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Incontinence in DPPOS

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Long-term prevalence and predictors of urinary incontinence among women in the Diabetes Prevention Program Outcomes Study

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Abstract

Objectives—This study examined the long-term prevalence and predictors of ≥ weekly urinary incontinence (UI) in the Diabetes Prevention Program Outcomes Study (DPPOS).

Methods—DPPOS is a follow-up study of the DPP randomized clinical trial of overweight adults with impaired glucose tolerance. This analysis included 1,778 female participants of DPPOS who had been randomly assigned during DPP to intensive lifestyle intervention [ILS; n = (582)], metformin [MET; n = 589], or placebo [PLC; n = 607)]. DPPOS participants completed semi-annual assessments after the final DPP visit and for six years until October, 2008.

Results—At entry into DPPOS, the prevalence of weekly UI was lower in ILS compared with MET and PLC (44.2% vs. 51.8%, 48.0% UI/week, p=0.04); during the 6-year follow-up, these

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CONFLCITS OF INTEREST

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lower rates in ILS were maintained (46.7%, 53.1%, 49.9% UI/week; p = 0.03). Statistically adjusting for UI prevalence at the end of DPP, treatment arm no longer had a significant impact on UI during DPPOS. Independent predictors of lower UI during DPPOS included lower BMI (OR [95% CI] = 0.988 [0.982, 0.994]) and greater physical activity (OR = 0.999 [0.998, 1.000] at DPPOS entry, and greater reductions in BMI (OR = 0.75 [0.60, 0.94]) and waist circumference (OR = 0.998 [0.996, 1.0]) during DPPOS. Diabetes was not significantly related to UI.

Conclusions—ILS had a modest positive impact on UI that endured for years after the DPP trial and should be considered for the long-term prevention and treatment of UI in overweight/obese women with glucose intolerance.

Keywords

Diabetes Prevention Program Outcomes Study; lifestyle intervention; urinary incontinence; weight loss

INTRODUCTION

Overweight women with type 2 diabetes[1] or impaired glucose tolerance [2] have higher prevalence of urinary incontinence (UI) than women with normal glucose tolerance. Weight loss through lifestyle modification appears to help prevent incontinence in women with type 2 diabetes.[3] However, less is known about effects of weight loss on UI in women with impaired glucose tolerance. A study of women with impaired glucose tolerance enrolled in the Diabetes Prevention Program (DPP) after a mean of 3.2 years of follow-up revealed a lower prevalence of UI in those assigned to an intensive lifestyle modification program [4] compared to women assigned to metformin or placebo, suggesting a beneficial effect of that intervention. However, UI was only assessed at the end of DPP, so prospective effects of the treatment arms could not be evaluated.

Extensive research has identified risk factors for UI in women, including excess weight, increasing age, parity, and oral estrogen use. [5, 6] Risk factors specific for women with type 2 diabetes include microvascular damage,[7] duration of diabetes,[8] insulin treatment,[9] peripheral neuropathy, and retinopathy.[2, 8] However, risk factors for UI in women with impaired glucose tolerance remain less well described.

The purpose of this study was to determine the long-term effects of the DPP lifestyle intervention on the prevalence, incidence, and resolution of UI in overweight/obese women with impaired glucose tolerance or incident diabetes who participated in the Diabetes Prevention Program Outcomes Study (DPPOS). We hypothesized that, during the 6-year DPPOS follow up period, the prevalence and incidence rates of UI would be lower and resolution rates higher among women who were assigned the lifestyle intervention during the clinical trial phase of the DPP. A secondary aim was to identify demographic and behavioral predictors and correlates of UI during the DPPOS 6-year follow-up period.

METHODS

Study Setting, Patients and Design

The design, methods, baseline characteristics [10] and main findings [11] of the DPP and the DPPOS[12] have been published. Briefly, the DPP was a randomized controlled trial conducted at 27 clinical centers in the U.S. to evaluate whether an intensive lifestyle intervention or treatment with metformin would prevent or delay the onset of type 2 diabetes. Eligibility criteria at entry into DPP included age of at least 25 years, body mass index (BMI) of 24 kg/m^2 or higher (≥ 22 kg/m^2 for Asians), and plasma glucose 2 hours after a 75-g oral glucose load of 140 –199 mg/dl plus a fasting plasma glucose (FPG) of 95–125 mg/dl (or any fasting glucose ≤ 125 mg/dl for American Indians).

