Regression From Pre-Diabetes to Normal Glucose Regulation in the Diabetes Prevention Program

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OBJECTIVE — Participants in the Diabetes Prevention Program (DPP) randomized to intensive lifestyle modification (ILS) or metformin had a significantly reduced incidence of diabetes compared with those randomized to placebo, yet most were still at risk because they had pre-diabetes. We explored the effect of baseline characteristics, weight change, ILS, and metformin on regression from pre-diabetes to the lowest-risk state of normal glucose regulation (NGR) defined by American Diabetes Association criteria.

RESEARCH DESIGN AND METHODS — The DPP was a prospective randomized trial. Cox proportional hazards modeling was used to identify predictors of regression from pre-diabetes to NGR over 3 years of follow-up.

RESULTS — Lower baseline fasting (hazard ratio 1.52, $P < 0.01$) and 2-h (1.24, $P < 0.01$) glucose predicted regression to NGR, as did younger age (1.07, $P < 0.01$) and greater insulin secretion (1.09, $P = 0.04$). ILS (2.05, $P < 0.01$) and weight loss (1.34, $P < 0.01$) had significant and independent effects on regression. A nonsignificant trend for regression was also observed for metformin (1.25, $P = 0.06$), male sex (1.17, $P = 0.08$), and insulin sensitivity (1.07, $P = 0.09$). In those entering the study with both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), male sex and insulin sensitivity predicted regression to isolated IFG, whereas ILS, metformin, female sex, and greater insulin secretion predicted regression to isolated IGT.

CONCLUSIONS — Insulin secretion, and other biologic processes retained with younger age, are key in restoring NGR in people with pre-diabetes. However, NGR may also be attained through weight loss and additional aspects of ILS.

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The prevalence of type 2 diabetes increased 61% between 1990 and 2001 (1), and by 2005 it affected nearly 21 million Americans (www.cdc.gov/Diabetes/pubs/estimates05.htm). This trend shows no sign of abating, considering that there are currently an estimated 54 million Americans with pre-diabetes (i.e., impaired fasting glucose [IFG] and/or impaired glucose tolerance [IGT]), up to 70% of whom may develop diabetes in their lifetime (2–4). Consequently, a number of clinical trials (2,4–9) have examined the feasibility and efficacy of lifestyle and/or drug therapy at preventing diabetes in people with pre-diabetes. Together, these studies have demonstrated reductions between 25 and 67% in the incidence of diabetes over 2.5- to 6-year intervention periods, with most participants remaining in a pre-diabetic state. Less often discussed were the 20–50% of participants who not only did not progress but, in fact, returned to normal glucose regulation (NGR) (2,6–8). One could make the case that true risk reduction is in restoring NGR rather than in maintenance of pre-diabetes.

Whereas risk factors for diabetes are well established (3), far less is known about factors associated with reversal of the process. There are a large number of possible candidates, including a variety of genes, environmental exposures, and aspects of behavior, including diet, physical activity, and stress responses. Data from the Diabetes Prevention Program (DPP) offered a unique opportunity to explore some of these possible mediators. Thus, we aimed to examine the effect of basal biologic factors, weight change, and prevention strategies (intensive lifestyle modification [ILS] or metformin) on the incidence of regression from pre-diabetes to NGR.

RESEARCH DESIGN AND METHODS

— The DPP was a randomized clinical trial performed at 27 centers involving 3,234 subjects who were at high risk for diabetes. The detailed methods have been reported (10), and the protocol is available at http://www.bsc.gwu.edu/dpp. Institutional review boards at each center approved the protocol, and all participants gave written informed consent prior to participation.

Eligibility criteria included being age ≥25 years, having a BMI ≥24 kg/m^2 (≥22 kg/m^2 in Asian Americans), having a fasting plasma glucose concentration of 5.3–6.9 mmol/l (≤6.9 mmol/l in the American Indian clinics), and attaining a 2-h glucose of 7.8–11.0 mmol/l during a

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75-g oral glucose tolerance test. Thus, all participants had IGT at baseline. Subjects were excluded if they were taking medications known to alter glucose tolerance or had significant illness.

Interventions

Eligible participants were randomly assigned to one of three interventions: *1*) ILS, *2*) 850 mg metformin twice daily and standard lifestyle recommendations, or *3*) placebo twice daily and standard lifestyle recommendations. The goal for participants assigned to ILS was to achieve and maintain a weight reduction of at least 7% of their initial body weight through a healthy low-calorie, low-fat diet and physical activity of moderate intensity, such as brisk walking, for at least 150 min per week.

