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Exploring residual risk for diabetes and microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS)

Short title: Residual risk factors in the DPPOS

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What's new?

- The Diabetes Prevention Outcomes Study (DPPOS) is the largest global trial to date aimed at preventing or delaying diabetes onset in a high-risk group.
- We have retained ~ 85% of the original participants for nearly 20 years.
- At the time of the most recent data lock, ~ 50% of participants had developed diabetes, whereas the others had not. This analysis examines residual risk factors for diabetes and microvascular disease not formerly explored in the DPPOS.
- Simple clinical information, such as the number of medications taken and glycaemic variability, are associated with increased risk for diabetes and microvascular disease.
- Hypertension and use of anti-hypertensive medication predicted composite microvascular disease independent of diabetes status.

Abstract

Aim Approximately half of the participants in the Diabetes Prevention Outcomes Study (DPPOS) had diabetes after 15 years of follow-up, whereas nearly all the others remained with pre-diabetes. We examined whether formerly unexplored factors in the DPPOS coexisted with known risk factors that posed additional risk for, or protection from, diabetes as well as microvascular disease.

Methods Cox proportional hazard models were used to examine predictors of diabetes. Sequential modelling procedures considered known and formerly unexplored factors. We also constructed models to determine whether the same unexplored factors that associated with progression to diabetes also predicted the prevalence of microvascular disease. Hazard ratios (HR) are per standard deviation change in the variable.

Results In models adjusted for demographics and known diabetes risk factors, two formerly unknown factors were associated with risk for both diabetes and microvascular disease:

number of medications taken (HR = 1.07, 95% confidence intervals (95% CI) 1.03 to 1.12 for diabetes; odds ratio (OR) = 1.10, 95% CI 1.04 to 1.16 for microvascular disease) and variability in HbA_{1c} (HR = 1.02, 95% CI 1.01 to 1.03 for diabetes; OR = 1.06, 95% CI 1.04 to 1.09 for microvascular disease per SD). Total comorbidities increased risk for diabetes (HR = 1.10, 95% CI 1.04 to 1.16), whereas higher systolic (OR = 1.22, 95% CI 1.13 to 1.31) and diastolic (OR = 1.14, 95% CI 1.05 to 1.22) blood pressure, as well as the use of anti-hypertensives (OR = 1.41, 95% CI 1.23 to 1.62), increased risk of microvascular disease.

Conclusions Several formerly unexplored factors in the DPPOS predicted additional risk for diabetes and/or microvascular disease – particularly hypertension and the use of anti-hypertensive medications – helping to explain some of the residual disease risk in participants of the DPPOS. (Clinical Trial Registry Nos: DPP NCT00004992 and DPPOS NCT00038727)

Introduction

To date, the Diabetes Prevention Program (DPP) is the largest clinical trial in the world designed to determine whether an intensive lifestyle intervention or metformin could prevent or delay the onset of Type 2 diabetes in a high-risk multi-ethnic cohort [1]. Of the 3234 original participants in the DPP, 85% continue to be followed in the Diabetes Prevention Program Outcomes Study (DPPOS), 14–17 years post randomization at 10 July 2013, the closing date of this analysis. Approximately half the participants had developed diabetes and nearly all the others continued to have pre-diabetes, as they did from initial enrolment. The annual incidence rate of diabetes has decreased in all groups and has not differed significantly between the intervention groups in recent years, presumably due to depletion of susceptible individuals [2]. Thus, many participants have had persistent pre-diabetes, without the development of overt diabetes, over the past 15 years of study. This is the case despite the presence of significant baseline risk for progression based on traditional diabetes risk factors

(e.g. obesity, elevated fasting glucose, impaired glucose tolerance). The observation that nearly half remained free of diabetes despite the presence of substantive clinical risk raises the possibility that residual factors coexist with known risk factors that collectively protect from or exaggerate risk for diabetes. Identification of these formerly unexplored factors could aid with risk stratification, and thereby improve decision-making in the setting where resources are being directed toward prevention.

