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Symposium on 'Diet and diabetes'

Influences of weight loss on long-term diabetes outcomes

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Increasing rates of type 2 diabetes (T2DM) follow the obesity 'epidemic', with 86% of patients with T2DM being overweight and over half being obese. Literature has highlighted that being overweight or obese increases the risk of diabetes. Weight loss for obese patients is associated with clinical improvements, although this evidence is mostly from short-term studies. As part of a Health Technology Assessment systematic review the long-term ($\geq$2 years) effects of weight loss on change in diabetes-related outcome measures for those with diabetes, or risk of developing diabetes for those without diabetes, was investigated in obese individuals. Eleven studies published between 1966 and 2001 fulfilled the inclusion criteria (Caucasian, BMI >28 kg/m^2, adults, no eating disorders, weight loss and changes in diabetes-outcome measures). Results of these studies indicated that intentional weight loss reduces the risk of developing diabetes in the long term and those participants with T2DM often have reduced clinical symptoms and mortality risk. These results have been verified and enhanced by literature published since this review. A similar systematic review was conducted as part of a six-phase project, the PRevent Obesity GRowing Economic Synthesis Study. This review excluded BMI >34 kg/m^2 and was restricted to lifestyle interventions (or intentional weight loss). Limited information relating to diabetes was gained, with only a non-significant increasing trend for mortality from diabetes for severe weight cycling practices being suggested. Other results indicated a relationship between weight loss and fasting plasma glucose, but because of the heterogeneity of participation groups and lack of definition in relation to diabetes this relationship was not formalised. In summary, weight loss is beneficial for long-term diabetes outcomes for overweight, obese and morbidly-obese participants. There is little research evidence for those individuals who are overweight or just obese, indicating areas of future research in terms of prevention of both obesity and diabetes.

Weight loss: Overweight and/or obese: Long-term diabetes

The potential for being overweight or obese has been postulated as a genetic predisposition during the evolution of homo sapiens to protect against leaner times. Unfortunately, in the last 50 years such lean times have not been prevalent (certainly in the developed world and even now in the developing countries energy-rich foods are becoming common place) and labour-saving devices encourage more sedentary behaviour, thus tilting the whole energy-balance equation. However, the obesogenic environment is more complex, involving not just genetic and environmental factors but also other interconnecting factors such as biochemical, neurological, physiological, cultural and socio-economic factors[1]. Obesity prevalence has risen alarmingly, especially in the last 20 years (Table 1), and if trends continue it has been forecast that in the UK 33% of men and 28% of women will be obese by 2010[2].

Along with the rise in obesity is the notable increase in the numbers of those individuals with diabetes, and the projected rise in obesity suggests that in England the current 2·35 million individuals who have diabetes will increase to 2·5 million, i.e. 150 000 more in 3 years, most of whom are expected to have type 2 diabetes (T2DM)[3].

Abbreviations: PROGRESS, PRevent Obesity GRowing Economic Synthesis Study; T2DM, type 2 diabetes.

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Table 1. Obesity prevalence (%) in England (from Health Survey for England[32], updated for 2005[33])

	1980	1993	2004	2005
Men	6	13·2	22·7	22·1
Women	8	16·4	23·2	24·3

It has been claimed that 75% of the risk of developing T2DM is a result of obesity[4]. Of those with T2DM 86% are overweight or obese, with 52% being obese[5]. There seems to be a gender effect in the consequences, with women who have diabetes having a four- to five-fold higher risk of coronary artery disease compared with men with diabetes who have a two- to three-fold higher risk of coronary artery disease[6]. It is estimated that if there were one million fewer individuals who were obese in the UK, then there would be 34 000 fewer individuals developing T2DM[3].

For diabetes, however, it is more than just the increase in weight that is important. Weight distribution also plays a role, with the upper-body or central distribution of body fat being associated with increased risk. One way to assess this body-fat distribution is by the waist:hip ratio, which as a marker of upper-body obesity independently predicts development of T2DM in several ethnic groups[7].

There is extensive literature showing that being obese or even overweight increases the risk of developing T2DM, whilst physical activity and weight loss (even small amounts, approximately 5% voluntary weight loss) have been shown to reduce this risk[8,9]. For those individuals already with diabetes it is commonly reported that the quantity of medication required may be reduced with weight loss, and in some instances a resolution of their diabetes is possible[8,9]. However, most research has examined such effects in the short term (generally <1 year follow up). The present paper examines the long-term effects of weight loss on diabetes health outcomes, defined here as ≥2 years, using systematic reviews and meta-analysis and a consideration of the relevant literature.

