Factors Affecting the Decline in Incidence of Diabetes in the

Diabetes Prevention Program Outcome Study (DPPOS)

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Abstract

During the first 7 years of the Diabetes Prevention Program Outcomes Study (DPPOS), diabetes incidence rates when compared to DPP decreased in the placebo (PLB) (-42%) and metformin (MET) (-25%) groups compared to the rates in the intensive lifestyle (ILS) (+31%) group. Participants in PLB and MET groups were offered group ILS prior to starting DPPOS. Two hypotheses were explored to explain rate differences: ‘effective intervention’ (changes in weight and other factors due to ILS) and ‘exhaustion of susceptibles’ (changes in mean genetic and diabetes risk scores).

No combination of behavioral risk factors (weight, physical activity, diet, smoking, antidepressant or statin use) explained the lower DPPOS rates of diabetes progression in PLB and MET whereas weight gain was the factor associated with higher rates in ILS. Different patterns in the average genetic risk score over time were consistent with ‘exhaustion of susceptibles’.

Results were consistent with ‘exhaustion of susceptibles’ for the change in incidence rates, but not the availability of ILS to all persons before the beginning of DPPOS. Thus, ‘effective intervention’ did not explain the lower diabetes rates in DPPOS among PLB and MET groups compared with DPP. ClinicalTrials.Gov: DPP - NCT00004992; DPPOS - NCT00038727
**Introduction**

The Diabetes Prevention Program (DPP) (1) showed that intensive lifestyle intervention (ILS) and metformin (MET) reduced diabetes incidence compared with placebo treated controls (PLB). At the end of the three years of active intervention, the DPP was closed and was converted to a long-term follow-up study, the Diabetes Prevention Program Outcome Study (DPPOS), to determine if reductions in diabetes incidence observed with ILS and MET were maintained (2). Because the ILS intervention produced the largest reduction in diabetes incidence, it was offered to all participants during a six month “bridge” period before the follow-up (3).

Over a ten year follow-up period from randomization in DPP, diabetes risk was reduced by 34% in the original ILS group, and by 18% in the MET group compared with the original PLB group (2). The smaller long-term differences between treatment in progression to diabetes that were observed during the DPPOS phase of the study were due to two factors: an increase in the incidence rates among those in the ILS group over the 10 year period, and a substantial decrease in rates in the MET and PLB groups. We considered two hypotheses to explain these results. The ‘effective intervention’ hypothesis, posits that substantial numbers in the MET and PLB groups achieved weight loss (and related lifestyle changes) due to ILS classes following DPP, and reduced their annual incidence rates during DPPOS. The ‘exhaustion of susceptibles’ hypothesis, posits that persons most susceptible to diabetes in the MET and PLB groups developed it during DPP, and the remaining participants were less susceptible, leading to overall lower incidence rates for these groups during DPPOS. We present several analyses designed to explore these hypotheses.
Research Design and Methods

The DPPOS objectives were to evaluate long-term effects of DPP interventions on the development of diabetes and its complications. The protocol and informed consent procedures were approved by all responsible institutional review boards and all participants provided written informed consent.

Participants

Details of methods have been presented previously (1;2;4). A total of 3,324 participants enrolled in DPP between 1996 and 1999 and were randomized to one of three treatment arms: ILS, MET or PLB. Participants were ≥ 25 years of age, overweight or obese, and had impaired glucose tolerance (IGT) and elevated fasting glucose levels (5). A detailed flow chart of enrollment has been published (2). All 3,150 surviving DPP participants who had not withdrawn consent were eligible for DPPOS. Enrollment began in September 2002 and was largely completed within one year. By August 27, 2008, the closing date for this report, 88% (2,766) had enrolled and were followed for a median 10.0 year (IQR 9.0–10.5) period post randomization.

