Volume 11 • Number 7 • 2008
VALUE IN HEALTH

Cost-Effectiveness of a Low-Calorie Diet and Orlistat for Obese Persons: Modeling Long-Term Health Gains through Prevention of Obesity-Related Chronic Diseases

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ABSTRACT

Objective: Our study estimated the cost-effectiveness of pharmacologic treatment of obesity in combination with a low-calorie diet in The Netherlands.

Methods: Costs and effects of a low-calorie diet-only intervention and of a low-calorie diet in combination with 1 year of orlistat were compared to no treatment. The RIVM Chronic Disease Model was used to project the differences in quality adjusted life years (QALYs) and lifetime health-care costs because of the effects of the interventions on body mass index (BMI) status. This was done by linking BMI status to the occurrence of obesity-related diseases and by relating quality of life to disease status. Probabilistic sensitivity analysis was employed to study the effect of uncertainty in the model parameters. In univariate sensitivity analysis, we assessed how sensitive the results were to several key assumptions.

Results: Incremental costs per QALY gained were €17,900 for the low-calorie diet-only intervention compared to no intervention and €58,800 for the low-calorie diet + orlistat compared to the low-calorie diet only. Assuming a direct relation between BMI and quality of life, these ratios decreased to €6000 per QALY gained and €24,100 per QALY gained. Costs per QALY gained were also sensitive to assumptions about long-term weight loss maintenance.

Conclusions: Cost-effectiveness ratios of interventions aiming at weight reduction depend strongly on assumptions regarding the relation between BMI and quality of life. We recommend that a low-calorie diet should be the first option for policymakers in combating obesity.

Keywords: cost-effectiveness analysis, modeling, obesity, orlistat.

Introduction

Obesity is a major cause of morbidity and mortality [1,2]. The prevalence of overweight, defined as a body mass index (BMI) ≥25 kg/m^2, is increasing worldwide. Reversing this trend is a major health policy aim in many countries [3]. It has been estimated that in The Netherlands overweight causes yearly 40,000 new cases of heart disease, type 2 diabetes, and cancer, and is responsible for approximately 7% of all mortality [4]. Successful treatment of obesity thus may dramatically lower the burden of disease.

To be effective, obesity treatment should aim to achieve a modest weight loss (5–15%) that can be sustained in the long term [5,6]. Treatment options include lifestyle programs, such as a low-calorie diet, exercise, behavioral therapy, pharmacologic treatment, and even surgery. Generally, an integrated, multimodal, approach is recommended, such as a combination of lifestyle programs and pharmacologic treatment [7].

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10.1111/j.1524-4733.2008.00328.x

The most frequently used weight-reducing drugs are orlistat and sibutramine. Many studies have shown that pharmacologic treatment of obesity in combination with life-style changes achieves a modest weight loss [8]. Moreover, economic evaluations mostly concluded that pharmacologic treatment of obesity is cost-effective compared to lifestyle changes only. Reported cost-effectiveness ratios range from approximately €10,000 to €35,000 per quality adjusted life year (QALY) gained [9–12]. It should be noted, however, that in all of these studies effects on BMI were directly translated into changes in quality of life [13,14]. In our study, by contrast, we aimed to assess the cost-effectiveness of pharmacologic treatment of obesity in combination with a low-calorie diet by linking quality of life to the occurrence of obesity-related diseases rather than assuming a direct effect of obesity on quality of life. This way, gains in length and quality of life can be ascribed to the prevention of chronic diseases such as diabetes, cardiovascular disease, and osteoarthritis [15].