Active treatment during DPP resulted in rapidly apparent, persistent treatment-specific effects to prevent or delay diabetes [1,3], and the prevention/delay of diabetes was associated with a lower prevalence of microvascular disease 14–17 years post randomization [4]. Surprisingly, the treatment-specific differences in rates of diabetes have not produced corresponding differences in the overall prevalence of microvascular disease to date, with the exception that among women only, the prevalence of microvascular disease was lower in the intensive lifestyle group [4]. This observation has been ascribed to the minimal degree of hyperglycaemia experienced to date among most DPPOS participants who developed diabetes [4]. It may also suggest that the interventions used in the DPP, although effective at minimizing glycaemia, have been insufficient to mitigate important non-glycaemic determinants of microvascular disease, such as habitual diet or social factors. The possibility that non-glycaemic biomarkers could inform us about risk, for both diabetes and related complications, needs further elucidation.

Only part of the risk for diabetes [5], and the risk for microvascular [6] and macrovascular [7] complications associated with diabetes is explained by known risk factors. This gap in the current knowledge led to a search for residual factors with diabetogenic or anti-diabetogenic potential. The objective of the current analysis was to examine the effects of factors formerly unexplored in the DPP to reduce or augment risk for diabetes and/or microvascular disease in this high-risk cohort. We hypothesized that formerly unexplored factors may be protective,

rendering a state of non-progressive pre-diabetes with a lower cumulative glycaemic exposure and lower risk for microvascular disease.

Patients and methods

Participants

The DPP was a randomized clinical trial performed at 27 research centres in the USA that enrolled overweight or obese adults with pre-diabetes determined on one occasion. BMI $\geq 24 \text{ kg/m}^2$ ($\geq 22 \text{ kg/m}^2$ in Asian Americans), elevated fasting glucose 95–125 mg/dl (5.3–6.9 mmol/l; $< 6.9 \text{ mmol/l}$ in the American Indian Centers) and 2-h plasma glucose levels of 140–199 mg/dl (7.8–11.0 mmol/l) were eligibility criteria. The DPPOS is the follow-up to the DPP and includes 2775 people (85% of the original cohort at the data lock on 10 July 2013).

Detailed methods have been published previously [8] and the protocol is available at <http://www.bsc.gwu.edu/dpp>. Institutional review boards at each centre approved the protocol, and all participants gave written informed consent prior to participation.

Interventions

During the DPP, participants were randomized to: (1) an intensive lifestyle intervention (low-fat diet and exercise $> 150 \text{ min/week}$ for a goal of 7% body weight reduction); (2) metformin 850 mg twice daily; or (3) matching placebo (Fig. 1). Median follow-up during the DPP was 3.2 years followed by a 10-month ‘bridge’ period when all participants were offered group-implemented lifestyle sessions prior to the start of DPPOS, including those who had been randomized to the intensive lifestyle arm during DPP [3]. Open-label metformin was also continued in participants initially randomized to metformin during DPP, and discontinued when progression to diabetes required management outside the protocol, or for reasons of

safety and/or tolerability. Median follow-up in the DPPOS was 15 years from randomization to the closing date of this analysis (10 July 2013; range 14–17 years).

Outcomes

The primary outcome of the DPP and DPPOS is the development of diabetes, defined as a fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/l; tested twice a year) and/or 2-h glucose ≥ 200 mg/dl (≥ 11.1 mmol/l; tested annually) during a 75-g oral glucose tolerance test (OGTT). Once diabetes is confirmed on a second test, the participant is classified as having diabetes regardless of subsequent plasma glucose values. Persistent normoglycaemia is defined as fasting plasma glucose levels of < 100 mg/dl (5.6 mmol/l) and 2-h plasma glucose levels of < 140 mg/dl (7.8 mmol/l) on every annual OGTT after enrolment. Persistent pre-diabetes [9] is defined as fasting plasma glucose levels of 100–125 mg/dl (5.6–6.9 mmol/l), 2-h plasma glucose levels of 140–199 mg/dl (7.8–11.0 mmol/l), or both on an OGTT at baseline and at least once thereafter, but not developing diabetes and not achieving persistent normoglycaemia during follow-up. Approximately 50% of participants achieved normoglycaemia at some time during the trial [10], however, its persistence was uncommon. To focus on predictors of diabetes vs. persistent pre-diabetes, 45 participants (1.4%) who achieved and maintained normoglycaemia throughout the DPP and DPPOS were excluded from the present analysis. Predictors of normoglycaemia and its protection from diabetes have been reported previously [10,11].

