

# What works for obesity?

A summary of the research behind obesity interventions

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[www.clinicalevidence.com](http://www.clinicalevidence.com)

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# Executive summary

## Background

Increasing obesity is alarming health experts, politicians, and the public. Latest estimates in the United States indicate that 64% of adults are overweight and 31% are clinically obese. The rise of obesity in children has been especially rapid: 10-15% of children in the United States are overweight, compared to 5-6% in 1976-80. Other developed and developing countries are experiencing similar trends.

Obesity in adults is associated with higher mortality, increased risk of high blood pressure and cardiac disease, diabetes, gallbladder disease, osteoarthritis, and some forms of cancer. In children, obesity is associated with short- and long-term health consequences, including diabetes, increased blood pressure, the development of cardiac risk factors, and orthopedic disorders. For both adults and children, obesity has powerful social and psychological effects, including low self-esteem and discrimination.

It is not known why the prevalence of obesity has increased so suddenly and markedly. Experts agree that the rise is unlikely to be related to a sudden shift in genetic or biological factors within individuals. The causes are largely environmental or a consequence of the mismatch between our physiology and an environment where food is abundant and physical activity unnecessary. Apart from recreational exercise, daily energy expenditure is probably much less than in the past because of technological change and the abundance of labor-saving devices. Calorie intake may also have increased recently, although this is controversial.

Irrespective of the reasons for obesity's increase, interventions for its prevention and treatment are urgently needed. Many experts recommend a two-pronged approach: treating the already overweight and obese while directing efforts to prevent obesity, particularly during childhood.

## Objective

The purpose of this paper is to summarize the research evidence behind interventions to treat and prevent obesity. In the manner of *Clinical Evidence*, we will present and summarize up-to-date research on studies that aim to prevent or treat obesity in individuals or groups. It is intended that this paper will be a useful tool for primary care physicians, professionals, and policy-makers. It is beyond the scope of this paper to carry out systematic reviews so instead we will report their results and assess the amount and quality of research found.

## Methods

We searched Medline, the Cochrane Library, Embase, PsycInfo, and the ERIC database for relevant systematic reviews, references, and studies through March 2004. We also consulted a panel of experts for additional studies on the prevention and treatment of obesity in adults and children.

We searched within each category of intervention. So lifestyle interventions included specific searches on dietary maneuvers, exercise programs and behavioral treatments, and surgical interventions included specific searches for each type of procedure used. After gathering the research, we summarized the studies found and described the conclusions reached by authors of the systematic reviews. Where research was

lacking or poor in quality, we also state those findings. Individual sections were sent to advisors and editors for review.

For the background sections on incidence and prevalence, health consequences of obesity, and the etiology of obesity, we referred to high-quality systematic reviews where they were available. If systematic reviews were not found, findings from reputable, objective sources based on large, controlled surveys were included.

## Results

For the treatment of obesity in adults, there are several types of interventions that have very modest efficacy in bringing about weight loss.

**Surgical interventions:** Surgery is only appropriate for adults with morbid obesity (BMI  $\geq 40$ ) or with BMI  $\geq 35$  and a serious obesity-related co-morbidity. In these people, surgery is the most effective intervention for producing weight loss. On average, gastric surgery for obesity results in weight loss of 25-44 kg (55-97 lbs) after 1-2 years (compared with matched participants who did not have surgery) and sustained weight loss of 20 kg (44 lbs) up to 8 years later. The risk of death from obesity surgery is estimated to be 0-1.5% but rates of surgical complications are considerable. Up to 20% of patients who receive gastric bypass had wound infections and 25% of patients who received gastroplasty required re-operation. The research is insufficient to recommend one procedure over another but rates of surgical complications and length of hospital stays may be less with laparoscopic techniques compared to open surgery. Nearly all patients require prolonged follow-up and vitamin supplementation, and gastrointestinal symptoms may be common in the majority of patients who have surgery for obesity.

Most randomized studies of surgery involve comparisons between procedures so it is difficult to quantify the benefit of surgery compared to nonsurgical management. Severely obese adolescents are also receiving surgery in some centers, but no randomized or controlled trials of this group have been published.

**Pharmacological interventions:** Of the medications that have been used to treat obesity, sibutramine and orlistat appear to have modest effects (weight loss of 3-5 kg, or 6-11 lbs) with frequent but not serious side effects. Treatment up to two years helps to maintain the weight loss. Phentermine and mazindol have similar efficacy, but only up to six months. Metformin, diethylpropion, and fluoxetine have questionable efficacy and are more likely to have adverse effects.

Many of the trials for medications lasted less than one year (including follow-up) so the effectiveness of medical therapy is probably exaggerated. Longer trials showed less weight loss, suggesting that weight regain is common, perhaps rapidly after the medication is discontinued. Many of the drug trials had very high attrition rates (up to 50%) without documentation of the reasons for the losses to follow-up.

Studies of dietary supplements and herbal products were limited but suggest that pyruvate and conjugated linoleic acid may prove to be safe and effective.

**Lifestyle interventions:** Dietary interventions produce modest weight loss of about 2-3 kg (4-7 lbs) compared to controls and 5-6 kg (11-13 lbs) relative to baseline. (The control groups often also lose weight in these studies.) The calorie content seems more important than the composition of the diet; low-carbohydrate diets or low-fat diets were not more effective at producing weight loss than high-carbohydrate or high-fat diets, as long as the total caloric content was equivalent. Meal replacement

strategies (often used in commercial diet plans), such as replacing one meal a day with a liquid shake, may help dieters to adhere to the diet and lose weight.

A smaller pool of evidence suggests that physical activity programs help patients lose about 4 kg (8-9 lbs) compared to usual care. However, lifestyle interventions in any setting (community, clinic, or workplace) seem most effective for adults if they combine dietary change *and* physical activity instruction with behavioral therapy to assist participants in making and sustaining changes in their habits. The average weight lost with these interventions was 3-5 kg (6-11 lbs) compared to usual care. As the intensity of the intervention increased (more frequent meetings, for example) the effectiveness also increased; programs that involved meeting less than once a month were generally ineffective. Interventions with longer follow-up often had less effect, suggesting at least partial regain.

There were many fewer studies aiming to prevent rather than treat obesity in adults who were not already overweight or obese. The large-scale interventions aiming to improve the health of a community used mostly educational campaigns that advocated individual behavior change. A few studies also described some environmental modifications, such as changing food options in grocery stores and schools. These studies did not demonstrate a measurable effect.

**Childhood obesity:** The research on the treatment and prevention of obesity in children is limited and has often been poor in quality. Experts and authors of systematic reviews found the research inadequate to make specific recommendations for the prevention or treatment of childhood obesity. Strategies to reduce sedentary activities, particularly television watching, hold promise and seem more effective than active exercise programs. Studies suggest that parents should be involved and perhaps even act as primary agents for change. School programs that included both dietary change and increased physical activity may be effective, especially for girls. Despite worries among health professionals that obesity interventions may inadvertently provoke eating disorders among children, studies did not report data on the harms of interventions. Follow-up of children for more than one year was rare.

## Conclusions

Even effective treatments for adult obesity only produce very modest weight loss (about 3-5 kg, or 6-11 lbs) compared to no treatment or usual care. Surgery is perhaps the exception but is only appropriate for a subset of patients with severe obesity.

Studies of obesity interventions need to be rigorously performed:

- Participants should be randomized (or well-controlled)
- Authors should state an *a priori* hypotheses and document that the study has sufficient power to determine a clinically important effect
- Participants and interventions should be described in detail
- Standard outcome measures should be reported
- Results should include intention-to-treat analysis and document characteristics of participants lost to follow-up
- Patients should be followed longer than one year to determine rates of weight regain.

Despite a recognized need for obesity prevention and for early treatment, high-quality research on obesity prevention or childhood obesity is scarce. As policy-making organizations put into place public health

measures such as bans on food advertising to children or subsidies on healthy foods, they should simultaneously apply research principles to evaluate these interventions. They should be conducted rigorously and the results should be published.

Although most experts agree that the obesity epidemic is environmental, the research has not been. The interventions for which there is good evidence of efficacy are likely to help individual patients lose some of their weight but alone are unlikely to halt the epidemic of obesity. Obesity prevention, particularly during childhood, and environmental, public health solutions deserve immediate attention.

# Introduction

*“We're just too darned fat,” Thompson, the secretary of health and human services, said at a news conference where he previewed the government's new, humorous advertising campaign aimed at motivating an overweight nation to look in the mirror and lose those love handles, the potbelly, and the double chin.”*

Boston Globe, March 10, 2004

*“The Bush administration is challenging a World Health Organization report that outlines steps for nations to take to reduce obesity. In a letter to the United Nations agency that is meeting next week, Health and Human Services official William Steiger questioned the organization's findings, said they were based on faulty science, and called for changes to the report.”*

Associated Press, January 16, 2004

The headline above portrays just one of the most recent controversies about obesity. The World Health Organization (WHO) has recognized obesity as an international health problem of staggering magnitude. In an effort to curb obesity's impact, WHO convened experts to compose an initiative: a plan to fight obesity globally. The plan includes public health measures such as restricting food advertising aimed at children, increasing the price of junk food through taxes and changes in farm subsidies, limiting unhealthy foods in schools, and encouraging manufacturers to reduce sodium, fats, and sugars in certain foods.

Tommy Thompson, the Secretary of Health and Human Services, has drawn attention to the problem of obesity, but advocates individual change rather than supporting WHO's public health approach. Part of the White House's objection to WHO's plan is the claim that the interventions proposed are not based on scientific evidence. In other words, WHO does not know that the measures will *work* to decrease obesity. In this paper, we will present the scientific evidence behind interventions for obesity. We have rigorously searched the scientific literature to find what the evidence proves and what it does not. In this way, interventions can be based on science whenever possible. When research is found to be scant or of poor quality, the results are not meant to justify inaction. Instead, the lack of research can be used to direct future research efforts. We intend to show where we stand currently in terms of research, and how to move forward, in both practice and research.

As highlighted above, health officials and obesity experts continue to debate the relative importance of individual responsibility versus public interventions. In order to be inclusive, we will present both: interventions aimed at individuals and those aimed at larger groups. We recognize that successful interventions in either domain may have implications for individuals and groups. For instance, one school successfully prevented overweight among its students by limiting television viewing.<sup>1</sup> This might be successful for an entire community or just a single individual.

Successfully tackling obesity will require a two-pronged approach: treating the already obese and overweight, and preventing obesity in others. As such, there is not always a clear line where prevention stops and treatment begins. In addition, treatment of obese people is also secondary prevention of further weight gain and complications. In many cases there will be little distinction between the interventions themselves; the same approach will be used to lessen obesity among those who already suffer from it as well as to prevent it among lean individuals. (Surgery and medications may be the notable exceptions to this: one would not perform surgery on someone as a preventive measure.) Therefore, we will include both treatment and prevention interventions in this review, and describe the appropriate population for each.

## **Objective**

This paper was produced by the BMJ Publishing Group at the request of Reed V. Tuckson MD, vice president of the United Health Foundation. The purpose of this paper is to answer the question “What works for obesity?” in a systematic way, based on the evidence. Using the methodology of *Clinical Evidence*, we have constructed a summary of the research about interventions to combat obesity, in adults and in children. In order to fully describe the problem of obesity and consider interventions within the proper context, we have also summarized research about the etiology, prevalence, and impact of obesity using reliable sources and systematic studies whenever possible. From the research we have made statements about the efficacy of obesity interventions as well as describing where research is lacking.

Our intended audience is primary care physicians although we hope other professionals and policy makers will find this paper readable and useful.

It is beyond the scope of this paper to perform systematic reviews for each type of intervention. Instead, like *Clinical Evidence*, we have reported the results of systematic reviews performed by obesity experts. Where systematic reviews were lacking, we have summarized research findings very briefly. We have also purposely not considered studies of cost-effectiveness, instead concentrating on efficacy.

# Definitions and abbreviations

## Definitions of obesity

To most non-professionals, obese means very fat, and overweight means either less fat or, sometimes, a euphemism for fat or obese. To health professionals and researchers, however, both these terms have definitions that specify the degree of excess fat. Overweight is defined as a body mass index (BMI) of 25.0-29.9 kg/m<sup>2</sup> and obese is a BMI  $\geq 30.0$  kg/m<sup>2</sup>. BMI is defined as weight in kg/(height in m)<sup>2</sup> and is independent of gender and age.<sup>2,3</sup> Morbid obesity is defined by a BMI  $\geq 40.0$  kg/m<sup>2</sup>.

<b>BMI</b>	<b>Description</b>
<18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight
$\geq 30$	Obese
$\geq 40$	Severe or morbid obesity

Physiologically, obesity actually refers to excess fat or adipose tissue, not necessarily excess weight. The gold standard for assessing the amount of body fat is a process called dual X-ray absorptiometry (DXA). However, this technique is expensive and inconvenient, and needs frequent cross-standardization. DXA is used in small research studies but is impractical for common clinical use or large clinical studies in measuring obesity.<sup>4</sup>

BMI is inexpensive, reproducible, and convenient. It is a reasonable approximation of amount of body fat for most adults and has thus come to be the standard for assessing obesity, both in the United States and internationally. BMI is falsely high in individuals with a great deal of muscle mass (such as bodybuilders) and falsely low in those that have lost muscle mass, such as the elderly.

## Obesity measures in clinical trials for adults

Simple weight measurements are a useful way to assess changes in weight.<sup>3</sup> They have been used together with BMI in many of the trials of obesity treatment. Most well-designed studies allowed only measured weight, BMI, or other measure of obesity. Self-reporting for weight status has been shown to be unreliable.<sup>5,6</sup>

## Definitions of obesity in children

For children, the terms obesity and overweight have historically had different meanings. They have been defined at times according to weight, weight/height, percentage of ideal body weight, percentage BMI and skinfold thickness. Furthermore, some researchers have used the terms “obese” and “overweight” at times interchangeably, but at other times to indicate that “obese” was a more severe form of excess fat than “overweight”. “Morbidly obese” and “superobese”, indicating increasing levels of excess adiposity in adults, have generally not been used for children.

