Effect of Weight Loss With Lifestyle Intervention on Risk of Diabetes

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OBJECTIVE — Diabetes Prevention Program (DPP) participants randomized to the intensive lifestyle intervention (ILS) had significantly reduced risk of diabetes compared with placebo participants. We explored the contribution of changes in weight, diet, and physical activity on the risk of developing diabetes among ILS participants.

RESEARCH DESIGN AND METHODS — For this study, we analyzed one arm of a randomized trial using Cox proportional hazards regression over 3.2 years of follow-up.

RESULTS — A total of 1,079 participants were aged 25–84 years (mean 50.6 years, BMI 33.9 kg/m^2). Weight loss was the dominant predictor of reduced diabetes incidence (hazard ratio per 5-kg weight loss 0.42 [95% CI 0.35–0.51]; $P < 0.0001$). For every kilogram of weight loss, there was a 16% reduction in risk, adjusted for changes in diet and activity. Lower percent of calories from fat and increased physical activity predicted weight loss. Increased physical activity was important to help sustain weight loss. Among 495 participants not meeting the weight loss goal at year 1, those who achieved the physical activity goal had 44% lower diabetes incidence.

CONCLUSIONS — Interventions to reduce diabetes risk should primarily target weight reduction.

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The Diabetes Prevention Program (DPP) reported a 58% reduction in the incidence of diabetes over almost 3 years in subjects treated with an intensive lifestyle intervention (ILS) compared with participants treated with placebo (1). The ILS involved changes in diet and physical activity aimed at producing weight loss, but the study did not randomly assign each component of the intervention. However, there was variation in the change in diet, physical activity, and weight loss among ILS participants (2). Thus, we analyzed the relative contributions of changes in diet, physical activity, or weight loss to the reduction in diabetes incidence and assessed the contribution of diet and activity changes on weight loss. This report extends the understanding of how the ILS resulted in lower diabetes incidence (1) by assessing the impact of meeting intervention goals and on the changes in risk factors among individuals randomized to the ILS.

RESEARCH DESIGN AND METHODS

— The design, methods, recruitment, and characteristics of the DPP participants have been reported elsewhere (3,4). In summary, participants were aged ≥25 years, had a BMI of ≥24 kg/m^2 (≥22 kg/m^2 in Asian Americans), and had impaired glucose tolerance during an oral glucose tolerance test, based on DPP criteria (5). Participants were excluded if they had diabetes or a number of other conditions or medications. All participants gave written informed consent after approval by the appropriate institutional review board.

ILS

The ILS has been described (6). Goals were to reduce weight by 7% from baseline, to achieve and/or maintain at least 150 min per week of moderate physical activity, and to reduce total dietary fat to <25% of calories; if weight loss was not achieved by lowering fat, calorie goals were introduced. Participants met with a lifestyle counselor weekly over a 16-session curriculum and at least bimonthly thereafter. Periodic group classes and campaigns were used to reduce weight regain and maintain activity levels.

Outcomes

Incident diabetes was identified by an annual 75-g oral glucose tolerance test or semiannual fasting glucose levels, with confirmation (3), using American Diabetes Association criteria (7). The 30-min Δ insulin–to–Δ glucose ratio (IGR) was used as a marker of insulin secretion (8), and fasting insulin level was used as a marker of insulin resistance. Weight was measured semiannually.

Diet information was collected by interview at baseline and at year 1 using a modified Block food-frequency questionnaire (9). Complete diet data were avail-

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Abbreviations: DPP, Diabetes Prevention Program; IGR, insulin-to-glucose ratio; ILS, intensive lifestyle intervention.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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able for 98.2% of participants at baseline and 92.4% at year 1 (10).

Total MET hours per week of physical activity was assessed by the 1-year recall Modifiable Activity Questionnaire (11) and the 1-week Low Level Physical Activity Recall (12).

