Determinants of HbA1c in non-diabetic children and adults

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Interventions for treating obesity in children Cochrane Review

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ABSTRACT

Background: Child and adolescent obesity is increasingly prevalent, and can be associated with significant short- and long-term health consequences. The aim of this review is to assess the efficacy of lifestyle, drug and surgical interventions for treating obesity in childhood.

Methods: We searched eight databases from 1985 to May 2008. We selected randomised controlled trials (RCTs) of lifestyle (i.e. dietary, physical activity and/or behavioural therapy), drug and surgical interventions for treating obesity in children (mean age under 18 years) with a minimum of six months follow up. Two reviewers independently assessed trial quality and extracted data following the Cochrane Handbook.

Main results: We included 64 RCTs with 5230 participants. Lifestyle interventions focused on physical activity and sedentary behaviour in 12 studies, diet in 6 studies, and 36 concentrated on behaviourally orientated programs. Two drug trials involved metformin, two orlistat and five sibutramine. No surgical intervention was eligible for inclusion. The studies included varied greatly in intervention design, outcome measurements and methodological quality. Meta-analyses indicated a reduction in overweight at 6 and 12 months follow up in: i) lifestyle interventions involving children; and ii) lifestyle interventions in adolescents with or without the addition of orlistat or sibutramine. A range of adverse effects was noted in drug RCTs.

Authors' conclusions: While there is limited quality data to recommend one treatment program to be favoured over another, this review shows that combined behavioural lifestyle interventions can produce a significant and clinically meaningful reduction in overweight in children and adolescents. In obese adolescents, consideration should be given to the use of either orlistat or sibutramine, as an adjunct to lifestyle interventions, although this approach needs to be carefully weighed up against the potential for adverse effects.

BACKGROUND

The prevalence of obesity and overweight is increasing in both adult and child populations throughout the world[1]. Using the IOTF standard definition of paediatric overweight and obesity, the worldwide prevalence of overweight (including obesity) in children and young people aged 5-17 years is approximately 10%, with that of obesity alone being 2-3%. Certain regions and countries have particularly high rates of paediatric obesity: more than 30% of children and adolescents in the Americas, and approximately 20% of those in Europe, are overweight or obese.

Overweight and obesity in childhood are known to have significant impact on both physical and psychosocial health. For example, hyperlipidaemia, hypertension, insulin resistance and abnormal glucose tolerance occur with increased frequency in obese children and adolescents[2]. Overweight children are known to become targets of early discrimination[3]. In addition, obesity in childhood is an independent risk factor for adult obesity[4]. Furthermore, there is evidence of an association between adolescent obesity and increased risks for health in adult life[5].

Treatment of childhood overweight and obesity is important, given the significant health and social consequences both in the short- and long-term. Ultimately treatment shares the same fundamental principles as treatment in adults i.e. to decrease caloric intake and increase energy expenditure. However, the primary goal of treatment (i.e. weight reduction or deceleration of weight gain) and the recommended mode of intervention are variable and dependent on the child's age and initial level of overweight, among other considerations. In order to support clinicians in determining the most appropriate form of treatment, paediatric weight management guidelines exist in many countries to promote best practice, but at present many of these recommendations are based on low grade scientific evidence.

The first version of this systematic review was published in 2003[6] and included analysis of childhood obesity treatment studies published up until July 2001. Many of the studies included in the review had small sample sizes, high drop-out rates, unreliable or limited outcome measurements or sampling problems, raising concerns about validity and generalisability of the findings. Furthermore, the wide range of interventions tested made comparison of studies difficult. No direct conclusions could be drawn from the review.

The aim of this current review was to update the previous 2003 review. A new feature of this review is the consideration of drug trials and surgical interventions for the treatment of obesity in children and adolescents, reflecting both the increasing use of such therapies in clinical management and the emergence of published studies.

The aim of this review was to assess the efficacy of any combination of lifestyle (dietary, physical activity, behavioural therapy), drug or surgical intervention, compared with any other combination

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of these interventions or no treatment, designed to treat obesity in children and adolescents. The results of the current review will provide information on which to underpin clinical guidelines and health policy on the treatment of childhood obesity.