The three interventions included an intensive lifestyle (ILS) intervention, metformin (MET) 850 mg twice daily, or placebo (PLC) twice daily with standard lifestyle recommendations provided to all participants at entry into DPP and annually. The goals of the intensive lifestyle intervention were to lose and maintain at least 7% of initial body weight through a low fat diet and to engage in moderate-intensity physical activity for at least 150 minutes each week. The clinical trial was halted earlier than planned because the incidence of diabetes had been significantly reduced in participants assigned to the ILS and MET groups compared to PLC.[11] On the basis of the benefits from the intensive lifestyle intervention in the DPP, all participants were informed of the main results from DPP and offered a group-administered version of the 16-session lifestyle curriculum as a “bridge” protocol.

DPPOS was a follow-up study of participants from the DPP trial. All active DPP participants were eligible for continued follow-up in DPPOS. The DPPOS started in 2002 and enrolled 2,766 (86%) of DPP participants and 1,878 (86%) of female DPP participants. Lifestyle sessions were offered to all participants every 3 months. DPP lifestyle participants were also offered additional group classes twice each year to reinforce weight control behaviors. Metformin treatment was continued in the original metformin group (850 mg twice daily as tolerated), with participants unmasked to assignment.

For the purposes of this incontinence sub-study, only women (N = 1,778) who provided UI data at the first DPPOS assessment were included in this analysis. The data include semi-annual clinic assessments performed for 6 years until data collection was locked in October, 2008. All of the DPPOS clinical centers as well as the DPP Coordinating Center had institutional review board approvals. All participants gave written informed consent.

Data Collection

Our primary outcome was frequency of weekly or more frequent incontinence overall and by type.[3, 4] UI was assessed at each annual visit during DPPOS and was determined using a self-administered questionnaire modified from validated questions. [13–15] Demographic predictors were assessed at entry into DPP and included sex, age, and self-identified race/ethnicity. Anthropometric measures (weight, body mass index [BMI], waist circumference), physical activity, biological factors (glucose, albumin to creatinine ratio) and parity were assessed at entry into DPPOS and each year for the six years of follow-up. C-reactive protein [CRP] was measured at DPPOS year 1 and year 5. Weight was measured in

kilograms using a standard balance beam scale; height was measured in centimeters, using the height rod attached to the standard balance beam scale or a stadiometer. Waist circumference was measured using a flexible tape measure at the minimum circumference between the iliac crests and lower ribs. Physical activity was assessed with the Modifiable Activity Questionnaire,[16] and was calculated as the product of the duration and frequency of each activity, weighted by an estimate of the metabolic equivalent of that activity, and summed for all activities resulting in an estimated average metabolic equivalent (MET) hours per week. One MET represents the energy expenditure for an individual at rest (1 MET = 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ of oxygen consumption), whereas a 10-MET activity requires 10 times the resting energy expenditure. Incident diabetes, the primary DPP and DPPOS outcome, was diagnosed by annual oral glucose-tolerance test or a semiannual fasting plasma glucose test according to the 1997 American Diabetes Association criteria.[17]

Statistical Analyses

In all analyses, incontinence was a binary outcome. Prevalent incontinence was defined as proportion of participants who reported ≥ weekly UI (vs. < weekly UI). Incidence was defined as proportion of participants who reported < weekly UI at the previous visit but ≥ weekly UI at the current visit. Resolution was defined as the proportion of participants reporting ≥ weekly UI at the previous visit but < weekly UI at the current visit. Resolution and incident UI were assessed in relation to the immediate prior visit at each annual visit during DPPOS. A sensitivity analysis was conducted examining stability of incident or resolved UI across two annual consecutive visits; 85–88% of classifications remained constant between any two-year window of DPPOS.