Methods

Incremental cost-effectiveness ratios (ICERs) were first calculated by comparing treatment with orlistat in

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Table 1 Costs per patient during year of intervention (2005 euros)

Type of costs	Units	Unit price	Costs
GP time	15 min	2.07	20.70–41.40
Dietician time	180 min	0.85	102–204
Food diary	1 manual	12.85	12.85
Orlistat (three tablets per day)			
Minimum only 3 months	50%	45 (45 tablets of 120 mg)	270
Maximum for 12 months	50%		1080

GP, general practitioner.

combination with a low-calorie diet, and, second, by comparing a low-calorie diet only to no treatment at all. The target population consisted of all Dutch individuals between 20 and 70 years of age with a BMI $\geq$30 who were not being treated for obesity. We chose "no treatment" as comparator because it best reflects current primary care practice in The Netherlands. A recent nationwide study showed that 22% of patients diagnosed with obesity in primary care receive pharmacologic treatment, although only 5% are referred to a dietician [16]. All other patients received no treatment, or were given only informal lifestyle advice of low intensity [16]. It was assumed that those who did not respond to the orlistat treatment discontinued treatment after 3 months [8]. Nonreponse to orlistat treatment was defined as a weight loss of less than 5% within the first 3 months of treatment. Based on the literature, we used a nonreponse rate of 50% [8]. By evaluating the interventions from a health-care perspective, we assumed that the interventions would be paid for by parties belonging to the health-care system. In accordance with the Dutch guidelines for pharmacoeconomic research, effects and costs were discounted at a yearly rate of 1.5% and 4.0%, respectively [17,18].

We employed the RIVM Chronic Disease Model (CDM) to translate from weight loss as a result of treatment to life years and QALYs gained, and to calculate lifetime health-care costs [15,19–22]. To calculate ICERs, discounted yearly differences in outcomes between the intervention and the current practice scenarios were added over the time interval modeled of 80 years. This resulted in net present values for life years gained, QALYs gained, and incremental health-care costs. All cost data were presented in euros, for the price level of 2005. Costs taken into account were the costs of the interventions, the savings (negative costs) because of a reduced incidence of obesity-related diseases as well as the costs of unrelated diseases occurring during life years gained [21].

Costs of the Interventions

Table 1 presents the intervention costs for the orlistat plus low-calorie diet intervention. These costs were calculated by using a so-called bottom-up method as advocated in the Dutch pharmacoeconomic guidelines [23]. This means that first the intervention was analyzed in detail to identify all of its elements and thereby the resources used. The units of resources used were then multiplied by standardized unit costs. In calculating the costs, it was assumed that patients visit the dietician every 3 months, and that nonresponders to orlistat treatment stop after two visits. Furthermore, as part of the low-calorie diet intervention, it was assumed that each patient was provided a food diary. The medication costs per patient were determined on the basis of national reference prices (GIP, http://www.gipdatabank.nl; CVZ, http://www.medicijnkosten.nl). Orlistat tablets are taken three times daily.

Effects of the Interventions on Weight

Estimates of weight loss because of the two interventions were based on meta-analyses published in the international literature. The weight loss resulting from the interventions after 1 year [8,24] was translated into long-term weight loss by assuming that 23% of the weight loss achieved after 1 year can be maintained in the long run [25].

Effects of Weight Loss on Life Years, QALYs, and Lifetime Health-Care Costs

The health gains and the effects of long-term weight loss on lifetime health-care costs were estimated using the CDM [15,19,21,22,26,27]. As mentioned above, the CDM is a dynamic population model that describes the life course of cohorts in terms of transitions between risk factor classes and disease states over time. BMI is modeled as a discrete variable divided intro three classes: $18.5 \leq \text{BMI} < 25$ (normal), $25 \leq \text{BMI} < 30$ (overweight), $\text{BMI} \geq 30$ (obesity). Obesity-related diseases in the CDM are coronary heart disease, stroke, diabetes, osteoarthritis, low back pain, and some forms of cancer [15]. The link between risk factors and diseases is modeled by assigning relative risks of disease incidence to each risk factor class. Because the presence of a disease increases mortality rates, risk factor levels ultimately influence mortality. To estimate incidence, prevalence, and mortality rates, three types of data sources were used: general practitioners' registrations, national registries, and population surveys. For cancers, national registries were considered the most reliable source. Data for most

