 years. (63)

Whilst monogenic studies have been helpful in gaining a better understanding of adipose tissue metabolism, they have not resulted in big advances in explaining the genetic causes of obesity. To date, studies have only identified relatively small numbers of patients with single gene mutations, and these have only explained a small degree of variance in weight.

Genome-wide association studies (GWAS) have allowed hypothesis-generating analyses of the whole genome to identify possible candidate genes to explain a relationship between BMI and identified loci. Despite highly significant associations, each of these loci has only explained a small variance in body

weight, with variations in the fat and obesity gene (FTO) having the strongest effect in adults, but only increasing BMI by 0.26-0.66 kg/m^2 in adults and increasing obesity odds by 1.25-1.32-fold. In children, single nucleotide polymorphisms (SNPs) in FTO have an effect on BMI as early as two weeks of age (64) and near-MC4R mutations have similar effect sizes compared to FTO alleles, having twice the impact on childhood BMI compared to adults. (65)

A recent systematic review and meta-analysis of GWAS and Metabochip data (selective genotyping of 200,000 SNPs of cardio-metabolic interest) from 339,224 individuals (236,231 GWAS, 103.047 Metabochip) identified 97 BMI-associated loci. (66) This meta-analysis provided key insights:

1. Conservative estimates suggest that these 97 loci account for 2.7% of BMI variance in the studied population. The influence of these loci were tested in one sample population of 8,164 individuals of European descent; a difference of +1.8 kg/m^2 and -1.5 kg/m^2 were seen between those carrying the most BMI-increasing and least BMI-increasing alleles and median number of alleles, respectively. Less conservative estimates suggest that these loci could predict 21% BMI variation.

2. These 97 loci had significant associations with thirteen metabolic phenotypes, including some that were associated with a reduced risk of metabolic disease despite being associated with increased BMI.

3. These loci were mostly associated with gene expression in brain tissue, including the hypothalamus and pituitary which are critical in central appetite regulation, and more strongly in the hippocampus and limbic

system, both of which have a role in learning, cognition, emotion and memory.

4. Identified loci influenced specific pathways affecting BMI, including synaptic plasticity and glutamate receptor activity.

1.6.1.2 Energy homeostasis

An undisputed factor in obesity is a mismatch between energy intake (dietary) and expenditure (basal metabolic rate, thermogenesis and physical activity). (67) This is often wrongly considered to be a simple "energy in versus energy out" phenomenon. One estimate calculated that simple laws of thermodynamics would predict yearly gains of 68 pounds for men and 47 pounds for women using estimates of changes in physical activity and dietary intake in recent times; clearly this has not occurred. (67) Rather, energy homeostasis is the result of highly complex interactions with physiological adaptions to changes in energy balance. (68)

Energy balance is highly regulated and relies on complex communication from the executive, reward and autonomic circuits in the brain and circulating homeostatic signals. (68) The hypothalamus is the most studied region of the brain in regards to energy regulation and co-ordinates signals from the gastro-intestinal tract, adipose tissue, muscle and liver(69),(70) The arcutate nucleus (ARC) and ventromedial hypothalamus (VMH) express high levels of receptors for many of the hormones and neuropeptides that regulate feeding, with the signalling pathways promoting termination of eating (satiety signals) much better understood than those promoting eating.

The gastrointestinal tract largely sends satiety signals to the brain indicating sufficient food intake via gut hormones (enterokines) and efferent neurons, with only ghrelin sending hunger signals. Increasing numbers of sensing cells are being detected in the GI tract which are able to detect macro- and micro-nutrient components of food ingested.

1.6.1.3 Weight loss physiology

A common perception is that negative energy balance leads to continuing ongoing weight loss. (71) There is good evidence to show that individuals possess highly regulated physiological mechanisms to prevent and reverse weight loss. (2) Body weight is affected by biological, environmental and behavioural pressures, all of which are influenced by genetics; the resulting effect establishes a "steady state" weight in adults.

The hunger associated with weight loss has been shown to be closely associated with changes in satiety hormones (GLP-1, PYY, GLP1) and fat storage signals (leptin). These changes are still persistent one year after weight loss, thereby promoting weight re-gain. (72, 73)

Weight loss results in changes in energy expenditure disproportional to the degree of weight loss (muscle becomes more efficient), autonomic nervous system, neuroendocrine function (particularly leptin and thyroid hormones) and energy intake behaviours (delayed satiation, decreased perception of how much food has been eaten, increased food reward and decreased food restraint) to promote weight regain. (59) These changes are seen even if subjects are in a

state of energy balance following weight loss but can be partially reversed with administration of leptin.

 It was initially thought that bariatric surgery (techniques described later) worked due to physical restriction of food intake and malabsorption. It has since been shown that the mechanisms are more likely to be due to physiological changes that promote weight loss, and the variation in outcomes is likely due to the differing physiological changes between procedures. These include changes in vagal stimulation, altered gut hormone response to food (PYY, GLP-1, ghrelin) improving insulin secretion and promoting satiety, bile acid changes in the gut and serum, and changes to the gut microbiome.(74) (75) Furthermore, bariatric surgery results in changes in food preference with preference for healthier foods, higher acuity to sweet taste and a lower preference for sweet fatty foods. (76)
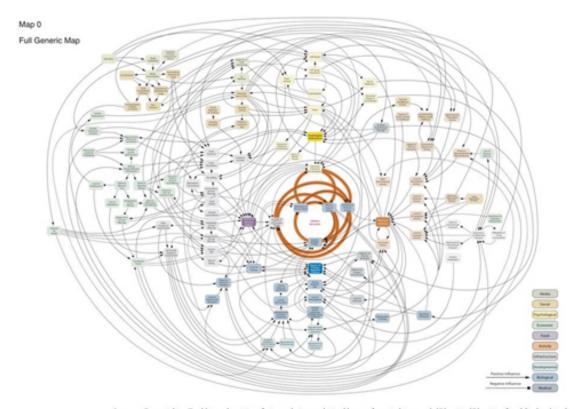
1.6.2 Extrinsic moderators

There is currently little evidence that human genotype, epigenetics or physiology has changed in the last 50 years. The interaction between changes in extrinsic factors and an individual's physiology are most likely the cause of the obesity epidemic. In addition to physiologically-driven behaviours including appetite, food choice and exercise, it is clear that external triggers have an influence on each individual's behaviours. However, we see variations in individuals' response to external triggers raising the point that this relationship is bi-directional.

Systems science has helped to understand the multitude of factors involved in the causation of obesity.(77) Systems science aims to understand the complex relationships between multifactorial problems such as obesity and both their causative factors and potential solutions. System science emphases that obesity in an individual does not occur in isolation but rather it occurs "within a particular genetic, social and environmental mileu".
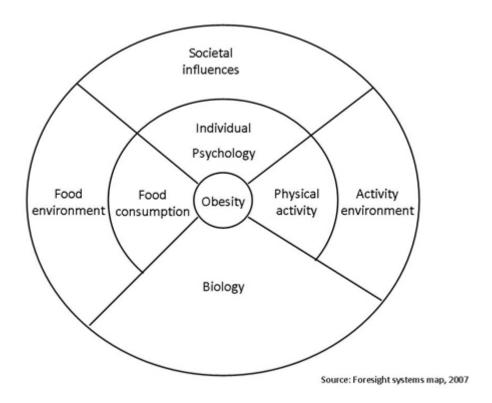
The British Government commissioned the Foresight report to understand the contributing factors that promote obesity. It produced a complex model that interconnected disciplines as disparate as the built environment, group psychology, individual physiology and individual physiology to develop an overall causative model for obesity. (78) It showed that an individual's physiology, diet and physical activity are intricately related with individual and group psychology, societal influences, food production, and the environment (figures 1.6 and 1.7 below).

Figure 1.6 Foresight report summary diagram showing the complex interconnecting web of factors causing obesity. From Foresight report. (78)

Source: Foresight - Tackling obesities: future choices - http://www.foresight.gov.uk/Obesity/Obesity_final/Index.html

Figure 1.7 Simplified foresight report showing categories of factors influencing obesity.

Source: Foresight systems map, 2007

Without attempting to summarise all the evidence and interactions shown in the diagram, some key areas merit attention.

1. The relative contribution of physical activity, sedentary activity and diet to the development of obesity, together with the inter-individual effect of this balance is unclear, and hard to measure. (79)There has been an arguably disproportionate focus on energy intake and physical activity as causative factors.

2. Child measuring programme data have shown strong correlations between obesity prevalence and socio-economic status. Prevalence is falling in reception aged children in the least deprived communities but is unchanged in the most deprived children and in year 6 children, prevalence is stable in the least

deprived but increasing in the most deprived areas. Variation is also seen by ethnic grouping. Across both age strata and both sexes, Black African and Black Other ethnicities have the highest prevalence of obesity, except for year 6 boys, where Bangladeshi boys have higher prevalence, and Pakistani and Asian Other groups (not including Indian) have similar prevalence to Black African and Black Other. Across all groups, White British children are amongst those with the lowest prevalence of obesity.

3. Data from the Framingham Study showed that an adult had increased risk of becoming obese if a same-sex friend, spouses or adult sibling became obese (increase of 57%, 40% and 37% respectively) but not a neighbour, suggesting that social networks are more important than built environment in obesity risk. (80) In children, the home and school environments, parental eating behaviours, and food availability are likely to influence their adiposity status (known as the ecological model). (81)

4. There is increasing evidence that the uterine millieu, and even the mother's pre-conception physiology have an influence on fetal growth and health (known as fetal programming). Maternal smoking, maternal weight gain and blood glucose control during pregnancy appear to promote obesity (82) whereas breastfeeding is likely protective, although the latter is controversial with conflicting data reported. (83) (82) (84) Conversely, the Thrifty Phenotype hypothesis suggests that reduced fetal growth can result in fetal physiological changes that pre-dispose it to increased lifelong risk of cardiovascular disease and diabetes.(85)

4. Sleep, both in terms of timing and duration, is increasingly being recognised as having an important impact on energy regulation. Changes in melatonin due to night-time light exposure and sleep disturbance can lead to weight gain through changes in brown adipose tissue metabolism as well as insulin resistance.(86-88)

5. Animal studies have shown that the gut microbiota is capable of secreting and altering the production of molecules that affect both energy balance and energy stores. (89) Germ-free mice are inefficient at weight gain, but subsequently gain weight when innoculated with gut microbes with ultimate weight being reflective of the donors, despite their energy intake being less than when in their germ-free state. (90). Studies are ongoing to evaluate the impact of fecal microbiota transplantation in humans (clinicaltrials.gov identifier NCT02530385).

6. There are strong associations between obesity and mental health problems. These are likely bidirectional and include eating disorders.

1.7 Evidence base for current available treatments

In this section I shall discuss the evidence base for the main types of obesity interventions. Most of the evidence base derives from adult studies, and for each type of intervention I shall first describe the evidence base for adults and then for children and young people.

I shall not be focussing on the evidence base for either prevention programmes or public health interventions as these lay outside the domain of this thesis.

1.7.1 Lifestyle interventions

1.7.1.1 Adults

The current mainstay of obesity interventions is the lifestyle intervention. These aim reduce the weight of participants by enabling them to change their diet and physical activity. These are usually community-based and delivered to groups of participants. Although they are outside the remit of this thesis, much of the evidence base is relevant to the lifestyle advice and interventions provided within secondary and tertiary care.

Data from two large randomised controlled trials, Look AHEAD (91) and the Diabetes Prevention Study(92), have provided important insights into the outcomes of lifestyle interventions. I will describe both studies in detail as their components and outcomes are of relevance to this thesis.

The Diabetes Prevention Study (DPP)(92) was a three group RCT comparing the effects of intensive lifestyle intervention, metformin with standard care, and

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placebo with standard care. A total of 3234 participants aged 25 years or over were recruited with inclusion criteria of BMI > $24kg/m^2$ and fasting hyperglycaemia or impaired glucose tolerance but not diabetes. The intensive lifestyle programme participants received 16 individual lessons over 24 weeks covering diet, exercise and behaviour modification with the goal of achieving 7% weight loss. Recommendations included a low calorie, low fat diet and 150 minutes of moderate intensity exercise per week. Those in the lifestyle group lost greatest weight at one year, followed by the metformin group. However, weight regain was seen in the intensive lifestyle group and the weight difference between groups at 10 years was minimal. The study also found that highly intensive lifestyle treatment reduced the risk of developing diabetes; the incidence of diabetes at 4 years was 58% lower in the lifestyle group and 31% lower in the metformin group than the control group, and group differences persisted at ten years.

The Diabetes Prevention Study Outcome Study (DPPOS) continued to monitor 88% of DPP participants following the end of the study; all were given lifestyle support (less intensive than earlier phase) and the metformin group continued to receive metformin.(93) Those in the control group who were subsequently given lifestyle support subsequently showed no subsequent difference in diabetes risk compared to the original intensive or metformin groups. These findings suggest that the diabetes-preventing effect of the initial treatment persisted for 10 years; however, once lifestyle intervention was given to all groups, their subsequent risk was equivalent.

Look AHEAD (Action for Health in Diabetes) assessed the effects of intentional weight loss on cardiovascular mortality and morbidity in 5,145 overweight and obese adults with type two diabetes aged 45 – 74 years. (91) Recruits were randomised to either standard care or an intensive lifestyle intervention delivered over 8 years. The intensive lifestyle programme (ILI) was adapted from the Diabetes Prevention Programme but was more intensive and longer-lasting. For the first year it consisted of monthly individual sessions together with 3 weekly sessions per month in the first 6 months and 2 in the second 6 months. Reduced calorie intake of 1200-1800 kcal (depending on initial weight) was recommended with <=30% calories from fat and >= 15% from protein. Structured meal plans were provided and replacements of 2 meals and 1 snack with liquid shakes or meal bars were encouraged each day for the first 6 months and one meal and one snack for the subsequent 6 months. Participants were prescribed >=175 minutes of unsupervised moderate activity exercise (mostly walking) and instructed to keep daily records of food intake, physical activity and other targeted behaviours. Support was ongoing for the subsequent 7 years, with monthly group meetings (education, support, weighing) and individual lifestyle counselling which was followed by email or phone contact after two weeks. Individual sessions used cognitive behavioural therapy and elements of motivational interviewing, problem solving and cultural tailoring to enable behaviour change. Those assigned to standard care receive three group education sessions per year in first 4 years and then one session per year. These consisted of group education on diet, physical activity and social support but not behavioural strategies for adhering to the recommendations.

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The ILI group had much greater weight loss in the first year compared to controls (8.5% loss vs 0.6%) but subsequently regained weight. In contrast, the control group demonstrated a slow gradual loss over the 8 years. At 8 years, a more modest difference in weight loss was seen between the two groups (4.1% versus 2.1%, respectively). Greater attendance at behavioural sessions, higher numbers of meal replacements and more physical activity in the first year predicted outcomes at 4 and 8 years. Despite improved weight loss, fitness, diabetes control, and greater reductions in cardiovascular risk factors in the intensive intervention group, no differences were found in the primary outcome measure of cardiovascular morbidity and mortality at a median follow-up of 9.6 years and the study was stopped early.(94).

Systematic reviews and meta-analyses have found similar findings across lifestyle interventions. (95) (96) (97) Leblanc *et al.* found that lifestyle interventions had no effect of mortality, hospitalizations or depression, although they noted that data on these outcomes were sparse. (96) They detected reductions in diabetes incidence, particularly in those with elevated risk.(98, 99) Weight change in these reviews have been of the same magnitude as those reported in DPP and LookAHEAD; interventions largely result in modest weight loss with subsequent weight regain. (97) Meta-analyses show high levels of heterogeneity, which is not surprising given that they combine heterogenous interventions with differing components (caloric restriction, macronutrient composition, exercise types and behavioural models), inclusion criteria (different thresholds and different normative data), age group, outcome criteria,

duration of study and post-intervention follow-up, and control groups (waiting list, no treatment, usual care or written education).

In one systematic review, data from 37 studies which included 16,000 participants were meta-analysed; at one year, a mean loss of −2.8 kg (95%CI −3.6 to −2.1) was detected. (95) The authors extracted data from individual studies with the additional aim of identifying the successful components of these interventions. Meta-analysis showed no evidence that supervised physical activity, more frequent contact, or in-person contact were related to effectiveness at 1 year. In meta-regression, calorie counting, contact with a dietician and use of behaviour change techniques that compare participant's behaviour with others were associated with greater loss (-3.3 kg, −1.5 kg and −1.5 kg respectively).

The interventions described are not widely available in comparison with commercial interventions such as Weight Watchers and Slimming World. A systematic review and network meta-analysis of "named diet" programmes including Weight Watchers, Slimming World and Aitkens diets showed all resulted in greater weight loss than controls; no difference was found between low-carbohydrate diets and low-fat diets. (100)

Commercial interventions are usually not as one-off interventions with long periods of subsequent monitoring (as occurs in RCTs) but as intermittent and repetitive interventions as a way to achieve recurrent weight loss after weight regain. No study has measured the outcomes to this approach.

1.7.1.2 Paediatrics

There have been have been no large-scale, long-term, multi-centre RCT studies
of a multi-component intervention in children equivalent to studies such as
LookAHEAD or DPP. Randomised controlled trials have predominantly been
carried out with small sample sizes in the academic hospital setting, with
smaller numbers in primary care and community settings. (101) A 2012 review
found only seven studies had been performed in adolescents, of which 4
specifically targeted girls. (101)

Various systematic reviews have evaluated the outcomes of paediatric and
adolescent interventions.(101-106) Studies that compared an intervention to a
wait-list or no-treatment control group had mean change of BMI of -1.0 kg/m^2 in
children (95%CI 1.91, -0.08) and -1.45 kg/m^2 (-3.02, -0.12) in adolescents at
latest follow-up (3 months to 2 years), with a large amount of variation between
studies (high heterogeneity). (101)

No long-term data on the impact of lifestyle interventions on mortality or
diabetes risk exist in children and young people. Reporting on cardiometabolic
changes associated with interventions has been variable, with less than half of
eligible RCTs reporting any cardio-metabolic outcomes.(101) Lifestyle
interventions which had longer follow-up were associated with improvements in
cholesterol (-0.24 mmol/L, 95% CI -0.30 to -0.17), triglycerides (-0.09 mmol/L,
-0.11 to -0.07) , LDL (-0.3 mmol/l, -0.45 to -0.15), fasting insulin (-55.1 pmol/L,
-71.2 to -39.1), systolic blood pressure (-3.72 mm Hg, -4.74 to -2.69) but not

fasting glucose, HDL cholesterol or diastolic blood pressure. The clinical significance of these short changes in risk factors is unclear.

The individual components of the studies have varied widely, as seen in adults.(103) One systematic review separated out the benefits of dietary and exercise interventions;(107) fourteen studies compared diet-only to diet plus exercise, and 4 studies compared diet-only to exercise-only interventions. The combination of diet plus resistance training led to the greatest gain in lean body mass and reduction in body fat compared to diet alone. When considering macronutrient composition, no difference was detected between low-carbohydrate and low-fat diets. (108)

Family involvement is a key difference between adult and paediatric studies. Epstein undertook seminal work which showed that inclusion of the family in education and behaviour change improved outcomes up to ten years later. (109) Different behavioural approaches have been used, including interventions focussing solely on parents, cognitive behavioural therapy, and family therapeutic approaches. (102, 110, 111). There are insufficient data to compare these different approaches.

Commercial companies such as Slimming World and Weight Watchers both allow adolescents to join their programmes. Slimming World has undertaken evaluation of their adolescent programme, (112) but not weight watchers.

1.7.2 Anti-obesity drugs

The development of drugs as anti-obesity agents has been challenging, with many removed from the market due to side-effects.(113)Previous attempts at anti-obesity drugs have largely targeted the central nervous system to moderate appetite and energy balance. Cardiovascular side-effects (raised blood pressure and heart rate) and changes in mood (particularly increased suicidality) have resulted in the cessation of their development or withdrawal of many of these drugs.

Phentamine, a norepinephrine, dopamine and serotonin releasing agent, was first used in 1959 and continues to be approved for short term adult use in the US but not in the EU. Its combination with fenfluramine, a serotonin releasing agent, (known as fen-phen) was initially found to reduce both their side-effect profiles whilst maintaining their efficacy.(114) However, this agent was subsequently found to result in pulmonary hypertension and valvulopathies and removed from the market.(115)

Sibutramine, a serotonin-noradrenaline reuptake inhibitor was licensed for use in children and resulted in BMI changes of -2.20 (-2.83,-1.57) kg/m^2.(116) It was withdrawn from the market after the SCOUT trial reported increased risk of myocardial infarction and stroke in adults with pre-existing ischaemic heart disease.(117)

Currently only one medication, orlistat (Xenical) is licenced for use in children. Orlistat works by inhibiting lipase activity, thereby lowering fat absorption and

reducing caloric intake. Increased faecal fat results in common side-effects (or treatment effects) such as abdominal pain, urgency and occasionally incontinence when a high-fat diet is consumed.(116) A meta-analysis of orlistat trials showed mean loss of -0.83 kg/m^2 (95% CI −1.19, −0.47) but no differences in triglyceride, cholesterol, glucose or insulin measures in the two RCTs eligible for inclusion.(116)
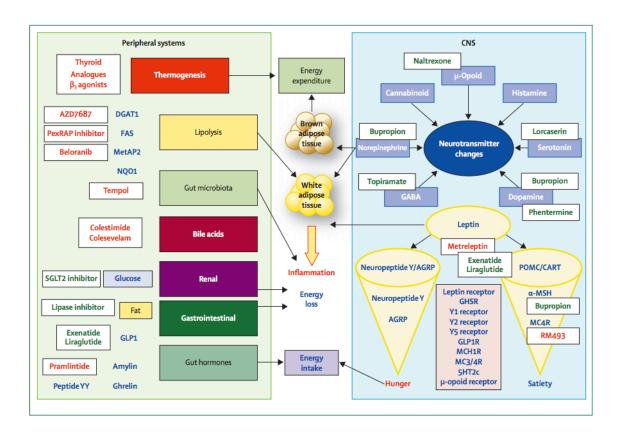
Drugs developed for other conditions have been found to result in weight loss, including metformin and GLP-1 agonists developed for use in diabetes; topiramate and zonisamide in epilepsy; naltrexone used in alcohol and drug dependency; and venlaflaxine and buprion, used as mood stabilisers and anti-depressants.(118, 119) Given the proven safety of many of these drugs, their weight-loss properties have led to them undergoing trials as anti-obesity drugs. Recently approved anti-obesity drugs for adults (but not children) include the naltrexone-buprion combination (known as Mysimba in the EU and Contrave in the US),(120) phentermine-topiramate(121) (known as Qsimia in the US but not approved in the EU) and liraglutide, a GLP-1 agonist. (122, 123)

Metformin is used off-label to treat obesity, predominantly in patients with polycystic ovarian syndrome or insulin resistance.(124) Evidence from the Diabetes Prevention Study showed use of metformin reduced the incidence of type 2 diabetes with modest weight loss. (93) There is modest evidence to support its use in adolescents; a meta-analysis of 5 RCTs lasting at least 6 months showed mean BMI loss of −1.42 kg/m^2 (95% CI −2.02, −0.83). (125) Cardio-metabolic changes associated with metformin use have been reported

less often in studies in children and young people and the meta-analyses of trial data show modest improvements in fasting insulin, but no changes in fasting glucose, HDL cholesterol or blood pressure. (125) There are currently no data to assess the long term effects of metformin in this age group.

Many novel drug targets are being trialled and summarised in figure 1.8 below.

Figure 1.8 White boxes indicate specific drugs located next to the target upon which they are acting. Inside the white boxes green names stand for already approved drugs, whereas red names represent drugs in phase 1–3 development. The right hand panel summarises the neurotransmitters and pathways in the CNS in energy homoeostasis, whereas the left hand panel represents the mechanisms operative in the periphery. The intermediate area represents where the eff ects of both central and peripheral actions converge—namely, on the two main components of the energy balance equation: energy intake and expenditure. From Bray et al 2016. (118)
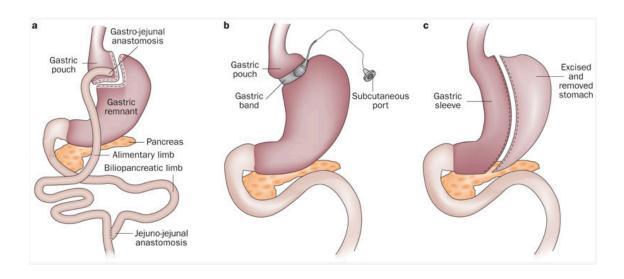
1.7.3 Bariatric surgery

Bariatric surgery describes a group of surgical procedures that intentionally result in weight loss. The jejuno-ileal bypass was first used in the 1950s but has

since been superceded by more modern procedures. The most common

procedures currently being undertaken are the adjustable gastric band (AGB),

sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). (126) Nearly

half a million bariatric procedures were performed globally in 2013 of which 45%

were RYGB, 37% SG and 10% AGB. All procedures are usually carried out

endoscopically and summarised in figure 1.9 below.

Figure 1.9 Summary of bariatric procedures. A = Gastric bypass B = Adjustable gastric band C = Sleeve Gastrectomy. From Miras, Le Roux 2013. (58)

The adjustable gastric band (AGB) is an adjustable silicon band placed around

the upper part of the stomach. It is connected by tubing to a subcutaneous port;

insertion or removal of fluid into this port adjusts the pressure around the band

which influences the size of stomach and the amount of food that can be

ingested at any one time. Many people incorrectly assume that this is the only

bariatric procedure performed and is seen to be a simple, reversible procedure.

The device is removable, but can result in irreversible damage to the stomach wall.

The sleeve gastrectomy involves the irreversible removal of approximately 85% of the stomach along the greater curvature, to form a narrow "sleeve"-like stomach.

The Roux-en-Y gastric bypass is the most studied bariatric procedure and also the most complex of these three procedures. It involves the dissection of the upper stomach resulting in a 15-30ml functioning stomach (known as a "pouch"). The jejunum is divided and anastomosed to this newly formed small stomach so that food passes directly into the jejunum from the stomach pouch. The distal end of the "remnant" (disconnected) gut is re-connected to the jejunum below the gastric-jejunal anastomosis to ensure that secretions from the stomach, biliary tree and pancreas return to the functioning gut. There are various forms of this procedure, depending on the position at which the jejunum is dissected, the positioning of the reconnection of the remnant limb, and the anastomosis type. In addition, a "Fobi ring" can be attached around the stomach pouch to prevent distention.

Surgical complications are largely related to leakage of anastamoses in the peri-operative period, and spontaneous perforation or strictures at a later time. (127) The SG and RYGB require lifelong vitamin supplementation to avoid micronutrient deficiency due to malabsorption. The SG and RYGB are associated with challenging non-surgical complications, including dumping syndrome, gastro-oesophageal reflux and hypoglycaemia. (128)

As with most obesity research, the evidence base is primarily from adult studies and I shall first summarise these before summarising the data from adolescent studies.

1.7.3.1 Adults

The Swedish Obese Study (SOS) was the first long term, prospective trial to provide data on the outcomes of bariatric surgery. The outcomes of this study have been widely published over the last 20 years,(129) and laid the foundations for multiple subsequent randomised studies. It followed up 4047 obese subjects over 20 years, of whom 2010 underwent a bariatric procedure (AGB, RYGB, vertical banded gastroplasty). Patients undergoing surgery were matched with 2037 patients undergoing standard care which involved largely lifestyle treatment and medical treatment of co-morbidities.

The outcomes of SOS were striking, with 20-year weight loss of −18% in those undergoing surgery compared to −1% in the control group. The benefits were not limited to weight loss; those undergoing surgery had reduced mortality (hazard ratio 0.71), diabetes (0.17), myocardial infarction (0.71) and stroke (0.66). Those with diabetes were 8.4 times more likely to be in remission 2 years after surgery and 3.5 times at 10 years.(129-131)

Two recent systematic reviews of RCTs examining bariatric surgery provide strong evidence of the short term benefits of bariatric surgery; one compares bariatric procedures to non-surgical treatment(132) whilst the second additionally compares individual procedures (133). Both show similar results;

bariatric surgery is more effective at achieving weight loss than non-surgical treatments.

Gloy *et al.* performed a meta-analysis using pooled participants from ten studies; those undergoing a surgical procedure had 26 kg (95% CI, −31 to −21) greater weight loss compared to non-surgical treatment. (132) No difference was seen between either AGB and other techniques, or AGB and RYGB when comparing them to non-surgical treatments. In addition to greater weight loss, the relative risk of diabetes remission was 22 times higher (3.2 to 154.2) and metabolic syndrome remission was 2.4 times (1.6 to 3.6) compared to conservative treatments. Furthermore, quality of life was improved in all three studies that measured these domains, with consistent improvements in general health subdomains and physical role in two studies.

Colquitt et al reported similar trends in improvements in weight, diabetes control and quality of life in surgical compared to non-surgical treatments although they did not perform a meta-analysis.(133) They performed comparisons between surgical procedures; RYGB resulted in 5 kg/m^2 greater weight loss compared to AGB (3 studies), although it had longer hospital admissions and a greater number of late major complications. No difference was seen between RYGB and SG, in terms of weight change, quality of life, co-morbidities or complications.

1.7.3.2 Paediatrics

Evidence supporting bariatric surgery in adolescents is limited. Separate to this thesis, I was the second author of a systematic review examining published outcomes of bariatric surgery. (134) We found only a limited number of high-quality studies in this age group including one randomised control trial and two high quality longitudinal studies. The remaining had small cohorts, limited descriptions, and short follow-up duration. Meta-analysis of BMI outcomes at around 1 year after bariatric surgery showed a mean loss of 10.5 kg/m^2 (95%CI −11.8, - 9.14) after adjustable gastric band, 14.5 kg/m^2 (-17.33, −11.73) after sleeve gastrectomy, and 17.2 kg/m^2 (-20.09, −14.31) after Roux-en-Y gastric bypass. (135) . These are similar to those seen in adult meta-analyses described earlier.

The one completed RCT randomised 50 adolescents to either AGB or intensive lifestyle intervention (25 per arm). (136) Two-year outcome data showed greater improvement in BMI z-scores (1.07 v 0.15 respectively), obesity-related co-morbidities and quality of life in those undergoing AGB. Data were limited to two years' follow-up with no ongoing surveillance planned.

Two high-quality ongoing prospective longitudinal cohorts are examining the longer term outcomes of bariatric surgery: Teenlabs, led by Dr Thomas Inge in Cincinnati (OH, USA) and AMOS, led by Dr Torsten Olbers in Gothenburg (Sweden). (137, 138) Teenlabs propectively enrolled 242 adolescents from 5 US centres between March 2007 and February 2012, with 161 (67%) undergoing RYGB, 67 (28%) SG and 14 (6%) AGB. Outcome data at 3-years

were published in 2016 and provide the most complete data available on both complications and changes in BMI, cardio-metabolic health and quality of life in this age group. Mean BMI fell from 53 to 38 kg/m^2 with outcomes between the procedure types not formally compared. In line with adult studies described earlier, co-morbidity resolution was high, with remission of type 2 diabetes in 95% of those with the condition at baseline, hypertension in 74% and dyslipidaemia in 66%.

The AMOS (Adolescent Morbidity Obesity Surgery) study has taken a whole-country approach, and bariatric surgery in Sweden between February 2006 and June 2009 was only offered within this study. (138) It operated from 3 centres with planned follow-up at 1, 2, 5 and 10 years. Only the RYGB procedure was offered, and 81 young people have undergone surgery within this study. Outcome data at 2 years were published in 2012 and 5-year data due for publication. High levels of psychiatric co-morbidities were seen, including 31% having a neuropsychiatric diagnosis and 41% having previous contact with paediatric psychiatric units.

Bariatric surgery for adolescents is potentially fraught with medical and ethical dilemmas. (ref) Optimal timing of surgery is hotly debated, with some arguing that surgery should be postponed until adulthood, and others suggesting that delay results in poorer outcomes and increased health risks. The AMOS-RCT aims to understand the best age to undertake the RYGB and is currently recruiting adolescent participants to received surgery either in early

adolescence (13-16 years) or undergo intensive conservative treatment with delayed surgery at 18 years. (ClinicalTrials.gov identifier: NCT02378259)

1.8 Role of secondary and tertiary care

The NHS commisioning board and the NHS England and Public Health England (PHE) defined a tiered system of weight management services. Tier 1 covers universal services (such as health promotion), tier 2 covers lifestyle interventions, tier 3 covers specialist services, and tier 4 covers bariatric surgery and super-specialist medical services.