Currently, many experts agree on definitions for obesity in children. The term “obese” is avoided, because of its considerable negative repercussions and fear of stigma with the label. “Overweight” is used to indicate a child whose BMI is above the 95th centile for his or her age and sex. A child between the 85th and 95th centiles is considered “at risk for overweight.” As such there is no definition for “obese” in a child.

It is still controversial, however, which of the standardized charts to use as a reference. The NCHS growth and BMI charts are based on children in the United States from 1963-1988, before the trend of increasing childhood obesity was present.<sup>7</sup> These charts may not accurately reflect the ethnic diversity in the United States today. Cole and colleagues have derived charts for use in the United Kingdom and internationally based on the growth trajectories of children in six diverse regions (Brazil, the United Kingdom, Hong Kong, the Netherlands, Singapore, and the United States).<sup>8</sup> There is not yet consensus that each country should use international rather than country-specific charts, although universal use of international charts could make international comparisons and tracking less difficult.

Because of these problems with defining obese and overweight uniformly in children, we have included the various definitions of obesity used in the studies, as long as they were based on measured and not reported weight measures. In this paper, we use the terms overweight and obese interchangeably in children as they are used in the studies. For adults, however, we use the common BMI cut-offs of 25 for overweight and 30 for obese.

## Abbreviations

BMI	Body mass index: weight in kg/(height in m) <sup>2</sup>
BMI z score	Number of standard deviations above or below the mean.
NCHS	National Center for Health Statistics
%OW	Percentage overweight
RCT	Randomized controlled trial

## Methods

Our methods are largely based on those of *Clinical Evidence*. We searched broadly for systematic reviews of interventions for both the treatment and prevention of obesity in adults and children. We searched within each category of intervention (lifestyle interventions included searches for diet, exercise, and behavioral therapy, for example) and for both prevention and treatment for adults and children. In contrast to *Clinical Evidence*, we also extracted additional information about the participants, setting, interventions, and recommendations for practice and research from the systematic reviews and randomized controlled trials (RCTs).

### Searching the literature

For each question, the literature was first searched using the Cochrane Library, Medline, Embase, PsycInfo, and Eric. Then we searched other sources for evidence-based medicine, including Dare (database of abstracts of reviews of effects), HTA (health technology assessment), Bandolier, and Trip (turning research into practice). See Appendix A for more details.

We also consulted with members of the advisory group about other sources for systematic reviews of the literature.

For each source, we looked first for good systematic reviews of RCTs, then for good RCTs published since the search date of the review. Where we found no good recent systematic reviews, we searched for individual randomized controlled trials back to 1966. This search strategy, from *Clinical Evidence*, is heavily based on strategies developed by Brian Haynes and Anne McKibbin at McMaster University in Canada,<sup>9</sup> and strategies developed by Carol Levebvre and colleagues at the UK Cochrane Centre.<sup>10</sup> These strategies are described in Appendix B. The date of the search for systematic reviews is recorded for each search question.

Of the studies that are identified in the search, we select and summarize those with sound methodology. This selection is done by critically appraising the abstracts of the studies identified in the search, a task performed jointly by the author (AJ) and information scientist (TR) using validated criteria similar to those of Sackett et al<sup>11</sup> and Jadad<sup>12,13</sup> (see Appendix C). Where the search identifies more than one or two good reviews or trials, we select those we judge to be the most recent, detailed, and robust. We also compare the results of reviews to ensure consistency of results. Where we identify few or no good reviews or trials, we identify areas for needed research. Advisors, chosen for their clinical expertise in the field, were asked to review our selection of studies and presentation of their results.

Several of the recent, high-quality systematic reviews used in this paper came from the Cochrane Library and the OOPS (Optimizing Obesity Prevention Strategies) study.

### The Cochrane Library

The Cochrane Library is widely recognized as one of the best sources for evidence-based medical research, being based on rigorous searches including grey and non-English language literature together with electronic and hand-searching of medical journals. Protocols for Cochrane reviews in progress are also included together with contact details for the principal investigator. The Cochrane Library contains a comprehensive collection of trials (more than on Medline).

The Cochrane Collaboration is an international, independent, nonprofit organization whose purpose is to provide evidence-based healthcare information. Started in 1993, it produces and disseminates systematic reviews (about 1700 reviews currently available in full in the library; 1300 protocols published for reviews in progress). Its aim is to have 10 000 systematic reviews to cover all interventions studied in RCTs, update 5000 each year and promote research on health care interventions.

The major product is the Cochrane Database of Systematic Reviews, produced quarterly by the Cochrane Library. Reviews are mostly produced by health care professional volunteers with editorial teams overseeing the reviews. The Cochrane Library also includes the Cochrane Central Register of Controlled Trials (CENTRAL), a bibliography of clinical trials. The Register provides a summary of the trial, often with details of where it was published. Three-fifths of the trials come from Medline; the rest are identified by specialty groups that are part of the Cochrane Collaboration or found by hand-searching. CENTRAL includes unpublished sources.

### **The OOPS study**

The OOPS (optimizing obesity prevention strategies) study aims to identify and review studies that were conducted over the last 40 years, with the aim of learning more about controlling weight and preventing weight gain. The goal is to develop evidence-based guidelines for the prevention of obesity for use by public health professionals, although “prevention” in this case includes both weight loss in obese participants and prevention of weight gain. The Yale Prevention Research Center received funding from the Centers for Disease Control and Prevention to conduct the study. The funding supported the systematic review of nonsurgical, non-pharmacological interventions for the prevention and control of obesity in adults and children. This review did not rely on previous systematic reviews but instead searched for primary data from published (searched since the beginning of databases such as Medline) and unpublished sources. The search date was February 2002. Four systematic reviews have emerged from this project, categorized according to setting (workplace, school, health care systems, and community settings).

The author of this paper, Dr. Jain, served as a consultant for this project and was thus aware of its completion although the findings have not yet been published. The results of the systematic reviews will be published in the medical literature and will be incorporated into the United States Preventive Services Task Force’s Guide to Community Preventive Services. As it is a recent and very comprehensive review of lifestyle interventions, the OOPS study was a significant source of evidence for lifestyle interventions in adults.

## Advisory group

We formed an advisory group of obesity experts to guide and broaden our search for obesity studies as well as to ensure that our interpretation of the research is both reasonable and accurate.

Members of the group served as peer-reviewers for relevant sections of the paper.

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## **Background: the incidence and prevalence of obesity**

Epidemic is a word that has traditionally been used to describe contagious infectious diseases, where a few cases of a disease spread rapidly to affect many who enter its sphere. There seems to be no better word, however, to describe the rapid rise of obesity, a complex multifactorial condition, that spreads by our common exposure to an environment that encourages eating and inactivity.

### ***Obesity in the United States***

The Centers for Disease Control and Prevention's (CDC) 1999-2000 National Health and Nutrition Examination Survey (NHANES) estimated that 64% of U.S. adults are either overweight (33%) or obese (31%).<sup>14</sup> Severe or morbid obesity (BMI  $\geq 40$ ) affects 4.7% of the U.S. population. Current estimates show that obesity has dramatically increased from 46% overweight or obese and 14.4% obese (no data on severe obesity) during 1976-80.

Although more women than men are obese, more men than women are overweight. Both men and women have become more overweight, obese, and severely obese over the last two decades. Native Americans, African-Americans, and Mexican Americans have an increased prevalence compared to white Americans. Obesity has increased across all education levels but is highest among those with the lowest educational levels. In the United States, obesity is least common in the New England states (Northeast) and highest among mid-western and mid-southern states. The prevalence of obesity increases with age.

Perhaps more worrying is the rapid rise in numbers of overweight and obese children and adolescents. Current estimates are that 10.4% of children aged 2-5, 15.3% of children aged 6-12, and 15.5% of children aged 12-19 are overweight. This has increased from figures of 5.0%, 6.5%, and 5.0% during the 1976-80 surveys and 7.2%, 11.3%, and 10.5% during the 1988-94 surveys.<sup>15</sup>

Boys and girls are equally affected. Overweight is more common among ethnic minorities. Prevalence rates for African-Americans are 8.4% (ages 2-5), 19.5% (6-11), and 23.6% (12-19). For Mexican Americans the rates are 11.1% (2-5), 23.7% (6-11), and 23.4% (12-19). African-Americans and Mexican Americans have experienced more dramatic increases in the prevalence of obesity during the last 20 years than white Americans.<sup>15</sup>

Two other CDC surveys, the Behavioral Risk Factor Surveillance System (BRFSS) and the Youth Risk Behavior Surveillance System (YRBSS), revealed that self-reported obesity prevalence has also shown similar trends and increases. Estimates based on self-report, however, are consistently lower than prevalence estimates based on measured weight and height from NHANES.

### ***Obesity in developed countries***

Outside the United States, other developed countries are showing similar trends. The International Obesity Task Force estimates that the prevalence of obesity in Europe is 10-20% for men and 10-25% for women, having increased 10-40% in the last decade.<sup>16</sup> The most dramatic increase has been in the United Kingdom, where the prevalence of obesity doubled between 1980 and 1995 (from 6% to 15% in men and from 8% to 15% in women).<sup>2</sup> There is some evidence that the trend may be leveling off among women, particularly in Scandinavian countries.<sup>16</sup> In Japan, obesity has doubled among men in the last two decades,

and almost doubled for young women (age 20-29). In China, obesity is more common in urban areas and among women.<sup>16</sup>

### ***The global epidemic of obesity***

Although the increase in obesity has been most dramatic in developed countries, developing countries are affected. The International Obesity Task Force estimates that 1 billion people worldwide are overweight and 300 million are obese, 115 million of these in developing countries.<sup>16</sup> The increases in obesity may be particularly rapid in developing countries compared to developed countries.

Although current data are limited in many developing countries, regional studies indicate that the prevalence of obesity is rising in developing countries, particularly among the more affluent families. Under- and over-nutrition coexist in many developing countries in roughly equal proportions.

In parts of South Africa, up to 44% of black women may be obese. Similarly, the prevalence of obesity is high in the Middle East and the Caribbean, especially in women. Brazil's national survey showed an increasing prevalence, especially among lower income groups. Obesity has been traditionally considered desirable among Pacific islanders. In 1991, more than 75% of urban males in Samoa were obese. About 23% of school children in Tonga were obese in 1986.<sup>16</sup>

## The health consequences of obesity

In this section, we will present information on the health consequences of obesity in adulthood and childhood. As randomized studies are not feasible or ethical in assessing the naturally occurring consequences of obesity, we will instead seek evidence from high-quality systematic reviews or from rigorously conducted controlled observational cohorts whenever possible.

A note about causation: as these studies are observational and not experimental, most studies show an *association* between obesity and a health outcome, without proving that obesity actually *causes* the outcome. Often, however, the obesity arises first temporally and there is a reasonable and reproducible mechanism to explain how obesity results in the health consequence, suggesting a causal relationship. When the prevalence of a disease increased with worsening obesity, such as diabetes, the evidence that obesity is causal is fortified. Some diseases, such as diabetes and hypertension, improve with weight loss.

### **Adult obesity**

We did not find any systematic reviews about the health consequences of adult obesity. Instead, we used sources where reported adverse effects are based on large surveys comparing the health of obese and non-obese adults. We also relied on authoritative sources, without conflicts of interest or known bias in reporting obesity's effects. In most cases, these reliable experts relied on surveys comparing obese and non-obese participants, rather than case series or case reports.

### **Medical consequences of adult obesity**

Mortality (all causes) worsens as the severity of obesity increases. The lowest risk of mortality is in the normal BMI range for men and the normal-to-overweight range for women.<sup>17</sup> Afterward, mortality increases slightly with BMI >31, and rapidly with BMI >35.<sup>18</sup> In the United States, the association between excess weight and mortality may be weaker for African-Americans than for white Americans. The risk of mortality from obesity probably lessens with age; the health risks of obesity beyond 74 years are unclear.<sup>17</sup>

Obesity is associated with hypertension, dyslipidemia, type 2 diabetes, coronary artery disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, and cancers of the endometrium, breast, prostate and colon.<sup>18</sup> Data from NHANES show that hypertension is the most common weight-related health condition, and that rates of hypertension increase with worsening obesity.<sup>14 19</sup> Overweight and obese adults are also at risk of type 2 diabetes, gallbladder disease, and osteoarthritis, and are more likely to have one or more of these conditions as their weight increases. High blood cholesterol and coronary heart disease were common among overweight men and women but did not increase in prevalence with worsening weight category.<sup>19</sup>

### **Quality of life**

In the medical literature, quality of life encompasses physical, psychological and functional components of well-being. Reliable measures of quality of life and health-related quality of life have been based mostly on the individual's perception of their own well-being.

Studies that measured the quality of life in obese people have found overall that quality of life worsens as the severity of obesity worsens. Most studies have been based on obese people who present for treatment

and want to lose weight, and may not reflect the general obese population. However, studies have generally shown the same result: obese individuals experience a poorer quality of life than their non-obese counterparts. In one study severely overweight patients preferred having a major physical disability such as deafness or blindness to being obese. Obese people who have pain reported the greatest impairments in functioning. Obese women describe a poorer quality of life than obese men, especially at younger ages. Weight loss improves quality of life, but has a greater effect on physical health than on emotional or psychological well-being.<sup>18</sup>

### **Psychological consequences of adult obesity**

In the United States, obesity is more common among minority groups and poorer people although the causal relationship is not well-characterized and is likely bidirectional. Prejudice and resulting discrimination against the obese have been documented, even among health professionals.

In well-controlled studies, obese individuals were rated as less qualified for jobs and were less likely to be admitted to prestigious jobs and professions. Obese people also have less income and lower rates of marriage.

### **Childhood obesity**

We found one systematic review about the health consequences of childhood obesity.<sup>20</sup> This review included results from studies that had a “low risk of bias” and were mostly based on observational cohort studies where health consequences were compared between obese and non-obese groups. Case studies and case series were excluded from this review.

