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Outcome of lifestyle intervention in relation to duration of pre-diabetes: the Pathobiology and Reversibility of Prediabetes in a Biracial Cohort (PROP-ABC) study

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ABSTRACT

Introduction In studies that enrolled people with prevalent pre-diabetes of unknown duration, lifestyle intervention (LI) delayed progression to type 2 diabetes (T2D) but did not reverse pre-diabetes in most participants. Here, we assessed the effects of LI among individuals with pre-diabetes of known duration to determine whether outcomes are related to duration of pre-diabetes.

Research design and methods The Pathobiology and Reversibility of Prediabetes in a Biracial Cohort study initiated LI in subjects with incident pre-diabetes during follow-up of initially normoglycemic African Americans and European Americans with parental T2D. Participants were stratified into those initiating LI after <3, 3–5, or >5 years of pre-diabetes diagnosis. Assessments included anthropometry, body fat, fasting and 2-hour plasma glucose (FPG, 2hPG), and insulin sensitivity and secretion. The outcomes were normal glucose regulation (NGR; ie, normal FPG and 2hPG), persistent pre-diabetes, or T2D. Participants who maintained normal FPG and normal 2hPG levels during follow-up served as the control. The control subjects did not receive lifestyle or other intervention to alter the course of glycemia or body weight.

Results Of 223 participants (age 53.3±9.28 years, body mass index 30.6±6.70 kg/m^2), 72 (control) maintained normoglycemia during follow-up and 138 subjects with incident pre-diabetes initiated LI after 4.08±2.02 years (range 3 months–8.3 years) of diagnosis. Compared with control, LI participants showed decrease in glucose, weight, and body fat; 42.8% reverted to NGR, 50% had persistent pre-diabetes, and 7.2% developed T2D after 5 years. These outcomes were similar across race and pre-diabetes duration strata, but greater glycemic decrease occurred when LI was initiated within 5 years of pre-diabetes diagnosis.

Conclusions Ninety-three per cent of adults with parental T2D who initiated LI within 3 months to 8.3 years of developing pre-diabetes did not progress to T2D; nearly half reverted to NGR.

Trial registration number NCT02027571.

Significance of this study

What is already known about this subject?

- Previous studies have shown that lifestyle intervention can prevent or delay type 2 diabetes (T2D) in people with pre-diabetes, but data on the reversibility of the pre-diabetes state are scant.
- Previous studies enrolled individuals with prevalent pre-diabetes, of unknown duration, who were identified during cross-sectional community screening.

What are the new findings?

- The Pathobiology and Reversibility of Prediabetes in a Biracial Cohort study offered lifestyle intervention to initially normoglycemic individuals with parental T2D who developed incident pre-diabetes during longitudinal follow-up.
- The study design enabled timing of incident pre-diabetes to a window of 3–6 months in high-risk African Americans and European Americans.
- The findings showed that ~93% of participants who initiated lifestyle intervention within 3 months to 8.3 years of developing pre-diabetes did not progress to diabetes and ~43% reverted to normal glucose regulation.

How might these results change the focus of research or clinical practice?

- Most people with pre-diabetes are discovered incidentally instead of during regular blood glucose screening.
- Our findings suggest that routine clinical practice of proactive screening and prompt lifestyle intervention in people with incident pre-diabetes would be effective in preventing T2D or reversing pre-diabetes in most individuals.

INTRODUCTION

Type 2 diabetes (T2D) accounts for 90%–95% of the diabetes burden, currently estimated at 30 million adults in the USA and more than 400 million adults worldwide.[1–3] Pre-diabetes, characterized by impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT),[4 5] affects approximately 90 million US adults and is associated with increased risk of T2D, heart disease, and other

complications.[4–7] Landmark studies have demonstrated that lifestyle intervention can prevent T2D in people with pre-diabetes,[8–12] with risk reductions ranging from ~30% to ~60% compared with placebo.[8–12] However, persistent pre-diabetes was more likely than reversal to normal glucose regulation (NGR) (as defined by the American Diabetes Association and the WHO[4 13]) among lifestyle intervention responders.[8–12 14]