There are currently no agreed national specifications for tier 3 services in children and young people. NICE guidance describes the need for tier 3 services that are "multi-component, multidisciplinary and specialist" and are able to assess obesity-related co-morbidities. (139) NHS England is currently reviewing the service provision for tier 3 services across England.

1.8.1 Burden

The current burden of children and young people with obesity is unclear; there are few data and these do not identify if the presentation was related obesity treatments or due to a co-morbidity (associated or not) in a person with obesity.

1.8.1.1 Presentation to primary care

Data from an evaluation of the NCMP showed that families continue present to medical professionals each year wanting obesity-related support; 15% of families with obese children identified in the National Child Measurement Programme (NCMP) had presented to their general practitioner (GP) due to weight concerns. (140) There are qualitative data to suggest that families with

obese children present late due to concerns about being blamed for their

weight, or concerns that the consultation may have a negative impact on their

emotional wellbeing. (141)

1.8.1.2 Hospital admissions

The burden on hospital services has increased greater than four-fold increase in

obesity-associated admissions in England between 2000 and 2009.(142) This

increase was highest in young people aged 15 to 19 years. Similar findings

have been reported internationally, with a near-doubling of obesity-related

hospitalisations seen in the US between 1999-2005. (143) There are few data

about the associated healthcare costs of obesity in childhood with data only

available for US-hospital admissions which have risen from $126 million to $238

million between 1999 and 2005 (143) There are no data estimating the lifelong

financial burden of childhood obesity.

1.8.1.3 Anti-obesity drug prescribing

Anti-obesity drug prescribing data in the UK come from primary care as the vast

majority of drugs are prescribed by general practitioners, either independently

or at the request of specialist doctors. Pharmaco-epidemiology data show very

low prevalence of AOD prescribing in the UK in this age group, (144) with an

estimated rate of 0.091 per 1000 (95% CI 0.07, 0.11) prescriptions for orlistat,

sibutramine and rimonabant in 2006.

1.8.1.4 Bariatric surgery

UK data on incidence of bariatric surgery are available from the UK National Bariatric Surgery Registry (NBSR) and HES data. A total of 62 bariatric procedures in those under 18 between 2011 and 2013 were reported on the NBSR, although it is important to note that it was a voluntary database until 2013. (145). HES data shows an increase from 34 procedures in 2009-2010 to 44 in 2011-2012 in those aged 10-19 years in England (no data available for those under 18 years). (146).

It is not clear where the procedures reported by the NSBR are being performed, what services are provided or their outcomes. To my knowledge, only four centres in the UK are performing bariatric surgery in adolescents: University College Hospital London, Kings College London Hospital, Bristol Children's Hospital and Sheffield Children's Hospital. Three of these centres have published outcomes in conference abstracts reporting a total of 20 patients, which included 11 of the cohort that I will be describing in this thesis. (147) (148) (149). It is most likely that the remainder are being performed in young people aged over 16 years in adult bariatric services in both the NHS and private sector.

The incidence of adolescent surgery in the UK is low compared to the US. Using the National Inpatient Sample, Tsai et al estimated that the numbers of adolescent (<20 years) bariatric procedures performed nationally was stable between 1996 and 2000 but subsequently tripled between 2000 and 2003 to an estimated incidence of 771 procedures nationally or 2.3 (95%CI 1.8-2.9) per

100,000. (150). Subsequent analyses from a different database estimated that that had risen to 1615 procedures nationally in 2009. (151)

1.8.2 Current guidelines

Recommendations in both the US and UK suggest that the role of medical professionals is largely the assessment and management of reversible causes and co-morbidities associated with obesity. In the US, this is largely performed by primary care paediatricians, and in the UK within secondary care. (139, 152, 153) The assessment for causes and co-morbidities associated with obesity is summarised in a document developed by the Obesity Services for Children with Obesity Group (OSCA). (154) Secondary causes of obesity such as hypothalamic tumours, Cushings disease and hypothyroidism are very rare.

The role of the paediatrician in weight control beyond assessment and management of co-morbidities is less clear. In Australia, paediatricians working across secondary and private primary healthcare have reported low confidence in being able to make a difference to a child's weight, despite reporting high confidence in being able to assess and discuss obesity. (155)Primary care paediatricians in New England (USA) perceived that competency in treating obesity was positively correlated with paediatricians counselling families themselves, and negatively correlated with referring families to other professionals.(156) Those who had specialist training were more likely to feel competent, with perceived barriers being lack of time and lack of specialists to whom patients could be referred. A study of paediatricians, paediatric nurses and paediatric dieticians revealed that areas of self-perceived low proficiency

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were the use of behavioural management strategies, guidance in parenting techniques and addressing family conflicts. (157)

A multitude of guidelines have been produced to support the identification and management of obesity including the American Academy of Pediatrics (AAP), (158) The Endocrine Society,(159) the National Institute of Clinical and Care Excellence (NICE)(139) and the Scottish Intercollegiate Network (SIGN). (160) In addition, the Obesity Services for Children and Adolescents Network (OSCA) has produced a guidance focussing specifically on the assessment of childhood obesity in UK secondary care.(153) They largely focus on lifestyle change, and note that drug or surgical treatment should only be used in rare circumstances in children.

1.8.2.1 Lifestyle interventions

Multi-component interventions are the treatment of choice recommended by NICE. (139) Their recommended strategies include:

- Behavioural control strategies including stimulus control, self-monitoring, goal setting with rewards for reaching goals and problem solving.
- Physical activity strategies include 60 minutes of at least moderate physical activity each day in sessions lasting at least 10 minutes each (both structured exercise and incorporation of exercise into daily routines such as more walking), reduction of inactive behaviours such as television or computer games

- Dietary strategies include energy intake below energy expenditure and consistent with "healthy eating advice". The guidelines do not stipulate micronutrient dietary composition.

- Parents who are overweight or obese should be encouraged to lose weight.

Recommendations from SIGN are very similar. Additionally, they recommend that a parent or carer should attend and aim to change the whole family's lifestyle, regardless of their weight status.

Mapping of existing services by NHS England has found that these are usually short-term lasting 12 weeks but ranging from 6 to 52 weeks. (161) These consisted of a range of components, withg 66% being "multi-component" including diet, activity and behavioural change, 17% having two of these components, and 16% having a single component. They were typically commissioned by local authorities and considered to be a "tier 2" intervention. Access to these programmes was via the National Child Measuring Programme, health professionals or self-referral.

1.8.2.2 Anti-obesity drugs

NICE recommends only orlistat in its current guidance(139) following discontinuation of sibutramine since its previous recommendations.(162) The guidance is brief, and is summarised below:

- Drug treatment is not generally recommended for children younger than 12 years.

- In children younger than 12 years, drug treatment may be used only in exceptional circumstances, if severe comorbidities are present. Prescribing should be started and monitored only in specialist paediatric settings.

- In children aged 12 years and older, treatment with orlistat is recommended only if physical comorbidities (such as orthopaedic problems or sleep apnoea) or severe psychological comorbidities are present. Treatment should be started in a specialist paediatric setting, by multidisciplinary teams with experience of prescribing in this age group.

- Do not give orlistat to children for obesity unless prescribed by a multidisciplinary team with expertise in: drug monitoring, psychological support, behavioural interventions, interventions to increase physical activity interventions to improve diet.

- Drug treatment may be continued in primary care for example with a shared care protocol if local circumstances and/or licensing allow.

- Adults and children: If there is concern about micronutrient intake adequacy, a supplement providing the reference nutrient intake for all vitamins and minerals should be considered, particularly for vulnerable groups such as older people (who may be at risk of malnutrition) and young people (who need vitamins and minerals for growth and development).

- If orlistat is prescribed for children, a 6–12-month trial is recommended, with regular review to assess effectiveness, adverse effects and adherence.

Its overall tone is that orlistat should largely be avoided, and when it is used, it should only be prescribed by experienced specialist teams to adolescents with obesity-related co-morbidities. This contrasts to adult guidance (within the same guideline) that states that orlistat can be used in primary care for weight control, without the presence of obesity-related co-morbidities.

SIGN recommendations for use of orlistat are similar to those by NICE, but they recommend a more stringent BMI threshold of BMI > 3.5SD if no co-morbidities are present, or BMI >99.6[th] centile in those with co-morbidities. This contrasts with the standard obesity threshold (>98th centile) used by NICE.(160)

Metformin is not recommended (or even mentioned) in either NICE or SIGN guidance. In the US, it has been recognised as a therapeutic agent in a scientific statement on severe obesity by the American Heart Association (AHA) (163) and guidelines by the Endocrine Society(164) and Institute for Clinical Systems Improvement(165) but not the American Paediatric Association. (158) Given that the APA guidance is the oldest of all current guidelines, their lack of recommendation is possibly due to the evidence-base available 9 years ago. All statements note that metformin is not FDA approved for use in obesity.

1.8.2.3 Bariatric surgery

Existing guidelines for bariatric surgery were reviewed by Aikenhead et al in 2014.(166) They found 15 sets of guidelines including NICE 2006 and 2014 guidance (2014 recommendations for bariatric surgery remain largely

unchanged). The guidelines largely focussed on eligibility criteria rather than focus on details of pre- and post-operative care.

There was a general consensus that bariatric surgery was appropriate for adolescents with severe obesity, although some guidelines stressed that it should be performed only in exceptional circumstances. Previous attempts at weight loss were necessitated by most. The guidelines differed in their eligibility criteria particularly BMI thresholds (mostly 35-40 kg/m^2) and developmental thresholds; most used measures of physical development rather than absolute ages, including Tanner pubertal stage (3 to 5) and bone age.

UK recommendations regarding bariatric surgery in adolescents come from the National Institute of Clinical Excellence (NICE) clinical guideline 43(167) and the Scottish Intercollegiate Guideline Network (SIGN). (160) NICE guidance key recommendations are displayed below. Key points are that bariatric surgery is not generally recommended for children or young people under 18 years, that bariatric surgery should only be considered in exceptional circumstances and that patients should have achieved or nearly achieved physical maturity. SIGN guidelines are largely similar but less explicit, namely that puberty must have been completed, have BMI should be >3.5 SDS and participants must have severe co-morbidities.

NICE guidance states:

- Surgical intervention is not generally recommended in children or young people. [2006]

- Bariatric surgery may be considered for young people only in exceptional circumstances, and if they have achieved or nearly achieved physiological maturity. [2006]

- Surgery for obesity should be undertaken only by a multidisciplinary team that can provide paediatric expertise in:

  - preoperative assessment, including a risk-benefit analysis that includes preventing complications of obesity, and specialist assessment for eating disorder(s)

  - information on the different procedures, including potential weight loss and associated risks

  - regular postoperative assessment, including specialist dietetic and surgical follow up

  - management of comorbidities

  - psychological support before and after surgery

  - information on or access to plastic surgery (such as apronectomy) when appropriate

  - access to suitable equipment, including scales, theatre tables, Zimmer frames, commodes, hoists, bed frames, pressure-relieving mattresses and seating suitable for children and young people undergoing bariatric surgery, and staff trained to use them. [2006]

  - Coordinate surgical care and follow-up around the child or young person and their family's needs. Comply with the approaches outlined in the Department of Heath's A call to action on obesity in England. [2006, amended 2014]

- Ensure all young people have had a comprehensive psychological, educational, family and social assessment before undergoing bariatric surgery. [2006, amended 2014]

- Perform a full medical evaluation, including genetic screening or assessment before surgery to exclude rare, treatable causes of obesity. [2006]

1.9 Thesis overview

In summary, obesity is a complex, persistent, and potentially intractable disease with impact across the lifecourse. New approaches are clearly needed. In this thesis I will focus on a range of interventions that aim to improve weight control and health in adolescents attending health services.

2   Methods

The methods used in each chapter are described within each chapter.

Further details of quality of life and mental health questionnaires are outlined in appendix 9.1.

3 Feasibility and acceptability of a brief office-based adolescent weight management programme

3.1 Abstract

Background: The mainstays of obesity interventions are community-based group programmes and multidisciplinary programmes. Some have been developed for the lone practitioner in the outpatient (office) setting, but not specifically for adolescents. No adolescent interventions exist for the lone clinician in the outpatient (office) setting. We adapted HELP, an existing lifestyle modification to develop a novel brief intervention and conducted an early feasibility and acceptability study. We used tools from motivational interviewing and solution focused therapy to optimize engagement and behaviour change.

Methods: HELPclinic consisted of 5 sessions delivered monthly. We initially aimed to test this intervention using a randomized control trial with waiting-list control. Due to recruitment issues, we changed this to a simple pre-post study and widened eligibility criteria; ultimate eligibility criteria being young people aged 12-18 years, BMI between 98th centile and 45 kg/m^2 seen for the first time in an obesity service between 17th October 2010 and 3rd April 2012. Exclusion criteria included monogenic obesity syndromes, conditions known to promote obesity and significant mental health problems. Primary outcomes: a) Feasibility: measured in terms of recruitment, ability of all staff members to deliver the intervention and attrition; b) Acceptability: measured using semi-

structured telephone interview participants and staff. Secondary outcomes were BMI change over the course of the programme.

Results: A total of 111 new patients were seen; 55.9% were eligible (n=62), 59 were invited to join the study of which 26 (44.1%) enrolled. Patients aged above 16 years appeared less likely to be eligible, and those from deprived populations less likely to enrol. Half of participants (13/26) completed the programme. The specialist nurse was the only permanent member of staff to successfully deliver the intervention. Senior doctors believed they had inadequate skills and time, and all staff members felt that a specialist nurse was the most appropriate intervention provider. Four overlying themes were captured in participant interviews: HELPClinic relationships enabled discussions of a difficult topic; lack of novel medical approaches polarised participants' acceptance of HELPclinic; School vs HELPclinic – it's hard to do both; and ongoing support is crucial. Mean BMI change was -0.15 (95% CI -0.54, 0.2) kg/m^2 with individual BMI trajectories +/- 2.5 kg/m^2.

Conclusions: Early trialling of HELPclinic shows encouraging potential for a subgroup of participants who want support to achieve lifestyle changes aligned with mainstream lifestyle recommendations.

3.2 Introduction

The current gold standard of obesity interventions recommended in the UK by the National Institute for Health and Care Excellence is the multi-component lifestyle intervention. (139) Despite this, families continue to present to medical professionals each year wanting obesity-related support; 15% of families with obese children identified in the National Child Measurement Programme (NCMP) had presented to their general practitioner (GP) due to weight concerns. (140) The details of their weight concerns are not known, nor are there estimates of how many of them have accessed tier two community programmes prior to seeking medical support.

There are few data related to primary care attitudes towards managing obesity in the UK. In the US and Australia, where primary care is often delivered by paediatricians rather than general physicians, surveys have shown that paediatricians have little confidence in managing weight. In Australia, paediatricians working across secondary and private primary healthcare have reported low confidence in being able to make a difference to a child's weight, despite reporting high confidence in being able to assess and discuss obesity. (155) Primary care paediatricians in New England (USA) perceived that competency in treating obesity was positively correlated with paediatricians counselling families themselves, and negatively correlated with referring families to other professionals. (156) Those who had specialist training were more likely to feel competent, with perceived barriers being lack of time and lack of specialists to whom patients could be referred.

Some of these children may be referred to specialist tier 3 services if available. The range of interventions for young people available once in specialist services is limited; recent service mapping by Public Health England found little evidence of tier 3 service across the country, with the majority of respondents in a survey reporting having no service, and only 9% of local authorities and 2% of clinical commissioning groups (CCG) reporting a tier 3 service. (161)

Public Health England are in the process of undertaking a systematic review of the evidence base for tier 3 services in the UK (unpublished). (168) It included only twelve studies, of which four were camp interventions, one school-based, two pilots of group-based lifestyle interventions, (169, 170) (171), one commercial group programme (Slimming World) (112), one small individualised programme for children with severe obesity, (172) one study using a mandometer to retrain eating behaviours, (173) and two studies from a hospital-based obesity service (174, 175) including one that compared hospital and primary-care delivery of obesity services. (175).

As described earlier, the majority of adolescent interventions included in systematic reviews have been trialled within the complex obesity clinic (176-179). They are usually multi-component and multi-disciplinary interventions with high associated costs which are usually not available in standard settings.

We developed HELPclinic to fill this gap. HELPClinic is a brief outpatient lifestyle obesity intervention for a solitary practitioner in the office (outpatient) setting. We challenged the belief that obesity interventions need to be prolonged and high-intensity to be successful, and developed a low intensity

pragmatic adolescent programme that could be delivered by a single clinician in any outpatient (office) setting.

We used techniques from two brief therapy techniques, motivational interviewing (MI)(180, 181) and solution focused therapy (SFT)(182, 183), that have been developed with the aim of enabling behaviour change within a brief intervention. Neither use analytical tecniques, and have been used by non-mental health professionals in a variety of health settings, including obesity. (184) These techniques encourage participants to resolve ambivalence about behaviour change, and develop their own solutions to solving their own solutions. (184)

3.2.1 Motivational interviewing (MI)

MI is a type of conversation about change, particularly ambivalence about change. (185-187) The "spirit" of MI is based on three key elements: collaboration (equal status between clinician and participant, rather than expert-recipient); evocation (seeks to arouse and strengthen the participants own motivation and commitment rather than imposition of motivation); and autonomy (the patient ultimately makes the decisions, not the clinician). The principles that guide the practice are expressing empathy, supporting self-efficacy (belief that participants have the capabilities to change for themselves), "rolling with resistance" (avoiding and de-escalating conflict) and developing discrepancy (mismatch between participants current actions and both their current beliefs and future goals).

Key tools used are:

1 Agenda setting: the participant rather than the clinician defines the agenda for the consultation, focusing on the issue of behavior they are most able to tackle.

2 Affirmations: clinician notices actions and behaviors that promote change towards the desired goal, noticing the resources that made them possible and acknowledging the difficulties that they have experienced.

3 Decisional balance: discussion and comparison of the advantages and disadvantages of changing, and staying the same.

4 Readiness to change: participants use a 10-point Likert scale (10 being the highest) to rate the importance of change, their confidence in being able to change, and its priority against other pressures. Breaking down readiness to change into these 3 measures allows discussion of likely factors that will allow and inhibit changes.

5 Reflective listening: clinician summarizes what they have heard and understood, as a way of developing an empathetic and correct interpretation of the participant's situation.

6 Sharing expert advice: any advice or medical opinion is conveyed not as an instruction from the clinician, but as a piece of evidence to be discussed and considered.

3.2.2 Solution focussed therapy (SFT)

SFT seeks to enable the participants to find their own solutions to problems rather than understand the underlying causes of these problems. (182, 188)

The clinician aims to help the participant uncover intrinsic skills and strengths that can enable these solutions, without making any therapeutic interpretations. Key tools used are:

1   Problem-free talk: the clinician aims to develop an understanding relationship with the participant, evoking their skills, strengths and life situation that is unrelated to the problem, enabling a relationship that is not solely about the problem.

2   Exception-seeking: times that problem has been less severe or absent are discussed in detail, noticing the participant's own skills, resources and abilities that have enabled these actions.

3   Identifying solutions: participant identifies their own solutions to problems, rather than being told by the clinician how to solve the problem.

4   Scaling questions: a ten-point Likert scale is used to rate their current position against the desired future where the problem is solved. Questions are used to elicit the factors that made it possible to be at their current position, describe the changes they would notice should they find themselves higher up the scale, and understand what situation would be good enough for them.

5   Miracle question: a future scenario without the problem is imagined and richly described by the participant, including the changes that they would see, and the impact it would have on themselves and those around them.

6   Scaling questions: a ten point Likert scale is used to rate their current position against the desired future where the problem is solved. Questions are used to elicit the factors that made it possible to be at their current

position, describe the changes they would notice should they find

themselves higher up the scale, and understand what situation would be

good enough for them.

7   Externalisation: a problem is personified as if it were a third party allowing

detachment of the problem from the person.

3.2.3 Existing literature

Similar brief interventions for obesity have undergone RCT evaluation using

techniques from motivational interviewing (189-192) and solution focused

therapy (193) although these studies have largely been in younger children

seen in primary care.

The High Five for Kids Study used MI techniques within nurse-led consultations

as part of a complex intervention for children aged 2-7 years, including service

re-configurations, clinical support tools, the training of paediatricians in

negotiation skills at routine medical visits and seven additional nurse contacts

over the first year. (190) They found a small, non-significant reduction in BMI at

one year and some improvements in obesity-related behaviours compared to

controls, (190) but these differences disappeared at two years. (192)

The BMI[2] study (Brief Motivational Interviewing to reduce Body Mass Index) is

the intervention most similar to HELPclinic. Participants aged 2-8 years were

allocated to three groups; standard care (group 1), standard care plus 4

additional counselling sessions from their primary care physician (group 2) and

group 2 plus an additional six MI sessions from a research dietician over two

years (group 3). There was a modest, but statistically significant difference between groups, with the greatest change seen in group 3 (4.9 BMI percentile points) followed by group 2 (3.8) and finally group 1 (1.8). Dieticians had difficulties providing sessions to those in group 3, with greater differences seen in patients with higher attendance rates. No other outcome measures were reported.

An adolescent intervention (CHOOSE HEALTH) using predominantly cognitive behavioural techniques used a single session of motivational interviewing at the start of the programme as part of a cross-over study design. (194) No difference in final outcomes was detected between those whose initial session included MI techniques and those who had a standard assessment interview.

Solution focussed techniques were used in the LEAP (Live, Eat and Play) trial in children aged 5 to 10 years. (193) Participants attended 4 consultations over 12 weeks with their GP after being given an individualised plan based on screening baseline questionnaires. No differences in BMI status between intervention and control groups were detected at 15 months. Small improvements in fat consumption in milk, and physical activity levels were detected but not self-reported child health status, body satisfaction or appearance/self-worth. The intervention was further tested in the LEAP 2 trial within similar limited findings. (195)

A study of primary care paediatricians in Italy delivering 5 sessions of MI over the course of a year to families with children aged 4-7 years detected improvements in BMI at 1-year but not 2-years compared to controls who

received standard care. (191, 196) Greater improvements were seen in children

of mother with high and medium education and a negative effect in those with a

low level of education.

3.3 Methods

HELPclinic was developed and evaluated using research methodologies set out by the Medical Research Council guidance for developing and evaluating complex interventions. (197) Changes were made to study design and eligibility during the evaluation in line with MRC recommendations to ensure the intervention and its evaluation fulfilled the needs of the clinical population.

3.3.1 Content development

HELPclinic was derived from HELP (Healthy Eating Lifestyle Programme), a lifestyle programme developed for clinical psychologists using behavioural tools from motivational interviewing and solution focused therapy to promote behavior change. It has been delivered both in the clinical setting by psychologists and the community by health care graduates. (198, 199)

Dietary and exercise advice adhered to NICE (162) and contemporary macronutrient composition recommendations (200, 201). Box 1 summarizes the behavioural tools used in HELP and HELPclinic.

Written materials are used to facilitate exercises, promote later recall and provide further information. Diary templates are provided to enable monitoring of dietary intake and physical activity.

HELPclinic is a shortened version of the HELP programme, cut from twelve sessions delivered every two weeks to five sessions delivered monthly. We (BW & DC) retained and condensed the key lifestyle components from HELP

reported to be most helpful by prior participants, namely promotion of regular physical activity and healthy eating and discussion of the impact of restrictive diets.

Prior to this evaluation, we conducted pre-trial development and early evaluation of the HELPclinic programme within a regional weight management clinic. (202) We added two additional components, specifically discussion of medical screening results and tracking of weight and height at each session. Appendix 1 describes the individual components of the original HELP intervention, and identifies components retained in HELPclinic.

3.3.2 Eligibility

All new patients attending an outpatient (office) weight management service between 17th October 2010 and 3rd April 2012 were invited to participate in the study. Our initial eligibility criteria were as follows: patients aged 12-18 years inclusive with a BMI greater than 98th centile but below 40 kg/m^2 were initially eligible to enrol. (8) We excluded patients with monogenic obesity syndromes, any chronic illness or medication known to promote obesity, significant mental health problems, poor command of spoken English, and those unwilling to take part with a family member or who had taken part in a weight management programme within the previous year. Due to poor recruitment we subsequently widened our criteria on 1st July 2011 to include those with BMI up to 45 kg/m^2 and included those who had previously been prescribed an anti-obesity drug.

3.3.3 Study design

We initially aimed to conduct a randomized controlled pilot of HELPClinic, using waiting list controls who would wait 4 months to start the intervention. After 6 months and only 2 patients initiating the study, we changed the trial methodology from a waiting list control randomized trial to an uncontrolled mixed methods observational study. Neither had been randomized to the control arm. Pre-existing waiting lists for physician assessment and medical investigations together with control arm waits were deemed both clinically inappropriate and incompatible with recruiting sufficient participants in the study period.

3.3.4 Consent

Consent was gained from parents and assent from young people. Patients were offered appointment times to suit their schedule, where possible. In the event of non-attendance, patients were contacted and offered a further appointment to cover the session they missed. We assumed attrition if participants missed a session and we were unable to contact them on two separate occasions.

3.3.5 Outcome Measures

3.3.5.1 Primary outcome measures

The primary outcome measures were feasibility and acceptability. Feasibility was measured in terms of participant recruitment and retention, and ability of staff members to deliver the intervention. Baseline characteristics of participants

and eligible non-participant were compared to assess for possible barriers to enrolment.

Acceptability was measured using qualitative semi-structured telephone interviews with participants (young people and parents) and clinicians. One clinician delivering the intervention was also the main investigator(BW), and as such, was not interviewed to minimise bias. Interview outlines are presented in appendices 2-3 and included questions to ascertain opinions about active components, reasons for drop out, efficacy, ideas for improvement and which participants would be most suited to this intervention. Three questions from the Session Rating Scale were used to quantify acceptability and adherence to MI principles. (203) Participants were interviewed by KD, and clinicians by JD; both were from the same institution but not the same clinical team as the clinicians. Up to three attempts on three different days were made to contact all families. Detailed notes were taken during and after the interviews, but due to limited resources, interviews were neither recorded nor transcribed.

3.3.5.2 Secondary Outcome Measures

The secondary outcome measure was BMI change between first and last session. Since this was not a feasibility and acceptability trial, it was not designed to have sufficient statistical power to detect BMI changes or improvements in health usually seen in obesity lifestyle interventions. Body weight and height were measured at each session using a Tanita BC-418MA scale and wall mounted stadiometer, respectively. BMI was calculated as

weight /height^2 (kg/m^2) and zBMI calculated using the LMS method and UK reference data.(8)

We had initially planned to collect further secondary outcomes, namely change in cardio-metabolic risk factors and psychological function. We removed these measures due to high attrition from the programme, and subsequent non-attendance in the clinical service making collection of post-intervention measures challenging.

3.3.6 Baseline measures

Baseline measures were collected to characterize the sample. These included demographic data, cardio-metabolic makers and psychological function.

We initially established glucose tolerance status with a standard [1.75 g/kg body weight (up to 75 g)] oral glucose tolerance test (OGTT). Plasma glucose and insulin concentrations were measured at 0, 30, 60, 90, 120 minutes after a 12–hour overnight fast. In an attempt to shorten and simplify the investigation pathway, we subsequently use only baseline HbA1c, fasting glucose and insulin to measure glucose tolerance and an OGTT only undertaken in those with HbA1c >6.5% (204). Blood pressure was measured using automated blood pressure monitor (Datascope Accutor Plus) (205) with appropriately sized cuff. High blood pressure was defined as above 98th centile. (206) Lipid levels were stratified following US National Heart, Heart, Blood and Lung Institute recommendations. (207) Metabolic syndrome was diagnosed using International Diabetes Federation criteria. (208)

Baseline ethnicity, socio-economic status, and mental health status were routinely collected for all new patients attending the clinic. Socio-economic status was derived from the patient's home postcode using the 2007 Index of Multiple Deprivation (IMD) score and rank (England only), grouped into ten deprivation deciles (decile 10 = most deprived).(209) Ethnicity was self-reported using a standard list used by the hospital.

Quality of life and mental health status was measured using validated questionnaires. Generic quality of life was measured using the PedsQL 2.0 questionnaire (210, 211) and weight-specific quality of life using the IWQOL-kids. (212) Psychological distress was measured using the Strengths and Difficulties Questionnaire (SDQ). (213, 214) Depressive symptomatology was measured using the Short Moods and Feelings questionnaire (SMFQ) (215) using thresholds derived from UK data. (216) Self-esteem was measured using the Rosenberg Self-Esteem Scale (RSE). (217, 218) Disordered eating was measured using the Eating Disorder Examination - Questionnaire (EDE-Q) (219, 220). We compared questionnaire scores of those enrolling to both eligible non-enrollers and normative data using two tailed student t-test.

3.3.7 Clinician training

All long-term team members (consultant paediatricians, specialist nurse) and the research medical Fellow were trained to deliver the intervention in two half-day workshops delivered by a consultant clinical psychologist trained in MI and SFT. Ongoing clinical supervision from a clinical psychologist was provided to those delivering the intervention.

3.3.8 Data analysis

3.3.8.1 Primary outcomes

Feasibility was evaluated through descriptive analyses of recruitment, retention and numbers of session attended. Access to HELPclinic was assessed by comparing baseline demographics, and psychological function questionnaire scores using student t-test and chi squared test.

Qualitative data were analysed using thematic analysis. (41) Anonymised notes taken from telephone interviews with participants were read and coded independently by KD and BW (participant interviews) and by JD and BW (clinician interviews). Memos were written to summarise and synthesise emerging themes. BW, JD and KD developed models through an iterative process, in which the initial model was reviewed using constant comparison techniques (in which successive items of data are appraised and compared to ensure the code is reflective of all) and the models revised accordingly.

3.3.8.2 Secondary outcome

Paired t-tests were used to compare change in BMI from baseline to last-attended session.

3.3.9 Study approval

The study was reviewed and approved by the West London REC3 NRES Committee (reference 10/H0706/53), and registered at the UCLH Research & Development Department.

3.4 Results

3.4.1 Recruitment

A total of 111 young people aged 12 to 18 years were referred to the clinical service during the recruitment period. Of the 111 assessed, 62 (55.9%) were eligible for the intervention. Medical co-morbidities resulting in exclusion were Prader-Willi syndrome (n=1), hypothalamic-pituitary dysfunction (n=3), type two diabetes (n=1), achondroplasia (n=1), and complex unexplained symptoms (n=3). Mental health co-morbidities were depression with suicidal ideation (n=2), severe anxiety (n=2), ADHD requiring special schooling (n=2) and complex emotional difficulties not clearly defined (n=3).

Recruitment flow is shown in Figure 3.1 below. Fifty-nine young people (95% of eligible) were therefore invited to join the programme (the remaining 3 were not invited due to administrative errors). Of 59 invited, 26 (44.1%) enrolled in the study. Reasons for non-enrolment were not formally collected.

Table 3.1 below shows patient eligibility and recruitment by age and by deprivation. Three patterns are noted. First, older patients appeared less likely to be eligible, particularly those aged 15 years and older. Second, uptake in those eligible appeared fairly constant across all ages, with the exception of those aged 14-15 years who had higher uptake. Third, eligible subjects from the most deprived populations (lowest decile) appear less likely to enrol.