### **Immediate health consequences of childhood obesity**

**Psychological:** Obese children are more likely to suffer from low self-esteem and behavior problems during childhood compared to non-obese children. In one study, 34% of children with a BMI above the 95th centile had low self-esteem compared to 8% of non-obese girls. Prejudice against obesity begins in children as young as 6.<sup>18</sup>

**Medical:** Many high-quality studies have shown associations between obesity (defined as above either the 85th or 95th centiles) and cardiovascular risk factors, including hypertension, dyslipidemia, abnormalities in left ventricular mass or function, endothelial function abnormalities, hyperinsulinemia, or insulin resistance. The presence of risk factors were 2.4-fold (raised diastolic blood pressure) to 12.1-fold (hyperinsulinemia) more likely among obese children compared to non-obese children. More than half of obese children aged 5-10 had at least one risk factor already.

Several well-conducted studies also found a positive relationship between obesity and asthma in childhood. One study reported that becoming obese increased the risk of developing asthmatic symptoms in girls who were not originally diagnosed as having asthma.

From other well-designed studies, childhood obesity was found to be associated with type 1 diabetes, low-level systemic inflammation (indicated by raised levels of C-reactive protein) and structural abnormalities of the foot.

Other medical consequences of childhood obesity, such as type 2 diabetes, polycystic ovary syndrome, and orthopedic, hepatic, and respiratory disorders, are considered well-established but were found to have a limited body of supportive evidence in this review. This was mostly because they were older associations, with low prevalence in non-obese children, and were thus discovered through case reports and case-series. For instance, obstructive sleep apnea occurs almost exclusively in very obese children.

Other health consequences of childhood obesity include:

- Adult eating disorders, smoking to lose weight
- Slipped capital femoral epiphyses and Blount's disease
- Pseudotumor cerebri
- Obstructive sleep apnea
- Gallstones, liver steatohepatitis
- Irregular or early menarche, polycystic ovary syndrome.

### **Long-term health consequences of childhood obesity**

**Persistence of obesity:** Obese children are more likely to become obese adults. The older the obese child is, the more likely he or she will become an obese adult. Persistence of a child's obesity is also more likely if the child is very obese and if at least one parent is obese. Overall, about 40-70% of obese children will become obese adults. However, most of these estimates are based on older data, when obesity in both childhood and adulthood were less prevalent than they are now, so persistence of obesity may be even higher than these percentages.

**Psychological consequences:** Obesity in adolescent females, not males, was found to be related to low educational attainment and income, even after controlling for intelligence and socioeconomic status at baseline. Effects were present even if the teen was no longer obese. Discrimination against the obese was thought to account for this effect.<sup>21 22</sup>

**Medical consequences:** Obesity at age 18 was associated with increased mortality 20 and 32 years later. Estimates indicate an increased relative risk of approximately 1.5 for all-cause mortality, and 2.0 for cardiovascular disease mortality.<sup>19</sup> Obesity in childhood leads to a higher risk of cardiovascular disease in adulthood, although it is not clear how much childhood obesity contributes to cardiovascular risk independent of adult obesity or the persistence of obesity from childhood into adulthood.

There are few long-term, well-controlled studies of the consequences of becoming obese at different ages. As the prevalence of obesity increases, the health consequences are likely to increase in both childhood and adulthood. As with type 2 diabetes in childhood (formerly called adult-onset diabetes), new phenomena associated with obesity may arise. As obesity becomes more common, the associated stigma has not lessened, and may actually be increasing.<sup>23</sup>

# Etiology

On the simplest level, the cause of obesity is clear. Obesity results when energy intake or food is greater than energy expended (or physical activity): when you eat more than you use up. The simplicity ends here; what we eat, how much, when, where, and why we eat depend on a thousand other factors, from our genes and inherent biological makeup to our socioeconomic status, from our mood to our family heritage and more. The way these factors relate to one another in a particular individual at a particular moment is also unpredictable. How much exercise we do also depends on many other variables, internal and external. It is affected by who we spend time with, what our jobs are, how much money we have, how strong our muscles are, and whether we live in a cold or warm climate. The list goes on.

It can be helpful to separate causes or contributing factors into biological factors and environmental factors. Although more true in some individuals than in others, generally speaking, our bodies are efficient machines to store fat, to become obese.<sup>24</sup> This is likely the result of thousands of years of evolution, an adaptation that was suited to the environment in which humans developed, where food was often scarce. In this sense, our biology has everything to do with why we are becoming obese.

However, the current problem of obesity is a modern phenomenon: the increased prevalence has been especially marked within the last three decades. On the timescale of evolution, this is much too short a time to reflect a significant change in our biology. We simply cannot evolve that quickly. In contrast, our environment has changed dramatically to one where food is plentiful and physical activity nonessential to survival. Experts agree that the current epidemic of obesity is due to environmental causes. In an individual, obesity results from an interaction or even a mismatch between our biology and the environment.

## **Biological factors**

Figures of 30-70% are oft-quoted as the size of the contribution made by biology or genetics (as opposed to the environment) to obesity.<sup>25</sup> It can be difficult to understand what a numerical estimate like this means, especially in the context of an obesity epidemic, when we are trying to stop its progression, not to attribute all of obesity to biological factors that are extremely difficult or impossible to change.

The higher estimates for the heritability of obesity (the largest contribution of biology) have been based on studying the prevalence of obesity in monozygotic or identical twins. These studies have found that identical twins are very likely to reflect one another's adiposity - if one is obese then the other is also. Similar levels of adiposity between monozygotic twins are present even when they are raised apart, or irrespective of environment. These studies suggest that 70% of obesity is genetic. Other studies of adopted children suggest otherwise; adoption studies show that children's adiposity reflects the adiposity of their parents, whether they are the biological or the adopted parents. Studies like this suggest a more important role of the environment, and yield a lower estimate of 30% of the contribution to obesity coming from a biological predisposition. Studies of the prevalence of obesity among family members suggest estimates between 30% and 70% for the biological or genetic contribution to obesity.<sup>25</sup>

There are several genetic disorders where obesity is nearly always present. These include Prader-Willi syndrome, Laurence-Moon-Biedl-Bardet syndrome and Albright's hereditary osteodystrophy. Rare syndromes with genetic abnormalities of leptin or the leptin receptor have also been found recently. Usually, in these disorders obesity is expressed almost regardless of the environment. Indeed, these

disorders probably have little to do with the current epidemic, although the study of individuals with these disorders can help us to understand the complex pathways that result in obesity.

Although common obesity is not entirely biological or genetic, and individual behavior plays an important role for most obese individuals, the importance of biology is not to be minimized. Between individuals the tendency to gain weight in an obesity-promoting environment varies greatly.<sup>25</sup> Some individuals are likely to be overweight even in a healthy environment and others remain lean despite easy access to high-calorie foods and a sedentary lifestyle. Biological factors may also govern behavioral responses to environmental conditions. For instance, one individual may prefer the sour taste of fruits compared to the sweetness of baked desserts. Another individual may have physical abilities in sports that make exercise more enjoyable and easier to sustain. Factors traditionally considered important in the amelioration of obesity, such as willpower and metabolic rate, may be mostly biologically mediated.

## ***Environmental factors***

Many environmental factors have been suggested as major causes of the obesity epidemic. However, because measurements of energy intake and expenditure are flawed (often based on self-report) and imprecise (both in individuals and in groups) it is still unproven what has contributed most to the current problem, eating more than in the past or exercising less. Even the dramatic rise in obesity we see today could be due to the accumulation of very small changes in energy intake or expenditure over long periods in time, differences that are well within the margin of error for current instruments used to measure the energy intake and activity level in individuals.

Based on self-report, large surveys of dietary intake in the United States have generally shown two conflicting results: that Americans are either eating slightly less or slightly more than in the past.<sup>26,27</sup> The evidence is perhaps stronger that the overall decrease in physical activity has been the primary cause of the obesity epidemic.<sup>26-28</sup> Although it is extremely difficult to measure energy expenditure in individuals, or to prove that the average American does less physical activity than in the past, studies have suggested that most jobs (where much of adult waking time is spent) require less movement and physical exertion than in the past, mostly because of technological advances. Recreational physical activity for adults has probably increased, but sedentary activity such as television viewing and computer work has also increased.<sup>24,26,28</sup> In addition, recreational activity for children is less common within the school day, and changes outside the school day are not well documented.<sup>24</sup>

We found one systematic review that evaluated the strength of scientific evidence behind environmental etiological factors.<sup>2</sup> However, this review also considered a factor's effectiveness as a treatment for obesity as evidence of its etiological role. We will present the findings of this review in terms of important causative etiological factors. Interventions and the evidence behind effective interventions for obesity will be presented in the results section as the main purpose of this paper.

In the review, *convincing* causative, etiological factors included:

- Sedentary lifestyles
- High intake of energy-dense, micronutrient-poor foods.

*Probable* etiological factors were:

- The heavy marketing of fast-food outlets and energy-dense, micronutrient-poor foods and beverages
- A high intake of sugars-sweetened beverages
- Adverse socioeconomic conditions, especially for women in high-income countries.

*Possible* (lower strength of evidence) etiological factors included:

- Large portion sizes
- Food eaten outside the home
- Psychological eating patterns including rigid restraint/periodic disinhibition.

### **Breastfeeding and obesity**

This WHO report described breastfeeding as a probable *protective* etiological factor for obesity.<sup>2</sup> There is no evidence that breastfeeding *per se*, or a recent change in breastfeeding habits has contributed to the obesity epidemic. Breastfeeding rates have generally increased in the United States, concurrent with the rise in obesity. However, a few large, retrospective studies have found that breastfeeding protects against obesity. Many other studies have shown no relationship, and two found that breastfeeding predicts obesity.

### ***Etiological factors versus interventions for obesity***

The causes of the obesity epidemic may not necessarily be the best targets for interventions to treat and prevent obesity in the current environment. Effective interventions, whether or not they've caused the current epidemic, may have to include strategies to deal with very recent environmental phenomena such as the omnipresence of computers and the need for seated work in almost every profession, as well as the inexpensive nature of high-calorie foods.

Although inactivity may have played a larger role than dietary intake in causing obesity in the population, it may be easier to decrease energy intake in an individual than to increase energy expenditure enough to compensate for the availability of high-calorie foods. In other words, it may be easier to keep someone from eating a piece of chocolate cake than to make them jog for an hour, although calorically equivalent. Ideally, interventions will use an individualized, two-pronged approach that includes both dietary change and increased physical activity for maximum health benefit.

# Treatment of adult obesity

## *Pharmacological interventions*

Medications as described in this section include medications approved by the Food and Drug Administration (FDA) for use in obesity, including both prescription and over-the-counter drugs. In addition, we've included off-label drugs, or medications approved for other, non-obesity indications, that may have efficacy for weight loss.

Prescription medications include sibutramine, orlistat, metformin, phentermine, mazindol, and diethylpropion. Off-label medications include fluoxetine.

Drugs withdrawn from the market in the United States and/or the United Kingdom due to harmful side effects (fenfluramine, dexfenfluramine, and phenylpropanolamine) have not been included.

The research for each of these medications will be presented in summary form below. At the end of this section, overall conclusions and recommendations will be given.

### **Sibutramine**

We found three high-quality systematic reviews of sibutramine (search dates: April 2002, December 2002, and February 2003).<sup>17 29 30</sup> Since February 2003, we found one additional study.<sup>31</sup> In total, the results described here include 29 trials, with a total of more than 4800 participants.

**Study sizes:** Studies varied in size from 19 to 1102 participants. Studies were published between 1991 and 2003, and varied in length from 8 weeks to 12 months.

**Characteristics of participants:** Most participants were healthy obese adults, mean ages 34-54, with baseline BMI above 30 (mean baseline BMI = 32-39). Some studies included participants with BMI 27-30 and a cardiovascular risk factor such as hypertension, diabetes, or dyslipidemia. Several trials specifically recruited participants with hypertension (four studies), type 2 diabetes (five studies), hyperlipidemia (two studies), or obstructive sleep apnea (one study). Most studies excluded patients with known cardiovascular disease.

Three studies included only women. In addition, women comprised the majority of the participants in most of the studies that also included men. Ethnicity and socioeconomic status were not described in most of the studies. When reported, most participants were described as white.

**Settings:** Of the 29 trials, 14 took place in Europe and six took place in the United States. The rest were in Mexico (4), Brazil (2), Turkey (1), South Korea (1), and China (1). Most studies were funded by pharmaceutical companies or did not specify; the Chinese study was funded by the Chinese government.

**Interventions:** The participants in most of the studies (in treatment and control groups) also received lifestyle interventions for obesity consisting of dietary modification, physical activity, behavior therapy, or a combination. In 25 of the studies, participants were also prescribed a low-calorie diet.

Most trials began with a sibutramine dose of 5 mg daily, increasing to 20 mg daily by week 8. One study included doses of 10 mg and 15 mg.

**Outcomes assessed:** Studies measured weight loss, percentage weight lost, and numbers of patients achieving at least 5% and 10% weight loss.

**Treatment effects:** On average, patients lost 4.3 kg (or 4.6%) more with sibutramine than with placebo. The attrition rate was 43%. One study looked at sibutramine for weight maintenance in 605 patients.<sup>30</sup> After two years, patients taking sibutramine kept off more weight (4 kg) than those receiving placebo. One comparative study found that persons treated with sibutramine lost significantly more weight (13.4 kg) than those treated with orlistat (8 kg) or metformin (9 kg).

**Adverse effects:** Sibutramine caused increases in both systolic and diastolic blood pressure (0.8 mm Hg and 0.7-3.3 mm Hg, respectively), and increases in pulse rate (4-6 beats per minute). Insomnia, nausea, dry mouth, and constipation were more common in people taking sibutramine than those taking placebo. These effects occurred in 7-20% of patients.

**Follow-up:** All studies followed participants for one year.

**Quality of studies:** High attrition rates making data difficult to interpret, details of randomization usually not given, and true intention-to-treat analysis not reported because of high attrition rate, could bias results in either direction.

## Orlistat

We found two high-quality systematic reviews (search dates: end of 2002 and February 2003).<sup>17 29</sup> Both these reviews included only RCTs with a placebo or medication control group and with at least one year of follow-up since randomization. In total, the results represent 17 studies, with more than 6000 patients in total.

**Study sizes:** Studies varied in size from 218 to 892 participants.

**Characteristics of participants:** At baseline, study participants had an average BMI of 35.7 kg/m<sup>2</sup>, weight of 100 kg, and age of 49 years; 72% were women and 79% were white. Six of the 11 studies included patients with co-morbidities, including type 2 diabetes (three studies), or a cardiovascular risk factor (hypertension, hyperlipidemia, type 2 diabetes, or impaired glucose tolerance) (three studies).