Analysis

The 1,079 ILS participants were enrolled from June 1996 to May 1999 and followed until 31 July 2001, 4 months longer than previously reported (1). Of these, 1,026 were observed at year 1, 999 at year 2, and 638 at year 3 or beyond. The declining sample size resulted from patient recruitment over a 2.7-year period ending in June 1999. Thus, subjects entering in (e.g.) 1999 had only 2 years of follow-up and were censored in the analysis at that time. Overall, 92.4% of participants completed scheduled annual visits over the 3-year period.

Risk of diabetes was assessed using Cox proportional hazards models with time-dependent covariates (13). For each covariate of interest (e.g., weight), a baseline model was fit using the baseline value and those of other adjusting covariates; those not nominally significant were removed. Proportionality assumptions were verified using time-by-variable interaction terms. Time-dependent covariates were then added, with values updated at each annual assessment with no time lag. Relevant interactions were assessed. Madalla's partial R^2 was used to estimate the proportion of variation in risk of diabetes over time explained by a covariate in the model (14) and indicates the ability to predict which participants would develop diabetes and exactly when this would occur.

Factors predicting weight change from baseline were assessed using separate linear regression models at years 1, 2, and 3. The mean change in physical activity from baseline reported from the Modifiable Activity Questionnaire was used in the model at each year. Diet change, assessed from baseline to year 1, was used in all models. The SAS analysis system was used (version 8.2; SAS Institute, Cary, NC).

RESULTS — A total of 153 participants developed diabetes over the 3.2-year mean follow-up period among the 1,079 at baseline, a rate of 5.0 per 100 person-years. Participants were aged 25–84 years at baseline (mean 50.6 years), and 68% were women. Their race/

Table 1—*Weight, physical activity, and diet at baseline and annual changes from baseline among participants in the ILS group: DPP, 1996–2001*

	Baseline	Year 1	Year 2	Year 3
	Mean (25th–75th percentile)*	Mean change (25th–75th percentile)*	Mean change (25th–75th percentile)*	Mean change (25th–75th percentile)*
Weight				
n	1,079	1,023	999	638
Weight (kg)	94.1 (79.2–105.1)	−6.8 (−10.0 to −2.6)†	−5.4 (−8.5 to −1.10)†	−4.1 (−7.3 to 0.0)†
BMI (kg/m^2)	33.9 (28.9–37.2)	−2.4 (−3.5 to −1.0)†	−1.9 (−3.0 to −0.4)†	−1.5 (−2.7 to 0.0)†
Percent weight loss	—	7.2 (3.0–10.5)†	5.8 (1.2–9.8)†	4.5 (0–8.5)†
Energy expenditure				
n	1,077	1,013	995	635
Modifiable Activity Questionnaire (MET hours/week)‡	15.5 (3.8–19.3)	+6.6 (−0.1 to +14.4)†	+5.7 (−0.7 to +13.9)†	+4.3 (−2.3 to +13.1)†
Low Level Physical Activity Recall (MET hours/week)§	67.1 (36.3–91.1)	+8.3 (−15.1 to +30.9)†	+8.0 (−17.0 to +33.9)†	+8.1 (−19.3 to +35.2)†
Energy intake‖				
n	1,054	987	—	—
Total kcal/day	2,137 (1,452–2,550)	−452.3 (−803.3 to +29.0)†	—	—
Total fat/day (g)	83.0 (49.3–102.5)	−30.3 (−47.6 to −6.3)†	—	—
Percent of calories from fat	34.1 (29.6–38.5)	−6.6 (−10.9 to −1.9)†	—	—

*Twenty-fifth to 75th percentile of change in variable. †$P < 0.0001$ compared with baseline value by paired t test. ‡One-year recall using Modifiable Activity Questionnaire (see RESEARCH DESIGN AND METHODS). §Seven-day recall using Low Level Physical Activity Recall (see RESEARCH DESIGN AND METHODS). ‖Diet information was not collected after year 1 (see RESEARCH DESIGN AND METHODS).