Landmark diabetes prevention studies enrolled individuals with prevalent pre-diabetes identified during cross-sectional screening programs.[8–12] Thus, neither the time of onset of pre-diabetes nor its duration could be determined in participants.[8–12] The Pathobiology of Prediabetes in a Biracial Cohort (POP-ABC) study enrolled initially normoglycemic African American (AA) and European American (EA) adults and followed them every 3 months for 5.5 years, the primary outcome being incident pre-diabetes.[15 16] The POP-ABC study did not offer any intervention and thus has provided valuable insights into the natural history of pre-diabetes.[17–22] The sequel, Pathobiology and Reversibility of Prediabetes in a Biracial Cohort (PROP-ABC) study, re-enrolled original POP-ABC participants for continued follow-up every 6 months for 5 years. Unlike the POP-ABC study, the PROP-ABC study offered lifestyle intervention to participants with incident pre-diabetes observed during the POP-ABC or subsequent PROP-ABC follow-up period. Thus, we were able to time the onset of pre-diabetes to within a window of 3–6 months during follow-up in the combined POP-ABC/PROP-ABC program.

Given the known temporal worsening of the pathophysiological defects (beta-cell dysfunction and insulin resistance) during transition from NGR to pre-diabetes and T2D,[23 24] the question arises as to whether people with recent-onset pre-diabetes respond differently to lifestyle intervention compared with those whose pre-diabetes has been present for longer duration. Our unique POP-ABC/PROP-ABC study population has enabled us to address this question by evaluating the efficacy of lifestyle intervention in metabolic and glycemic outcomes in relation to the chronicity of pre-diabetes before initiation of intervention.

RESEARCH DESIGN AND METHODS

The design, baseline characteristics, and primary results of the POP-ABC study have been published.[15–17] Eligibility criteria for POP-ABC study included self-reported non-Hispanic white or EA or non-Hispanic black or AA ancestry; history of T2D in one or both parents; normal fasting plasma glucose (FPG) (<100 mg/dL; 5.6 mmol/L); normal 2-hour plasma glucose (2hPG) (<140 mg/dL; 7.8 mmol/L) during a screening 75 g oral glucose tolerance test (OGTT); and absence of exposure to medications or interventions known to alter body weight, glucose, or lipid metabolism.[15–17] The initially normoglycemic POP-ABC study participants were followed passively every 3 months for 5.5 years (from September 2006 until March 2012) for the primary outcome of incident pre-diabetes.[15–17] Funding for the extension PROP-ABC study was received in September 2013. Consenting POP-ABC participants were screened and re-enrolled in the PROP-ABC study between October 2013 and April 2015 and followed up every 6 months until April 2019. Participants with incident pre-diabetes during the initial POP-ABC or subsequent PROP-ABC follow-up period received lifestyle intervention during the PROP-ABC study period. Incident pre-diabetes was defined as the occurrence of IFG (FPG >100–125 mg/dL; >5.6–6.9 mmol/L) and/or IGT (2hPG level of 140–199 mg/dL; 7.8–11 mmol/L) based on the American Diabetes Association criteria.[4] All pre-diabetes endpoints were confirmed with OGTT within 3 months and adjudicated by an independent institutional data and safety officer (Murray Heimberg, MD, PhD). The POP-ABC participants who had maintained normoglycemia since enrollment (non-progressors) continued routine follow-up assessments for incident pre-diabetes. Individuals with newly occurring pre-diabetes during the PROP-ABC follow-up period were promptly enrolled in the lifestyle intervention. Online supplemental figure S1 illustrates the design of the PROP-ABC study and its relationship to the antecedent POP-ABC study. Study participants were offered an honorarium of $25 per visit (up to $100/year), reimbursement for parking expenses, and sundry small incentive items (including baseball caps, umbrellas, and key chains).

All participants gave written informed consent prior to initiation of the study, which was conducted at the General Clinical Research Center.

Assessments

Serial assessments during study visits included medical history and physical examination; measurement of height, weight, waist circumference, and FPG every 6 months; and OGTT, body fat analysis by dual energy X-ray absorptiometry (Hologic Discovery A80044A, Hologic, Bedford, Massachusetts), lipid profile, insulin sensitivity, insulin secretion, and resting energy expenditure annually. We derived the body mass index (BMI) as the weight in kilogram divided by the height in meter squared. Insulin sensitivity was measured using hyperinsulinemic euglycemic clamp during the POP-ABC phase,[15 16 25] and subsequently by calculating the Matsuda Index[26] and the homeostasis model assessment of insulin resistance (HOMA-IR)[27] during the PROP-ABC phase. Insulin secretion was measured as the insulin response to glucose using the frequently sampled intravenous glucose tolerance test (15.16), and by calculating the insulinogenic index[28] and the homeostasis model assessment of beta-cell function.[27] Resting energy expenditure was measured by indirect calorimetry (Cardio Coach, KORR Medical Technologies, Salt Lake City, Utah).