Table 2 Stochastic parameters

	Low-calorie diet-only intervention	Low-calorie diet + orlistat intervention
GP time	Uniform distribution: 10–20 min	Uniform distribution: 10–20 min
Dietician time	Uniform distribution: 120–240 min	Uniform distribution: 120–240 min
Weight loss (in kg) after one year due to low-calorie diet [26]	Normal distribution Mean: 3.2 SD: 0.54	Normal distribution Mean: 3.2 SD: 0.54
Weight loss (in kg) after one year due to orlistat [8]		Normal distribution Mean: 2.89 SD: 0.32
Proportion successful weight loss maintenance [27]	Normal distribution Mean: 0.23 SD: 0.015	Normal distribution Mean: 0.23 SD: 0.015

GP, general practitioner.

noncancerous diseases were based on a combination of up to five different general practitioners' registrations or other medical care registrations. Relative risks of morbidity and mortality for BMI were based on several observational studies. Details on the methods and input data employed in the CDM have been discussed in depth elsewhere [15].

Differences in QALYs and lifetime health-care costs because of the interventions were assessed by translating long-term weight loss into differences in the prevalence of obesity. This was done by first subtracting the average long-term weight loss achieved by the intervention from the weights of each of the individuals making up the target population. Next, the resulting weights were converted to BMI values, allowing comparison between prevalences before and after the interventions. For the conversion from weight to BMI, we used the weight and length distributions reported in the so-called second Dutch general practice study [16]. To compute health effects in terms of QALYs, the CDM couples disability weights from the Dutch Burden of Disease Study [28] to disease prevalence rates [15,20,29]. Disability weights reflect the severity and impact of a disease relative to death and optimal health, defined as absence of disability or disease, and ranges from 0 (no disability) to 1 (death) [30]. The Dutch Burden of Disease Study estimated disability weights for 48 different disease categories, using the person trade off method [28]. Obesity itself was not considered a disease, and therefore, improvements in BMI status only result in improvements in quality of life if BMI-related diseases are avoided. For diseases causally related to BMI, we used the CDM to estimate diseases prevalence rates as a function of time. To capture the impact on quality of life of diseases not related to obesity during life years gained, we used age- and gender-specific prevalence rates as reported in the Dutch Burden of Disease Study [31]. Cost-of-illness data from the Netherlands for the year 2003 [32] served to estimate health-care expenditure conditional on disease status and age [20,21]. Annual disease costs per patient were multiplied by the projected future prevalence numbers for each obesity-related chronic disease in the model. Costs of all other—obesity-unrelated—diseases, incurred during life years gained, were calculated as the product of the numbers of "survivors" and the category of "remaining costs." These latter equal the difference between total health-care costs and the costs of the obesity-related diseases incorporated in the model. They include, for instance, the costs of mental and behavioral disorders. Finally, these two categories of costs, one related and the other unrelated to the risk factor under study, were added to estimate annual costs.

Probabilistic Sensitivity Analysis

We employed probabilistic sensitivity analysis (PSA) and ran the model 500 times to assess the effect of uncertainty regarding some of the input parameters on outcomes. Results of the PSA are displayed in a costs versus effects plane and a cost-effectiveness acceptability curve [33]. Table 2 describes the stochastic input data used in the PSA.

Sensitivity Analyses

Besides the PSA, we carried out a series of univariate sensitivity analyses to investigate the robustness of our results to some key parameters and assumptions. Mean incremental costs per QALY were calculated for the following scenarios:

- Quality of life exclusively determined by BMI status: in this scenario, quality of life did not depend on disease but solely on BMI status. For this scenario, the study by Hakim et al. [13] was employed, which estimated that for each unit increase in BMI quality of life decreases by 0.017 points;
- Fifty percent weight loss maintenance in both interventions: in this scenario, it was assumed that for both interventions 50% of the weight loss after 1 year is maintained in the long run;