Table 2—*Univariate and multivariate association of weight loss, behavioral, and metabolic variables on lower diabetes incidence in participants in the ILS group: DPP, 1996–2001*

		Models assessing one characteristic at a time*			Multivariate model†		
Variables (unit change)	Model	HR (95% CI)‡	*P*	R^2 (%)§	HR (95% CI)‡	*P*	R^2 (%)§
Baseline variables							
Lower weight (10 kg)	1	0.81 (0.75–0.86)	<0.0001	3.46	0.88 (0.81–0.96)	0.003	0.82
Higher leisure physical activity (MAQ) (5 MET hours/week)	2	1.00 (0.96–1.05)	0.89	0.00	1.00 (0.96–1.04)	0.98	0.00
Higher recreational activity (LoPAR) (20 MET hours/week)	3	1.12 (1.01–1.23)	0.03	0.42	1.08 (0.97–1.20)	0.16	0.19
Lower percent of calories from fat (5%)	4	0.96 (0.84–1.10)	0.57	0.03	0.91 (0.79–1.05)	0.19	0.16
Follow-up variables							
Weight loss (5 kg)	1	0.49 (0.43–0.57)	<0.0001	7.55	0.42 (0.35–0.50)	<0.0001	8.09
Higher leisure physical activity (MAQ) (5 MET hours/week)	2	0.95 (0.88–1.02)	0.17	0.17	0.97 (0.90–1.05)	0.50	0.04
Higher recreational activity (LoPAR) (5 MET hours/week)	3	0.99 (0.97–1.02)	0.66	0.01	0.99 (0.96–1.02)	0.45	0.05
Lower percent of calories from fat (5%)	4	0.75 (0.63–0.88)	0.0007	1.06	0.93 (0.77–1.12)	0.42	0.06

*Baseline proportional hazards models (1–4) include baseline and follow-up (time-dependent) variables for each characteristic and are also adjusted for baseline demographic factors (age, sex, race/ethnic group, and weight). Separate models are shown with numbers. †Multivariate proportional hazards model includes all baseline and follow-up (time-dependent) variables shown, as well as age, sex, ethnic group, HbA_{1c}, and baseline fasting measures of insulin, glucose, and IGR. ‡HRs for specified unit differences: <1 indicates less diabetes at follow-up; >1 indicates more diabetes. §Partial R^2 indicates the proportion of explained variance in predicting the development of diabetes at a specified time point. LoPAR, Low Level Physical Activity Recall questionnaire; MAQ, Modifiable Activity Questionnaire.

ethnicity was Caucasian (53.7%), African American (18.9%), Hispanic American (8.6%), American Indian (5.7%), and Asian/Pacific Islander (5.3%).

Table 1 describes the changes in weight, physical activity, and diet over each year. At year 1, the mean weight loss was 6.8 kg (7.2%). The 638 participants who completed the year 3 assessment lost a mean of 4.1 kg from baseline. Both measures of leisure physical activity showed significant increases at each of the 3 years. Percent of calories from fat was reduced from 34.1 to 27.5% at year 1.

We explored the association of diabetes incidence over time with weight loss, lower energy or fat intake, and increases in energy expenditure in separate Cox models adjusting for baseline factors (Table 2). Baseline weight and weight loss were most strongly associated with lower diabetes incidence (model 1), with hazard ratios (HRs) of 0.81 per 10-kg–lower baseline weight ($P < 0.0001$) and 0.49 per 5-kg weight loss ($P < 0.0001$), with a partial R^2 of 7.55%. Figure 1 illustrates the effect of weight loss on the incidence of diabetes (rate per 100 person-years of follow-up). On average, there was a 16% reduction in diabetes risk per kilogram weight loss.

Neither change in physical activity nor total kilocalories per day were related to incidence of diabetes (models 2 and 3). The largest dietary association was seen using percent fat, which integrates kilocalories and fat grams. For every 5% reduction in percent fat during follow-up, diabetes incidence was reduced by 25% ($P = 0.0007$). This variable was used in multivariate models, since it explained the largest fraction of risk among the dietary variables.