Biochemical measurements

Plasma glucose was measured with YSI glucose analyzer (Yellow Springs Instruments, Yellow Springs, Ohio).

Plasma insulin was measured at our Endocrine Research Laboratory with a chemiluminescent assay using a commercial kit (Immulite, Siemens, Llanberis, Gwynedd, UK). The sensitivity of the insulin assay was 2 uIU/mL and the within-run and between-run coefficients of variation were 4.7% and 8%, respectively. Fasting plasma lipid profiles and hemoglobin A1c (HbA1c) levels were measured in a contract clinical laboratory.

Definition of pre-diabetes duration

The time from the date of first observation of confirmed pre-diabetes events to the date of the first visit for lifestyle intervention counseling was recorded as the duration of pre-diabetes.

Lifestyle intervention

The PROP-ABC lifestyle intervention design has been published.[29] Briefly, participants with incident pre-diabetes received counseling sessions (focused on increased physical activity and weight-based calorie reduction) delivered by registered dietitians. The goal was to encourage participants to accrue 180 min/week of moderate-intensity physical activity. Participants with baseline weight <113.4 kg (<250 pounds) were counseled to limit calorie intake to 1200–1500 kcal/day (40–50 g fat) and those with baseline weight ≥113.4 kg (≥250 pounds) were encouraged to limit intake to 1500–1800 kcal/day (50–60 g fat). These weight-based targets were adopted from the Look AHEAD study.[30] Overweight or obese participants were encouraged to lose weight (up to ~10% from enrollment weight). Along with lifestyle counseling, a study behaviorist (RR) provided psychological support to participants as needed. The lifestyle intervention program was delivered to groups of 5–10 participants during monthly face-to-face counseling sessions for the initial 6 months, followed by quarterly visits during the study period. The protocol specified 20 face-to-face counseling sessions over 5 years for PROP-ABC study participants and adopted flexible scheduling at participants' convenience. Adjunctive strategies included self-monitoring, meal replacements, and special campaigns.[29]

Definition of outcome

The primary outcome of the PROP-ABC study was the proportion of participants with reversal of pre-diabetes, persistent pre-diabetes, or incident T2D, following lifestyle intervention. Reversal of pre-diabetes was defined as the attainment of NGR, as indicated by normal FPG (<100 mg/dL or <5.5 mmol/L) and normal glucose tolerance (NGT) (2hPG level of <140 mg/dL or <7.8 mmol/L) during OGTT.[4 13] Persistent pre-diabetes was defined as the presence of IFG (FPG ≥100–125 mg/dL; ≥5.6–6.9 mmol/L) and/or IGT (2hPG level of 140–199 mg/dL; 7.8–11 mmol/L). Diabetes was diagnosed as FPG >126 mg/dL (≥7.0 mmol/L) and/or 2hPG >200 mg/dL (≥11.1 mmol/L).[4] Participants who maintained normal FPG and normal 2hPG levels throughout the combined POP-ABC and PROP-ABC follow-up period served as the control. The control subjects did not receive lifestyle or other intervention to alter the course of glycemia or body weight.

Statistical analysis

Data are reported as mean±SD for continuous variables and frequencies and per cent for categorical variables. Serial changes in clinical and biochemical variables were analyzed using repeated measures analysis of variance (ANOVA). Spearman correlation coefficients were used to analyze the association between weight change and physical activity. The study was powered to detect differences in the outcome of lifestyle intervention by intervals of pre-diabetes duration (<3 years, 3–5 years, >5 years) before the intervention. Assuming a 40% reversal rate from pre-diabetes to NGR, as reported in the Diabetes Prevention Program,[12] and an attrition rate of 20%, we calculated that a sample size of 120 subjects would provide ~85% power to detect medium to large differences. Outcome data were analyzed according to the intention to treat principle. The associations between duration of pre-diabetes and glycemic and metabolic variables were analyzed using linear regression models and Pearson correlation coefficients. In univariate analysis, categories of final glycemic status were compared using t-test and ANOVA for continuous variables and χ^2 test for categorical variables. In multivariate analysis, variables considered in univariate models were included in a logistic regression. OR, 95% CI, and p values were reported. Analyses were run on SAS (V.9.4) software. P<0.05 was accepted as significant.

