Long-Term Effectiveness of Weight-Loss Interventions in Adults with Pre-Diabetes

A Review

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Objective: To assess the effectiveness of weight-loss and weight-control interventions for adults with pre-diabetes (impaired fasting glucose and impaired glucose tolerance), an important risk factor for the development of type 2 diabetes.

Methods: Computerized searches were conducted of multiple electronic bibliographic databases up to August 2003. Randomized controlled trials in any language were selected that examined weight-loss or weight-control strategies using at least one dietary, physical activity, or behavioral intervention, and with a follow-up interval of â‰¥12 months. Effects were combined using a random effects model.

Results: Studies were identified, with a total of 5168 participants. Follow-up ranged from 1 to 10 years. Quantitative synthesis was limited by the heterogeneity of populations, settings, and interventions, and by the small number of studies that examined outcomes other than weight. Overall, compared to usual care, four studies with a follow-up of 1 year reduced weight by 2.8 kg (95% confidence interval [CI]=1.0–4.7) (3.3% of baseline body weight) and decreased body mass index by 1.4 kg/m^2 (CI=0.5–2.3). Weight loss at 2 years was 2.7 kg (CI=1.9–3.4) (two studies). Modest improvements were noted in the few studies that examined glycemic control, blood pressure, and lipid concentrations ($p>0.05$). The incidence of diabetes was significantly lower in the intervention groups versus the controls in three of five studies examining this outcome at 3 to 6 years follow-up.

Conclusions: Overall, weight-loss strategies using dietary, physical activity, or behavioral interventions produced significant improvements in weight among persons with pre-diabetes, and a significant decrease in diabetes incidence. Further work is needed on the long-term effects of these interventions on morbidity and mortality and on how to implement these interventions in the community setting.

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Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), now referred to collectively as pre-diabetes, dramatically increase the risk for progression to clinical diabetes,[1] incident cardiovascular disease, and cardiovascular mortality.[2] Data from the Third National Health and Nutrition Examination survey (1988 to 1994) projected to the year 2000 revealed that pre-diabetes is highly prevalent, affecting almost 12 million overweight persons aged 45 to 74 years in the United States.[3]

Weight loss and control are key goals for persons with diabetes. Weight loss improves insulin sensitivity and glycemic control,[4] lipid profiles, blood pressure,[5] mental health, and quality of life[6,7]; moderate intentional weight loss sustained over time may be associated with reduced mortality.[8,9] Similarly, several large randomized controlled trials (RCTs) have shown that weight loss is also a potentially important management strategy for overweight persons with pre-diabetes, as it may delay or prevent the progression to clinically defined type 2 diabetes.[10,11] The American Diabetes Association's recent position statement recommends that "individuals at high risk for developing diabetes need to become aware of the benefits of modest weight loss and participating in regular physical activity."[12]

To assess the effectiveness of dietary, physical activity, and behavioral interventions for weight-loss or weight

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control in adults with pre-diabetes on the outcomes of weight, other cardiovascular risk factors, and the incidence of diabetes, a systematic review was conducted of RCTs of these interventions. The systematic review and synthesis of all available data allowed the exploration of heterogeneity and applicability of interventions and outcomes, the potential achievement of pooled estimates of effect with increased precision over single studies, the increase of power to explore relationships between intervention characteristics and outcomes, and the identification of gaps in the existing literature.

Methods

Data Sources

Following the Cochrane Collaboration's methods,[13] a systematic review protocol was developed. In consultation with a medical research librarian, search strategies were devised using an iterative process that involved medical subject headings (MeSH) and text words. The following databases were searched between the date indicated and August 2003: MEDLINE (1966), EMBASE (1980), CINAHL (1982), ERIC (1966), PsychInfo (1967), Web of Science (1981), Biosis (1969), Nutrition Abstracts and Reviews (1979), Cochrane Library (2003, issue 3), and the Cochrane Register of Controlled Trials (2003, issue 3). Search strategies are available from the authors. The following journals (expected to have the highest relevance) were manually searched for articles, from 1980: *Diabetes Care*, *International Journal of Obesity and Related Metabolic Disorders*, *Obesity Research* (commenced in 1993), *American Journal of Clinical Nutrition*, and *Journal of the American Dietetic Association*.

Finally, systematic searches were performed for relevant reviews of weight-loss or weight-control interventions among persons with pre-diabetes. Reference lists of all included studies and the identified reviews were examined and experts in obesity research were consulted for additional citations. There was an attempt to contact authors of original studies if data were unclear or missing.

Study Selection

Searches were performed for published and unpublished RCTs in any language that examined weight-loss or weight-control strategies using dietary, physical activity, or behavioral interventions in populations with pre-diabetes. Prediabetes could be defined by an abnormal oral glucose tolerance test (OGTT), IFG, or a combination of the two. Because criteria for defining IGT and IFG have changed in the last 20 years, studies were included in which participants met criteria for abnormalities at the time of the study, but which now may be considered in a different category (e.g., fasting blood sugar 126 mg/dL to 139 mg/dL is now considered diabetes,[14] but at the time of many of the studies was considered IFG). The included populations were adults (persons aged >18 years), and either weight or body mass index (BMI) was measured as an outcome. The intervention could be of any duration, but the follow-up interval was â‰¥12 months.