Changes in Interventions

At the termination of DPP in July 2001 (1), there was a two-week drug “washout period” (6). Following this, all participants were offered the ILS intervention modified for groups (3) and 57% of PLB, 58% of MET, and 40% of ILS participants attended some of these sessions. From the end of DPP until the start of DPPOS, MET participants lost about 1.5 kg, when weight regain began to occur. PLB participants lost about 2 kg, whereas ILS participants gained ~1 kg on average (3). This “bridge period” was conducted until the DPPOS protocol began in September, 2002. During DPPOS, quarterly lifestyle sessions were offered to all participants and. ILS participants received additional group classes, and MET participants received
unmasked drug (850 mg twice a day, as tolerated) unless discontinued for safety reasons or diabetes development.

Risk factors

Variables in this analysis included demographic factors; obesity measures (weight (kg), height (m), waist circumference (cm), body mass index (kg/m$^2$)); measures of glycemia (fasting and two hour glucose, A1c (%)); insulin sensitivity (1/fasting insulin) and secretion (insulinogenic index: ($\text{Insulin}_{30}-\text{insulin}_0$) / ($\text{glucose}_{30}-\text{glucose}_0$) (7)). In addition, dietary intake data were collected by modified Block food frequency questionnaire (8) at regular intervals. Physical activity was self-reported using the Modified Activity Questionnaire (MAQ) (9) as total MET-hours per week. Goals were defined annually for the weight goal ($\leq$7% weight loss), exercise goal ($\geq$ 150 min/week of moderate physical activity (6 met hrs/wk or more, based on the MAQ)), and the fat intake goal (total dietary fat less than 25% of calories). Biochemical tests were analyzed in the Northwest Lipid Research Laboratories, Seattle, Washington using methods reported previously (1).

Exploration of the ‘exhaustion of susceptibles’ hypothesis used the genetic risk score (GRS), comprised of 34 type 2 diabetes associated genetic variants, weighting each risk allele by its reported effect size on diabetes risk and summing these values (10). We also calculated a clinical diabetes risk score (DRS) using baseline sex, age, BMI, sex-specific waist circumference, hypertension medication, history of GDM, smoking, and family history of diabetes (11) as well as analyzing fasting and 2 hour glucose levels. We used these scores and glucose levels to explore whether the intervention group (ILS, MET, PLB) average risk profile became lower over time by calculating the mean of the baseline assigned scores and levels every
6 months for those participants in each group who did not develop diabetes. Thus, an individual’s score or level was the same in each time period, but the group average changed as participants developed diabetes and were no longer included in the mean for the treatment group.

Outcome

The DPP/DPPOS outcome was development of incident diabetes according to ADA criteria (fasting glucose $\geq 126$ mg/dl and/or 2-hour OGTT glucose $\geq 200$ mg/dl), measured annually and confirmed by repeat testing. Participants were followed until they developed diabetes, withdrew, or were administratively censored as of their last follow-up visit.

Analyses

Time Intervals

Analyses used a common DPPOS start date of September 1, 2002, although most participants were not seen on exactly that date. The baseline visit for DPPOS was the last yearly visit that occurred between August 1, 2001 and August 31, 2002. Follow-up time was divided into two periods: 1) July 31, 1996 to July 31, 2001: DPP to the end of the masked intervention phase, and 2) August 1, 2001 through August 27, 2008: all visits following the completion of the masked intervention phase, combining the washout period, bridge and the DPPOS follow-up period.

Analytic methods

Data from participants at DPPOS baseline were described using means (± SD) for quantitative variables and frequencies (%) for qualitative variables. The effect of weight change over time on diabetes risk was assessed within each treatment group using proportional hazard regression
models after adjusting for other factors. Conditional independence of time periods in DPP and DPPOS for diabetes risk was assumed, as any incident diagnosis of diabetes could occur only once, either in DPP or DPPOS, to a given participant. The proportional hazards assumption did not hold, therefore the Lin-Wei robust covariance estimates were used in estimating corresponding standard errors (12). To assess whether diabetes risk in DPP was different than in DPPOS, hazard ratios (HRs) were computed using Poisson regression models with the log link function using a time dependent binary covariate for each subject to designate DPP vs. DPPOS within each treatment group. SAS 9.2 (Cary, N.C., USA) was used for all analyses. Two-sided p-values are reported with alpha=0.05. No adjustments were made for multiple testing.