Figure 3.1 CONSORT diagram summarising recruitment into HELPclinic
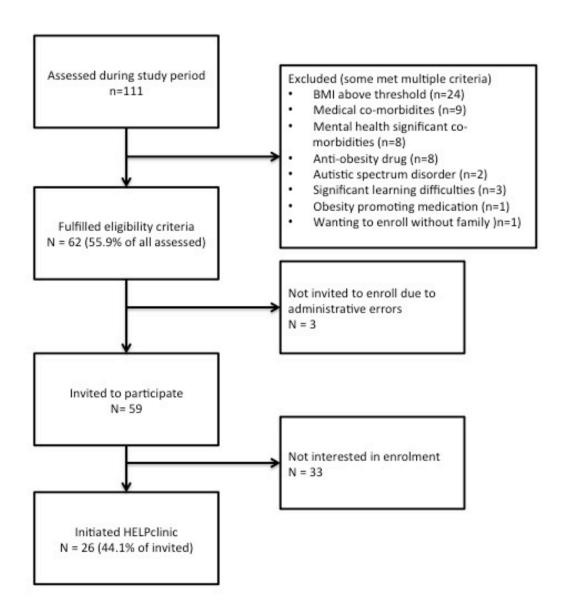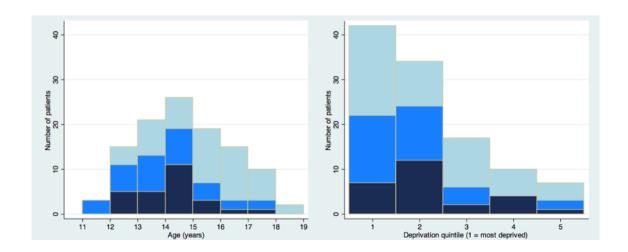
Table 3.1 (next page) Demographics of whole group, eligible v non-eligible, and recruited vs not recruited. Deprivation quintile 1 = most deprived. P values reported are for student-t or chi2 tests comparing recruited and non-recruited groups.

	Whole group	Eligible	Not eligible	HELPclinic recruited	Not recruited	p
N	111	62	49	26	33	
Female (n,%)	70 (63.1)	35 (56.5)	35 (71.4)	13 (50.0)	20 (60.6)	0.4
BMI (mean, SD)	39.0 (7.6)	35.9 (4.3)	42.9 (9.0)	35.0 (3.3)	36.3 (4.5)	0.2
zBMI (mean, SD)	3.47 (0.57)	3.21 (0.40)	3.71 (0.67)	3.23 (0.33)	3.31 (0.43)	0.4
Age (mean, SD)	14.8 (1.6)	14.3 (1.5)	15.4 (1.6)	14.2 (1.2)	14.2 (1.6)	1
Distance (mean, SD)	25.0 (58.5)	15.5 (18.9)	37.0 (84.3)	13.7 (12.6)	13.9 (20.5)	1
Ethnicity (n,%)						
British	50 (45.1)	23 (37.1)	27 (55.1)	10 (38.5)	11 (33.3)	
African &/or Caribbean	24 (21.6)	11 (17.7)	13 (26.5)	6 (23.1)	5 (15.2)	
Asian	12 (10.8)	9 (14.5)	3 (6.1)	1 (3.9)	7 (21.2)	0.1
Other	16 (14.4)	13 (21.1)	0	9 (34.6)	0	
Missing (n,%)	9 (8.1)	6 (9.7)	3 (6.1)	0	6 (18.2)	
Deprivation (n,%)						
Quintile 1	42 (37.8)	23 (37.1)	19 (38.8)	7 (26.9)	15 (45.5)	
Quintile 2	34 (30.6)	24 (38.7)	10 (20.4)	12 (46.2)	12 (36.4)	
Quintile 3	17 (15.3)	8 (12.9)	9 (18.4)	2 (7.7)	4 (12.1)	
Quintile 4	10 (9.0)	4 (6.5)	6 (12.2)	4 (15.4)	0	0.09
Quintile 5	7 (6.3)	3 (4.8)	4 (8.2)	1 (3.9)	2 (6.1)	
Missing	1 (0.9)		1 (2.0)	0	0	

Figure 3.2 below shows patient eligibility and recruitment by age and by deprivation. Three patterns are noted. First, older patients appeared less likely to be eligible, particularly those aged 15 years and older. Second, uptake in those eligible appeared fairly constant across all ages, with the exception of those aged 14-15 years who had higher uptake. Third, eligible subjects from the most deprived populations (lowest decile) appear less likely to enrol.

Figure 3.2 Eligibility and recruitment into HELPclinic by age (left) and deprivation status (right). Grey = not eligible, light blue = eligible but did not enroll, dark blue = enrolled in HELPclinic

Quality of life and mental health data were available for 23 participants (88.4% of cohort) and 26 eligible non-participants (78.8% of cohort) with varying levels of questionnaire completion. Compared to non-enrolling eligible participants, there was evidence that girls who enrolled into HELPclinic had higher levels of food restraint. There was no other difference in any scale.

3.4.2 Participant details

All 26 participants had baseline blood pressure measurement and 24 had cardio-metabolic blood tests at UCLH (1 refused and the other had recent blood testing prior to referral). 23 young people and 23 parents completed baseline quality of life and mental health questionnaires. Results are summarised in Table 3.2 below and table 9.5 (appendix).

Additional co-morbidities were non-alcohol fatty liver disease (n=3), hyperlipidaemia (1) hypertension (2), insulin resistance (7), hypothyroidism (1), pubertal delay (2), precocious puberty (1), developmental delay (1), dyspraxia (1), mild learning difficulties (2), iron deficient anaemia (1), irritable bowel syndrome (1), constipation (1), gastro-oesophageal reflux disease (5), chronic lower back pain (3), chronic knee pain (1), nocturnal enuresis (2), tension headaches (6), gynaecomastia (6), asthma (5), eczema (2), acne (1), vitamin D deficiency (4) and social anxiety (1).

Table 3.2 Summary of cardiometabolic, quality of life and mental

health status of HELPclinic participants**.**

	Questionnaire completant (where applicable)	Incidence (percentage)
Cardio-metabolic		
High blood pressure		6/26 (23.1%)
Raised lipids		10.24 (41.7%)
Impaired glucose tolerance / pre-diabetes		4/24 (16.7%)
Quality of life and mental health		
Low quality of life	Young person	7/23(30.4%)
	Parent	12/23(52.2%)
Low self-esteem	Young person	9/23(39.1%)
Raised psychological distress	Young person	6/23(26.1%)
	Parent	8/23(34.8%)
Raised risk of depression	Young person	6/23(26.1%)
	Parent	9/23(39.1%)
Raised levels of disordered eating	Young person	6/22(27.2%)
Raised levels of eating secondary to external triggers	Young person	7/23(30.4%)
Raised levels of eaten secondary to emotional triggers	Young person	7/22(31.8%)
Raised levels of food restraint	Young person	13/23(56.5%)

All families were invited to participate in qualitative telephone interviews, with 54.8% (14/26) participating. This comprised 5 young person and parent dyads, 5 young people alone without their parents, and 4 parents without their children. Patients of both treating clinicians were represented, 9 from one clinician and 5 from the other. Both completers and non-completers were represented, being 8/14 (57.1%) attending all 5 sessions, 3/14 (21.4%) attending one session and one each (7.1%) attending 2, 3 and 4 sessions. Participant details are summarized in table 9.6 (appendix).

3.4.3 Feasibility - programme delivery and retention

Half of all participants (13/26; 50.0%) attended all sessions (designated as completers) over a median time of 5.2 months (range 3.9 to 7.0 months) of whom only 3 missed a session which was later conducted. Of the non-completers, 3 (11.5%) attended 4 sessions, 5 (19.2%) attended 3 sessions, 1 (3.9%) attended 2 sessions and 4 (15.4%) attended 1 session.

There appeared to be no difference between completers and non-completers in terms of sex, baseline BMI or age, or deprivation status although this was not formally tested due to risk of type 2 error.
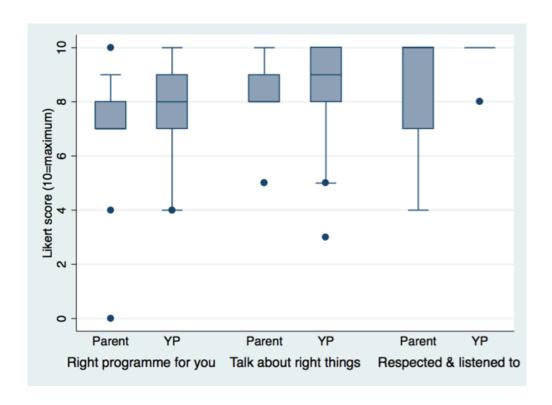
The medical research fellow and clinical nurse specialist completed training and delivered the intervention. Consultants undertook the training but were unable to deliver the intervention. We were unable to train dieticians or junior paediatric trainee doctors as they undertook 6-month rotational posts that were deemed to be of insufficient duration to allow patient continuity or develop sufficient skills.

3.4.4 Acceptability – participants.

3.4.4.1 Quantitative feedback

Median (interquartile range) likert scores for feeling respected and listened to were 10 (7,10) for parents, and 10 (10,10) for young people (10=highest score). Median (IQR) scores for talking about the right things were 8 (8,9) for parents, and 9(8,10) for young people. Median (IQR) scores for the programme being right for participants were 7(7,8) for parents, and 8(7,9) for young people. Scores are summarised in Figure 3.3 below.

Figure 3.3 Acceptability of programme. Bars show median (horizontal line in box), interquartile range (upper and lower hinge of box), upper adjacent value (adjacent line of whiskers) and outside values (single points beyond whiskers).

3.4.4.2 Qualitative feedback

Four themes were identified in the participant interviews.

3.4.4.2.1 Theme 1: HELPclinic relationships enabled discussion of a difficult topic

Almost all participants expressed some form of difficulties in addressing their weight. Comments such as "I was nervous before coming", "it is daunting and stressful being weighed", and "sometimes it's embarrassing, talking about things with an adult" (mother of participant 10) summed up many participants'

attitudes about HELPclinic and past experiences. Mediators included previous unhelpful experiences with clinicians, multiple clinicians in a consultation, having a staff member who was not their clinician performing weight measurements, and both the body habitus and gender of the clinician.

"No-one wants to talk about being overweight" (participant 2)

"On the second appointment it was [with] a man because the lady wasn't in. I found it easier to talk to a man. [prompt]. Yeah, I really didn't want to talk to a woman. (male participant 3)

For most, the relationship between participant and clinician was of key importance and it allowed them to tackle this difficult topic. Almost all appreciated the nature of the relationship between the family and their clinician, in particular its holistic, non-critical, and supportive nature that focused on the young person but included the parents. For one young person, the nature of the relationship was insufficient to overcome the difficulty in talking about obesity.

"It was nice to have something that was non-critical. We talked about the good things, and I didn't fear having a bad day because I wouldn't get told off. I felt really included." (YP21)

"It wasn't the programme, it was me. I was too embarrassed." (YP6)

The positive relationships that participants developed with their clinicians were contrasted with previous critical, prescriptive and parent-focused interactions with healthcare professionals.

"It was a really good positive atmosphere [in HELPclinic]. Doctors aren't always nice but [name] was" (YP21)

"Previously we has seen dieticians and people like that and they just tell you what to do and tell you that you are fat with a chart in their hand. This approach was not helpful." (mother of participant 25)

3.4.4.2.2 Theme 2: Lack of novel medical approaches polarised participants acceptance of HELPclinic

Participants described the programme as having a lack of new medical approaches to managing obesity, with varying acceptance of this.

Some were looking for novel ways to control weight, and were unhappy that the activites used in HELPclinic were all alighned with contemporary weight control advice. One mother described her daughter as having difficulty leaving the house and wanted more emotional support. One father found the solution-focused approach unhelpful; he felt the team should be providing answers, not himself, particularly new solutions to control his daughter's obesity.

"Not to be rude but it was condescending. No I mean patronising. She knew all of the information. It was very basic." (Parent 4)

 "She has a problem with eating. No talking is going to help that. There were more questions asked to us than answers. We went to the hospital for them to tell us not for us to tell them…

For others, the activities and behavioural approaches that were used to enable contemporary weight control advice were sufficient for them to value the intervention. They wanted help in adhering to standard weight management advice and found regular weighing, monitoring, use of food and activity diaries, the opportunity to discuss weight loss advice, weight targets (including BMI) and medical results to be helpful components. In addition, the use solution-focused approaches, where participants are encouraged to develop with their own solutions rather than be told what to do, were seen by some as beneficial.

"It was useful to write things, and that way she could come up with ideas of what she could do or add ….She would try and impress [name of clinician] and please him. She wanted to show him how determined she was and that she could do it. He didn't tell her what to do." (Mother of participant 25)

3.4.4.2.3 Theme 3: School vs. HELPclinic; it's hard to do both

Third, conflicting demands were described as having critical importance, both in terms of being able to attend the session and being able to make changes between the sessions. Many described a decisional balance between attending the programme and missing school. Key mediators were availability of after-school appointments, time taken to get to the hospital and differences in school stage (time of year and school year). After-school appointments at a location nearer home were suggested to minimize impact on school and avoid the unacceptable cost of travelling to the sessions.

"Appointments during school time are not ideal as it is embarrassing to explain that you need to go to the hospital because you are fat. After school appointments would have been preferable." (Mother of participant 21)

"At the time I was doing GCSEs at school so I lost track and missed appointments…. School was just more important at that time." (Participant 3)

"Our appointment times were after school which was ideal. I think that they should only offer first thing in the morning or after 4pm, specifically for this age group" (Mother of participant 5)

3.4.4.2.4 Theme 4: Varying needs for ongoing support

Almost all described the importance of the supportive nature of HELPclinic. They wanted differing levels of support, in terms of frequency of contact, forms of contact, and overall duration of contact.

The frequency of sessions was deemed important, with the perceived ideal interval being influenced by both the perceived level of ongoing support to enable behavior change, and the time needed between sessions for change to occur independently. Most liked monthly sessions, although one suggested that this permitted a brief period of relapse after each session.

"I liked that the sessions were once a month. They gave something to work towards" (Mother of participant 10)

"The frequency was just right for me. I didn't exactly look forward to the sessions but it was good to be able to go every month. I was good to be able to

have a week to let my hair down but still have enough time to get back on track for the next appointment." (Participant 21)

Some wanted access to more frequent support between sessions, although this was not necessarily in the form of additional fixed sessions; they suggested more frequent sessions, emails and tweets as ways of optimizing motivation. None of the interviewees referred to the summary letters that were sent to participants after each session that were devised to enhance motivation.

"Because the sessions were so long between one another it meant that if something came then I could not get the help quick enough" (Participant 25)

"Emailing between sessions I think would improve the programme. I think every month is fine for visits but some other contact in between would be good to keep it in mind. Contact between would help with the motivation because the monthly session is the goal but a reminder to keep motivation around would have been good" (Mother of participant 10)

Many of those who completed the programme wanted ongoing support after the end of the programme. They described how their difficulties addressing obesity described previously meant that five sessions were insufficient to fully engage with the programme and enable sufficient behaviour change.

"The first session was scary because [name of clinician] is obviously very [physically] fit. This can be quite depressing for people who are overweight. However, we warmed to [clinician's] approach and now we miss him. I do not

think the programme was long enough for it make a change." (Mother of participant 21).

Group sessions were suggested as a way of providing support. These were deemed by some to be less embarrassing than individual sessions, and could be used for peer support, and education.

"Maybe if it was to be in a group of people in the same situation and then I saw other people asking questions and then if they got an answer that I thought was helpful, then maybe I would have been able to ask my own questions. This would have increased my confidence I think. Maybe not at first but after some time. [Name of clinician] was always asking me if I had any questions and I think that even if I did have a million questions I don't think I would have been able to ask them." (Participant 2)

3.4.5 Acceptability – clinical staff

All three consultants and the specialist nurse were interviewed. Recall of the programme was generally good. Overall, clinicians described a sense of unease about the role of HELPclinic within a specialist obesity service and described a need to carefully consider its content and role. Three themes arose.

3.4.5.1 Theme 1: HELPclinic is too different to usual practice

All three consultants described their inability to deliver the programme was due to it being too different to their usual practice. They described how it "takes doctors out of their comfort zone" and is "a big departure for doctors". They all felt inadequately skilled, and needed more training than had been offered. One

described the transition between training and delivering the intervention as " a big jump" and others described needing "more time to practice and develop micro-skills". In addition to lack of skills and increased training needs, they described HELPclinic as a greater burden than usual practice due to its longer and more frequent sessions. It required "a different pace to normal clinics", and as such did not fit into their standard medical clinics. One suggested that HELPclinic sessions should be ring fenced into separate clinics. The medical fellow and specialist nurse had been able to do this, but other clinicians did not have the time and job flexibility to be able to do so. All clinicians believed that a specialist nurse was the most appropriate team member to deliver this intervention.

3.4.5.2 Theme 2: HELPclinic is not enough for weight loss

Clinicians did not consider HELPclinic to be a weight loss intervention. One clinician reported "some good weight losses" but noted "these are often not sustained". Rather, they saw it as a programme that was often effective at achieving weight neutrality and "help[ing] people to stop gaining weight". The key components were the "motivational and solution focused approaches used". One clinician described himself as "a big believer in motivational interviewing" and another described the relationship that it nurtured as being "key" its success. There were suggestions that changes to the programme could result in improved outcomes. "My belief is that with behavior change people need regular support", described one clinician. Clinicians hypothesized that patients needed to be seen every one to two weeks for the intervention to be successful,

as is practice in interventions such as weightwatchers and slimming world. "Offering something less than is offered on the outside [i.e. weightwatchers/slimming world] doesn't make sense", reported on clinician.
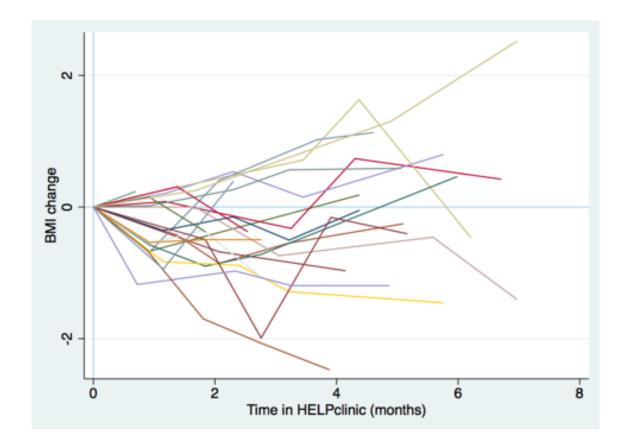
3.4.5.3 Theme 3: Where does this fit in obesity management?

Third, there was a lack of consensus about the role of HELPclinic within a complex obesity service. Clinicians were confused about patient pathways, and described a need for "a more consistent approach". There was a general sense that HELPclinic was not appropriate for the most complex patients, such as those with severe obesity who would benefit from bariatric surgery or those with significant mental health problems. Rather, it was seen as an "entry level intervention" that could be used in schools, primary or secondary care, or within specialist nurse or dietetic clinics "as a formalized way of approaching conversations around weight with a light touch".

3.4.6 Secondary outcomes

Mean BMI change between first and last attended sessions was -0.15 (95% CI -0.54, 0.2) kg/m^2 and zBMI was -0.04 (-0.08, 0.00). Individual BMI trajectories are shown in Figure 3.4 below. BMI changes ranging from -2.5 to 2.5 kg/m^2 were seen over the course of the programme.

Figure 3.4 Individual change in BMI over time from start of intervention.

3.5 DISCUSSION

3.5.1 Main findings

HELPclinic was successfully delivered in the paediatric outpatient setting by a specialist nurse and medical fellow but not by more senior doctors. The intervention was deemed worthwhile by some participants, but not others. The relationship and activities helped those who wanted to initiate behaviour change aligned with routine paediatric weight control advice, and needed support doing so. In contrast, the programme was deemed insufficient for those who wanted medication, prescriptive advice, increased understanding of underlying causes of obesity, novel treatments, or more practical support.

The style of interaction resulting from the behavioural approach was popular and resulted in good patient-clinician relationships. Techniques from MI and SFT were effective in making young people feel heard and allowed them to make their own decisions. Participants largely valued the nature of the relationship between clinician and family. Participants had varying perceived needs, and expressed desire for differing levels of ongoing support, with suggestions of additional support through email and group sessions.

Clinic referral rates and study enrolment rates were all lower than expected. Enrolling patients into this intervention was challenging, despite active promotion with local general practitioners and general paediatricians using invitation letters, hospital newsletters, and educational programmes. We recruited at a time of changing local services, with increased funding for local

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community-based group interventions. As such, patients who were ultimately referred to our service had more complex needs than had been anticipated when we developed this programme. Only half of all new patients seen in clinic were eligible, with eligibility being particularly low in those aged 15 and above.

Less than half of eligible patients enrolled in the intervention. Few baseline differences were seen between eligible participants and non-participants. Patients from deprived populations appeared less likely to enrol, but this was not statistically significant and girls who enrolled had higher levels of eating restraint. Informal feedback collected during patient recruitment suggested multiple reasons for non-enrolment, including travel times and cost, lack of suitable appointment times, and wanting other treatment modalities such as a low calorie meal plan and exercise programme.

Difficulties in recruiting and retaining study participants, and waiting lists for initial assessments and investigations resulted in the decision to abandon the control arm, and use an observational methodology to better understand the feasibility and acceptability of the intervention. The choice of a waiting list RCT to measure the intervention resulted in a further 4-month wait in those who were allocated to the control arm; this was deemed clinically unacceptable to staff and patients and alternative control groups should be used in future studies. This change in methodology impacted on our ability to estimate the weight change associated with the intervention however other valuable lessons were learnt.

Half of all participants completed the interventions. Qualitative feedback suggests that school pressures together with the cost and time taken to travel to our centre were major causes of attrition. Attrition was markedly higher compared to the earlier pilot of this intervention where all participants completed the intervention. (202) Patients in the earlier pilot were existing patients in the clinical service rather than new patients, and were selectively invited to join the intervention. Given this, it is likely that careful patient selection is key to successful completion.

Senior doctors were unable to deliver the intervention due to time pressures and perceived insufficient skills. Everyone felt that a specialist nurse was the most appropriate professional to deliver the intervention. They were unsure of the role of the programme within a complex obesity service, and felt it was more suited for patients in primary and secondary care who need support to stabilize weight gain.

Although this feasibility study was not specifically designed to evaluate weight loss outcomes, the intervention was associated with a modest decrease in zBMI over the course of the programme. Paired t-test suggests this intervention is associated with a small decrease in zBMI over the course of the programme. At the individual level, we saw a wide range of BMI change (+/- 2.5 kg/m^2). Qualitative evaluation showed some participants were gaining weight prior to the intervention, and even a cessation of weight gain was deemed a success. Future inclusion of pre-intervention BMI trajectories could allow a more detailed analysis of the trajectories associated with this intervention.

3.5.2 Comparison with the literature

Unpublished pilot data for 20 patients undergoing HELP in the clinical setting and delivered by clinical psychologists showed a mean reduction of 1.7kg/m^2 over 6 months. No change in BMI was detected in its evaluation in the community setting with graduate health workers.(199) It should be noted though that HELP was delivered by graduate health workers rather than trained health professionals, and did not include feedback of medical results or serial weight monitoring.

Few brief interventions for single practitioners have been tested in this age group, with the majority being trialled on younger children. The one adolescent intervention discussed in the introduction detected no change in BMI. (221)

Previous pilot studies of obesity interventions undergoing development have shown modest pilot data but subsequently showed positive outcomes in a larger randomized controlled trial. (222, 223) This should encourage ongoing development of this intervention.

Both frequency and causes of attrition were in line with those reported in other weight management programmes. (224, 225) Attrition in specialist obesity programmes ranges from 32% to 73%, and conflicting school and work demands, appointment timing and cost were also reported across different programmes.

3.5.3 Strengths and Limitations

The use of mixed methods has resulted in important insights into the practicalities of delivering this intervention within a complex obesity service. The qualitative interviews delivered rich data that will allow further development of this intervention. A range of opinions were heard, making sampling bias less likely.

We were unable to record or transcribe the qualitative interviews due to limited resources. Analyses were based on notes taken during the interviews, and as such, are potentially open to misinterpretation. To minimize error, the researcher undertaking the interviews took extensive notes during and after each interview and was involved in interpretation of the data. Interviews were analysed by one of the clinicians delivering the study together with the interviewer who was external to the clinical team as a way to minimise bias.

We did not have the resources to record the sessions and record their fidelity to MI principles, and further evaluations could include this.

We were unable to measure change in BMI or cardio-metabolic risk factors post intervention due to high levels of attrition, and limited capacity within the clinical service to easily monitor patients after the intervention.

3.5.4 Implications

In line with most obesity interventions, we aimed to recruit a uniform patient group into this study in order to produce results that were comparable, generalizable and reproducible. As such, we excluded subjects with co-

morbidities such as diabetes, mental health problems, or obesity-promoting conditions. Patients had higher levels of co-morbidities and greater body mass than expected and as a result, less than half fulfilled pre-determined eligibility criteria. Arguably, we excluded those attending a weight management serice who were most in need of a weight management program, and further work is needed to ensure that the needs of this group are met.

Both levels and causes of attrition were in line with those reported for other weight management programmes. (224) As with most studies, we aimed for rapid recruitment, and we did not actively address common causes of attrition when recruiting. Further iterations could ensure that timing, competing commitments (especially education), financial restraints, and perceived needs are incorporated into programme planning and delivery. This would require careful consideration of the trial methodology and could potentially make testing the intervention within a RCT challenging.

Part of the aim of this study was to test the feasibility of delivering the intervention within the context of a randomised control trial so that lessons could be learnt about trial methodologies for future large scale trials. Having a waiting list as a control arm was not popular with potential recruits who had already waited for their clinic appointment and again their medical investigations. We partly resolved this by replacing oral glucose tolerance tests with a single HbA1c measure as a way to exclude type 2 diabetes; these tests were performed on the day of the medical assessment and eliminated further waits. Either way, neither patients nor clinicians found a wait list control group to be

acceptable and it was abandoned. Future iterations could consider the use of a standardised single education session as a control arm.

Obesity interventions are ultimately about improving health, and mean BMI change is a crude measure of change in health status. We attempted to repeat cardio-metabolic blood markers post-intervention however this failed due to post-intervention attrition from our service and difficulty getting them back for blood tests. Similar difficulties have been experienced in adolescent bariatric surgery trials, and researchers have needed to go to the home of patients to collect blood samples and undertake measurements. (137) Some patients appeared to not be able to differentiate between the clinical service and the trial, and did not want to return for follow-up or consider other therapies

Other non-invasive reliable repeatable measures could be included at appointments to monitor changes in health status and gain a better understanding of the true outcome of this study, such as simple fitness tests. (226) This could allow tracking of progress through the programme and could potentially be seen as a motivator, in the way that regular weighing is perceived. We attempted to track waist circumference with varying success due to variability of measures between clinical staff. Other measures of body anthropometry could be used in future evaluations.

We followed contemporary paediatric obesity treatment recommendations and did not restrict macronutrient intake below recommended standard daily requirements. It is maybe not surprising that we did not see large magnitudes of weight loss over the course of this programme. Baseline questionnaires showed

high levels of pre-existing dietary restraint, and disordered eating; it is not clear if this programme is sufficient to reverse these habits. Larger studies that are powered to allow subgroup analyses are needed to better understand which subgroup may benefit from this approach.

The findings of this study are compatible with benefit, and future iterations should be undertaken taking the findings of this study into consideration. Results from this study suggest that future iterations of this programme should:

- Be offered at the right time within the context of the adolescent's willingness to change and conflicting priorities, especially education.

- Include better explanation of programme components prior to enrolment, to ensure it aligns with participant expectations, particularly weight loss expectations.

- Those wanting novel approaches should be offered alternative programmes, and we should consider other approaches including meal replacement, trialing of new satiety medications, and other behavioural approaches.

- Consider individualization of programme (both content and frequency), to ensure it fulfils the needs and expectations of participants. Systematic reviews and our own qualitative feedback show a range of expectations from participations that cannot be addressed within a single uniform intervention

- Include a broader range of participants, especially those at high risk of future cardiovascular poor health, such as those with type 2 diabetes and obesity syndromes.

- Consider delivery of the intervention in primary and secondary care. Alternative approaches such as teleconferencing could also be considered as this could eliminate the financial and time burdens of travel. However, it should be noted that the HELP trial was delivered close to the home, and did not produce outcomes that were different to controls.

- Use of other RCT trial methodologies to avoid the difficulties associated with introducing delays into a clinical service, such as testing of the intervention against standard care or against written advice.

- Ensure that the needs of those from deprived populations are met to allow them to partake in the intervention.

- Be delivered by specialist nurses rather than doctors, and possibly other allied health professionals such as dieticians, exercise physiologists, or physiotherapists.

3.6 CONCLUSIONS

Early trialing of HELPclinic within a secondary care outpatient obesity service shows encouraging potential. Behavioural techniques from motivational interviewing and solution focused therapy resulted in supportive relationships between participants and clinicians, particularly for those wanting support to adhere to mainstream lifestyle recommendations. Some families attending a tertiary obesity clinic wanted novel lifestyle approaches and were dissatisfied with this approach. All clinicians believed that allied health professionals rather than doctors were the most appropriate to deliver this intervention. The BMI outcomes were consistent with modest benefit which were deemed acceptable by some participants, particularly those who had previously been gaining weight. Further development and evaluation are warranted to explore the potential role of this intervention.

4 Understanding Young People's Experiences of Anti-Obesity Drugs

4.1 Abstract

Background: Only two anti-obesity drugs (AOD) are frequently prescribed in paediatric obesity, orlistat and metformin. Meta-analyses show modest benefit in clinical trials yet analyses of prescribing databases show high levels of discontinuation in routine clinical practice. Increased understanding of young people's experiences taking AOD could result in improved prescribing and outcomes.

Methods: Semi-structured interviews with young people aged 13 to 18 years and their parents from 3 specialist obesity clinics, analysed using a general thematic coding methodology.

Results: Theme saturation was achieved after interviews with 15 young people and 14 parents (13 parent-child dyads). Three models were developed. Model 1 explored factors influencing commencement of AOD. Six themes emerged: medication as a way out of obesity, enthusiasm and relief at the prospect of pharmaceutical treatment, last ditch attempt for some but not all, passive acceptance of medication, fear as a motivating factor, and unique treatments needed for unique individuals. Model 2 described the inter-relationship between dosing and side-effects; side-effects were a significant experience for many young people and few adhered to prescribed regimens, independently changing lifestyle and dosage to tolerate medications. Model 3 described the patient-led

decision process regarding drug continuation, influenced primarily by side-effects and efficacy.

Conclusion: Use of anti-obesity drugs is challenging for many adolescents. Multiple factors were identified that could be targeted to improve concordance and maximise efficacy.

4.2 Introduction

The role of medications in the management of obesity in children and young people is unclear. In the UK, the National Institute of Health and Clinical Excellence (NICE) suggests anti-obesity drugs (AOD) may have a role in treatment of young people over 12 years of age with very high BMI or obesity comorbidities. (139) Currently only one drug, orlistat, is licensed in the UK as an AOD in children. In addition, metformin is used off licence predominantly in obese subjects with insulin resistance. (125) There are no current data to compare relative usage of these two drugs, however it is likely that metformin is more widely prescribed, especially by endocrinologists and gynaecologists in subjects with type 2 diabetes, insulin resistance and polycystic ovarian syndrome. Systematic reviews of metformin and orlistat, show small reductions in BMI; orlistat by 0.83kg/m^2 (116) and metformin by 1.4kg/m^2.(125) Whilst these clinical trials suggest the benefits of AOD may be very small, even small reductions in BMI can be important in growing children and adolescents. Primary care prescribing of these drugs has increased 15-fold in the UK between 1998 and 2007. (144)

Despite encouraging trial results which have evaluated the safety and efficacy of AODs, pharmacoepidemiological studies show that medication discontinuation rates outside the trial environment are very high in both children (144) and adults. (227) Analysis of a national primary care prescribing database found 45% of orlistat prescriptions were discontinued after one month, and approximately 10% of children and young people remained on the drug for 6

months after initiation. (144) The reasons for these high rates of discontinuation are unclear. Metformin and orlistat have high rates of gastrointestinal side-effects which may limit their use. (228, 229) However there are no published data regarding patient experience of AODs in young people. Qualitative investigation of young people's experiences allows the generation of hypotheses regarding reasons for early discontinuation.

We undertook a qualitative investigation of experiences associated with AOD prescribing and use in adolescents in the UK in order to inform potential strategies to improve AOD use and therefore efficacy in young people.

4.3 Methods

We used a qualitative design utilising an in-depth, semi-structured interview schedule for young people and parent/carers developed by a multi-disciplinary team (two psychologists, two paediatricians, a pharmacist and a patient representative). The schedule contained questions regarding decision processes to take the AOD, expectations of AOD outcomes, experiences of AOD usage, understanding of mechanism of drug action, outcomes of AOD usage and suggestions for improved outcomes.

