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Use of metformin following a population-level intervention to encourage people with pre-diabetes to enroll in the National Diabetes Prevention Program

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ABSTRACT

Introduction The National Diabetes Prevention Program (NDPP) and metformin are interventions to slow progression from pre-diabetes to type 2 diabetes. When coverage for the NDPP was offered by a public research university's health insurance plan, proactive strategies were used to combat historically low enrollment. Although not specifically targeted by these strategies, metformin use was higher than expected, leading to this evaluation.

Research design and methods We used insurance enrollment, claims, pharmacy, and laboratory data for 64 131 adult employees, dependents, and retirees to identify individuals with pre-diabetes and invite them to enroll in the NDPP at no out-of-pocket cost. The characteristics of individuals with pre-diabetes who used metformin before and after their invitation were compared with NDPP enrollees.

Results 8131 individuals with pre-diabetes were identified. Of these, 776 (9.5%) enrolled in a NDPP and 802 (9.9%) used metformin. Metformin users were younger, had higher body mass index, were more likely to have comorbidities, and had higher baseline hemoglobin A1c levels than non-users. Timing of metformin use varied with 107 (13%) discontinuing, 426 (53%) continuing, and 269 (34%) initiating metformin use after their NDPP invitation. Of NDPP enrollees, 13 (2%) discontinued, 56 (7%) continued, and 34 (4%) initiated metformin use when they enrolled.

Conclusions Despite no active encouragement, use of metformin was similar to the rate of enrollment in the NDPP. Metformin use was higher for individuals with higher likelihood of responding. With the proven cost-effectiveness of metformin, targeted strategies to increase metformin use in individuals with pre-diabetes who are likely to respond, but not willing to enroll in a lifestyle intervention, are needed.

Significance of this study

What is already known about this subject?

- Both the National Diabetes Prevention Program (NDPP) and metformin decrease progression from pre-diabetes to type 2 diabetes.
- Historically, few primary care physicians refer patients with pre-diabetes to the NDPP and even fewer prescribe metformin for their patients with pre-diabetes.

What are the new findings?

- Metformin use for diabetes prevention was substantially more common than previously reported (10% vs 4%).
- Following invitation to enroll in the NDPP, younger people with pre-diabetes, men, and individuals with higher body mass index were more likely to initiate metformin than to enroll in the NDPP.
- Of those who ever used metformin, 13% discontinued, 53% continued, and 34% initiated metformin after they were invited to participate in the NDPP.
- Of those who enrolled in the NDPP, 2% discontinued, 7% continued, and 4% initiated metformin use.
- Compared with those who enrolled in the NDPP without ever using metformin, metformin users were younger, more likely to be men, have higher BMIs, higher hemoglobin A1c, to be more likely to be obese/overweight and have hypertension, and to live in neighborhoods with lower incomes and higher proportions of Supplemental Nutrition Assistance Program recipients.

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

- Targeted interventions are needed to increase metformin use in individuals with pre-diabetes who are likely to respond but not willing to enroll in lifestyle interventions.

INTRODUCTION

Pre-diabetes is estimated to affect over 88 million Americans, over one-third of the adult US population.[1] Unfortunately, fewer than one in six Americans with pre-diabetes are aware of their diagnosis, with lower rates among men and adults under the age of 45 years. The Diabetes Prevention Program (DPP), a lifestyle intervention first described in 2002, was shown to delay or prevent the development of type 2 diabetes among individuals with pre-diabetes.[2 3] This has been translated into several community-level interventions, including the National Diabetes Prevention Program (NDPP), that use behavior changes with goals of weight loss and aerobic

physical activity to decrease progression from pre-diabetes to type 2 diabetes.[4 5]

Pharmaceutical intervention with metformin has also been shown to significantly decrease the incidence of type 2 diabetes in those with pre-diabetes, although this remains an off-label use of metformin. In the largest study to date, the DPP, metformin had a smaller impact than lifestyle intervention, although the use of metformin still reduced the incidence of type 2 diabetes by 31%.[2] This effect was heterogeneous, with greater risk reduction in those at the highest risk at the time of enrollment in the DPP.[6] Post hoc analysis of the DPP has shown that the greatest risk reduction occurred in those in the top quartile of risk, with the lowest quartile receiving no significant reduction in type 2 diabetes incidence from using metformin.[7]