**Results**

Overall, 2,766 participants joined DPPOS (Table 1), of whom 22 had no baseline visit, leaving an effective sample size of 2,744 for analyses. Of these, 68% were female, and the average age was 55.2 years. Seventy-two percent (72%) did not have diabetes at the start of DPPOS. A higher proportion of the ILS group entered DPPOS without diabetes (81.2%), with lower fasting insulin levels, better insulin secretion (higher insulinogenic index), lower BMI, waist circumference, fewer daily calories, and higher physical activity, and they met more of the DPP goals than the other groups, consistent with the results of DPP.

The impetus for this analysis was that diabetes incidence rates during DPPOS for all three groups were similar (2). In the DPPOS period (approximately 4-12 years post-randomization), the HR for incidence in the ILS to PLB groups was 1.01 (95% CI: 0.84-1.22), for ILS to MET was 0.95 (0.79-1.15), and for MET to PLB was 0.96 (0.79-1.17), indicating no differences in the rates
between the three groups. We also explored rate change patterns by sex, baseline age, BMI group, and initial IGT or IGT+IFG, each having similar patterns to the entire group (see supplementary data).

We examined the average annual incidence rates from randomization over time to assess when changes began to occur (Figure 1). Annual incidence rates in the ILS group (bottom panel) rose slowly through year 4 post-randomization, then declined to steady levels at year seven. Among participants in the MET group (middle panel), annual rates were steady until year five, then fell and remained lower than rates during DPP with a continuing downward trend late in DPPOS. The PLB group (top panel) showed a very different trend, rising to the highest rate early in DPP, with a relatively steady decline through the end of DPP and into DPPOS, leveling late in DPPOS. Figure 1 also shows the HRs for the average annual incidence rates during the DPPOS period compared with DPP. There was a significant increase in incidence rates (of 31%) for ILS participants in DPPOS compared with DPP (HR=1.31, 95% CI=1.07-1.61), whereas both MET (HR=0.75, 0.62-0.90) and PLB (HR=0.58, 0.48-0.69) had significant decreases in rates after the DPP period (25% and 42%, respectively). The declines in absolute cases per 100 person-years were largest for the MET and PLB groups (-2.9 and -5.4 cases / 100 person-years respectively), compared to the increase in the ILS group (+1.1 /100 person-years). The pattern of rate changes in the MET and PLB groups does not correspond with, or follow a consistent time lag of, the bridge period transition when all participants were offered lifestyle intervention.

We explored the ‘effective intervention’ hypothesis several ways. Since weight change was the primary variable explaining the difference between the treatment groups in DPP (13), we
explored whether the effect of changes in weight in both time periods were similar. Hazard ratios (HR) for a 1 kg weight change were nearly identical in DPP and DPPOS within each treatment group (data not shown), indicating that weight loss was acting similarly in both study periods within each treatment group.

We next asked whether differences in weight change patterns between groups could partially or fully explain the trends in rates between DPP and DPPOS. Figure 2 compares the HR of the DPPOS to DPP rates, first unadjusted (model 1, ILS HR=1.31; MET HR=0.75; PLB HR=0.58), as in Figure 1), and then adjusted for various behavioral variables, added one at a time to prior models, in each treatment group separately. In the ILS group, addition of age, sex and race/ethnicity and baseline weight did not reduce the HR (model 2: 1.34; model 3: 1.39). However, starting with model 4, which added time dependent weight change, the HR was 1.04, no longer different than 1.0 (p=0.851) and the HR remained so with addition of time dependent leisure time physical activity and % of calories from fat, suggesting that resulting weight regain explained the increased ILS incidence rates in DPPOS compared to DPP. However, the same models for MET and PLB participants showed no such pattern. Each HR remained significantly different from 1.0 (MET: 0.75 to 0.76; PLB: 0.58-0.61 over models 2-6) and very close to the unadjusted values. Because the greater number of study goals met, the lower the risk (13;14), we added meeting study goals (model 7), which also did not explain the MET (HR=0.74, p=0.002) and PLB (HR=0.62, p<0.001) differences. Finally, we explored a series of other risk factors which predict diabetes (15) and might have differed by treatment group, including changes in waist circumference (model 8), other aspects of diet (model 9), alcohol consumption (model 10), smoking status (model 11), (17) use of antidepressants (model 12) and depression score
(model 13), (18) use of statins (model 14), (19;20) and a final model including all these variables (model 15). None of these variables materially changed either the MET (model 15 HR=0.76, p=0.009) or PLB (HR=0.54, p<0.001) HRs. Finally We added the GRS to the full behavioral model (model 16=model 6 plus GRS) with no significant change in HR estimate and little change in statistical significance for each treatment group. Thus, weight gain explained the change in diabetes risk between the two periods in the ILS group but accounting for weight changes and other clinical variables did not explain the differences between study periods in the MET and PLB groups. These observations argue against ‘effective intervention’ in these groups as an explanation for the reduction in incidence in the MET and PLB groups during DPPOS.