Assessments

Self-reported levels of leisure physical activity were assessed semiannually with the Modifiable Activity Questionnaire (10). The physical activity level was calculated as the product of the duration and frequency of each activity (in hours per week) weighted by an estimate of the metabolic equivalent (MET) of that activity and summed for all activities performed with the result expressed as the average MET hours per week for the previous year. Usual daily caloric intake during the previous year, including calories from fat, carbohydrate, protein, and other nutrients, was assessed at baseline and at 1 year with the use of a modified version of the Block food frequency questionnaire (10). Weight was measured using a standardized calibrated scale, and blood pressure was measured using a manual sphygmomanometer.

Venous blood was obtained and processed at each clinical site using a standardized manual of operations. Participants randomized to metformin did not take the medication the morning of blood testing. Serum and plasma samples were stored at –20°C for several days and then shipped in batches on dry ice to a single central laboratory. Measurement methods for glucose, insulin, triglycerides, and HDL cholesterol have been published (11). Measures of insulin secretion (corrected insulin response [CIR] = [100 × 30 min insulin]/[30 min glucose × {30 min glucose − 70}]) and insulin sensitivity (1/fasting insulin) were calculated using validated indices (12).

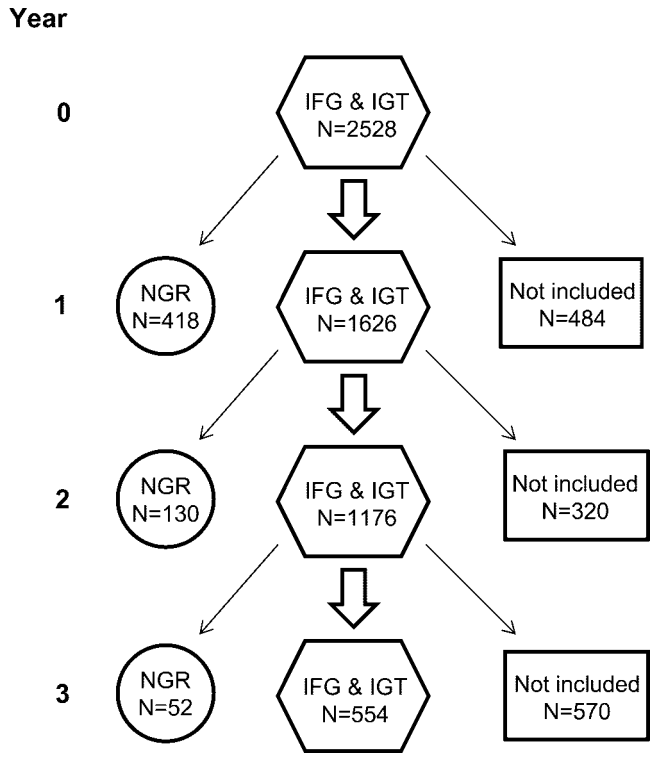

Figure 1—*Flowchart for primary data analysis illustrating handling of the data from years 1 to 3. IFG, fasting glucose = 5.6–6.9 mmol/l; IGT, 2-h glucose = 7.8–11.1 mmol/l; NGR, fasting glucose <5.6 mmol/l; and 2-h glucose <7.8 mmol/l. Data "not included" were censored from subsequent analyses due to regression to NGR (in year prior), isolated IFG or IGT, progression to diabetes, or missing data.*