METHODS

Criteria for considering studies for this review

For lifestyle interventions, only RCTs that were specifically designed to treat obesity and observed participants for a minimum of six months follow-up from baseline were included. The rationale for introducing this criterion arose from the belief that many interventions appear to be effective in the short term (up to three months), but not in the long term[7]. For drug trials, we included trials that had at least three months of drug therapy and follow up at six months. For bariatric surgery, we considered RCTs, as well as published reports of controlled clinical trials, controlled before and after studies and interrupted time series studies. Alternative therapies were not considered in this review. Data were extracted for outcomes at 6, 9, 12 and 24 months where possible, and other time points where appropriate. Participants in study groups with a mean age less than 18 years at the commencement of the intervention were included.

The primary outcome measures were measured (not self-reported) height and weight. To account for sex- and age-related changes over time, we chose body mass index standard deviation score (BMI-SDS or BMI-Z-score) and percentage overweight to compare results between studies.

Data collection and analysis

We searched eight electronic databases from 1985 to May 2008. Assessment of search strategy data was undertaken independently by two reviewers (the first author screened all; the second review was performed by all other authors by dividing all titles and abstracts into equal batches). Study data extraction and information on a number of measures of methodological quality of the included studies was assessed independently by two reviewers. Most of the included studies were too small to have the power to detect efficacy. In an attempt to overcome this problem, we compared studies that included children in the same age group, dealt with comparable interventions, and had a similar duration of intervention at the follow up moment for meta-analysis. Data needed to be reported at 6, 9, 12 or 24 months for the same outcome measurements (BMI-SDS or percentage overweight). Since few data on BMI-SDS were available in adolescents, we chose absolute changes in BMI as a second measure of fatness to compare results obtained in adolescents. Only studies

providing similar analyses based on intention-to-treat principles (for example with baseline- or last-observation-carried-forward or imputed data by mixed model analysis) were considered. Studies fulfilling all these criteria were pooled in meta-analyses.

RESULTS

Results of the search

The updated search of electronic databases performed in 2008 found 6496 abstracts. From these the full text of 206 papers was assessed. The results of the 2008 searches are detailed in Figure 1. All papers for which hard copies were obtained but which failed to meet the inclusion criteria (n=136 papers) were excluded from this review. The remaining 70 papers (55 on lifestyle interventions, 15 on drug interventions) reported 49 different studies (39 on lifestyle interventions, 10 on drug interventions). One lifestyle intervention paper was an additional report of an existing included study.

Eighteen studies were included in the first version of the review[6]. They all involved lifestyle interventions to treat obesity in children or adolescents. An additional 46 studies that met the inclusion criteria were found in 2008. Therefore a total 64 studies are included in the current review. Two additional papers were ongoing trials, both involving lifestyle interventions. Overall, 54 studies reported on lifestyle interventions, ten on drug interventions (with or without combination with lifestyle intervention) i.e. sibutramine (n=5), orlistat (n=3) and metformin (n=2). None of the surgical intervention studies met the inclusion criteria.

The total number of participants in the 64 included studies with outcome data was 5230, of which 3806 participated in the lifestyle studies and 1424 in the drug trials. Ages ranged from 3 to 21 years. Thirty-four lifestyle studies included children with a mean age below 12 years. All but one drug trial involved adolescents aged 12 to 19 years. One study included children aged 9 to 18 years, but the mean age of children was 12.5 years.

Of the lifestyle intervention studies, 12 focused on exercise, physical activity or the reduction of sedentary behaviours, 6 focused on diet and 36 concentrated on behaviourally orientated treatment programs. The lifestyle interventions ranged in duration from 1 month to 24 months, with 14 having a duration less than 6 months. Forty interventions lasted 6 months or longer, six of which continued for one year. Four interventions lasted at least two years.

In most studies (n=40) the target of intervention was the family or the child with a parent. In the drug trials the drugs were only administered to the child.