Development of microvascular disease is a co-primary outcome of DPPOS

Microvascular disease was defined as follows:

- retinopathy; diagnosed on 7-field stereoscopic fundus photography by the Early Treatment of Diabetic Retinopathy Study (ETDRS) as ≥ 20 in either eye, or treatment of retinopathy with laser photocoagulation or intravitreal injections, assessed during the DPPOS in 2012 or 2013;
- neuropathy; defined as loss of light touch sensation (< 8 of 10 applications detected on the dorsum of the great toe) measured with a 10-gram Semmes–Weinstein monofilament [12], assessed annually throughout DPPOS; and/or
- nephropathy; assessed by albuminuria ≥ 30 mg/g creatinine in a spot urine collection on two consecutive tests, or an eGFR < 45 ml/min/1.73 m², based on annual serum creatinine using the CKD-EPI equation [13] on two consecutive tests, or renal failure (end-stage renal disease, dialysis or transplantation, assessed annually throughout the DPPOS). Participants taking antihypertensive drugs at the final assessment who did not meet albuminuria or estimated GFR criteria at that time were considered to have reached the nephropathy outcome if the nephropathy criteria were met at two consecutive prior visits.

Predictors of interest

We examined the influence of formerly unexplored factors in the DPPOS in the context of factors that have been shown as related to diabetes in the DPP and/or DPPOS. A complete list of all predictors explored, their measurement interval(s) and method of derivation are presented in Table 1. Quality of life used the composite score from the SF6D, a truncated version of the SF-36 Health Survey Questionnaire [14]. Values were taken from the baseline of the DPP, with the exception of time-varying change in the major predictors of diabetes in

the DPP and/or DPPOS (variability in weight, i.e. standard deviation in weight over the DPP and DPPOS, regression to normal glucose regulation (NGR; defined during DPP) and variability in HbA_{1c}, i.e. root mean square HbA_{1c} over DPP and DPPOS). The baseline characteristics of the randomized cohort have been published previously [15].

Statistical analyses

Selected factors were examined for their prediction of diabetes and microvascular disease (Table 1). Univariate Cox proportional hazards regression models were constructed for each potential predictor and adjusted for age, sex and race/ethnicity, and DPP treatment arm (model 1). The subsequent multivariable model (model 2) adjusted model 1 for factors formerly shown to predict diabetes in the DPP (baseline fasting and 2-h plasma glucose, insulin secretion and sensitivity, BMI, history of gestational diabetes, use of antidepressants and plasma adiponectin concentration, as well as time-varying BMI, HbA_{1c} and regression to NGR). Hazard ratios (HRs) in these models represent the comparison of a categorical variable to its reference category, or per standard deviation difference in a continuous variable. We applied a parallel approach to evaluate the association of the candidate prognostic factors with microvascular disease, applying logistic regression rather than Cox proportional hazards modelling because composite microvascular disease prevalence data were available at only one point in time. Duration of diabetes was also included as a covariate for model 2 predicting microvascular disease. The model building procedure used to derive models 1 and 2 (above) was repeated to examine the predictive value of candidate factors on prevalence of nephropathy, neuropathy and retinopathy, as well as the composite microvascular complication outcome (i.e. one or more of these complications), occurring at a median time of 15 years since initial enrolment in the DPP. Using the methods of Bonferroni, a *P*-value of ≤ 0.002 was used to denote significance accounting for multiple comparisons.

Thus, the 95% confidence intervals (95% CI) may not cross 1.0 and still be considered not significant.

Results

By 10 July 2013, diabetes had been diagnosed in 50.4% of participants, 48.2% had pre-diabetes (without ever meeting the diagnosis of diabetes), and 1.4% returned and remained normoglycaemic (the latter were excluded from this analysis; see above). Those with persistent pre-diabetes had plasma glucose values consistent with the diagnostic thresholds for pre-diabetes 77% of the time (vs. 93% in those who progressed to diabetes) and normoglycaemia 23% of the time (vs. 7% in those who progressed to diabetes).