We next explored the ‘exhaustion of susceptibles’ hypothesis. While conceptually simple in an infectious disease context, it is not straightforward to test, because nearly all measures of susceptibility or change in susceptibility to diabetes over time are confounded by treatment effects. We explored changes in average GRS (10) and DRS (11) for each group over time. Figure 3 (top panel) shows the results of calculation of the mean GRS among the group of persons who remained without diabetes at every six month visit over the course of DPP and DPPOS. There was a declining trend in the group mean GRS over time, which began to diverge near the start of DPPOS visits. There was little decrease in the mean GRS among participants in the ILS group, but both the MET and PLB groups had lower average scores over time, suggesting that persons remaining non-diabetic had somewhat lower genetic susceptibility. There were small non-significant declines in the DRS over time with no difference between treatment groups (data not shown). Since fasting and 2 hour glucose levels are strong predictors of diabetes, we calculated the baseline group mean glucose levels at each visit, removing persons
who became diabetic over time. The middle (fasting) and bottom (2 hour) panels in Figure 3 show small declines over time, suggesting less persons at higher risk, but there is little difference between treatment groups, unlike that seen for GRS.

Next, we explored whether participants randomized over the ~3-year period from July 1996 - May 1998 had different levels of baseline diabetes risk. If participants entering DPP earlier were at higher risk than those recruited later, they would have entered DPPOS first, followed by lower risk subjects, who would have had lower incidence rates later in follow-up. Such a pattern would have to be differential by treatment group to aid in understanding incidence patterns. Figure 4 shows both the DRS (Panel A) and the GRS (Panel B) patterns, stratified into three recruitment periods with approximately equal recruitment numbers in each. Within each period, there were no statistically significant differences between treatment groups; however, there were statistically significant decreasing trends in the estimated DRS in both the MET and PLB groups, but not in the ILS group. While significant, the magnitude of the decline was small. No temporal trend was seen for GRS during the randomization period.

Discussion

Diabetes incidence rates in the DPPOS time period were similar across the three intervention groups (2), resulting from increasing rates in the ILS group but larger declines in both the MET and PLB groups. We examined two hypotheses to explain these patterns: ‘effective intervention’ and ‘exhaustion of susceptibles’. In the former, we postulated that participants in the MET and PLB groups experienced weight loss sufficient to account for the change in diabetes risk following the group lifestyle classes that were offered during the bridge period between DPP and
the start of DPPOS (3). Importantly, weight change had a similar association with diabetes risk in each treatment group during both DPP and DPPOS, providing evidence that weight reduction retained its clinical significance throughout the study period. Models including weight change as a time dependent variable did explain the increase in rates in the ILS group from DPP to DPPOS. However, weight change, or combinations of other risk factors, did not explain the lower rates seen in either the MET or PLB groups. These observations argue against the ‘effective intervention’ hypothesis, contrary to our expectation.

Alternatively, we hypothesized that the decline in incidence rates among MET and PLB groups might have been due to ‘exhaustion of susceptibles’. This concept has a long history in the explanation of infectious disease transmission e.g. (21) and has been invoked to explain incidence patterns in selected cancers, e.g. (22). In diabetes epidemiology, the concept has been proposed as a possible explanation for the observed lower diabetes incidence rates over 50 years of age among the Pima Indians, together with a possible cohort effect, where older cohorts were less exposed to risk earlier in life (23). In the context of the DPP/DPPOS, a small cohort effect appears to have occurred in the PLB and MET groups during randomization (Figure 4), but it did not explain the lower incidence rates in those groups during DPPOS.