Two reviewers (SLN and TJ Brown) independently identified potentially relevant titles and abstracts from MEDLINE and CINAHL, and the remaining databases were reviewed by one author (SLN). One of the authors (SLN) reviewed each full-text article to ensure that it fulfilled inclusion criteria. Where there was uncertainly about inclusion, a second person (AA) reviewed the paper, and consensus was achieved.

Data Extraction

For studies that met inclusion criteria, two reviewers independently abstracted relevant data, and consensus was achieved through discussion. Data abstracted from each study included participant characteristics, setting, intervention characteristics, behavioral techniques used, intensity of the intervention, and study design. Outcomes examined included weight, percent weight change (based on individual data), BMI, glycated hemoglobin (GHb), blood pressure, lipid levels, and cumulative incidence of diabetes.

Interventions were classified as dietary, physical activity, or behavioral. Dietary interventions include low-calorie diets (LCD) (800 to 1500 kcal/day) and very low-calorie diets (VLCD) (<800 kcal/day).[15] Physical activity interventions include a specific approach to increasing activity levels, including counseling, an exercise prescription, or participation in either a supervised or unsupervised exercise program. Behavioral therapy includes strategies based on learning principles (such as reinforcement) that provide approaches for overcoming barriers to dietary and physical activity interventions. These approaches include self-monitoring of activity levels and diet, stress management, stimulus control, problem solving, and social support.[15]

Internal validity was assessed based on individual components of quality according to Cochrane Collaboration methodology.[13] Each study was examined for potential selection, attrition, and detection bias, because these factors are thought to influence measured outcomes in intervention studies.[16] Studies were not excluded on the basis of potential bias, but a sensitivity analysis was planned to compare results between studies with potential bias and those without.

Data Analysis and Synthesis

A meta-analysis was performed to combine continuous data when two or more studies reported an outcome of interest and the interventions were similar. The mean difference between baseline and follow-up measures for the comparison and intervention groups and the standard error of each difference were recorded. If the standard error of the difference for each group was not given in the original study, sensitivity analyses were performed by assuming correlations between baseline and follow-up of 0.25, 0.50, 0.75, and 1.0. (The pooled estimates presented assume a correlation of 0.75.) If data were presented in graphical form only, point estimates were determined from enlargements of the published graphs. If only the range was given as the measure of variation, then the standard deviation was estimated as the range divided by 5.88 (99.7% confidence interval [CI], assuming a normal distribution).[17] If the interquartile range was given, standard deviation was estimated.[18] Pooled effects were determined using the DerSimonian and Laird random effects model.[19]

Meta-regression was performed to determine whether various study-level characteristics (follow-up interval, duration of the intervention, number of intervention contacts, total attri-

tion, year of publication) affected the between-group change in weight. Interaction terms were examined for all models. A chi-square test was performed for heterogeneity to examine between-study variance.[20] SAS, version 8.02 (SAS Institute, Cary NC, 2001), was used for the meta-regression, and Cochrane Review Manager software, version 4.2.2 (Cochrane Collaboration, 2003), for calculating pooled effects.

Results

Nine eligible RCTs were identified in the published literature[10,11,21–27] (Table 1). These were all weight-loss studies among overweight or obese people with prediabetes. No unpublished studies were identified and no studies focused exclusively on weight control. The study flow diagram is available from the authors. The studies included a total of 5168 participants (range, 31 to 3234) and the follow-up interval averaged 3.2 years. The study populations varied somewhat in terms of how abnormal glycemia was defined, with a number of studies using IGT (variably defined).[24,26–28] One study[21] specified only fasting glucose, overlapping both normal, IFG, and the current American Diabetes Association definition of diabetes,[14] and two other studies[11,25] also overlapped with the current criteria for diabetes.[14] It was not possible to exclude these patients from analyses as they were not presented as subgroups in the original papers. Some studies combined restrictions on fasting glucose with IGT.[10,11,23,25]

Mean age, weight, and BMI at baseline, as well as ethnicity and gender all varied considerably among the studies. Overall, the mean age was 51.2 years and studies contained 50% females, on average. Mean baseline weight was 82.2 kg (range, 69.7 to 94.2); mean BMI, 28.7 kg/m^2 (range, 25.8 to 34.0); and mean GHb, 5.8% (range, 5.7 to 5.9%).

The sampling frame for study participants was a community in four studies,[11,22,24,27] a medical clinic population in one,[21] a combination of a clinical population and a community in one,[10] and was not reported in two studies.[23,26] Only one trial reported on how the randomization sequence was generated,[11] and the same study was the only one that reported adequate concealment of allocation. Attrition ranged between 4% (at 1-year follow-up)[24] and 43% (10-year follow-up).[22] The nine interventions included in this review were heterogeneous in components, content, and intensity, but the intervention group used at least one dietary, physical activity, or behavioral intervention (Table 2). The duration of interventions ranged from 4 weeks[24] to 10 years,[22] although the latter study involved only annual contacts for the last 5 years of the study. The total number of contacts ranged from four[21] to 78,[23] and one study[24] involved a 28-day in-residence lifestyle intervention. Both individual and group sessions were used. A variety of facilitators or educators were involved, but most studies involved a dietitian as a member of the care team.