Formerly unexplored predictors of diabetes and microvascular disease in the DPPOS

In fully adjusted models (model 2), two formerly unidentified factors were associated with risk for both diabetes and microvascular disease: greater number of medications taken (HR = 1.03, 95% CI 1.03 to 1.12 for diabetes; odds ratio (OR) = 1.10, 95% CI 1.04 to 1.16 for microvascular disease) and variability in HbA_{1c} (HR = 1.02, 95% CI 1.01 to 1.03 for diabetes; OR = 1.06, 95% CI 1.04 to 1.09 for microvascular disease). The most common types of medication reported were hormones (oral contraceptives or post-menopausal hormone therapy) and anti-hypertensives, accounting for 24.8% and 17.7% respectively, of the total medications reported. We performed a sensitivity analysis to determine whether the use of anti-hypertensive medication explained the association between total medications reported and diabetes and microvascular disease. After omission of anti-hypertensive drugs, numbers of medications taken were no longer significantly related to diabetes (HR = 1.07, 95% CI 1.02 to 1.11) or microvascular disease (OR = 1.06, 95% CI 0.99 to 1.13). Anti-hypertensive use was associated with microvascular disease (OR = 1.41, 95% CI 1.23 to

1.62), independent of blood pressure, with a similar trend seen for diabetes (OR = 1.17, 95% CI 1.05 to 1.31).

Formerly unexplored predictors of diabetes or microvascular disease, but not both, in the DPPOS

Total comorbidities increased risk for diabetes (HR = 1.10, 95% CI 1.04 to 1.16) with a similar trend observed for microvascular disease (OR = 1.12, 95% CI 1.04 to 1.20). Greater time varying triglyceride (TG)/HDL ratio predicted diabetes and microvascular disease in model 1, but not in model 2 (Table 2). Both systolic (OR = 1.22, 95% CI 1.13 to 1.31) and diastolic (OR = 1.14, 95% CI 1.05 to 1.22) blood pressure were associated with an increased risk of microvascular disease, whereas systolic blood pressure alone was associated with diabetes in model 1 (OR = 1.12, 95% CI 1.07 to 1.18). Higher quality of life appeared to protect against diabetes in the univariate model, but failed to maintain significance in the multivariable model.

Formerly unexplored predictors of retinopathy, nephropathy and/or neuropathy in the DPPOS

To account for differences in ascertainment intervals, mixed models were used to estimate prevalence of retinopathy (11%), nephropathy (14%) and neuropathy (12%). Greater number of comorbidities reported (OR = 1.23, 95% CI 1.10 to 1.38; OR = 1.19), associated with nephropathy, in the fully adjusted model, as observed with diabetes and composite microvascular disease. As with composite microvascular disease, the relationships between the subtypes of microvascular disease and numbers of medications reported did not retain significance after omission of anti-hypertensive medications (OR = 0.94, 95% CI 0.78 to 1.13 for nephropathy; OR = 0.91, 95% CI 0.71 to 1.17 for retinopathy; OR = 1.20, 95% CI 0.95 to

1.52, $P = 0.12$ for neuropathy). Variability in HbA_{1c} was the only formerly unexplored factor that associated with retinopathy after full adjustment (OR = 1.09, 95% CI 1.04 to 1.14). Both systolic (OR = 1.47, 95% CI 1.30 to 1.65) and diastolic (OR = 1.31, 95% CI 1.17 to 1.48) blood pressure associated with an increased risk for nephropathy, as they did for composite microvascular disease. The associations between quality of life, household income and weight variability with neuropathy were only observed in the univariate model.

A subset of these known and formerly explored factors and their association with the various outcomes in the DPPOS are shown in Table 2. Data for all the selected variables on the outcomes are shown in univariate and multivariate models in Tables S1–S6.

Discussion

Approximately half of participants in the DPPOS have persistent pre-diabetes since their enrolment over 15 years ago. We sought to determine whether protective factors coexisted with known risk factors to retard development of overt diabetes and/or microvascular disease, or, alternatively, if formerly unidentified novel risk factors compounded known risk in those who developed diabetes and/or microvascular disease. Major findings from the current analyses suggest that the number of medications taken, as well as variability in HbA_{1c}, proved to be formerly unidentified predictors of both diabetes and microvascular disease in the DPPOS. Hypertension and the use of anti-hypertensive medications appeared particularly relevant to microvascular disease, but far less so to diabetes. Collectively, formerly unexplored factors appear to provide additional information for the prediction of microvascular disease rather than diabetes in our well-described DPPOS cohort.

