

# Early Response to Preventive Strategies in the Diabetes Prevention Program

Nisa M. Maruthur, MD, MHS<sup>1,2</sup>, Yong Ma, PhD<sup>3</sup>, Linda M. Delahanty, MS, RD<sup>4</sup>, Julie A. Nelson, RD<sup>5</sup>, Vanita Aroda, MD<sup>6</sup>, Neil H. White, MD, CDE<sup>7</sup>, David Marrero, PhD<sup>8,9</sup>, Frederick L. Brancati, MD, MHS<sup>1,2,10</sup>, and Jeanne M. Clark, MD, MPH<sup>1,2,10</sup> for the Diabetes Prevention Program Research Group

<sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA; <sup>2</sup>Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, MD, USA; <sup>3</sup>George Washington University, Rockville, MD, USA; <sup>4</sup>Massachusetts General Hospital Diabetes Research Center and Harvard Medical School, Boston, MA, USA; <sup>5</sup>Southwest American Indian Center-Arizona, NIDDK, Phoenix, AZ, USA; <sup>6</sup>Department of Medicine, University of California, San Diego, CA, USA; <sup>7</sup>Washington University School of Medicine, St. Louis, MO, USA; <sup>8</sup>Regenstrief Institute for Health Care, Indianapolis, IN, USA; <sup>9</sup>Diabetes Translational Research Center, Indiana University School of Medicine, Indianapolis, IN, USA; <sup>10</sup>The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA.

**BACKGROUND:** Recommendations for diabetes prevention in patients with prediabetes include lifestyle modification and metformin. However, the significance of early weight loss and glucose measurements when monitoring response to these proven interventions is unknown.

**OBJECTIVE:** To quantify the relationship between early measures of weight and glucose and subsequent diabetes in patients undergoing diabetes prevention interventions.

**DESIGN:** Analysis of results from a randomized controlled trial in 27 academic medical centers in the United States.

**PARTICIPANTS/INTERVENTIONS:** 3,041 adults with hyperglycemia randomized to lifestyle ( $n=1,018$ ), metformin ( $n=1,036$ ), or placebo ( $n=987$ ) with complete follow-up in The Diabetes Prevention Program.

**MAIN MEASURES:** Independent variables were weight loss at 6 and 12 months; fasting glucose (FG) at 6 months; hemoglobin A1c (HbA1c) at 6 months; and post-load glucose at 12 months. The main outcome was time to diabetes diagnosis.

**KEY RESULTS:** After 6 months, 604 participants developed diabetes in the lifestyle ( $n=140$ ), metformin ( $n=206$ ), and placebo ( $n=258$ ) arms over 2.7 years. In the lifestyle arm, 6-month weight loss predicted decreased diabetes risk in a graded fashion: adjusted HR (95% CI) 0.65 (0.35–1.22), 0.62 (0.33–1.18), 0.46 (0.24–0.87), 0.34 (0.18–0.64), and 0.15 (0.07–0.30) for 0–<3%, 3–<5%, 5–<7%, 7–<10%, and  $\geq 10\%$  weight loss, respectively (reference: weight gain). Attainment of optimal 6-month FG and HbA1c and 12-month post-load glucose predicted >60% lower diabetes risk across arms. We found a significant

interaction between 6-month weight loss and FG in the lifestyle arm ( $P=0.038$ ).

**CONCLUSION:** Weight and glucose at 6 and 12 months strongly predict lower subsequent diabetes risk with a lifestyle intervention; lower FG predicts lower risk even with substantial weight loss. Early reduction in glycemia is a stronger predictor of future diabetes risk than weight loss for metformin. We offer the first evidence to guide clinicians in making interval management decisions for high-risk patients undertaking measures to prevent diabetes.

**KEY WORDS:** diabetes prevention; diabetes risk; type 2 diabetes.

J Gen Intern Med 28(12):1629–36

DOI: 10.1007/s11606-013-2548-4

© Society of General Internal Medicine 2013

## INTRODUCTION

The Diabetes Prevention Program (DPP) demonstrated that lifestyle modification and metformin decrease diabetes risk, by 58% and 31%, respectively, relative to control over 3.2 years and by 34% and 18%, respectively, at 10 years of follow-up.<sup>1,2</sup> Prior research in the DPP established that weight loss (more than physical activity) mediates the beneficial effects of lifestyle change,<sup>3</sup> and that both weight loss and reduced glycemia mediate the beneficial effects of metformin.<sup>4</sup> These analyses indicate the contribution of average weight loss over a 3-year period to the success of the trial's interventions. However, clinicians see their patients at high risk of diabetes at least yearly, if not more frequently. Our current analysis builds on the previous ones to identify intermediary markers of success with regards to weight and glucose parameters for the prevention or delay of diabetes over a 3-year period.

---

Clinical Trials Registration: NCT00004992

**Electronic supplementary material** The online version of this article (doi:10.1007/s11606-013-2548-4) contains supplementary material, which is available to authorized users.