RESULTS

Cohort characteristics

The 343 participants who completed the previous 5.5-year observational POP-ABC study were invited to join the interventional PROP-ABC study and 223 subjects (65%) agreed to re-enroll and were followed up for 5 years (mean 3.38±0.80 years). Of the 223 participants who re-enrolled in the PROP-ABC study, cumulatively 151 subjects developed incident pre-diabetes: 101 participants reached that endpoint during POP-ABC and 50 subjects did so during the PROP-ABC follow-up period. All participants with incident pre-diabetes initiated lifestyle intervention during the PROP-ABC phase. Of the 151 lifestyle intervention participants, 138 (91.3%) had evaluable follow-up data that were analyzed for the present report. Of the remainder, 12 lifestyle intervention participants dropped out of the study and 1 subject died from causes unrelated to the study (figure 1).

The study cohort was 70% women, 52.5% AA, and 47.5% EA; the mean age was 53.3±9.28 years and the mean BMI was 30.6±6.70 kg/m^2. Table 1 summarizes the characteristics of the study participants at enrollment in the PROP-ABC study. Compared with PROP-ABC participants who maintained normoglycemia during follow-up (control), participants with incident pre-diabetes had

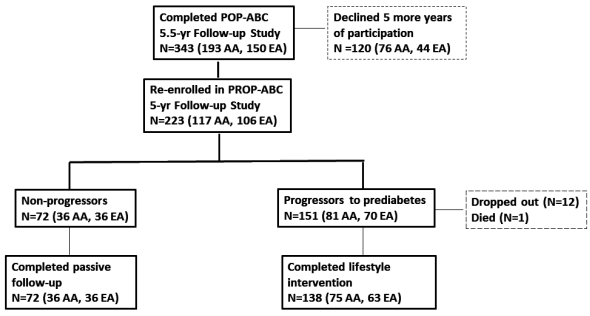

Figure 1 Enrollment data showing flow of participants from POP-ABC to PROP-ABC study. AA, African American; EA, European American; POP-ABC, Pathobiology of Prediabetes in a Biracial Cohort; PROP-ABC, Pathobiology and Reversibility of Prediabetes in a Biracial Cohort.

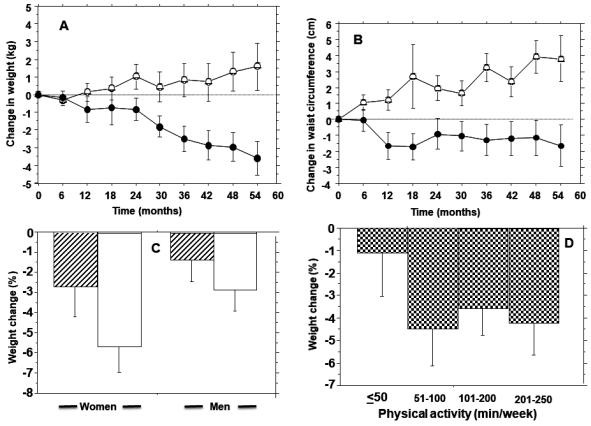

Figure 2 Changes in (A) body weight and (B) waist circumference in participants receiving lifestyle intervention (closed circles) versus control subjects (open circles); (C) weight change in African Americans (striped bars) and European Americans (open bars) and (D) in relation to physical activity during 5 years of lifestyle intervention. Repeated measures ANOVA p=0.037 for weight change, p=0.03 for change in waist circumference; weight change did not differ significantly by sex or race/ethnicity. ANOVA, analysis of variance.

higher baseline adiposity (weight, BMI, waist circumference, body fat) and glycemic (FPG, 2hPG, HbA1c) measures. The pre-diabetes group also had higher levels of triglycerides and insulin resistance (HOMA-IR, Matsuda Index) than the normoglycemic control group (online supplemental table S1). The pre-diabetes group initiated lifestyle intervention after a mean duration of 4.08±2.02 years (range 3 months–8.3 years) from the diagnosis of pre-diabetes.