As momentum builds in support of widespread preventive interventions in people with pre-diabetes [16–18], important counter-arguments must be addressed. Yudkin and Montori wrote a recent counterpoint to the medicalization of pre-diabetes [19], citing over-diagnosis

by current criteria and unnecessary treatment for the ~ 50% of people with pre-diabetes never destined to develop diabetes. Data from the Baltimore Longitudinal Study of Aging suggest that two-thirds of people with pre-diabetes will either spontaneously regress or remain with pre-diabetes for long durations, leaving only the remaining one-third at risk for diabetes itself [20]. In diabetes prevention studies, including the DPP, diabetes risk is determined primarily by elevated plasma glucose levels (fasting and/or post-OGTT). Current findings highlight the deficiencies of this approach and indicate a clear need for risk stratification beyond glycaemia. In the present analysis, we demonstrate higher incidences of both diabetes and microvascular disease in participants who reported a greater number of medications taken from the outset of the DPP, with only two medications needed to go from the 25th to the 75th percentile for risk (data not shown). This was particularly relevant when participants reported using anti-hypertensives. In addition, variability in HbA_{1c} (as a measure of glycaemic variability [21]) over time, also appeared to influence risk for diabetes and microvascular disease beyond traditional risk factors. Ongoing clinical trials hope to prove this point [22,23] making both the absolute HbA_{1c} and glycaemic variability relevant to patient care. Collection of this basic historical and laboratory information, which is already performed routinely, may improve our risk assessment for people with pre-diabetes where access to other information is limited.

In pursuit of novel risk-conferring or protective factors for diabetes and microvascular disease, some factors exhibited discordance associating with one or the other, but not both. Total comorbidities increased the risk for diabetes with a similar trend observed for microvascular disease. Given the close correlation between numbers of medications taken and numbers of comorbidities reported, this information likely reflects overall health status and deserves greater appreciation as a metric of health risk [24]. By contrast, both SBP and DBP increased the risk of microvascular disease with little association with diabetes.

Although hypertension is widely recognized as a risk factor for microvascular disease and cardiovascular disease [25,26], this is the first report of these associations in the DPPOS.

Importantly, these results highlight the risk for microvascular disease associated with hypertension that may precede the onset of diabetes [27]. Accordingly, the management of hypertension remains central in the prevention of both micro- and macrovascular disease.

The DPPOS used a composite microvascular disease outcome as its primary endpoint for long-term complications [4], in part, with the expectation of a shared mechanism for retinopathy, nephropathy and neuropathy [28]. Although greater number of comorbidities reported and variability in HbA_{1c} associated with both diabetes and composite microvascular disease, they did not associate uniformly with each individual microvascular disease subtype.

Specifically, a greater number of comorbidities reported predicted nephropathy, whereas variability in HbA_{1c} predicted retinopathy, in the fully adjusted models. The latter observation is consistent with the highly specific association between retinopathy and plasma glucose concentration [29,30]. By contrast, hypertension appeared specific to nephropathy.

Together, these preliminary post hoc results cast a degree of uncertainty on the prevailing paradigm that development of microvascular disease is relatively homogenous [28].

Expanding our knowledge of the pathogenesis of microvascular diseases will likely lead to new approaches to prevent them.

Several limitations of our analysis warrant mention. This analysis is post hoc and the results can be viewed as hypothesis generating. Associations do not confirm causation. Thus far, rates of complications, especially for the individual components of microvascular disease, have been very low and different ascertainment schedules, as well as the sensitivity of our methods of detection, for the microvascular disease endpoints complicate direct comparisons of individual microvascular disease outcomes.

In conclusion, the current analysis highlights several formerly unexplored factors that associate with risk for diabetes, but did not heighten our understanding as to why approximately half of our high-risk cohort has developed diabetes since enrolment into DPP, whereas the other half has not. Several of these factors predicted composite microvascular disease, whereas some were associated with either diabetes or microvascular disease, but collectively only improved prediction for microvascular disease. Importantly, our findings were comprised of basic information (e.g. use of blood pressure lowering medication) routinely collected in a clinical setting providing additional information about who may be at risk for the complications of diabetes.

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Competing interests

None declared.

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FIGURE 1 CONSORT diagram (adapted from American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004; **27(Suppl 1)**: S5–S10). DPP, Diabetes Prevention Program; DPPOS, Diabetes Prevention Program Outcomes Study. *The DPP enrolled participants over a 3-year period ending June 1999, therefore participants had varying duration of DPP follow-up depending on their year of enrolment. †DPP participants alive at 1 September 2002 were eligible for the DPPOS. OGTT, oral glucose tolerance test.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. DPPOS research group investigators.