**Interventions:** All studies used the standard dose of orlistat: 120 mg three times a day. Several studies also tested other doses, including 30 mg, 60 mg, and 240 mg three times a day. All patients were instructed to follow a low-fat diet (fat comprising less than 30% of daily caloric intake). Other co-interventions in studies varied and included dietary and exercise counseling, keeping a food diary, and educational material.

**Outcomes assessed:** Studies reported weight loss, percentage of weight lost and numbers of patients achieving at least 5% and 10% weight loss.

**Treatment effects:** In all studies, treated patients reported more weight loss than those receiving placebo. On average, patients lost 2.8-4.5 kg more with orlistat than with placebo, kept off their weight more successfully with orlistat treatment for 1-2 years, but discontinuing treatment led to excess weight gain

compared to placebo. Attrition rate averaged 22% for the orlistat trials. Orlistat was slightly less effective among participants with cardiovascular risk factors.

**Adverse effects:** Gastrointestinal side effects were common among orlistat users; 15-30% of patients experienced oily stools, fecal urgency, or oily spotting, and 7% reported fecal incontinence (compared to 1% in the placebo group). Levels of fat soluble vitamins were lower in those taking orlistat, occasionally requiring vitamin supplementation.

**Follow-up:** Studies followed patients for six months to one year.

**Quality of studies:** High attrition rates making data difficult to interpret, details of randomization usually not given, and true intention-to-treat analysis not reported because of high attrition rate, could bias results in either direction. Side effects of orlistat make blinding unlikely.

## **Metformin**

We found one high-quality systematic review that identified three studies of metformin (850 mg twice a day) in more than 3000 patients.<sup>17</sup>

The largest study (3234 patients; 55% white; 68% women; baseline BMI = 34 kg/m<sup>2</sup>) showed a weight loss of 2 kg at 2.8 years, but this was less than the group that received the lifestyle intervention (5.6 kg).

Another study showed no effect of metformin, and the last study was a multidrug comparison and showed that patients lost 9 kg at the end of six months, more than the weight loss seen with orlistat (8 kg) but less than with sibutramine (13.4 kg).

## **Phentermine**

We found one systematic review (search date: 1999) that included six RCTs with a total of 368 participants, followed for 2-24 weeks.<sup>32</sup> Overall, participants receiving phentermine lost significantly more weight (0.6-6.0 kg) than those receiving placebo, but there was no difference in weight loss compared to other obesity medications.

## **Mazindol**

We found one systematic review (search date: 1999) that included 22 RCTs with 906 participants in total.<sup>32</sup> Mazindol (1-3 mg daily) produced modest weight loss (0.1-7.3 kg) compared to placebo after 2-20 weeks, and no significant difference in weight loss compared to other medications, including diethylpropion, fluoxetine, orlistat, phentermine, and fluoxetine. In a multidrug comparison, sibutramine had a significantly greater effect on weight loss.

The systematic review did not comment on adverse effects. Case series have reported episodes of pulmonary hypertension, atrial fibrillation, and syncope, but the frequency of adverse events is unknown.

## **Diethylpropion**

One systematic review included nine RCTs with 353 people total. Participants received 75 mg daily of diethylpropion for 6 weeks to 1 year.<sup>32</sup> Participants treated with diethylpropion lost more weight (1.6-11.5

kg) than those on placebo but no more than those on other obesity medications in a multidrug comparison.

Case reports have described pulmonary hypertension and psychosis.

## **Fluoxetine**

One systematic review (search date: 1999) included 11 RCTs with 1219 participants in total.<sup>32</sup> Fluoxetine (32.5-60 mg daily) was associated with greater weight loss (0.2-7.4 kg) than placebo after 6-60 weeks (mean follow-up was 28 weeks). There was no difference in weight loss between fluoxetine and other obesity medications in a multidrug comparison.

An older systematic review found that selective serotonin-reuptake inhibitors (SSRIs) such as fluoxetine were associated with increased incidence of anxiety, diarrhea, dry mouth, headache, nausea, and rare but serious events such as bradycardia, bleeding, granulocytopenia, seizures, hyponatremia, hepatotoxicity, serotonin syndrome, and extrapyramidal effects.<sup>33</sup>

## **Conclusions and recommendations**

- Sibutramine and orlistat appear to have modest efficacy of 3-5 kg of weight loss, and frequent but not serious side effects. Treatment up to two years helps maintain the weight loss.
- Phentermine and mazindol have similar short-term efficacy.
- Metformin, diethylpropion, and fluoxetine have questionable efficacy, possible adverse effects, or both.

## **Research limitations**

- The short duration of pharmacotherapy trials may exaggerate their efficacy.
- Attrition rates in pharmacotherapy trials were very high, and the diversity of participants was limited.
- Long-term benefit and adverse effects are unknown.

## ***Dietary supplements and herbal products***

We found one systematic review (search date: May 2003) that included single-agent randomized blinded studies of dietary supplements and herbal products used to treat obese or overweight participants.<sup>34</sup> Studies of sufficient rigor were included and studies of combination products were excluded.

## **Conjugated linoleic acid**

Conjugated linoleic acid is found in dairy products and beef and is thought to work by inhibiting lipoprotein lipase, an enzyme that breaks down fat for absorption, and increasing the breakdown of stored fat.

Three RCTs with a total of 126 patients used conjugated linoleic acid for weight loss. Typical doses were 3.0-3.6 grams per day in three divided doses with meals for 12 weeks or less. None of these showed changes in weight or BMI, but did report significant decreases in abdominal diameter, body fat mass and percent body fat. Adverse effects included mild gastrointestinal symptoms but were not different from placebo.

### **Ephedra, ephedrine (Ma Huang)**

Ephedra is an extract or powdered formulation of a plant or stem containing ephedrine. Shekelle et al published a meta-analysis of 22 studies of ephedrine, ephedrine and caffeine, ephedra, or ephedra and herbs containing caffeine, each lasting 8 weeks to 4 months.<sup>35</sup> Rates of weight loss was 0.6-1.0 kg per month, and 21 of 22 studies found 5-11% weight loss at 4 months compared to placebo. However, ephedrine and ephedra had 2-3 times the risk of adverse effects, including psychiatric symptoms, autonomic symptoms, gastrointestinal symptoms, and heart problems. Another reviewer reported that of ephedra-related adverse effects reported to the FDA, 47% were cardiovascular and 18% central nervous system symptoms. Hypertension was the most common adverse effect. A disproportionate number of adverse events due to ephedra were reported to poison control centers. Although effective, ephedra is not considered safe for use in obesity treatment.

### **Chromium**

Chromium is an essential nutrient that aids metabolism of carbohydrates and lipids. The recommended daily allowance (RDA) of chromium is 50-200 µg, but 200-400 µg per day is used for weight loss. Four studies of chromium for weight loss were poor in quality and had mixed results.

### **Hydroxycitric acid (Garcinia cambogia)**

This supplement comes from a fruit rind that is used in Indian and Thai cooking and is thought to inhibit enzymes that prevent fat storage.

We found one RCT (119 women, 16 men) that evaluated 1500 mg/day hydroxycitric acid for 12 weeks with a high-fiber, low-calorie diet and found no effect compared to placebo. Adverse effects were mild and not significantly different from placebo.

### **Chitosan**

Chitosan comes from the shells of crab, lobster, shrimp, and other shellfish. It is thought to inhibit fat absorption.

Two studies (103 participants in total) used 3.0-4.5 grams twice daily compared to placebo for 4-8 weeks and found mixed results (one found positive effect, the other no effect). Adverse effects are unknown.

### **Pyruvate**

Pyruvate is a breakdown product of carbohydrate and protein metabolism and is thought to increase the metabolism of fat.

Five RCTs (121 participants total) evaluated doses of 6-44 g for 3-6 weeks. All participants also followed low-calorie diets or took exercise. All five studies showed a positive effect compared to placebo: weight loss ranged from 0.05-1.1 kg at 3 weeks to 2.5 kg at 6 weeks. Pyruvate appeared to be safe in the RCTs, but has been associated with gastrointestinal symptoms at higher doses. One child with restrictive cardiomyopathy died when given pyruvate intravenously.

## **Effective interventions**

From limited clinical evidence, conjugated linoleic acid appears to have positive effects on body composition without significant harms. Also, pyruvate appears to be safe and effective in short-term studies. More research is needed to make definite recommendations.

## **Quality of studies**

Almost all studies of supplements and herbal products were small in size and thus underpowered to show efficacy or safety. Furthermore, most were short in duration.

## ***Surgical interventions***

Studies only included obese patients for whom surgery is indicated: participants with a BMI >40, or with BMI > 35 and a significant obesity-related morbidity.

To evaluate the efficacy and safety of bariatric surgery for weight loss in morbidly obese adults, we examined RCTs comparing different surgical procedures and both RCTs and non-randomized controlled trials comparing surgery with nonsurgical treatment for morbid obesity. We excluded studies that compared variations of surgical techniques and studies that included jejunioileal bypass.<sup>36,37</sup> This procedure is no longer recommended in the United States and Europe due to high morbidity and mortality.

We found three high-quality systematic reviews of bariatric surgery.<sup>36-38</sup> The first comprehensively reviewed 16 RCTs comparing different bariatric procedures, one large non-randomized controlled trial (the Swedish obese subjects [SOS] study), and one RCT comparing bariatric surgery to nonsurgical treatment (Search date: October 2001; published twice).<sup>36,37</sup> Since October 2001, there have been three additional RCTs comparing different surgical procedures.<sup>39-41</sup> The second reviewed only trials comparing bariatric surgery to nonsurgical treatment and compiled data from six separate reports of the SOS study (search date: August 2003).<sup>38</sup> The third systematic review was a broad review of all interventions for obesity in adults (search date: February, 2003) with less detail about specific trials. Hence, the surgery-specific reviews were used to describe details of studies and interventions, and the broad review for overall conclusions. When the systematic reviews had similar and consistent conclusions, those are presented here. When they differed, the uncertainty is presented. In total, the results described here include about 21 trials, with a total of 3830 participants.

## **Details of studies**

**Study size (number of participants), length of follow-up, and publication dates:** Studies varied in size from 30 to 2188 participants. Studies were published between 1981 and 2004. The duration of included studies was 1 year (eight trials), 18 months (two trials), 2 years (two trials), 5 years (one trial), 6.5 years (two trials), and 8 years (one trial; SOS).

**Characteristics of participants in the studies:** Most participants were female with a mean age of between 33 and 47 years. Baseline BMI was >35; mean or median baseline BMIs ranged between 41 and 52, when reported. Most studies excluded patients with known cardiovascular disease. Ethnicity and socioeconomic status were not described in most of the studies. We did not identify any RCTs or non-randomized controlled studies of bariatric surgery in adolescents.

**Settings:** Of the 21 trials, seven took place in the United States, 10 took place in Europe, with one trial each in Australia, Canada, Mexico, and New Zealand. Most studies did not specify the source of funding.

**Interventions:** The interventions and comparisons fell into three groups (see table).

- Bariatric surgery (any type) versus nonsurgical treatment (1 RCT and 1 non-randomized trial)
- Comparisons of different bariatric procedures: gastric bypass versus vertical banded gastroplasty (4 RCTs); gastric bypass versus horizontal gastroplasty (5 RCTs); vertical banded gastroplasty versus horizontal gastroplasty (1 RCT); gastric banding versus vertical banded gastroplasty (2 RCTs); gastric bypass versus vertical banded gastroplasty versus gastric banding: (1 RCT); gastric bypass versus vertical gastroplasty versus gastrogastrostomy (1 RCT)
- Open versus laparoscopic bariatric procedures: open versus laparoscopic gastric bypass (3 RCTs); open versus laparoscopic vertical banded gastroplasty (1 RCT); open versus laparoscopic gastric banding (1 RCT).

**Outcomes assessed:** Studies measured weight loss (mean change in weight or BMI, percentage of body weight lost, percentage of excess body weight lost), and quality of life.

**Quality of studies:** Rates of follow-up were generally high (>80%) but overall quality ratings of these trials are poor. The details of randomization and concealment were usually not given, and true intention-to-treat analyses were not usually reported. Outcome assessors were rarely blinded (or blinding not stated) to treatment allocation. Some trials did not adequately report attrition.<sup>37</sup>

## **Bariatric surgery versus nonsurgical treatment**

Compared to nonsurgical treatment, bariatric surgery was more effective at producing weight loss among morbidly obese adults. Surgical patients lost 25.8-44 kg at 1-2 years follow-up compared to 1.6-9 kg weight loss among randomized or non-randomized matched controls. The mean difference in body weight after 8 years between surgical and nonsurgical participants in the large non-randomized study was 20.7 kg ( $p < 0.01$ ).<sup>36</sup> After eight years the surgical group (all three procedures combined) had lost  $16.3 \pm 12\%$  body weight (232 people) and the usual care group had gained  $0.9 \pm 11\%$  body weight (251 people).

## **Comparisons of different bariatric procedures**

Two of the four RCTs that compared gastric bypass with vertical banded gastroplasty found significantly greater weight loss with gastric bypass<sup>37</sup>: 78% and 68% versus 52% and 43% excess weight lost at 12 months, and similar significant result at 2-3 years. The other two RCTs (32 adults with BMI  $\geq 40$ ; 106 adults) found no significant difference in weight loss between these two procedures at 36 months, 3 years and 5-6 years.<sup>37</sup>

All five RCTs (387 adults) comparing gastric bypass with horizontal gastroplasty demonstrated significantly greater weight loss for those undergoing gastric bypass<sup>37</sup>: 35-42% weight loss with gastric bypass compared with 16-29% with horizontal gastroplasty at 12 months' follow-up.