For comparison of participant characteristics at the DPPOS 1st annual visit, Kruskal Wallis test[18] was used for the continuous variables and chi-square test for categorical variables. Repeated measures with general estimating equations were used to examine differences in prevalent UI among the treatment groups overall and by subtype. Repeated measures analysis with generalized estimating equations[19] was used in a single multivariable model to identify independent predictors (assessed at entry into DPPOS or prior) and correlates (assessed concurrently over DPPOS) in relation to the prevalence of UI and its subtypes during the 6 year follow-up; ll variables shown in Figure 1 were included; these were selected based on prior published relationships with UI.[20, 21] Cox's proportional hazard models[22] were used to model the time to the first event of incidence and resolution of UI with the same covariates (used in modeling UI prevalence); variables that changed over time were coded as time-varying covariates. Analyses followed the intention-to-treat (ITT) principal. All analyses were conducted using SAS (version 9.2, Cary, N.C., USA).

RESULTS

Women in this DPPOS sub-cohort were older (49.1 [43.2–56.3] vs. 45.1 [39.3–51.8] years; p<0.0001), leaner (BMI 33.7 [29.6–38.5] vs 34.3 [30.0–40.0] kg/m^2; p=0.02) and less likely to be a current smoker (6.2% vs. 9.9%; p=0.02) than women who did not enroll into DPPOS[12] but were comparable in fasting plasma glucose, glycated hemoglobin (HbA1C),

albumin to creatinine ratio and leisure activity (p>0.05). Characteristics of the 1,778 women by treatment assignment are shown in Table 1. Median duration of follow-up was 5.5 years.

Over the 6 year DPPOS follow-up examination, generalized estimating equations yielded average weight gains (as a percentage of total body weight at entry into DPPOS) of 0.4% in the ILS group, 0.5% in MET and 0.1% in the PLC group (p=0.40 for group comparison); mean waist circumference (WC) increased by 1.84 cm, 1.90 cm, and 1.61cm (p=0.61 for group comparison); mean fasting glucose increased by 1.40 mg/dl, 1.57 mg/dl and 1.57 mg/dl (p=0.97 for group comparison); and, mean activity (met-hours) decreased by 1.66, 1.62 and 0.79 met-hours (p=0.20 for group comparison) in ILS, MET, and PLC, respectively, over the DPPOS study period.

Prevalence, Incidence, and Resolution of Urinary Incontinence

Similar to DPP end trial data,[4] at the beginning of DPPOS, the overall prevalence of UI was significantly lower in ILS compared with MET and PLC (44.2% vs. 51.8%, 48.0%, p=0.04); prevalent stress incontinence (37.1% vs. 44.1%, 40.4% p =0.08) and urgency incontinence (33.1% vs. 40.4%, 36.8%; p =0.06) were also both numerically but not statistically significantly lower in ILS vs. MET and PLC, respectively.

Over the 6 years of DPPOS follow-up (Figure 1), all three groups demonstrated a significant (p=0.006) increase in overall prevalence of any UI. However, the prevalence of any UI remained significantly lower in women assigned to ILS compared with MET and PLC, respectively (46.7%, 53.1%, 49.9%, p= 0.03). Similarly, subgroups of prevalent stress (39.3% 45.1% 42.6% p=.06) and urgency (36.2%, 42.6%, 39.6%; p=0.04) UI were consistently lower in those assigned to ILS.

After adjusting for UI at end of DPP, the effects of treatment assignment were no longer statistically significant (p <0.60), suggesting that the benefits associated with the ILS treatment were maintained during this follow-up time but were not augmented relative to the other groups. Similarly, during DPPOS there was no significant impact of treatment group on incidence or resolution rates of any UI (Figure 1) or by subtype of UI. Both average incidence (12.1%, 10.8% and 11.0%, p=0.2) and average resolution rates (10.5%, 10.0% and 10.4%, p=0.8) were very similar for ILS, MET and PLC, respectively, over the DPPOS follow-up.