- One hundred percent weight loss maintenance in both interventions: in this scenario, it was assumed that for both interventions 100% of the weight loss after 1 year is maintained in the long run;
- Fifty percent weight loss maintenance in the orlistat intervention: in this scenario, it was assumed that 50% of the initial weight loss after 1 year because of the orlistat intervention is maintained in the long run. Weight loss maintenance because of low-calorie diet treatment is the same as in the base case analysis;
- Target population with a BMI between 30 and 35: in this scenario, only persons with a BMI between 30 and 35 were offered the interventions;
- Excluding costs of unrelated medical care: in this scenario, incremental medical costs of diseases not related to obesity incurred during life years gained were excluded;
- Excluding costs of unrelated medical care and savings in BMI-related diseases: in this scenario, only the 1-year costs of the diet and orlistat interventions were included. Savings in costs because of a reduction in BMI-related diseases as well as costs of unrelated medical care were excluded.

Results

Figure 1 presents histograms displaying the proportions of individuals in the target population who move from the obese to the overweight class because of the diet respectively the diet + orlistat interventions. On average, this proportion equals 1% for the diet-only intervention and 1.9% for the diet + orlistat intervention.

Figure 2 presents average differences in diabetes and osteoarthritis prevalence because of the diet-only intervention compared to no care. It illustrates the importance of the factor time in evaluating the effects of the interventions. After the intervention, the prevalence numbers of diabetes and of osteoarthritis first decrease because of a reduction in the incidence of these diseases. In the long run, however, prolonged life expectancy results in an increase of the prevalence of osteoarthritis. Ultimately, differences in prevalence over time vanish as more of the target population die.

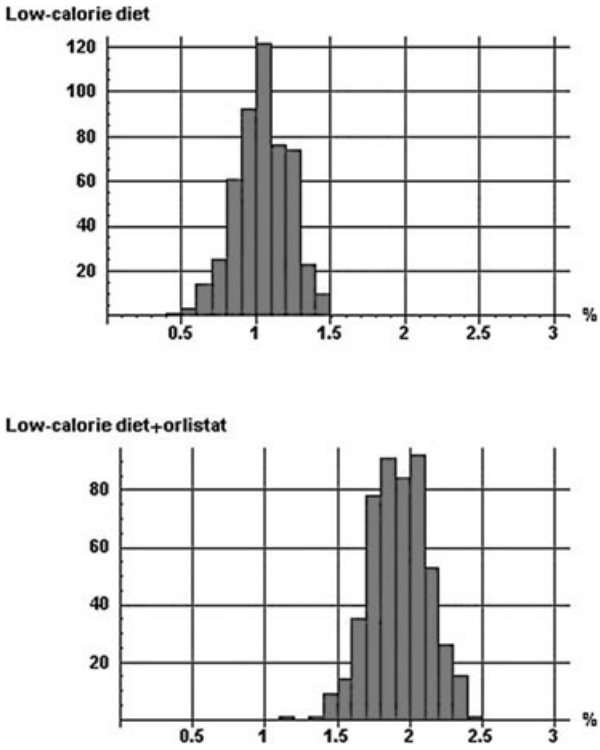

Figure 1 Histograms of the proportions of individuals in the target population who move from the obese to the overweight class because of the diet respectively the diet + orlistat interventions.

Table 3 shows incremental life years, QALYs, and health-care costs as well as ICERs for the target population.

Mean incremental costs per QALY were €17,900 for the low-calorie diet compared to no care and €58,800 for low-calorie diet + orlistat compared to the low-calorie diet only. Nevertheless, a low-calorie diet alone results in more modest health gains than a low-calorie diet in combination with orlistat.

To represent uncertainty around the ICER, Figure 3 displays a costs (differences in intervention + lifetime health-care costs) and effects (QALYs gained) plane for low-calorie diet and low-calorie diet + orlistat compared to usual care, for different values of the input parameters as specified in Table 2.