Several of our observations were consistent with the ‘exhaustion’ hypothesis. First, patterns of annual incidence rates in the untreated PLB group rose rapidly and then began to decline midway through DPP to even lower rates in DPPOS, consistent with ‘exhaustion’. Whereas, the slower rise and fall in the MET group and the absence of a rise in the ILS group likely reflect delays in the onset of diabetes, since higher risk subjects would have been delayed to later time periods
through effective interventions and some would have been prevented for the duration of observation. Second, the mean GRS (Figure 3) declined in both PLB and MET groups similarly, and were both lower over time than in the ILS group. Very small declines in fasting and 2 hour glucose were also seen, though not different between groups. Third, participants randomized early to MET or PLB had somewhat higher mean baseline DRS that declined significantly over the randomization period, whereas little change was seen in the ILS group (Figure 4). The magnitude of this decline was small, however.

As previously reported (10), the GRS was significantly associated with diabetes risk, but in the highest quartile of GRS, ILS was effective in reducing risk. We interpret the lack of decline in the ILS GRS to mean that genetically high risk subjects were retained in this group for a longer period due to an effective intervention, but were lost from the other two treatment groups because they developed diabetes. While consistent with the ‘exhaustion’ hypothesis, the magnitude of the changes in the mean GRS over time are relatively small, predicting only a 1.1% decrease in risk (10). Similarly, Figure 2 shows that addition of the GRS to model 6 (model 16) does not materially change the HRs, suggesting limited impact of this score. Nonetheless, these results are consistent with an ‘exhaustion’ hypothesis. There was small decline in the DRS over time but there were not differences between groups. We did, however, see a baseline difference in the DRS during the recruitment period (Figure 4). This would have resulted in fewer higher risk participants entering DPPOS in the later time intervals, and would have reduced the treatment group risk profile in a manner similar to ‘exhaustion’.
We also reviewed the long-term follow-up experience of similar studies of persons with IGT to determine if a decline in rates over time occurred among the control or placebo groups, which would lend additional support for the ‘exhaustion’ hypothesis. Studies reviewed included the long-term follow-up of Pima Indians with IGT (24), the Finnish Diabetes Prevention Study (14), the DREAM (25;26) and DREAM-ON follow-up (27), the Da Qing Prevention Study (28) and the ADDITION-Denmark study (29). Only in the latter study were lower rates of diabetes seen 1.5-3 years after screening for high risk impaired fasting glucose (IFG) and IGT (29) with the highest rates among those with combined IFG plus IGT, a pattern similar to ours. None of the other reports showed evidence of lower incidence rates of diabetes within 4-6 years and up to 20 years after randomization; however, none reported annual incidence rates as we and ADDITION have done. When examining only cumulative incidence, it is often difficult to ascertain the underlying pattern of incidence rates, and we were not aware of such patterns in the PLB group until this analysis was undertaken. Thus, lack of agreement between other studies may be an artifact of data presentation. Only 1 of 6 studies directly supports the phenomenon of ‘exhaustion’ as we postulated; In addition, most of these studies enrolled subjects with either a single impaired glucose tolerance (IGT) result on an OGTT (24;30), or two IGT results (31) but they did not require a separate fasting glucose elevation at entry, as was done in the DPP (fasting glucose ≥ 5.3 mmol/l; ≥ 95 mg/dl). Only in the DREAM Trial did the majority of participants have both IGT and impaired fasting glucose (IFG), or IFG alone (25;26). Persons with IGT and elevated fasting glucose levels have subsequent rates of new diabetes higher than those with lower levels of fasting glucose (29;32). It seems unlikely that requiring an elevated fasting glucose level is responsible, since among persons with isolated IFG or IGT in ADDITION, a pattern of exhaustion was also seen, as it was in our data (see supplementary data).
Other possible explanations deserve mention. The incidence rates in the MET group during the DPPOS period were significantly lower than during DPP. Whether long-term use of metformin has effects different from those following shorter periods of use, as seen initially in DPP, is unknown. However, only 57% of the non-diabetic MET group took 80% or more of the prescribed metformin dose in DPPOS (2), lower than that during DPP (72%) (1). Similarly, it is unlikely that use of metformin among the PLB group accounted for their lower rates, since only 3% reported taking metformin prescribed outside the study (2). It is also possible that long-term population changes in diabetes risk occurring outside the trial might have affected DPPOS participants, but this seems unlikely since this effect would need to be different by treatment group to explain the observed differences.