Determinants of UI during 6 year follow-up

As shown in Figure 2, significant independent predictors of lower prevalence of any UI during DPPOS included younger age, non-smoking, Hispanic or African-American self-reported ethnicity (vs Caucasian), fewer previous pregnancies and more physical activity and lower initial BMI at entry into DPPOS. Significant correlates of lower UI during DPPOS were greater decreases in BMI and waist circumference over the 6 years. Every 1% reduction in BMI over the 6 year follow-up was associated with an approximate one quarter reduction in prevalent UI (Figure 2). Examining predictors and correlates of prevalent stress and urgency UI, similar variables emerged, including lower initial BMI at entry into DPPOS and greater reductions in BMI and WC over the 6 years of follow-up being independently

related to less prevalent stress and urgency UI; one exception was that reductions in WC were not significantly (p = 0.08) related to less prevalent stress UI (data not shown).

Neither diabetes at entry into DPPOS nor receiving a diagnosis of diabetes during DPPOS was significantly related to UI. Entry level or changes during DPPOS in glucose and albumin to creatinine ratio or changes during DPPOS in activity were also not significantly related to prevalent UI overall or by any of the subtypes of UI.

We similarly examined predictors of resolution and incidence of UI. Among women with UI at entry into DPPOS, resolution was more likely in women with younger age (HR = 0.97 [0.95–0.98]; p=0.0001), African American race (HR = 1.44 [1.0–2.1]; p=0.04), and greater reductions in BMI during DPPOS (hazard ratio [HR] = 0.013 [0.001–0.15; p=0.0005). No significant predictors or correlates emerged in analyses of incidence of UI. Sample sizes were too small to examine predictors of incidence and resolution by type of UI.

DISCUSSION

This is the first, long-term description of UI in women with impaired glucose tolerance and incident diabetes. We previously reported that overweight women at risk for diabetes assigned to intensive lifestyle intervention had significantly lower prevalence of weekly UI compared with women assigned to metformin or placebo (38% vs. 48.1% and 45.7%, respectively) at the end of the approximately 3 year DPP trial; this effect was accounted for by weight loss during DPP. [4] During the 6 years of follow-up of this cohort, the prevalence of any weekly incontinence increased across all groups but remained lower in the ILS group compared with MET and PLC (44.2% vs. 51.8% and 48.0%, respectively). Thus, the beneficial effects of DPP lifestyle intervention on incontinence appeared to extend for years beyond the end of the DPP trial.

During DPPOS, ILS did not result in additional improvements in UI above and beyond those observed at end of DPP. The diminished effect of ILS during DPPOS might have been due to a decrease in intensity of ILS during DPPOS. As noted earlier, a “bridge” protocol was offered to all participants between DPP and DPPOS, which included a group-administered version of the 16-session lifestyle curriculum. Subsequently, during DPPOS, lifestyle sessions were offered every three months to all participants, and additional special sessions (four sessions per year) were offered to ILS group. Participation rates of at least several sessions were modest in each group (40% in ILS, 58% in MET, and 57% in PL), and less than 20% of ILS participants attended the additional special sessions. Thus, a decline in both treatment intensity and adherence to ILS might explain the diminished effect on UI during DPPOS. It is also possible that the addition of lifestyle sessions to the PL and MET groups improved UI during DPPOS. Indeed, other work has shown positive effects of the MET group emerging during DPPOS that were not apparent during DPP.[12] However, throughout DPPOS, the MET group had a numerically *higher* prevalence of UI compared with PL and ILS. MET is known to activate AMP-activated protein kinase (AMPK), leading to improved insulin sensitivity.[23] However, the physiological role of AMPK in the lower urinary tract and pelvic floor muscles remains to be elucidated and merits further research.[24]

Notably, lower BMI at entry into DPPOS and decreases in BMI and waist circumference during 6 year follow up were strong determinants of less prevalent UI overall and by type. Other research in overweight women [25] and those with type 2 diabetes[3] has documented the benefits of weight loss in reducing prevalent[25] and incident[3] incontinence. Among overweight/obese women with type 2 diabetes in the Look AHEAD trial, a lifestyle intervention that promoted an average 8 kg weight loss also reduced 1-year prevalent and incident incontinence compared to the Diabetes Support and Education control group. [3] The current study is the first prospective study to examine and document the benefits of weight loss on UI in women with impaired glucose tolerance. Although mechanisms linking BMI and UI remain poorly understood, decreasing weight and/or abdominal adiposity may reduce intra-abdominal pressure and decrease intravesicular pressure and urethral mobility, thereby improving UI. [26]

Interestingly, higher leisure time physical activity at entry into DPPOS (median was ~120 minutes per week) was related to *less* prevalent 6-year UI. This finding is in contrast to earlier research showing a positive association between exercise and urine leakage. [27, 28] However, more recent data indicate that most types of exercise, particularly low impact exercises, do not appear to adversely affect urinary incontinence [29]. The low impact activities promoted as part of the lifestyle intervention in DPP and DPPOS may account for this association between higher activity and subsequently less UI.