One RCT (77 adults) found greater mean excess weight loss with gastric bypass (76.6%) than with gastric banding (65.5%) or vertical banded gastroplasty (59.8%) at 18 months (statistical significance not reported).<sup>37</sup>

One RCT (74 adults) compared vertical banded gastroplasty with horizontal gastroplasty at 12 months and found significantly greater weight loss for vertical banded gastroplasty (48.5 kg versus 32.6 kg;  $p < 0.02$ ).<sup>37</sup>

Another RCT demonstrated that patients undergoing gastric bypass were more likely to achieve 50% excess weight loss compared to vertical gastroplasty or gastrogastrostomy.<sup>37</sup>

Two RCTs found conflicting results regarding the efficacy of vertical banded gastroplasty versus adjustable gastric banding.<sup>37 40</sup>

### **Open versus laparoscopic bariatric procedures**

Three RCTs (310 adults) found no significant differences in weight loss at 1-2 years between open or laparoscopic gastric bypass.<sup>37 41</sup>

One RCT (30 adults; BMI = 40-50) found no difference in weight loss between open and laparoscopic vertical banded gastroplasty at 12 months.<sup>39</sup>

One RCT (50 adults with BMI  $\geq 40$ ) found no significant difference in weight loss between open and laparoscopic gastric banding at 12 months (34.4 kg and 35.0 kg).<sup>37</sup>

### **Adverse effects**

One systematic review also included surgical case-series for determination of adverse effects.<sup>17</sup> Those results are presented here with the results from controlled randomized and non-randomized trials.

**Risk of death:** True risk of death from bariatric surgery is not yet clear as no surgical deaths were reported by the RCT comparing surgery to nonsurgical treatment.<sup>37</sup> From 38 case series, including patients with substantial co-morbid conditions or mild health problems, perioperative mortality rates were low and similar across procedures: 0.0-1.5% among patients who received gastric bypass, vertical banded gastroplasty, or gastric banding. To date, the SOS study has reported five postoperative deaths in 2010 operated patients (0.25%); three due to leakage, one from a technical mistake during laparoscopic surgery and one from postoperative myocardial infarction.<sup>42</sup>

**Morbidity or non-fatal adverse effects:** In the large SOS study comparing surgical to nonsurgical treatment, perioperative complication rates were: subphrenic abscess (7%), atelectasis, or pneumonia (4%) and wound infection (4%). The RCT comparing surgery to low-calorie diet reported that no patients required reoperation, while 2.2% of SOS patients required re-operation.<sup>37</sup>

From the review of surgical case series, morbidity was common.<sup>17</sup> Wound infection was reported in 8-20% of patients who had gastric bypass and in 8-32% who had vertical banded gastroplasty. Reoperation was required in 20-25% of patients who received vertical banded gastroplasty over 3-5 years. Less frequent were gastric leaks, stomal stenosis, and pouch dilatations. Other single studies reported vitamin B-12 deficiency (40%), staple failure (15%), diarrhea (13%), and gastrointestinal bleeding (3%). Patients who received gastric banding often required reoperation (1-20%) or band dislocation, leakage, or slippage (0.4-8%).

Although RCTs had somewhat mixed results, studies suggested that patients undergoing laparoscopic versus open procedures had fewer surgical complications and possibly shorter hospital stays.<sup>17 37 41</sup> In three RCTs, minor complications (including vomiting, colicky pain, and wound infection) were not significantly different across groups.<sup>37</sup>

Mild adverse effects after surgery (all procedures) included the need for prolonged follow-up and vitamin supplementation. In addition, surgical patients described dysphagia, vomiting, hunger, and esophagitis. In the large SOS study, vomiting was the only complication that differed significantly across groups (52% for the surgery group; 0% for the nonsurgical group;  $p < 0.05$ ).

## **Recommendations for practice**

Two systematic reviews identified limited evidence that surgery is more effective than conventional management for weight loss in morbid obesity. The weight loss from bariatric surgery appears to be maintained up to eight years and is associated with reductions in obesity-associated co-morbidities, such as hypertension and diabetes. There are a number of different operative procedures available. However, due to the limited evidence and poor quality of the RCTs, the comparative safety and effectiveness of these procedures is not clear. We did not identify any comparative studies of bariatric surgery in adolescents.

## **Recommendations for research**

Good-quality RCTs comparing different operative techniques and comparing surgery with nonsurgical treatment are needed. Studies of adolescents are also needed.

## ***Lifestyle interventions to treat obesity***

Lifestyle interventions include changes in diet, physical activity (or sedentary activity), behavior therapy to help make those changes, or any combination of the above. We will discuss the effectiveness of lifestyle interventions as a whole, and then divide lifestyle interventions into those that focus primarily on dietary changes, physical activity changes, or a combination. Studies of lifestyle interventions are divided into treatment studies, community prevention studies, and workplace studies.

**Treatment studies:** Systematic reviews did not always clearly separate studies intended to prevent obesity from those intended to treat already obese and overweight individuals; weight loss was the goal in both situations. Often, studies included adults who were overweight, felt to be at risk of becoming obese, were mildly or moderately obese, or had a cardiovascular risk factor such as high normal blood pressure or increased insulin resistance. As the difference between obesity prevention and treatment is overlapping in such studies, and both the nature of the interventions and the results they produced are similar, we have grouped these studies together.

**Prevention and treatment interventions:** The vast majority of studies were intended to treat obesity in adults. Within the systematic reviews, however, there were a few studies and interventions that attempted to affect weight status of a group that included both lean and obese individuals. The interventions used in these studies did not always differ markedly from those aimed to treat obesity, but the number of studies and the results did differ significantly. Thus, lifestyle interventions to prevent obesity in adults are described separately below.

**Workplace interventions:** These are lifestyle interventions but in a different setting. They included both obesity prevention and treatment.

**Results of literature search:** We found six high-quality systematic reviews. There was considerable but not complete overlap between the systematic reviews because of differences in inclusion and exclusion criteria, how interventions were classified, and the manner in which the quality of studies was rated. We describe the results here of the two most recent high quality systematic review (search dates February, 2001, and February 2003) because they were the most recent<sup>17</sup>, most inclusive<sup>17,43</sup>, and most detailed about the interventions and settings.<sup>43</sup> The broadest review of RCTs with at least one year of follow-up included three previous systematic reviews (with 29, 24, and 6 trials in each) and 17 additional RCTs.<sup>17</sup> We have also included studies found since the date of most recent search (February 2003). In addition, we checked the previous systematic reviews to ensure that we are not missing any important research findings as well as to make sure the messages from the experts in the reviews are consistent.

## **Dietary interventions**

One systematic review assessed the effectiveness of all interventions that primarily improve dietary intake in two settings, within healthcare systems (22 studies) and community settings (17 studies).<sup>43</sup> Because the interventions themselves and the results found did not differ greatly between these two settings, the details of the studies will be presented together. Another systematic review assessed the efficacy of low fat diets in particular<sup>44</sup> and a systematic review assessed the efficacy of low-carbohydrate diets.<sup>45</sup> These results will be presented after the review of dietary interventions as a whole.

**Study characteristics:** Studies varied in size from 36 to 956 participants. Most studies followed participants for 6-18 months, but a few determined outcome at 3-5 years post-intervention. Studies were published between 1980 and 2001.

**Characteristics of participants:** Most studies included overweight or obese adults. Eleven studies specifically targeted adults with hypertension or diabetes and one targeted adults with obstructive sleep apnea secondary to obesity (and assessed weight loss as an outcome measure). Some studies included only men (three studies) or only women (10 studies). Studies were generally designed for adults of all ages, although one study included only postmenopausal females. One study was specifically designed for native Hawaiians and included cultural health education and a traditional diet. Another study specifically enrolled women of low socioeconomic status (white and African-American). Most studies did not specify socioeconomic status or ethnicity of participants.

**Settings:** Most studies took place in the United States. Other settings included Canada, Finland, Germany, Japan, Sweden, and the United Kingdom.

**Outcomes assessed:** Outcome measures were weight or BMI units.

**Description of interventions:** The interventions used in the studies varied a great deal. All studies gave dietary advice or prescription, often with behavioral therapy (most often cognitive), in a group setting as well as individually. Most often diets were low in fat and calories (1000-1500 kcal/day) and the American Heart Association diet was often used. A few studies tested short-term very low-calorie diets. Two studies tested the effectiveness of low-carbohydrate diets. Participants were often required to keep food diaries.

Some interventions also included: meal replacements, shopping, and cooking instruction, weighing multiple times a day, comparisons between medications and dietary change, lactovegetarian diet, simple and complex carbohydrates, use of a small plate and bowl for all meals, monetary incentives, food provisions, varying degrees of spouse involvement, peer pressure, public announcing of weight, monitoring number of bites of food, and comparisons between eating breakfast and skipping breakfast.

**Effect of dietary interventions:** There is strong evidence that dietary lifestyle interventions produce weight loss in adults, in both health care settings and community settings. Mean weight loss (pooled effect sizes) from these studies was 5.25 lbs and 6.5 lbs (clinical and community settings, respectively) compared to controls and 15.1 lbs and 13.2 lbs from baseline.

**Low-fat diets:** One systematic review evaluated the efficacy of low-fat diets (search date: February 2002).<sup>44</sup> This review included six studies (with a total of 594 participants) that were randomized, included either obese or overweight adults, compared a low-fat diet with another type of diet, and followed participants for at least six months. The participants were mostly (92%) women and three trials were restricted to women. The age range was 18-66, with mean ages 40-50. Trials took place in the United States or the United Kingdom, and participants were recruited from the community.

Low-fat diets consisted of 20-30 g of fat per day or less than 20% of calories from fat. Low-fat diets were compared to low-calorie diets, and moderate fat (low calorie) diets. All participants received nutritional education as well as group or individual meetings. Three studies also included behavioral therapy and physical activity advice as part of the intervention; no studies included medications.

There was no significant difference in weight loss between low-fat diets and other diets. The overall weight loss at 12-18 months was 2-4 kg.

**Low-carbohydrate diets:** One systematic review evaluated the efficacy of low-carbohydrate diets (search date: February 2003).<sup>45</sup> This review included the analysis of 107 studies, of which 24 were RCTs. Participants included healthy volunteers, obese participants or patients with diabetes. About two-thirds were women. The interventions were either lowest-carbohydrate diets ( $\leq 20$  g of carbohydrates per day) or low-carbohydrate diets ( $\leq 60$  g of carbohydrates per day), with a mean calorie content of 1446 kcal/day, and lasted for less than 90 days in all but five studies. Weight loss was associated with calorie content, duration of the diet, but not with amount of carbohydrate content of the diet. Among RCTs, the mean weight loss was not statistically different between low-carbohydrate diets (3.6 kg) and high-carbohydrate diets (2.1 kg). Low-carbohydrate diets were not associated with adverse cardiovascular effects.

**Meal replacement strategies:** One systematic review (search date: January 2001) evaluated the efficacy of using partial meal replacements as a dietary intervention to lose weight.<sup>46</sup> This review included six RCTs (487 participants total) of at least three months' duration where at least one meal per day of a low-calorie diet (800-1600 kcal/day) was replaced by a commercially available, reduced-calorie product. Participants were 75% women, with mean age 46.1 years, and baseline BMI = 31. Participants who received partial meal replacement lost 6.2-6.5 kg, compared to 3.2-4.0 kg by those who received conventional reduced-

calorie diet, with no adverse effects in either group. Forty-seven percent of the patients on partial meal replacements dropped out compared to 64% in the conventional diet group. The 119 patients who were diabetic in these studies had less weight loss at one year and higher drop-out rates than the non-diabetic participants.

## **Physical activity interventions**

The systematic review found six studies of physical activity lifestyle interventions, all in the community setting.<sup>43</sup> The studies, published between 1986 and 1991, included 30-357 participants.

One study was conducted among attendees at a YMCA and compared self-directed change in exercise habits to individual sessions and peer support. Another study compared gym based exercise to home exercise. Another trial used behavioral therapy and financial incentives to promote aerobic exercise in 90 obese adults. Two studies were conducted among Zuni native Americans, both testing the effect of aerobic exercise classes 1-5 times a week for participants with diabetes. The final trial was a small study of 13 obese women who were asked to participate in high-intensity exercise (initially walking, then cycling, dancing, and swimming) for 90 minutes, 4-5 times a week.

**Effect of interventions:** There was sufficient evidence to suggest that physical activity interventions in the community setting can be effective for losing weight. All studies showed positive results, with a pooled weight loss of 8.1 lbs (range: 7.1-14.3 lbs).

## **Multi-component interventions**

One systematic review assessed the effectiveness of all interventions to both improve dietary intake and promote physical activity in two settings: health care systems (54 studies) and community settings (30 studies).<sup>45</sup> Because the interventions and the results did not differ greatly between these two settings, the details of the studies will be presented together.

**Study characteristics:** Studies varied in size from 15 participants to 12 472 participants in the largest community interventions. The largest studies described interventions to improve dietary intake and physical activity in a large community such as an entire town. One study described a community intervention that lasted for 13 years, although most studies lasted 6 months to 1 year. Studies were published between 1974 and 2001.

**Characteristics of participants:** In the health care systems setting, where participants were drawn from patient populations, participants often had hypertension or type 2 diabetes and weight loss was intended to improve the cardiovascular disease. One study only included patients with knee osteoarthritis, one study separated participants with adult-onset and child-onset obesity in the analysis. Several studies focused on an elderly population (for example: post-menopausal women or adults greater than 60); one study specifically targeted postpartum mothers with residual pregnancy weight gain. Many studies were designed specifically for men (eight studies) or women (12 studies). The socioeconomic status of the participants was not well described in the studies.

**Settings:** Most studies took place in the United States. Three studies only included African-Americans, and one specifically native Americans. Studies also took place in Australia, Denmark, Finland, Greece, Israel, and the United Kingdom.

**Outcomes assessed:** Weight loss and BMI were the main outcome measures.

**Description of interventions:** Most interventions included both dietary and exercise counseling with supportive behavioral therapy and some form of group meetings. A few studies compared diet, exercise, or both. Recommended diets were often 1000-1500 kcal per day, usually with an emphasis on decreasing fat intake. Keeping food diaries was a common component of dietary modification, as was instruction on shopping and cooking. Physical activity often included a half-hour or more of aerobic exercise (walking was mentioned most often, although one study conducted among the indigenous people of northwest Australia included hunting and sports) at least three times a week. Some studies tested different forms of exercise, such as lifestyle versus aerobic. Different forms of behavioral therapy were also used; cognitive behavioral treatments were probably most common. Several studies compared group and individual treatment and various levels of support. Many studies employed some form of financial incentive for attendance or for meeting goals. Programs often included meetings several times a week initially and then gradually decreasing in frequency to every month or less often at six months or a year. Participants usually weighed themselves daily or weekly.