Young people aged 12-18 years were eligible if they had BMI $\geq 98^{th}$ centile(230)and were prescribed orlistat or metformin for weight control within the last 3 years. Exclusion criteria were 1) use of metformin for management of diabetes, pre-diabetes or polycystic ovarian syndrome in non-obese young

people 2) inability to participate in a face-to-face interview or 3) insufficient English to participate.

Young people were recruited from 3 paediatric obesity clinics in England (London, Bristol and Liverpool) through the Medicines for Children Research Network. We anticipated requiring approximately 10-20 families to achieve theme saturation. (231) Based on our previous difficulties recruiting participants into obesity studies, all one hundred and nine subjects fulfilling eligibility criteria were invited by their hospital doctor to enroll in the study. Those consenting were invited to interview, together with one parent and each given a £10 gift voucher as participation compensation.

Face-to-face interviews were conducted in the participant's own home by one researcher (LJ) experienced in interviewing young people. Parent/young person dyads were independently interviewed unless either of the dyad opted out or wished to be interviewed together. Written assent for under 16 year olds and consent for those over 16 were obtained from both the young person and parent/carer. Interviews were audio recorded and field notes written immediately after the interview.

4.3.1 Analysis

Audio recordings from each interview were transcribed verbatim and anonymised by LJ. Transcripts and field notes were read and coded independently by LJ and a sample coded by BW using a general thematic coding methodology(232) Memos were written to summarise and synthesise

emerging themes. This initial coding framework was used to code the

subsequent transcripts and new codes were added as they emerged using a

constant comparative technique to compare new and previously collected data

to understand emerging themes. To ensure reliability, BW read all transcripts

and reviewed the coding. BW and LJ developed models through an iterative

process, in which the initial model was reviewed using constant comparison

techniques (in which successive items of data are appraised and compared to

ensure the code is reflective of all) and the models revised accordingly. The

qualitative analysis was facilitated by the use of NVivo software - QSR

International (UK) Limited, Southport, UK.

4.3.2 Study approval

The study was reviewed and approved by the NRES Committee London –

Surrey Borders REC reference number 11/LO/1020.

4.4 Results

The interviews took place between January and May 2013; each lasted between 24 minutes and 1 hour 35 minutes. Theme saturation was reached after views from 16 families were collected. There were 13 parent and young person dyads, two young people without parents (one carer was not available and one did not speak English) and one parent alone (the young person did not wish to be interviewed). Four families (25%) were recruited from Bristol, 1 (6%) from Liverpool and 11 (69%) from London. Self-reported weight change ranged from no change to 12.7kg loss.

Young people were aged 13 to 18 years, 12 (75%) were female, and 12 identified themselves as white British (the remaining identified themselves as White Jewish, Caribbean, British Bangladeshi, and British African). All carers interviewed were female.

Ten participants (63%) were prescribed metformin only; 8 continue to take metformin. Four were prescribed (25%) orlistat only; none continue on the drug. Two were prescribed both (13%) both metformin and orlistat; two continue on metformin and one continues on orlistat. Participants continued with the medication for between 1 month and 8 years. 9 of 12 prescribed metformin, and 1 of 6 participants prescribed orlistat continued beyond 6 months. 7 young people discontinued an AOD.

Participant-reported co-morbidities included insulin resistance, type 2 diabetes, asthma, hypothyroidism, epilepsy, androgen excess, obsessive-compulsive

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disorder, depression and hypertension. Participant demographics are summarised Table 4.1 below.

Three conceptual models were developed from the emerging themes. Models were a) the factors influencing the commencement of an AOD, b) the management of side effects, and c) decision to terminate the drug including balancing efficacy and side-effects. Below we relate the emergent themes within each model.

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Table 4.1 Self-reported demographics, comorbidities and weight trajectories whilst on an anti-obesity drug

ID	Interviewees	Age (Years)	Sex	Ethnicity	Self-reported co-morbidities	AOD + Duration	Self-reported weight change
1	YP + Mother (together)	18	F	White British	Underactive thyroid, borderline diabetes. Polycystic ovaries.	Metformin (4 years: ongoing) Sibutramine (1 year: stopped) Orlistat (1 month: stopped)	2 stone (12.7kg)
2	YP + Mother (separately)	17	F	White British	None	Orlistat (9 months: stopped)	1.5 stone (9.5 kg)
3	YP + Mother (separately)	16	F	White British	Underactive thyroid,suspected polycystic ovaries	Orlistat (3 months: stopped)	None
4	YP + Mother (separately)	16	F	White British	None	Orlistat (6 months: stopped)	None
5	YP + Mother	13	M	White British	None	Metformin (2 years:	None
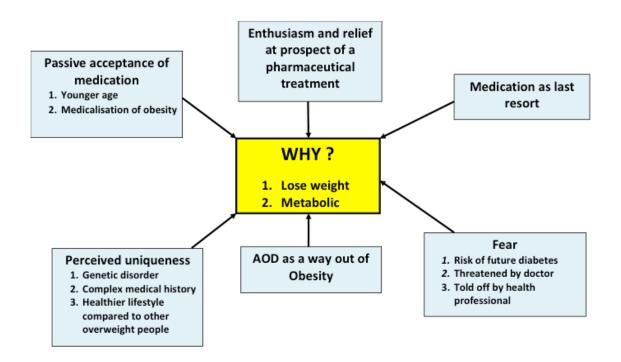
ID	Interviewees	Age (Years)	Sex	Ethnicity	Self-reported co-morbidities	AOD + Duration	Self-reported weight change
	(separately)					stopped)	
6	YP + Mother (separately)	14	F	White British	Genetic disorder (leptin receptor missing)	Sibutramine (1 year: stopped) Orlistat (2 months: stopped)	Maintenance only
7	YP + Mother (together)	14	M	White British	Raised blood sugars	Metformin (3-4 months: ongoing)	Unknown
8	YP only	16	F	British Bangladeshi	Type 2 diabetes, high level of male hormone	Metformin (4 years: ongoing)	Dropped a clothes size
9	YP + Mother (separately)	17	F	White British	Glucose intolerant, depression	Metformin (4 years: ongoing)	None
10	YP + Mother (separately)	14	F	White Jewish	Underactive thyroid, insulin resistant	Metformin (15 months: ongoing)	Weight maintenance
11	YP + Mother (together)	14	F	White British	Osgood-Schlatter, Insulin dependent [not on insulin]	Metformin (18-24 months: ongoing)	No weight loss but possibly clothes size

ID	Interviewees	Age (Years)	Sex	Ethnicity	Self-reported co-morbidities	AOD + Duration	Self-reported weight change
12	YP only	16	F	Caribbean	Asthma, need to regulate insulin levels	Metformin (2 years: ongoing)	About a quarter of a stone (1.6kg)
13	YP + Mother (separately)	13	F	African/ British	Complex medical conditions including seizures and insulin resistance	Metformin (9 years with 4 year intermission: ongoing) Orlistat (18 months then 15 months: ongoing)	Weight maintenance/ small amount of weight loss at times
14	Mother only	17	F	White British	Bone condition	Metformin (6 months then 7 years: ongoing)	7-8 pounds (3.2-3.6 kg)
15	YP + Mother (separately)	15	M	White British	Periodic fevers, anaemia	Metformin (1 month: stopped)	None
16	YP + Mother (separately)	14	M	White British	High blood pressure	Metformin (4 months: ongoing)	4 kg

4.4.1 Model 1: Factors influencing why young people commenced on an AOD

Model one is summarised in Figure 4.1 below. Six themes fed into the decision by young people to take the AOD: passive acceptance of the AOD, enthusiasm and relief at the prospect of a drug treatment, medication as a last resort, fear as a motivating factor, AOD as a way out of obesity and their own perceived uniqueness.

Figure 4.1 Model 1 - factors influencing the commencement of an anti-obesity drug

4.4.1.1 Theme 1: Passive acceptance of medication

In all cases the doctor suggested an AOD to the young people. Young people's views were mixed; many had reservations about initiation and there was a

general feeling that they should follow the doctor's advice. Passive acceptance was especially likely when the doctor medicalised obesity by highlighting the increased risk of co-morbidities such as type 2 diabetes, and where patients were younger.

"At the time I was thinking, well if it is stopping her from becoming totally diabetic, then the best thing for her to do is to take it, I suppose" (Parent 9)

"I remember them saying to me 'you haven't lost any weight, you have gone up, so let's use this' and I am like 12/13 years old, what am I supposed to do at this age?" (Young person 12, aged 16)

4.4.1.2 Theme 2: Enthusiasm and relief at the prospect of a pharmaceutical treatment

Many participants wanted a novel solution for obesity control and described the potential of a medicine helping them with weight control as "*awesome*"' (Young person 12, aged 16 years) and "*exciting*" (Young person 8, aged 16 years). One participant described how the doctor "*made it sound like a miracle cure – he made it sound like it was going to fix all of my problems*" (Young person 9, aged 17 years). However, some young people felt disappointed that they were not able to lose the weight without medication.

"I felt incredibly relieved that there was something that could help her" (Parent 14)

4.4.1.3 Theme 3: Medication as a last resort.

Timing of drug initiation was an important factor, both in terms of timing in relation to other treatments, and in relation to readiness to controlling obesity. Many viewed an AOD as a "last resort" in obesity management. Some had tried all other treatment modalities with insufficient long lasting benefits, including changes in diet and exercise, partaking in programmes such as "Slimming World" and "Weight Watchers", and "gastric band hypnotherapy" (Young person 5).

> "I think I was at my wits end so anything was better than nothing" (Parent 13).

In contrast, others felt that they were put on the medication before they had had a chance to fully explore other treatment modalities, including management of eating disorders. One young woman said, "if I wasn't binge eating I think there would have been an impact [on my weight]" (Young person 6, aged 14 years).

Families saw an AOD as an alternative to, rather than part of, a treatment package that included lifestyle changes.

> "... and it was just about like, well okay then, if this is the last resort, but in some ways I don't think it was" (Young person 12, aged 16 years).

The importance of controlling weight at the time of drug initiation was varied. This ranged from the belief that they would be able to control weight in the future without a drug to others wanting additional support immediately.

"if I was referred to it a year later or two years later I don't think it would make too much difference" (Young person 15, aged 15).

4.4.1.4 Theme 4: Fear as a motivating factor

Participants initiated AOD due to three types of health-related fears. Firstly, parents and young people were both concerned and confused by discussions with clinicians about diabetes; any mention of diabetes increased their acceptance of the AOD. Young people's concerns were amplified if their parents or grand-parents had obesity-related conditions.

"It is because I am concerned that [my son] does not set up health problems for himself in later life and if we can avoid diabetes that to me seems a very good thing to do indeed while he is struggling to get his weight down, not only for diabetes itself, but all the related things that come in its wake. So that seemed to be absolutely excellent." (Parent 15)

"…I know that I have to get the weight off for health reasons, because like family members in the past have had lots of health things, especially on my Mum's side and being overweight will affect those things and make them worse or make me more susceptible to them which I don't want" (Young person 9, aged 17).

Secondly, some young people described feeling threatened by their doctor who told them that they would have to undergo bariatric surgery if weight loss was not achieved; they saw surgery as a "*last resort*" (Young person 6, aged 14

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years) or "*final straw*" (Young person 9, aged 17 years) which they wished to avoid.

Thirdly, participants described a fear of being told off or patronised by clinicians, particularly dieticians, in regard to either continued weight gain, lack of exercise, or diet.

> "I didn't really find her [the dietician] very helpful. I think I need guidelines. And it was just oh, you need to eat healthily. I didn't really find her useful...... [she] ask(ed) me what I eat and it made me feel guilty then. I know that that is kinda what the aim is but do that as well as help me. Not just make me feel bad." (Young person 3, aged 16 years)

> "For the first two years they wanted me to see the dietician and all you ever got were these really skinny bitches (mind my language) who just patronized you and said eat healthily and I am, like I have been coming here two years already, I already know what I am meant to do, and no matter how hard I try nothing is happening and you are not helping." (Young person 9, aged 17 years)

4.4.1.5 Theme 5: AOD as a way out of obesity

For some young people, an AOD was seen as a 'way out' of obesity. Young people had their own personal reasons for wanting to lose weight. Some were emotional, and in these cases they saw the AOD as a way out of being bullied, feeling self-conscious or a way to alleviate their feeling of "desperation" (young

person 9, aged 17 years). Others had lifestyle reasons for wanting to lose weight, which included improved fitness and ability to wear certain clothes.

> "Just to help me lose weight because at the time I was feeling really self-conscious." (Young person 13, aged 13 years)

> "I want to just fit into a medium [sized clothes]". (Young person 8, aged 16 years)

4.4.1.6 Theme 6: Perceived uniqueness
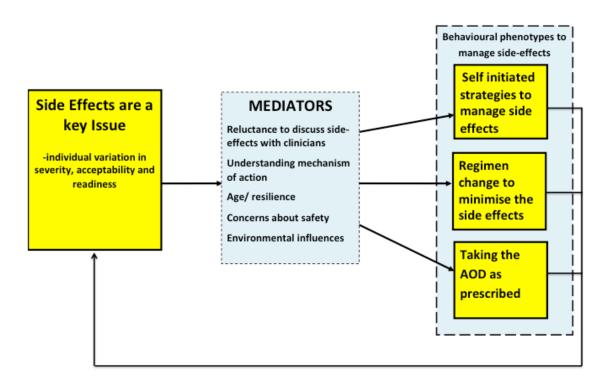
Some young people considered themselves to be "unique" either because they had a complex medical history or a genetic tendency to obesity and thus felt they needed specialised treatment to help them with their weight. Some believed that they were unlike other overweight young people, in that they did not have a sedate lifestyle or poor diet, but were incorrectly judged by others as doing so.

> "It is not that I eat a lot, it is just because of my…I can't remember what it is called, they think it has something to do with my complex medical issues 'cos I don't eat that much" (Young person 13, aged 13 years)

4.4.2 Model 2:   Management of side effects

Model 2 is summarised in figure 4.2 below.

Figure 4.2 Model 2 - management of side-effects

Side effects from AODs were a key issue for many young people, although a

minority did not experience any. Side effects of both metformin and orlistat were

usually gastro-intestinal, particularly abdominal cramps and diarrhea. For some,

this involved spending "many, many hours on the loo" (Young person 15, aged

15 years, metformin), and "really weird, intense pain" (Young person 1, aged 18

years, metformin). Some were taken aback by the severity of the side effects;

one young person reported "I have never seen diarrhea like it" (Young person 6,

aged 14 years, orlistat), while another said "we were told that there could be

mild stomach upsets or whatever but I didn't expect it to be as uncomfortable as

it was" (Young person 15, aged 15 years, metformin). A few young people

attributed unusual symptoms to metformin, including hand tremor, headaches

and change in moods.

Parents expressed concern about their children having to experience such unpleasant side effects. One mother felt that it was "*totally wrong*" for her daughter to have such side effects at her age (Parent 6 - Orlistat).

> "It was awful and he would do it [faecal incontinence] in his trousers and he would phone me up and say Mum, I need to come home."
> (Parent 5)

4.4.2.1 Mechanisms to manage side-effects

Nearly all young people were prepared to endure some side effects as their doctor had forewarned them. However, there was variation as to how much each individual tolerated these side effects; some continued taking the medication despite episodes of faecal incontinence while others stopped with much milder side effects. Some young people appeared more resilient than others in coping with side effects.

Some initiated self-devised lifestyle strategies or changes in drug regimen to minimise side effects; we identified a number of key likely mediators that influenced how these side effects were managed.

4.4.2.2 Regimen change to minimize the side effects

Regimen changes were devised and initiated by both doctors and families. Some young people used orlistat flexibly and omitted doses to minimize side-effects at pre-determined important times. Firstly, this allowed them dietary freedom at special occasions such as birthdays and secondly, it minimized side-effects in certain environments or events, such as school-time or during exams.

"I stopped [the medication] because I didn't want to take them during the exams in case I had a bad stomach it would take time off [the exam]" (Young person 2)

Doctors at times recommended changes in formulation, dosage and frequency to minimise side-effects.

"They [doctors] changed her metformin dose and changed it to slow release. Then after that they changed the time she was taking it. It would help her a bit more." (Parent 1, metformin)

"With the higher [initial] dosage I was vomiting more….. by breaking it down to two in the morning and two in the evening, I think it [vomiting] is a lot better. " (Young person 8, aged 16 years, metformin)

In contrast, some young people reported discussing side-effects with their doctors but were told that their symptoms would improve if they continued with the current regimen.

[I was] "…just told to take it and get on with it really" (Young person 5, aged 13 years).

4.4.2.3 Alternative self-initiated strategies to manage side effects

Families reported a range of self-initiated strategies to cope with the side-effects, particularly diarrhea and faecal incontinence. These included taking

spare clothes to school in case of incontinence, not leaving the house or taking additional medication to counteract the effects.

> "….she would start taking loperamide [anti-diarrheal medication] to counteract the effects of it … a few times because she was like, I have got to go to school, I have got the runs and I can't keep going out of the lessons, so it was a bit difficult that one" (Parent 2, orlistat).

> "I was asked to bring in spare things because she kept having accidents [faecal incontinence]. She had [already taken] a few herself which she had taken in her bag" (Parent 13, orlistat).

> "It made me stop going out for a while as I was worried that it might come over me and I might have to dash off and it would be embarrassing." (Young person 4, aged 16, orlistat)

Only a minority of young people taking Orlistat reported that the "side effects" they were experiencing were in relation to the fat they had consumed and changed their diet.

> "I went back to the really healthy stuff" (Young person 13, aged 13, orlistat).

4.4.2.4 Mediators in dealing with side-effects

Young people identified certain mediators that influenced how side effects were managed.

4.4.2.4.1 Reluctance to discuss side-effects with clinicians

Despite reporting trust in their doctors, some participants were disinclined to talk to them at planned appointments or initiate additional interim appointments. Some did not feel their GP had sufficient expertise to support AOD usage.

> "I probably would have liked more support – however, my consultant is very good and I do prefer her to the local GP. She [consultant] sees loads of people with the same condition. Helping them to change their ways and this and that. But at the GPs they do loads of different things..." (Young person 10, aged 14 years)

Few turned to other healthcare professionals such as pharmacists for support, and sometimes these interactions heightened familial concerns, particularly if the professional questioned the appropriateness of the medication.

> "… when I picked up his prescription the pharmacist said "the child is only 13" and I thought oh, is there a reason...He just thought it was unusual, it was normally for older people. He thought it was a bit odd and he said maybe you should ask that question. And he also said it would be helpful for me to give him some feedback after he takes them" (Parent 7)

4.4.2.4.2 Understanding mechanism of action

Understanding of food content, in particular fat content, was also variable and some young people reported not having received any dietetic advice prior to commencement of the AOD. This included patients prescribed orlistat. Many

had familial experience of AOD usage that increased their own understanding; this was often grandparents taking Metformin for control of type 2 diabetes or mothers who had taken orlistat for weight control.

Some perceived their drug-related symptoms as "side effects" whilst others realized that they were a consequence of high fat intake. The majority of participants who correctly understood the mechanism modified either their diet or drug regimen.

> "if I was eating the fat, I would have to go to the toilet" (Young person 3, aged 16, orlistat).

4.4.2.4.3 Age

Young people reported that if they had been early adolescents at the time the AOD was introduced, they did not listen to the information given by the Doctor, preferring to leave understanding to the parent.

> "I was at that age where I don't need to know" (Young person 6, aged 14 years).

4.4.2.4.4 Concerns about safety

A few had concerns about the safety of the medicine because of the side effects whilst others felt that the medicines must be safe because a doctor had prescribed them.

"I thought that it couldn't be, like, safe if it was keeping me awake all night and making me like go a lot" (Young person 5, aged 13 years, metformin).

4.4.2.4.5 Environmental influences
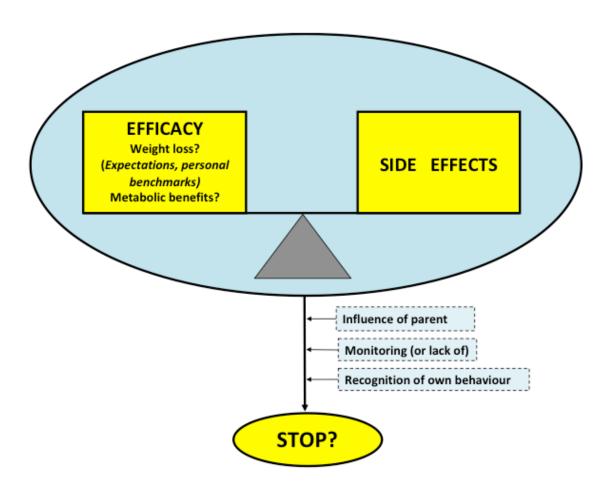
Many had heightened awareness of toilet facilities, particularly their proximity and the impact of sharing toilets. This was driven by concerns about faecal urgency, risk of incontinence and the embarrassment related to the staining of toilets with oily faeces.

> "She felt she couldn't be comfortable taking them at school and college, because she just couldn't rush out, and when she said she did, it was like an orangey/yellow oil that goes into the toilet and it doesn't flush away. So that is very embarrassing if you are out somewhere." (Parent 1, orlistat)

4.4.3 Model 3: Drug continuation: efficacy versus side-effects

Model 3 is summarised in Figure 4.3 below. The decision to either continue with, or stop, the AOD was frequently based on a decisional balance between the efficacy of the AOD and ongoing side effects. The decision to terminate treatment was frequently described as a balance between the perceived benefits of the AOD and its side effects.

Figure 4.3 Model 3 - patient-led decision process regarding drug continuation

Various mediators influenced this decision, including perceived benefits and expectations, lack of support and understanding of drug action.

"I don't want to take something that I don't think was working and making me ill" (Young person 6, aged 14 years)

"I just thought what is the point of taking it if it is not working and I am not eating the rubbish foods, there is no point as it weren't really doing anything". (Young person 3, aged 16 years)

Participants described efficacy in terms of body weight, body shape and metabolic parameters. Individual goals varied from going down a clothes size, to weight stabilisation. Most young people had expectations of weight control that were aligned with published outcomes, although some hoped for outcomes that were faster, more extreme or more guaranteed. Weight stabilisation was acceptable for some, and they continued to take it fearing that it would increase faster if they stopped taking the medicine.

> "He [clinician] said that they may help me lose weight and my mind crossed out the word 'may' and replaced it with the word 'will'.
> (Young person 9, aged 17 years)

> " It is keeping her weight not going up." (Parent 10)

There was significant variation in the understanding of drug action, in terms of mechanism and efficacy. Some perceived that the AOD required a restricted diet and increased exercise to be effective, whilst others believed that lifestyle changes were not necessary. These views seemed unrelated to the drug prescribed. Some described the futility of taking an AOD as they were unable to undertake healthy behaviours, and subsequently stopped the drug.

> "….. they said this [the medicine] is not a miracle worker it doesn't help you lose weight. You help yourself to lose weight and it just gives you a little pat on the back every so often to help you carry on what you need to do…." (Young person 10, aged 14 years)

"I don't know whether the tablet actually makes you lose weight or just because it makes you stop eating, it makes you lose weight".

(Young person 2, aged 17 years)

Drug termination was an active decision by young people and their families, and not by their doctor. The decision was taken by the young person alone, or with the advice and support of their parent. Very few young people or parents reported adequate drug monitoring and support from the obesity specialist; this influenced their decision to independently stop the drug.

"She (Mum) advised me not to take them because it wasn't very nice for me experiencing this" (Young person 6, aged 14 years)

"I just stopped taking them, went cold turkey". Interviewer: "What put you off ringing up the clinic to discuss it?" Young person: "I just didn't think it was important." (Young person 15, aged 15 years)

Support was a theme that spanned across all 3 models. One mother described the period taking the AOD as a "*lonely*" time. Few reported adequate support from their obesity specialist, primary care physician or pharmacist. Two participants described disheartenment after being discharged from a specialist service due to inadequate progress, and reported subsequent weight gain. General practitioners mostly only issued repeat prescriptions. Many young people said that they would be happy to be monitored by their GP if they could not get an appointment at the specialist clinic, yet others felt that GPs had insufficient experience to support them. Emotional support mainly came from

friends and family. Parental supervision, usually from a mother, ensured that younger adolescents took the medication. As young people matured, parents were more likely to step back and let the young person take responsibility for their medication.

> "I think there were times when she tried skipping it, but she had a dragon as a mother. So as long as I am aware it happens, and what I do now is put it all out in individual pill boxes for the day." (Parent 13)

4.5 Discussion

4.5.1 Main findings

These are the first published qualitative data on adolescent experiences of AOD use. In this sample, AOD prescriptions were uniformly suggested and initiated by specialist paediatricians, with passive acceptance by young people and families. After initiation, families mostly described receiving minimal support from the specialist prescriber as well as from local clinicians including GPs and pharmacists. There was a wide variation in the experience and tolerance of side effects, which were largely managed by families independently of clinicians using self-directed strategies. Although doctors made the decision to start the drug, we saw that patients decided to terminate the drug, usually because of insufficient benefit to justify the side-effects.

Participants had a range of co-morbidities, including depression and hypothyroidism, which may have impacted on their experience of AOD usage. Due to the wide range of co-morbidities and small numbers of each, it was not possible to explore more fully the interaction between these individual conditions and AOD usage.

4.5.2 Comparison with literature

Similar findings have been demonstrated in the adult studies exploring AOD usage. Qualitative study participants from three primary care practices reported that doctors initiated AOD, giving patients little choice in the decision and inadequate information about the drugs and related lifestyle changes. (233)

Similar patterns of use have been reported in adults. Two previous studies showed that side-effects were a major factor influencing adherence, and many adults report using the medication flexibly to fit in with their lifestyles, and minimize side-effects at inappropriate times. (234, 235) The highly visual side effects also encouraged some adults to consider their behaviour as a cause of their obesity and to adopt a healthier diet. (234) Similar themes for drug discontinuation were reported in these previous studies; participants who benefitted from the drug continued with, or adapted the medication, and those who did not lose weight abandoned it. (235) Similar themes have also been demonstrated in the adolescent generic adherence literature, with insufficient clinician support, embarrassment, insufficient belief in drug efficacy, interference with usual activities and side-effects all being reported as barriers to medication adherence in other chronic conditions (236).

4.5.3 Implications

Results from this study offer insight into the experiences of young people who are taking AODs, and offer potential targets for change that could potentially improve drug adherence and outcomes in this patient population. They suggest that more careful approaches are needed to improve drug initiation and ongoing support. Potential strategies include:

I.   Ensure that families accept the need for medication, with alternative options discussed, and drug initiated only when it fits in with the families own treatment ladder.

II.   Initiate the medication at a time that is right for the family, with consideration of the school day, week and year, and avoidance of periods where side effects may be problematic (e.g. examinations).

III.   Ensure that those prescribed orlistat are fully informed and understand the difference between treatment effects and side effects. This could include dietetic input to enable its use as an educational tool to identify high fat foods, and subsequently enable a low fat diet.

IV.   Provide sufficient information about side-effects at initiation, with written advice related to side-effect management strategies

V.   Provide sufficient ongoing support from specialist services, particularly related to management of side effects. Active monitoring of non-weight related benefits, e.g. cardio-metabolic risk factors, may reduce drug cessation.

Obesity is likely to be a life-long disease for this cohort, given that current treatments have modest efficacy. Long-term drug use is likely to be an integral treatment modality in addition to behaviour modification strategies at both the individual and population level. Effective prescribing habits are needed to support both current and future generations of anti-obesity medications.

4.5.4 Limitations

Participants were recruited from three hospital clinics in England, with the majority from one hospital in which two of the authors are clinicians. This has the potential of limiting generalisability and introducing bias. However AOD in young people are largely initiated in specialist centres and those centres

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included in this study were amongst the largest of a very small number of specialist paediatric obesity clinics in the UK. To minimize bias, all data were collected by an independent researcher not part of any clinical team and responses were anonymised before analysis.

Delays in the study may have led to problems with recall for those patients who stopped the medication some time previously. As with all qualitative studies, the researcher's presence during interviews could have affected the subjects' responses; every effort was made to reassure the participants that the researcher was both non-judgmental and not part of the clinical team, and their responses would be fully anonymised prior to analysis by the team.

We aimed to include patients who were prescribed AOD, but never commenced it. However, no such young people responded to recruitment invitations. We are therefore unable to comment on those who were prescribed an AOD but who never initiated medication.

Only a small minority of eligible subjects enrolled in the study, despite thorough attempts to contact them using clinical research nurses. It is highly possible that those with negative experiences felt more motivated to participate in the study. Largely negative responses indicate that participants are likely to have felt reassured about their anonymity, and did not fear reprisal from their clinicians.

4.6 Conclusions

Use of anti-obesity drugs is challenging and complex for many adolescents, and few young people in our study described positive experiences. Multiple factors

were identified that could be targeted to improve medication concordance and maximise efficacy, including improved clinician-patient partnership in decision making, and better patient education and subsequent support. Many of these are not unique to the current generation of anti-obesity drugs, and are likely to be relevant to novel drugs.

5 Survey of anti-obesity drug prescribing for obese children and young people in UK primary care.

5.1 Abstract

BACKGROUND: Anti-obesity drug (AOD) prescribing in children and young people (CYP) in primary care is rising with high rates of discontinuation. Little is known about prescribing in this group in terms of patient demographics and co-morbidities, reasons for initiation and discontinuation, or adherence to national guidelines.

Methods: Questionnaire survey to GPs prescribing an AOD to patients aged <=18 years between 31st May 2010 and 31st May 2014, identified using a nationally representative primary care database covering 5.7% of UK population. We audited orlistat prescribing against NICE guidance.

Results: Total of 151 patients identified with 78.8% response rate. A total of 94 subjects were eligible (females 86.2%, 65% were >=16 years). 46.8% were prescribed metformin, 58.5% orlistat and 5.3% both drugs. Metformin was initiated for treatment of polycystic ovarian syndrome (70.5%), insulin resistance (25.0%) and impaired glucose control (9.1%).

Drug discontinuation was high; 5% orlistat and 57% metformin prescriptions were active at time of survey. Median supply of metformin was 10.5 months (IQR 4-18.5 months) and 2.0 months (1.0-4.0) for orlistat (p=<0.001). 45.5% of orlistat treatment lasted a single prescription and none lasted more than a year.

Most drug terminations were due to families not requesting repeat prescriptions (96.2% orlistat and 89.5% metformin) rather than medically-led discontinuations.

Adherence to NICE paediatric guidance for prescribing of orlistat was low:17% of prescriptions were initiated in the specialist setting, and 56% had evidence of obesity-related co-morbidity; orlistat was largely prescribed in those over 16 years of age without physical co-morbidities; and 89.1% (49/55) of orlistat prescriptions were initiated in primary care independent of specialist advice.

GPs reported lower confidence in prescribing AOD to CYP compared with adults (10-point Likert score median 3 vs 8, p<0.001). GPs requested additional support in managing behavior change interventions and drugs.

Conclusions: Prescribing of AOD for CYP does not mirror national guidelines. Use of AOD in primary care is rare, particularly in males and those below 16 years. High rates of discontinuation were seen, primarily in those prescribed orlistat. GPs report low confidence in their usage, and want further support in managing obesity.

5.2 Introduction

Little is known about use of medication for obesity in children and adolescents in the UK, particularly use in primary care. Orlistat is currently the only licensed anti-obesity drug in the UK since sibutramine was withdrawn due to concerns about cardiovascular safety.(139, 237) However, the most commonly used drug for obesity in children and young people (CYP) is metformin, an anti-diabetes drug used off-licence to treat the metabolic sequelae of obesity in CYP, although not formally classed as an anti-obesity drug. (238-240) Both orlistat and metformin appear to offer small benefits for BMI loss in CYP; systematic reviews show small reductions in BMI compared with placebo, orlistat by 0.83 kg/m^2 (116) and metformin by 1.4kg/m^2 (at 6-12 months, and 6 months, respectively)(125)

In the UK, the National Institute for Health and Care Excellence (NICE) guidance recommends community-based lifestyle modification programmes as the first tier of weight management for childhood obesity, with pharmacotherapy as a second line treatment.(139) Their guidance only covers use of orlistat which should be prescribed only in exceptional circumstances for those with obesity-related co-morbidities (life-threatening in those under 12 years of age) and only prescribed by teams with expertise in these conditions.