Received February 22, 2013

Revised May 13, 2013

Accepted June 24, 2013

Published online July 17, 2013

The American Diabetes Association recommends that clinicians refer patients with impaired glucose tolerance, impaired fasting glucose, or a hemoglobin A1c (HbA1c) of 5.7 % to 6.4 % for lifestyle interventions aimed at 7 % weight loss and 150 min per week of moderate physical activity.<sup>5</sup> Metformin is recommended for very high-risk patients.<sup>5</sup> To date, evidence is lacking on how to evaluate the response to diabetes prevention interventions, which high-risk patients should be considered candidates for metformin, and at what point a given intervention should be intensified.

We analyzed data from the DPP with the following aims: 1) To quantify the association between early changes in body weight, fasting glucose, HbA1c (first 6 months), and post-load glucose (first 12 months) and the subsequent risk of diabetes at 3 years; and 2) To identify joint patterns of weight loss and glycemic reduction that indicate that diabetes risk has been minimized. We hypothesized that greater reductions in weight and glycemic markers after 6 and 12 months of intervention would be associated with lower diabetes risk at 3 years and could help guide physicians and patients in their diabetes prevention efforts.

## METHODS

The DPP was a multi-center, randomized, placebo-controlled trial that compared the effect of two active interventions (intensive lifestyle modification or metformin) to a placebo medication condition combined with standard lifestyle recommendations on diabetes risk.<sup>1</sup> Recruitment of overweight participants in the United States with both impaired glucose tolerance and elevated fasting glucose occurred between 1996 and 1999, and mean follow-up was 3.2 years.<sup>1</sup> The methods and main results of the DPP were published previously.<sup>1</sup> The current study evaluates the relationship between early ( $\leq 12$  months) measures of weight and glucose homeostasis and 3-year diabetes risk in the DPP.

### Setting and Participants

We included participants randomized to the intensive lifestyle modification, metformin, or placebo arm without incident diabetes at the follow-up time point of interest. For analyses of weight, fasting glucose, and HbA1c at 6 months, we excluded participants with incident diabetes at 6 months; for the analysis of glucose tolerance at 12 months, we excluded participants with incident diabetes at 12 months. Participants missing data on variables of interest were excluded. Final sample size was 3,041 for 6-month analyses and 2,853 for 12-month analyses (Fig. 1).

### Randomization and Interventions

Randomization was adaptive and stratified by site.<sup>6</sup> Investigators and participants were masked to metformin and placebo, but not the lifestyle intervention.<sup>1</sup>

The goals of the intensive lifestyle intervention were  $\geq 7$  % weight loss and  $\geq 150$  min/week of moderate-intensity physical activity.<sup>1</sup>

Metformin was started at 850 mg by mouth once daily and increased to twice daily, and control arm participants took a placebo twice daily.<sup>1</sup> Participants in the metformin and placebo arms received standard lifestyle recommendations at brief annual in-person sessions.<sup>1</sup>

Fasting glucose (FG) and weight were measured every 6 months in the DPP.<sup>1</sup> Hemoglobin A1c was measured at 6 months and then annually.<sup>1</sup> Oral glucose tolerance tests were performed annually and consisted of administration of a 75-g glucose load orally after a 12-h fast.<sup>1</sup> The glucose measured 2 h after the oral glucose load is the measure of glucose tolerance that we term the “post-load glucose.” Weight was measured in duplicate by trained, certified staff using a balance scale and a standardized protocol.

Participants self reported age, sex, race/ethnicity (Caucasian, African American, Hispanic, Asian, and American Indian), education ( $\leq 12$  years, 13–16 years,  $\geq 17$  years), and annual household income ( $< \$50,000$  and  $\geq \$50,000$ ) at the baseline visit.<sup>1</sup>

The primary outcome of the DPP and the current study was time to new diagnosis of diabetes defined by a FG  $\geq 126$  mg/dL or post-load glucose  $\geq 200$  mg/dL, with confirmation by a second test.<sup>1</sup> Investigators, participants, and their physicians were informed of results if a diagnosis of diabetes was made.<sup>1</sup>

Participants provided informed consent, and the study protocol was approved by the Institutional Review Board at each site. The funding source did not have a role in this sub-analysis of the DPP.

### Statistical Analysis

We compared baseline characteristics and differences in glucose, percent weight change, and hemoglobin A1c using Wilcoxon rank sum tests for continuous measures and chi-square tests for categorical measures.

We used separate Cox proportional hazard models to estimate hazard ratios for time to diabetes for four independent variables: Percent weight change at 6 months, FG at 6 months, HbA1c at 6 months, and post-load glucose at 12 months. These were modeled continuously and categorically. We defined clinically-relevant categories based on current and past recommendations<sup>5,7,8</sup>: percent weight loss,  $< 0$  % or weight gain (reference), 0 to  $< 3$  %, 3 to  $< 5$  %, 5 to  $< 7$  %, 7 to  $< 10$  %, and  $\geq 10$  %; fasting glucose,  $\geq 110$  mg/dL (reference), 100 to  $< 110$  mg/dL, and  $< 100$  mg/dL; hemoglobin A1c,  $\geq 6.5$  % (reference), 5.7 to 6.4 %, and  $< 5.7$  %; and post-load glucose,  $\geq 140$  mg/dL (reference) and  $< 140$  mg/dL. We performed global tests for interactions between these independent variables (treated as continuous variables) and treatment arm, and then stratified analyses by arm if  $P$  for interaction between the independent variables and treatment arms was  $< 0.05$ . When the proportional hazards assumption