In studies designed for patients with hypertension, sodium restriction was a common component of dietary change. Other studies designed to improve cardiovascular disease also advocated smoking cessation and reduction in alcohol intake.

Some unusual interventions included in studies were: strict enforcement of attendance (with withdrawal from group for any infraction); comparison of different levels of spouse involvement (and one study included marital therapy); provision of accelerometers; provision of home treadmills; inpatient treatment; telephone, television, or correspondence-based intervention; alternating levels of calories in the diet; inclusion of spouse and children in the intervention; and comparison of daily versus weekly goal-setting.

**Effects of interventions:** In both clinical and community settings, there was strong evidence to support the effectiveness of combined dietary and physical activity interventions to prevent and control obesity. The mean change in weight (in lbs) ranged from +0.9 lbs to -21.88 lbs in either setting, with the pooled effect as -6.4 lbs in the clinical setting and -7.74 lbs in the community setting (compared to controls). This may be a conservative estimate as the control groups in most studies also lost weight (with a lesser intervention) and studies that measured change from baseline had a mean weight loss of -8.8 lbs (clinical and community setting). This is consistent with the effect found for lifestyle interventions overall of 3 kg (6.6 lbs) compared to controls, and 3-5 kg (6.6 lbs to 11 lbs) from baseline.<sup>17 37</sup>

### ***Lifestyle interventions to prevent obesity***

Three studies described interventions specifically to prevent weight gain among non-obese participants.<sup>43</sup> Two studies took place in Minnesota (70-90% women) and the other study took place in Finland (men only). The interventions were mostly educational and included advice on diet and exercise and two programs included financial incentives. Outcomes were assessed at 1-3 years but found no significant effect compared to controls. The reviewers considered the evidence insufficient to show effectiveness of obesity prevention interventions in the community setting.

**Large community interventions:** Within the systematic reviews, four studies described very large scale community interventions in Rhode Island, Minnesota, Germany, and the Stanford 5-city project.<sup>43</sup> The largest of these, the Stanford 5-city project, weight outcomes were compared between two intervention

cities (122 800 individuals) and two control cities (197 500). These interventions included all or members of the community, including children. The interventions were designed to make changes in food supply sources (grocery stores, restaurants), physical activity opportunities, as well as community organizations such as churches, neighborhood centers, or schools. Media campaigns using mailings and advertising in buildings and during community events were also directed towards healthier lifestyles. These large community interventions described above found a small overall *gain* in BMI.

## **Workplace interventions**

We found one high-quality systematic review, search date February 2001.<sup>43</sup> The systematic review included controlled studies of well-described interventions conducted in a workplace setting, with weight outcomes, and at least six months of follow-up. Studies were then judged according to quality criteria. This review found 20 good-quality studies, with over 30 000 participants total. Nineteen interventions were intended to help obese or overweight workers lose weight, and one study intended to prevent weight gain among all employees.

### **Details of studies**

**Study sizes:** Studies varied in size tremendously, from 24 participants to 12,500.

**Characteristics of participants:** Out of 20 studies, one study included only women, seven studies only men, and the others varied from 14-90% female. Baseline weight, ethnicity and socioeconomic status were not reported in the review.

**Settings:** Ten out of 20 studies took place in the United States. The others took place in Australia (2 studies), Italy (1), Japan (3), the United Kingdom (2). Two studies did not describe the location. Workplaces included factories (five studies), aerospace, and oil companies, police department, university, retail stores, public services offices, ambulance service, and the military.

**Interventions:** No two interventions were alike. Eleven interventions targeted both dietary intake and physical activity, four studies physical activity alone, and two studies diet alone. Some common components of the interventions were: group counseling, didactic instruction by nutritionist or trained lay person, specific dietary prescription, specific exercise prescription, group exercise, provision of on-site exercise facilities, behavioral training, general health assessment and education, use of nutritional software, and provision of self-help materials. Four studies used financial incentives.

**Outcomes assessed:** Studies measured change in weight, percent overweight, percent weight change, percentage fat, and BMI after six months or more.

**Treatment effects:** All studies using a combination of nutrition and physical activity interventions achieved positive results, ranging from mean weight loss of 4.4-26.4 lbs. However, studies with longer follow-ups had less weight loss, suggesting that the effects of the intervention wear off, and weight regain is common. Interventions using either physical activity or nutrition interventions (but not both) or using other types of interventions (non-nutrition and physical activity) achieved very small positive effects on weight loss. But there were too few studies to determine effectiveness.

**Harms:** Adverse effects were not reported in the studies.

**Quality of studies:** Among studies included, high attrition rates were common preventing data interpretation. The details of randomization were usually not given, and true intention-to-treat analysis was not performed because of high attrition rate, which could bias results in either direction.

**Conclusions:** Studies with positive effects combined dietary instruction with a structured approach to increasing physical activity.

### **Research recommendations**

The authors recommend additional research on the prevention of obesity in the workplace, testing the effects of environmental change (such as making stairs more accessible, modifying the food supply), on dual interventions that combine worksite and are supported outside (such as in the supermarket or school), and recommend consideration of targeting adolescents in the worksite.

# Treatment of childhood obesity

As described earlier, obesity in children has almost doubled in the United States in the last decade. And there is fear that childhood obesity may have even greater implications on the quality and quantity of life than obesity acquired in adulthood.

## Treatment versus prevention

It may be useful to separate interventions to treat children who are already overweight from those designed to prevent children from becoming overweight. Treatments for children who are already overweight or obese are usually individually based or small-group based although they may also have similar effects on lean or normal weight children. These treatments are also likely to be in a clinical setting.

Interventions aimed at lean or normal weight children (as well as overweight children) to prevent obesity are often large group-based, and may occur in either a clinical or non-clinical setting such as a school or community center.

As a way of organizing the evidence, we have divided the research into these two general categories, treatment and prevention, recognizing there may be some overlap between the two.

## ***Lifestyle interventions to treat childhood obesity***

Lifestyle interventions include exercise, dietary change, behavior therapy, or some combination of these components. We found three high-quality systematic reviews of lifestyle interventions for childhood obesity treatment, each with considerable but not complete overlap between included studies.<sup>47-49</sup> The results of the EHC bulletin (search date: June 2002) will be described here in detail as it includes and updates the previous reviews by Glenny et al (search date: prior to February 1997) and Summerbell (search date July 2001).<sup>47, 48</sup> Since June 2002, we found three additional RCTs on lifestyle interventions. In total, there were 24 studies of obesity treatment (10 on prevention are discussed later), with approximately 1398 children treated for overweight.

## Details of studies

**Study sizes:** Studies varied in size from 19 children total up to 197, although one study did not specify the number of participants.<sup>50</sup> Fifteen out of 24 studies included less than 50 participants, and the two studies with more than 100 participants were conducted outside the United States: in Italy (185 participants) and Germany (197).<sup>51, 52</sup> Many studies were underpowered and did not include power calculations among the published papers.

**Characteristics of children:** Studies included children aged 3-19 but most interventions targeted children of school age prior to adolescence (7-12). Most interventions included both boys and girls but included more girls than boys; two studies included only girls. Ethnicity was either not specified or was mostly or exclusively white. Prior to the intervention, participants were about 20-80% overweight, with most studies describing their participants to be an average of 50% overweight.

**Settings:** Most studies (16 of 24) were conducted in the United States. Other settings included Australia, western Europe and Israel. All the studies took place in a clinical setting, most often within a specialist obesity treatment center, and seven came from the same research group.

**Outcomes assessed:** Most of the treatment studies assessed the change in percent overweight (%OW) from baseline to end of treatment or follow-up. Studies also reported weight loss in kg, percent weight loss, BMI, BMI z score, percentage of ideal body weight, and other scales.

**Length of follow-up:** Most studies followed participants for a year, and a few for only for six months. Shorter studies were excluded from the systematic reviews. A few studies followed participants longer: (three for two years, one for five years, and one with 10 year follow-up).

Interventions will be divided into three categories and are described below, followed by the treatment effect of those interventions as found in the studies.

### **Interventions primarily aimed toward increasing energy expenditure (exercise, physical activity or decreasing inactivity)**

Physical activity interventions studied in trials for obesity treatment included:

- Diet and exercise versus diet alone
- Comparisons between different types of physical activity: calisthenics versus aerobic exercise versus lifestyle exercise
- Comparisons between increased activity or exercise and decreased sedentary activity (primarily aimed toward reducing television time).

In studies comparing the different types of exercise or comparing exercise to reduced sedentary behaviors, all participants also received dietary education and advice on behavioral modification.

Exercise added to diet was not beneficial over diet alone in helping children lose weight. Both aerobic and lifestyle exercise (with diet and behavioral modification) were more beneficial than calisthenics (with diet and behavioral modification) at 10 years (range of effect was +10.9 to -19.7 %OW). Reducing sedentary behaviors had greater effect than increasing physical activity in one study (-18.7 %OW at 1 year) but no significant difference from increasing physical activity in another study.

### **Interventions primarily aimed toward decreasing energy intake (diets or dietary interventions, nutritional interventions)**

Types of dietary interventions in studies included:

- Nutrition education by written materials or by a health professional
- Specific dietary guidelines
- Use of a food diary
- Instructions about a particular diet called the Traffic Light Diet.

Only one study compared the Traffic Light Diet with no treatment. One study compared general diet and physical activity guidance with specific instructions to keep a food diary and follow a prescribed 1400

calorie diet (with active parental commitment).<sup>52</sup> Other obesity treatment studies did not compare dietary interventions with one another or with no treatment. Most often, dietary change was included as a component of a multifaceted program that included physical activity and behavior modification. The multifaceted program was compared to no treatment or waiting list controls.

The Traffic Light Diet (with or without exercise) helped children lose weight at 12 months compared to a waiting list control group. Families given the more detailed and specific instructions about diet and keeping a food diary lost more weight than those given general, less intense guidance (size of effect was -8.50 %OW).

### **Multifaceted interventions incorporating behavior modification strategies**

As behavior modification strategies either aim to increase physical activity or decrease energy intake, it is artificial to distinguish between the technique of changing the behavior and the behavior itself.

Many studies used approaches that combined diet, physical activity and additional assistance to make behavior changes. The studies we found included interventions where parents were given additional training or responsibility to help their children lose weight, compared with a general weight loss program (with behavior modification) focusing on the child. Many studies tested different forms of “family-based” interventions to treat obesity in children. In all cases, this meant that at least one parent (most often the mother) was included as part of treatment.

Studies evaluated:

- Treating the child or parent separately versus together
- Behavioral interventions given rapid and intense scheduling compared to gradually decreasing appointments
- The addition of family therapy to conventional treatment
- The addition of cognitive behavioral treatment (versus relaxation placebo)
- Group therapy versus individual therapy
- The addition of cognitive behavioral treatment to inpatient multifaceted treatment.

A family-based multifaceted program including diet, physical activity, or reduction of sedentary behavior and behavior therapy helps children to lose weight compared to no treatment, especially if parents are actively involved in treatment (range of effect: -5.5%OW to -20.5%OW at 1 year). Family-based, multifaceted interventions with the mother and child treated separately had a greater effect on weight loss (-20.5 %OW) than those where mother and child were treated together (-5.5 %OW) or the child was treated alone (-6.0 %OW). The other studies that tested variations of a family-based behavioral approach found no significant differences between interventions.

### ***Pharmacological interventions for childhood obesity***

We found one systematic review (search date: June 2002) that included one RCT of metformin.<sup>53</sup> We found one additional study of metformin<sup>54</sup> and a further study on the use of sibutramine combined with behavioral therapy.<sup>55</sup>

## **Metformin**

The RCTs were conducted in North Carolina and Tennessee and were published in April and December of 2001. They included a total of 53 adolescents. Both studies specifically tested the effectiveness of metformin in hyperinsulinemic non-diabetic adolescents.

One study specified that participants also have a family history of type 2 diabetes, were on a normal diet, and were treated with metformin 500 mg twice daily.<sup>53</sup> The other study also treated all participants with a low-calorie diet and assessed weight outcomes after only 8 weeks of treatment with metformin (850 mg twice daily) or placebo.<sup>54</sup> Both studies found that metformin produced small but statistically significant changes in weight at 6 months: -0.12 BMI z score relative to baseline for the metformin group; +0.23 BMI z score for the placebo group. In the shorter study, the treated group lost 6.1 kg relative to the start of the study (8 weeks), compared to 3.2 kg in the placebo group.

## **Sibutramine**

We found one double-blinded RCT of 82 adolescents aged 13-17 with a BMI range of 32-44.<sup>55</sup> Participants were treated for 6 months with either behavior therapy and sibutramine, or behavior therapy and placebo. The group taking sibutramine lost 7.8 kg at 6 months, compared with 3.2 kg in the placebo group. At the end of the 6 months, both groups received open-label sibutramine; the sibutramine group gained 0.8 kg and the placebo group lost 1.3 kg during months 7-12. Adverse events, including elevations in blood pressure or pulse rate, occurred more often among patients receiving sibutramine, although differences were not quite significant. Elevations in blood pressure or pulse caused reductions in dose in 23 participants and discontinuation of the drug in 10 participants. More safety and efficacy data are needed before a combination of sibutramine and behavior therapy can be recommended for as a treatment for obesity in adolescents.

## ***Surgical interventions for childhood obesity***

We found no systematic reviews or RCTs.

## **Prevention of childhood obesity**

Primary prevention interventions target children who are not already overweight or obese. Interventions are designed either for a population of children (including both lean and overweight children) or for a group of children at high risk of becoming obese, such as those with an obese parent or of a specific ethnic group (native American or African-American, for example).

Schools have been a popular site for obesity prevention programs because of the easy access to so many children irrespective of background in one setting, with food and exercise facilities on-site.