Randomised trial data on orlistat and metformin come from specialist clinical settings and largely from outside the UK. Very little is known about how these AOD are prescribed and used in clinical practice. Pharmaco-epidemiology studies of AOD prescribing in primary care in the UK show both increasing use

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of AODs, but also high levels of drug discontinuation, with approximately half the prescriptions of orlistat not being continued beyond 1 month.(116) The one qualitative study examining adolescent use of AOD showed frequent cessation by families independent of their doctors, usually because the perceived advantages did not outweigh the medication side effects that they endured with often minimal professional support.(241) These data suggest that the effectiveness of AOD in 'real life' settings may be considerably less than shown in trials, and suggests a need to identify strategies to improve the effectiveness of AOD for CYP.

We undertook a questionnaire survey of GPs prescribing AODs to CYP to better understand their use in primary care in the UK. We sought to characterize patient demographics, quantify adherence to NICE guidance, and identify primary care perceptions of AOD with the longer-term aim of optimizing AOD prescribing and efficacy.

5.3 Methods

A questionnaire survey was used to gather individualized prescribing data from general practitioners in the UK. We followed recommendations for good practice in survey research.(242)We used routinely collected primary care data from The Health Improvement Network (THIN) database to identify children and young people aged up to and including 18 years prescribed orlistat or metformin between 31st May 2010 and 31st May 2012. We excluded patients prescribed metformin for type 2 diabetes.

THIN covers approximately 5.7% of the UK population with 3.6 million active patients from 587 general practices using the Vision General Practice System.(243) These practices are broadly representative of practices in the UK in respect of patients' demographics and characteristics.(244) Questionnaire administration was undertaken by THIN Additional Information Services (THIN AIS), an independent research organisation affiliated with THIN, with data protection firewalls.

A paper questionnaire was sent to the GP practices of all identified CYP in order to collect patient-level data(see appendix for full questionnaire). The questionnaire was designed by a multi-disciplinary study team comprising of an academic GP, two paediatricians, a psychologist, a pharmacist and GP representative. GPs prescribing an AOD were contacted up to 3 times over 3 months until the questionnaire was returned. GPs received a £35 payment for each completed and returned questionnaire. THIN AIS anonymised questionnaires prior to analysis by the study team.

Year of birth, practice ID and region were provided by THIN AIS. All other data were provided by GPs within prescribing practices for each identified patient using existing medical records. The questionnaire contained questions regarding patient demographics and co-morbidities, height and weight measurements, indications for treatment and outcomes. Furthermore, GP experiences and opinions related to AOD usage in children, regardless of their involvement with the patient.

Body Mass Index (BMI) was calculated from GP-derived height and weight measurements when available, and zBMI calculated using the LMS method and UK reference data.(8) We assumed AOD termination if no prescription had been issued within 3 months of the survey. Age at first prescription was calculated from the midpoint of birth year, as month and day of birth were not provided due to data protection restrictions.

We audited orlistat use against NICE 2006 recommendations which remain unchanged in the 2014 update, bar some text clarifications(139, 162). NICE criteria were specified earlier in section 1.8.2.2 (page 71).For audits against NICE, we used assumed birthdate of 1st January to ensure that no subjects were misclassified as children if they were 18 years of age.

5.3.1 Analyses

Analyses were conducted using STATA 11.0 (STATA Corp, College Station, Texas, USA). Simple descriptive statistics were used for the majority of data.

Duration of drug use was compared using Wilcoxon-Mann-Whitney test (highly skewed data) and paired likert-scores usingWilcoxon-Signed rank test.

Handwritten free text comments from each questionnaire were transcribed verbatim. Transcripts were read and coded using a general thematic coding methodology(232). Memos were written to summarize and synthesize emerging themes. This initial coding framework was used to code the subsequent transcripts and new codes were added as they emerged using a constant comparative technique to compare new and previously collected data to understand emerging themes. Models were developed through an iterative process, in which the initial model was reviewed using constant comparison techniques (in which successive items of data are appraised and compared to ensure the code is reflective of all) and the models revised accordingly.

5.3.2 Governance

The study was reviewed and approved by the NRES Committee London – Surrey Borders REC reference number 11/LO/1020.

5.4 Results

5.4.1 Patient demographics

Figure 5.1 below summarizes patient sampling. A total of 151 eligible patients were identified by THIN. GP-response rate was 78.8% (119/151). GPs identified 21/119 as ineligible. We further excluded 4 subjects after inspection of questionnaires, due to duplicate questionnaires received for the same drug with inconsistent responses (n=1), missing patient demographics and drug details (n=2), and empty questionnaire (n=1).

Figure 5.1 Patient sampling

A total of 99 AODs initiations occurred in the 94 subjects (5 subjects were prescribed both orlistat and metformin), consisting of 44 metformin (46.8% of

sample) and 55 orlistat (58.5%) prescriptions. Drugs were initiated in 68

practices, with 46 practices prescribing one drug each, 15 practices two drugs

each, 6 practices three drugs each and 1 practice prescribing five drugs.

Table 5.1 summarizes baseline demographic and co-morbidities by drug. Co-

morbidities appeared higher in those taking metformin. Sufficient data were

provided to calculate BMI & zBMI during study period for 90.9% (40/44)

prescribed metformin and 89.1% (49/55) prescribed orlistat. All had BMI above

98th centile (>2SD).

Table 5.1 Demographics and co-morbidities by drug

	Metformin	Orlistat
Demographics		
N	44	55
Female (%, N)	90.9% (40)	83.6% (46)
BMI (mean kg/m^2, SD)	35.9 (6.1)	37.6 (6.5)
zBMI (mean, SD)	3.2 (0.7)	3.2 (0.6)
Median age (range)	15.7 (6.5,19.2)	17.3 (13.8,18.8)
<12 years (n)	5	0
12-15 years (n)	17	9
16-17 years (n)	16	29
>=18 years (n)	4	17
Missing age (n)	2	0
Co-morbidities		
Hypertension (n,%)	1 (2.3%)	0
Hyperinsulism / insulin resistance (n,%)	13 (29.5%)	0
Type 2 diabetes (n,%)	0	3 (5.5%)
Dyslipidaemia (n,%)	1 (2.3%)	3 (5.5%)
Emotional distress (n,%)	12 (27.3%)	17 (30.9%)
Sleep apnoea (n,%)	0	1 (1.8%)
Polycystic ovarian syndrome (n,%)	32 (72.7%)	6 (10.9%)
Orthopaedic issues (n,%)	3 (6.8%)	3 (5.5%)
Pervasive developmental disorder (n,%)	3 (6.8%)	0
Hypothyroidism (n,%)	1 (2.3%)	3 (5.5%)

5.4.2 Drug initiation

Figure 5.2 below summarizes frequency of drug prescription by age and drug initiator.
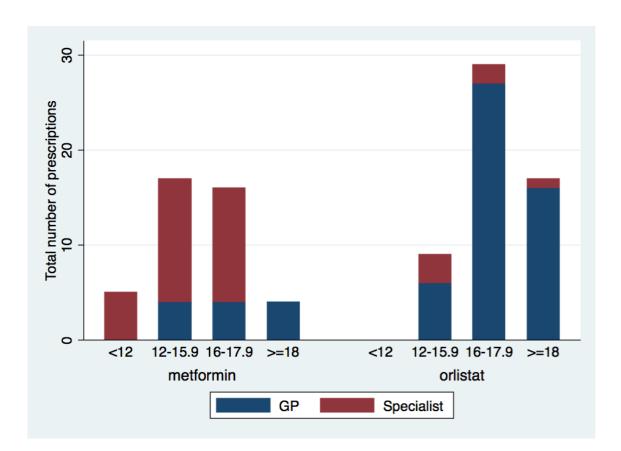
Figure 5.2 Frequency of drug prescription by age and drug initiator

Of 55 orlistat prescriptions, 89.1% (n=49) were initiated in primary care independent of specialist advice. This comprised of 66.7% prescriptions to those aged 12 to 15.9 years, 93.1% from 16 to 17.9 and 94.1% over 18 years. Orlistat was not prescribed to any patient aged less than twelve years. In six cases where orlistat was initiated in primary care on specialist recommendation, three (50%) were from a paediatrician, and one each (16.7%) from an adult physician, lipid clinic and dietician.

Of 44 metformin prescriptions, 27.3% (n=12) were initiated in primary care independent of specialist advice. This comprised no metformin prescriptions to those under 12 years, 23.5% to those aged 12 to 15.9 years, 25% from 16 to 17.9 and 100% over 18 years. In the 32 cases where metformin was initiated in primary care on recommendation of a specialist, 59.4%(19) were from a paediatrician, 21.9% (7) from a gynaecologist, 12.5% (4) an adult physician and 3.1% (1) an endocrinologist (some had multiple/joint consultations).

Indications for metformin initiation were obesity together with 1) polycystic ovarian syndrome (70.5%, 31/44), 2) insulin resistance (25.0%, 11/44), 3) impaired glucose tolerance/impaired fasting glucose (9.1%, 4/44) and 4) obesity without known co-morbidity (6.8%, 3/44).

5.4.3 Drug monitoring

Of the 61 prescriptions initiated independently by a GP, 67.2% (n=41) were subsequently reviewed by a GP (75% of metformin, and 65.3% of orlistat prescriptions), including 3 who were additionally reviewed by their practice nurse. One was reviewed by a gynaecologist but not their GP after drug initiation to confirm appropriateness of drug prescription.

Of the 38 prescriptions initiated by a GP on specialist recommendation, 26.3% (n=10) had a GP consultation related to the drug for "supervision" (1), weighing (2), psychological support (1), prescribing (2), answering queries (1) and to discuss efficacy (6). None discussed side effects with their GP. GP were aware

of monitoring with a clinician in 84.2% (32/38) cases, including 81.8% (18/22) follow-up by paediatricians and 40% (2/5) by adult physicians.

GPs were made aware of adverse drug effects by two patients, both prescribed metformin; one had diarrhea and the other nausea.
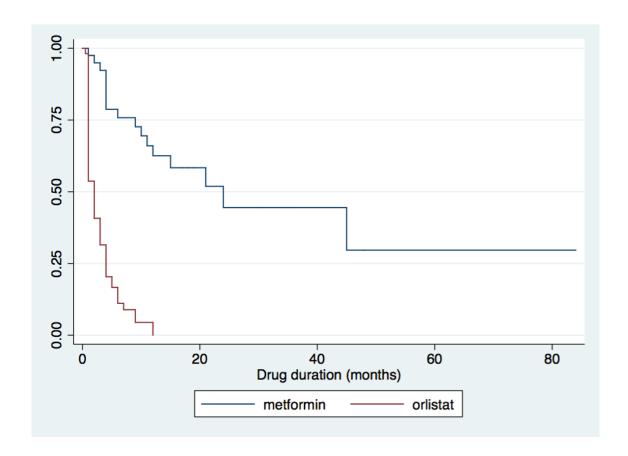
5.4.4 Drug duration and termination

Duration of drug prescription is summarized in Figure 5.3 below.

The median supply of metformin was 10.5 months (IQR 4-18.5 months) compared to 2.0 months (1.0-4.0) for orlistat (p=<0.001). Over half of all metformin prescriptions (25/44) but only 5.5% of orlistat prescriptions (3/55) were active at the time of survey, defined as a new prescription issued within the preceding 3 months. There was a disparity between reported length of drug prescription and the amount of drug prescribed, suggesting non-continuous use at dose prescribed.

Twenty-seven patients had only a single prescription issued from primary care, being 45.5% (25/55) of all orlistat and 4.5%(2/44) metformin treatments. None of these single prescriptions were issued in the three months prior to the survey, and all were given a maximum of one-month supply making ongoing use highly unlikely.

Figure 5.3 Kaplan-Meyer survival curve demonstrating treatment duration of metformin and orlistat. Figure shows proportion still actively prescribed AOD for orlistat and metformin by time since initiation, beginning from time 0 (100% active prescriptions) to 80 months.

The majority of all drug terminations were due to families not requesting repeat prescriptions (96.2% of all orlistat and 89.5% of metformin) rather than medically-led terminations or shared decision making. GP reported possible orlistat cessation in three cases due to lack of drug supply in pharmacies. Of four prescriptions actively terminated by a doctor (metformin=2, orlistat=2), two were due to lack of efficacy, one for lack of drug adherence and the other two for reasons unknown.

5.4.5 Adherence to NICE guidance

We restricted NICE compliance analysis to recommendations for children (see background). Using 1st January as their assumed birthday, 23 subjects could be identified to be definitely aged less than 18 years at drug initiation.

In this group, the following criteria were fully met; all subjects were aged over 12 years (recommendation 1.8.4); and no participants were prescribed orlistat for over 12 months (1.9.11)

The following criteria were partially met; first, four (17.4%) were prescribed orlistat following specialist advice (1.8.5), Recommending specialists were paediatricians (n=3) and an adult physician, with one known to be part of a specialist multi-disciplinary team (1.8.7). All prescriptions recommended by specialists were continued in primary care (1.8.8).
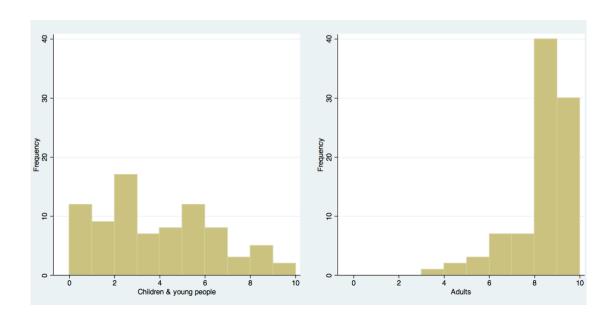
Second, co-morbidities were reported in 56.5% of the sample (13/23) despite NICE requiring co-morbidities to be present (1.8.6). These were emotional distress (7/23), hypothyroidism (3/23), type 2 diabetes (1/23), medulloblastoma (1/23), Polycystic ovarian syndrome (1/23), or worsening of another chronic disease secondary to obesity (1/23). No patients had sleep apnoea. Low levels of co-morbidity screening in primary care were reported suggesting that higher number of co-morbidities may have existed (6 of 23 were screened for psychosocial distress, 5 for hypertension, 2 each for type 2 diabetes, and dyslipidaemia, and none for sleep apnoea).

No patients were prescribed a multivitamin (1.9.2). We did not assess screening for micronutrient intake or risk of vitamin deficiencies.

5.4.6 Improving prescribing in primary care

GP confidence in prescribing AOD to CYP and adults is summarized in Figure 5.4. It shows an inverse relationship between prescribing in adults and CYP. Confidence was higher for prescribing to adults (median=8, interquartile range 8-9) than children (3, 1-5), p<0.001.

Figure 5.4 GP confidence in prescribing AOD to children and young people (left) and adults (right). Scores are likert-scores (10=highest confidence**)**

The most popular resources used by GPs to support prescribing were NICE guidance (orlistat n=20, metformin n=7), British National Formulary (orlistat 17, metformin 8), local prescribing guidelines (orlistat 8, metformin 11) and specialist guidance (orlistat 1, metformin 7).

GPs perceived that 27.3% (n=12) of patients prescribed metformin and 12.7% (7) prescribed orlistat benefitted from the drug, with half (50% metformin, 52.7% orlistat) reporting not knowing if there had been any benefits for the patient.

Thirty-five general practitioners provided brief free text reflections of their experiences prescribing orlistat (n=20) and metformin(n=14). Three main themes arose. First, the use of metformin was mostly ascribed to polycystic ovarian syndrome rather than as a weight loss drug. One GP stated that (s)he "wouldn't normally prescribe this just for weight loss".

Second, there was controversy about whether AODs should be prescribed in primary care in this age group, with one saying (s)he "usually not prescribe for children" and another saying (s)he avoided orlistat "where possible". Metformin was used either "on advice of specialist only", or had specialist follow-up after initiation.

Third, GPs noted concern about the efficacy of these drugs. "Inadequate counseling", lack of drug availability and patient compliance ("clearly patient was not able to comply") were hypothesized reasons for ineffectiveness.

Sixty-two GPs wanted improved support, primarily split into two main themes. First, they requested improved age-related guidance for prescribing AOD that is "realistic", with "clear [and] concise" advice including "flow diagrams" and "stepwise advice". This would include instructions on assessment prior to initiation, indication indications, contra-indications, monitoring, safety advice, duration, targets and indications for stopping treatment. Second, they wanted

improved guidance for managing patients with obesity, namely advice about lifestyle management and details of available interventions. GPs requested details of "non-drug treatments" including "community support for adolescents" and "special clinics for monitoring and support of patients." One GP highlighted that "non-drug treatments need to be key alongside drug treatment."

5.5 Discussion

5.5.1 Summary of results

This is the first detailed study of primary care prescribing of anti-obesity drugs in CYP at individual patient level. Small numbers of prescriptions were issued in this age group, with most practices surveyed prescribing just a single AOD to a child or young person. However, clear patterns were detected that can help guide prescribing of current and future generations of anti-obesity drugs. Our findings augment the very limited existing data relating to AOD rates of initiation and cessation and experiences of children and young people prescribed an AOD.(241)

Recipients of an AOD were largely female. Prescribing to those under 12 years was rare, with AOD prescribing rates increasing with age. Two-thirds (65%) of the sample was aged 16 or over, including 84% of those prescribed orlistat. Metformin was largely initiated by specialists, and orlistat by general practitioners.

Comparison with NICE guidelines showed low compliance with national prescribing recommendations, namely low prevalence of co-morbidities and drug initiation without specialist advice. Given that most orlistat prescriptions were for those above 16 years, it could be hypothesized that those aged 16 years and over were treated as adults, with drugs prescribed in line with adult guidelines that do not necessitate presence of co-morbidities.

Metformin was largely recommended by specialists to those with obesity and either PCOS or insulin resistance. GPs were divided about whether they consider metformin to be an anti-obesity drug despite it being used for the co-morbidities of obesity, and shown to have to have weight loss benefits.

Drug cessation was high with only 1 in 18 patients prescribed orlistat continuing to take it at the time of survey, and half requesting only a single prescription. Metformin treatment was more longstanding, with half continuing at time of survey. It is not clear from this study why these prescriptions were short lived. GPs reported that termination was due to families not requesting repeat prescriptions rather than clinicians ceasing the drugs.

GP reported low confidence in prescribing AOD to children and young people, despite high levels of confidence when prescribing to adult. They reported a desire for improved guidance not only on drug initiation and monitoring, but also on lifestyle interventions suggesting possible low overall confidence in managing obesity in children.

5.5.2 Strengths and Limitations

We used data from a nationally representative dataset to identify patients prescribed an AOD. There was a high rate of completion of questionnaires by GPs.

Our data is subject to a number of limitations. Data collection relied on retrospective notes-based recall by GPs, increasing the likelihood of missing data. Individual item completion rates were variable, with some having only a

few questions answered. We assumed that unanswered questions implied lack of evidence to support the questions. As such, rates of co-morbidities and screening may have been higher than reported.

Free-text answers were brief. Given this, we were cautious in our analysis of their responses and themes were kept simple. Future interview studies could allow a better understanding of GP experiences.

We were unable to ascertain exact age of subjects resulting in risk of misclassification bias. Given this, we were cautious in analyzing NICE compliance, and we are likely to have underestimated the number of subjects who were prescribed orlistat under 18 years of age.

GPs were not asked to justify exclusion of patients into this study. Given some freetext comments about metformin not being an AOD, we hypothesise that some may have inappropriately excluded.

5.5.3 Comparisons to the literature:

We found similar low incidence of AOD initiation and high levels of discontinuation as previously published.(144) This is unsurprising given that we used the same GP prescribing database as previous studies to identify patients. Use of a different database, such as the General Practice Research Database (GPRD) could be used if needed to substantiate these data.

A paired study by our research team investigating patient experiences of AODs found high levels of side-effects, low levels of professional support managing these side-effects, and ultimately families deciding to stop the AOD due to the

disadvantages of the side-effects outweighing the perceived benefits of the drugs.(241) This contrasts with findings from this study where no patients actively discussed side-effect profiles with their GPs, and GPs being aware of side-effects in only two patients. This study does not explain the disconnect between patients' and clinicians' experiences, and further work should examine ways to support families so they are able to access support to manage the side-effects of these drugs. Low confidence described by GPs in prescribing AOD to this age group is likely to have an influence.

5.6 Conclusions

Use of AOD including metformin in primary care is rare, particularly in males and those below 16 years. High rates of discontinuation were seen, primarily in those prescribed orlistat. Rates of compliance with NICE guidance for orlistat were low and GPs report low confidence in the use of AOD in this age group. Improved training and support for GPs is needed to guide AOD use in primary care, both for current and future generations of drugs.

6 Systematic review of psychological and social outcomes of adolescents undergoing bariatric surgery, and predictors of success

6.1 Abstract

Background. The psychological and social outcomes of bariatric surgery in adolescents, together with psychological and social predictors of success, were systematically reviewed.

Methods. PubMed, EMBASE, ISI Web of Science, and PsychInfo, were searched to July 2014.

Results. Existing data were sparse; 15 were suitable for qualitative review and 6 for meta-analysis (4 quality of life, 2 depression). 1 study was a randomized control trial. 139 subjects underwent Roux-en-Y gastric bypass, 202 underwent adjustable gastric band and 64 underwent sleeve gastrectomy. Overall quality of life improved after bariatric surgery, regardless of surgical type with peak improvement at 6-12 months. Meta-analysis of 4 studies showed changed in overall QOL at latest follow-up of 2.80 SD (95% CI 1.23-4.37). Depression improved across all studies, regardless of procedure (effect size -0.47 SD (95% CI - 0.76, -0.18) at 4-6 months). Two cohorts reported changes in both overall QOL and depression following a quadratic trajectory, with overall improvement over 2 years and deterioration in the second post-operative year. There were limited data on other psychological and social outcomes.

Summary. There were insufficient data on psychosocial predictors of outcome to form evidence-based recommendations for patient selection for bariatric surgery at this time.

6.2 Introduction

Bariatric surgery in adults is the most effective treatment option for long-term weight loss, and has been shown also to be an effective treatment of medical co-morbidities with resulting improvement in psychological and social functioning (132, 245-247). Increasing numbers of obese adults are turning to bariatric surgery with smaller numbers of adolescents following suit (248, 249). In the UK, the National Institute of Health and Care Excellence (NICE) advises that bariatric surgery in adolescents is a potential treatment for young people where BMI is above 40kg/m^2, or above 35kg/m^2 together with other significant disease that could be improved by weight loss, and where multi-disciplinary lifestyle interventions lasting at least 6 months have failed (162).

Evidence supporting bariatric surgery in adolescents is limited. Adolescence is a complex period of biological, psychological and social development(250) and outcomes of bariatric surgery in adolescents are potentially different to adults. Bariatric surgery for adolescents is potentially fraught with medical and ethical dilemmas(251). Optimal timing of surgery is hotly debated, with some arguing that surgery should be postponed until adulthood, and others suggesting that delay results in poorer outcomes and increased health risks(166, 252). Systematic reviews have identified significant benefits for BMI loss in adolescence but have not thoroughly addressed psychological, social or quality of life outcomes after surgery(135, 166, 253). To date, only two systematic reviews have evaluated the psychosocial outcomes of surgery; one was limited to outcomes of gastric banding, included only 6 studies with psychosocial data,

and did not include the other more common weight loss procedures currently performed in adolescents(253) and the other only evaluated quality of life(135).

Obese adolescents seeking bariatric surgery report impaired quality of life and significant levels of psychological morbidity(254, 255) and these problems are regarded as part of the rationale for surgery. However we know little about the benefits of surgery for psychological function and quality of life in adolescence and existing evidence has not been systematically reviewed across all surgery types. Furthermore, it has been suggested that certain psychological problems may be contraindications for bariatric surgery, although this is controversial. Again, existing evidence on psychological predictors of outcomes of bariatric surgery in adolescents, whether weight-related or psychological and social outcomes, has not been systematically examined. Knowledge of both the psychological and social outcomes of surgery and of psychological predictors of outcome are necessary to improve the effectiveness of bariatric surgery by allowing clinicians to offer surgery to those for whom the intervention is likely to be most effective, and protect those unlikely to benefit.

We undertook a systematic review of both these issues, reviewing existing literature on children and adolescents up to the age of 21 who have undergone bariatric surgery to answer the questions:

1.   What psychological and quality of life factors are associated with outcomes of bariatric surgery?

2.   What are the psychological and quality of life outcomes of surgery in

adolescence?

6.3 Methods

We report methods according to the PRISMA statement.(256)

6.3.1 Eligibility criteria

Studies were eligible if they fulfilled the following criteria:

1.   Subjects were children, adolescents, or young adults up to 21 years undergoing bariatric surgery of any type

2.   Reported either:

Psychological outcomes of bariatric surgery, including quality of life.

Psychological or social predictors of outcomes of surgery. Outcomes were defined in the broadest sense, and included changes in weight, medical co-morbidities as well as psychological outcomes.

3.   Used either:

Validated questionnaires before and after surgery, or questionnaires that compared post-operative to pre-operative state or qualitative studies

Validated diagnostic system to detect prevalence of mental health disorders

6.3.2 Study type

All study types were included with the exception of non-sequential case-series and studies with less than 10 cases, with the aim of minimising selection bias.

Publication status: We included only studies published in peer-reviewed journals. Conference abstracts and letters to editors were excluded.

6.3.3 Search strategy

6.3.3.1 Sources

Electronic searches were conducted in PubMed, EMBASE, ISI Web of Science and PsychInfo using the PubMed or equivalent search terms presented in figure 1(mapped and exploded terms used). No date limits were set during the search. The reference lists of all included studies and reviews were searched for additional studies. Only papers written in English were retrieved. The same procedure was repeated in July 2014, covering publications after 6 February 2013. Figure 6.1 below summarises the searches undertaken on 6 February 2013 and repeated on 28 July 2014.

Figure 6.1 Search terms for MEDLINE via Ovid SP. Equivalent terms and MESH terms used for other EMBASE and PsychINFO via OVID SP and Web of Science

1. exp Obesity/
2. obes*.mp
3. exp overweight/
4. overweight.mp
5. exp weight loss/
6. weight loss.mp
7. overweight*.mp
8. exp Body Mass Index/
9. body mass index.mp
10. body mass.mp
11. bmi.mp
12. obese,mp
13. exp body fat distribution
14. exp Child/
15. child*.mp
16. exp Adolescent
17. adol*.mp
18. adolescen*.mp
19. pediatr*.mp
20. paediatr*.mp
21. exp Bariatrics/
22. exp Bariatric Surgery/
23. bariatric*.mp
24. lagb*.mp
25. gastric band.mp
26. lap band*.mp
27. lap-band*.mp
28. Gastric Bypass/
29. Gastric bypass*.mp
30. Roux-en-y*.mp
31. Exp Jejunoilieal Bypass
32. Jejuno-ileal bypass*.mp
33. Malabsorptive surgery.mp
34. Weight loss surgery.mp
35. Weight reductions surgery.mp
36. Exp Biliopancreatic Diversion/
37. Bilipancreatic bypass.mp
38. Exp Gastric Balloon/
39. Gastric balloon.mp
40. Exp Quality of Life/
41. Quality of life.mp
42. Exp Depression/
43. Depression.mp
44. Exp Mental Health
45. Mental health.mp
46. Psychosocial.mp
47. Exp Anxiety
48. Anxiety.mp
49. Exp Self Concept/
50. Self concept.mp
51. Exp Anger/
52. Anger.mp
53. Exp Eating Disorders/
54. Eating disorder.mp
55. Exp Bulimia Nervosa or exp Bulimia/
56. Bulimia.mp
57. Ednos.mp
58. Eating disorder not otherwise specified.mp
59. Exp Anorexia Nervosa
60. Anorexia nervosa.mp
61. Or/1-13
62. Or/14-20
63. Or/21-39
64. Or/40-60
65. And/ 61-64

6.3.3.2 Study selection

The electronic search was performed by BW and SC. The initial exclusion by title and abstract was performed independently by BW and SC and any disagreements discussed. Papers selected for full text review were reviewed by both BW and either SC, DC or RV. Provisionally eligible papers were then independently reviewed by two authors (BW, RV) and eligibility agreed. The reviewers were not blinded to study authors, affiliations or journal name (257).

6.3.3.3 Data collection process

Data were extracted from eligible studies independently by 2 authors (BW and SC), with differences harmonized. Where inadequate data were available, authors were contacted by email and any further data included in this review where appropriate.

6.3.4 Summary measures

The majority of studies were uncontrolled pre-post studies and used a variety of validated questionnaires to measure quality of life and mental health. To allow synthesis of results across studies, we followed guidance from the Cochrane Collaboration and calculated Cohen's d standardised mean difference for each questionnaire outcome, defined as difference in mean pre-test to post-test divided by the pre-test standard deviation. (258, 259) We calculated estimates of the standard error (SE) of the SMD using published formulas (260) due to insufficient detail in included studies. Given that correlations between pre- and post- scores were not provided by any included study, we followed guidance

from the Cochrane Collaboration in assuming a correlation of 0.5.(261, 262)Where questionnaires gave two separate summative scores (e.g. SF-36 physical component and mental component scores), the more conservative outcome was used in the meta-analysis. We have defined a large effect as ≥0.8 (four fifths of a SD), a medium effect as 0.5 (half a standard deviation) and a small effect as 0.2 (one fifth of a standard deviation)(263).

6.3.5 Synthesis of results

Meta-analyses were conducted using the metan commands in Stata 12 (Stata Corp, College Station, TX, USA) (264) specifying a DerSimonian and Laird random effects model (265). Heterogeneity between studies was measured using the I^2 measure in addition to Cochran's Q test, as the latter has been shown to be a poor test of heterogeneity, especially in meta-analyses with small numbers (266).

6.4 Results

Figure 6.2 below summarizes the PRISMA paper selection process.

Figure 6.2 PRISMA summary of study selection

15 papers from 10 different patient cohorts met the inclusion criteria and are summarized in tables 6.1 and 6.2 below. Four cohorts published outcomes at multiple time points across separate publications. Five cohorts were based in the US, and one each in Austria, Australia, Israel, Saudi Arabia and Sweden. Four cohorts published high-quality prospective longitudinal outcomes, using well-validated measures at uniform time points with clear reporting and high retention rates(138, 267-272). The remaining cohorts either used poorly validated outcome measures (273-276), reported incomplete data (277, 278) or reported outcomes at non-uniform time points (273-276, 279). A variety of different measures were used, at different time points, making comparison and meta-analysis difficult. Median cohort size was 32, ranging from 11 to 101 adolescent participants. Sufficient data were available to perform meta-analysis for change in quality of life (4 studies) and change in depressive symptoms (2 studies).

Three studies used control groups; one was a randomised controlled trial (RCT)(271),one used both matched adolescents undergoing non-surgical treatment and adults undergoing similar surgery (138), and another used non-weight matched intra-family controls(280)

Outcomes of 405 patients undergoing surgery were evaluated. In terms of surgical type, 139 underwent Roux-en-Y gastric bypass (RYGB), 202 underwent adjustable gastric band (AGB), and 64 underwent sleeve gastrectomy (SG). Age of participants was 9 – 20 years. Baseline BMI appeared higher in studies of RYGB (RYGB mean 50.9, AGB 46.5, SG 46.4

kg/m^2) with similar mean age (RYGB 16.7 years, AGB 16.2, SG 16.0). Change

in mean BMI in studies of RYGB ranged from -9.3 kg/m^2 at 4 months (272)

follow-up to -24.1kg/m^2 at 12 months (281). Mean BMI change in studies of

ABG ranged from -8.0 kg/m^2 at 9 months (277) to -12.7 kg/m^2 at 24

months(271). Mean BMI change was only reported in 1 study evaluating SG,

with a difference of -20.3kg/m^2 at 1 year(280).

Table 6.1 Summary of eligible studies. Studies grouped by cohort. NR= not reported, RCT = randomized control trial, n/r = not reported, AGB=Adjustable gastric band, RYGB = Roux-en-Y gastric bypass, SG= sleeve gastrectomy. Studies are grouped by research cohort.