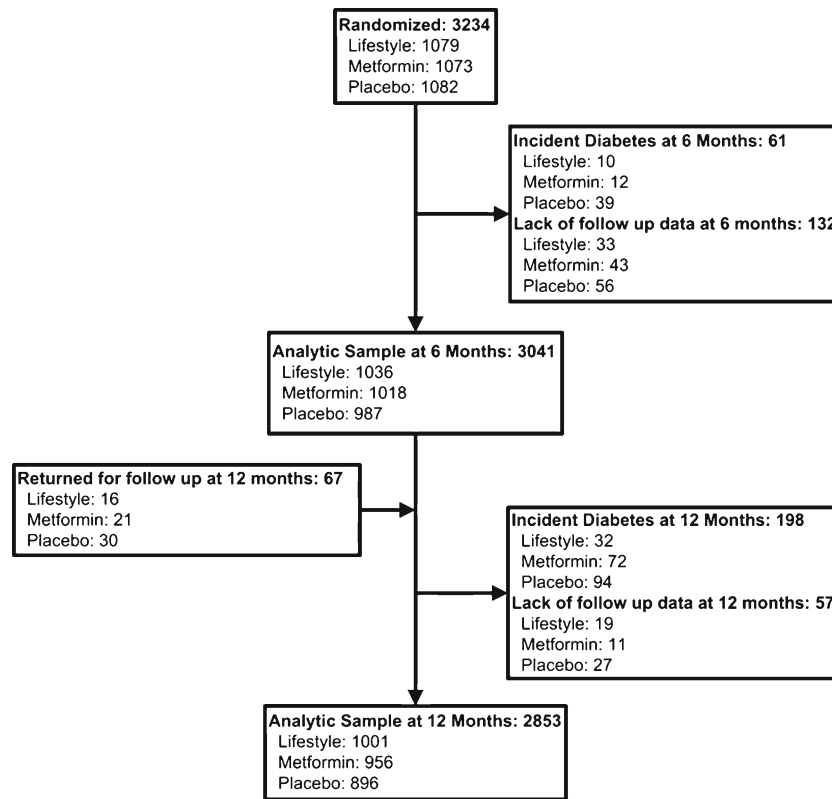


Figure 1. Selection of study participants.

was violated, we adjusted the covariance matrix using Lin and Wei’s robust sandwich estimates.<sup>9</sup> We adjusted Cox proportional hazards models for age, sex, race/ethnicity, education, income, and the baseline measure of the independent variable. When models were not stratified by treatment arm, we included treatment arm as a covariate. The starting time point for each model was as follows: 6 months for analyses of 6-month weight change, fasting glucose, and HbA1c and 12 months for analyses of post-load glucose.

We also calculated crude incidence rates of diabetes by percentage of weight change and glucose categories and used unadjusted Poisson regression to assess the statistical significance of interactions between percent weight change and glucose homeostasis.

We performed all analyses with SAS, version 9.2 (Cary, North Carolina).

## RESULTS

Baseline characteristics of the 3,041 study participants were similar in the three treatment arms (Table 1). Compared to the 193 participants excluded because of diabetes at 6 months or lack of follow-up data, the included participants were on average older; more likely to be Caucasian and less likely to be

African American or Hispanic; and mean HbA1c, FG, and weight were lower (Online Appendix Table 1).

### Short-Term Weight Loss, Fasting Glucose, and Post-Load Glucose

Mean percent weight loss at 6 months was 7.2 %, 2.4 %, and 0.4 % in the lifestyle, metformin and placebo arms, respectively (Table 2). Almost all (92 %) participants in the lifestyle arm lost weight at 6 months, while >25 % of participants in the metformin arm and nearly 50 % of those in the placebo arm gained weight at 6 months. Six-month FG and HbA1c were similar across arms, and 12-month post-load glucose was significantly lower in the lifestyle compared to metformin and placebo arms (Table 2).

### Relationship Between Short-Term Weight Loss and Glucose Measures and Diabetes Risk

After the 6-month visit, 604 participants ( $n=140, 206, \text{ and } 258$  in the lifestyle, metformin, and placebo arms, respectively) developed diabetes over the course of the study (mean follow-up 2.7 years). Diabetes risk decreased by 10 % for each percentage point of weight loss at 6 months in the lifestyle arm (HR, 0.90 (95 % CI, 0.87 to 0.94)) independent of FG or HbA1c achieved. This graded benefit of 6-month weight loss

**Table 1. Baseline Characteristics of Diabetes Prevention Program Participants Without Diabetes at 6 Months (Participants Without Complete Data Excluded from Analysis) (N=3,041)**

