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# Impact of Lifestyle and Metformin Interventions on the Risk of Progression to Diabetes and Regression to Normal Glucose Regulation in Overweight or Obese People With Impaired Glucose Regulation

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## OBJECTIVE

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Both lifestyle and metformin interventions can delay or prevent progression to type 2 diabetes mellitus (DM) in people with impaired glucose regulation, but there is considerable interindividual variation in the likelihood of receiving benefit. Understanding an individual's 3-year risk of progressing to DM and regressing to normal glucose regulation (NGR) might facilitate benefit-based tailored treatment.

## RESEARCH DESIGN AND METHODS

We used the values of 19 clinical variables measured at the Diabetes Prevention Program (DPP) baseline evaluation and Cox proportional hazards models to assess the 3-year risk of progression to DM and regression to NGR separately for DPP lifestyle, metformin, and placebo participants who were adherent to the interventions. Lifestyle participants who lost  $\geq 5\%$  of their initial body weight at 6 months and metformin and placebo participants who reported taking  $\geq 80\%$  of their prescribed medication at the 6-month follow-up were defined as adherent.

## RESULTS

Eleven of 19 clinical variables measured at baseline predicted progression to DM, and 6 of 19 predicted regression to NGR. Compared with adherent placebo participants at lowest risk of developing diabetes, participants at lowest risk of developing diabetes who adhered to a lifestyle intervention had an 8% absolute risk reduction (ARR) of developing diabetes and a 35% greater absolute likelihood of reverting to NGR. Participants at lowest risk of developing diabetes who adhered to a metformin intervention had no reduction in their risk of developing diabetes and a 17% greater absolute likelihood of reverting to NGR. Participants at highest risk of developing DM who adhered to a lifestyle intervention had a 39% ARR of developing diabetes and a 24% greater absolute likelihood of reverting to NGR, whereas those who adhered to the metformin intervention had a 25% ARR of developing diabetes and an 11% greater absolute likelihood of reverting to NGR.

## CONCLUSIONS

Unlike our previous analyses that sought to explain population risk, these analyses evaluate individual risk. The models can be used by overweight and obese adults with fasting hyperglycemia and impaired glucose tolerance to facilitate personalized decision making by allowing them to explicitly weigh the benefits and feasibility of the lifestyle and metformin interventions.

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\*A complete list of the DPP Research Group Investigators can be found in the Supplementary Data online.

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The Diabetes Prevention Program (DPP) demonstrated that over 3 years, intensive lifestyle intervention and metformin treatment reduced the incidence of diabetes mellitus (DM) in high-risk participants with impaired glucose regulation. In addition to reporting average benefit by randomized treatment group, the DPP reported treatment effectiveness by age, sex, race/ethnicity, baseline BMI, and baseline measures of glycemia. Lifestyle intervention was effective in all age groups, both sexes, all racial and ethnic groups, in overweight, obese, and severely obese participants, and in participants with lesser and greater degrees of fasting and postglucose load hyperglycemia (1). In contrast, metformin was more effective in participants <60 years of age, in those with BMI  $\geq 35$  kg/m<sup>2</sup>, and in those with greater degrees of fasting hyperglycemia than in those who were older, less obese, and who had fewer degrees of fasting hyperglycemia (1).

A better understanding of who is more likely to benefit from these effective interventions could inform individual treatment decisions and help make treatment more effective and cost-effective. Although ~100 risk models and scores for DM have been published (2), few have developed multivariable models to facilitate tailoring preventive interventions to individuals, and none has reported the impact of interventions on both progression to DM and regression to normal glucose regulation (NGR). Recently, Sussman et al. (3) described the use of prediction models to estimate a person's likelihood of benefit, describing this approach as "benefit-based tailored treatment." They subsequently argued that treatment decisions should be based on the best estimate of absolute risk reduction (ARR) considering all of the patient and treatment factors that determine an individual patient's chances of benefiting (4). An individual's ARR can be calculated as the difference between an individual's risk without treatment and the risk with treatment. These risks may vary substantially among individuals, even in seemingly homogeneous study populations (4). Although Sussman et al. (3) developed multivariable models to predict progression to DM for individuals in the DPP population with and without interventions, they assessed some variables not routinely assessed in clinical practice (such as waist circumference and waist-

to-hip ratio [5]), did not account for treatment adherence, and did not assess the possibility of regression to NGR (3).

The purpose of this paper was to use baseline data from the DPP to develop risk equations that use routinely assessed clinical variables and predict progression to DM and regression to NGR among individuals who adhere to the interventions. These equations can be used in clinical practice by patients >25 years of age who are overweight or obese and have fasting hyperglycemia and impaired glucose tolerance (IGT) to answer the question, "What will happen to me over 3 years if I adopt the DPP lifestyle intervention or metformin intervention or do nothing?" The answer should facilitate individual benefit-based tailored treatment and personalized decision making.

## RESEARCH DESIGN AND METHODS

### Study Population

The study population included overweight and obese adults with IGT and fasting hyperglycemia enrolled in the DPP, a randomized, controlled clinical trial comparing the impact of intensive lifestyle intervention, metformin, and

placebo on the development of DM over an average 3.2 years. Inclusion criteria included age  $\geq 25$  years, BMI  $\geq 24$  kg/m<sup>2</sup> ( $\geq 22$  kg/m<sup>2</sup> in Asian Americans), plasma glucose 2-h after a 75-g oral glucose load (2-h PG) of 140–199 mg/dL, and fasting PG (FPG) of 95–125 mg/dL (no lower limit in the American Indian centers). The DPP was conducted between 1996 and 2001 at 27 sites in the U.S. The design, rationale, and outcomes have been described in detail elsewhere (1,6).