Seven of the nine studies involved caloric restriction; one[23] involved a diet intended to be isocaloric, with specification of the percent of total intake contributed by fats and carbohydrates, and one involved carbohydrate restriction intended to produce weight loss.[22] Diets often included a weight-loss goal,[10,25] or restrictions on fat intake.[10,21,25] The physical activity interventions varied from counseling to encourage increased activity[26,27]; to supervised sessions several times a week[10,11,23,25]; to a daily 2.5-hour aerobic session in an in-residence program.[24] In one study there was no physical activity intervention.[22] Behavioral interventions were used in five studies, and such interventions were very intensive in the Diabetes Prevention Program (DPP) study,[10] which included a variety of behavioral techniques. The other four studies were much less intensive, consisting of goal setting,[11,25] self-feedback with food or exercise diaries,[11,21,23] stress management, or improved coping skills.[24]

The comparison group interventions were fairly minimal, consisting of "usual care" or general information and counseling on diet and physical activity.[10,11,21,22,24–27] One study[23] prescribed a diet to the comparison group, but it was less restrictive than that of the intervention group, which also received a supervised physical activity intervention.

The effects of interventions on net change in weight are shown in Figure 1 and Table 3. The range of weight loss was 0.2 to 6.0 kg for the six studies with a follow-up of 1 year. Compared with usual care, the four studies with a follow-up interval of 1 year and with complete data for obtaining a pooled estimate[11,21,24,25] reduced weight by 2.8 kg (95% CI=1.0–4.7) (3.3% of baseline body weight) and decreased BMI by 1.4 kg/m^2 (95% CI=0.5–2.3).[24,25] Statistically significant heterogeneity was noted for change in weight at the 1-year follow-up. The pooled weight loss for the two studies that examined outcomes at 2 years and for which a standard error was reported[11,23] was 2.7 kg (95% CI=1.9–3.4). The most marked mean weight change was in the lifestyle arm of the DPP,[10] with a loss of 5.5 kg at an average follow-up of 2.8 years. This study population was larger than all the other study populations combined, and constituted 63% of the total population examined. Weight loss at other follow-up intervals in the DPP was 6.0 kg at 1 year; 4.9 kg at 2 years, 4.0 kg at 3 years, and 3.2 kg at 4 years (results obtained from a graphical display of the original data). No measures of uncertainty were available for these estimates; therefore, they are not included in the pooled analyses.

Only a few studies examined other outcomes, and it was felt these were insufficiently representative of all nine studies to justify pooling the effects. Changes ranged from 0.0% to −0.2% for GHb,[10,21,25] and generally corresponded to changes in weight (Table 3).

Table 1. Characteristics of study participants

Citation	Sample size	Length of follow-up (years)	Age at baseline (years) Mean (SD)	Gender (% female)	Setting; race/ ethnicity	BMI at baseline (kg/m^2) Mean (SD)	Inclusion criteria	Sampling method	Attrition (%)
Diabetes Prevention Program Research Group (2002)[10]	3234	Mean 2.8 (range, 1.8–4.6)	50.6 (10.7)	67.7	Multicenter, USA trial; 55% white, 20% African American	34.0 (6.7)	BMI>24 kg/m^2 FPG 95–125 mg/dL (5.2–6.9 mmol/L) and 2-h 75-g OGTT PG 140–199 mg/dL (7.8–11.0 mmol/L)	Self- and provider-selected from clinic and community	8%
Dyson (1997)[21]	227	1	50 (9)	59.0	NR	NR	FPG on two occasions 5.5–7.7 mmol/L (99–139 mg/dL). There is some overlap with this population and diabetes (as defined by the American Diabetes Association.[14] Also, at baseline 27% had diabetes as defined by OGTT (World Health Organization[29])	Self-selected from clinics	11%
Jarrett (1987)[22]	204	10.0	55.0 (7.6)	0.0	NR	25.8 (3.4)	Random capillary BG 110–199 mg/dL (1.6–11.0 mmol/L), followed by 50-g OGTT with peak >180 mg/dL (9.0 mmol/L) and 2-h 120–199 mg/dL (6.6–11.0 mmol/L) and/or 2 values >180 mg/dL (9.0 mmol/L) and/or mean 2-h >120 mg/dL (6.6 mmol/L)	Self-selected, community recruitment	43%
Liao (2002)[23]	64	2.0	54.0 (10.2)	55.0	USA; Americans of Japanese ancestry	26.1 (4.5)	FPG<127 mg/dL (<7.0 mol/L) and 2-h post 75-g glucose load of >140 mg/dL (7.8 mmol/L) and <200 mg/dL (11.1 mmol/L)	Unclear	17%