	Lifestyle arm	Metformin arm	Placebo arm
N	1,036	1,018	987
Age, median [IQR], y	50 [42, 59]	51 [44, 57]	50 [44, 57]
Sex, %			
Women	69	66	69
Race, %			
Caucasian	54	56	55
African American	18	20	20
Hispanic	16	15	15
Asian	6	3	5
American Indian	6	5	6
HbA1c, median [IQR], % <sup>†</sup>	5.9 [5.6, 6.2]	5.9 [5.6, 6.2]	5.9 [5.6, 6.2]
<5.7	29	30	29
5.7 to <6.5	59	57	58
≥6.5	12	13	12
Fasting glucose, median [IQR], mg/dL	105 [100, 111]	105 [100, 112]	105 [100, 111]
<100	20	21	21
100 to <110	49	46	48
≥110	31	33	31
Post-load glucose, median [IQR], mg/dL <sup>†</sup>	162 [150, 177]	163 [150, 179]	162 [149, 177]
Weight, median [IQR], kg	91 [79, 105]	91 [80, 105]	91 [79, 105]
Education, %			
≤12 years	26	25	27
>12 years	74	75	73
Household income, % <sup>§</sup>			
<\$50,000	56	53	52
≥\$50,000	44	47	48

IQR 25th percentile, 75th percentile; HbA1c hemoglobin A1c

\*HbA1c results available for 3,034 participants

<sup>†</sup>Glucose level 2 h after administration of 75 g of an oral glucose load

<sup>§</sup>2,802 (92 %) of participants provided income information

persisted over the course of the study (Fig. 2). Weight loss also predicted lower diabetes risk in the placebo [HR, 0.95 (95 % CI, 0.92 to 0.98)], but not metformin arm [HR, 0.98 (95 % CI, 0.94 to 1.02)] (*P* interaction between treatment arms and weight loss=0.0051; Fig. 2).

Lower 6-month FG and HbA1c and post-load glucose at 12 months were associated with similar, substantial graded reductions in diabetes risk across arms (Table 3). In the lifestyle and placebo arms, these glycemic measures predicted diabetes risk independent of weight loss. Six-month HbA1c and 12-month post-load glucose predicted diabetes risk independent of weight loss in the metformin arm.

### Interactions Between Short-Term Weight Loss and Glucose Measures

In the lifestyle arm, attainment of FG <100 mg/dl at 6 months predicted a similar diabetes risk reduction across 6-month weight loss categories, whereas diabetes risk decreased with increasing weight loss in those with FG ≥110 mg/dl at 6 months (Fig. 3, *P* interaction from Poisson regression=0.038). Diabetes risk was similar for those with the combination of ≥10 % weight loss and FG ≥110 mg/dL at 6 months (4.3, 95 % CI 1.5 to 12.4

cases/100 person-years) and those with a combination of weight gain and fasting glucose <100 mg/dL at 6 months (3.4, 95 % CI 1.1 to 10.3 cases/100 person-years) (Fig. 3). Poisson models did not reveal significant interactions between 6-month FG and weight loss in the metformin or placebo arm or a significant interaction between 6-month HbA1c and weight loss or 12-month post-load glucose and weight loss in any arm.

## DISCUSSION

In a population at high risk for type 2 diabetes undergoing intensive lifestyle change, 6-month weight loss predicted lower 3-year diabetes risk in a graded fashion; compared with weight gain, ≥10 % weight loss at 6 months was associated with an 85 % reduction in diabetes incidence at 3-year follow-up, and early weight loss was especially important in reducing diabetes risk among those with FG ≥110 mg/dl at 6 months. The effect of ≥10 % weight loss at 6 months was not significant in the metformin and placebo arms. Results for glucose and HbA1c were similar across treatment arms (lifestyle, metformin, and placebo); compared with higher values, achievement of fasting glucose <100 mg/dl or HbA1c <5.7 % at 6 months or 12-month post-load glucose <140 mg/dl was associated with a 62 to 70 % diabetes risk reduction.

Several points deserve mention regarding the interpretation of our findings. Few participants receiving metformin lost >7 % of their baseline weight at 6 months with many gaining weight, and more than 80 % of participants in the placebo arm either gained weight or lost little weight at 6 months. This relative difference in weight loss across the arms likely explains the clear graded benefit of weight loss observed in the lifestyle arm compared to that in the metformin and placebo arms, especially since early weight loss in this lifestyle arm predicted maintenance of weight loss over the course of the study.<sup>10</sup> Also, we did not find a statistically significant diabetes risk reduction for participants with less than 5 % weight loss at 6 months in the lifestyle arm although HRs were suggestive of a benefit; this lack of statistical significance is likely related to the small samples for the 0–<3 % and 3–<5 % weight loss categories in that arm. Therefore, it is likely that 6-month weight loss of any amount is beneficial. Additionally, participants in the lifestyle arm had much more in-person contact with case managers which generally improves the effect of lifestyle interventions.<sup>11,12</sup> Participants experiencing substantial weight loss in the lifestyle arm despite a high FG at 6 months may have been more successful in continuing lifestyle modification and eventually reducing diabetes risk as suggested by prior analysis of the DPP<sup>10</sup>; this may partly explain the interaction between weight loss and fasting glucose at 6 months in predicting diabetes risk. Another important consideration when comparing the three arms is that attainment of the physical activity and dietary goals at