Adherence to interventions

In all, 70.6% of participants attended 50% or more of the protocol-specified 20 face-to-face lifestyle counseling sessions over 5 years; 55.8% attended 75% of the sessions and 42.5% attended 100% of the scheduled sessions. Syllabus materials with visit-specific content were mailed to all participants who missed face-to-face sessions.[29] The study protocol recommended a physical activity target of 180 min/week. The mean self-reported weekly physical activity level was 129±67 min/week (71.7% of target). Objective data downloaded from participants' pedometers showed average movement activity of 6564±3053 steps/day. There was a significant correlation between self-reported exercise minutes and daily steps recorded by pedometers (r=0.47, p<0.0001). Dietary change was assessed only at 1 year. Self-reported energy intake decreased insignificantly from 1549±207 kcal/day at baseline to 1485±263 kcal/day at 1 year (p=0.17), but fat intake decreased significantly from 56.0±21.9 g/day to 47.4±16.3 g/day (p=0.029) during the same period.

Adiposity measures

Lifestyle intervention participants showed significant decrease from baseline in body weight, waist circumference, and trunk fat mass, and a downward trend in total fat mass, during 5 years of intervention. In contrast, the control group showed temporal increase in these adiposity measures (online supplemental table S2 and figure 2). The mean weight loss was −2.91±6.56 kg (3.06%±6.90%) among lifestyle intervention participants, with an insignificant trend toward sex and ethnic differences (women: −5.71%±8.25% in EA vs −2.73%±10.9% in AA, p=0.15; men: −2.88%±4.93% in EA vs −1.36%±5.53% in AA, p=0.79) (figure 2). Participants who reported 50 min/week or less of physical activity experienced less

Table 1 Changes in adiposity and glycemic measures in relation to duration of pre-diabetes before lifestyle intervention

	Duration of pre-diabetes before lifestyle intervention			
Outcome	**<3 years**	**3–5 years**	**>5 years**	**ANOVA p value**
Weight (kg)	−5.18±9.58	−1.07±6.35	−3.20±4.81	0.19
Waist circumference (cm)	−1.52±9.93	−1.33±6.22	−2.05±4.77	0.862
Total fat mass (kg)	−2.33±7.56	−1.27±5.66	−1.79±3.66	0.862
Trunk fat mass (kg)	−2.68±5.97	−1.72±4.32	−1.70±3.09	0.554
FPG (mg/dL)	−3.30±8.66	−13.0±8.66	−4.23±8.60	<0.0001
2hPG (mg/dL)	−14.9±38.3	−7.77±30.5	−7.41±28.3	0.052

To convert the values for glucose to mmol/L, multiply by 0.056.
ANOVA, analysis of variance; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose.

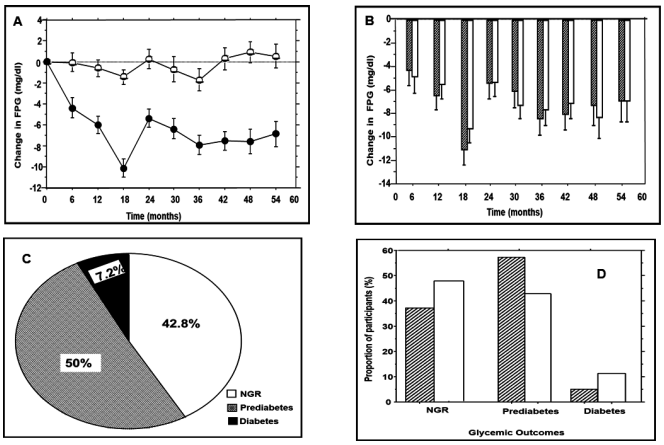

Figure 3 (A) Serial changes in FPG in participants receiving lifestyle intervention (closed circles) versus control subjects (open circles). (B) Changes in FPG among African American (striped bars) and European American (open bars) lifestyle participants. Proportion of (C) all lifestyle participants and (D) African Americans (striped bars) and European Americans (open bars) with NGR, pre-diabetes, and diabetes after lifestyle intervention. Repeated measures ANOVA p=0.0008 for FPG change in lifestyle intervention participants versus control subjects. ANOVA, analysis of variance; FPG, fasting plasma glucose; NGR, normal glucose regulation.

weight loss than those with higher exercise levels, but the differences were not statistically significant due to wide variability (figure 2). The correlation coefficient between self-reported exercise minutes and per cent weight change was significant in men (r=−0.50, p=0.0026) but not in women (r=−0.02, p=0.87).