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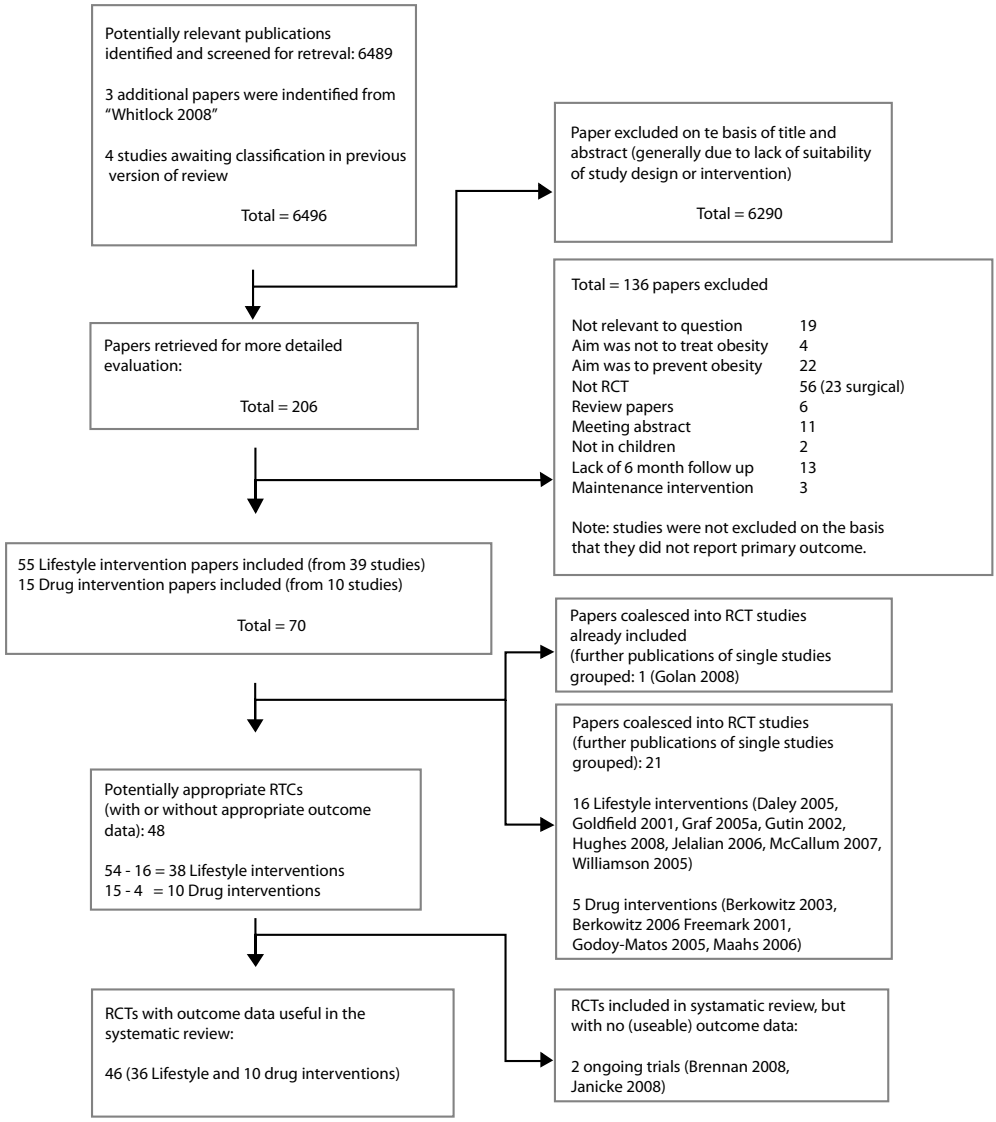

Figure I. 2008 Quorom statement flow diagram [revised 29/08/08] Interventions for Treating Obesity in Childhood

Risk of bias in included studies

All 64 included studies were RCTs. All studies included in this review had some methodological weaknesses according to the criteria set out in the Cochrane Handbook[8], and thus did not fulfil all quality criteria.

Allocation to the intervention or control group was reported to be concealed in 14 of 54 lifestyle studies. However, allocation concealment was unclear in 38 of 54 studies and two studies reported that allocation was not concealed. In all but two drug intervention studies allocation to intervention or control was concealed. Blinded outcome assessment was reported in only five of the 54 lifestyle intervention studies and in seven of the drug trials.

Dropout rates reported at the end of intervention ranged from 0 to 42%. Twenty-seven studies reported a completion of intervention rate of more than 80%. Twenty-one lifestyle intervention studies reported analysis based on intention-to-treat principles to account for missing data. In general, dropout rates in drug intervention trials were higher; at the end of intervention they ranged from 4 to 35%, but in only four of the drug trials, data at follow up measurements represented more than 80% of the baseline sample. All but three drug trials performed analysis based on intention-to-treat principles.