### Candidate Predictor Variables

Nineteen routinely assessed clinical variables measured at DPP baseline and known to be associated with progression to DM or regression to NGR were selected as candidate predictor variables. These variables included sociodemographic characteristics (age, sex, race/ethnicity, education, and household income); health behaviors (smoking and self-reported physical activity assessed as minutes per week); selected medications (antihypertensive medications and statins); medical history (polycystic ovarian disease, pregnancy, and gestational DM [GDM]); family history of diabetes (DM in parents, siblings,

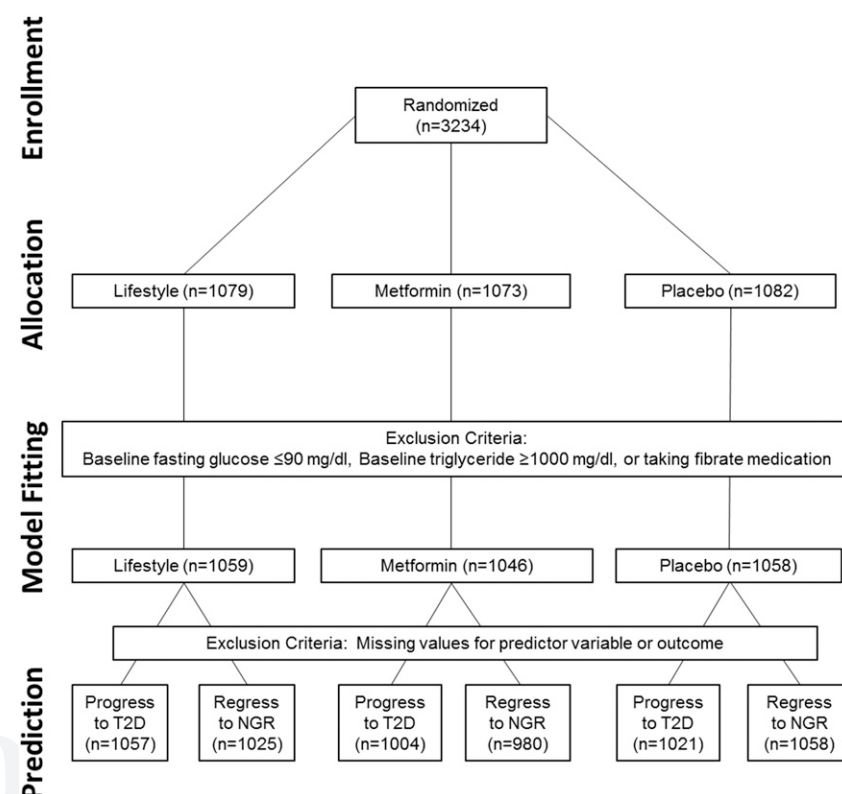


Figure 1—Consort diagram.

Table 1—Baseline characteristics of the DPP population by adherence status

	Lifestyle			Metformin			Placebo		
	Total (N = 1,059)	Adherent (N = 661 [62%])	Nonadherent (N = 398 [38%])	Total (N = 1,046)	Adherent (N = 713 [68%])	Nonadherent (N = 291 [32%])	Total (N = 1,058)	Adherent (N = 766 [72%])	Nonadherent (N = 238 [28%])
<b>Sociodemographic characteristics</b>									
Mean age $\pm$ SD (years)	50.6 $\pm$ 11.3	52.0 $\pm$ 11.4	48.4 $\pm$ 10.9	50.9 $\pm$ 10.3	51.3 $\pm$ 10.2	50.5 $\pm$ 10.4	50.3 $\pm$ 10.4	51.1 $\pm$ 10.4	50.5 $\pm$ 10.4
Sex [N (%)]									
Male sex [N (%)]	339	226 (34)	113 (28)	352	251 (35)	85 (29)	328	238 (31)	75 (32)
Female with no history of pregnancy	111	62 (9)	49 (12)	102	73 (10)	25 (9)	97	74 (10)	18 (8)
Female with history of pregnancy but no GDM	474	298 (45)	176 (44)	464	306 (43)	140 (48)	485	347 (45)	113 (47)
Female with history of pregnancy and GDM	104	57 (9)	47 (12)	103	65 (9)	35 (12)	111	77 (10)	26 (11)
Race/ethnicity [N (%)]									
White	576	401 (61)	175 (44)	589	429 (60)	142 (50)	575	445 (58)	102 (43)
African American	202	94 (14)	108 (27)	218	135 (19)	72 (25)	218	138 (18)	69 (29)
Hispanic	176	107 (16)	69 (17)	159	96 (13)	53 (18)	166	112 (15)	43 (18)
Asian	55	32 (5)	23 (6)	35	21 (3)	11 (4)	47	34 (4)	11 (5)
American Indian	50	27(4)	23 (6)	45	32 (4)	13 (4)	52	37 (5)	13 (5)
College graduate [N (%)]	490	318 (48)	172 (43)	490	358 (50)	113 (39)	489	359 (47)	108 (45)
Annual household income [N (%)]									
<\$30,000	144	88 (13)	56 (14)	134	77 (11)	51 (18)	156	105 (14)	39 (16)
\$30,000–\$50,000	405	244 (37)	161 (40)	377	263 (37)	97 (33)	396	290 (38)	86 (36)
>\$50,000	510	329 (50)	181 (45)	534	372 (52)	143 (49)	506	371 (48)	113 (47)
<b>Health behaviors [N (%)]</b>									
Current smoking	70	33 (5)	37 (9)	72	46 (6)	23 (8)	84	64 (8)	13 (5)
Physical activity									
>150 min/week	514	310 (47)	204 (51)	521	365 (51)	145 (50)	528	377 (49)	122 (51)
90–150 min/week	163	101 (15)	62 (16)	154	110 (15)	33 (11)	166	125 (16)	33 (15)
<90 min/week	380	248 (38)	132 (33)	371	238 (33)	113 (39)	364	264 (34)	83 (35)
<b>Past history and family history</b>									
Polycystic ovary disease (among women)	18	7 (1)	11 (3)	26	19 (3)	6 (2)	20	12 (2)	5 (2)
Family history of diabetes	739	448 (68)	291 (73)	719	494 (69)	198 (68)	738	529 (69)	172 (72)
<b>Medications</b>									
Antihypertensive medication	177	113 (17)	64 (16)	161	104 (15)	52 (18)	160	129 (17)	26 (11)
Statin	31	21 (3)	10 (3)	39	31 (4)	7 (2)	49	41 (5)	7 (3)
<b>Anthropometric measures (mean <math>\pm</math> SD)</b>									
Weight (kg)	94.3 $\pm$ 20.8	93.8 $\pm$ 20.8	95.1 $\pm$ 20.9	94.4 $\pm$ 19.8	94.5 $\pm$ 19.3	93.2 $\pm$ 19.1	94.5 $\pm$ 20.1	94.7 $\pm$ 20.1	93.8 $\pm$ 19.8