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Table 1. *(continued)*

Citation	Sample size	Length of follow-up (years)	Age at baseline (years) Mean (SD)	Gender (% female)	Setting; race/ ethnicity	BMI at baseline (kg/m^2) Mean (SD)	Inclusion criteria	Sampling method	Attrition (%)
Lindahl (1999)[24]	194	1.0	55.4 (8.9)	63.0	Residential wellness facility in Sweden; NR	30.6 (3.3)	BMI>27 Kg/m^2 Abnormal OGTT (World Health Organization[29])	Subset of a community intervention registry	4%
Mensink (2003)[25]	114	1.0	56.6 (7.2)	43.0	The Netherlands; Caucasian	29.4 (3.6)	Mean 2-h 75g OGTT BG>140 mg/dL (7.8 mmol/L) and <225 mg/dL (12.5 mmol/ L); FBG<140 mg/dL (7.8 mmol/L)	Patients in existing community cohort who were at high risk for diabetes were given OGTT	10%
Page (1992)[26]	31	2.0	39.3 (10.7)	NR	United Kingdom; NR	26.6 (4.0)	IGT based on two continuous infusions of glucose with model assessment (CIGMA) tests, or FBG>5.6 mmol/L (101 mg/dL)	Unclear	26%
Pan (1997)[27]	577	6.0	45.0 (9.1)	47.0	China; community cohort	25.8 (3.8)	2-h postprandial BG≥ 120 mg/dL (6.7 mmol/L) and <200 mg/dL (11.0 mmol/ L), followed by 75-g OGTT (abnormal by 1985 WHO criteria[29])	87% of target population (a community in China) were screened	8%
Tuomilehto (2001)[11]	523	Mean 3.2 (range, 1.6–6.0)	55.0 (7.0)	67.0	Finland; NR	31.1 (4.6)	BMI≥25 kg/m^2 IGT (2-h post prandial plasma glucose 140–200 mg/ dL [7.8–11.0 mmol/ L]) and FG<140 mg/ dL (7.8 mmol/L)	Epidemiologic surveys and opportunistic population screening	8% at 3.2 years
Mean	5168 (total)	3.2	51.2 (9.9)	50.2		28.7 (5.9)			15.6%
Range	31–3234	1–10	39.3–56.6	0.0–67.7		25.8–34.0			4.0%–43%

ADA, American Diabetes Association; BMI, body mass index; BG, blood glucose; FBG, fasting blood glucose; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; NR, not reported; OGTT, oral glucose tolerance test; PG, plasma glucose; SD, standard deviation; WHO, World Health Organization.

Table 2. Intervention characteristics

Study[a]	General intervention characteristics	Dietary intervention	Physical activity intervention	Behavioral intervention	Comparison group care
Diabetes Prevention Program Research Group (2002),[10] (2002),[32] (2002),[33] (2000),[31] (1999)[30]	**Duration:** Average 2.8 years; range 1.8 to 4.6 years **Frequency:** 16 lessons in first 24 weeks, then monthly **No. of contacts:** 40 **Group/individual:** Lessons individual; some follow-up group sessions **Medium:** In person **Facilitator:** Case manager ("lifestyle coach"), usually a dietitian	Sixteen lessons covering diet, exercise and behavioral modification; goal 7% weight loss; low calorie, low fat	Intensive lifestyle arm: moderate-intensity exercise for 150 minutes a week; supervised sessions twice a week, with supplemental group classes	Goal setting, individual case managers, individualization, culturally sensitive materials and strategies, motivational strategies	Standard lifestyle: written information and annual 30-minute individual session on healthy lifestyles
Dyson (1997)[21]	**Follow-up interval:** 32 months **Duration:** 52 weeks **Frequency:** Every 3 months **No. of contacts:** 4 **Group/individual:** Individual **Medium:** In person **Facilitator:** Dietitian, fitness instructor **Follow-up interval:** 12 months	500–700 kcal/day deficit if BMI>22 kg/m^2; decrease fat; increase fiber	Encouraged to exercise starting at two to three times a week for 20 minutes with a variety of aerobic exercise; increase to five or six times a week; seen by fitness instructor every 3 months	Food and exercise diaries	Written information; weight loss and activity advice if BMI>25 kg/m^2 visits every 3 months
Jarrett (1987)[22] Jarrett (1979)[28]	**Duration:** 10 years **Frequency:** Every 6 months for 5 years, then every year **No. of contacts:** 15 **Group/individual:** Unclear **Medium:** In person and written **Facilitator:** NR	120 g/day carbohydrate	None	None	Recommended to reduce use of table sugar
Liao (2002)[23]	**Follow-up interval:** 120 months **Duration:** 2 years **Frequency:** Three times per week for 6 months, then unsupervised **No. of contacts:** 78 sessions **Group/individual:** Individual **Medium:** In person **Facilitator:** Exercise physiologist, dietitian **Follow-up interval:** 24 months	American Heart Association step 2 diet: <30% fat, 55% carbohydrate; <200 mg cholesterol; individual prescription by dietitian; intended to be isocaloric with prior intake	Supervised treadmill for 1 hour three times a week for 6 months; initial goal 50% maximum heart rate reserve, then increase to 70%; continued unsupervised for next 18 months	Food records for feedback	Stretching exercises in a group three times a week and American Heart Association step 1 diet (30% fat, 50% carbohydrate, <300 mg cholesterol); intended to be isocaloric with prior intake