We did not find a relationship between the diagnosis of diabetes (at any time) glucose-related variables (fasting glucose, HbA1C), or an inflammatory marker (CRP) and incontinence. This was not unexpected since most women were at the early stage of disease and did not commonly experience microvascular complications that could damage innervation of the bladder or alter detrusor muscle function. [30] Moreover, the blood glucose levels in this population may not have been high enough to cause an osmotic diuresis.

During the DPPOS follow-up, the prevalence of ≥ weekly UI remained relatively stable, increasingly overall by only ~2% per year with an annual incidence rate of ~12% and resolution rate of ~10%. Few epidemiologic data in general populations are available on the development or natural history of UI and its types. Existing research suggests somewhat lower incidence rates (ranging between 3 and 6%)[31, 32] and generally higher resolution rates (although varies from 6% to 38%)[33–35] than the rates observed in the current study. Overall, the current study is consistent with higher incident rates of UI in individuals with impaired glucose or type 2 diabetes than in comparison groups, as found in other research.[36]

This study is the first to prospectively show that intensive lifestyle intervention had a modest positive impact on UI that appeared to endure for years beyond the end of the DPP trial. Nonetheless, a notable limitation is that UI was not assessed until the end of DPP; thus, we could not evaluate changes in prevalent, incident, and resolved UI over the full study (DPP plus DPPOS). Our study participants were clinical trial volunteers who agreed to long-term follow-up, thus findings may not generalize to other populations or lifestyle interventions. Also, our assessment of parity did not include evaluation of type of delivery (vaginal vs. c-section), which may differentially impact UI. Although UI information was based on self-

report, the reliability and validity of self-reported incontinence has been demonstrated in previous studies.[13]

Women at high risk for diabetes who were randomly assigned to a comprehensive lifestyle intervention involving weight loss, dietary changes, and exercise had lower long-term prevalence of UI that persisted even after the end of the trial. Reducing BMI and waist circumference may be an effective means of lowering the prevalence of UI in women with impaired glucose tolerance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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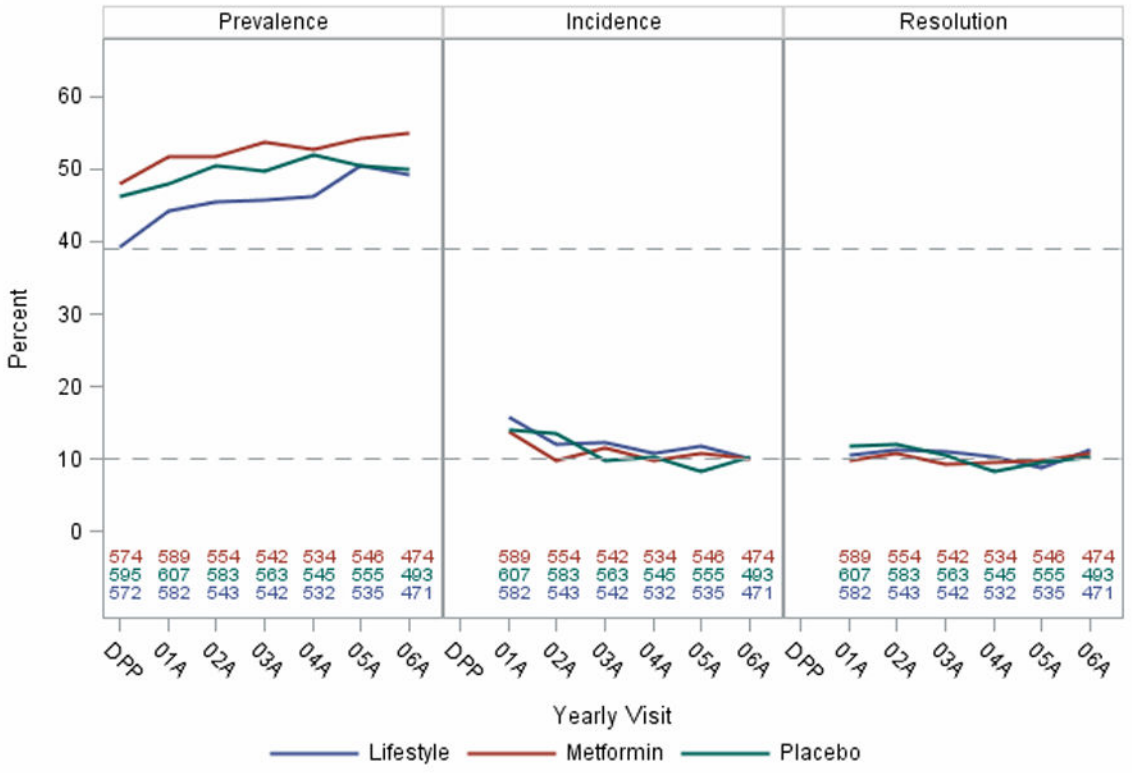