Continued on p. 4



and determined the magnitude of the deviation using the D'Agostino and Nam statistic (12). Nonsignificant *P* values from this test indicate good model fit. Finally, we used the decision-curve analysis of Vickers and Elkins (13) to identify the range of threshold probabilities in which the models had added value for predicting progression to DM and regression to NGR and the magnitude of benefit.

All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and R 3.0.0 (The R Foundation).

## RESULTS

The DPP randomized 3,234 participants: 1,079 to the lifestyle, 1,073 to the metformin, and 1,082 to the placebo intervention. A total of 71 participants (2%) with extreme values of baseline FPG (FPG  $\leq 90$  mg/dL) or TG (TG  $\geq 1,000$  mg/dL) or who were

taking fibrates for hypertriglyceridemia were excluded from the analyses (Fig. 1). Because of missing values for predictor variables and outcomes covariates, a few additional participants were excluded when we developed the prediction models. Figure 1 shows the data sets used for our analyses.

Table 1 shows the baseline characteristics of the study participants by DPP intervention group and adherence. Mean age was  $\sim 50$  years, approximately one-third of participants were men, and slightly more than half were white. Almost half of participants were college graduates. Approximately 7% of participants reported current smoking. At baseline, approximately half of participants reported engaging in  $>150$  min/week of moderate physical activity. Approximately 15% were taking medications for hypertension, and  $<5\%$  were taking

statins for hypercholesterolemia. Mean BMI was  $\sim 34$  kg/m<sup>2</sup>, and mean SBP was 124 mmHg. Mean FPG was 107 mg/dL, and median fasting TG was 141 mg/dL.

Sixty-two percent of lifestyle participants, 68% of metformin participants, and 72% of placebo participants were adherent to the interventions at 6 months (Table 1). In general, adherent participants were more likely to be older and of white race/ethnicity (Table 1). One hundred forty-one (14%) adherent lifestyle participants, 218 (21%) adherent metformin participants, and 296 (28%) adherent placebo participants developed DM. Four hundred twenty-three (40%) adherent lifestyle participants, 272 (26%) adherent metformin participants, and 214 (20%) adherent placebo participants regressed to NGR.

Table 2 shows the baseline predictor variables included in the final prediction

**Table 2—Multivariable models**

A: Multivariable models predicting progression to diabetes at 3 years

Predictors	Hazard ratio (95% CI)		
	Lifestyle	Metformin	Placebo
Age		1.016 (1.002, 1.029)	
Sex and GDM status			
Female with no history of pregnancy vs. male			0.745 (0.453, 1.225)
Female with history of pregnancy but no GDM vs. male			1.120 (0.847, 1.482)
Female with history of GDM vs. male			1.566 (1.080, 2.272)
College graduate vs. non-college graduate			1.322 (1.044, 1.673)
Current smoking: yes vs. no		1.590 (0.998, 2.531)	
Physical activity $>150$ min/week: yes vs. no	1.304 (0.935, 1.818)		
Polycystic ovarian disease: yes vs. no		1.920 (0.944, 3.905)	
Family history of diabetes: yes vs. no		1.311 (0.964, 1.783)	
BMI (kg/m <sup>2</sup> )	1.050 (1.028, 1.072)		1.019 (1.002, 1.035)
SBP (mmHg)			1.009 (1.000, 1.018)
Fasting glucose (mg/dL)	1.074 (1.054, 1.094)	1.057 (1.042, 1.073)	1.089 (1.075, 1.103)
Natural log-transformed TG (mg/dL)	1.506 (1.104, 2.053)	1.717 (1.305, 2.260)	1.279 (1.005, 1.627)
Adherence at 6 months: yes vs. no	0.366 (0.264, 0.507)	0.819 (0.614, 1.094)	1.243 (0.928, 1.665)