The sample sizes of studies ranged from 16 to 218 participants in the lifestyle interventions, and from 24 to 539 participants in the drug trials. Power calculations were only discussed in 15 lifestyle studies included in this review. Thirty-eight of 54 lifestyle interventions randomised less than 30 children to at least one study arm. Four of the drug intervention studies did not discuss power. Most drug trials included in this review had small sample sizes; six out of ten drug trials randomised less than 30 children to at least one study arm.

Baseline differences between intervention and control groups were discussed in most studies, four lifestyle studies found a significant difference in body composition between the experimental and control group. Two drug studies found a significant difference in body composition between the experimental and control group at baseline. None of these baseline differences between groups were taken into account in analyses reported in the original papers, neither in the lifestyle, nor in the drug trials.

No conflicts of interest of any note were reported. Most studies were funded by national health institution research grants. All drug trials reported funding sources. Most of these studies were industry-sponsored but four studies reported non-industry sources of funding.

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Effects of interventions

The studies included in this review varied greatly in intervention design, outcome measurements and methodological quality. Most studies demonstrated beneficial effects of interventions on child adiposity from baseline to the end of intervention or follow up. Due to heterogeneity only a small number of studies could be included in the meta-analysis (Table 1). Also the drug intervention studies varied greatly, but showed a consistent beneficial effect. A few studies could be pooled, as shown in Table 2.

Adverse effects

Reporting of harm was noticeably absent in lifestyle studies. In contrast, the majority of drug studies reported total adverse events and possible medication-related adverse events. In the orlistat trials, the most commonly reported adverse events were associated with the gastrointestinal tract (fatty/ oily stool or evacuation, oily spotting, increased defecation, cramps and abdominal pain). In the sibutramine trials, adverse events included increased pulse rate and increased blood pressure, as well as dry mouth and dizziness.

Table I. Meta-analysis of lifestyle interventions to treat obesity in children.

	No. of studies	No. of participants	Mean difference in BMI-SDS or BMI
Children younger than 12 years			
- change in BMI-SDS at 6 months follow up	4	301	-0.06 [-0.12, -0.01]
- change in BMI-SDS at 12 months follow up	3	264	-0.04 [-0.12, 0.04]
Children 12 years and older			
- change in BMI-SDS at 6 months follow up	3	291	-0.14 [-0.17, -0.12]
- change in BMI at 6 months follow up	4	362	-1.27 [-1.61, -0.93]
- change in BMI-SDS at 12 months follow up	2	231	-0.14 [-0.18, -0.10]
- change in BMI at 12 months follow up	2	231	-2.29 [-2.96, -1.62]

Table II. Meta-analysis of drug treatment for obesity in children.

	No. of studies	No. of participants	Mean difference in absolute BMI
Children 12 years and older			
- Orlistat: change in BMI at 6 months follow up	2	579	-0.76 [-1.07, -0.44]
- Sibutramine: change in BMI at 6 months follow up	2	111	-2.21 [-2.92, -1.50]

DISCUSSION

Sixty-four randomised controlled studies were included in this review, sharing similar overall goals and objectives. However, there were multiple differences in terms of study design (particularly intervention comparisons), quality (particularly sample size and thus power) and outcome measures. Most studies reported beneficial effects of the intervention on adiposity from baseline to end of intervention or follow up. The challenge is to ascertain which intervention is more effective than another. Although we have not been able to fully answer this, we have identified further evidence as to the effectiveness of various strategies for treating childhood obesity. The importance of a combined dietary, physical activity and behavioural component has been highlighted by several studies included in this review. Parental involvement has been recognised as an important feature of behavioural programs, particularly in pre-adolescent children.

Meta-analysis in children under twelve years of age showed that family-targeted behavioural lifestyle interventions decreased BMI-SDS more than did standard care at six months follow up. The effect size was small but statistically significant and clinically relevant. In these studies new behavioural interventions were compared to established standard care, thus providing an additional effect. The effect size found in meta-analysis at 12 months was no longer significant, although decreases in BMI-SDS persisted in the three pooled studies. In adolescents, a similar pattern was seen, albeit with an even greater effect size, given that behavioural interventions were compared to a self- help condition. In adolescents the effect size remained significant at 12 months after beginning of the intervention, demonstrating that beneficial effects of the behavioural program persisted in the longer-term. In addition, in the meta-analyses of included drug trials, both orlistat and sibutramine, as an adjunct to a lifestyle intervention, led to significant improvements in adiposity in adolescents, although a range of adverse events was also noted.