Glycemic and metabolic measures

The mean FPG was 106±9.89 mg/dL and 2hPG was 153±31.9 mg/dL among participants with incident pre-diabetes at initiation of lifestyle intervention. During 5 years of follow-up, FPG values decreased in lifestyle intervention participants but increased slightly among subjects in the control group (−7.76±10.8 mg/dL vs 1.23±1.43 mg/dL, p=0.0008) (online supplemental table S2). There were no significant differences by sex or race/ethnicity in mean changes in FPG among the lifestyle participants (women: −5.40±8.05 mg/dL in EA vs −5.80±7.45 mg/dL in AA, p=0.51; men: −5.56±8.88 mg/dL in EA vs −7.93±14.9 mg/dL in AA, p=0.79). Figure 3 shows the serial changes in mean FPG in the lifestyle intervention and control groups. The changes in FPG during lifestyle intervention were similar in AA and EA participants (figure 3B). The 2hPG values decreased in the lifestyle intervention and control groups, with a trend toward greater reduction in the former (−6.60±33.1 mg/dL vs −3.90±15.6 mg/dL, p=0.48) (online supplemental table S2). The temporal changes in plasma lipid profile tended to be more favorable overall in the lifestyle intervention group compared with the control group (online supplemental table S2).

Duration of pre-diabetes versus changes in adiposity and glycemia

The participants with incident pre-diabetes were classified into three strata by duration of pre-diabetes prior to initiation of lifestyle intervention: <3 years (n=32; 23.2%), 3–5 years (n=59; 42.8%), or >5 years (n=47; 34%). Table 1 summarizes the changes in adiposity and blood glucose measures in relation to pre-diabetes duration before initiation of lifestyle intervention. There were no significant differences in mean changes in weight, waist circumference, and total and trunk fat mass across the three strata of pre-diabetes duration (<3 years, 3–5 years, >5 years) before initiation of lifestyle intervention.

We observed a significant interaction between duration of pre-diabetes before lifestyle intervention (categorical variable) and change in FPG levels (and a similar trend for 2hPG), indicating greater glycemic decreases when lifestyle intervention was initiated within 5 years of pre-diabetes diagnosis than after 5 years of diagnosis (table 1). In linear regression, duration of pre-diabetes before lifestyle intervention (continuous variable) correlated inversely with insulin secretion (insulinogenic index: r=−0.21, p=0.019) and with insulin secretion corrected for insulin sensitivity (disposition index: r=0.20, p=0.028), but showed no correlation with insulin sensitivity assessed either by the Matsuda Index (r=0.04, p=0.96) or HOMA-IR (r=0.019, p=0.83).

Final glycemic classification

The final glycemic outcomes after 5 years (mean 3.38±0.80 years) of lifestyle intervention showed that 59 participants (42.8%) had reversed from pre-diabetes to NGR, 69 participants (50%) had maintained persistent pre-diabetes, and 10 participants (7.2%) had progressed to T2D (figure 3C). With an average follow-up period of 3.38 years, the diabetes incidence among the 138 lifestyle intervention participants was 2.14 cases per 100 person-years. Glycemic outcomes did not differ significantly by race/ethnicity (p=0.21) (figure 3D). Comparing AA versus EA participants, regression from pre-diabetes to NGR occurred in 37.3% vs 47.6%, persistent pre-diabetes occurred in 57.3% vs 42.9%, and T2D occurred in 5.33% vs 9.52%.

Approximately similar proportions of participants who initiated lifestyle intervention less than 3 years, 3–5 years, or longer than 5 years after diagnosis of pre-diabetes experienced reversal of pre-diabetes or persistent pre-diabetes without progression to diabetes (table 2).

Reversal to NGR versus persistent pre-diabetes

Compared with participants who had persistent pre-diabetes after lifestyle intervention, those who experienced reversal of pre-diabetes to NGR had significantly lower waist circumference (p=0.041) and 2hPG (p=0.0007) and higher insulin sensitivity (Matsuda Index, p=0.0081; HOMA-IR, p=0.014) at baseline. In a logistic regression model that included all three variables as potential predictors of pre-diabetes reversal, we

Table 2 Glycemic outcomes in relation to duration of pre-diabetes before lifestyle intervention among participants with incident pre-diabetes

Outcome	All n (%)	Duration of pre-diabetes before lifestyle intervention		
		<3 years n (%)	3–5 years n (%)	>5 years n (%)
NGR	59 (42.8)	14 (43.8)	24 (40.7)	21 (44.7)
Pre-diabetes	69 (50)	17 (53.1)	30 (50.8)	22 (46.8)
T2D	10 (7.2)	1 (3.1)	5 (8.5)	4 (8.5)
Total	138 (100)	32 (100)	59 (100)	47 (100)