B: Multivariable models predicting regression to NGR at 3 years

Predictors	Hazard ratio (95% CI)		
	Lifestyle	Metformin	Placebo
Age	0.989 (0.981, 0.998)	0.984 (0.971, 0.996)	0.991 (0.978, 1.004)
Sex and GDM status			
Female with no history of pregnancy vs. male		0.610 (0.388, 0.960)	
Female with history of pregnancy but no GDM vs. male		0.771 (0.585, 1.016)	
Female with history of GDM vs. male		0.594 (0.370, 0.955)	
College graduates vs. non-college graduates		1.301 (1.010, 1.667)	
SBP (mmHg)		0.992 (0.983, 1.001)	
Fasting glucose (mg/dL)	0.950 (0.936, 0.963)	0.945 (0.928, 0.962)	0.919 (0.898, 0.940)
Natural log-transformed TG (mg/dL)	0.765 (0.634, 0.923)	0.733 (0.578, 0.929)	0.727 (0.550, 0.961)
Adherence at 6 months: yes vs. no	1.867 (1.496, 2.331)	1.093 (0.831, 1.438)	0.753 (0.556, 1.018)

Adherence is defined as losing 5% of initial body weight at 6 months in the lifestyle group or reporting taking pills  $\geq 80\%$  of the time in the metformin and placebo groups. For categorical variables, 1 = yes and 0 = no.



models for progression to DM and regression to NGR for participants in each of the three treatment groups. All participants, adherent and nonadherent, were used to estimate the coefficients for the models. The coefficients for adherence represent the conditional log hazard ratios for adherent versus nonadherent participants. To calculate the risk for an adherent participant, the coefficient for adherence is set to 1.

Eleven of the 19 variables assessed at baseline remained in any of the three models predicting progression to DM, with little overlap across intervention groups. Only FPG and TG entered all three models (Table 2A). In the lifestyle intervention group, greater physical activity (>150 min/week) at baseline (before lifestyle intervention was implemented), higher BMI, higher FPG, and higher TG predicted greater risk of progression to DM. The seemingly paradoxical finding that greater reported physical activity at baseline was associated with greater risk of progression to DM in the lifestyle intervention group may be explained by the observations that those participants increased the physical activity less and

lost less weight than participants who reported less physical activity at baseline. In the metformin intervention group, older age, smoking, history of polycystic ovarian disease, family history of diabetes, higher FPG, and higher TG predicted greater risk of progression to DM. In the placebo group, female sex and having a previous pregnancy with or without GDM, being a college graduate, and higher BMI, SBP, FPG, and TG predicted greater risk of progression to DM.

Table 2B shows the baseline predictor variables associated with regression to NGR. Only 6 of the 19 variables entered any of the 3 NGR prediction models, and only 3 of the 6 (younger age, lower FPG, and lower TG) were common to all 3 models. In both the lifestyle and placebo intervention groups, no other variables predicted regression to NGR, whereas in the metformin intervention group, regression to NGR was also associated with male sex, being a college graduate, and lower SBP.

The 3-year probability of progression to DM and regression to NGR for the three intervention groups was calculated using the equations presented in Table 3A

and B, respectively. The Harrell C-statistic was used to assess the discriminative ability of the models. The C-statistic indicates the proportion of all pairs of subjects that can be ordered such that the subject with the higher predicted risk is the one who experiences the outcome earlier. In other words, the C-statistic assesses the ability of the model to correctly distinguish those at higher risk from those at lower risk of progression or regression. Two of the three diabetes progression models had fair discrimination (Harrell C-statistic 0.753 for the lifestyle intervention model and 0.721 for the placebo intervention model). Discrimination of the diabetes progression model for the metformin intervention group was not as good (Harrell C-statistic: 0.652). When the outcome was regression to NGR, Harrell C-statistics were generally lower: 0.673 for the lifestyle model, 0.674 for the metformin model, and 0.681 for the placebo model.

Figures 2A and B show the calibration curves of the observed versus predicted probabilities of progression to DM and regression to NGR, respectively. A nonsignificant *P* value from the D'Agostino and Nam (12)  $\chi^2$  statistic indicates good fit of a

**Table 3—Equations**

A: Equation to calculate probability of progression to DM at 3 years

Equation	Probability (progression to DM) = $1 - S_0^{\exp(F(X))}$	
Treatment	$S_0$	F(X)
Lifestyle	0.824	$0.048 \times (\text{BMI} - 34) + 0.071 \times (\text{fasting glucose} - 107) + 0.409 \times (\log(\text{TG}) - 5) + 0.266 \times \text{PA} - 1.005 \times \text{Adherence}$
Metformin	0.821	$0.015 \times (\text{age} - 51) + 0.271 \times \text{FH} + 0.056 \times (\text{fasting glucose} - 107) + 0.541 \times (\log(\text{TG}) - 5) + 0.463 \times \text{SM} + 0.652 \times \text{Polycystic} - 0.199 \times \text{Adherence}$
Placebo	0.825	$-0.294 \times \text{FNP} + 0.114 \times \text{FP} + 0.449 \times \text{GDM} + 0.018 \times (\text{BMI} - 34) + 0.085 \times (\text{fasting glucose} - 107) + 0.009 \times (\text{SBP} - 124) + 0.246 \times (\log(\text{TG}) - 5) + 0.279 \times \text{CG} + 0.217 \times \text{Adherence}$