Table S1. Formerly unexplored factors examined for their association with diabetes in the DPPOS.

Table S2. Established factors examined for their association with diabetes in the DPPOS.

Table S3. Formerly unexplored factors examined for their association with composite microvascular disease in the DPPOS.

Table S4. Established factors examined for their association with composite microvascular disease in the DPPOS.

Table S5. Formerly unexplored factors examined for their association with retinopathy, nephropathy and neuropathy in the DPPOS.

Table S6. Established factors examined for their association with retinopathy, nephropathy and neuropathy in the DPPOS.

Table 1. Established and formerly unexplored factors examined for their association with diabetes and/or microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS)

Parameter	Definitions	Units
	Historical information	
h/o GDM	History of gestational diabetes	Y/N
<i># comorbidities</i>	<i>Number of comorbidities reported</i>	<i>Number</i>
<i># meds used</i>	<i>Number of medications used</i>	<i>Number</i>
ADM	Use of anti-depressant medications	Y/N
<i>House income</i>	<i>Annual household income</i>	<i>per \$10,000</i>
<i>Amount of education</i>		<i>years</i>
<i># people in the home</i>		<i>Number</i>
<i>Quality of life</i>	<i>Based on SF6D</i>	<i>Number</i>
Smoking	Never/current/past	
	Plasma measures	
Ever NGR	Achieved normoglycaemia in Diabetes Prevention Program	<i>Number (%)</i>
	<i>Variability in HbA_{1c}</i>	
Fasting glucose		mg/dl
2-hour glucose	2-hours post-OGTT	mg/dl
Proinsulin		pmol/l
Adiponectin		g/ml
C-reactive protein		mg/dl
TG	Triglycerides	mg/dl

HDL	High-density lipoprotein cholesterol	mg/dl
<i>TG/HDL</i>	<i>Ratio TG/HDL</i>	*
CIR	Index of insulin secretion	pmol/l
1/[insulin]	Index of insulin sensitivity	ml/□U
Metabolic measures		
BMI	Body mass index	kg/m ²
Waist circumference		cm
<i>Weight variability</i>	<i>SD</i>	<i>kg</i>
<i>SBP</i>	<i>Systolic blood pressure</i>	<i>mmHg</i>
<i>DBP</i>	<i>Diastolic blood pressure</i>	<i>mmHg</i>
Reported diet and activity		
Activity	Leisure time physical activity	MET/h/wk
Total calories		kcal/day
Servings of alcohol		#/day
Calories from carbohydrate		%
Calories from protein		%
Calories from fat		%

Established factors are in regular font, whereas unexplored factors are in italics. Values are taken from the baseline of the Diabetes Prevention Program (DPP), regression to normal glucose regulation (NGR) is defined during the DPP, and time-varying analyses across DPP and DPPOS were conducted for weight and HbA_{1c}.