Figure 1. Prevalence, incidence, and resolution of UI in DPPOS by Treatment Group

Prevalence is defined as proportion of participants reporting “yes” to the question “in the past 7 days did you leak even a small amount of urine?” at each annual visit. Incidence is defined as proportion of participants reporting “yes” to the above question at the current visit and “no” in the previous visit. Resolution is defined as proportion of participants reporting “no” to the above question at the current visit and “yes” in the previous visit.

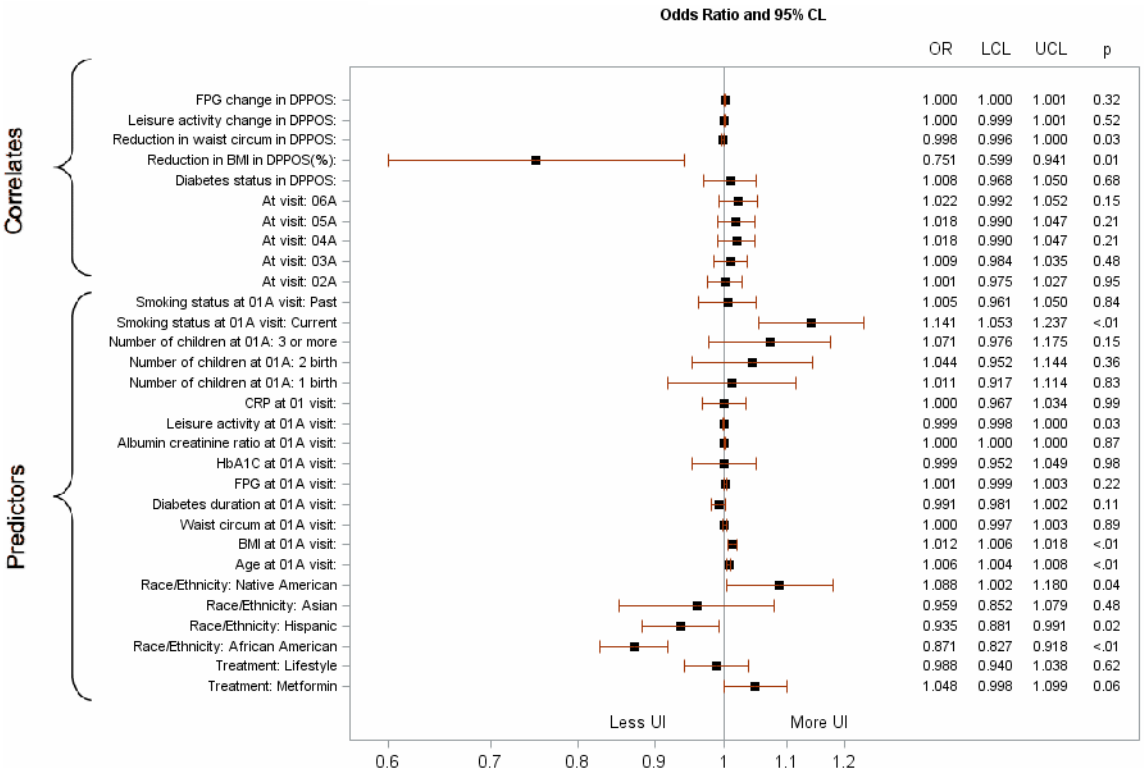

Figure 2. Predictors and Correlates of UI during DPPOS

Odds ratios are calculated as per unit increase in UI based on unit change in the predictors for the continuous predictors, or verse the reference group for the categorical predictors. Note that for BMI change, the unit was % reduction in BMI; and, for WC change, the unit was cm reduction in WC. Also note that X axis is logarithmic scale.

References for the categorical variables are: Placebo for the treatment group; 01A visit for the visit year; Non-Hispanic White for the Race/Ethnicity groups; no children for Parity; never smoked for the smoking status at 01A visit.

Abbreviations: OR, odds ratio; LCL, lower 95% confidence limit; UCL, upper 95% confidence limit; p, p value; FPG= Fasting plasma glucose; Waist circum= waist circumference; CRP= C-reactive protein; DPPOS= Diabetes Prevention Program Outcomes Study; DPP= Diabetes Prevention Program

Table 1