B: Equation to calculate probability of regression to NGR at 3 years

Formulas	Probability (progression to DM) = $1 - S_0^{\exp(F(X))}$	
Treatment	$S_0$	F(X)
Lifestyle	0.737	$-0.011 \times \text{Age} - 0.052 \times \text{fasting glucose} - 0.268 \times \log(\text{TG}) + 0.624 \times \text{Adherence}$
Metformin	0.729	$-0.017 \times \text{Age} - 0.494 \times \text{FNP} - 0.260 \times \text{FP} - 0.521 \times \text{GDM} - 0.056 \times \text{fasting glucose} - 0.008 \times \text{SBP} - 0.311 \times \log(\text{TG}) + 0.263 \times \text{CG} + 0.089 \times \text{Adherence}$
Placebo	0.775	$-0.009 \times \text{Age} - 0.085 \times \text{fasting glucose} - 0.319 \times \log(\text{TG}) - 0.284 \times \text{Adherence}$

CG, 1 if a subject is a college graduate, 0 otherwise; FH, 1 if a subject has family history of diabetes, 0 otherwise; FNP, 1 if a subject is female and has never been pregnant, 0 otherwise; FP, 1 if a subject is female and has been pregnant but no history of GDM, 0 otherwise; GDM, 1 if a subject is female and has had GDM, 0 otherwise; PA, 1 if physical activity >150 min/week, 0 otherwise; Polycystic, 1 if a subject is female and has polycystic syndrome, 0 otherwise;  $S_0$ , 3-year survival probability for a participant with reference covariate pattern (continuous covariates equal the sample average and categorical covariates equal male or no); SM, 1 if a subject is a current smoker, 0 otherwise.

model. Five of the six models had nonsignificant  $P$  values, indicating that in general, the models had good fit at year 3.

Vickers and Elkin (13) decision-curve analyses were used to identify the range of threshold probabilities in which the models added value for predicting progression to DM and regression to NGR. Both models added value for decision making: the lifestyle model added value for the full range of threshold probabilities, and the metformin model added value for threshold probabilities from ~10 to 70% (data not shown).

Figure 3A shows the 3-year predicted probabilities of progression to DM in DPP participants who adhered to the lifestyle, metformin, and placebo interventions stratified according to their quartile of risk of progressing to diabetes if they had been assigned to the placebo intervention. For those at lowest risk of progression to DM (quartile 1) who adhered to the lifestyle intervention, the predicted 3-year probability of progression to DM was only 4%. The corresponding probability was 11% for those in the lowest quartile of risk who adhered to the metformin intervention and

12% for those in the lowest quartile of risk who adhered to the placebo intervention. The ARR was thus 8% for low-risk participants who adhered to the lifestyle intervention but 0% for low-risk participants who adhered to the metformin intervention. For those in the highest quartile of risk, the predicted 3-year probabilities of progression to DM were 19% for individuals who adhered to the lifestyle intervention, 34% for those who adhered to the metformin intervention, and 59% for those who adhered to the placebo intervention. The ARR was thus 39% for those at highest risk who adhered to the lifestyle intervention and 25% for those at highest risk who adhered to the metformin intervention. These results indicate that the lifestyle intervention was effective in adherent participants regardless of baseline risk, and substantially more effective than the metformin intervention in those at highest risk, whereas the metformin intervention was only effective in adherent participants who were at higher risk (quartiles 3 and 4).

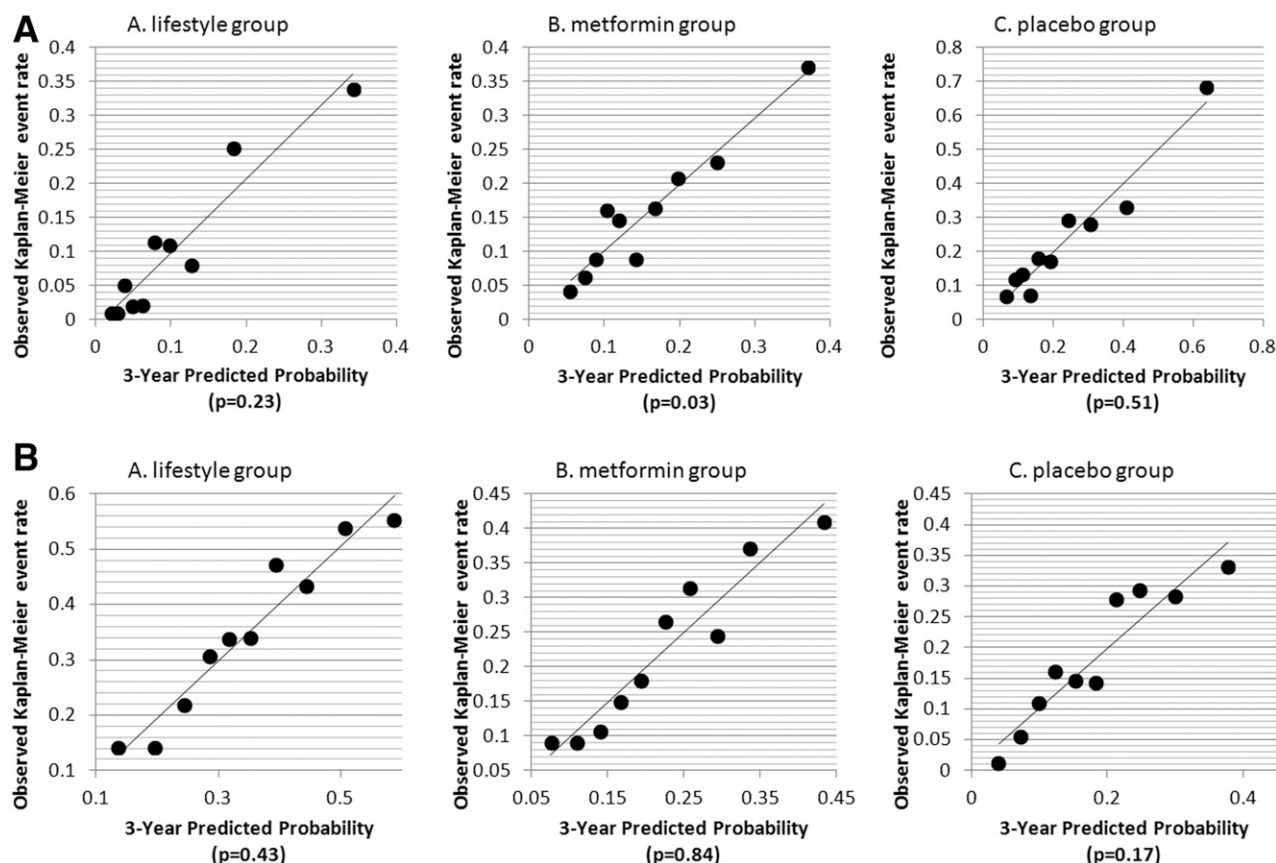
Figure 3B shows the 3-year predicted probabilities of regression to NGR by