For this purpose the WHO definitions have been used, such that BMI ≥25 kg/m^2 represents 'overweight', while BMI ≥30 kg/m^2 denotes those who are 'obese'[10]. Results from the Health and Technology Assessment review, other data sources published since the 2001 Health and Technology Assessment review and the ongoing PRevent Obesity GRrowing Economic Synthesis Study (PROGRESS) will be discussed.

Health and Technology Assessment review

The *Systematic Review of the Long-term Outcomes of the Treatments for Obesity and Implications for Health Improvement*[11], commissioned by the National Health Service programme, is a monograph for the Health and Technology Assessment resulting from a three-phase study conducted between 2001 and 2002. The three parts were: a systematic review of treatment studies in the long term; a systematic review of long-term effects of weight loss on several health outcomes for overweight and obese participants; an economic evaluation.

Here, only the second review is utilised in relation to the effects of weight loss on diabetes outcomes. For this particular review a systematic literature search was undertaken on Medline, Embase and Cinahl electronic bibliographic databases. The review included literature published between 1966 and 2001 with no language restrictions. Mesh terms and text words for 'cohort studies', 'obesity', 'overweight', 'weight changes' and 'diabetes' were used and appropriately combined. The inclusion criteria covered all prospective studies and trials carried out on participants with a BMI ≥25 kg/m^2. Cohort studies and randomised controlled trials with weight-change measurements, diabetes information and a follow-up of ≥2 years were included. Initially the follow-up had been set at 5 years. However, this time period tended to be limited to surgical interventions and hence was reduced to ≥2 years for the non-surgical interventions.

Participant criteria included adults between 18 and 70 years. Studies on Caucasian, Afro-American, Japanese American and British Asian populations were included in the review. It should be noted that the ethnic minorities in Western cultures may adopt the culture and dietary habits of their Caucasian counterparts and may, therefore, have similar risks of obesity. General population studies, animal studies and studies with <20% follow-up were excluded.

Results of the Health and Technology Assessment Review

Of the 7567 abstracts identified, this review included in total thirty-seven papers (of both cohort studies and trials), of which eleven involved diabetes outcomes. Longitudinal analyses were conducted to investigate the relationship between weight loss and the long-term changes in diabetes measures. The results break down into two broad areas for (1) those without diabetes but at risk and (2) those with diabetes.

Risk of developing diabetes

Three cohort studies (the National Health and Nutrition Examination Survey I[12], the Framingham (weight loss recorded as two weight changes, e.g. loss–loss, loss–stable etc., so could be classed as weight cycling)[13], and the British Regional Heart Study[14]) described studies with no intervention. These studies had recorded family history of diabetes and included those participants who had impaired glucose tolerance but did not actually have diabetes at baseline. Those participants with weight loss (>3·4 kg) showed non-significant reductions in the risk of developing diabetes when compared with those whose weight was stable. The combined fixed effect model indicated a risk of 0·85 (95% CI 0·69, 1·04).

Also included were two non-surgical intervention trials, the Finnish Diabetes Prevention Study[15] that used a lifestyle intervention and a USA study that was described as considering diet and exercise combinations[16]. Again, family history of diabetes and/or impaired glucose tolerance was recorded. In these studies some weight loss (3–5 kg) was associated with a reduced risk of developing