Characteristics of 1,778 women participants at DPPOS first annual visit

	Treatment groups			
	Lifestyle N = 582	**Metformin N = 589**	**Placebo N = 607**	**p-value**
Age, years	54.0 (47.5–62.0)	54.6 (48.8–61.2)	53.7 (48.2–60.4)	0.32
Race				
Caucasian	298 (51.2%)	312 (53.0%)	326 (53.7%)	0.65
African American	128 (22.0%)	138 (23.4%)	132 (21.7%)	
Hispanic	89 (15.3%)	90 (15.3%)	88 (14.5%)	
American Indian	43 (7.4%)	37 (6.3%)	44 (7.2%)	
Asian	24 (4.1%)	12 (2.0%)	17 (2.8%)	
Smoking				
Current smoker	30 (5.2%)	36 (6.1%)	44 (7.2%)	0.51
Past Smoker	181 (31.1%)	167 (28.4%)	172 (28.3%)	
Diabetes diagnosis (%)	143 (24.6%)	195 (33.1%)	225 (37.1%)	<0.0001
BMI, kg/m^2	32.7 (28.7–38.4)	33.2 (28.4–38.4)	33.8 (29.4–39.0)	0.06
Waist Circumference, cm	99.6 (90.2–111.0)	100.6 (91.0–110.4)	102.0 (91.2–112.8)	0.12
Leisure Physical Activity (MET-hr/wk)	10.4(5.2–19.6)	8.9(4.5–18.4)	8.9(4.0–18.1)	0.04
Fasting Glucose, mg/dl	104.0 (97.0–114.0)	103.0 (96.0–111.0)	105.5 (98.0–117.0)	<.0001
HbA1C, %	5.8 (5.6–6.2)	5.8(5.6–6.1)	5.9 (5.6–6.3)	0.02
Albumin:creatinine	5.9(4.1– 10.2)	6.2(4.3– 11.0)	6.3(4.3– 10.1)	0.39
Parity				0.95
0	28 (5.8%)	25 (5.0%)	28 (5.3%)	
1	88 (17.8%)	95 (19.0%)	90 (17.2%)	
2	159 (32.4%)	172 (34.4%)	188 (35.9%)	
3 or more	209 (43.9%)	208 (41.6%)	218 (41.6%)	
Any UI (% ≥ weekly)	257 (44.2%)	304 (51.8%)	290 (48.0%)	0.04
Stress UI (%≥ weekly)	191 (37.1%)	223 (44.1%)	213 (40.4%)	0.08
Urgency UI (%≥ weekly)	160 (33.1%)	192 (40.4%)	183 (36.8%)	0.06

Numbers are medians (Inter-quartile range) or N(%); UI= urinary incontinence