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Table 2. *(continued)*

Study[a]	General intervention characteristics	Dietary intervention	Physical activity intervention	Behavioral intervention	Comparison group care
Lindahl (1999)[24]	**Duration:** 4 weeks **Frequency:** Daily **No. of contacts:** Daily for 4 weeks **Group/individual:** Combined **Medium:** In person **Facilitator:** NR	Residential treatment with 1800 kcal/day for males, 1500 for females	2.5 hours/day aerobic activity	Stress management, coping and relapse prevention strategies	Usual care
Mensink (2003)[25] Mensink (2003)[38]	**Follow-up interval:** 12 months **Duration:** 1 year **Frequency:** Every 3 months for dietary intervention, weekly for physical activity training **No. of contacts:** Five for dietary; 52 for supervised physical activity **Group/individual:** Combined **Medium:** In person **Facilitator:** Exercise physiologist, dietitian	Goal: 5%–7% weight loss; carbohydrate 55%, 30%–35% fat, and <300 mg cholesterol daily	Encouraged to do moderate activity 30 minutes for â‰¥5 days a week; 1-hour weekly training sessions with trainer	Goal setting	Initially given written information about healthy diet and physical activity
Page (1992)[26]	**Follow-up interval:** 12 months **Duration:** 26 weeks **Frequency:** NR **No. of contacts:** NR **Group/individual:** Group **Medium:** In person **Facilitator:** Dietitian **Follow-up interval:** 24 months	Dietary advice to participant and spouse to increase fiber, increase carbohydrate, decrease fat, decrease energy intake if appropriate; advice and support for 6 months, then asked to continue on own	Advice to exercise for â‰¥20 minutes three times a week	None	Usual care
Pan (1997)[27] Li (2002)[34]	**Duration:** 6 years **Frequency:** Both diet and exercise interventions: weekly for 1 month, then monthly for 3 months, then every 3 months for both diet and activity counseling **No. of contacts:** 30 **Group/individual:** Both **Medium:** In person **Facilitator:** Physician and team **Follow-up interval:** 72 months **Group/individual:** Combined	Diet and diet-plus-exercise groups: if BMI<25 kg/m^2, 25–30 kcal/day with 50%–65% carbohydrate, 10%–15% protein, 15%–30% fat; if BMIâ‰¥25 kg/m^2, goal to lose 0.5 to 1.0 kg/month until BMIâ‰¤23 kg/m^2	Exercise and diet-plus-exercise groups: counseled regarding daily aerobic exercise; duration dependent on intensity	None	General information; usual care

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Table 2. *(continued)*

Study[a]	General intervention characteristics	Dietary intervention	Physical activity intervention	Behavioral intervention	Comparison group care
Tuomileho (2001)[11] Eriksson (1999)[35] Eriksson (1999)[36] Uusitupa (2000)[37]	**Duration:** Mean 3.2 years **Frequency:** Seven sessions with dietitian first year, then every 3 months **No. of contacts:** 15 **Group/individual:** Individual dietary advice **Medium:** In person **Facilitator:** Dietitian, other unclear **Follow-up interval:** Mean 38 months (range, 17–72 months)	Low-fat, high-fiber diet; goal BMI<25 kg/m^2 5- to 10-kg weight loss; <50% carbohydrate, <30% fat, <300 mg/day cholesterol, increase fiber	Individual counseling regarding moderate activity 30 minutes/day; supervised strength training; frequency and availability varied among study centers	Food records; goal setting	General written and oral information at baseline and annually

[a]The primary study is listed first, followed by additional citations for related publications.
BMI, body mass index; NR, not reported.

Systolic and diastolic (data not shown) blood pressure were measured in four studies, and a small decrease was noted in most studies. Lipids were examined in four studies, and minor improvements were noted.

Five studies examined the effect of interventions on the incidence of diabetes[10,11,22,23,27]; three of these demonstrated a significant decrease in the cumulative incidence of diabetes[10,11,27] (Table 4). These three large trials were adequately powered to detect effects and involved intensive, sustained, multicomponent interventions.

Sensitivity analyses were performed to examine the effect of different assumed values of the correlation between the study groups before and after the intervention and no significant changes were noted in pooled estimates and 95% CIs. The characteristics of study quality were not sufficiently heterogeneous for us to examine the effects of randomization procedure, allocation concealment, or blinding on change in weight. Study level characteristics (including length of follow-up, duration of intervention, and attrition) were examined using meta-regression, and no significant effects on weight change were noted. The total number of intervention contacts correlated positively with a decrease in weight ($p = 0.015$).

The performance of stratified analyses was limited by sparse data. The number of studies was insufficient to examine whether a physical activity intervention added to the effectiveness of dietary interventions.

A funnel plot was created to examine the relationship between total sample size and weight change. The plot was visually asymmetric, but there were too few studies for us to draw conclusions about small sample effects and outcomes.

Discussion and Conclusions

Randomized controlled trials of weight-loss interventions using dietary, physical activity, or behavioral interventions produced statistically significant between-group weight loss of 2 to 3 kg (3% of initial body weight) at 1- and 2-year follow-ups. In two studies where weight was examined at longer follow-up intervals (up to 10 years), similar weight reduction was maintained. The number of intervention contacts with subjects was significantly correlated with weight loss. Data are limited, but the small number of available studies demonstrated improvements in GHb, blood pressure, and triglycerides, although these changes were for the most part not statistically significant. Although the weight loss demonstrated in this review is small, even modest loss in general populations may have health benefits; blood pressure, blood glucose, and serum lipid levels have been positively associated with weight loss,[39] including at the magnitudes noted here.