This analysis has some limitations. It was a *post-hoc* exploratory analysis, with multiple analytic comparisons made. Whether there remain important unmeasured risk variables is an open question, though the primary ones used in this analysis are strong and widely predictive across studies. The ‘exhaustion’ analysis was limited to a few approaches. The GRS analysis and the lower risk for participants randomized later in the MET and PLB groups were consistent with ‘exhaustion’. However, there are few well established approaches to test this hypothesis and we are left with limited evidence to support it.

**Conclusions**

No combination of risk variables explained the decline in MET and PLB rates compared with the ILS group between DPP and DPPOS. Thus, it does not appear that ‘effective intervention’ was
the reason for the decline in rates. There was support for the ‘exhaustion of susceptibles’ hypothesis, since the mean GRS did decline more in MET and PLB groups than in the ILS group and there was a significant trend of recruitment of lower risk participants later in the MET and PLB groups. Only 1 of 6 long-term studies of high risk persons was consistent with the exhaustion hypothesis. Thus, we identified some internal support for the ‘exhaustion’ hypothesis, and no support for the ‘effective intervention’ one as the reason for the lower rates in the MET and PLB groups in DPPOS. Importantly, weight loss remained an effective strategy to reduce diabetes risk over the entire study period, and the long-term diabetes relative risk reductions seen in the DPPOS in the ILS group (2) would have been larger, had not the MET and PLB group rates declined over time. These findings have implications for treatment intervention duration and diabetes prevention trial planning, as the long-term observed effects of the treatments, while remaining highly significant (2), were reduced over time by increases in rates in the ILS and even larger absolute decreases in rates in the MET and PLB groups.
Acknowledgments

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R.F.H and E.H. conceived of and wrote the manuscript, and are the guarantors of this work. C.C. and J.L. developed the analysis plan and analyzed data, E.B.C., G.B., J.C., J.F., S.F., R.G., S.E.K., W.C.K., M.B.M., E.V. and R.F.H. conducted the study and reviewed and critically edited the manuscript. Members of the DPP Research Group are shown in the on-line supplementary material.

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**Role of the funding source**

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.

**Conflict of interest statement**

We declare that we have no conflicts of interest.

**References**


Figure legends

Figure 1. Average annual incidence rates (per 100 person-years) by time since randomization by initial treatment group.

Figure 2. Hazard ratios for DPPOS to DPP time period, by treatment group using sequential adjustment for risk factors. Model 1 is unadjusted, model 2 is model 1 plus factors listed, etc. TDC=time dependent covariate; leisure=leisure time physical activity; % fat=percent of calories from fat; goals=number of 5 study goals met; waist=waist circumference; %CHO= percent of calories from carbohydrate; %PRO= percent of calories from protein; ETOH=alcohol intake; smoking=current, former, never cigarette smoker; SSRI=selective serotonin reuptake inhibitors; CES-D=Center for Epidemiologic Studies of Depression score; statin= HMG-CoA reductase inhibitors.

Figure 3. Mean baseline genetic risk score (top panel), baseline fasting plasma glucose (middle panel) and baseline 2 hour plasma glucose (bottom panel), at each visit among groups of persons remaining non-diabetic at each visit.