We found four high-quality systematic reviews of childhood obesity prevention programs, each with considerable but not complete overlap between included studies.<sup>43 47-49</sup> The results of the most recent (search date: June 2002) will be described here in detail as it includes and updates two of the other reviews.<sup>49</sup>

We found one high-quality systematic review (search date: February 2001) that summarized the research on community programs designed to prevent and treat obesity among children and adolescents.<sup>43</sup> This review included a few studies not included in the NHS Centre for Reviews and Dissemination study.<sup>49</sup> Where there was overlap between the two reviews, the findings, conclusions, and recommendations are consistent.<sup>43,49</sup> Since June 2002, we found one additional RCT on obesity prevention interventions.<sup>56</sup>

## **School-based programs**

Seven randomized trials (3424 children in total) examined the effect of school-based programs.

**Study sizes:** Studies varied in size from 110 to 1295 children (the largest being across 10 schools).

**Characteristics of children:** Mean age of participating children was 4.5-15.9. All studies included roughly equal proportions of boys and girls.

**Settings:** Four studies took place in the United States, and one each in Germany, Thailand, and the United Kingdom.

**Outcomes assessed:** Studies reported change in BMI, prevalence of obesity, change in triceps skinfold thickness, and waist circumference.

**Follow-up:** One study followed children for only 12 weeks, the rest lasted for 6-18 months.

**Description and effects of interventions:** One intervention was a 6-month curriculum designed to reduce time spent watching television and playing videogames. This intervention included the use of an electronic device to monitor and record use of the television at home. Change in BMI was  $-0.45$  at the end of 6 months.

Two programs were designed to incorporate increased physical activity into the school curriculum, with no significant change found in weight status at follow-up.

Four programs used multifaceted interventions, combining physical activity and dietary education, and two of these showed a significant change in BMI ( $-1.1$ ) or in the prevalence of obesity ( $-5.5\%$ ) for girls only.

One program also involved teachers, catering staff, and parents, and made actual changes in the school environment such as the modifying school meals, but did not find an effect on weight measures.

## **Family-based programs**

Two U.S. studies (81 children in total) used a family-based program to target children at risk of obesity. One study tested a culturally specific program for African-American girls (ages 7-12) and their mothers. (62% of mothers were obese at baseline). The other program used a multifaceted approach including the Traffic Light Diet and different dietary goals. Neither program showed an effect on children's weight measures.

## **Community programs**

In one Russian study, two Moscow school districts were selected and used to randomly select control and intervention schools from which fifth-grade boys were selected.<sup>57</sup> The intervention group received a group counseling session with parents taking place outside of school. Boys with cardiovascular risk factors received an additional session which included counseling on rational diet, physical activity, and smoking hazards. The outcome was an overall decrease of 0.1 BMI units, which was not significant.

Another study included 12 obese female African-American adolescents in Michigan.<sup>58</sup> Participants were enrolled in Weight Winners, a multi-component after-school program of behavioral modification. The program included a focus on eating and exercise habits, aerobics, food-modeling activities, field trips to restaurants and supermarkets, and food preparation. Subjects met for 1.5 hours twice a week for three months. At the end of the intervention, weight loss was 1.4 kg.

In the last community study, 57 inner-city African-American adolescent girls from four housing developments in Atlanta, Georgia were enrolled in a 6-month intervention including educational behavior activity, 30-60 minutes of physical activity, and preparation of low-fat meals.<sup>59</sup> Outcome was reported by level of attendance. High attendance gained 2.6 kg and 0.7 BMI units and low attendance gained 2.4 kg, or 0.9 BMI units.

## **Breastfeeding**

There are reasonable mechanisms to explain how breastfeeding might prevent obesity: it may allow the children to better regulate their own intake or develop a variety of tastes, for example. But there are many confounding factors that could also explain the association, such as maternal weight or socioeconomic status. Our search strategy for obesity interventions did not yield controlled prospective studies of breastfeeding as an effective intervention to prevent obesity. Nevertheless, because of its other health benefits and few negative consequences, breastfeeding is often recommended as an obesity prevention intervention by experts.

## Implications for future research

The executive summary states the findings from our review of obesity interventions, measures designed to both treat and prevent obesity, in adults and children. In this section, we summarize the quality and limitations of the research that was found and outline specific gaps for future research.

Obesity is a common problem with significant effects on both the quantity and quality of life. Only surgery causes substantial weight loss, but is only appropriate for the most severely obese. For adults, lifestyle programs and medications produce modest weight loss. For the treatment of children and for the prevention of obesity in adults and children, the research provides no answers at all.

In this paper, in a manner similar to *Clinical Evidence* and other systematic reviews, we considered systematic reviews, RCTs and well-described controlled prospective studies as “evidence” for the effectiveness of obesity interventions. When held to the ideal of a double-blinded, placebo-controlled randomized trial, many, if not all, studies fell short. In the case of surgical studies, randomization was not feasible or ethical. Even when groups were randomized, the allocation method was not documented. Participants were often too few in number and not well characterized at baseline. They were seldom diverse; studies typically included mostly white, educated women. Blinding of participants or observers was often not reported. True intention-to-treat analysis was rarely conducted and attrition rates were high. And participants were not followed long enough to ensure that weight regain did not occur. Many of these flaws could potentially bias the results, and most of them would result in exaggerating the size of the effect that was found. Authors of systematic reviews lamented the lack of high-quality clinical trials and recommended that future studies more closely fulfill these ideals.

The range of interventions used in studies was remarkable. Although a few programs involved fairly simple, one-component interventions, most did not. The trials of drugs or surgery usually also included advice on diet, exercise, or both. Most of the other interventions studied addressed both diet and physical activity. They often also included an educational component, behavioral therapy, complicated systems of rewards and incentives for both attendance and weight loss results, or the involvement of other family members and health professionals. In short, they were extremely time- and labor-intensive. Compared to the size of the effect (weight loss of 3-5 kg over 1-2 years) the endeavor seems disproportionate. Future research should determine the minimal intervention that would have this effect. Although this amount of weight loss is not insignificant, and has been shown to have some health benefits<sup>18</sup>, it remains a question whether the obese person or his doctor sees the intervention as successful. For most obese or overweight individuals, losing 3-5 kg may not be worth the effort. For society at large, interventions such as these are not likely to alter the obesity epidemic in a major way.

Part of the problem may be that most of the interventions involve shielding the individual against the environment. Programs generally try to create a microcosm for particular individuals, where they develop enough motivation and discipline to continually fight both their own instincts (their human instincts to eat and rest, and feed each other) and the obesity-promoting environment. It is hardly surprising, therefore, that such behaviors cannot be sustained: participants often do not continue to lose weight after an intervention ends despite having gained knowledge and skills. In most studies with long-term follow-up, even the weight lost from an intervention gradually comes back. Thus, interventions that had continued positive effects after the end of active treatment deserve particular attention.

We did not find evidence that researchers were using success stories to help design feasible interventions. Currently, almost half of the adult population in the United States is not overweight, despite an environment that makes it very easy to gain. It seems worth conducting qualitative and quantitative research to investigate the factors that protect certain individuals from becoming obese, especially those that seem at high risk biologically (a family history of obesity, for example). The National Weight Control Registry has detailed information on individuals who have lost substantial amounts of weight and kept it off.<sup>60</sup> Lessons from these sources could be used to design feasible and successful interventions.

We did not find research evaluating the effectiveness of environmental or policy initiatives. Swinburn argues that in order to change the force of the epidemic, obesity interventions need to be environmental as well as individual.<sup>61</sup> He states, “the key role of environmental change is to make the healthy choices the easy choices....the default choices.” A few interventions included in our search results had an environmental component but the environmental part of the intervention was not well-described and its impact was not separated from that of the active intervention. There are reviews of environmental interventions reported in the literature but none that assessed weight measures as outcome variables.<sup>62</sup> As policy-making organizations in the United States and internationally attempt anti-obesity initiatives, it is imperative that these be evaluated rigorously and reported in the medical and scientific literature.

Despite the stated need and urgency to address eating and activity habits during childhood, research in the areas of prevention and treatment of childhood obesity is meager.<sup>48 63</sup> Summerbell, Campbell, and other reviewers of the pediatric obesity literature were unable to recommend any particular intervention with confidence.<sup>48 63</sup> The research on pediatric obesity has several unique limitations. First, studies did not use a consistent definition of obesity in children, making it especially difficult to differentiate normal growth from the excessive weight gain that may lead to obesity. Summerbell et al speculated that because there is continued uncertainty about how to define abnormal weight gain in childhood, perhaps interventions should concentrate on making sustained changes to eating and activity habits.<sup>48</sup> However, the very weak measures of both dietary intake and energy expenditure/physical activity hamper our ability to assess changes in either. Even when a child (or adult) loses weight, we cannot tell for certain which was the more important mechanism.

We noted that many obesity interventions for children were designed with careful attention to factors that might damage a child's self esteem or cause him to feel labeled or stigmatized. For example, non-overweight children were sometimes included in order to avoid overweight children feeling different from their peers, or words such as "diets" were not used. In other words, researchers implied that they were cautious not to provoke or cause eating disorders among treated children. Actually, there is very little evidence that an obesity treatment program could trigger or cause an eating disorder and obesity is much more common than eating disorders. On the other hand, researchers on the whole did not assess harms of treatment and prevention programs and thus missed an opportunity to clarify a link if it exists between obesity treatment and eating disorders.

# Appendix A: Sources of systematic reviews, RCTs, controlled studies

## Cochrane Library

The Cochrane Library and Cochrane Controlled Clinical Trials Register is widely recognized as some of the best, being based on rigorous searches including grey and non-English language literature together with electronic and hand searching of medical journals. Protocols for Cochrane reviews in progress are also included on the disc together with contact details for the principal investigator. This contains a comprehensive collection of trials (more than on Medline).

The Cochrane Collaboration is an international, independent, nonprofit organization whose purpose is to provide evidence-based healthcare information. Started in 1993, it produces and disseminates systematic reviews (about 1700 reviews currently available in full in the library; 1300 protocols published for reviews in progress). Its aim is to have 10 000 systematic reviews to cover all interventions studied in RCTs, update 5000 each year and promote research on health care interventions.

The major product is the Cochrane Database of Systematic Reviews, produced quarterly by the Cochrane Library. Reviews are mostly produced by health care professional volunteers with editorial teams overseeing the reviews. The Cochrane Library also includes the Cochrane Central Register of Controlled Trials (CENTRAL), a bibliography of clinical trials. The Register provides a summary of the trial, often with details of where it was published. Three-fifths of the trials come from Medline; the rest are identified by specialty groups that are part of the Cochrane Collaboration or found by hand-searching. CENTRAL includes unpublished sources.

## Medline

Medline is the National Library of Medicine's (NLM) bibliographic database. It contains bibliographic citations and author abstracts from more than 4600 biomedical journals published in the United States and in 70 other countries. The database contains well over 12 million citations dating back to the mid-1960s, including more than 130 000 population-related journal citations. Although coverage is worldwide, most records are derived from English-language sources or have English abstracts. Abstracts are included for more than 75% of the records.

## Embase

The Excerpta Medica database (Embase) produced by Elsevier Science, is a major biomedical and pharmaceutical database indexing over 3500 international journals in the following fields: drug research, pharmacology, pharmaceuticals, toxicology, clinical and experimental human medicine, health policy and management, public health, occupational health, environmental health, drug dependence and abuse, psychiatry, forensic medicine, and biomedical engineering/instrumentation. There is selective coverage for nursing, dentistry, veterinary medicine, psychology, and alternative medicine. Embase is one of the most widely used biomedical and pharmaceutical databases because of its currency and in-depth indexing. Approximately 375 000 records are added yearly.

## **PsycInfo**

PsycInfo contains citations and summaries of journal articles, book chapters, books, dissertations, and technical reports, all in the field of psychology and the psychological aspects of related disciplines, such as medicine, psychiatry, nursing, sociology, education, pharmacology, physiology, linguistics, anthropology, business and law. Journal coverage, spanning 1887-present, includes international material selected from more than 1500 periodicals written in over 35 languages. Current chapter and book coverage includes worldwide English-language material published from 1987-present. Over 60,000 references are added annually through weekly updates.

## **Eric**

The Educational Research Information Centre (ERIC) database is the world's largest source of education information. The database contains more than 1 million abstracts of education-related documents and journal articles. ERIC updates the database monthly.

## **CINAHL**

The Cumulative Index to Nursing & Allied Health (CINAHL) database provides authoritative coverage of the literature related to nursing and allied health. Virtually all English-language publications are indexed along with the publications of the American Nurses Association and the National League for Nursing. Selected journals are also indexed in the areas of consumer health, biomedicine, and health sciences librarianship. In total, more than 1200 journals are regularly indexed; online abstracts are available for more than 800 of these titles. There are more than 7000 records with full text now included and 1200 records with images. The database also provides access to healthcare books, nursing dissertations, selected conference proceedings, standards of professional practice, educational software and audiovisual materials in nursing.

## **Dare**

Dare (database of abstracts of reviews of effects) is produced by the NHS Centre for Reviews and Dissemination and forms part of the Cochrane Library. It contains abstracts of quality-assessed systematic reviews located by Medline and Embase searches from 1994 onwards. There is coverage of earlier reviews but this is not complete. It also contains abstracts of all the systematic reviews included in American College of Physicians' Journal Club and gives bibliographic details of other reviews identified in searches but not meeting the quality criteria for inclusion in the main database.

## **NHS EED**

The National Health Service Economic Evaluation Database (NHS EED) was set up by the NHS Centre for Reviews and Dissemination (CRD) in 1995. The database also includes records from the United Kingdom Department of Health Cost-Effectiveness Register, which was published in 1994. The database consists of abstracts of economic evaluations including cost-benefit analyses, cost-utility analyses, and cost-effectiveness analyses. Cost-minimization analyses and cost-consequence analyses are also included. The NHS EED database is funded by the U.K. Department of Health and managed by staff based at CRD. Abstracts are commissioned by the staff at CRD from health economists around the world. New abstracts are added at the end of each month.

## **HTA**

The Health Technology Assessment (HTA) database contains information on healthcare technology assessments and is produced in collaboration with the International Network of Agencies of Health Technology Assessment (INAHTA) Secretariat, based in Sweden.