The findings in this review are consistent with other reviews of educational interventions for weight loss

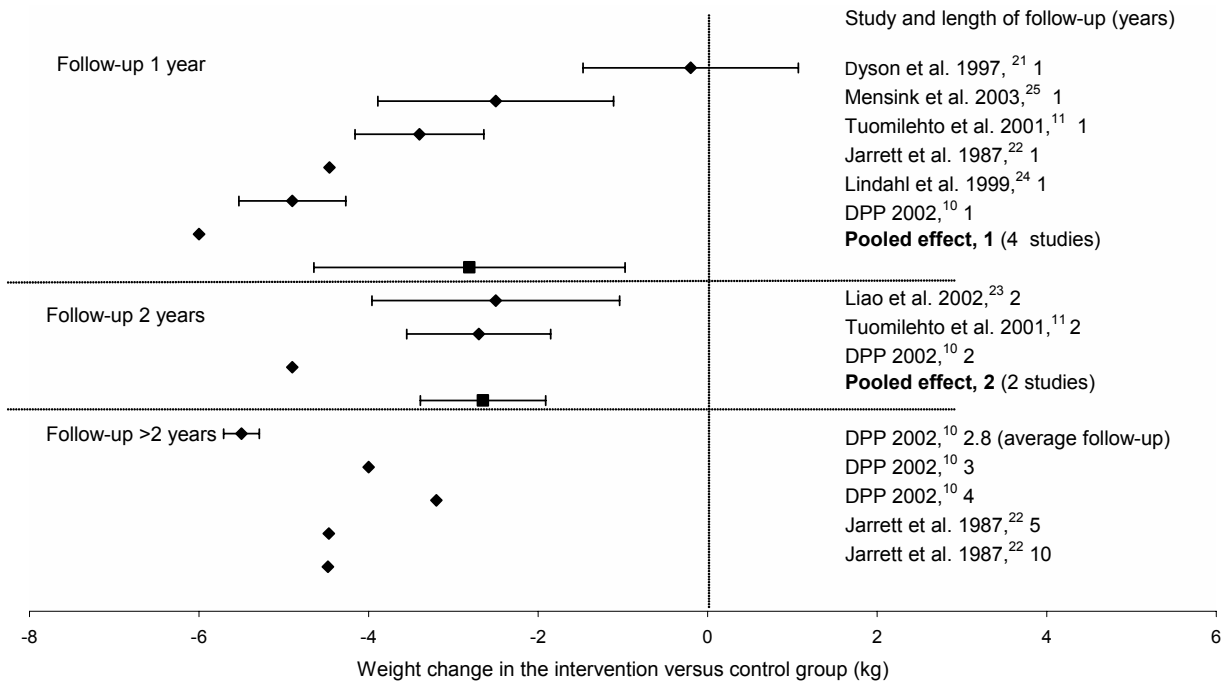

Figure 1. Effect of interventions on weight change. Confidence interval for the DPP study[10] at 2.8-year follow-up was provided by S. Edelstein (personal communication, October 13, 2003). Corrected standard error for the study by Liao et al.[23] was obtained from D. Liao (personal communication, October 8, 2003). Studies are presented on the y-axis, ordered by follow-up interval. The pooled estimates assume a correlation of 0.75. DPP, Diabetes Prevention Program Research Group.

among persons with diabetes[40] and in nondiabetic populations where comprehensive, intensive group dietary and behavioral programs produced a mean loss in weight of 8 to 10 kg at 6 months with a regain of 30% to 35% of weight loss at 1 year.[41,42] The number of contacts with patients has also been shown to correlate with glycemic control in diabetes education, where attempts are made to change complex behaviors and lifestyle.[40]

The three studies with effective interventions for decreasing the incidence of diabetes were associated with weight loss, although the change in BMI in Pan et al.[27] was only -0.4 kg/m^2 (95% CI=-0.9–0.1). These effective interventions demonstrate that diabetes prevention is achievable in a variety of settings in populations with pre-diabetes, but sustained, long-term, intensive, multicomponent interventions are required. It is noteworthy, however, that Tuomilehto et al.[11] had somewhat fewer contacts with participants (15 over 3.2 years on average), yet achieved a 58% relative risk reduction ($p<0.001$) in diabetes incidence over the course of the study.

Attrition is an important issue in weight-loss studies because of selective loss to follow-up.[43] In this review, however, attrition was on average 9.6%, perhaps because participants were most commonly self-selected, and thus perhaps more motivated to complete the study. Jarrett et al.[22] noted sustained weight loss at the 10-year follow-up, but their attrition rate was 43%, which likely contributed to the large measured weight loss among participants who persisted with the intervention over the long term.

The successful interventions that were examined in this review[10,11,27] had prolonged frequent contacts, low attrition rates, and evidence of persisting behavior change, which likely contributed to effectiveness. Few data are available on changes in patterns of behaviors over time. At the last follow-up of the DPP[10] (follow-up range, 1.8 to 4.6 years), 58% of participants continued to meet the goals of â‰¥150 minutes of self-reported physical activity per week. Total caloric and fat intake, examined at 1 year, decreased by 450 kcal/day in the lifestyle group and 249 kcal/day in the placebo group. Tuomilehto et al.[11] also reported significant between-group behavior change at 1 year. Pan et al.[27] noted no significant differences between treatment groups at the 6-year follow-up for daily caloric intake and calorie composition, but physical exercise was increased significantly in both the exercise group and the diet-plus-exercise group. In smaller studies, Mensink et al.[25] and Page et al.[26] demonstrated improved dietary habits at 1 and 2 years. Considering both attrition from study programs and recidivism with respect to positive lifestyle changes, the applicability of the results of these studies to general populations of people with pre-diabetes is unclear. Behavioral[44] and environmental[45] barriers to weight loss abound; populations that are not self-selected or participating in a research study might demonstrate less pronounced improvements in behavior and weight.