Outcome measures and statistical analyses

Of 3,234 participants in the DPP, 2,528 had a baseline fasting glucose concentration >5.6 mmol/l (and <7.0 mmol/l) and, thus, according to American Diabetes Association (ADA) criteria were considered to have IFG in addition to IGT (13). The primary outcome measure was regression from combined IFG/IGT to NGR (fasting glucose <5.6 mmol/l and 2-h glucose <7.8 mmol/l), with secondary outcome measures such as regression from IFG/IGT to isolated IFG (fasting glucose 5.6–6.9 mmol/l and 2-h glucose <7.8 mmol/l) or isolated IGT (fasting glucose <5.6 mmol/l and 2-h glucose 7.8–11.1 mmol/l), again using ADA criteria (13). Analyses also examined predictors for regression from IFG/IGT to NGR, isolated IFG, or isolated IGT within each treatment group. Another set of models was constructed analyzing regression in the DPP cohort (those who had IGT with a fasting plasma glucose concentration >5.3 mmol/l [and <7.0 mmol/l] [n = 3,143] and regressed to NGR [n = 468], isolated IFG [n = 1,150], or isolated IGT [n = 279]). Quantitative characteristics are presented as the median (25th and 75th percentiles) and qualitative characteristics as n (%). The effect of baseline characteristics, as well as the effect of weight change, ILS, and metformin versus placebo, on the incidence of regression was estimated using Cox proportional hazards modeling. In circumstances where variables had significant colinearity (e.g., weight and BMI), only one variable was included. Cox proportional hazards models included only participants with IFG/IGT and modeled time to first incidence of regression to NGR, isolated IFG, or isolated IGT using yearly visits. Those who had progressed to diabetes, had missing data, or, depending on the outcome measure of the model, regressed to NGR, isolated IFG, or isolated IGT were censored from subsequent analyses (Fig. 1). Hazard ratios (HRs) for continuous variables are presented per SD for each variable of interest (except age, which is for an increase of 5 years). An HR >1 indicates greater risk for regression (i.e., favors regression), whereas the opposite is true for HR <1 (i.e., impedes regression). P values for individual covariates were calculated using the Wald

Table 1—*Baseline characteristics of participants with both IFG and IGT, defined by the ADA*

	ILS	Metformin	Placebo
n	850	832	846
Age (years)	50 (42–59)	51 (44–57)	50 (44–58)
Female	555 (65.3)	528 (63.5)	559 (66.1)
Race/ethnic group			
White	456 (53.6)	474 (57.0)	458 (54.1)
African American	164 (19.3)	183 (22.0)	184 (21.7)
Hispanic	143 (16.8)	125 (15.0)	132 (15.6)
American Indian	36 (4.2)	21 (2.5)	31 (3.7)
Asian American	51 (6.0)	29 (3.5)	41 (4.8)
Systolic blood pressure (mmHg)	122 (113–133)	123 (113–134)	122 (114–132)
Diastolic blood pressure (mmHg)	79 (73–85)	79 (72–85)	78 (71–84)
Waist circumference (cm)	104 (95–115)	105 (96–114)	105 (96–115)
BMI (kg/m^2)	33 (29–37)	33 (29–37)	33 (29–38)
Activity (MET/h per week)			
Leisure	9.5 (3.7–20)	10 (3.9–21)	9.8 (4.1–21)
Recreational	62 (36–91)	63 (38–91)	62 (39–90)
Caloric intake (kcal)	1,881 (1,463–2,573)	1,902 (1,472–2,568)	1,874 (1,443–2,474)
Fasting plasma glucose (mmol/l)	5.9 (5.7–6.3)	5.9 (5.7–6.3)	5.9 (5.7–6.3)
2-h plasma glucose (mmol/l)	9.1 (8.3–9.9)	9.2 (8.4–10.0)	9.1 (8.3–9.9)
Triglycerides (mmol/l)	1.6 (1.1–2.3)	1.6 (1.1–2.2)	1.7 (1.2–2.4)
HDL cholesterol (mmol/l)	1.1 (1.0–1.3)	1.1 (1.0–1.3)	1.1 (0.9–1.3)
Insulin secretion	0.52 (0.35–0.74)	0.51 (0.34–0.74)	0.53 (0.34–0.78)
Insulin sensitivity	0.04 (0.03–0.06)	0.04 (0.03–0.06)	0.04 (0.03–0.06)

Data are *n* (%) for categorical variables and median (25th–75th percentile) for continuous variables. Twenty Pacific Islanders were included in the Asian American group. Insulin secretion was estimated using the CIR ([100 × 30 min insulin]/[30 min glucose × {30 min glucose −70}]). Insulin sensitivity was estimated using 1/fasting insulin.

test and the likelihood ratio test for the overall model. Stratified analyses were conducted first by treatment group with a test for heterogeneity, checking whether the effect of a covariate is the same across treatment groups. Significance was set at $P < 0.05$. All analyses were conducted using SAS software (version 8.01; SAS Institute, Cary, NC).

RESULTS

Demographics

Baseline characteristics for the entire DPP cohort have been previously published (11). Baseline characteristics for the ADA-defined IFG/IGT cohort (fasting glucose 5.6–6.9 mmol/l and 2-h glucose 7.8–11.1 mmol/l as opposed to fasting glucose 5.3–6.9 mmol/l and 2-h glucose 7.8–11.1 mmol/l for the entire DPP cohort) are summarized in Table 1 by treatment group. No significant differences were observed between the randomized groups by treatment assignment for the variables shown, except for diastolic blood pressure and HDL cholesterol that were borderline significant. Further, there was no significant difference between the treatment groups in baseline characteristics (except HDL cholesterol) using a fasting glucose cut point of 5.3 mmol/l (data not shown).