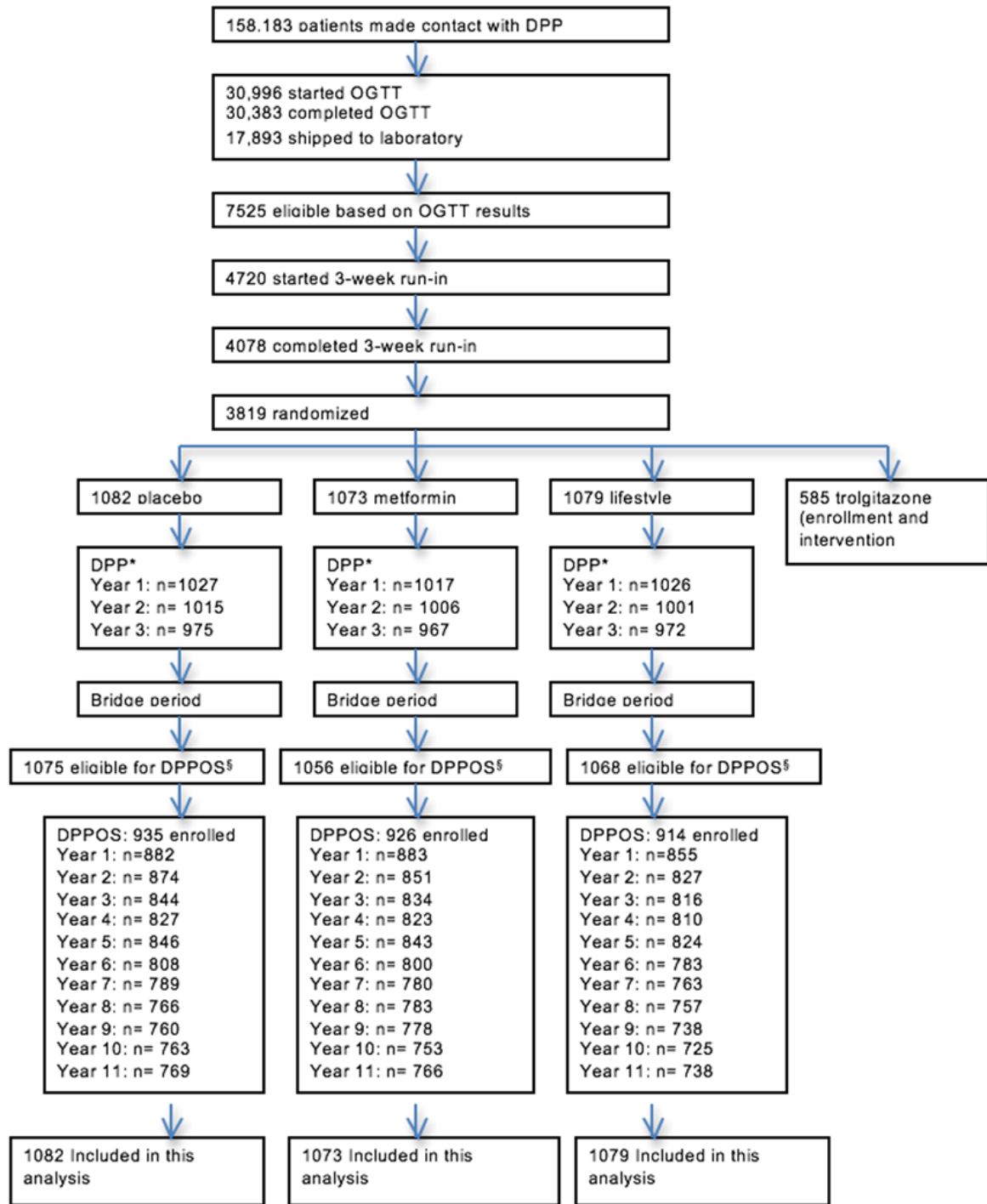
*TG and HDL are both measured in mg/dl, so the ratio units cancel mathematically.

Table 2. Selected Known and Formerly Unexplored Factors Examined for their Association with Outcomes in the Diabetes Prevention Program Outcomes Study (DPPOS)

Variable	Diabetes	MVD	Retinopathy	Nephropathy	Neuropathy
No. of comorbidities	1.095	1.115	0.946	1.232	1.188
No. of medications used	1.073	1.100	1.021	1.158	1.190
Variability in HbA _{1c}	1.020	1.064	1.091	1.037	1.091
SBP	1.031	1.215	1.073	1.466	1.087
DBP	0.998	1.135	1.062	1.313	0.983
BMI	1.061	1.179	1.113	1.267	1.157
Fasting glucose	1.199	1.029	1.086	0.079	1.034
C-reactive protein	0.983	1.095	1.132	1.048	1.142

Numbers represent hazards ratio for diabetes and odds ratios for other outcomes in fully adjusted models. Each variable is adjusted for fasting plasma glucose, 2-hour glucose, HbA_{1c}, BMI, history of GDM (coefficient for GDM is the difference between females with GDM vs. females without GDM; coefficient for female is the difference between females without GDM vs. male), use of anti-depressant medication, ever NGR, adiponectin, CIR, 1/[insulin].

See Table 1 for descriptions of the variables shown in Table 2. Using the methods of Bonferroni, a *P*-value of ≤ 0.002 was used to denote significance in order to account for multiple comparisons. Numbers in bold denote $P \leq 0.002$.



CONSORT diagram: Figure is adapted from reference 9. DPP = Diabetes Prevention Program. [§]DPPOS = Diabetes Prevention Program Outcomes Study. *DPP enrolled participants over a 3-year period ending June 1999; therefore participants had varying duration of DPP follow-up depending on their year of enrollment. [§]DPP participants surviving as of September 1, 2002, were eligible for DPPOS.