**Table 2. Body Weight, Fasting Glucose, and HbA1c at 6 Months and Post-Load Glucose at 12 Months Following Randomization in the Diabetes Prevention Program (Participants Without Complete Data Excluded from Analysis)**

	Lifestyle arm	Metformin arm	Placebo arm
Weight loss at 6 months			
N	1,031	1,012	981
Median [IQR] weight loss, % <sup>†</sup>	7.2 [3.7, 10.5]	2.0 [-0.1, 4.7]	0.0 [-1.9, 2.3]
Category of weight loss <sup>†</sup>			
<0 %, N (%)	79 (8)	264 (26)	481 (49)
0 to <3 %, N (%)	144 (14)	342 (34)	310 (32)
3 to <5 %, N (%)	137 (13)	179 (18)	88 (9)
5 to <7 %, N (%)	146 (14)	100 (10)	45 (5)
7 to <10 %, N (%)	232 (23)	80 (8)	33 (3)
≥10 %, N (%)	293 (28)	47 (5)	24 (2)
Fasting glucose at 6 months			
N	1,035	1,017	984
Fasting glucose, median [IQR] mg/dL <sup>b</sup>	101 [95, 107]	101 [95, 108]	104 [98, 112]
Category of fasting glucose <sup>†</sup>			
≥110 mg/dL, N (%)	184 (18)	211 (21)	333 (34)
100 to <110 mg/dL, N (%)	396 (38)	362 (36)	363 (37)
<100 mg/dL, N (%)	455 (44)	444 (44)	288 (29)
HbA1c at 6 months			
N	1,031	1,012	980
HbA1c, median [IQR], % <sup>†</sup>	5.8 [5.5, 6.1]	5.8 [5.6, 6.1]	5.9 [5.6, 6.3]
Category of HbA1c			
≥6.5 %, N (%)	75 (7)	87 (9)	154 (16)
5.7 to 6.4 %, N (%)	497 (48)	502 (50)	487 (50)
<5.7 %, N (%)	459 (45)	423 (42)	339 (35)
Post-load glucose at 12 months			
N	1,001	956	896
Post-load glucose, median [IQR], mg/dL <sup>†,‡</sup>	137 [114, 160]	153 [127, 176]	150 [128, 174]
Category of post-load glucose <sup>b,c</sup>			
≥140 mg/dL, N (%)	449 (46)	575 (63)	574 (64)
<140 mg/dL, N (%)	520 (54)	336 (37)	320 (36)

IQR 25th percentile, 75th percentile; HbA1c hemoglobin A1c

<sup>a</sup>*P* < 0.0001 comparing lifestyle, metformin, and placebo arms using Wilcoxon rank sum tests to compare medians and chi square tests to compare proportions

<sup>†</sup>Glucose level 2 h after administration of 75 g of an oral glucose load

12 months by participants in the lifestyle arm decreased diabetes risk over the course of the study even in the absence of attainment of the weight goal.<sup>3</sup>

A major strength of our analysis is that the DPP was a well-conducted randomized trial with high overall follow-up (92.5 %) and standardized measurement of all variables reducing measurement error and enhancing internal validity.<sup>1</sup> The study population was diverse by race/ethnicity and age making our results generalizable to the U.S. population at risk for type 2 diabetes. Also, the DPP assessed weight, fasting glucose, and HbA1c at 6 months to evaluate success of the interventions, a practice that can be readily assimilated in clinical practice.

While the glucose measures collected at 6 and 12 months are part of the case definition of diabetes and are therefore expected to predict diabetes risk, these measures are recommended in clinical practice to screen for diabetes.<sup>5,7</sup> Thus, quantifying the association between these measures and longer-term risk of diabetes is paramount in understanding the impact of preventive efforts. The lifestyle participants enrolled in the DPP maintained substantial weight loss over 10 years, as demonstrated in the DPP-Outcomes Study,<sup>2</sup> which may be more difficult for patients in clinical practice. At the time of their most recent visit prior to the end of the DPP (mean follow-up 2.8 years), 38 % percent and 58 % of lifestyle

participants had achieved the intervention weight loss and physical activity goals, respectively,<sup>1</sup> and 72 % of those in the metformin arm took ≥80 % of the medication during the DPP.<sup>1</sup> We conducted an intention-to-treat analysis and did not exclude participants based on adherence. This approach should reflect the clinical effectiveness of these interventions in practice.

Previous work in the Diabetes Prevention Program showed a graded benefit of weight loss averaged over the approximately 3 years of total follow-up in reducing diabetes risk in the lifestyle, metformin, and placebo arms.<sup>3,4</sup> Lachin et al. demonstrated that change in fasting glucose over the study duration was the strongest predictor of diabetes risk in the metformin and placebo arms, accounting for 14 % and 25 % of the decrease in risk over the course of the study in these two arms, respectively.<sup>4</sup> Among participants who had both impaired fasting glucose and impaired glucose tolerance at baseline, each standard deviation of mean weight loss was associated with a 34 % increased probability of regression to normal glucose regulation.<sup>13</sup> We now extend our understanding of these benefits by quantifying the predictive value of weight, glucose and HbA1c during the first 12 months of a preventive effort, and thereby inform approaches to intensifying preventive therapies in clinical practice.