Predictors for regression to NGR

Results from the final multivariate model, shown in Table 2, included treatment group, age, sex, ethnicity, baseline weight and change in weight, baseline fasting and 2-h plasma glucose concentrations, and indices of the β-cell's insulin response and tissue insulin sensitivity, as each were significantly and independently predictive of regression to NGR in a univariate analysis. As expected, lower baseline fasting and 2-h glucose predicted regression to NGR, as did younger age and a greater insulin secretion to the oral glucose load. ILS and greater weight loss had significant and independent effects on regression. A nonsignificant trend for metformin, male sex, and greater insulin sensitivity on incidence of regression was also observed. The cumulative incidence of regression to NGR in each treatment group is shown in Fig. 2. When the model was run using the entire DPP cohort (fasting glucose 5.3–6.9 vs. 5.6–6.9 mmol/l), the results were similar (data not shown).

When examining the data by treatment group, Caucasian self-reported ethnicity was significantly associated with less likelihood of regression (HR 0.68, $P = 0.02$), but only in the metformin group, and therefore is of uncertain significance. Contribution from a positive family history of diabetes, lipids, blood pressure, use of lipid- and/or blood pressure–lowering medications, selective serotonin reuptake inhibitors, or hormone replacement therapy, dietary calories from fat, and MET/h per week of physical activity were also explored and found to not be significantly related to regression to NGR (data not shown).

Predictors of regression to isolated IFG

Higher fasting and lower 2-h glucose, as well as male sex and greater insulin sensitivity, were associated with regression to isolated IFG, as defined by ADA (Table 2). The relationship between ILS and regression to IFG was of borderline significance. When the entire DPP cohort was analyzed, higher fasting glucose (HR 1.14, $P < 0.01$), lower 2-h glucose (1.43, $P < 0.01$), male sex (1.35, $P < 0.01$), and greater insulin sensitivity (1.08, $P = 0.02$) remained similarly predictive. The power gained by using the entire cohort increased the ability to detect an effect of ILS

Table 2—*Predictors of regression to NGR, isolated IFG, or isolated IGT using ADA criteria in a multivariate model*

	HR (95% CI)	*P*
Regression to NGR		
ILS versus placebo	2.05 (1.66–2.53)	<0.0001
Metformin versus placebo	1.25 (0.99–1.58)	0.0601
Younger age	1.07 (1.02–1.11)	0.0031
Male versus female sex	1.17 (0.98–1.40)	0.0784
Caucasian versus non-Caucasian	1.00 (0.84–1.19)	0.9986
Lower fasting plasma glucose	1.52 (1.36–1.68)	<0.0001
Lower 2-h plasma glucose	1.24 (1.13–1.35)	<0.0001
Greater insulin sensitivity (l/fasting insulin)	1.07 (0.99–1.16)	0.0934
Greater insulin secretion (CIR)	1.09 (1.01–1.17)	0.0353
Higher baseline weight	1.01 (0.92–1.11)	0.8229
Greater weight loss	1.34 (1.21–1.49)	<0.0001
Regression to isolated IFG		
ILS versus placebo	1.20 (0.99–1.46)	0.0576
Metformin versus placebo	0.98 (0.81–1.19)	0.8560
Younger age	1.03 (0.99–1.07)	0.1590
Male versus female sex	1.27 (1.08–1.50)	0.0037
Caucasian versus non-Caucasian	1.07 (0.91–1.26)	0.4088
Higher fasting plasma glucose	1.29 (1.19–1.40)	<0.0001
Lower 2-h plasma glucose	1.48 (1.36–1.61)	<0.0001
Greater insulin sensitivity (l/fasting insulin)	1.09 (1.00–1.18)	0.0441
Greater insulin secretion (CIR)	1.05 (0.96–1.15)	0.2591
Higher baseline weight	1.03 (0.95–1.13)	0.4467
Greater weight loss	0.98 (0.89–1.07)	0.5962
Regression to isolated IGT		
ILS versus placebo	1.30 (1.01–1.67)	0.0397
Metformin versus placebo	1.50 (1.18–1.91)	0.0009
Younger age	1.01 (0.96–1.06)	0.7587
Female versus male sex	1.58 (1.25–1.99)	0.0001
Caucasian versus non-Caucasian	1.13 (0.93–1.38)	0.2259
Lower fasting plasma glucose	1.67 (1.47–1.89)	<0.0001
Higher 2-h plasma glucose	1.19 (1.08–1.31)	0.0004
Greater insulin sensitivity (l/fasting insulin)	1.01 (0.91–1.12)	0.8854
Greater insulin secretion (CIR)	1.11 (1.01–1.23)	0.0257
Higher baseline weight	0.93 (0.83–1.03)	0.1733
Greater weight loss	1.13 (1.00–1.28)	0.0558

HRs for continuous variables are per 1 SD (or per 5 years for age).