The database contains records of ongoing projects being conducted by members of INAHTA as well as publications reporting completed technology assessments carried out by INAHTA members and other health technology assessment organizations. Many different types of research are included in the HTA database. As well as systematic reviews, the database contains ongoing and completed research based on trials, questionnaires and economic evaluations. Where possible, the research type is stated in the title or abstract. In some cases there will be an overlap between the Dare database (systematic reviews) and the NHS EED database (economic evaluations).

## **Bandolier**

The first issue of Bandolier, an independent journal about evidence-based healthcare, was printed in February 1994. It has appeared monthly ever since and has become a source of evidence based healthcare information in the United Kingdom and worldwide for both healthcare professionals and consumers. Bandolier is also a source of high quality information for many patients and their carers, as well as for organizations that commission and pay for healthcare. The impetus behind Bandolier was to find information about evidence of effectiveness (or lack of it), and put the results forward as simple bullet points of those things that worked and those that did not. Information comes from systematic reviews, meta-analyses, randomized trials, and from high quality observational studies. For other web content (such as the specialist resource areas) we search over all times, and where necessary, do systematic reviews ourselves. Other types of information, like large epidemiological studies, may be included if they shed important light on a topic.

## **TRIP**

The TRIP (turning research into practice) database is a meta-search tool that simultaneously searches up to fifteen sources of health related information (including some of the sources above) when a search term is entered. The results are categorized by source and level of evidence. The TRIP database does not offer original content but is a valuable tool for double checking search results or performing a high quality simple search within a short amount of time.

## Appendix B: Search strategies used for questions about interventions

### ***Searching Medline for systematic reviews and randomized controlled trials***

These search strings were written for use with OVID software. Once loaded and saved on a Medline computer these searches can be easily re-run. Having run these search strings for study methodology, we combined them with sensitive subject searches initially, tightening the focus of the subject search as appropriate in order to yield a manageable set of references for browsing.

The search strings were adapted for the various resources, Medline as the largest database required the most detailed search. For the smaller databases, a more general adaptation was used to retrieve more results.

### **Obesity**

The following search strategy demonstrates the terms used to describe the concept of obesity.

1. exp OBESITY/ or exp OBESITY, MORBID/
2. (fat or overweight).tw.
3. (excess\$ adj3 (weight or fat)).tw.
4. overweight.ti. or overweight.ab. /freq=2
5. (excess\$ adj3 (weight or fat)).ti. or (excess\$ adj3 (weight or fat)).ab. /freq=2
6. ((weight adj3 gain) or (weight adj3 loss)).mp. [mp=title, abstract, name of substance, mesh subject heading]
7. or/1-6

### **Non-drug interventions**

The following search strategy demonstrates the terms used to describe all non-drug, non-surgical interventions (dietary, behavioral, physical activity):.

1. exp OBESITY/dh [Diet Therapy]
2. exp Diet, Fat-Restricted/
3. exp Diet, Reducing/
4. exp Diet Therapy/
5. exp FASTING/
6. (diet or diets or dieting).mp. [mp=title, abstract, name of substance, mesh subject heading]
7. (diet\$ adj (modif\$ or therapy or intervention\$ or strateg\$)).mp. [mp=title, abstract, name of substance, mesh subject heading]
8. (low calorie or calorie control\$ or healthy eating).mp. [mp=title, abstract, name of substance, mesh subject heading]
9. exp Dietary Fats/
10. (fruit\$ or vegetable\$).mp. [mp=title, abstract, name of substance, mesh subject heading]
11. (high fat\$ or low fat\$ or fatty food\$).mp. [mp=title, abstract, name of substance, mesh subject heading]

heading]

12. Food, Formulated/ or formula diet.mp.

13. exp EXERCISE/

14. exp Exercise Therapy/

15. (aerobics or physical therapy or physical activity or physical inactivity).mp. [mp=title, abstract, name of substance, mesh subject heading]

16. (fitness adj (class\$ or regime\$ or program\$)).mp. [mp=title, abstract, name of substance, mesh subject heading]

17. (aerobics or physical therapy or physical training or physical education).mp. [mp=title, abstract, name of substance, mesh subject heading]

18. sedentary behavior\$ reduction.mp.

19. sedentary behavior\$.mp.

20. or/1-19

## Children

The following search strategy demonstrates the terms used to describe our population.

1. exp CHILD/ or child\$.mp.

2. exp Adolescent/ or Adolescen\$.mp.

3. Infant/ or Infan\$.mp.

4. (teenage\$ or young) adj people) or young) adj person) or young) adj adult).mp. [mp=title, abstract, name of substance, mesh subject heading]

5. (school adj children).mp. [mp=title, abstract, name of substance, mesh subject heading]

6. p\$ediatr\$.mp.

7. or/1-6

## Drug treatment

The following search strategy demonstrates the terms used to describe pharmacotherapy interventions.

1. exp Anti-Obesity Agents/

2. exp Serotonin Uptake Inhibitors/ or exp Fluoxetine/ or exp Serotonin Antagonists/

3. Appetite Depressants/ or sibutramine.mp.

4. exp PHENTERMINE/

5. exp MAZINDOL/

6. orlistat.tw.

7. exp DIETHYLPROPION/

8. exp DEXFENFLURAMINE/ or exp Fenfluramine/

9. exp PHENTERMINE/

10. exp PHENYLPROPANOLAMINE/

11. lipase inhibitor.mp.

12. (xenical or tetrahydrolipstatin).mp. [mp=title, abstract, name of substance, mesh subject heading]

13. bulking agent.mp.

14. (methylcellulose or celevac).mp. [mp=title, abstract, name of substance, mesh subject heading]

15. guar gum.mp.

16. ((antiobesity or anti obesity) adj (drug\$ or agent\$)).mp. [mp=title, abstract, name of substance, mesh subject heading]
17. exp EPHEDRA SINICA/ or exp EPHEDRA/ or ephedra.mp.
18. bupropion.mp. or exp BUPROPION/
19. (Wellbutrin or Wellbutrin XI or Zyban or Bupropin or Buprion Hydrochloride or Amfebutamone Hydrochloride).mp. [mp=title, abstract, name of substance, mesh subject heading]
20. zonisamide.mp.
21. (Excegran or Zonegran).mp. [mp=title, abstract, name of substance, mesh subject heading]
22. sertraline.mp. or exp SERTRALINE/
23. (Serad or Serlain or Tresleen or Zoloft).mp. [mp=title, abstract, name of substance, mesh subject heading]
24. exp LEPTIN/ae, tu [Adverse Effects, Therapeutic Use]
25. topiramate.mp.
26. or/1-25

## Surgery

The following search strategy demonstrates the terms used to describe all surgical interventions.

1. exp GASTROPLASTY/
2. Gastrectomy/ or gastric surgery.mp.
3. exp Gastric Bypass/ or gastric band\$.mp.
4. lap-band.mp.
5. roux-en-y.mp. or exp Anastomosis, Roux-en-Y/
6. exp Biliopancreatic Diversion/
7. biliopancreatic bypass.mp.
8. gastro\$gastrostomy.mp.
9. restrictive surgery.mp.
10. malabsorptive surgery.mp.
11. bariatric surgery.mp.
12. (jejunoileal bypass or jejuno-ileal bypass).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
13. or/1-12

## Systematic reviews and randomized controlled trials

Combined search for systematic reviews and randomized controlled trials in Medline. This strategy is adapted from one designed by Ann McKibbin and others at McMaster University, Canada.<sup>9</sup> It limits the very broad set of review articles by using terms indicating literature searches, meta-analysis or systematic reviews. When there were particular databases relevant to an area of interest (PsycInfo or Sociofile, for example) then these were included after line 5 as textword searches, adjusting the numbering of later lines accordingly.

1. exp review/
2. (medline or medlars or embase).tw,sh.
3. (scisearch or psychlit or psychlit).tw,sh.
4. (psycinfo or psychinfo or science citation index).tw,sh.
5. cinahl.tw,sh.

6. ((hand adj2 search\$) or (manual\$ adj2 search\$) or (literature adj2 search\$)).tw,sh.
7. (electronic database\$ or bibliographic database\$ or online database\$ or computerized database\$).tw,sh.
8. ((pooled or pooling) and analys\$).tw,sh.
9. (peto or dersimonian or der simonian or fixed effect or mantel haenszel).tw,sh.
10. or/2-9
11. 1 and 10
12. exp meta analysis/
13. meta?analys\$.tw,sh.
14. (systematic\$ adj5 review\$).tw,sh.
15. (systematic\$ adj5 overview\$).tw,sh.
16. (quantitativ\$ adj5 review\$).tw,sh.
17. (quantitativ\$ adj5 overview\$).tw,sh.
18. (methodologic\$ adj5 review\$).tw,sh.
19. (methodologic\$ adj5 overview\$).tw,sh.
20. ((integrative adj5 research adj5 review\$) or (research adj5 integrat\$)).tw.
21. (quantitativ\$ adj5 synthesi\$).tw,sh.
22. or/12-21
23. 11 or 22
24. exp randomized controlled trial/
25. (random\$ or placebo\$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
26. ((double or single or triple or treble) and (blind\$ or mask\$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
27. "##'Controlled clinical trial\$.mp.##"/ or Controlled study/ or "controlled clinical trial\$.mp.
28. or/24-27
29. 23 and 28
30. 1 or 22
31. exp randomized controlled trial/
32. (random\$ or placebo\$).ti,ab,sh.
33. ((double or single or triple or treble) and (blind\$ or mask\$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
34. controlled clinical trial\$.tw,sh.
35. exp Clinical trial/
36. clinical trial.ti,ab,hw,tn,mf.
37. or/31-36
38. exp OBESITY/
39. overweight.ti. or overweight.ab. /freq=2
40. (excess\$ adj3 (weight or fat)).ti. or (excess\$ adj3 (weight or fat)).ab. /freq=2
41. or/38-40
42. 37 and 41
43. 23 and 41

Line 23 gives a set of systematic reviews.

Line 29 gives a set of systematic reviews about therapy.

Line 30 gives an unfiltered set of review articles.

Line 37 gives a set of randomized controlled trials.

Line 41 describes a population of obese and overweight people.

Line 42 gives a set of randomized controlled trials about obesity.

Line 43 gives a set of systematic reviews about obesity.

## **Cohort studies**

A maximally sensitive search strategy for etiology, causation or harm. Developed by Haynes et al at McMaster University (82% sensitivity 70% specificity).<sup>9</sup>

1. (odds and ratio\$.tw.
2. (relative and risk).tw.
3. (case and control).tw.
4. exp cohort studies/
5. exp risk/
6. exp case control studies/
7. or/1-6
8. exp OBESITY/
9. overweight.ti. or overweight.ab. /freq=2
10. (excess\$ adj3 (weight or fat)).ti. or (excess\$ adj3 (weight or fat)).ab. /freq=2
11. or/38-40
12. 7 and 11

Line 12 represents cohort studies about obesity.

## ***Searching Cochrane Library for studies not indexed in Medline or Embase***

1. OBES\* or OBESITY/
2. OVERWEIGHT
3. (EXCESS\* near (WEIGHT OR FAT)) or (EXCESS\* next (WEIGHT or FAT))
4. #1 or #2 or #3
5. (MEDLINE or EMBASE) not ((MEDLINE:AB or EMBASE:AB) or COCHRANE:AB))
6. #4 not #5

Line 4 represents our population.

Line 5 represents trials that were found in Medline or Embase.

Line 6 are all those trials remaining in the Cochrane Library that are not also indexed in Medline or Embase. Trials that may be indexed in other commercial databases or as a result of hand-searching the literature.

## Appendix C: Criteria for appraising studies

Our aim, like that of *Clinical Evidence*, was to summarize evidence on medical interventions from high quality systematic reviews and large well-designed randomized controlled trials, and other studies when these are not available. There are numerous checklists for assessing study quality, some of which are summarized below. No study - or checklist - is perfect, but we have aimed for transparency and reproducibility in the appraisal process rather than a perfect and universal set of appraisal criteria. perfect a and it is not possible to lay down hard and fast criteria for inclusion.

In general, we have described what studies have accomplished in terms of their methodology. The methodology fell into three categories: Sound, suboptimal, and unsound. When studies of sound methodology for each question were found, they are described and summarized. If no studies with sound methodology were found, then suboptimal studies were summarized with reservations cited. When only unsound or no studies were found, the research is described but not as evidence of an effective intervention, but as an area for future research efforts.

The soundness of the methodology was judged according to criteria primarily from Sackett et al.<sup>11</sup> These criteria are described below.

### Quality criteria for systematic studies

- Questions and methods clearly stated.
- Comprehensive search methods described.
- Explicit methods used to determine which studies were included in the review.
- Methodological quality of primary studies was assessed.
- Selection and assessment of primary studies reproducible and free from bias.
- Differences in individual study results adequately explained.
- Results of primary studies combined appropriately.
- Reviewers' conclusions supported by data cited.

### Quality criteria for randomized controlled trials

- Were the setting and study patients clearly described?
- Was assignment randomized and similarity between groups documented?
- Was allocation to study groups adequately concealed from patients and investigators, including blind assessment of outcome?
- Were all clinically relevant outcomes reported?
- Were > 80% of patients who entered the study accounted for at its conclusion?
- Were they analyzed in the groups to which they were randomized (intention to treat)?
- Were both statistical and clinical significance considered?

### Quality criteria for other controlled studies

The rules of evidence on harm are the same as the rules of evidence on the beneficial effects of treatment. The best evidence on the harmfulness or otherwise of treatments comes from large randomized controlled

trials (or reviews thereof). However group sizes have to be large and follow up prolonged for rare side effects to be detected and evidence on harm from randomized controlled trials may not be available. Bias due to non-comparability of groups is more likely in cohort studies and more likely still in case control studies. Case series or case reports are the weakest forms of evidence, though associations in case reports have often been subsequently confirmed.

### **When considering evidence on harm**

- Was the study the strongest that could have been performed under the circumstances?
- Were study groups sufficiently comparable in respects other than exposure?
- Was determination of exposure free from bias?
- Was the determination of outcomes (in cohort studies) or the distinction between cases and controls (in case control studies) free from bias?
- Were both clinical and statistical significance considered in reporting the strength of the association?
- Is the association consistent in different studies?
- Is the temporal sequence of exposure and outcome in the right direction?
- Is there a dose response gradient?
- Does the association make sense?

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