Table 3. Outcomes: mean difference between intervention and control groups (95% confidence interval)

Study	Follow-up interval (years)	Weight (kg)	BMI (kg/m²)	GHb (%)	Systolic blood pressure (mm Hg)	Total cholesterol concentration (mmol/L)	Lipoprotein (mmol/L)	Triglyceride concentrations (mmol/L)
Diabetes Prevention Program Research Group (2002)[10]	2.8	−5.5 (−5.7–5.3)	NR	−0.2	NR	NR	NR	NR
Dyson (1997)[21]	1.0	−0.2 (−1.4–1.0)	NR	0.0 (−0.1–0.1)	−2.0 (−6.0–2.0)	0.0 (−0.1–0.1)	0.1 (0.0–0.2)	−0.14 (−0.4–0.1)
Jarrett (1987)[22]	1.0	−4.5 (NR)	NR	NR	−8.4	NR	NR	NR
Jarrett (1987)[22]	5.0	−4.5 (NR)	NR	NR	−6.8 (NR)	NR	NR	NR
Jarrett (1987)[22]	10.0	−4.4 (NR)	NR	NR	10.4 (NR)	NR	NR	NR
Liao (2002)[23]	2.0	−2.5 (−4.0–1.0)	−0.9 (−1.4–0.4)	NR	NR	NR	NR	NR
Lindahl (1999)[24]	1.0	−4.9 (−5.5–4.3)	−1.8 (−2.0–1.6)	NR	−6.2 (−9.2–3.2)	−0.15 (−0.4–0.1)	NR	−0.07 (−0.4–0.2)
Mensink (2003)[25]	1.0	−2.5 (−3.8–1.2)	−0.9 (−1.4–0.4)	−0.1 (−0.4–0.2)	NR	NR	NR	NR
Page (1992)[26]	2.0	NR	0 (−2.2–2.2)	NR	1.0 (−7.0–9.0)	−0.1 (−0.7–0.5)	−0.2 (−0.7–0.3)	−0.5 (−1.6–0.6)
Pan (1997)[27]	6.0	−0.1 (NR)	−0.4 (−0.9–0.1)	NR	NR	NR	NR	NR
Tuomilehto (2001)[11]	1.0	−3.4 (−4.2–2.6)	NR	NR	−4 (−6.5–1.5)	−0.03 (−0.2–0.1)	NR	−0.19 (NR)
Tuomilehto (2001)[11]	2.00	−2.7 (−3.6–1.9)	NR					

BMI, body mass index; GHb, glycated hemoglobin; NR, not reported.

Two thirds of all participants studied in the meta-analyses were from the DPP, so this study has the largest impact on the meta-analyses results. However, the use of a random effects model to combine studies accounts for between-study heterogeneity, thus weighting each study more equally than pure sample size would indicate. This approach recognizes potential heterogeneity among the different interventions and settings in which the research was conducted, and increases generalizability of the results.

Pharmacotherapy and surgery have been used to help prevent the progression of IGT to diabetes and may be important adjuncts to lifestyle interventions in the future. In the DPP,[10] the study group receiving metformin lost a mean 2.1 kg at an average follow-up of 2.8 years, and the incidence of diabetes decreased by 31%. These outcomes were less pronounced than those achieved with the lifestyle intervention. The weight-loss agent orlistat, a pancreatic lipase inhibitor, is currently under study in the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study: a comparison of a lifestyle intervention with orlistat revealed a significant decrease in weight (2.8 kg compared to the control group) and a relative risk reduction of 37.2% in the cumulative incidence of type 2 diabetes at the 4-year follow-up.[46] The Troglitazone in Prevention of Diabetes (TRIPOD) study has shown a 56% relative reduction in the progression to diabetes in Hispanic women with previous gestational diabetes at median follow-up of 30 months.[47] In the Study to Prevent Non-Insulin-Dependent Diabetes (STOP-NIDDM), a 25% relative risk reduction in progression to diabetes was noted at 3.3 years in the group using the alpha-glucosidase inhibitor acarbose.[48] Other drugs have been associated with a decreased incidence of diabetes in post hoc analyses of initially normoglycemic populations, including captopril,[49] ramipril,[50] and pravastatin,[51] and with estrogen progestin combination therapy.[52] Weight loss from bariatric surgery has also been shown to significantly decrease the progression of IGT to diabetes.[53,54]

This review is limited to published studies; although subject experts were contacted for additional unpublished literature, none was obtained. The quality of individual studies in this review varied, and some common deficiencies were noted: in particular, randomization procedures and allocation concealment were rarely reported.

Further, the studies included were heterogeneous with respect to population, setting, and intervention, and the data were very limited for most outcomes. Quantitative synthesis was therefore not justified for most outcomes, and the pooled effect for weight loss at 1 year must be interpreted with caution.