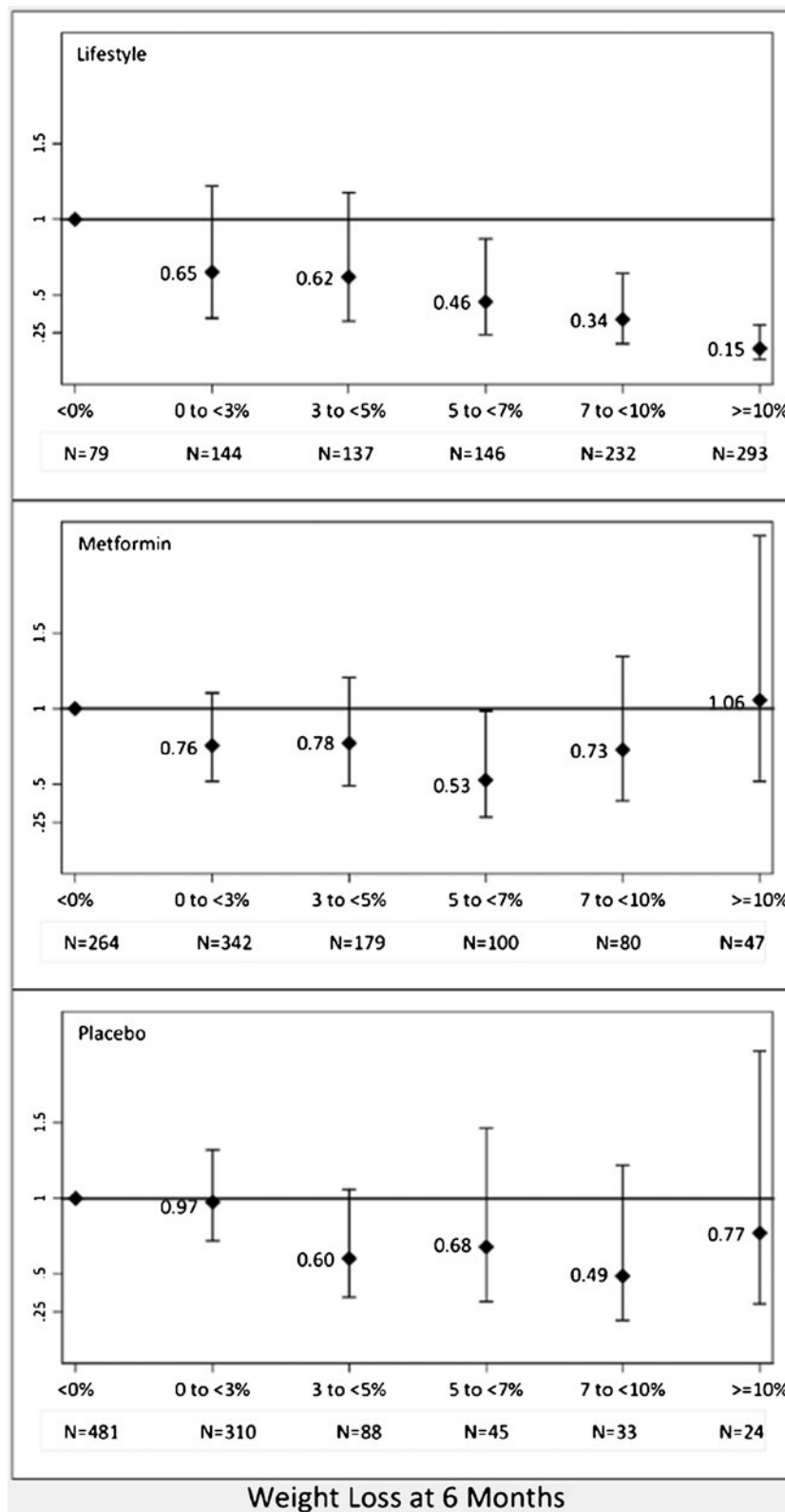


Figure 2. Diabetes risk in the Diabetes Prevention Program in each treatment arm by percent weight loss at achieved at 6 months. Hazard ratios for diabetes after 6 months in the Diabetes Prevention Program (mean follow-up 2.7 years) adjusted for the following: Age, sex, race/ethnicity, education, income, and baseline weight. Each category of percentage of weight loss achieved at 6 months is compared to the reference group consisting of participants who gained weight (weight loss <0 %) at the 6-month visit. Participants with incident diabetes at the 6-month follow-up visit are excluded.