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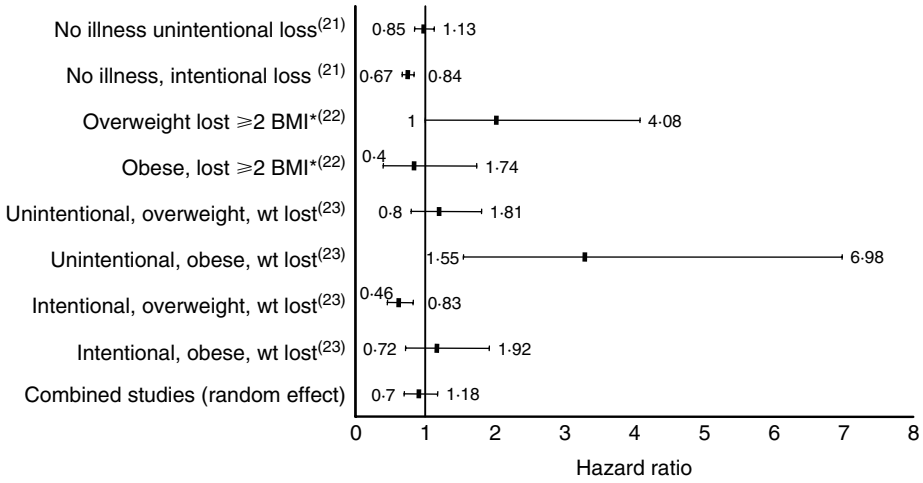

Fig. 1. Mortality risks for participants of three studies[21–23] who had diabetes and either intentional or unintentional weight loss. Values are hazard ratios and 95% CI represented by horizontal bars. *Weight loss represented by a drop in BMI of ≥ 2 kg/m^2.

diabetes when compared with the weight-stable group, by ≥10% (upper CI). A combined fixed-effect model indicates the risk to be 0·68 (95% CI 0·59, 0·80).

Surgical interventions for obesity had the greatest weight loss, as represented by two studies, one from USA[17] and the other representing the Swedish Obesity Study[18]. These studies both compare participants with large weight losses (62% of the excess weight) with those that did not have surgery and were weight stable. The individual studies indicate reductions of ≥63% (upper CI) for the risk of developing diabetes. These studies did use differing methodologies, both in terms of study design and analysis. Consequently these studies were not combined.

Participants with type 2 diabetes

From the USA there were two studies[19,20] reporting on obesity surgery interventions, where patients with diabetes showed an 80% improvement in their metabolic handling of glucose after massive weight loss. These results were not otherwise quantified.

Two non-surgical studies, the USA Cancer Prevention Study[21] and the WHO Multinational Study of Vascular Disease in Diabetes (non-insulin-dependent diabetes mellitus)[22] used records to follow-up patients in relation to mortality rates for those participants with diabetes. This part of the review was updated in 2006 to include just one more relevant study that used the US National Health Interview Survey with a supplemental survey asking about 'intention to lose weight'[23].

Initially, the mortality results seem mixed (Fig. 1); however, once the subgroups have been separated into intentional or non-intentional (or not known) weight loss a pattern emerges. Those participants with diabetes who claim to have had intentional weight loss benefited from a significant mortality reduction of 25% compared with those who were weight stable (Fig. 2). Specifically, weight loss of 9–13 kg was found to be the most protective.

Other data sources since the 2001 Health and Technology Assessment review

Other randomised controlled trials on the risk of developing diabetes since 2001 that fully fulfilled the inclusion criteria (for review, see Gillies *et al.*[24]) are summarised in Table 2.

Interestingly, for the US Diabetes Prevention Program[25] evidence is now emerging that lifestyle interventions are, in the long term, more effective in reducing the risk of developing diabetes than using the diabetes mellitus-specific drug Metformin. The XENDOS study[26] used an obesity drug intervention for weight loss rather than lifestyle changes. However, the similarity of the results for these two studies may indicate that it is weight loss that is important for the prevention of diabetes as well as other lifestyle changes.

Studies that did not fully fulfil the inclusion criteria were identified as being nonetheless interesting in relation to the evidence of weight-loss benefits for patients with diabetes.

The Diabetes Treatment Study[27] from Northern Ireland was an uncontrolled trial that indicated that the 9 kg average weight loss in the first 6 months of the trial by means of a lifestyle intervention had sustained effects over 6 years in relation to diabetes management. Of the participants 87% and 71% were able to manage their diabetes by diet alone after 1 and 6 years respectively.

The United Kingdom Prevent Diabetes Study[28] was a randomised controlled trial that compared the diabetic drug Metformin with diet only. Although the weight loss of 5 kg was not sustained, the intensive Metformin regimen decreased the risk of diabetes-related end points.