(1.28, $P < 0.01$) and revealed a tendency for younger age (1.03, $P = 0.07$) to positively influence regression to isolated IFG. Within–treatment group comparisons noted a stronger effect of low 2-h glucose on regression in placebo (HR 1.64) and metformin (1.61) groups than in the ILS group (1.25) (test for interaction, $P = 0.03$).

Predictors of regression to isolated IGT

Lower fasting and higher 2-h glucose, female sex, a greater insulin secretion, as well as both ILS and metformin were associated with regression to isolated IGT in the ADA-defined IFG/IGT cohort (Table 2). Greater weight loss was marginally associated with regression to isolated IGT. When the same analysis was performed in the entire DPP cohort, lower fasting glucose (HR 2.36, $P < 0.01$), higher 2-h glucose (1.15, $P = 0.02$), female sex (1.54, $P < 0.01$), ILS (1.46, $P = 0.02$), and metformin (1.89, $P < 0.01$) remained similarly predictive. In contrast, insulin response was no longer significantly related (1.01, $P = 0.86$), but younger age was (1.06, $P = 0.05$). In addition, marginal associations emerged for lower baseline weight (1.13, $P = 0.09$) and greater weight loss (1.17, $P = 0.07$) influencing regression to isolated IGT. No difference in predictors for regression within treatment groups was observed.

CONCLUSIONS — As the epidemic of diabetes continues to worsen, developing and implementing preventive strategies has become critical. A number of clinical trials (2,4–9) have demonstrated the effectiveness of lifestyle and/or drug therapy at preventing diabetes in people with pre-diabetes, but none have examined the effectiveness of an intervention on returning those with pre-diabetes to NGR. To expand the paradigm of diabetes prevention, the aim of the current study was to examine the effect of basal biologic factors, weight change, and prevention strategies (ILS or metformin) on the incidence of regression from pre-diabetes to NGR. The major findings from this analysis were that *1*) insulin secretion, and other biologic processes that are retained with younger age, are key in the restoration of NGR in people with pre-diabetes; however, *2*) NGR may also be attained through weight loss and additional aspects of ILS, such as healthy eating and exercise.

ILS and metformin both have been shown to be effective strategies for diabetes prevention, but in the DPP only ILS restored NGR significantly more frequently than did placebo (2). Different impact of ILS versus metformin on parameters of insulin sensitivity or secretion did not explain these results. This observation lends support for the notion that aspects of ILS beyond insulin sensitization per se are key in truly reducing diabetes risk.

Weight loss appears to be the most important component of ILS predicting regression, with every 1 kg lost associated with a 16% reduction in diabetes risk (14). Weight loss strategies inclusive of exercise preferentially mobilize fat from the visceral depot, inducing more favorable metabolic results than would fat mobilized from the subcutaneous depot (15). Interestingly, however, ILS, independent of weight loss, also predicted regression to NGR in our study. This finding implies a role for the other aspects of ILS, such as healthy eating or exercise, in restoring NGR. Indeed, healthy eating (16) and exercise (17) without weight loss have been previously and independently demonstrated as positive effectors on the metabolic milieu; however, we found no predictive effect toward regression for either in the current analysis. The combination of healthy eating with exercise or other pleiotropic effects of exercise may explain these findings but were not assessed in DPP participants.