First author Year	Cohort location	Cohort notes	Type of study / Data analysis	Bariatric procedure	% Female	Number at start (number completing questionnaire)	Number at latest follow-up (number completing questionnaire)	Baseline mean (SD) age (years)	Baseline age range (years)	Baseline mean (SD) BMI (kg/m^2)
O'Brien 2010	Melbourne, Australia	RCT: AGB v lifestyle	RCT	AGB	68	AGB: 25 (25) Control: 25(25)	AGB: 24 (24) Control: 18(18)	AGB: 16.5 (1.4) Control: 16.2 (1.2)	14.0-18.0	AGB: 42.3(6.1) Control: 40.4 (3.1)
Silberhumer 2006	Salzburg & Vienna, Austria		n/r	AGB	62	50(NR)	50(50)	17.1 (2.2)	9.0 - 19.0	45.2 (7.6)
Silberhumer 2011			n/r	AGB	NR	50(NR)	45(NR)	17.1 (2.2)	9.0 - 19.0	45.2 (7.6)
Jarvholm 2012	AMOS, Sweden	AMOS subgroup only (defined time period)	Prospective	RYGB	68	37(37)	37(37)	16.6 (1.3)	14.5-18.6	46.5 (5.9)
Olbers 2012		Full AMOS cohort	Prospective	RYGB	65	81(NR)	81(NR)	16.5 (1.2)	13-18	45.5 (6)

First author Year	Cohort location	Cohort notes	Type of study / Data analysis	Bariatric procedure	% Female	Number at start (number completing questionnaire)	Number at latest follow-up (number completing questionnaire)	Baseline mean (SD) age (years)	Baseline age range (years)	Baseline mean (SD) BMI (kg/m^2)
Loux 2008	Birmingham Children's Hospital, AL, US		Not reported	RYGB	NR	16(13)	12(9)	18.6 (1.7)	14.0 - 20.0	54.1 (7.6)
Ratcliffe 2012	Cincinnati Children's Hospital, OH, US	Consecutive subgroup within limited timeframe	Prospective	RYGB	69	16(16)	NR	16.3 (1.2)	NR	66.2 (12.0)
Zeller 2009		Full cohort	Prospective	RYGB	63	31(31)	29(28-29)	16.4 (1.4)	13.7-18.4	63.5 (10.6)
Zeller 2011		First 16 subjects with data at 18 & 24 months	Prospective	RYGB	65	16(16)	14(14)	16.2 (1.4)	n/a	59.9 (8.7)
Sysko 2012	New York, US		Prospective	AGB	72	101(NR)	NR (NR)	15.8 (1.1)	14-18	47.2 (0.89)*
Collins 2007	Pittsburgh, US		Retrospective	RYGB	64	11 (n/a)	9 (NR)	16.5 (0.2)	15.0-18.0	50.5 (2.0)

First author Year	Cohort location	Cohort notes	Type of study / Data analysis	Bariatric procedure	% Female	Number at start (number completing questionnaire)	Number at latest follow-up (number completing questionnaire)	Baseline mean (SD) age (years)	Baseline age range (years)	Baseline mean (SD) BMI (kg/m^2)
Holterman 2007	Univ. of Illinois at Chicago, IL	First 10 with 9 month data	Prospective	AGB	100	10 (10)	10(10)	16.0 (0.8)	15.0 - 17.0	50.0 (13.0)
Holterman 2010	Univ. of Illinois at Chicago, IL	Full cohort, except for n=1 who developed a comorditity, and n=5 who did not attend follow-up	Prospective	AGB	75	26(20)	12(12)	16.0 (1)	14.0 - 17.0	50.0 (10.0)
Aldaqal 2013	Jeddah, Saudi Arabia	32 young people, with intra-familial controls (not weight-matched).	Prospective	SG	68%	SG: 32 (32) Control 25(25)	32(32)	15.2 (1.2)	13-17	49.6 (4.9)
Raziel 2014	Tel Aviv, Israel		Prospective	SG	63	32(n/a)	31(22)	16.75	14-18	43.23

Table 6.2 Summary of mental health measures used in included studies. M-A = Moorehead-Ardelt Quality of Life Questionnaire, SF-36 = Short Form Health Survey, CHQ CF-50 = Child Health Questionnaire - Child Form, SFRS = Stunkard Figure Rating Scale, IWQOL-Kids = Impact of Weight on Quality of Life Kids, BDI = Beck Depression Inventory, BYI-D = Beck Youth Inventory Depression subscale, SPP = Harter's Self-Perception Profile for adolescents, EDE-Q = Eating Disorders Examination Questionnaire, FES = Family Environment Scale * model estimated means and standard error

First author & Year	QOL questionnaire	Depression questionnaire	Other questionnaire	Outcome analysis at uniform time points	Uniform time points (months)	Other time points (months)	Eligible for meta-analsyis?	Psychosocial assessment reporting issues
O'Brien 2010	CHQ CF-50	Nil	Nil	Yes	0, 24	No	No -no summative QOL scores	No CF-50 summative score results published
Silberhumer 2006	M-A	Nil	Nil	No	n/a	Mean 34.7 SD 17.5 range 3.6-85	Yes	
Silberhumer 2011	M-A	Nil	NIl	No	n/a	Two waves: 1.mean follow-up 34.7 2: at least 5 years follow-up	No – inadequate baseline data	

First author & Year	QOL questionnaire	Depression questionnaire	Other questionnaire	Outcome analysis at uniform time points	Uniform time points (months)	Other time points (months)	Eligible for meta-analsyis?	Psychosocial assessment reporting issues
Jarvolm 2012	Nil	BDI BDI-Y	BYI	Yes	0,4	No	Yes - depression	
Olbers 2012	SF-36	Nil	Nil	Yes	0, 12, 24	No	No – summative data not quantified	
Loux 2008	SF-36 IWQOL	Nil	Nil	No	n/a	mean 17 SD 12 range 1-39	Yes	Incomplete dataset
Ratcliffe 2012	IWQOL	Nil	SFRS SPPA	Yes	0, 6, 12	No	No – no QOL summative score	Full data collected for 14/16.
Zeller 2009	PedsQL IWQOL	BDI	Nil	Yes	0, 6, 12	No	No – Zeller 2011 longer follow-up	
Zeller 2011	PedsQL IWQOL	BDI	SPPA	Yes	0, 6, 12, 18, 24	No	Yes – QOL + Depression	

First author & Year	QOL questionnaire	Depression questionnaire	Other questionnaire	Outcome analysis at uniform time points	Uniform time points (months)	Other time points (months)	Eligible for meta-analsyis?	Psychosocial assessment reporting issues
Sysko 2012	PedsQL	BDI	EDE-Q FES	Yes	0, 1, 3, 6, 9, 12, 15	No	No - modelled outcomes published only	.
Collins 2007	M-A	Nil	Nil	No	n/a	Mean 11.5 SD 2.8 range 3-32	No – no summative score	
Holterman 2007	PedsQL	BDI	Nil	Yes	0, 3, 6, 9	No	No – only results of those with impaired function published	Not clear if sequential patients
Holterman 2010	PedsQL	Nil	NII	Yes	0, 6, 12, 18	No	No – inadequate data	Data only from attenders and those with impaired baseline scores
Aldaqal 2013	PedsQL	No	RSE	Yes	0, 12	No	Yes – QOL	Excluded if past or family history of psychiatric disorder
Raziel 2014	M-A	No	No	No	n/a	Range: 1-2 years	No – no summative scores	

6.4.1 Psychological and social outcomes of surgery

6.4.1.1 Quality of life

QOL outcomes of 405 adolescents undergoing bariatric surgery and 138 adolescent controls (25 randomised, 103 matched) were available. One study was an RCT. QOL was measured using 5 validated tools PedsQL (4 cohorts) (282), Moorehead-Ardelt Quality of Life Questionnaire (3 cohorts)(283, 284), Short Form Health Survey (SF-36) (2 cohorts) (285), Child Health Questionnaire - Child Form (CHQ CF-50) (1 cohort)(286) and Impact of Weight on Quality of Life Kids(IWQOL-Kids) (2 cohorts)(212).

6.4.1.1.1 Adjustable Gastric Band (AGB)

In the only RCT, O'Brien et al. compared 2-year outcomes of AGB compared to intensive lifestyle intervention(271). CHQ CF-50 summative scores were neither reported nor available from the study authors and so were not included in the meta-analysis. Compared to the intensive lifestyle control arm, physical functioning and change in health scores were significantly improved 2 years after ABG, but there were no significant between group differences for self-esteem, mental health, family activities, family cohesion, general behaviour or general health scores. Subjects undergoing AGB showed significant improvements (within group differences) in QOL related to family activities (p=0.006), general health (p=0.003), physical functioning (p=<0.001), self-

esteem (p=0.01) and change in health (p<0.001) but not general behaviour, family cohesion or mental health.

Sysko et al. used latent curve modeling to examine QOL changes of 101 adolescents over the first 15 months after AGB(269). PedsQL modeled mean (SE) total score improved from 77.22 (3.33) pre-surgery to 86.36 (4.96) at 12 months. All PedsQL mean subscores improved over the duration of the study. Linear models provided the best fit for total score and all QOL subscales with the exception of emotional functioning score where a quadratic model provided a better fit indicating a gradual deceleration in improvement over time. There was a significant variance in baseline emotional functioning subscores across the subjects, but improvement in PedsQL emotional function over time was independent of baseline scores.

Silberhumer et al. reported outcomes for 50 adolescents firstly at mean follow-up duration of 34.7 months and subsequently at 3- and 5-years(274) (275). Moorehead-Ardelt mean (SD) scores improved from 0.8 (0.3) at baseline to 2.11 (0.8) at a mean follow-up duration of 34.7 months. No change was seen between 3- and 5-year scores (mean (SD) 2.13 (0.8) and 2.11 (0.8)). Holterman et al. published 9-month follow-up data for the first 10 adolescents undergoing AGB(277) and subsequently data for 20 adolescents who reached 12-month follow-up and 12 adolescents who reached 18-month follow-up (287). 75% of adolescent-reported and 80% of parent-proxy PedsQL scores were impaired at baseline compared with two-thirds of adolescent-reported and half of parent-

proxy at latest follow-up, although numerator and denominator were not reported.

6.4.1.1.2 Roux-en-Y Gastric Bypass (RYGB)

Zeller et al. firstly reported 1-year follow-up data for 31 young people(281) and subsequently, data for the first 16 who have had 2-year assessments(267). All HRQOL measures improved after surgery, and with the exception of the social life subscore of IWQOL, log-linear models provided the best fit over the first year, indicating a deceleration in rate of improvement over time. Change in the social life subscore was linear, and showed no deceleration over time. PaedsQL physical health summative scores improved at a faster rate compared to psychosocial health (Slope (SE) 12.10 (1.11) v 7.62 (1.15)), and IWQOL physical comfort scores faster than body esteem (20.58 (1.38) v 11.75 (1.41)). Changes in PedsQL summative scores were deemed to be clinically meaningful over the first 6 months post-surgery, but not the subsequent 6 months. The authors suggest that these changes coincide with maximal weight loss in the first 6 months and subsequent deceleration in the next 6 months.

Quadratic models best fitted two-year data for all PedsQL subscores and three of four IWQOL sub-scores (Physical Comfort, Body Esteem, Social Life) indicating initial improvement in QOL, with subsequent deceleration in improvement and then decline over the two year period (physical health p=<0.0001, psychosocial health p=0.013, social life p=0.002, body esteem p=0.0007, physical comfort p=<0.0001, total score p=0.0001)(267). The authors suggest that these changes again coincide with weight loss in the first year and

subsequent minor weight regain in the second year. Clinically meaningful improvements were seen from baseline to 6 months for both PedsQL subscores and three IWQOL sub-scores (IWQOL: Physical Comfort, Body Esteem, Social Life), for weight-related IWQOL scores only from 6- to 12-months, but not between 12 to 18-months and 18 to 24-months.

Olbers et al. reported outcomes of 81 young people at 12- and 24-months. Compared to baseline, SF-36 physical component summary score and all four physical health domains were improved at 1 year and 2 years. Compared to baseline, three of four mental health sub-scales were improved at 1 year (vitality, social functioning, and mental health but not role-emotional), and two of four subscales were improved at 2 years (vitality and social functioning, but not role-emotional and mental health). Minor decreases were detected between 12- and 24-months, but these changes did not reach statistical significance.

Loux et al. reported outcomes of 16 patients(279). 4 of the 13 patients who completed pre-operative questionnaires were lost to follow-up, and follow-up data included those who did not have baseline assessments. The authors reported significant changes between preoperative and postoperative means for all quality of life domains (p<0.001). Collins et al. reported outcomes of 9 of 11 adolescents at mean follow-up duration of 11.5 +/- 2.8 months. Only the results of 3 of the 5 Moorehead-Ardelt questions were reported; all 9 reported physical function, social interactions and function at work as "improved" or "greatly improved" compared to before surgery(273).
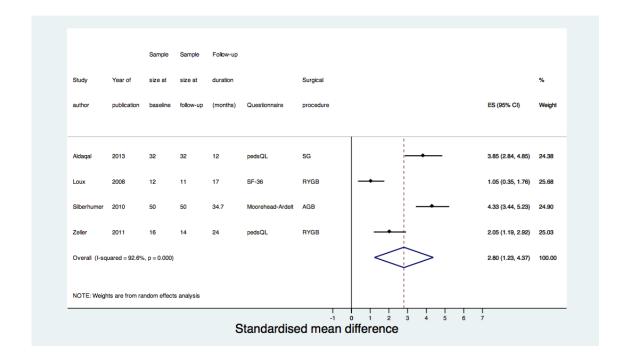
6.4.1.1.3 Sleeve gastrectomy

Aldaqal et al reported prospective 1-year outcomes for 32 adolescents(280), and quality of life improved across all PedsQL domains. 1-year total score have been included in the meta-analysis. Raziel et al reported 1-2 year outcomes for 22 of the 31 young people (71%) undergoing sleeve gastrectomy using 4 of the 5 Moorehead-Ardelt questions (question related to sexual activity was omitted)(276). Mean (SD) scores for each question were general feeling 5.0 (0.0), exercise satisfaction 2.6(1.3), social activity 4.8(0.4), work capability 4.8 (0.3) and food perception 3.8(1.1) using a 5-point likert scale (5=highest improvement compared to pre-surgery).

6.4.1.1.4 Meta-analyses

Figure 6.3 below summarises the studies eligible for meta-analysis. Mean change in QOL scores were 2.52 SD (95% CI 2.10-2.94) with I2 of 92.6%, indicating a "large" effect(263) with high heterogeneity between studies(266). We undertook further sub-group analysis, investigating the effect of only including studies that utilitised questionnaires with a single summative score, and found mean change in QOL scores of 3.40 SD (1.99-4.82) with I^2 of 86.0%.

Figure 6.3 Forest plot showing change in quality of life scores at
latest follow-up

Study author	Year of publication	Sample size at baseline	Sample size at follow-up	Follow-up duration (months)	Questionnaire	Surgical procedure	ES (95% CI)	% Weight
Aldaqal	2013	32	32	12	pedsQL	SG	3.85 (2.84, 4.85)	24.38
Loux	2008	12	11	17	SF-36	RYGB	1.05 (0.35, 1.76)	25.68
Silberhumer	2010	50	50	34.7	Moorehead-Ardelt	AGB	4.33 (3.44, 5.23)	24.90
Zeller	2011	16	14	24	pedsQL	RYGB	2.05 (1.19, 2.92)	25.03
Overall (I-squared = 92.6%, p = 0.000)							2.80 (1.23, 4.37)	100.00

NOTE: Weights are from random effects analysis

Standardised mean difference

6.4.1.2 Depression

Data on change in depressive symptoms following bariatric surgery were
available for 180 young people in 5 papers reporting outcomes of 4 prospective
cohorts(269, 272, 277, 281, 287). All five studies used the Beck Depression
Inventory (BDI); one of these additionally used the Beck Youth Inventory
Depression subscale (BYI-D). No data were available for clinical diagnoses of
depression.

6.4.1.2.1 Adjustable Gastric Band (AGB)

Sysko et al. used latent curve modeling to examine changes in depression
scores in the first 15 months after AGB(269). A quadratic model best fitted
changes in BDI score, indicating that BDI scores improved after surgery (i.e.

less depressive symptomatology), but with a deceleration in improvement over time, and subsequent decline from around 9 months post-surgery. There was significant variance in baseline BDI score, but it was the change in BMI after surgery rather than baseline BDI that predicted the change in BDI after surgery. Only modeled BDI-scores were reported and as such, could not be included in the meta-analysis.

Holterman et al. reported depression data only for the first 10 of 26 subjects who completed 9 months follow-up (277), but not for the remaining in the cohort(278). Data were reported for the 3/10 adolescents who had BDI scores in the clinical range at baseline (suggestive of a diagnosis of depression); at 9 months 0/3 had depression scores in the clinical range and mean (SD) scores in this subgroup had fallen from 25.3 (7.8) at baseline to 2.2(2.7) at 9 months.

6.4.1.2.2 Roux-en-Y Gastric Bypass (RYGB)

Zeller et al. reported firstly outcomes of 31 young people at 12-months(281), and subsequently, outcomes of the first 16 who reached 2-year follow-up(267). 12/31 adolescents (38.7% of cohort, 45% females, 27.3% males) had BDI scores in the "clinical range" indicating likely clinical depression at baseline compared to 2/31 (6.5%, both females) at 12 months(288). At 2 years, 2/16 (12.5%) had levels in the clinical range compared to 10/16 (62.5%) at baseline. Log-linear models provided the best fit for one-year data, indicating a deceleration in rate of improvement over time (intercept 15.11 (SE 2.14), Slope -3.87 (0.78), p<0.001). Quadratic models best fitted data for the first two years (t

(1.15) = 3.38, p=0.004), showing that the rate of improvement slowed at the end of the first year, with a slight deterioration in the second year.

Jarvolm et al. reported early subgroup data of the larger AMOS cohort. Mean scores of the 37 fell from mean 15.8 (SD 10.3) at baseline to 12.3 (9.5) at 4 months post-surgery (p=0.02). At baseline, 27% of adolescents (10/37) had scores above a threshold where everyday life is substantially affected (>90th centile of normative data(288)); at 4 months this figure was 11% (4/37), although significance of change was not reported. 4/37 adolescents (11%) had substantially more depressive symptoms on BYI-D at 4 months compared to baseline (defined as falling outside the 95% confidence interval of the baseline score), and were reported as impaired compared to baseline, whereas the rest (33/37, 89%) had unchanged or improved scores. Further data from this cohort have not been published to date.
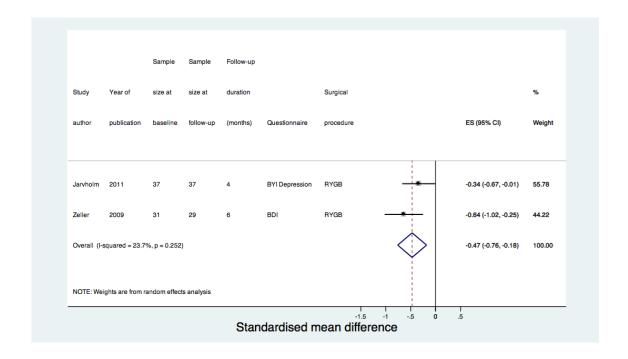
6.4.1.2.3 Sleeve gastrectomy

No data available.

6.4.1.2.4 Meta-analysis

Figure 6.4 below summarises the studies eligible for meta-analysis. Mean changes in depression scores were -0.47 SD (95% CI -0.76, -0.18) with I^2= 23.7%, indicating a "medium" effect with low heterogeneity.

Figure 6.4 Forest plot showing change in depression scores at 4-6 months after surgery

Study author	Year of publication	Sample size at baseline	Sample size at follow-up	Follow-up duration (months)	Questionnaire	Surgical procedure	ES (95% CI)	% Weight
Jarvholm	2011	37	37	4	BYI Depression	RYGB	-0.34 (-0.67, -0.01)	55.78
Zeller	2009	31	29	6	BDI	RYGB	-0.64 (-1.02, -0.25)	44.22
Overall (I-squared = 23.7%, p = 0.252)							-0.47 (-0.76, -0.18)	100.00

NOTE: Weights are from random effects analysis

Standardised mean difference

6.4.1.3 Other psychological and social outcomes

Outcomes for other psychological and social outcomes in adolescents were sparse. 4 papers reported outcomes using the Beck Youth Inventory (BYI)(272) (one study), Stunkard Figure Rating Scale(268) (one study), Harter's Self-Perception Profile for adolescents (SPPA)(289) (two studies) and Rosenberg Self-Esteem Scale (RSE) (one study).

Jarvolm et al. reported early subgroup data of the larger AMOS cohort. (272).8/37 (21.6%) had a clinically significant BYI-anxiety score at baseline; at 4 months, 4/37 (10.8%) had a clinically significant score and 4/37 (10.8%) had significantly increased anxiety scores. 8/37 (21.6%) had a clinically significant BYI-anger score at baseline; at 4 months 5/37 (13.5%) had significantly

increased anger scores (incidence of raised scores at 4 months not reported). 5/37 (13.5%) had a clinically significant BYI-disruptive behaviour score at baseline, with 7/37 (18.9%) having significantly increased disruptive behaviour scores (incidence of raised scores at 4 months not reported). 7/37 (18.9%) had impaired self-concept scores at baseline; at 4 months 3/37 (8.1%) had impaired scores, with 6/37 (16.2%) reporting significantly reduced (i.e. worse) self-concept scores. Improvements in mean domain scores between before and after bariatric surgery were significant for BYI-anxiety (p=0.004, student-t test), BYI-depression (0.02) and BYI-self concept (0.004).

Zeller et al. reported changes in self-concept subscores over the first 2-years(267). Quadratic models best fitted social acceptance [t(1,69) = -2.42, p=0.02], physical appearance [t(1,69) = -3.19, p=0.02] and close friendship scores[t(1,30) = -2.76, p=0.008]. Substantial improvement was seen over time across these domains, but with deceleration towards the end of the first year, and deterioration in the second post-operative year. Linear models best fitted global self-esteem [t(1,69) = 2.98, p=0.004], athletic competence [t(1,69) = 2.37, p=0.02], job competence [t(1,69) = 2.24, p=0.03] and romantic appeal scores [t(1,69) = 2.98, p=0.004), indicating continued improvement over 24 months post-operatively, with no evidence of deceleration. Changes in scholastic and behavioral conduct were not reported.

Ratcliff et al. reported changes in body image dissatisfaction (BID) in the first year(268). BID, defined as the difference between perceived and desired body shape, fell in the first 6 months post-surgery but not in the subsequent 6

months. This coincides with the maximal weight loss seen in the first 6 months (mean loss 22.4kg/m^2) and much smaller loss in the subsequent 6 months (4. 7kg/m^2). Change in perceived body shape was correlated with change in BMI. Discrepancy between current and ideal body size, rather than current body size alone, was negatively correlated with weight related quality of life (WRQOL), indicating that the difference between the actual body weight and the ideal body weight most influences QOL, and those with the smallest discrepancy have the best weight-related QOL. No other correlations were detected between current body size or body image dissatisfaction and either IWQOL, body esteem or physical appearance attitudes as measured by the SPPA.

Aldaqal et al analysed changes in self-esteem over the first year follow SG(280). Mean group scores significantly increased from 16.01 (2.7) pre-operatively, to 24.66(2.36) at the end of the first year, indicating improved self-esteem.

6.4.2 Psychological and social predictors of success after bariatric surgery

6.4.2.1 BMI outcomes

We identified only two studies that analysed associations between pre-operative psychological, quality of life or social measures and weight-related outcomes after surgery.

Sysko et al. examined baseline predictors of both initial and post-operative BMI trajectory over the first year post-surgery including gender, age, race/ethnicity,

median household income, distance from treatment centre, "clinically significant symptoms" (self-injurious behaviours, loss of control eating, BDI and PedsQL scores), family factors (involvement with social services, Family Environment Scale scores), DSM-IV diagnoses, and current and past psychiatric treatment) (269). Only higher levels of loss of control eating (as measured by the EDE-Q) and family conflict (as measured by the conflict subscale of the Family Environment Scale) were significant predictors of rate of weight change over time, and both predicted a lower rate of change over time.

Jarvholm found no significant relationship between changes in BMI in the 4 months post-RYGB and any baseline psychological parameter(272).

6.4.2.2 Psychological and social outcomes

Loux et al. reported a correlation between pre-operative QOL scores and change in QOL after surgery (Physical Component Score (PCS) r=-0.94, p<0.001, Mental Component Score (MCS) r=-0.9, p<0.005), indicating those with increased impairment at baseline benefitted the most from surgery(279). In a larger and more complete dataset, Sysko et al. found no correlation between baseline QOL or depression scores and change in QOL(269). Importantly, after controlling for baseline BMI and PedsQL score, improvement in PedsQL was significantly correlated with change in BMI after surgery. A similar pattern was seen for BDI scores.

6.5 Discussion

6.5.1 Summary of results

This is the first systematic review of psychological and social outcomes of all types of bariatric surgery in adolescents. We found moderate but consistent evidence that bariatric surgery in adolescents resulted in overall improvement in quality of life and in depressive symptoms in the first two years. Overall quality of life improved from before to after bariatric surgery in all studies identified in this review, regardless of surgical operation performed. In meta-analysis, overall QOL improved by 2.8 SD at latest follow-up, although only 4 studies were eligible for inclusion. Improvement in QOL was greater in the domains relating to physical function compared to emotional/mental function. In the only RCT, adolescents who underwent ABG had superior self-reported physical function and overall health compared to controls who underwent intensive lifestyle intervention.

Depressive symptomatology improved across all studies in the first year after bariatric surgery, and meta-analysis showed 0.52 SD improvement in depression scores 4-6 months after surgery. Depressive symptoms appear to follow a similar quadratic pattern to QOL, with significant improvement in the first 6 post-operative months, substantial deceleration by 12 months and suggestions of moderate deterioration at 24 months.(267) Depression scores in the clinical range were seen in up to 38.7% of cohort subjects at baseline; only 2 of 12 (16.7%) patients in this cohort had clinical range symptoms at last follow-up(281).

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A consistent theme emerged that QOL and depressive symptoms improved most in the first 6-9 months, with little further improvement and even some deterioration. One study reported that changes in QOL scores were only meaningful in the first 6 months, but not in the subsequent 18 months. Given that weight loss after bariatric surgery is most dramatic in the first 6 months, and is generally complete by 12-24 months post-operatively, this suggests that QOL improvement may be linked with timing and degree of weight loss post-operatively. Little is understood about this association. Only one study formally examined this association and reported that change in QOL and depression scores post-surgery was associated with change in BMI, rather than baseline score whilst another suggests that desired weight, and the mismatch between actual and desired weight is an important factor in changes in quality of life.

Limited outcome data for other psychosocial measures were available. 4-month outcomes of the AMOS cohort show improvement in mean anxiety and self-concept scores, but not disruptive behaviour or anger(272). Improvements were seen across all self-perception domains over two years in one study, with mean levels across all domains except for Athletic Competence lying within normative ranges at 2 years. As seen in QOL and depression scores, some domains showed a quadratic trend, notably social acceptance, appearance and close friendship(267). There are no data describing the impact of surgery on disordered eating behaviours and cognitions in this age group.

We found only one study to report baseline psychosocial predictors of BMI or psychosocial outcomes of surgery(269). Multiple factors were measured, and

only loss of control eating and family conflict were predictors of BMI outcome; both predicted a reduced rate of change of BMI.

6.5.2 Discussion of results

Current data regarding the psychological impact of surgery are sparse, particularly beyond 24 months, with inconsistent and incomplete reporting. Compared to other outcomes, particularly BMI and metabolic parameters, psychosocial outcomes are both poorly measured, and poorly reported. Only one study provided RCT-level evidence, and multiple publications, including one reporting one-year outcomes of 890 adolescents, were not eligible because they did not provide adequate measures of psychological function(290).

Adolescents presenting for bariatric surgery have severely impaired quality of life with high rates of depression and disordered eating(254). Adolescents have not usually accumulated the medical co-morbidities seen in adults undergoing BAS and indications for surgery are likely to be predominantly related to psychosocial distress. This review shows that for the average subject undergoing bariatric surgery, quality of life, depressive and anxiety symptoms improve after surgery, with peak improvement at 6 months after surgery. There was some evidence that psychological function deteriorated thereafter.

The outcomes of the only RCT are interesting and merit attention(271). Although the group undergoing AGB lost 31.6kg more than controls, changes in quality of life across many domains (notably general behaviour, family cohesion and mental health) were not significant either within- or between-groups. This is

potentially due to the small sample size (only 25 in each group), and larger RCTs are needed to determine if surgery in adolescence results in superior quality of life change compared to intensive lifestyle intervention.

The QOL meta-analysis showed high levels of heterogeneity between studies. This is not surprising for two reasons. First, the studies used different time points and the review has shown a clear temporal change in QOL over time. Second, different measures were used across studies with differing validity in this population. Despite their heterogeneity, they all show large magnitudes of change in QOL after surgery.

The QOL domains with significant improvement after surgery are those closely related to the physical and physiological effects of substantial weight loss, namely change in physical health and physical functioning. These outcomes are seen across several studies and we hypothesise that improvement in quality of life is most closely linked to the physical and physiological benefits of substantial and prolonged weight loss, currently only achieved by bariatric surgery (106, 166)

Many questions remain unanswered, particularly the long-term outcomes, optimal time for undergoing surgery and psychosocial predictors. There are currently insufficient data to predict which patients will benefit most from surgery, and as such, no evidence-based recommendations can be made following this review. Some questions will be answered by ongoing studies but additional research is needed into this important patient group.

6.5.3 Limitations

Only a small number of studies were eligible for inclusion in the meta-analysis, due to two factors: a) lack of reporting of summative scores where summative score is available and b) use of questionnaires that does not included a summative score. Generally, psycho-social outcomes were poorly reported across all studies, requiring use of accepted measures for calculating unreported study parameters, e.g. no study reported correlation between baseline and post-surgery individual scores. A wide range of questionnaires was used, with varying quality, making comparison between different studies and procedures difficult. We chose to use the SMD approach to allow comparison across these different instruments. High heterogeneity observed in our meta-analyses is likely to reflect differences in instruments used as well as populations. Further, SMD is influenced by the baseline variance which differs between studies. Our inclusion of follow-up data from different time points, necessary due to insufficiency of data and lack of consistency across studies, together with some studies reporting outcomes only at latest follow-up is likely to obscure the time trends described earlier(255). Additionally, psycho-social outcomes were frequently poorly reported, and this may have resulted in misinterpretation of results.

6.5.4 Summary

High quality psychosocial outcome data for adolescent bariatric are lacking, with data restricted to 2 years post-surgery. These data suggest that mean quality of life and depressive symptomatology improve after bariatric surgery, although

not in all patients. Improvements in psychological function appear to be

associated with reduction in BMI rather than baseline psychological function.

Improvement appears to peak at 6-12 months. There is weak evidence that

psychological function predicts BMI outcomes after surgery; those with higher

baseline levels of loss of control eating and family conflict appear to have

poorer BMI outcomes.

7 Outcomes of fifty patients entering a NHS adolescent bariatric surgery programme

7.1 Abstract

Objective. Bariatric surgery is the most effective intervention for weight loss and obesity-related co-morbidities currently available. Little is known about adolescents entering NHS bariatric programmes. We aimed to characterize those entering a pathway, and report their outcomes.

Design. Prospective service evaluation of patients assessed within a single NHS adolescent bariatric service.

Results. 50 patients assessed between 26th July 2007 and 27th January 2014; 6 (12%) were not eligible for surgery, 7 (14%) actively opted out, 8 (16%) were lost to follow-up and 29(58%) underwent surgery (18 sleeve gastrectomy (SG) 11 Roux-en-y gastric bypass (RYGB) and 0 adjustable gastric band). Mean (SD) age at initial assessment was 16.0(1.3) years and 18.3(1.3) at surgery (youngest 15.7 years). Mean time taken to surgery was 1.8 years; longer in those with higher BMI and aged below 14 at first assessment. Mean (SD) BMI at surgery was 53.1 (8.3) kg/m^2, lower in those undergoing RYGB (-5.2, 95% CI -11.6, 1.13). Follow-up was inconsistent and challenging; 1 was transferred to a regional centre, 26.3% (10 of 28) attended ongoing follow-up within our protocol, 21.4% (6) had intermittent monitoring and 42.9%(12) were lost to follow-up. Mean BMI change at 1 year (-14.0 kg/m^2) and complications were

similar to published cohorts. Data from 11 lost to follow-up were obtained and outcomes appeared similar to those actively followed-up.