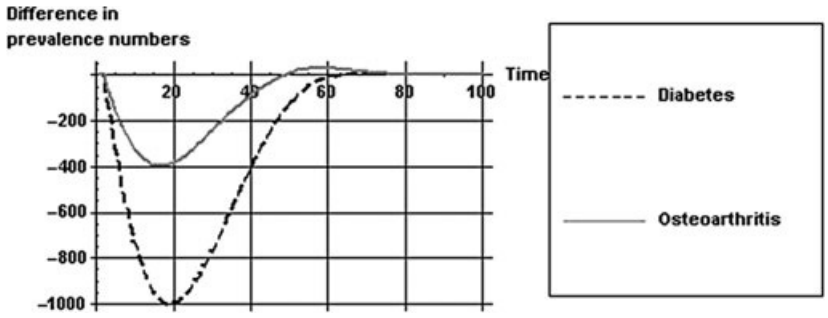

Figure 2 Average differences in diabetes and osteoarthritis prevalence over time because of the diet-only intervention.

Table 3 Estimates of total costs and effects of low-calorie diet and low-calorie diet in combination with Orlistat (95% confidence interval) for the target population (1,138,000 subjects)

	Low-calorie diet only	Low-calorie diet in combination with orlistat
QALYs gained	17	31
*1000 (discount rate 1.5%)	(11–23)	(25–39)
Life years gained	18	34
*1000 (discount rate 1.5%)	(12–25)	(27–41)
Incremental health-care costs	302	1136
*€1000,000 (discount rate 4%)	(236–373)	(1065–1209)
(Incremental intervention costs + incremental lifetime health-care costs)/(life years gained)*	€16,400	€53,600
(Incremental intervention costs + incremental lifetime health-care costs)/(QALYs gained)*	€17,900	€58,800

*Costs discounted at 4% and effects discounted at 1.5%.
QALYs, quality adjusted life years.

Figure 4 displays the cost-effectiveness acceptability curve for usual care, low-calorie diet, and low-calorie diet+orlistat.

Figure 4 indicates that for low monetary values placed on a QALY, neither a low-calorie diet nor a low-calorie diet + orlistat is likely to be cost-effective. For values placed on a QALY between approximately €18,000 and €58,000, low-calorie diet alone is probably the most cost-effective. For values higher than €58,000, low-calorie diet + orlistat is probably the most cost-effective option.

Table 4 shows results of the sensitivity analyses.

Table 4 clearly demonstrates that if quality of life increases linearly as a function of weight loss, although it is further assumed that the weight loss achieved lasts for a life time, ICERs decrease dramatically. In our base case analysis, ICERs are much higher due a time lag between the intervention and the effects on disease incidence. Moreover, we further assumed that quality of life decreases at older ages. ICERs are also sensitive to assumptions about long-term weight loss maintenance. If weight loss after 1 year can be sustained in the long run, ICERs decrease to €8100 and €23,400 per QALY gained for the two interventions. The ICER for the low-calorie diet-only intervention was €13,000 per QALY gained when only the intervention costs were taken into account. Including also the difference in costs of obesity-related diseases in future life years, the ICER for the low-calorie diet-only was €12,000 per QALY gained. Table 4 demonstrates that taking into account differences in lifetime medical costs increases cost-effectiveness ratios by roughly €5000 per life year or QALY gained.

Discussion and Conclusions

Obesity increases the risk of developing diseases such as diabetes and coronary heart disease. Prevention of obesity, by decreasing the incidence of such diseases, will therefore result in increases in life expectancy and decreases in health-care costs. Nevertheless, these life years gained come at a price. Later in life, people suffer other diseases that decrease quality of life and increase health-care utilization. In the simulation model employed, we estimated these effects by coupling disease incidence rates to changes in risk factor levels. In turn, having a particular disease or not determines quality of life and health-care costs. Using this approach, modeling the cost-effectiveness of treatment with orlistat in combination with a low-calorie diet resulted in an ICER of €58,800 per QALY gained. The cost-effectiveness of a low-calorie diet-only intervention was estimated at €17,900 per QALY gained.