treatment group stratified by the same quartiles of risk of progressing to diabetes if the participants had been assigned to the placebo intervention. For both those with the lowest probability of progressing to DM (quartile 1) and the highest probability of progressing to DM (quartile 4), the probability of regressing to NGR was substantially greater for those who were adherent to the lifestyle and metformin interventions compared with those who were adherent to the placebo intervention. Taken together, these results demonstrate the large variation in individual risk of progression to diabetes and regression to NGR even in this relatively homogeneous study population (14).

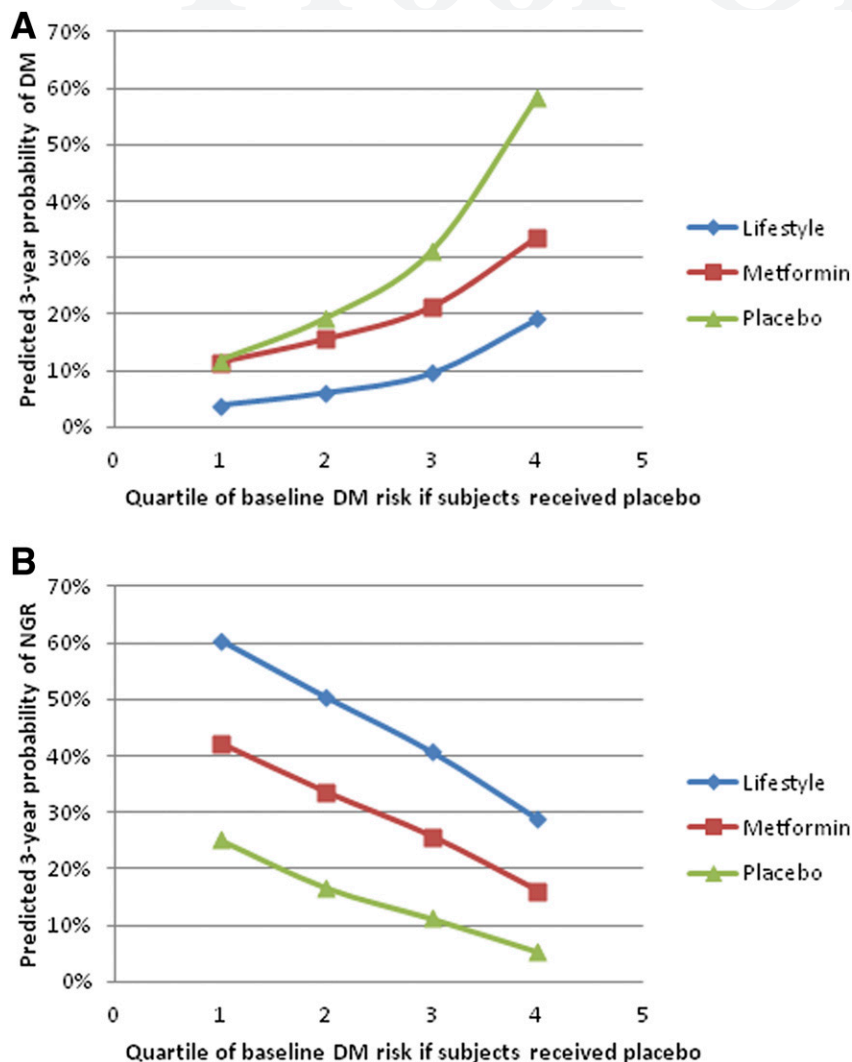
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## CONCLUSIONS

The DPP demonstrated the efficacy of lifestyle and metformin interventions for delaying progression to DM in diverse participants at high-risk for DM. Sussman et al. (3) previously demonstrated that the average benefit for DPP participants randomized to the metformin intervention



**Figure 2—A:** Calibration curves for progression to DM. Black dots represent deciles of risk for progression to DM. **B:** Calibration curves for regression to NGR. Black dots represent deciles of risk for regression to NGR.  $P$  values are for D'Agostino and Nam (12)  $\chi^2$  statistics.