Whether the benefits of weight loss in people with pre-diabetes differs from those in people with diabetes[6,8] in terms of macro- and micro-vascular disease remains to be seen. Is primary prevention of diabetes among high-risk adults any different from the treat-

Table 4. Effect of lifestyle and behavioral interventions among people with pre-diabetes on the incidence of diabetes

Study	Study group	Length of follow-up (years)	Definition of diabetes	Cumulative incidence, %, over duration of the study (95% CI)	Relative risk reduction (95% CI)	Incidence per 100 person years (95% CI)	Number needed to treat[b]	Comments
Diabetes Prevention Program Research Group (2001)[10]	Lifestyle Metformin Placebo	3.0	FPGâ‰¥126 mg/dL or 2-hour OGTTâ‰¥200 mg/dL, with repeat	14.4 (NR) 21.7 (NR) 28.9 (NR)	58 (48–66) 31 (27–43)	4.8 7.8 11.0	16.1 31.3	All three pairwise comparisons significant, number needed to treat over duration of the study was 6.9 (5.4–9.5) for the lifestyle group and 13.9 (8.7–33.9) for the metformin group
Jarrett (1979)[28]	Diet Control	5.0	2-hour blood glucose >200 mg/dL twice, or three nonsuccessive measures, or signs or symptoms of diabetes, or 2-hour 75-g OGTT â‰¥200 mg/dL	18.2 (NR) 13.3 (NR)	Not applicable, as intervention group had higher rate of diabetes than control group	3.6[a] 2.7[a]	Not applicable	No significant differences between each group
Liao (2002)[23]	Lifestyle Control	2.0	2-hour OGTTâ‰¥200 mg/dL	3.1 (NR) 6.3 (NR)	51[a]	1.6[a] 3.2[a]	62.5	One person developed diabetes in the intervention group (n=32) and two persons in the control group (n=32). Study not designed to demonstrate prevention of diabetes
Pan (2002)[27]		6.0	FPGâ‰¥140 mg/dL or PGâ‰¥200 mg/dL 2 hours after OGTT					
Li (2002)[34]	Diet plus physical activity Diet only Physical activity only Control			38.2 (NR) 44.4 (NR) 52.1 (NR) 67.4 (NR)	43[a] 34[a] 23[a]	8.0 (5.1–10.95) 10.1 (7.0–13.2) 10.7 (7.5–13.5) 15.2 (11.3–19.7)	13.9 19.1 22.2	Treatment groups differed significantly from controls: diet plus physical activity (p<0.005), diet only (p<0.03), and physical activity only (p<0.0005)

(continued on next page)

Table 4. *(continued)*

Study	Study group	Length of follow-up (years)	Definition of diabetes	Cumulative incidence, %, over duration of the study (95% CI)	Relative risk reduction (95% CI)	Incidence per 100 person years (95% CI)	Number needed to treat[b]	Comments
Tuomilehto (2001)[11]	Lifestyle intervention	2.0	FPGâ‰¥140 mg/dL or PGâ‰¥200 mg/dL 2-h after OGTT	6 (3–9)	58% (for all person-years accumulated)	3.2	21.7	For all person-years accumulated, lifestyle differed significantly from the control group (*p*<0.001)
	Control			14 (10–19)		7.8		
	Lifestyle intervention	4.0		11 (6–15)				
	Control			23 (17–29)				

[a]Calculated from the cumulative incidence and duration of study; thus, yearly incidence estimates are approximate.
[b]Calculated from the incidence per 100 person years.
CI, confidence interval; FPG, fasting plasma glucose; PG, plasma glucose; OGTT, oral glucose tolerance test; NR, not reported.

ment of diabetes? Certainly insulin sensitivity and glycemia represent a spectrum, and people with glucose levels below those defined for diabetes have significantly elevated cardiovascular disease risk over people with normoglycemia.[2] Preventing and treating diabetes are different, however: Current clinical approaches differ by frequency of laboratory and clinical testing, guidelines for blood pressure and lipid levels differ, people with diabetes are at risk for acute complications such as hyperglycemia, and microvascular complications are not well documented in pre-diabetes.[12] Thus, it is as yet unclear whether similar weight, lipid, glycemia, and blood pressure treatment strategies and goals are warranted in pre-diabetes.

Future research needs to focus on how best to sustain interventions and behavioral change, and long-term outcomes such as cardiovascular events and mortality need further study. Researchers need to explore the effectiveness of interventions shown to work in populations with IGT and in other populations (e.g., those with isolated IFG, the metabolic syndrome, type 2 diabetes, or overweight and obesity). There is some information available on the effectiveness of these interventions when nonselective community recruitment is used,[24,25,27] but further research needs to explore whether and how to translate these results to broadly defined communities. Should interventions focus on diet and physical activity change specifically, or more broadly on the social determinants of behavior and disease, such as social status or empowerment?[55] The role of diet versus physical activity interventions for weight loss in persons with pre-diabetes needs additional study. Physical activity interventions demonstrate benefits among persons with diabetes, independent of weight loss,[56] and there are some data to support a positive effect of physical activity on the incidence of diabetes independent of weight loss.[57] The role of other weight-loss strategies (in isolation or in combination with dietary, activity or behavioral interventions) such as pharmacotherapy,[58] surgical interventions, or public health interventions (such as changes in the physical and social environments), remains to be determined. Further research is needed on weight-control strategies and obesity prevention.

Small improvements in weight and in other cardiovascular disease risk factors appear achievable in populations with abnormal glycemia. Further research is needed to examine the effect of these interventions on morbidity and mortality and their effectiveness in other high-risk populations. Work is also needed to explore translation and implementation of these results in the community setting.

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What This Study Adds . . .

Pre-diabetes (impaired glucose tolerance and impaired fasting glucose) dramatically increases the risk of diabetes and cardiovascular disease.

Weight loss for persons with pre-diabetes may delay or prevent the progression to type 2 diabetes.

A systematic review was conducted to assess the effectiveness of dietary, physical activity, or behavioral interventions for weight loss in adults with pre-diabetes.

Overall, these strategies produced modest but significant improvements in weight and a significant decrease in diabetes incidence.

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