Weight loss was the dominant factor in a multivariate Cox model including behavioral and metabolic changes simultaneously (HR 0.42 per 5 kg; $P < 0.0001$; $R^2 = 8.09\%$) (Table 2). Simultaneous adjustment for changes in physical activity and percent fat, among other variables, had a negligible effect on the HR for weight loss compared with the unadjusted HR. At baseline, lower weight, a higher IGR, and lower fasting insulin were all significantly associated with lower diabetes incidence. Changes in IGR and fasting insulin over time, while significantly related to diabetes incidence when added to these models, did not change the coefficient for weight loss (models not shown).

Weight loss reduced diabetes inci-

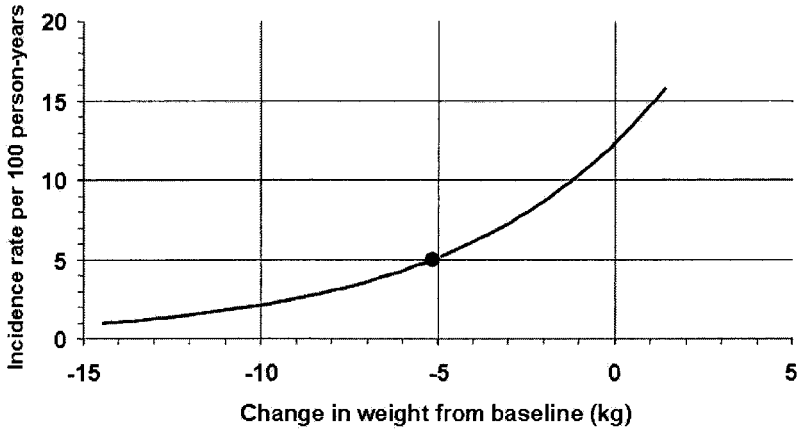
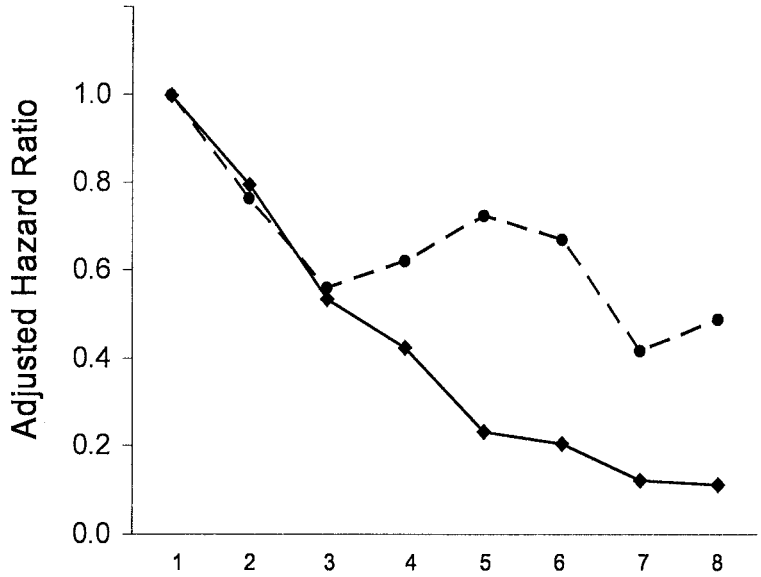


Figure 1—*Diabetes incidence (per 100 person-years) by change in weight after baseline among DPP ILS participants based on the multivariate model in Table 2. ●, overall risk in the group at the mean weight loss over an average of 3.2 years of follow-up.*



At weight goal	No	No	No	No	Yes	Yes	Yes	Yes
At exercise goal	No	No	Yes	Yes	No	No	Yes	Yes
At fat goal	No	Yes	No	Yes	No	Yes	No	Yes
Mean weight loss (Kg)	-1.5	-2.5	-2.2	-3.5	-11.5	-11.5	-11.8	-13.4
Sample size	134	32	226	103	51	34	208	187