**Table 3. Hazard Ratios (95 % CI) for Diabetes by Fasting Glucose or HbA1c Achieved at 6 Months or Post-Load Glucose Achieved at 12 Months Following Randomization (Mean Follow-Up for Analyses at 6 Months, 2.7 Years and Mean Follow-Up for Analyses at 12 months, 2.2 years) Across Arms [Results are Not Stratified by Treatment Arm Because the Association Between Glucose Measures and Diabetes Risk Did Not Vary Significantly by Treatment Arm (P for Global Test of Interaction 0.75 for Fasting Glucose, 0.42 for HbA1c, and 0.91 for Post-Load Glucose)] in the Diabetes Prevention Program**

	HR (95 % CI) for diabetes risk <sup>*</sup>
Per 5 mg/dL decrement of fasting glucose at 6 months	0.74 (0.70, 0.79)
Category of fasting glucose at 6 months	
<100 mg/dL	0.31 (0.24, 0.40)
100 to <110 mg/dL	0.37 (0.29, 0.46)
≥110 mg/dL	1.0
Per 0.5 % decrement of HbA1c at 6 months	0.58 (0.48,0.69)
Category of HbA1c at 6 months	
<5.7 %	0.38 (0.25, 0.57)
5.7 to 6.4 %	0.50 (0.38, 0.66)
≥6.5 %	1.0
Per 5 mg/dL decrement of post-load glucose at 12 months <sup>§</sup>	0.90 (0.88–0.92)
Category of post-load glucose at 12 months	
<140 mg/dL	0.30 (0.22, 0.40)
≥140 mg/dL	1.0

HbA1c hemoglobin A1c

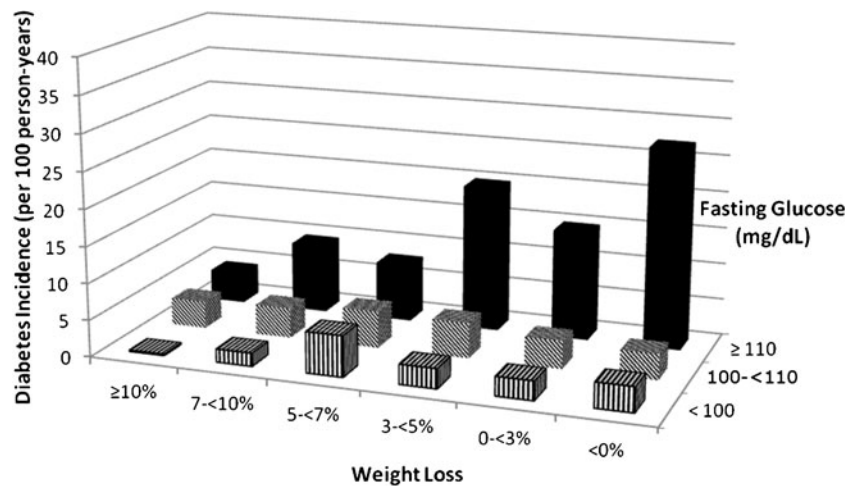
<sup>\*</sup>All hazard ratios are adjusted for treatment arm, age, sex, race/ethnicity, education, household income, and the baseline measure of the independent variable

<sup>§</sup>Glucose level 2 h after administration of 75 g of an oral glucose load

Current guidelines for diabetes prevention recommend weight loss and physical activity for at-risk patients and consideration of metformin for those at highest risk, but offer minimal guidance

on escalation of preventive therapy.<sup>5</sup> Our results suggest that both the weight loss and glycemic status achieved at 6 months are indicators of long-term success in diabetes prevention. Extrapolating to the clinic setting, these factors may be considered at 6 months to determine efficacy of the intervention. For example, our analyses suggest that individuals who achieve modest weight loss alone (e.g., 3–5 %) with intensive lifestyle intervention, but whose fasting glucose levels remain greater than 100 mg/dl at 6 months, would still be at increased risk of conversion to diabetes (Fig. 3), and addition of metformin may be considered. On the other hand, patients attaining ≥10 % weight loss and fasting glucose <100 mg/dl at 6 months have likely decreased their risk substantially (Fig. 3), and could be reassured about their preventive efforts. There is need for further study of the appropriate time points for and methods of escalation of therapy, and our analyses provide the data to support the design of such studies.

Evidence on type 2 diabetes prevention strategies is extensive,<sup>1,14–16</sup> and currently, clinicians in the United States seeking to help patients reduce their diabetes risk recommend lifestyle change and monitor weight, fasting glucose, and/or HbA1c levels periodically. Among persons undergoing lifestyle change, we show that greater weight loss at 6 months predicts decreased 3-year diabetes risk in a graded fashion and that achievement of fasting glucose <100 mg/dl at 6 months is beneficial regardless of weight loss. Glucose measures are the strongest indicators of successfully reduced diabetes risk with metformin. Our study offers the first evidence to guide clinicians in making interval management decisions for patients at high risk for diabetes undertaking preventive measures.