**Figure 3—A:** Predicted 3-year probabilities of progressing to DM in adherent participants by quartile of risk of developing DM if participants had been assigned to the placebo intervention. **B:** Predicted 3-year probabilities of regressing to NGR in adherent participants by quartile of risk of developing DM if participants had been assigned to the placebo intervention. (A high-quality color representation of this figure is available in the online issue.)

was distributed unevenly across the population with one-fourth of patients at the highest risk for developing DM receiving a dramatic benefit (22% ARR over 3 years), whereas the remainder of the study population received modest or no benefit. We have extended this approach evaluating “benefit-based tailored treatment” by developing multivariable models to predict individual risk of progression to DM and regression to NGR using variables routinely assessed in clinical practice and accounting for intervention adherence.

Our results demonstrate that compared with participants who adhered to the placebo intervention, the absolute reduction in the predicted 3-year probability of progression to DM is 20% for participants who

adhered to the lifestyle intervention and 9% for participants who adhered to the metformin intervention. However, only 62% of lifestyle participants, 68% of metformin participants, and 72% of placebo participants were able to adhere to their randomized intervention assignments at 6 months. Adherence to the lifestyle intervention, defined as achieving  $\geq 5\%$  weight loss at 6 months, was associated with reduced progression to DM across all four quartiles of baseline risk, with the greatest ARR relative to placebo occurring in the quartiles of participants at highest risk. Adherence to the metformin intervention was also associated with reduced risk of progression to DM. However, this benefit was strongly affected by baseline

DM risk: in the lowest-risk quartile, the metformin intervention reduced the predicted 3-year probability of progression to DM by  $<1\%$ , whereas in the group at highest risk, the ARR was 25% with metformin compared with placebo. Absolute risks of progression to DM were consistently lower among adherent lifestyle participants than among adherent metformin participants.

Among those who were adherent to the DPP interventions, lifestyle intervention was also more effective than metformin intervention in promoting regression to NGR (absolute increase in predicted probability of regression to NGR 30% for lifestyle and 14% for metformin). The predicted 3-year probability of regression to NGR by quartile of DM risk was greater with the lifestyle intervention than the metformin intervention, although the benefit of the lifestyle intervention relative to the metformin intervention in increasing the probability of regression to NGR was greatest in the quartile at highest risk of progressing to DM (35 vs. 17% and difference of 18%). In those at lowest risk of progressing to DM, the corresponding rates were 24 and 11% (difference of 13%). Better identification of individuals at low risk of progressing to DM may prevent overtreatment, reduce treatment-related adverse events, and encourage more appropriate resource utilization (15).

Recently, Davidoff (16) pointed out that although randomized trials can demonstrate whether treatments work, the benefits of treatment vary from patient to patient. Focusing solely on aggregate results for the randomized treatment groups may lead to the faulty inference that an effective treatment provides equal benefits to everyone who receives it. Understanding this phenomenon, termed “heterogeneity in treatment effects,” requires knowledge about which participants do and do not benefit from the treatment. Treatment benefits generally increase as an individual’s baseline risk increases, and “failure to explore differences in treatment effects among subgroups with different levels of baseline risk represents incomplete reporting of trial results” (16). Davidoff (16) goes on to recommend that investigators first determine the baseline risk for each trial participant and then develop disease-specific multivariable prognostic models to risk stratify the population. Then, by



assessing outcomes in study participants according to baseline risk, investigators can compare clinical outcomes directly between treated and untreated participants within each baseline risk subgroup.

There are a number of limitations to our analyses. First, it is important to recognize that the equations were developed and validated for individuals living in the U.S. who met DPP eligibility criteria. It is not clear how the equations will perform, for example, in individuals identified with prediabetes based on a risk-screening questionnaire alone. Second, it is important to recognize that individuals who participated in the DPP were likely more highly motivated to prevent diabetes than individuals with prediabetes in the general population and that the 3-year probabilities of progression to DM and regression to NGR that we reported are for adherent participants. To the extent that intervention participants are less motivated, and their adherence is less complete, the outcomes will be less favorable than we report. In addition, to the extent that long-term adherence to a medication intervention is better than long-term adherence to a lifestyle intervention, the apparent benefit of the lifestyle intervention relative to the metformin intervention will be attenuated. Finally, it should be recognized that the diabetes-prevention intervention being implemented in community settings today differs from that implemented in the DPP. For example, the National Diabetes Prevention Program lifestyle intervention lasts for only 1 year and is delivered in a

group format rather than one-on-one (17). To the extent that these differences reduce the efficacy of the lifestyle intervention, the apparent benefit of the lifestyle intervention will be overestimated.