Figure 2—*HRs for diabetes onset over 3.2 years of follow-up in DPP ILS subgroups defined by meeting intervention goals at 1 year compared with those meeting none of the goals (group 1). The solid line is adjusted for baseline covariates used in Table 2 (other than IGR and insulin); the dashed line is also adjusted for weight change over time.* ◆*, adjusted HRs;* ●*, adjusted HRs plus weight change.*

dence similarly across all race/ethnicity groups, for both sexes, for all ages, and for several levels of physical activity (all interaction $P > 0.4$), regardless of the level of initial obesity (interaction $P > 0.8$).

To explore the impact of meeting ILS goals on diabetes incidence, we defined eight subgroups based on whether goals were met at year 1. Figure 2 shows the HR for developing diabetes (solid line) for combinations of goals compared with the group meeting none (subgroup 1) as referent, adjusted for variables used in Table 2. Diabetes risk decreased as additional goals were met. The lowest risk was in the subgroup meeting all goals (subgroup 8), with an HR of 0.11 (95% CI 0.05–0.24; $P < 0.0001$) representing an 89% risk reduction.

Figure 2 also shows the effects of meeting goals adjusting for weight change (dashed line). In subgroups 1–3, adjusting for the small amount of weight loss had no effect. Starting with subgroup 4 and for subgroups 5–8, the adjusted HRs moved closer to 1.0, indicating that weight loss accounted for a substantial portion of the reduction in risk associated with meeting more goals. The estimated HRs ranged from 0.41 to 0.72 (~30–60% risk reduction), suggesting that meeting goals other than weight loss also reduced the risk of diabetes. Among 495 participants who did not meet the weight loss goal at year 1 (subgroups 1–4), there was no significant effect of meeting the percent fat goal on diabetes incidence (subgroups 1 and 3 versus 2 and 4) (adjusted HR 0.76 [0.35–1.67]; $P = 0.50$). However, there was a 46% reduction in diabetes incidence (0.54 [0.34–0.84]; $P = 0.007$) for participants who met the physical activity goal (i.e., 150 min of moderate intensity activity per week, as shown in subgroups 3 and 4 versus 1 and 2), adjusted for baseline variables only. Additional adjustment for weight change over follow-up (average of −2.6 kg) did not change the impact of physical activity (0.56 [0.36–0.89]; $P = 0.012$). The −2.6 kg of weight loss was significantly ($P < 0.0001$) and independently related to lower diabetes risk, suggesting that even small amounts of weight loss decrease risk.

We next explored the predictors of weight loss. Lower baseline percent fat and a reduction in percent fat at year 1 were each associated with short-term (year 1: $r = -0.78$ kg baseline and $r = -1.68$ kg/year per 5% reduction; $P < 0.0001$) and longer-term (year 2: $r = -1.75$ kg/year and year 3: $r = -1.52$ kg/year per 5% decrease to year 1, $P < 0.0001$) weight loss, adjusted for baseline BMI, age, sex, and race/ethnicity. Increased physical activity became a stronger predictor of weight loss at each subsequent year. By year 3, an increase in physical activity of 5 MET hours per week was associated with a loss of −0.43 kg ($P < 0.0001$), adjusted for other variables.

CONCLUSIONS — The DPP ILS included several lifestyle changes, but weight loss was the dominant determinant of the reduced risk of diabetes. Both increased physical activity and reduced percent fat predicted weight loss. We estimated that a 5-kg (~11-lb) weight loss over time could account for a 55% reduction in the risk of diabetes over the mean of 3.2 years of follow-up in this high-risk population. Contrasting those in the 90th versus 10th percentile of weight loss, there is a 96% reduction in risk. This suggests that subjects who lose even more weight than the DPP average (5–7%), and who meet physical activity and dietary fat goals, could reduce their diabetes risk by >90%. These estimates are consistent with the Finnish Diabetes Prevention Study among participants meeting four or five of their goals (15) and in a low-risk subgroup of the Nurse's Health Study, where women with the fewest risk factors had 91% lower risk than those in the rest of the cohort (16).