**Figure 3. Diabetes incidence during the Diabetes Prevention Program in each treatment arm by weight loss and fasting glucose achieved at 6 months. Crude diabetes incidence rates over the course of the Diabetes Prevention Program by weight loss and fasting glucose achieved at 6 months (mean follow-up 2.7 years). Test for interaction between weight loss and fasting glucose at 6 months from Poisson regression model: P=0.038 (lifestyle), P=0.586 (metformin), and P=0.285 (placebo). Participants with incident diabetes at the 6-month follow-up visit are excluded.**

**Acknowledgements:** The Investigators gratefully acknowledge the commitment and dedication of the participants of the DPP. The NIDDK of the NIH provided funding to the clinical centers and the Coordinating Center for the design and conduct of the study and collection, management, analysis, and interpretation of the data. The Southwestern American Indian Centers were supported directly by the NIDDK and the Indian Health Service. The General Clinical Research Center Program, National Center for Research Resources supported data collection at many of the clinical centers. Funding for data collection and participant support was also provided by the Office of Research on Minority Health, the National Institute of Child Health and Human Development, the National Institute on Aging, the Centers for Disease Control and Prevention, the Office of Research on Women's Health, and the American Diabetes Association. Bristol-Myers Squibb and Parke-Davis provided medication. This research was also supported, in part, by the intramural research program of the NIDDK. LifeScan Inc., Health O Meter, Hoechst Marion Roussel, Inc., Merck-Medco Managed Care, Inc., Merck and Co., Nike Sports Marketing, Slim Fast Foods Co., and Quaker Oats Co. donated materials, equipment, or medicines for concomitant conditions. McKesson BioServices Corp., Matthews Media Group, Inc., and the Henry M. Jackson Foundation provided support services under subcontract with the Coordinating Center. The opinions expressed are those of the investigators and do not necessarily reflect the views of the Indian Health Service or other funding agencies. See the [Online Appendix](#) for a complete list of Centers, investigators, and staff.

The authors dedicate this article to Dr. Frederick L. Brancati, the originator of the study question, who passed away on May 14, 2013. The authors are grateful to Dr. Christopher D. Saudek for his contribution to this study, as well as his contribution to the conduct of the DPP

**Funding:** Dr. Maruthur was supported by NIH/NCCR grant 1KL2RR025006-01.

**Author Contributions:** Development/refinement of objectives (NMM, FLB, JMC); study design (NMM, YM, LMD, JAN, VA, DM, FLB, JMC); data collection (LMD, JAN, VA, NHW, DM, FLB, JMC); analysis (YM); interpretation of results (NMM, YM, LMD, JAN, VA, DM, FLB, JMC); drafting of manuscript (NMM); critical review/revision of manuscript (NMM, YM, LMD, JAN, VA, NHW, DM, FLB, JMC). YM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentations:** None.

**Conflict of Interest:** LD has a financial interest in Omada Health, a company that develops online behavior-change programs, with a focus on diabetes. LD's interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies. The authors declare that they do not have a conflict of interest.

**Corresponding Author:** Nisa M. Maruthur, MD, MHS; c/o The Diabetes Prevention Program Coordinating Center, Biostatistics Center, George Washington University, 6110 Executive Blvd., Suite 750, Rockville, MD 20852, USA (e-mail: dppmail@biostat.bsc.gwu.edu).

## REFERENCES

1. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346(6):393-403.
2. Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet.* 2009;374(9702):1677-86. Epub 2009/11/03.
3. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care.* 2006;29(9):2102-7. Epub 2006/08/29.
4. Lachin JM, Christophi CA, Edelstein SL, et al. Factors associated with diabetes onset during metformin versus placebo therapy in the Diabetes Prevention Program. *Diabetes.* 2007;56(4):1153-9. Epub 2007/03/31.
5. Standards of medical care in diabetes—2012. *Diabetes Care.* 2012;35(Suppl 1):S11-63. Epub 2012/01/04.
6. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care.* 1999;22(4):623-34. Epub 1999/04/06.
7. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care.* 2011;34(Supplement 1):S11-61.
8. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care.* 1997;20(7):1183-97. Epub 1997/07/01.
9. Lin D, Wei L. The robust inference for the cox proportional hazards model. *J Am Stat Assoc.* 1989;1074-78.
10. Wing RR, Hamman RF, Bray GA, et al. Achieving weight and activity goals among Diabetes Prevention Program lifestyle participants. *Obes Res.* 2004;12(9):1426-34. Epub 2004/10/16.
11. Svetkey LP, Stevens VJ, Brantley PJ, et al. Comparison of strategies for sustaining weight loss: the weight loss maintenance randomized controlled trial. *JAMA.* 2008;299(10):1139-48.
12. Sarwer DB, von Sydow Green A, Vetter ML, Wadden TA. Behavior therapy for obesity: where are we now? *Curr Opin Endocrinol Diabetes Obes.* 2009;16(5):347-52. Epub 2009/07/23.
13. Perreault L, Kahn SE, Christophi CA, Knowler WC, Hamman RF. Regression from pre-diabetes to normal glucose regulation in the Diabetes Prevention Program. *Diabetes Care.* 2009;32(9):1583-8. Epub 2009/07/10.
14. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med.* 2001;344(18):1343-50.
15. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care.* 1997;20(Journal Article):537-44.
16. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia.* 2006;49(2):289-97. Epub 2006/01/05.