Conclusion. Adolescent bariatric surgery in the NHS appears effective, with outcomes similar to those reported internationally. Further work is needed to optimise post-surgical surveillance, and reduce age at surgery.

7.2 Introduction

Bariatric surgery is currently the only intervention resulting in clinically meaningful weight loss for obese children and young people.(135) In the UK, national guidelines for adolescent bariatric surgery are contained within the most recent NICE obesity guideline(139) summarized in section 1.8.2.3. It recommends that bariatric surgery is considered only in exceptional circumstances, and if young people have achieved or nearly achieved physiological maturity.

The largest and most complete bariatric research cohorts have come from the US(137, 255) and Sweden(138) with between 25 and 242 adolescents undergoing surgery, compared with only very small case reports totaling 20 adolescents published from the UK.(147-149) A recent systematic review of adolescent bariatric surgery showed mean loss of 13.5 kg/m^2 at 1 year post-surgery with greatest change seen in those undergoing the Roux-en-Y procedure (RYGB), followed by sleeve gastrectomy (SG) and adjustable gastric band (AGB).(135) Such changes are very much greater than those from with drug treatments such as metformin (mean loss 1.4 kg/m^2)(125), orlistat (-0.8 kg/m^2)(116) or lifestyle interventions (-1.25kg/m^2).(101)

Outcome studies have universally focused on those who received surgery.(135) Only one clinical service in Saudi Arabia has published outcomes of a clinical service. (291) It is unclear how many young people who are referred for surgery actually receive it, and the reasons for not receiving it in those referred. Furthermore, the outcomes of those entering a clinical programme compared to

a research cohort are largely unknown. Such data are important for planning and evaluating adolescent surgery programmes, particularly within state-funded systems.

Our aim was to characterize the patients referred to an adolescent bariatric surgery programme within the NHS in England and report their outcomes, including number reaching surgery, change in BMI and complications. We present data for the first 50 patients assessed within a single service.

7.3 Methods

We reviewed data on adolescent patients referred to University College London Hospitals (UCLH) for consideration of bariatric surgery by their general practitioner (GP), NHS paediatrician, or from our medical weight management service. Inclusion criteria were age less than 18 years at first assessment. Patients were identified prospectively, and included all patients seen from the start of our surgical programme in July 2007 until 27th January 2014.

Body weight was measured using a Tanita BC-418MA scale or SECA 645 scale where body weight exceeded 200 kg. Height was measured using a wall-mounted stadiometer. BMI was calculated as weight /height^2 (kg/m^2).

Socio-economic status was derived from the patient's home postcode using the 2007 Index of Multiple Deprivation (IMD) score and rank (England only), and grouped into five deprivation quintiles (1=most deprived).(209) Those coming from the bottom quintile were defined as "deprived". Ethnicity was self-reported using a list used by the hospital.

Baseline cardio-metabolic screening was undertaken in patients completing the initial evaluation process. We screened all participants for diabetes using HbA1c(292), fasting glucose and insulin levels, followed by a standard glucose tolerance test (OGTT) in those undergoing surgery.(204) Blood pressure was measured using automated blood pressure monitor (Datascope Accutor Plus)(205) with appropriately sized cuff. High blood pressure was as above 98th centile for age and gender.(206) Lipid levels were stratified following American

Heart Association guidelines.(293) Those eligible for surgery had a more complete assessment, including screening for sleep apnoea and polycystic ovarian syndrome if history and examination were suggestive.(154) Completeness of co-morbidity data varied by length of time in bariatric pathway; some of those who exited the pathway early did not have a full assessment. For the purpose of this publication, we used results of previous recent co-morbidity screening where we were unable screen ourselves due to early dropout.

Eligible patients were offered choice of RYGB or SG procedure, with those having higher BMI encouraged to undergo SG. We used clinic letters, electronic records and calls to families and GPs to collect BMI trajectories (patient-reported BMI outcomes not included in analyses) and co-morbidity data. We assumed that pre-operative participants were not interested in surgery if they missed two successive appointments and we were unable to contact them by phone or letter. We attempted to contact all post-operative patients who had not attended follow-up within the previous 6 months if they were in the first two post-operative years, or 1 year after that. Where we were unable to contact participants, we gathered information from their parent or GP. We wrote to the GPs of all patients lost to follow-up informing them of outcomes and recommended ongoing surveillance.

7.3.1 Analyses

We first used descriptive statistics to describe patients and comorbidities before and after surgery.

Group differences in demographics and BMI outcomes were analysed using student-t and chi^2 tests. Regression models were used to analyse time take to surgery from first assessment. To allow comparison of BMI outcomes, we calculated 1-year change using BMI measurements recorded nearest to one year (between 8 to 16 months after surgery)

7.3.2 Study approval

This study fulfilled National Research Ethics Service (NRES) criteria for service evaluation, and was registered in the UCLH Research & Development Department.

7.4 Results

7.4.1 Pre-operative patient flow:

The patient flow is summarised in Figure 7.1 below. A total of 50 patients were seen between July 2007 and 27th January 2014. As of 26th September 2016, all 50 young people had completed the pre-operative phase; 7(14%) actively withdrew from the pathway, 6 (12%) were deemed ineligible, 8 (16%) did not attend to complete the assessment process, and 29 (58%) underwent bariatric surgery. Reasons given for active withdrawal were the wish to pursue non-surgical interventions and stress of coming into a London hospital; none were due to lack of funding.

Figure 7.1 Patient assessment flowchart

Of the six who were deemed not eligible, principal reasons for exclusion were: residence outside the UK and as such deemed incompatible with safe post-

operative monitoring (n=1), inability to consent due to learning difficulties (n=2), severe needle phobia (n=1), inconsistent desire to undergo bariatric surgery (n=1), and complex behavioural difficulties (n=1). No patients were excluded because of psychiatric disorders. One patient deemed ineligible by our service subsequently had surgery in the private sector.

7.4.2 Patient characteristics:

Patient demographics and co-morbidities are in summarized in

Table 7.1(below) All subjects undergoing surgery underwent full baseline cardio-metabolic screening. Of the 21 not undergoing surgery, three did not have baseline cardio-metabolic screening within our service including two that only attended a single assessment and did not wish to pursue further investigations or assessment.

Three had hypothalamic obesity secondary to previous treatment of hypothalamic-pituitary tumours, the two with previous craniopharyngioma underwent surgery but given their outcome (described below), surgery was not offered to the subsequent patient with optic glioma. In addition, one with an identified obesity-promoting monogenic genetic variant (homozygous leptin receptor mutation) with one with achondroplasia underwent surgery.
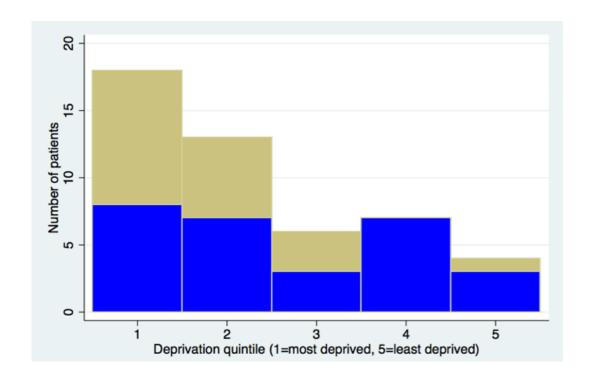
Table 7.1 Demographics and baseline co-morbidity data for complete cohort, those undergoing surgery, and those not undergoing surgery. NAFLD = non-alcholic fatty liver disease, n/a = not applicable (those not undergoing surgery did not have full evaluation).

	Whole cohort	No surgery	Surgery	p
Number	50	21	29	
Female n (%)	29 (58.0)	11 (52.4)	18(62.1)	0.5
Mean (SD) age at baseline	16.0 (1.3)	15.9 (1.3)	16.1 (1.3)	0.9
Age range at baseline	12.8-18.5	13.4-18.5	12.8-17.8	0.6
Mean (SD) baseline BMI (kg/m^2)	51.2 (7.5)	51.1 (7.4)	51.3 (7.8)	0.9
Mean baseline zBMI	4.21 (0.34)	4.21 (0.3)	4.20 (0.3)	1.0
BMI range (kg/m^2)	37.5-69.6	37.5-64.8	38.2-69.6	
British	29 (58.0%)	14 (66.7%)	15 (51.7%)	0.7
African/Caribbean	8 (16.0%)	3(14.3%)	5 (17.3%)	
Asian	5 (10.0%)	1 (4.8%)	4 (13.8%)	
Other	8 (16.0%)	2 (14.3%)	5 (17.2%)	
Low socio-economic status	18/48 (37.5%)	10/20 (50.0%)	8/28(28.6%)	0.3
High blood pressure	16/48 (33.3%)	7/21 (33.3%)	10/29 (34.4%)	
High lipids	17/43 (39.5%)	4/16 (25.0%)	6/27 (22.2%)	
Type 2 diabetes	5/50 (10.0%)	2/20 (10.0%)	3/29 (10.3%)	
Polycystic ovarian syndrome	n/a	n/a	5/18 (27.8%)	
Sleep apnoea	n/a	n/a	4/29 (13.7%)	
NAFLD	n/a	n/a	3/29 (10.3%)	

Regarding access to surgery, there was no difference in gender, BMI or age between those having surgery, and those not. Deprivation data were available for 48 participants (1 from Scotland, 1 postcode not registered on IMD). Graphically it appears that patients from more deprived populations were less likely to get to surgery (Figure 7.2 below) however there was no difference in access to surgery between those in the most deprived quintile and the remainder of the cohort.

Figure 7.2 Access to surgery by socio-economic status (1= most deprived quintile,5= least deprived). Green = assessed but did not undergo surgery, blue = underwent surgery.

Mean time from assessment to surgery was 1.8 years (range 0.5-4 years). All 4 patients entering the pathway below 14 years of age waited at least 2.5 years for surgery. There was moderate evidence that baseline BMI (0.04 years per kg/m^2 (95% CI -0.00,0.08)) but not duration of program (-0.08 per year (-
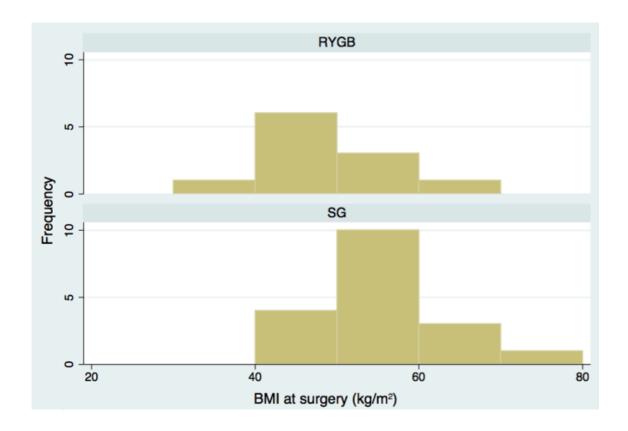
0.30,0.13)) or age (0.10 per year (-0.34,0.55)) was associated with time to surgery in those aged 14 years and over at programme entry. Temporary cessation of the programme for 6 months in 2013 due to reorganization of the service resulted in delays at that time.

7.4.3 Bariatric surgery details

A total of 18 patients underwent SG and 11 RYGB; none had an AGB. One RYGB procedure included use of a Fobi ring. All procedures were performed exclusively by bariatric surgeons fulfilling British Obesity & Metabolic Surgery Society (BOMSS) competencies, and reporting outcomes to National Bariatric Surgery Registry (NBSR). Participants fulfilled NICE criteria including BMI greater than 40kg/m^2 at the time of surgery planning. (139)

Figure 7.3 below shows BMI distribution by surgical procedure. Mean (SD) BMI was 49.8 (7.0) for those undergoing RYGB, and 55.0 (8.7) for SG. There was moderate evidence that those undergoing RYGB had lower BMI (difference in means -5.2, 95% CI -11.5, 1.1). Mean (SD) age at surgery was 18.3 (1.3) years with no difference between procedures (difference in means -0.6, 95% CI -1.5,0.4). The youngest patient was aged 15.7 years; a total of two were aged under 16 years, eight were aged 16-17 years and the remaining nineteen were aged 18 or over.

Figure 7.3 BMI at surgery by procedure (top = Roux-en-Y gastric bypass, bottom = Sleeve Gastrectomy)

7.4.3.1 Weight outcomes

Follow-up post-surgery was inconsistent. At the time of this analysis, patients were mean 4.0 years (SD 1.9) post-surgery (range 1.4-7.9). One patient was transferred to a regional centre for ongoing follow-up within the first 18 months. All others were offered follow-up at our centre; 26.3% (10/28) attended ongoing follow-up within our protocol, 21.4% (6/28) had intermittent monitoring and 42.9%(12/28) were lost to follow-up. Follow-up was achieved in 79.3% at 1 year post-surgery (23 of the 29 reaching 1 year since surgery), 59.1% at 2 years (13 of 22) and 33.3% at 5 years (3 of 9).

We successfully gained follow-up information on 16 of 17 participants with intermittent or inactive follow-up (8 from young person, 4 from parents and 4 from GPs); the remaining patient had no identifiable contact details or GP. Only one was attending bariatric follow-up at another centre, and none had monitoring of micronutrient status.
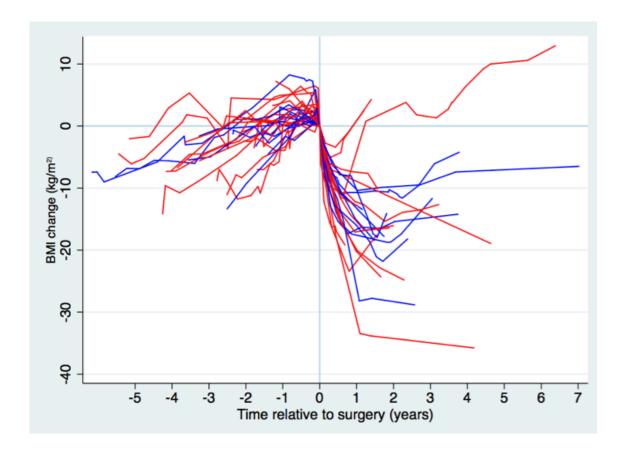
BMI data at 1 year were available for 23 patients (11 RYGB, 12 SG). There was no evidence of difference in means between the two surgical procedures (mean (SD) RYGB -14.8 (5.5), SG -13.4(10.8), p=0.7); however, greater variation in BMI change at 1 year was seen in patients undergoing SG than RYGB.

Figure 7.4 below and 9.1 (appendix) shows the BMI trajectory of each patient undergoing surgery and the change in BMI relative to the day of surgery. A substantial variability in BMI trajectories was seen across subjects. Data were predominantly limited to 3 years after surgery. In line with published studies, the majority of patients lost weight rapidly in the first 6 months (10-20kg/m^2), with subsequent deceleration in the rate of weight loss in the next 6 months and weight stability in the second year. The patient with achondroplasia lost over 30kg/m^2 in the first year after surgery; however his stature makes BMI hard to interpret.

Of those attending ongoing follow-up, three patients regained all weight loss. This included one with leptin receptor variant whose genetic variant was not expected to respond poorly to surgery (personal communication with Prof Sadaf Farooqi, University of Cambridge) and one with craniopharyngioma.

Those who had telephone reviews due to delayed or absent follow-up reported BMI trajectories similar to those attending follow-up (one GP was not aware of their patient's weight trajectory). One patient reported regain of all post-operative weight loss and one mother reported an unspecified amount of weight regain after removal of the Fobi ring; neither had any previous co-morbidities suggesting they may respond poorly to surgery.

7.4.3.2 Co-morbidities and complications

No patients died post-operatively; 2/29 (10.5%) patients had a gastric perforation, one identified in the immediate post-operative period after RYGB

and the second 1-year after surgery. Both were successfully repaired by laparoscopy with no further sequelae. 2/29 (10.5%) patients had a gastro-jejunal stricture, both treated after respectively one and two endoscopic dilatations.

The patient with pre-existing cerebral vascular disease and previous cerebral vascular events (CVE) had a further CVE in the peri-operative period resulting in hemiplegia, expressive and receptive dysphasia and loss of thirst. He required prolonged neuro-rehabilitation with residual loss of function. The following sequelae were also reported: gall stones requiring cholecystectomy (n=3), excess skin (10), pregnancy (2), gastro-eosophageal reflux (7), unexplained abdominal pain (2), constipation (1), oesophagitis resolved after removal of Fobi ring (1), hypotension (1 postural, 1 cause unknown), ulcerative colitis with biliary cirrhosis and gastroparesis (1), poorly controlled PCOS (2), skin infections (1) and dumping syndrome (1).

Data were insufficient to allow detailed analysis of resolution of co-morbidities or cardio-metabolic risk factors post-operatively, with the exception of diabetes. Diabetes control improved in all three patients with diabetes and two were able to stop all hypoglycaemic agents.

7.5 Discussion

7.5.1 Main findings

This is the first study describing the characteristics and outcomes of patients entering an adolescent bariatric surgical programme in the NHS. We found that over half of adolescents seen were both eligible and interested in surgery. Main reasons for non-eligibility were lack of capacity to consent, behavioural difficulties and inconsistent desire for surgery. Patients had relatively few identified co-morbidities and surgery was undertaken mainly for weight loss rather than control of obesity-related conditions.

Change in BMI compared well with that described in a recent systematic review (13.5 kg/m^2).(135) There was no operative mortality and surgery complication rates were within the range (4 to 33%) described for adolescent SG and RYGB in other centres internationally.(135) Patients undergoing SG had a higher baseline BMI and greater variation in BMI change after surgery compared to those having a RYGB. High rates of attrition to follow-up were seen after surgery, despite earlier careful identification and support of medical and psychological co-morbidities, and good adherence to the pre-operative preparation programme.

These data raise important issues. First, we were referred low numbers of adolescents with weight-related co-morbidities that respond well to bariatric surgery, such as type 2 diabetes, sleep apnoea and idiopathic intracranial hypertension.(129, 294, 295) The reasons for this are not clear, and we believe

that raised awareness of the safety and efficacy of bariatric surgery to control these conditions will increase referrals. Subsequent to this cohort, we have seen an increase in patient referrals, particularly those with type 2 diabetes.

Second, the mean age at surgery was 18 years of age and the youngest 15.7 years. This compares to a mean age of 16.5 and 17.1 years respectively in large Swedish and US cohorts described previously. (137, 138) This may reflect time taken from first assessment to surgery, or reluctance to refer younger patients in the NHS. NICE guidance recommends surgery in those who have "nearly reached physiological maturity", a conservative recommendation compared to other international guidelines.(296) Earlier referrals may help reduce the age at surgery, and change the BMI trajectory of this population.

Third, we encountered various dilemmas about eligibility for surgery, particularly for those who perceived that surgery was the only remaining treatment option. A systematic review undertaken by these authors has shown that there is a limited evidence base on psychosocial predictors of outcome after surgery in adolescence, with only two studies comparing baseline psychosocial variables and BMI outcomes. (134) In addition, we reviewed three patients with previous pituitary-hypothalamic tumours. Two underwent a bariatric procedure (SG) with disappointing results. A subsequently published small case series suggest improved outcomes after RYGB compared to SG in this cohort,(297) however small numbers and the non-randomised methodology limit generalizability. A registry has since been started to monitor the outcomes of those with obesity due to hypothalamic dysfunction undergoing surgery.(298)

Fourth, there was significant attrition both before and after surgery. Our data suggest a non-significant trend for those with lower SES to be more likely to drop out pre-surgery, and it will be important to monitor and facilitate access of deprived groups to surgery over time. Only post-operative attrition has been reported in research cohorts, with follow-up rates of 89-100% at 2 years, (136-138) with low attrition achieved through telephone surveillance and home visits.

Our telephone assessments in those not attending follow-up revealed that patients were largely doing equally well after surgery as those attending follow-up, and attrition was largely due to the practicalities of attending follow-up rather than poor outcomes. Attrition within the adolescent service has subsequently improved with appointment of a dedicated adolescent specialist nurse who provided email, SMS and telephone monitoring in addition to standard clinic appointments. The needs of young adults in adult bariatric services are not known, and merit investigation.

Lastly, patients frequently described issues with excess skin, with difficulty accessing plastic surgery in the NHS due to variations in funding and eligibility criteria.

7.5.2 Limitations

Our study is subject to the common limitations of service evaluation studies; e.g. data were not collected at standardised timepoints and collection of co-morbidity data at follow-up was also not standardized, limiting data availability. We did not routinely collect data on quality of life or psychosocial functioning.

We minimized bias due to attrition by contacting those not attending follow-up. Self-reported weight trajectories were similar to that of those attending follow-up, and their complications have been included in this report. The majority of those who decided against surgery did not remain within our service, and we are unable to compare their outcomes to those who had surgery.

7.6 Conclusions

Adolescent bariatric surgery in an NHS service compares favourably to international cohorts, and shows promise as an effective treatment for severe obesity. Further work is needed to improve patient selection, reduce age at surgery, and reduce pre- and post- surgical attrition.

8 Summary of studies performed

8.1 Feasibility and acceptability of a brief office-based adolescent weight management programme

I performed a feasibility and acceptability study to test a novel brief obesity intervention for use in the outpatient setting. We used behavioural techniques that were designed to enable behaviour change after a short intervention and contemporary weight management advice.

8.1.1 Key findings

It was feasible for a specialist nurse and a research fellow (who was not a permanent member of staff) to deliver the intervention. Consultants in the service did not believe they had achieved the required skills from the training provided to be able to deliver the intervention, or had sufficient time within the structure of their jobs, to deliver the intervention. The team believed that a nurse was the most appropriate person to deliver the intervention.

Participants largely liked the supportive nature of the relationship that was fostered; this was driven by the MI and SFT behavioural approaches which were non-blaming and allowed participants to discuss a difficult topic and decide their own course of action. Support was important to the participants, and each had varying needs in terms of frequency and duration. The lifestyle advice within the programme polarised opinion; some were happy to follow the contemporary lifestyle advice that was provided whilst others wanted novel

advice and were unhappy. Half of the participants completed the programme. School was a major barrier to attendance and influenced their ability to attend the programme (in terms of school year and time of day).

There was no mean change in BMI across attendees whilst attending the programme. Qualitative feedback suggests that cessation of weight gain seen during the programme was a valid outcome for some and changes in weight persisted after the programme.

8.1.2 Clinical implications

Participants and clinicians found this intervention to be feasible and acceptable in certain circumstances. Given the limited resources available within healthcare settings and the potential to trial different approaches in the clinical setting, the future of this intervention needs to be carefully considered. There is currently insufficient evidence to justify routine use of this intervention in clinical practice. However, this study suggests that it may have a role in clinical practice, particularly for those who find it hard to engage with clinicians and should be further evaluated.

Only half of new patients offered this intervention enrolled. It is not known what the remainder want from a weight management service and further insights into their needs are warranted.

8.1.3 Research implications

HELP was initially developed as an intervention to be delivered by clinical psychologists in the hospital setting with original pilot data showing encouraging

BMI changes. It was next trialled as a community intervention delivered by trained graduate health workers and tested using a RCT methodology; there was no change in weight or health status between those undergoing the intervention and those receiving a single education session. We trialled a shortened version of the intervention together with an additional session discussing medical results and weight targets, and included regular weighing. We found no change in BMI in our cohort and our estimates are compatible with both BMI gain and loss.

There are three main potential reasons for differences in outcomes between these three different cohorts. First, that MI and SFT needs to be delivered by a trained clinical psychologist, and that non-psychologist clinical staff or graduate health workers have insufficient skills to deliver the intervention effectively. Second, that skilled patient selection in clinical practice allowed clinical psychologists to offer the intervention to those who would benefit it whereas both the community RCT and our pilot did not select patients. Third, the therapist effect in the intervention delivered by psychologists was a key reason for its success rather than the MI and SFT tools that it employed.

One of the main challenges of lifestyle interventions is that advances in science have not found methods to help people achieve substantial long-term weight loss through conservative approaches. We know that some outliers manage to do so, but intervention studies have not managed to replicate these outcomes. The evidence that lifestyle interventions improve health is mixed; studies show a reduction in incidence of diabetes but no change in cardiovascular mortality.

This is associated with short-term weight loss with weight regain. This may be acceptable to some, such as those who specifically want to achieve short-term weight loss (such as those getting married) or those who want to promote future good health. However, it is not surprising that many give up on lifestyle interventions and resort to their usual lifestyle, especially given the strong physiological drives to maintain weight and the relatively small magnitudes of weight change associated with current lifestyle measures.

It is unclear if it is the behavioural approach or lifestyle advice in HELPclinic that is insufficient, or both. There is increasing evidence to suggest that focussing on intrinsic motivation is insufficient to enable behaviour change and that additional behavioural tools are needed as well as changes to the environment; these could include approaches that promote acceptance of obesity as a chronic condition (e.g. acceptance and commitment therapy(299)) and compare behaviour to peers (nudging(300)) as ways to promote behaviour change.

There is also increasing evidence that non-behavioural approaches are increasingly needed to achieve weight loss. New anti-obesity drugs and bariatric surgery offer outcomes that are superior to lifestyle interventions.

In practice, both are likely to be important. Given lack of current alternative approaches for the majority of patients with obesity, there is still a role for low intensity and low-cost lifestyle interventions.

The future of HELPclinic is not clear. It has a potential role for helping engage patients with clinical services. Based on feedback, we could further adapt the

intervention as described above and undergo further evaluation. The most obvious trial methodology appears to be a randomised controlled trial with all participants undergoing a medical assessment and single education session and half being offered HELPclinic. This would allow us to detect if the intervention confers additional benefits compared to a single education session. The first uniform session could share the evidence base related to obesity physiology, its impact health and the evidence base for different medical and lifestyle approaches. This approach would potentially placate reticent clinicians who feel the need to offer patients an intervention and would allow us to test its efficacy.

Inclusion of flexible timing of intervention initiation, individualised frequency of appointments and facilitation of teleconferencing (e.g. Facetime or Skype) could allow more patients to benefit from the intervention.

8.2 Improved usage of anti-obesity drugs

8.2.1 Key Findings

There are currently two drugs used in the UK for control of obesity and its complications. We detected a low prevalence of AOD prescribing in the UK, together with high rates of drug discontinuation in line with previously published data. Two major prescribing patterns were seen. First, orlistat was largely initiated independently by GPs to those aged over 16 years of age with few co-morbidities. Secondly, metformin was largely initiated by specialists for girls with obesity either polycystic ovarian syndrome or disturbances of glucose and/or insulin.

Families who were initiated an AOD from a specialist clinic reported that AODs were uniformly suggested by their specialist doctor. For some, there was a sense of enthusiasm and relief at the prospect of a pharmaceutical solution to obesity whilst others felt pressurised to take it.

Drug side-effects were a key issue for many young people. These were mostly gastro-intestinal in nature, particularly abdominal cramps and diarrhoea. Some managed to control these side-effects by changing dosing regimens, such as timing or strength, and others moderated their lifestyle. Mediators in side-effect management were embarrassment talking to health professionals, understanding of drug action, safety concerns and environmental influences (such as availability of clean toilets). Only a small minority of GPs reported being aware of side-effects, or involved in their modification.

Drug discontinuation rates were high, especially for orlistat where only half of patients were issued more than one prescription and median duration was 2 months. Drug termination was patient-led by not requesting repeat prescriptions rather than a joint decision between families and doctors. Families described this as a decisional balance between the perceived benefits of the drug, and the side-effect profile. For many, this resulted in termination of the drugs. Monitoring by professionals, parental influences and recognition of their behaviours influenced this decision. Families reported that this decision was made by themselves without medical input; GPs reported a similar story with none of them being involved in drug termination.

We found that GPs had low confidence in prescribing AODs to children and young people despite feeling confident prescribing them to adults. They wanted more support managing not just anti-obesity drugs, but also child obesity as a whole. These lack of skills and low confidence are likely to contribute to the experiences of some families who described health professionals in the community not being comfortable prescribing AODs.

GPs did not follow NICE guidelines for prescribing of orlistat to children and young people. One explanation for this pattern of orlistat prescribing is that young people aged 16 years and over were assumed to be adults, and as such, GPs both felt more confident in prescribing them and prescribed them according to adult prescribing guidelines.

Proposed causes (and solutions) include inadequate support from specialist clinicians, inadequate national prescribing guidelines, inadequate knowledge amongst GPs, and inadequate AOD efficacy.

8.2.2 Clinical Implications

These data suggest that families could benefit from:

1. Collaborative and supportive relationships with specialist clinicians to ensure that patients feel empowered to make their own decisions about drug initiation, and feel able to discuss side-effects and drug termination.

2. Appropriate education to increase understanding of drug mechanisms to optimise side-effect management and dispel safety fears

3. Increased awareness of AOD usage by community pharmacists and GPs. Strategies to deliver this could include improved prescribing guidelines, better communication between specialist clinicians and community clinicians, improved obesity education and support from specialist teams.

4. Improved national guidance on prescribing of anti-obesity drugs.

These data on real-life usage contrast with those seen in clinical trials. These differences are likely to be caused by the type of patients who enter randomised trials and the support and surveillance offered within these trials. These differences may suggest that specialist teams prescribing these drugs need to give greater support to both patients and GPs.

Only two different AODs are currently being used in the UK in children and young people. It is likely that newer agents will soon be approved by EU-regulators, partly due to EU regulations that mandate trialling of new drugs in all age groups. The next generation of AODs show promising results and our findings suggest that changes are needed to ensure that current and future generations of AODs are used effectively to mirror efficacy seen in clinical trials.

Attitudes in both health professionals and lay people about the roles of anti-obesity drugs are likely to be critical. There is still an ongoing perception that obesity can be cured by lifestyle changes alone, and that drugs are not only unnecessary but inappropriate in children and adolescents with obesity. Arguably, their use is more important in this age group rather than adults, especially if drugs are able to change obesity trajectories into adult life.

An analogy could be the medication for conditions such as attention-deficit hyperactivity disorder (ADHD). Today's environment is undoubtedly implicated as a contributory factor for ADHD behaviours, yet medical professionals largely agree that these behaviours should, and can, be moderated by the use of drugs to aid learning and development when changes to the environment are insufficient. Stimulant medications are now used in children of a young age with little ongoing controversy.

There are parallels with obesity. Some children are victims of physiology-enabled desire to choose unhealthy foods, not partake in exercise and gain excess weight. They are particularly susceptible to the environment, which can be sufficiently moderated for some, but not by all. New drugs that act on the

central nervous system have shown the ability to moderate this behaviour, and change eating behaviours and weight status.

Current prescribing recommendations from NICE are likely to influence attitudes. Current recommendations are very restrictive, in terms of their tight controls related to prescribing orlistat to children and young people and their lack of inclusion of metformin. This contrasts with recent guidelines from the American Endocrine Society recommending a wide-range of drugs and considering the impact of drugs on weight.

There are good long-term safety data for metformin in adults, including diabetes prevention, and a growing evidence base in adolescents. It is cheap, and its side-effect profile can usually be minimised if dosage is increased slowly. Guideline development committees in the US have found sufficient evidence base for its inclusion, and UK prescribing guidelines should consider its inclusion at their next review.

8.2.3 Research implications

Ongoing studies are being performed testing the new generation of anti-obesity drugs. Interventions should be developed and trialled to guide the practical usage of current and future AODs in children and young people. The challenges in medication adherence in adolescents are unlikely to be unique to anti-obesity drugs, and likely to include factors common to all drug usage in adolescence. (301) These include family conflict, adolescent focus on the "here and now" rather than the future, and the challenges of taking medications in addition to an

already challenging adolescence. Lessons should be learnt from existing adherence literature, while noting factors that are unique to AOD usage.

One such approach could be to limit the use of orlistat to those who want to achieve weight loss through a low fat diet, and use it as a biofeedback tool to help patients identify dietary fat. The side-effects could be used to help identify foods that contain high fat, and allow the user to remove them from their diet. This approach could be trialled within the clinical setting as a way to achieve better outcomes with current drugs.