Figure 4. Panel A: Mean diabetes risk score (DRS) at randomization by month of randomization, by treatment group (mean, 95% confidence intervals). Each time interval includes 1072, 1073, 1075 participants respectively, balanced in the three treatment groups. Panel B: Mean genetic risk score (GRS). Each time interval includes 947, 941, 955 participants, respectively, also well balanced in the three treatment groups.
Table 1. Characteristics of participants at DPPOS entry

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<th>Overall</th>
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<td>Lifestyle</td>
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**Non-diabetic participants**

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<td>Lifestyle</td>
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<td>Fasting glucose (mmol/L)</td>
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<td>Waist circumference (cm)</td>
<td>101.3 (13.8)</td>
</tr>
<tr>
<td>Total calories/day (Kcal)*</td>
<td>1775 (802)</td>
</tr>
<tr>
<td>Calories from fat (%)*</td>
<td>31.4 (7.4)</td>
</tr>
<tr>
<td>Physical activity (METS/wk)</td>
<td>18.2 (18.6)</td>
</tr>
</tbody>
</table>

| Met goals at DPPOS entry*†      |         |
| Weight (N, %)                   | 472 (23.9) | 238 (32.6) | 137 (21.2) | 97 (16.1)  |
| Exercise (N, %)                 | 1499 (76.6) | 610 (84.3) | 465 (72.7) | 424 (71.4) |
| Fat intake* (N, %)              | 382 (19.1) | 256 (34.7) | 56 (8.6)   | 70 (11.5)  |
| Number of goals met             | 1.00 (0.64) | 1.17 (0.65) | 0.94 (0.62) | 0.87 (0.62) |

Data are mean (SD) or number of participants (N) and percent of total (%).

Data were missing for 22 enrolled persons who had no DPPOS baseline examination (see methods). Data were missing for additional participants in varying numbers for some of the variables.

\[ \frac{(\Delta \text{Insulin}_{30 \text{ min-fasting}})}{(\Delta \text{glucose}_{30 \text{ min-fasting}})} \]

\*n=1995 – using the last available visit with dietary data before DPPOS baseline visit

\[ \Delta \text{Insulin}_{30 \text{ min-fasting}} \text{ / } \Delta \text{glucose}_{30 \text{ min-fasting}} \]
†Weight goal is defined as having lost 7% or more of the weight at randomization. Exercise goal is defined as leisure activity of 6 MET hrs / wk or more. 1 MET is 1 kcal/kg * hr. Fat intake is defined as per cent of calories from fat being 25% or less.
Average annual incidence rates (per 100 person-years) by time since randomization by initial treatment group.

Placebo (PLB): $HR_{PLB/PLB}=0.58$, $p<0.0001$

Metformin (MET): $HR_{MET/PLB}=0.75$, $p=0.0023$

Lifestyle (ILS): $HR_{ILS/PLB}=1.31$, $p=0.0086$
Hazard ratios for DPPOS to DPP time period, by treatment group using sequential adjustment for risk factors. Model 1 is unadjusted, model 2 is model 1 plus factors listed, etc. TDC=time dependent covariate; leisure=leisure time physical activity; % fat=percent of calories from fat; goals=number of 5 study goals met; waist=waist circumference; %CHO= percent of calories from carbohydrate; %PRO= percent of calories from protein; ETOH=alcohol intake; smoking=current, former, never cigarette smoker; SSRI=selective serotonin reuptake inhibitors; CES-D=Center for Epidemiologic Studies of Depression score; statin= HMG-CoA reductase inhibitors.

21x16mm (600 x 600 DPI)
Mean baseline genetic risk score (top panel), baseline fasting plasma glucose (middle panel) and baseline 2 hour plasma glucose (bottom panel), at each visit among groups of persons remaining non-diabetic at each visit.

30x53mm (600 x 600 DPI)
Panel A: Mean diabetes risk score (DRS) at randomization by month of randomization, by treatment group (mean, 95% confidence intervals). Each time interval includes 1072, 1073, 1075 participants respectively, balanced in the three treatment groups.

Panel B: Mean genetic risk score (GRS). Each time interval includes 947, 941, 955 participants, respectively, also well balanced in the three treatment groups.
Figures show average annual incidence of diabetes (per 100 person years) for the DPP time period and the DPPOS time period by subgroups of DPP participants at baseline. See methods for definitions of time periods. BMI=body mass index; IFG=impaired fasting glucose; IGT=impaired glucose tolerance, by 1997 American Diabetes Association criteria.
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