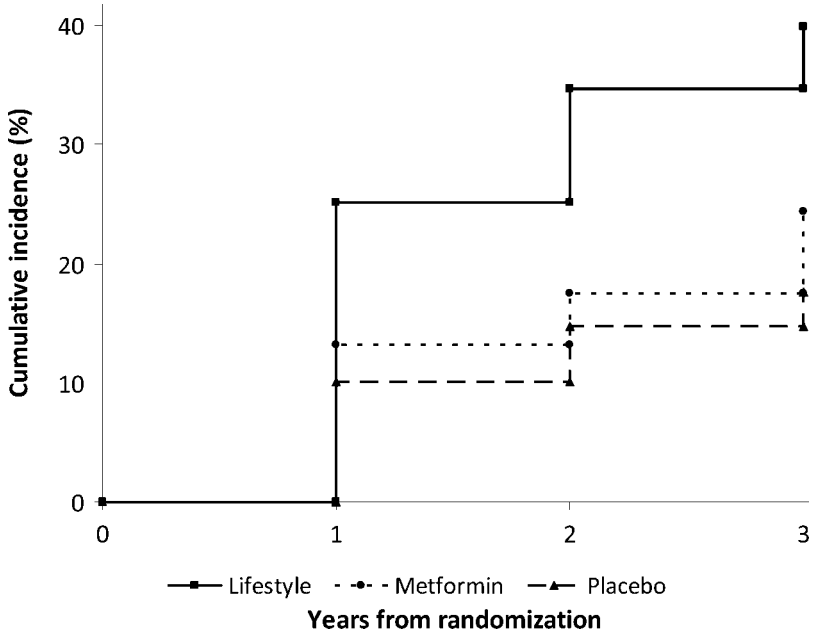

Figure 2—*Cumulative incidence of NGR according to treatment group, adjusted for baseline age, sex, ethnicity, weight, fasting and 2-h glucose concentrations, as well as insulin sensitivity (1/fasting insulin) and secretion (CIR).*

In contrast to lifestyle change, some predictors of regression to NGR are not modifiable. For example, younger age was associated with regression to NGR in the current study. This was seen despite the previous finding that older DPP participants had greater success meeting ILS goals and with it the beneficial effect of lower diabetes incidence (18). What age-related processes may be responsible is speculative. Considerable controversy exists as to whether age by itself (19) (versus age-related body composition change [20]) leads to the deterioration of insulin action and/or secretion.

Greater insulin secretion also predicted regression to NGR and may reflect the critical link between ILS, weight loss, and age in restoring and maintaining NGR. Weight loss and younger age either resulted in, or were associated with, lower baseline 2-h glucose levels in the DPP, likely reflecting the more robust β-cell responsiveness in these groups. Insulin sensitivity and secretion are integrally related, and the deterioration of each is felt to be requisite in the development of type 2 diabetes (21). Nevertheless, longitudinal data (22) clearly demonstrate the failure of the β-cell as the seminal event in this process. Therefore, one could surmise that the maintenance of insulin secretion is vital, as insulin sensitivity may be modified more readily than insulin secretion by ILS, weight loss, and/or age-related body composition changes.

All participants in the DPP had elevated 2-h and high-normal fasting glucose concentrations. As the combination of increasing fasting and 2-h glucose levels confers greater risk for diabetes than either in isolation (3), there is reason to believe that regression from IFG/IGT to isolated IFG or IGT may also decrease diabetes risk. Other than the expected predictive effects of glucose concentration itself (high fasting and low 2-h glucose for IFG and the converse for IGT) and intervention effects on glucose concentration (ILS on fasting and 2-h glucose, metformin on fasting), we observed distinct predictors for reversion to isolated IFG and isolated IGT, likely reflecting their different pathophysiology (23). Consistent with some, but not all, cross-sectional studies, those with isolated IFG were more likely to be insulin sensitive and male, whereas those with isolated IGT were more likely to have retained insulin secretion and be female (24,25).

Several limitations of the current study are worth noting. First, the primary analyses were conducted using the ADA definition of IFG, which reduced the sample size and power to find differences. Additionally, the considerable amount of missing data exacerbated this issue. Nevertheless, when the entire cohort was analyzed, the results were largely unchanged. Second, by virtue of our analysis plan, the fate of those who may have changed glucose tolerance status more than once, spontaneously regressed, or were incorrectly classified due to the inaccuracy of the oral glucose tolerance test, was not captured. Finally, analyses were post hoc and exploratory with the intention of generating hypotheses and discussion on this topic. Prospective studies are needed to confirm the current findings.

In conclusion, true diabetes prevention likely resides in the restoration of NGR rather than in the maintenance of a high-risk state, such as pre-diabetes. Some factors governing the return to NGR are modifiable, and others are not. For example, age-related changes, particularly when leading to diminished insulin secretion, may permanently impede restoration of NGR. In other circumstances, however, NGR may be attained through weight loss and the combined aspects of ILS. Establishing healthy habits early in life, before age-related changes occur, is most likely the best strategy for diabetes prevention.

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