PRevent Obesity GRrowing Economic Synthesis Study

The on-going study PROGRESS awarded by the National Prevention Research Initiative hopes to examine the benefits, at several different levels of lifestyle interventions, of weight loss on reducing risk of developing chronic

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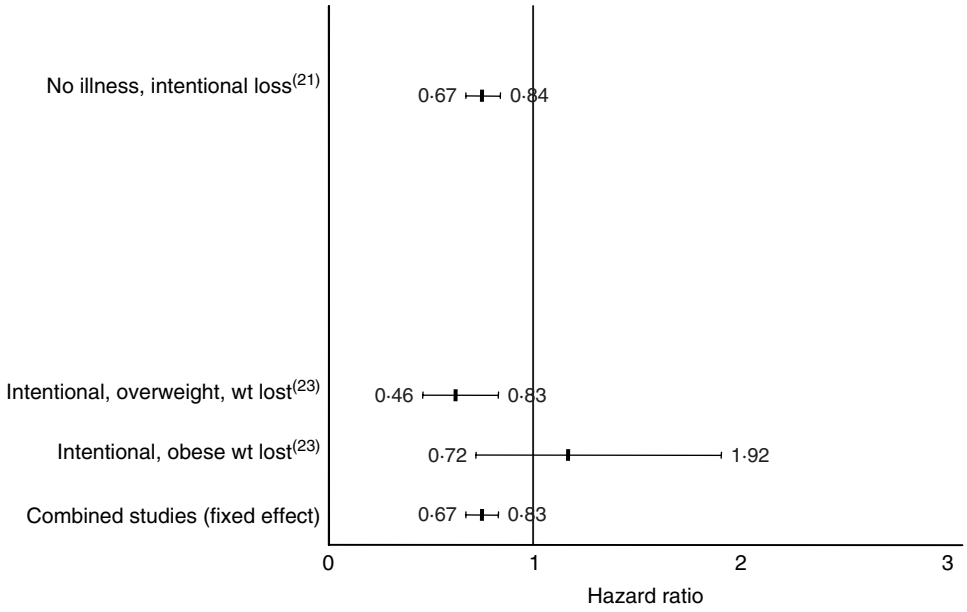

Fig. 2. Mortality risks for participants of two studies[21,23] who had diabetes and either intentional or unintentional weight loss. Values are hazard ratios and 95% CI represented by horizontal bars.

Table 2. Randomised controlled trials for diabetes that have fulfilled the inclusion criteria since 2001

Study	Intervention	Result	
		HR	95% CI
XENDOS (Sweden)[26]	Orlistat; obesity	0·48	0·26, 0·88
STOP-NIDDM (Canada)[34]	Arcarbose; DM	0·75	0·63, 0·90
DPP (USA)[25]	Metformin; DM	0·69	0·57, 0·84
DPP (USA)[25]	Lifestyle	0·42	0·34, 0·52
DPS (Finland)[35]	Lifestyle	0·40	0·26, 0·61

XENDOS, Xenical in the prevention of diabetes in obese subjects; NIDDM, non-insulin dependent diabetes mellitus; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; DM, diabetes mellitus; HR, hazard ratio.

Table 3. Results for participants in the Nurses' Health Study II that focused on the effects of weight cycling on the risk of developing type 2 diabetes (from Field *et al.*[30])

Subgroup	Follow-up no.	Cases	RR	95% CI
Non cyclers	36424	230	1·00*	
Mild cyclers (≥4·5 kg loss three or more times)	9461	160	1·07	0·87, 1·32
Severe cyclers (≥9 kg loss three or more times)	749	28	1·46	0·98, 2·17

RR, risk ratio.
*Referent.

disease such as cancer, CVD and diabetes. This multi-disciplinary approach has six phases, which will be described briefly (for more detail, see Vale *et al.*[29]): phase 1, systematic reviews; phase 2, qualitative analysis with three group types of focus interviews; phase 3, discrete choice experiment to examine which weight-loss interventions individuals would prefer; phase 4, econometric analysis of large-panel datasets (cancer, CHD and diabetes); phase 5, analysis of cost to the National Health Service of cancer, CHD and diabetes; phase 6, a cost–benefit analysis using phases 1–5.

Within phase 1 two systematic reviews similar to the Health and Technology Assessment review have been conducted whereby (a) the trial data of the interventions were reviewed and (b) the longitudinal effects of weight loss on health outcomes were investigated. There were, however, more restrictions in that both reviews required studies with a lifestyle intervention or at least some intention to lose weight and only studies with participants with an average BMI of <35 kg/m^2 at baseline were considered. Consequently, these reviews did not include the morbidly obese. In addition, for phase 1b the weight-change measure(s) were also set at ≥ 2 years in order to assess maintained weight loss.