χ^2 p=0.901.
NGR, normal glucose regulation; T2D, type 2 diabetes.

obtained the following OR and 95% CI: 2hPG, OR=0.977 (95% CI 0.960 to 0.994, p=0.02); waist circumference, OR=0.978 (95% CI 0.951 to 1.007, p=0.13); and Matsuda Index, OR=1.076 (95% CI 0.910 to 1.271, p=0.39). Thus, higher baseline 2hPG levels significantly predicted lower likelihood of pre-diabetes reversal. Baseline age, FPG, BMI, insulin secretion, and time from occurrence of pre-diabetes to initiation of lifestyle intervention (4.08±2.17 years vs 3.99±1.99 years, p=0.81) were not significantly different between the NGR group and the persistent pre-diabetes group.

Compared with the persistent pre-diabetes group, participants who reversed to NGR showed greater decrease in FPG (−10.2±10.8 mg/dL vs −5.29±6.10 mg/dL, p=0.04) and 2hPG (−18.5±22.1 mg/dL vs −1.29±19.0 mg/dL, p=0.0076) during lifestyle intervention. However, there were no significant differences between the NGR and persistent pre-diabetes groups with regard to mean changes in weight (−2.73±4.61 kg vs −1.90±8.31 kg, p=0.67) or waist circumference (−2.18±6.21 cm vs −1.67±4.87 cm, p=0.66) during lifestyle intervention.

DISCUSSION

In the present study, we assessed the impact of lifestyle intervention in normoglycemic offspring of parents with T2D who developed incident pre-diabetes during prospective follow-up. Our findings showed that the vast majority (~93%) of participants who received lifestyle intervention within 3 months to 8 years (mean ~4 years) of developing pre-diabetes did not progress to T2D during 5 years of follow-up. The diabetes incidence of 2.34 cases per 100 person-years in our study appears lower than the rates reported by lifestyle intervention studies in people with pre-diabetes of unknown duration.[8–12] In the Da Qing study, the diabetes incidence among participants assigned to diet, exercise, and diet-plus-exercise intervention groups was 10, 8.3, and 9.6 cases per 100 person-years, respectively.[9] The diabetes incidence (cases per 100 person-years) among lifestyle intervention participants was 4.8 in the Diabetes Prevention Programme (DPP),[8] 13.1 in the Indian DPP (IDPP)-1,[11] and 2.75 in the Finnish Diabetes Prevention Study (FDPS).[10]

Thus, except for the FDPS, previous lifestyle intervention studies in people with pre-diabetes of unknown duration reported at least twofold higher diabetes incidence rates compared with our PROP-ABC study, where lifestyle intervention was initiated within 3 months to 8 years of incident pre-diabetes. It is unknown how long participants in the DPP, FDPS, Da Qing study, and IDPP-1 had had pre-diabetes before starting lifestyle intervention.[8–12] Because ~85% of people with pre-diabetes are unaware of their condition, it is plausible that previous studies enrolled people with longer-duration pre-diabetes than PROP-ABC participants.[1] Direct comparison with previous studies is hampered by demographic and methodological differences; conceivably, people with undiagnosed pre-diabetes over protracted periods may suffer declines in insulin action or secretion that could decrease the efficacy of lifestyle interventions.[23 24]

In fact, we observed that the pre-diabetes duration before lifestyle intervention was inversely related to beta-cell function. Furthermore, we observed greater decrease in FPG and 2hPG when lifestyle intervention was initiated within 5 years of pre-diabetes diagnosis than after 5 years of diagnosis. However, when comparing the categorical outcomes of reversal or persistence of pre-diabetes, the rates were similar among participants who started lifestyle intervention at less than 3 years, 3–5 years, or greater than 5 years after the occurrence of pre-diabetes. Together, our findings suggest that initiating lifestyle intervention after up to ~8 years of pre-diabetes diagnosis would still be highly efficacious in preventing progression to T2D, but earlier intervention could have a greater glycemic impact.