Our modeling exercise resulted in a higher cost-effectiveness ratio for the treatment of obesity through a low-calorie diet in combination with orlistat than what has been reported in previous studies. One of the explanations for this difference lies in the methods

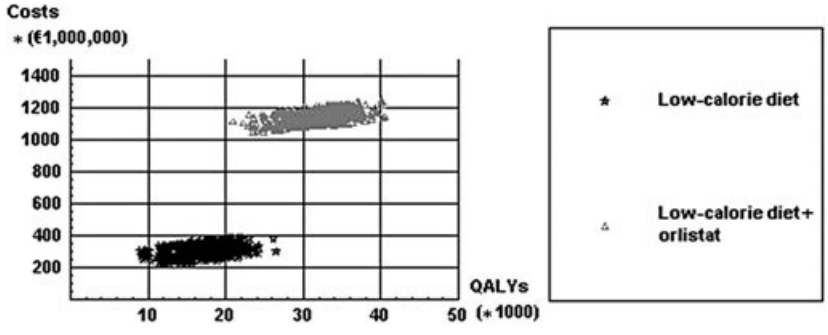

Figure 3 Incremental costs and effects of low-calorie diet and low-calorie diet + orlistat compared to usual care for the target population. QALYs, quality adjusted life years.

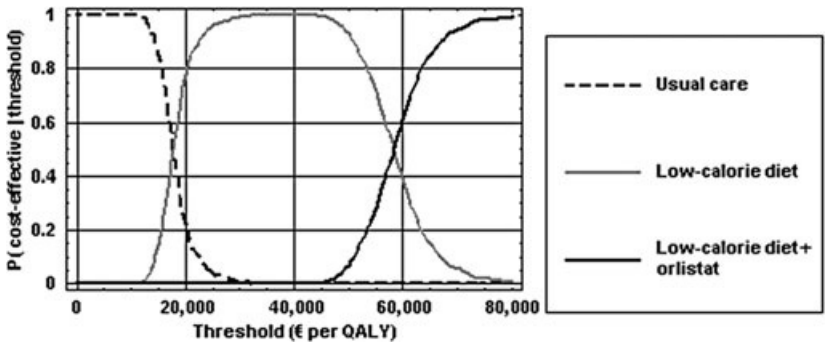

Figure 4 Cost-effectiveness acceptability curves for usual care, low-calorie diet, and low-calorie diet + orlistat. QALY, quality adjusted life year.

used to calculate QALYs. Studies by Lacey and Hertzman [12,34] used a much shorter time horizon (5 years) and assumed a direct effect of decreases in BMI on improvements in quality of life based on a earlier study by Hakim et al. [13]. They thus assumed instantaneous improvements in quality of life as a result of the intervention. In our model, we only assumed improvements in quality of life indirectly, namely through a reduced risk of the development of obesity-related diseases. The particular methodology we used accounts for much smaller gains in quality of life during the life years that would have been lived also without the intervention [15]. Furthermore, we took into account the fact that quality of life generally decreases with advancing age. This is important, because obviously most of the life years gained occur at advanced ages. Similar to Roux et al. [9], we used a lifetime perspective and tracked lifetime costs. We also assumed the same degree of long-term weight loss maintenance. Nevertheless, their study, in contrast to ours, assumed a direct relation between BMI level and quality of life. This may explain the large differences they reported between costs per life year gained and costs per QALY gained. We performed a health-economic evaluation from the health-care perspective and concentrated on effects of interventions on health and lifetime health-care costs and compared these with intervention costs. This is relevant information for the health-care decision-maker, who may be primarily concerned with health-care costs [35,36]. We did not include effects on the cost because of lost productivity and we did not take into account effects on informal care. Including these aspects would imply a societal perspective to be used in cost-effectiveness analysis to demonstrate the broader societal costs and benefits from the interventions [37]. Such a broader perspective is normally advocated in economic evaluations, because it gives a complete picture of welfare changes in society associated with a particular intervention [38]. A next step therefore would be to assess the cost-effectiveness of these interventions from a societal perspective.