The review in phase 1b of the longitudinal effects of weight loss has been completed in relation to the cohort studies and has been extended to trials for overweight and obesity prevention using a more pragmatic search strategy in which reviews have been searched to gain the primary papers.

Results of the PRevent Obesity GRrowing Economic Synthesis Study

For cohort studies 2154 papers were screened, resulting in fourteen unique cohort studies of which only one study[30] had diabetes-outcome changes. This study focused on the effects of weight cycling on the risk of developing T2DM rather than specifically examining weight loss; however, it

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has been included since some weight-cycling groups had intentional weight loss. Weight-cycling behaviour was assessed in these participants from the Nurses' Health Study II between 1989 and 1993. Originally, the medical history of the women was assessed and their lifestyle and health behaviours were determined. While the results were not significant (Table 3), there is a suggestion of a detrimental effect of severe weight cycling.

The 'trials' review conducted for phase 1a identified >100 papers, of which twelve were suitable for longitudinal analysis of weight loss with health outcomes. In relation to diabetes, however, there was only one measure, fasting plasma glucose. The participant groups varied greatly, with some being impaired glucose tolerant, some being obese, some having normal weight and diabetes status but of a particular type (e.g. premenstrual women). Since levels of fasting plasma glucose for diagnosing diabetes are not clearly defined, a detailed analysis has not been included. However, it would appear that larger weight losses (>5 kg) are associated with significant ($P<0{\cdot}05$) reductions in fasting plasma glucose.

Conclusions

The feature that is consistently seen to be beneficial in terms of diabetes-related outcome or risk of developing diabetes is intentional weight loss in obese patients. In these cases weight loss as a result of lifestyle, pharmaceutical and obesity surgical interventions reduces the risk of developing diabetes in the long term by approximately 32%, 10–74% and 63% respectively. Those participants with T2DM often have reduced clinical symptoms, reduced medication and/or a resolution of diabetes symptoms after intentional weight loss; for surgical intervention these reductions can be ≤80%. The long-term benefits increase with the amount of maintained weight loss.

Mortality risk for those participants with diabetes is reduced by 25% in the long-term in association with weight loss. This positive result for patients with diabetes differs from that for participant groups without diabetes. Men only without diabetes, and men and women grouped together, have a poorer mortality outcome after weight loss, even if overweight and obese participants are compared with a like weight-stable participant group[31]. Consequently, weight loss is of particular importance for those with diabetes.

These conclusions are mainly derived from the Health and Technology Assessment review and are in concordance with results from phase 1b of PROGRESS. Under PROGRESS's specific inclusion criteria (BMI <35 kg/m^2, weight change for ≥2 years) one cohort study focused on weight cycling. There are no clear definitions of weight cycling despite weight cycling perhaps being the true state for most individuals. However, there is an indication, albeit from just one study, that weight cycling does not significantly increase the risk of developing diabetes, although the trends may increase as the severity of the cycling increases.

The lifestyle trials from PROGRESS indicated that for fasting plasma glucose large sustained weight losses are required for any reductions to be significant, regardless of participant group. However, this aspect has been highlighted as an area to be further investigated within the review.

When assessed for quality both the Health and Technology Assessment review and PROGRESS indicate several methodological flaws in the conducting and reporting of long-term prospective studies, including: many studies rely on self-reporting; there is no current definition or even accommodating of weight cycling within studies; randomised controlled trials tend to be well managed but rarely incorporate a long follow-up; cohort studies tend to be run for longer but with considerable drop-out rates. Such factors need to be addressed and standardised in order to accurately assess the effects of weight loss on health for obese individuals and for the prevention of obesity.

Intentional weight loss seems to have a positive effect for diabetes outcomes in the long term, particularly if it is maintained. This long-term commitment seems to be more successful if multifaceted interventions are used that combine diet, physical activity and behaviour therapy. The current evidence is that lifestyle interventions are more effective than pharmaceutical interventions in preventing T2DM for some individuals. However, the evidence is mainly for those individuals who are already obese, and further information on the preventative effect of weight loss on diabetes also requires long-term assessment.

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