It is important to note that interventions to reduce obesity may vary in effect depending on the age of the child, due to differences in metabolism, nutritional needs, physical maturation and

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psycho-social development throughout childhood. Some studies reported delivering interventions separately to different age groups. Three studies developed interventions in line with their target group behaviour, such as a phone or internet-based facility or peer-enhanced activity training. It is very likely that the level of parental involvement will change with age and developmental stage. Therefore it is a priority to develop interventions that account for these differences throughout child and adolescent development. An important finding in this review was the lack of interventions for preschool-aged children and the relatively low number of lifestyle interventions targeted at adolescents.

Most studies were underpowered (44 out of 64 randomised less than 30 children to at least one group) and only 15 out of 54 lifestyle studies reported power calculations. In these circumstances it is possible that small study biases will arise, in particular a tendency to publish positive studies more than negative studies. As so few common interventions could be pooled it was not feasible to examine this formally using Funnel plots and Begg and Eggar tests. Most studies did not account for missing data in analyses and less than half of all included studies performed analysis based on intention-to-treat principles. This might be an important issue, since many of the studies dealt with high dropout rates; only 31 studies reported follow up of more than 80% of the baseline participants. It is possible that participants with a successful intervention experience or outcome may be more likely to return for follow up assessments, whereas participants who fail to change their adiposity status may not return for follow-up, leading to an overestimation of the treatment effect. However, in most studies dropout rates were not significantly different between comparison groups.

A new feature in this update was the inclusion of drug interventions and the consideration of surgical interventions for the treatment of adolescent obesity. While no surgical study met the inclusion criteria, several drug interventions were ultimately included in the review. In comparison with the lifestyle interventions, the drug trials generally met more of the CONSORT criteria[9] and several had relatively large sample sizes. We were also able to undertake meta-analyses for two of the drug interventions (orlistat and sibutramine). The adverse event profile of the drug trials was well documented.

The proposed relationship between treating obesity and eating disorders, particularly in young populations, is a vital area of consideration. In this review ten lifestyle studies that reported on measures of disordered eating, did not find any adverse changes. However, obesity treatments should make assessments of potential unintended effects since there is a lack of data on this aspect of treating obesity in children and adolescents.

While we agree that research in the area of obesity treatment is difficult to conduct, this must be considered against a background which acknowledges that obesity is now considered to be a global epidemic[10]. Halting this epidemic may ultimately be determined by the quality and co-ordination of a range of obesity treatment initiatives, alongside an effective obesity prevention strategy. It is desirable, from both ethical and fiscal perspectives, to understand how interventions can most effectively and appropriately halt the population trend to fatness. However, the heterogeneity of data at hand make it difficult to conclude that one particular strategy, or combinations of strategies, is or are more important than others in the treatment of child and adolescent obesity, although several strategies appear promising. The mismatch between the high prevalence and significance of the condition and the limited knowledge base from which to inform treatment strategies remains a feature of this review. The potential outcome of effective obesity treatment interventions for children and adolescents include both short and long-term health benefits. Studies are needed that are designed to disentangle the relative importance and effects of targeted antecedent behaviours in paediatric obesity treatment. In addition, study designs must adopt current knowledge regarding the most appropriate theoretical underpinnings of behavioural change. When interpreting the results of such studies the role of general health promotion programmes as potential confounding factors needs to be assessed. In assessing drug interventions in adolescents, the adjunctive role of lifestyle change interventions needs to be further investigated, and the effectiveness of intervention needs to be weighed up against the impact of potential adverse events. The role of surgical interventions in severely obese older adolescents also requires detailed study. All such issues are important in terms of identifying the most cost-effective and sustainable range of interventions.

In conclusion, while there is relatively limited quality data to ascertain which type of intervention is more effective than another in child and adolescent obesity treatment programs, this updated review allows us to be more confident about which strategies are potentially useful. A combined dietary, physical activity and behavioural component appears effective. Family-based, lifestyle interventions with a behavioural program provide significant and clinically meaningful decrease in obesity in both children and adolescents compared to standard care or self-help in the short- and the long-term. In obese adolescents, consideration should be given to the use of either orlistat or sibutramine, in the context of a lifestyle change program, although such therapy needs to be carefully weighed up against the potential for adverse events.

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