The strength of the model presented is that the causal effects of changes in BMI level on quality of life and health-care costs were estimated by coupling health-care costs and quality of life to diseases related to obesity instead of coupling them directly to BMI status. We only included diseases for which a causal relation to obesity has been established [1]. A limitation of our model is that three different BMI classes were used with average relative risks computed using the BMI distribution over these classes in the Netherlands. This is a rather crude classification, which may not be sensitive enough to capture small differences in weight. Assuming that BMI is a continuous risk factor this means that we have underestimated health gains for persons with extreme obesity and overestimated health gains for persons with moderate obesity. To what extent this approach results in biased estimates of health gains and therefore in biased estimates of the ICER is difficult to assess. For this to completely balance out would require an assumption that the sum

Table 4 Results of sensitivity analysis on ICER (costs discounted at 4% and effects discounted at 1.5%)

	Low-calorie diet only	Low-calorie diet in combination with orlistat
Base case	€17,900	€58,800
Quality of life exclusively determined by BMI status	€6,000	€24,100
100% weight loss maintenance both interventions	€8,100	€23,400
50% weight loss maintenance both interventions	€11,000	€33,300
100% weight loss maintenance orlistat	€17,800	€18,700
Target population BMI between 30 and 35	€13,400	€51,100
Excluding costs of unrelated medical care	€12,100	€53,000
Excluding costs of unrelated medical care and savings in BMI-related diseases	€13,300	€53,900

BMI, body mass index; ICER, incremental cost effectiveness ratio.

of the smaller continuous health effects for all those who lose weight is about equal to the sum of the threshold effects for those who cross the 30 BMI thresholds. This could work, more or less, if the benefits of weight loss are roughly linear with changes in BMI. Nevertheless, the literature tends to suggest that health risks increase quadratically with BMI [39,40]. On the other hand, the BMI distribution is known to be heavily skewed, meaning that there are more persons with a BMI of 31 than of 32 and so on. The effect of the skewness of the distribution would be to counteract the bias because of the nonlinearity of the relation between BMI and health risks, as there would be correspondingly more individuals for whom the benefits of weight loss would be underestimated than overestimated in the direction of being under-estimates of the effects of weight loss. Another crucial assumption was the estimate of the long-term effectiveness of interventions on BMI. In this study, it was assumed that 23% of the weight loss was maintained in the long run. If we did not take the relapse into account, costs would be substantially lower: €8100 per QALY gained for low-calorie diet only, and €23,400 per QALY gained for a low-calorie diet in combination with orlistat. It has been shown that longer and active follow-up can prevent weight regain [41]. Nevertheless, this would also involve additional costs. Finally, we neglected any possible side effects of orlistat. Although significant proportions of orlistat users suffer from adverse events because of the medication, such as diarrhea, flatulence, bloating, abdominal pain, and dyspepsia [8], we are not aware of studies that have linked these side effects to quality of life. Nevertheless, we believe that because we used a lifetime perspective while the orlistat treatment lasts for only 1 year, the influence of side effects on the cost utility ratios would be minimal.

In conclusion, both a low-calorie diet and low-calorie diet in combination with orlistat have a higher cost-effectiveness ratio if no direct effect of BMI on quality life is assumed and only effects of weight loss through obesity-related diseases are taken into account. As a result, especially the addition of orlistat to the treatment of obesity loses much of its attractiveness. We recommend that a diet alone should be the first option for policymakers in combating obesity.

We would like to thank the reviewers for their in depth review of the article. Furthermore, we would like to thank our colleague Wien Limburg for critical reading of the article.

Source of financial support: This work was funded by the Dutch Ministry of Health, Welfare and Sports.

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