In the future, we plan to upload the multivariable models for individual risk prediction on the DPP Outcomes Study (DPPOS) website. By entering the values for each individual's predictor variables, people meeting DPP eligibility criteria and their health care providers can calculate and compare their 3-year risk of progression to DM and likelihood of regression to NGR if they adhere to an intensive lifestyle intervention and lose at least 5% of their initial body weight or adhere to a metformin intervention by taking metformin 850 mg twice daily at least 80% of the time. They can also see the number of individuals who would need to be treated with the lifestyle or metformin intervention for 3 years to prevent one person from progressing to DM or to induce one person to regress to NGR (the numbers needed to treat). Use of these equations will also allow patients and providers to reassess the choice of intervention after 6 months in light of the intervention's demonstrated feasibility and side effects. For example, if an individual is unable to adhere to the lifestyle intervention after 6 months, the patient and provider may wish to consider metformin therapy. Similarly, if a patient experiences intolerable side effects with metformin therapy, the patient and provider may wish to consider the lifestyle intervention.

For example, a 40-year-old man with IGT, BMI of 27 kg/m<sup>2</sup>, FPG of 99 mg/dL, and TG of 67 mg/dL is substantially less likely to progress to DM and more likely to regress to NGR than a 40-year-old man with IGT, BMI of 41 kg/m<sup>2</sup>, FPG of 115 mg/dL, and TG of 245 mg/dL, regardless of which intervention he chooses (Table 4). Because of the substantially lower risk of progression to DM and the lower efficacy of the metformin intervention in a 40-year-old man with IGT and lower BMI, FPG, and TG versus higher BMI, FPG, and TG, 16 men would need to be treated with lifestyle (vs. 4 men) and 82 men would need to be treated with metformin (vs. 7 men) to prevent one case of diabetes over 3 years in the lower-risk compared with the higher-risk men (Table 4). However, in a 60-year-old man, adhering to a lifestyle intervention is as effective as in a younger man, but the metformin intervention is less effective in preventing progression to DM in a man with higher BMI, FPG, and TG and ineffective in a man with lower BMI, FPG, and TG (Table 4). Forty- and 60-year-old women with IGT and histories of pregnancy but no histories of GDM are as likely to benefit from the lifestyle and metformin interventions as 40- and 60-year-old men with the same risk-factor profiles. Compared with men, women are less likely to regress to NGR with the metformin intervention compared with the lifestyle intervention.

Clinical trials assess the efficacy of new treatments and often highlight the effects of an intervention on the relative risk

**Table 4—Impact of extreme values of predictor variables on 3-year predicted probabilities of progression to type 2 DM and regression to NGR for adherent participants**

Predictor variables					Progress		Regress			
					3-year predicted probabilities (%) if treated with placebo		Percent ARR (NNT)		3-year predicted probabilities (%) if treated with placebo	
Age (years)	Sex	BMI (kg/m <sup>2</sup> )	FG (mg/dL)	TG (mg/dL)			Lifestyle	Metformin	Lifestyle	Metformin
40	M	27	99	67	8		6 (16)	1 (82)	57	12 (7)
40	M	41	115	245	45		26 (4)	14 (7)	20	11 (9)
60	M	27	99	67	8		6 (16)	—2 (—)	45	7 (11)
60	M	41	115	245	45		26 (4)	6 (16)	15	7 (13)
40	F	27	99	67	8		6 (14)	1 (46)	47	2 (18)
40	F	41	115	245	47		28 (3)	16 (5)	16	7 (14)
60	F	27	99	67	8		6 (14)	—2 (—)	37	—1 (—)
60	F	41	115	245	47		28 (3)	8 (10)	12	4 (23)

—, not effective; F, woman with history of pregnancy but no history of GDM; M, male; NNT, number needed to treat.

reduction for a prespecified outcome, such as the development of DM. Treatment decisions should, however, be based on the best estimate of the ARR or risk difference associated with alternative courses of action for a particular patient. The purpose of this paper was to use baseline data from the DPP to develop risk equations to predict progression to DM and regression to NGR among individuals who adhere to the interventions. These simple equations can be used in clinical practice by patients and their providers to better understand the benefits of the alternative treatments to delay or prevent the development of DM and to induce regression to NGR in order to facilitate individual benefit-based tailored treatment and personalized decision making.

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The sponsor of this study was represented on the Steering Committee and played a part in study design, how the study was done, and publication. The funding agency was not represented on the writing group, although all members of the Steering Committee had input into the report's contents. All authors in the writing group had access to all data. The opinions expressed are those of the investigators and do not necessarily reflect the views of the funding agencies. A complete list of Centers, investigators, and staff can be found in the Supplementary Material. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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**Prior Presentation.** Parts of this study were presented in poster form at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 10–14 June 2016.

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Q:4

Q:7

# AUTHOR QUERIES

## PLEASE ANSWER ALL QUERIES

- Q1: A short running title “Impact of Lifestyle Interventions on Diabetes” has been created. If making changes, please note that the running title may not exceed 47 characters including spaces.
- Q2: Okay to change expansion for “DM” to “diabetes mellitus” to be consistent with abbreviation throughout? 
- Q3: Reference 14 was not cited in the text and has been added here temporarily. Please cite reference 14 at the appropriate location, renumbering references if necessary.
- Q4: Please confirm that any agencies (or individuals) that provided materials or support services to the DPP/DPPOS are listed in the Acknowledgments, whereas any financial support is listed under Funding. Information was shifted to the appropriate sections accordingly, but please confirm that each section is correct and complete as shown. 
- Q5: Should asterisk symbol be added after the two other *P* value headings in Table 1? Also, please confirm that *P* values that span multiple subcategories are placed correctly within the table.
- Q6: Please check that all equations in Table 3 are correct as shown, including all symbols.
- Q7: Check that the conflict of interest information for each author is presented in full in the Duality of Interest section.