The consistency of effects from the DPP (1), Diabetes Prevention Study (15), and other randomized trials including weight loss (17–19), as well as observational studies (20–23), shows that lifestyle changes that result in weight loss effectively reduce diabetes risk. This finding likely also extends to even lower-risk populations, as shown among nonsmoking men in the Multiple Risk Factor Intervention Trial (24); for every 1 kg of weight loss, there was a 25% lower diabetes risk among men in the intervention group and a 16% lower risk in the usual care group, consistent with our results.

In the ILS group, we found no inde-

pendent effects of increased physical activity or decreased percent fat on diabetes risk after adjustment for weight change (Table 2) when analyzed as continuous variables. This suggests that self-reported changes in physical activity or fat intake did not lead to additional reductions in diabetes risk after accounting for weight loss. However, in analyses using categories of meeting versus not meeting goals at year 1 (Fig. 2), diabetes risk was lower with each additional goal met. Moreover, among participants who did not meet the weight loss goal, those who met the activity goal had a 44% reduction in diabetes incidence, independent of the small weight loss (−2.9 kg) that occurred.

The Finnish Diabetes Prevention Study also reported that individuals who met their physical activity goal (>4 h/week), but who did not meet the weight loss goal (>5% weight loss), had a 70% reduction in diabetes incidence after adjustment for baseline but not follow-up BMI (15). Increases in moderate to vigorous leisure time physical activity and in strenuous, structured leisure time physical activity also resulted in 63–65% reductions in diabetes risk, even after adjustment for changes in weight (25). A similar effect of physical activity was also seen in the Da Qing Study (26).

The finding that the effects of quantitative measures of activity are negligible, whereas those based on meeting the defined goals are significant, may indicate that small changes in activity are overshadowed by the much stronger effect of weight loss. It may also reflect the measurement error of the self-reported quantitative diet and activity measures, which would tend to bias the estimated HR for their effects toward the null and underestimate the proportion of variance explained (27). Correction for imprecision of dietary intake or activity measures based on reliability estimates (9) increased the partial R^2 for percent fat (assuming the reliability coefficient is 0.4, i.e., 60% of the variation among the measurements is due to inherent random error) from 0.06% (Table 2) to 0.15% and for physical activity from 0.04 to 0.10%, far smaller than the partial R^2 for weight change (8.09%). Thus, the proportion of explained variance for weight change remains substantially higher than for either percent fat or physical activity. The results may also indicate that at least ~150 min a week of moderate activity are required before an effect on diabetes risk is achieved.

Weight loss at each year of follow-up was predicted by a reduction in the percent fat at year 1 and by increased physical activity at years 2 and 3, consistent with other studies (28). The reduction of 1.68 kg per 5% decrease in percent fat is consistent with the predicted loss of 1.4–2.8 kg over 6–12 months from a review of weight loss studies using low-fat diets (29). Higher levels of physical activity also significantly predict long-term weight loss (28).

Our analysis has limitations. Participants were not randomized to receive different components of the intervention that could result in residual confounding with the effects of measurements during follow-up. We attempted to account for this by adjusting all analyses for baseline characteristics. Dietary measures were chosen a priori to include calories, fat grams, and percent fat, but diet change was only measured at 1 year of follow-up. Both diet and activity measures were self-reported, without additional objective data; however, they were significantly associated with weight loss.

With the increasing prevalence of overweight and adoption of a Western lifestyle, many populations are at risk of developing diabetes and may be reasonable candidates for a prevention intervention like that of the DPP. Weight loss, largely determined by changes in diet and exercise, is the primary factor resulting in reduced diabetes incidence among those in the ILS group. An increase in physical activity helps sustain weight loss and independently reduces diabetes risk among those who do not lose weight. Interventions to reduce the incidence of diabetes should aim at weight loss as the primary determinant of success.

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