8.3 Systematic review of psychological and social outcomes of adolescents undergoing bariatric surgery, and predictors of success

8.3.1 Key findings

Existing data for the psychological and social outcomes of bariatric surgery were sparse with only one randomised control trial. We detected a substantial improvement in quality of life after surgery that persisted throughout follow-up, most notably in physical domains. Improvements in depressive symptoms were also detected, although the data was more limited and of shorter duration. Improvements in quality of life and depression peaked at 6 months post-surgery. This coincides with maximal weight loss, and we hypothesise cessation of improvement in these domains is limited by ongoing weight loss. Lack of further improvement in quality of life after maximal weight loss is not surprising. We hypothesise that this is partly driven by realisation that their new body habitus is not what they had wanted.

We found no data related to outcomes of disordered eating, and data were sparse for other psychological and social outcomes.

We identified only two studies that analysed pre-operative predictors of surgical outcomes; higher levels of loss of control eating and family factors predicted poorer BMI outcomes, and change in BMI was correlated with change in quality of life and depressive symptoms.

8.3.2 Clinical implications:

Previous studies have demonstrated high levels of psychopathology in those with severe obesity. In clinical practice, we see a complex group of patients who want bariatric surgery because they believe that weight loss will improve their mental health and quality of life. They can be out of education, training or employment, have low confidence and have severe social anxiety making them house-bound for much of the day. Current clinical practice excludes patients with these levels of co-morbidities driven by the theoretical belief that their psychopathology will limit their ability to adhere to post-operative dietary and physical activity recommendations.

These data are helpful in counselling potential patients who want bariatric surgery and perceive that it will improve their quality of life and mental health. However, study criteria excluded those with severe psycho-pathology and we found few data on outcomes other than quality of life and depression. As such, there are currently insufficient data to fully counsel patients on outcomes or allow patient selection based on mental health status.

8.3.3   Research implications

Given lack of data, further research is needed including evaluating the outcomes of those with more severe psychopathology. Given that the relationship between poor mental health and severe obesity is bi-directional, further experimental work is warranted for those in this cohort. This could

include use of temporary procedures such as a gastric balloon to promote weight loss.

Current practice believes that mental health needs to be supported and treated before bariatric surgery can be provided. Given that mental health and severe obesity are so enmeshed, it could be argued that both conditions need to be treated concurrently to offer a chance of success. This could include early bariatric surgery, given that it is the only treatment currently available that offers large magnitudes of weight loss.

Clinical experience suggests that post-operatively psychopathology is partly driven by unhappiness about excess skin after weight loss. Current clinical guidelines provide bariatric surgery on the NHS yet limit the availability of surgical removal of excess skin (apronectomy). There is no evidence in adolescents about the additional benefit of plastic surgery after bariatric surgery, and studies are needed.

8.4 Outcomes of fifty patients entering a NHS adolescent bariatric surgery programme

8.4.1 Key findings

We received a low number of referrals for assessment for bariatric surgery during the study period. Fifty patients were assessed, of whom 28 (58%) underwent a bariatric procedure, 6 (12%) were not eligible for surgery, 7 (14%) actively opted out, and 8 (16%) were lost to follow-up. There was some evidence that those from deprived populations were less likely to have surgery.

Mean age at surgery was 18.3 years compared to 16-17 years in Swedish and US cohorts. This was in part to the time taken from first assessment to surgery (mean 1.8 years). It is not clear if earlier referral would change outcomes given that those who were referred below age 14 years waited longer than older subjects.

BMI outcomes and complications were in keeping with other published cohorts and meta-analyses. High levels of attrition were seen after surgery without obvious impact on patient safety or outcomes.

8.4.2 Clinical implications

We were referred low numbers of patients whose health is likely to improve from weight loss, such as those with type 2 diabetes and sleep apnoea. The reasons for low referral rates are not clear. Hypothesised reasons include lack of knowledge about the role of bariatric surgery and of specialist services

offering it amongst paediatricians and general practitioners across the county Increasing the profile of services again through publication of these findings may increase awareness of services and offer treatments to those in need.

There was moderate evidence that those from more deprived populations were less likely to undergo surgery, and further attention is needed to ascertain the clinical needs of this group. Evidence described earlier shows that those with low socio-economic status are more likely to be obese and further work is needed to ensure that they can access treatment. This may include issues with transport cost, work pressures or other co-morbidities in the family.

High levels of attrition were seen in this cohort and further work is needed to support this group. Telephone interviews revealed that they were largely doing well after surgery. It is not known if attrition is associated with the transfer from adolescent services to adult services where there are fewer resources available to support this cohort.

Future models of working could include:

1. Development of a "Teenage and Young Adult" (TYA) service which supports the need of this population up to their 25th birthday. Similar models have been successfully used in cancer services in the UK.
2. Use of telephone and teleconference clinics to support those living far from clinic
3. Closer working with general practitioners to enable regular micronutrient screening and multi-vitamin adherence.

8.4.3 Research implications

These data suggest that young people struggle to attend follow-up after surgery. The reasons are not fully understood and further work is needed to understand the need of this challenging population.

8.5 Key themes across chapters

Obesity is a challenging and complex condition. This work was unique in providing insights into the role of a novel lifestyle programme, the complexities of anti-obesity drug prescribing and the outcomes of bariatric surgery in young people.

Lifestyle interventions alone are insufficient to combat the strong physiological mechanisms that exist to prevent weight loss. We evaluated various approaches, and found that bariatric surgery is the one intervention with the greatest outcomes in terms of BMI change. Furthermore, we showed good evidence for improvements in quality of life and depressive symptoms after surgery. These BMI outcomes can be achieved within an NHS service although further work is needed to monitor and support patients after surgery.

More research is needed to develop better treatments for obesity as a whole, with careful consideration of how these treatments are best used in the adolescent population.

9 Appendices

9.1 Background information on quality of life and mental health measures

9.1.1 Quality of Life

9.1.1.1 Generic Quality of Life

Health related quality of life is defined as the impact of health or disease on physical, mental, and social well-being from the patient's point of view. (302) Various QOL measures have been developed,(303, 304) with PedsQL being one of the shortest but with equivalent validity.(210)We measured quality of life (QOL) using the PedsQL 4.0 questionnaire (US version). It has been widely used in both healthy populations and those with health conditions, allowing comparisons between the two populations.(210, 305)

9.1.1.1.1 Questionnaire structure

PedsQL was completed both by the young person, and a parent-proxy. In an attempt to optimise comprehension and to measure age-appropriate QOL constructs, self-report and parent-proxy questionnaires are available for the following age groups: 5-7, 8-12 and 13-18 years. In addition, parent-proxy measures are available for the 2-4 year age bracket.

PedsQL is consists of 28 questions that map onto 4 domains: physical functioning (8 questions), emotional functioning (5 questions), social functioning

(5 questions) and school functioning (5 questions). Each question is reverse-Likert scored (100 – never, 75- almost never, 50 – sometimes, 25 –often, 0- almost always). Subscale scores indicate the mean score of all questions answered that map to that domain, and are transformed to a score of 0-100, with maximum score indicating best quality of life. Subgroups scores are invalidated if >50% of answers are missing. A psychosocial functioning score is the transformed mean of answers in the emotional, social, and school functioning subscales. The physical health score is the same as the physical functioning score. The total score is the transformed mean of all questions answered.

9.1.1.1.2 Normative Data

Both the US- and UK-versions of the PedsQL were used in 1399 children and young people (CYP) aged 8-18 years and 970 parents/carers from 23 schools in South Wales, completed both the original version of the PedsQL .(211)

No thresholds for impaired generic quality of life have been widely used. We identified patients as having low quality of life if their PedQL scores were greater than 1SD below the normative population mean.

9.1.1.2 Obesity-specific Quality of Life

Generic quality of life measures can insufficiently specific to provide data on disease-specific quality of life issues. IWQOL-Kids is a weight-specific quality of life tool, designed to measure quality of life issues that are likely to be directly associated with overweight.(212)

9.1.1.2.1 Questionnaire structure

IWQOL-Kids was completed both by the young person, and a parent-proxy.

IWQOL consists of 27 questions that map onto 4 domains: physical comfort (6

questions), body esteem (9 questions), social life (5 questions) and family

relationships (6 questions). Each question is Likert-scored (always true =1

point, usually true=2, sometimes true=3, rarely true=4, never true=5). The total

scores for questions completed in each subgroup are averaged, and then

transformed, whereby 0 indicates maximum impairment for that domain, and

100 indicates no impairment. The total score is a transformed mean of all

questions, again scored 0-100. The subgroup and total scores are invalidated if

more than 50% of questions mapped to each domain (or 50% of all questions

for total) are not answered.

9.1.1.2.2 Population normative data

There are no normative data available for non-treatment seeking community

samples. The tool was validated with 642 young people aged 11-19 years

pooled from psychosocial research cohorts, clinical protocols and a community

sample.(212) Data are only available from other clinical samples, such as a

population seeking bariatric surgery(306)

9.1.1.3 Self-esteem

We used the Rosenberg Self-Esteem (RSE) questionnaire to measure global

self-worth.(217) It is the briefest of all scales, but has been extensively

validated, and shown to have equivocal validity as more complex scales, and used widely over the last 45 years.(307)

9.1.1.4 Questionnaire structure

The RSE Scale is completed by the young person and consists of 10 questions. It was originally Gutmman scored, however, further evaluation has shown Likert scoring to be more appropriate. 5 questions are positively framed, i.e. relate to high self-esteem (0 - Strongly Disagree, 1 – Disagree, 2 – Agree, 3 – Strongly Agree) and 5 questions that are negatively framed, i.e. relate to poor self-esteem ,and so are inversely scored (0 – Strongly Agree, 1 – Agree, 2 – Disagree, 3 – Strongly Agree). A maximum score of 30 indicates the highest self-esteem.

9.1.1.5 Normative data

The most contemporary UK normative data is available for 1330 pupils aged 12 to 19 years, from 6 schools chosen to represent a wide socio-economic background (results in table below).(218) Individual scores were compared to UK population normative data using published means for sex-matched subjects aged 12-19 years. The reference data demonstrated a significant difference between male and female self-esteem scores so we have scored each sex separately. There was no significant difference between age bands so we have scored all subjects according to mean scores by sex.

No thresholds for impaired self-esteem have been consistently used. We identified patients as having low self-esteem if their RSE scores were less than 1SD below the population mean.

9.1.1.6 Eating behaviours

We used the Dutch Eating Behaviours Questionnaire (DEB-Q) to measure emotional, restrained and externally-driven eating behaviours. (308)

9.1.1.7 Questionnaire structure

The DEB-Q is completed by the young person and consists of 33 questions that map onto 3 domains: restrained eating (10 questions), emotional eating (13 questions) and external eating (10 question). Each sub-scale is Likert-scored (never =1 point, seldom=2, sometime=3, often=4, very often=5). Subscale scores indicate the mean score of all questions answered that map to that domain. A minimum of 12 of 13 questions in the emotional eating subgroup, 9 of 10 in external eating, and 9 of 10 in restrained eating need to be answered for the results to be valid. Scores of the individual domains are not totalled to give a single overall score.

9.1.1.8 Normative data:

The largest normative cohort is of 10,087 Dutch adolescents aged 11-16 years selected from 55 secondary schools across the Netherlands. (309) UK normative data is available for a smaller community sample of 846 school

children from 6 London schools chosen to represent a range of social and

ethnic backgrounds.(310)

Table 9.1 Normative data for DEB-Q

Author Year	Population	Country	Emotional eating Mean (SD)	External Eating Mean (SD)	Restrained Eating Mean (SD)
Snoek 2007 (309)	10,087 school-attending 11-16 yrs, 49% boys, 81% "Dutch" 0.9% obese	Netherla-nds	Boys: 1.85 (0.74) Girls: 1.97 (0.71)	Boys: 2.75 (0.72) Girls: 2.66 (0.67)	Boys: 1.87 (0.78) Girls: 2.25 (0.92)
Wardle 1992 (310)	846 secondary school-attending. 11-18 years 63% White-Caucasian, 16% Black, 20% Asian+ Oriental. Obesity %- n/a	UK	Boys: 1.94 (0.69) Girls: 2.11 (0.74)	Boys: 2.97 (0.74) Girls: 2.96 (0.70)	Boys: 1.94 (0.82) Girls: 2.52 (0.96)

Individual scores were compared to the Wardle population normative data.The

reference data demonstrated a significant difference between male and female

self-esteem scores so we have scored each sex separately. There was no

significant difference between age groups so we have scored all subjects according to mean scores for each sex.

- · 1. Z-scores were calculated for each individual using normative data (z-score = (subject score – population mean)/population SD)
- · 2. Patients were identified as having raised levels of eating in each domain if their DEBQ scores were 1sd above the population mean.

9.1.1.9 Depression

There are a number of depression screening tools that have been developed for children and young people. (311)The Short Moods and Feelings questionnaire (SMFQ) was developed as a briefer measure "where depression is not the primary focus of attention, but where at least a rough index of depression is needed". (215)

9.1.1.10   Questionnaire structure

SMFQ is completed independently by both the young person and parent/carer, and consists of 13 questions. The answers are Likert-scored depending on the frequency of the feelings or behaviours (True = 2, Sometimes True =1, Not True = 0). Scores for all questions are summed to give a maximum score of 26 points.

9.1.1.11 Normative data:

MFQ was primarily developed as a screening tool for depression, and as such, has been widely evaluated to derive appropriate threshold scores to achieve optimal sensitivity and sensitivity for detecting depression. The various studies have been summarised in the table 9.2 below:

Table 9.2 Normative data for MFQ questionnaire. DISC = Diagnostic Interview Schedule for Children (Costello et al 1982),CAPA = Child and Adolescent Psychiatric Assessment, DSM-III/IV = Diagnostic and Statistical Manual of Mental Disorders, 3rd / 4th edition, ICD-10 = International Classification of Diseases, 10th Revision.

Author + year	Age (years)	Population	Gold standard test	Questionnaire	AUC (95% CI)	Threshold	Sensitivity	Specificity
Rhew 2010 (312)	11-13	521 Middle school students, Seattle area.	DISC + DSM-IV	YP	0.73 (0.63-0.84)	4	0.66	0.61
				Parents	0.74 (0.62-0.85)	4	0.66	0.66
				Combined	0.86 (0.81-0.91)	10	0.76	0.78
Angold 1995 (215)	6-11	125 primary paediatric care patients, USA.	DISC + DSM-III	Child	n/a	8	0.6	0.85
				Combined	n/a	≥12	0.7	0.85
Thapar 1998 (216)	8-16	South Glamorgan (Wales) Twin Study	CAPA + ICD-10	Parent	0.82	9	0.75	0.73
				YP	0.63	5	0.75	0.74

We used the Thapar thresholds (parent proxy - 9, young person - 5) to define patients with significant depressive symptoms who are at high risk of clinical depression.(216) We have chosen these thresholds as the study population most closely mirrors our clinic population in terms of age and geography and uses contemporary international criteria for diagnosis of depression (ICD-10).

9.1.1.12 Psychological distress

The Strengths and Difficulties Questionnaire was developed to screen for overall psychological distress, with particular focus on emotional difficulties, conduct problems, hyperactivity and difficulty with peers.

9.1.1.13 Questionnaire structure

The SDQ is completed by parents and/or teachers of children aged 4-16 years, and young people aged 11-16 years. SDQ consists of 25 questions that map onto 5 domains; emotional difficulties scale (5 questions), conduct problems scale (5 questions), hyperactivity Scale (5 questions), peer problems scale (5 questions), pro-social scale (5 questions). The first 4 subscales aim to identify psychological distress, whereas the 5th identifies positive social skills. The questionnaires for each respondent are scored separately. Each question is Likert-scored (not true = 0 points, somewhat true = 1 point, certainly true = 2 points) with a maximum of 10 points for each domain. The 4 pathological subscales are summed to create a total score (total score 0- 40 points, maximum points indicating greatest distress). At least 3 of 5 questions for each

subscale need to be answered for the subscale to be valid; and scores for answered questions are prorated to give a score of out 10.

9.1.1.14 Normative data

UK normative data is available from a 1999 national survey by United Kingdom Office for National Statistics which measured the mental health of 10,438 children aged 5-15 years.(213) The risk of those in the top decile of each domain having a mental health diagnosis was calculated and we used these thresholds for identifying those at high risk of a mental health condition.(213)

Table 9.3 Threshold SDQ scores SDQ by sex and questionnaire respondent.

	Male		Female	
	Parent	Young person	Parent	Young person
Total score	≥18	≥18	≥16	≥18
Emotional score	≥5	≥6	≥6	≥7
Conduct Problems	≥5	≥5	≥4	≥5
Hyperactivity	≥8	≥7	≥7	≥7
Peer problems	≥5	≥4	≥4	≥4

9.1.1.15 Eating Disorders

We screened for eating disorders using the Eating Disorders Examination Questionnaire (EDE-Q). (219)

9.1.1.16 Questionnaire structure

The EDE-Q is completed by the young person. It EDE-Q consists of 28 questions which are mapped onto 4 domains: restraint (5 questions), eating concern (5 questions), shape concern (8 questions) and weight concern (5 questions). In addition, 6 further questions quantify key behavioural features of eating disorders (questions 13-18).

Each question is Likert-scored, depending on number of days in the last 28 days that the behaviours, attitudes or feelings in question have occurred (no days = 1 point, 1-5 days = 1 point, 6-12 days = 2, 13-15 days = 3, 16-22 days =4, 23-27 days =5, everyday = 6). Subgroup scores indicate the average number of days in which the particular behaviours, attitudes or feelings mapped to that domain have occurred. The subgroup score is invalidated if more than 50% of questions mapped to that domain are not answered. The global score is the mean score of all 4 domains. Scores of 4 or above (i.e. 16 or more days per month) are interpreted as more likely to be in the "clinical range".

9.1.1.17 Normative data

There are limited adolescent normative population data: a cohort of girls aged 12-14 years in Oxfordshire schools, (220) an inpatient obesity unit for young

people aged 10-16 years in Belgium,(313) and male psychology undergraduate students in the US. (314) Details of the cohorts and mean scores for each domain are summarised in table 9.4 below.

Table 9.4 Normative data for EDE-Q

Author	Population	Age	N & sex	Eating Restraint M (SD)	Eating Concern M (SD)	Weight concern M (SD)	Shape concern M (SD)	Global score M (SD)
Decaluwe 2003 (313)	Inpatient obesity unit,	10-16	51M 75F	1.19 (1.04)	1.99 (1.06)	3.26 (1.20)	3.34 (1.37)	n/a
Lavender 2010 (314)	College psychology students	Mean 19.02 SD 1.41	404M	1.09 (1.19)	0.43 (0.77)	1.29 (1.27)	1.59 (1.38)	1.09 (1.0)
Carter 2001 (220)	School, Oxfordshire	12-14	F	1.4 (1.5)	1.0 1.0)	1.8 (1.7)	2.2 (1.7)	1.6 (1.4)

We used data from the Carter population as theses were closest in age and social status to our cohort. There are no data for males in this age group and we chose to use Carter data for both sexes.

9.2 Additional tables and figures for chapter 3

Table 9.5 Summary of cardio-metabolic screening. OGTT = oral glucose tolerance test. SBP = systolic blood pressure. DBP= diastolic blood pressure.

	Diabetes			Lipids						Blood Pressure		
	OGTT	HbA1c	OGTT or HbA1c	Total	HDL	Non-HDL	LDL	Trig	Any category	SBP	DBP	SBP or DBP
Normal	6	15	19	15	12	12	17	11	9	17	13	11
Increased risk	1	3	4	7	3	9	5	9	5	5	8	9
Significant risk	0	0	0	2	9	3	2	4	10	4	5	6
Not undertaken	19	7	2	0	0	0	0	0	0	0	0	0
Missing data	0	1	1	0	0	0	0	0	0	0	0	0

Table 9.2 Participant qualitative interview details. YP = young person, GORD = gastro-oesophageal reflux disease, NAFLD = non-alcoholic fatty liver disease, PCOS = polycystic ovarian syndrome.

Participant ID	Age (Years)	Sex	Interviewees	Ethnicity	Co-morbidities	N sessions	BMI change	Self-reported weight trajectory		
								Before	During	After
1	14.4	M	YP	African	Tension headaches, asthma, muscular back pain, nocturnal enuresis	3	0.18	Stable	Down	Delayed regain
2	17.4	M	YP	British	Nil	4	2.52	Increasing	Down	Continuing loss& delayed regain

Participant ID	Age (Years)	Sex	Interviewees	Ethnicity	Co-morbidities	N sessions	BMI change	Self-reported weight trajectory		
								Before	During	After
3	15.6	M	YP	Other White	Gynaecomastia, pubertal delay, presumed NAFLD,	2	0.23	Gain	Stopped gain	Gain
4	15.1	F	Mother	British	Social anxiety, previous GORD	1	n/a	Stable	Stable	GainBrf
5	14.2	M	Mother	British	Asthma, GORD, dyspraxia	5	0.42	Unsure	Loss	Maintained
6	12.3	M	YP	British	Gynaecomastia, tension headaches	1	n/a	Stable	n/a	Loss
7	13.2	F	Mother	British	Nil	5	-0.26	Stable	Slow	Stable

Participant ID	Age (Years)	Sex	Interviewees	Ethnicity	Co-morbidities	N sessions	BMI change	Self-reported weight trajectory		
								Before	During loss	After
10	12.4	F	Mother	British	Precocious puberty, acne, PCOS	5	0.46	Slow gain	Stable	Stable
11	12.5	F	Father	British	Nil	1	n/a	Increasing	No loss	Stable
13	14.0	F	YP	Other White	Nil	5	-1.40	Stable	Loss	Ongoing loss (total 20kg)
15	15.4	F	YP + mother	Other White	Hypertriglyceridaemia	5	1.13	Stable	Stable	Stable

Participant ID	Age (Years)	Sex	Interviewees	Ethnicity	Co-morbidities	N sessions	BMI change	Self-reported weight trajectory		
								Before	During	After
20	14.8	F	YP + mother	British	Gynaecomastia	5	-1.10	Increasing	Stable	Loss
21	14.4	M	YP + mother	White British	Eczema, gynaecomastia, pubertal delay, iron deficient anaemia	5	-0.41	Increasing	Loss	Continuing loss with delayed regain
25	14.9	F	YP + mother	White other	Nocturnal enuresis, tension headaches, lower back pain	5	0.59	Increasing	Stable	Stable

9.3 Additional tables and questionnaires for chapter 4

9.3.1 Semi-structured questionnaire to young people.

Self-reported demographics:

- How old are you?

- What ethnicity do you consider yourself?

- Can you tell me about your health (prompts: medical problems, medications, impact of weight on   health)

- What have you tried to get overweight under control (prompt: *formal weight loss programs,   dieting, exercise)*

Section 1: Decision process to take AOD

- Can you tell me about the first time that you discussed medicines to control weight with a doctor   (prompt: who was this doctor, what type of doctor was he/she (e.g. paediatrician, endocrinologist,   GP), how old were you, who was with you)

- Whose idea was it to take a medicine to help you control your weight (prompt: was it your idea, a   parent, carer or relative or the doctor's idea?)

- Had you heard anything about this medicine before? (prompt: did you know anyone taking it, had   you seen or read anything about it?)

- What did you first think about taking a medicine for controlling overweight? (prompt: how   important was it for you to control overweight,

did you think that a medicine would help, did you think this was the right

time to take a medicine, did you want to take a medicine for overweight?)

- Did you decide to take the medicine?

Section 2: Expectations of AOD outcomes (all participants)

1. What sort of changes did you expect to happen with the medicine?
   (prompt: weight in kg or stone, change in clothes size, change in
   appearance to certain parts of the body)
2. How quickly did you think these changes would happen? *(prompt: hours,
   days, weeks)*

Section 3: Experiences of AOD usage (only if the YP tried AOD)

1. What support did you receive when you were first taking this medicine
   (prompt: from the prescriber, pharmacist, nurse etc).
2. Can you tell me about how you usually took/take this medicine? (prompt:
   certain times of day, certain days of the week, with certain foods)
3. Can you tell me about any immediate effects when you took/take this
   medicine, either good or bad. What I mean by immediate effects is
   changes that you noticed on the day you took the medicine *(prompt:
   some people may call these side-effects, pains, change in appetite or
   bowel habits, do they still persist)*
4. What did/do you think about these effects? (prompt: concerns about
   safety, understanding of why they were happening)

5. Did/do these effects make you decide to take the medicine in a different way? *(prompt: change frequency, change dose, stop taking)*

6. And did/do these effects make you decide to make any other changes in your life? *(prompt: dietary changes, activity changes)*

7. Which of these effects did you expect to happen, and which ones were a surprise?

8. What help or advice did you get with these effects? (prompt: parents/carers, peers, GP, specialist   team, pharmacist, internet)

9. How long did you use the medicine for?

10. Did you have any other problems or concerns with taking this medicine? (prompt: what were   these, what action did you take, outcomes etc)

11. People miss doses of their medicines for a range of reasons. Thinking of this medicine, how often   did/do you miss a dose? (prompt: *reasons for missing doses)*

12. Did you have any way of noticing if the medicine was helping you lose weight (prompt: weighing   (and how often), clothes size, looking in mirror, what others noticed)

13. Are you still taking the medicine?

Section 4: Understanding of mechanism of drug action (all participants)

1. Can you tell me anything about how this medicine works to control overweight? *(prompt: anything else, does)*

2. And does the person taking the medicine have to do anything to help the medicine work properly? *(prompt: change the type of food you eat, change amount of exercise/activity you do?)*

3. How did you find out about how this medicine worked? (prompt: what did the doctor/pharmacist/GP tell you, patient information leaflet in box, did you ask anyone else, did you look it up on the internet, discussed with someone who has taken the medicine)

4. Did anything you found out surprise you, or make you take the medicine differently?

Section 5: Outcomes of AOD usage (only if YP tried AOD)

1. Did this medicine help you to lose weight or change your body? (prompt: clothes size, weight, amount of muscle or fat)

2. If the YP stopped the medication: What made you decide to stop the medicine? (prompt: who stopped treatment – YP/parent/doctor, lack of efficacy, side-effects?)

3. If the YP continues to take the medication: Why are you still taking the medicine? (prompt: *continuing weight loss, weight maintenance, motivates lifestyle changes)*

Section 6: Suggestions for improved outcomes (all participants) 1. If any changes could be made to help you and other young people take weight-loss medicines,

what changes would you suggest? (prompt: discussion with doctor, information about medicine,

support while taking medicine – who from?) *Wrap up question:* Is there anything else that I haven't asked you that you think is important or that you want to add?

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9.3.2 Semi-structured interview schedule for parent/carer

Section 1: Decision process to take AOD

1. Can you tell me about the first time that you discussed medicines to control your child's weight with a doctor (prompt: who was this doctor, what type of doctor was he/she (e.g. paediatrician, endocrinologist, GP), how old was your child, who was with you)

2. Whose idea was it to take a medicine to help control your child's weight *(prompt: was it your idea, YP, relative or the doctor's idea?)*

3. Had you heard anything about this medicine before? (prompt: did you know anyone taking it, had you seen or read anything about it?)

4. What did you first think about your child taking a medicine for controlling overweight? (prompt: how important was it for your child to control their overweight, did you think that a medicine would help, did you think this

was the right time for them to take a medicine, did you want them to take

a medicine for overweight?)

5. Did your child decide to take the medicine?

Section 2: Expectations of AOD outcomes (all participants)

1. What sort of changes did you expect to happen with the medicine?

(prompt: weight in kg or stone,   change in clothes size, change in

appearance to certain parts of the body)

2. How quickly did you think these changes would happen? *(prompt: hours,*

days, weeks)

Section 3: Experiences of AOD usage (only if the YP tried AOD)

1. What support did you and your child receive when first taking this

medicine *(prompt: from the   prescriber, pharmacist, nurse etc).*

2. Can you tell me about how your child usually took/takes this medicine?

(prompt: certain times of   day, certain days of the week, with certain

foods)

3. Can you tell me about any immediate effects when he/she took this

medicine, either good or bad. What I mean by immediate effects is

changes that were noticed on the day of taking the medicine *(prompt:*

some people may call these side-effects, pains, change in appetite or

bowel habits, do they still persist)

4. How did/do you think about these effects? (prompt: concerns about

safety, understanding of why they were happening)

5. Did/do these effects result in you influencing the way your child took the medicine? *(prompt: change frequency, change dose, stop taking;)*

6. And did/do these effects result in your child making any other changes in his/her life *(prompt: dietary changes, activity changes)*

7. Which of these effects did you expect to happen, and which ones were a surprise?

8. What help or advice did you and your child get with these effects? *(prompt: friends, family, GP, specialist team, pharmacist, internet)*

9. How long did your child use the medicine for?

10. Did (s)he have any other problems or concerns with taking this medicine? (prompt: what were these, what action did you take, outcomes etc)

11. People miss doses of their medicines for a range of reasons. Thinking of this medicine, how often did/does (s)he miss a dose? (prompt: *reasons for missing doses)*

12. Did your child have any way of noticing if the medicine was helping them to lose weight *(prompt: weighing (and how often), clothes size, looking in mirror, what others noticed)*

13. Is (s)he still taking the medicine?

Section 4: Understanding of mechanism of drug action (all participants)

1. Can you tell me anything about how this medicine works to control overweight? *(prompt: anything else, does)*

2. And does the person taking the medicine have to do anything to help the medicine work properly? *(prompt: change the type of food you eat, change amount of exercise/activity you do?)*

3. How did you find out about how this medicine worked? (prompt: what did the doctor/pharmacist/GP tell you, patient information leaflet in box, did you ask anyone else, did you look it up on the internet, discussed with someone who has taken the medicine)

4. Did anything you found out surprise you, or make you want your child to take the medicine differently?

Section 5: Outcomes of AOD usage (only if YP tried AOD)

1. Did this medicine help your child to lose weight or change his/her body? (prompt: clothes size, weight, amount of muscle or fat)

2. If the YP stopped the medication: Why did (s)he stop the medicine? (prompt: who stopped treatment – YP/parent/doctor, lack of efficacy, side-effects?)

3. If the YP continues to take the medication: Why is (s)he still taking the medicine? (prompt: *continuing weight loss, weight maintenance, motivates lifestyle changes)*
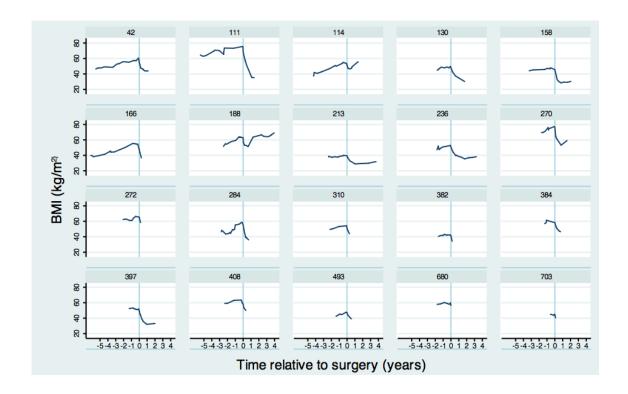
Section 6: Suggestions for improved outcomes (all participants) 1. If any changes could be made to help other young people take weight-loss medicines, what

changes would you suggest? (prompt: discussion with doctor, information about medicine, support while taking medicine – who from?)

Wrap up question: Is there anything else that I haven't asked you that you think is important or that you want to add?

9.4 Additional tables and figures from chapter 8

Figure 9.1 Individual BMI trajectories for all patients undergoing surgery. Numbers are patient anonymised identification numbers

9.5 Papers published from this PhD

White B, Jamieson L, Clifford S, et al. Adolescent experiences of anti-obesity drugs. Clin Obes 2015;5:116-26.

White B, Doyle J, Colville S, et al. Systematic review of psychological and social outcomes of adolescents undergoing bariatric surgery, and predictors of success. Clinical Obesity 2015;5:312-24.

9.6 Abstracts from this PhD

White B, Finer N, Adamo M, et al. Outcomes of an adolescent bariatric service. Archives of Disease in Childhood 2012;97:A63.

White B, Viner R, Christie D. 77. Outcomes of a Pilot Study of a Physician and Nurse Delivered Adolescent Weight Management Program. Journal of Adolescent Health 48:S57.

9.7 Papers published related to this PHD

Black J, White B, Viner R, et al. Bariatric surgery for obese children and adolescents: a systematic review and meta-analysis. Obes Rev 2013;14:634-44.

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