The mean weight loss from baseline of ~3% in the present study is comparable with the mean weight loss of ~4% and ~3% reported for the lifestyle intervention arms of the DPP and Malmo study, respectively.[8 31] The DPP data showed that participants who did not meet the weight loss goal but achieved the physical activity goal of 150 min/week or greater experienced a 44% decrease in diabetes incidence.[32] Furthermore, despite observing no weight loss in their participants, investigators in the Da Qing study and the IDPP-1 reported significant decrease in diabetes incidence following lifestyle intervention.[9 11 33]

Thus, even with modest or no weight loss, healthier lifestyle can protect against cardiometabolic risks, via mechanisms that include exercise-induced improvements in fitness and body composition.[34–37]

We observed that ~43% of lifestyle intervention participants reverted to NGR, whereas 50% had persistent pre-diabetes, consistent with ~30% to ~50% pre-diabetes reversal rates in previous reports.[8 12 31] Compared with the persistent pre-diabetes group, PROP-ABC participants who achieved NGR had lower FPG, 2hPG, and waist circumference, and higher insulin sensitivity at baseline, as also observed among DPP participants.[38 39] However, lifestyle intervention, independent of weight loss, also predicted reversal to NGR in the DPP.[38] Persistent pre-diabetes is associated with vascular complications,[5–7] and there is evidence that reversal of pre-diabetes to NGR (even transiently) may reduce the risk of developing diabetes and related complications.[40–43] In an observational study, reversion from pre-diabetes to normoglycemia, as compared with progression to T2D, was associated with ~22% lower incidence of cardiovascular events and 18% lower risk of death during a median follow-up period of 8.75 years.[43] By contrast, persistent pre-diabetes during the same follow-up period was not associated with significant differences in cardiovascular or mortality risk compared with progression to T2D.[43] Thus, restoration of NGR ought to be a primary goal in people with pre-diabetes. Because current lifestyle intervention strategies restore NGR only in ~50% of individuals with pre-diabetes, opportunity exists for novel interventions, including combined lifestyle and pharmacological approaches.[14 44]

The strengths of the present study include enrollment of high-risk AA and EA with parental T2D, the prospective design, and the rigorous adjudication of outcomes. Importantly, unlike previous diabetes prevention studies, we were able to time the onset of pre-diabetes to within a window of 3–6 months by monitoring blood glucose in initially normoglycemic POP-ABC and PROP-ABC participants. Despite the strengths of our study, the restriction of enrollment to offspring of parents with T2D limits the generalizability of our findings. Specifically, the similar glycemic outcomes in AA and EA participants are in discord with the reported ethnic disparities in diabetes prevalence.[45] However, the DPP, which was not restricted to people with parental diabetes, reported similar efficacy of lifestyle intervention on diabetes incidence and regression of pre-diabetes across ethnic groups.[8 38]

Another weakness pertains to the level of adherence to the lifestyle protocol: despite flexible scheduling aimed at maximizing convenience for participants, only 70.6% attended half or more of the scheduled 20 face-to-face counseling sessions over 5 years. Similarly, only 51% of participants reported physical activity of 100 min or greater per week during the study, despite the prescribed target of 180 min/week. Our experience with the PROP-ABC participants probably reflects real-world challenges of balancing the demands of work, family, and social life with active participation in longitudinal research. Per protocol, lifestyle intervention syllabus materials were mailed to all participants who missed face-to-face visits. However, mailed materials might not match physical attendance regarding the efficacy of lifestyle intervention, given the correlation between frequency of face-to-face contacts and weight loss.[29 46] Nonetheless, there is evidence that self-directed healthy lifestyle practices (including optimal diet and physical activity) are associated with increased likelihood of reversion to NGT among people with pre-diabetes.[47]

Face-to-face lifestyle intervention has limitations for translation of diabetes prevention for the >400 million adults with pre-diabetes worldwide.[1–3] Alternative modes, including internet-based delivery, have yielded mixed results regarding efficacy in weight control.[48 49] Until definitive data become available, inperson lifestyle counseling approach, supplemented with remote delivery methods, seems prudent. In conclusion, we have shown that starting lifestyle intervention within 3 months to 8 years of incident pre-diabetes was associated with robust prevention of progression to diabetes and reversal of pre-diabetes in high-risk AA and EA with parental T2D.

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Contributors SD-J (guarantor) conceived of and designed the study, analyzed the data, and drafted manuscript. NU, AAB, IO, VM, and RR collected the data and reviewed and revised manuscript. JW performed the statistical analysis and reviewed and revised manuscript. As guarantor, SD-J accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the University of Tennessee Health Science Center Institutional Review Board (reference number: 12-01970-FB). The study was conducted in accordance with the principles of the Helsinki Declaration. Participants gave informed consent to participate in the study before taking part.

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