The effect of metformin in reducing risk of progression from pre-diabetes to type 2 diabetes has been shown to be durable. Following a 1–2 week washout period, only 26% of the risk reduction was attributed to metformin's immediate pharmacological effect, yielding a persistent 25% relative risk reduction in type 2 diabetes incidence versus placebo.[8] With ongoing metformin therapy, this positive effect has been shown to be sustained for at least 10 years after the completion of the trial.[9] Both interventions have been shown to be financially advantageous, with lifestyle interventions being cost-effective and metformin being marginally cost-saving at 10 years.[10] Combination of metformin and lifestyle intervention has been evaluated in the Indian DPP as well as several smaller studies, with no evidence of additive benefits.[11]

Despite strong recommendations by the American Diabetes Association (ADA) for lifestyle intervention or metformin in pre-diabetes, both interventions have been found to have low uptake.[12] In a large sample of employed, insured Americans, only 3.7% of patients with pre-diabetes were prescribed metformin.[13] Likewise, many primary care physicians are not aware of the NDPP and its availability in many communities across the USA.[14] In qualitative analysis of primary care recommendations for intervention in those with laboratory values consistent with pre-diabetes, most physicians provide general guidance on improving diet and increasing physical activity with little utilization of metformin or referral to the NDPP.[15]

Herein, we describe the impact of proactive strategies to identify and increase enrollment in the NDPP on the use of metformin among individuals with pre-diabetes enrolled in a public research university's self-funded health insurance plan. Though metformin was not specifically promoted, we sought to understand the characteristics of individuals with pre-diabetes who used metformin only before their invitation to participate in the NDPP, both before and after their invitation, and only after their invitation. We also compared the characteristics of those who simultaneously took metformin and enrolled in the NDPP with those who only took metformin or only enrolled in a NDPP.

RESEARCH DESIGN AND METHODS

The University of Michigan (U-M) is a public research university located in Ann Arbor, Michigan, with additional regional campuses in Flint, Michigan, and Dearborn, Michigan. Among all campuses, approximately 45 000 individuals are employed by U-M. Approximately 85 000 individuals, including employees, dependents, and retirees, are insured by Premier Care, U-M's self-funded commercial health insurance program. Blue Care Network (BCN), the largest independent practice associate model health maintenance organization in Michigan, is the claims manager for Premier Care. In 2015, U-M Premier Care elected to begin coverage of the NDPP with no out-of-pocket cost for overweight or obese enrollees ≥18 years of age with pre-diabetes. Given historically poor uptake of the NDPP and high attrition among those who participate, a 3-year pilot initiative was undertaken to implement and evaluate three proactive strategies to encourage enrollment and completion of NDPP programs. Between August 2015 and July 2018, BCN used enrollment, claims, pharmacy, and laboratory data for 64 131 Premier Care members ≥18 years of age to identify and contact those with known pre-diabetes and those at high risk for pre-diabetes using two strategies, outlined further. A third strategy targeted all U-M employees. These strategies were described previously.[16]

Strategy 1 (members with pre-diabetes)

Enrollment, claims, pharmacy, and laboratory data were used to identify Premier Care members ≥18 years of age without evidence or diagnoses of diabetes mellitus but with one or more of the following: (1) claims for impaired fasting glucose (International Classification of Diseases, Ninth revison (ICD-9) 790.21 or ICD, Tenth revision (ICD-10) R73.01), impaired glucose tolerance (ICD-9 790.22 or ICD-10 R73.02), or other abnormal glucose (ICD-9 790.29 or ICD-10 R73, R73.0, R73.09, and R73.9), and (2) hemoglobin A1c (HbA1c) levels between 5.7% (39 mmol/mol) and 6.4% (46 mmol/mol) in the preceding 3 years (ADA criterion for pre-diabetes).[17] Every 6 months, these criteria were used to identify individuals with pre-diabetes. In total, 6736 individuals with pre-diabetes were identified and received mailed invitations to enroll in the NDPP. Second invitation letters were sent to 1372 previously identified individuals who had repeat HbA1c levels in the pre-diabetes range who had not enrolled in the NDPP. Primary care physicians identified 49 additional individuals who likely qualified based on fasting glucose or oral glucose tolerance test results who were not identified using claims or HbA1c results. All individuals received a single reminder letter 90 days following the initial invitation letter.

Strategy 2 (members at high-risk for pre-diabetes)

A previously described and validated algorithm using health plan members' demographic, claims, pharmacy, and laboratory data (not including HbA1c or fasting glucose levels) was used to identify Premier Care members 40–64 years of age at high risk for impaired fasting glucose (here defined as fasting glucose 110–125 mg/dL) or previously undiagnosed type 2 diabetes.[18] Four models were created, using increasingly complex risk factors including age, sex, obesity, hypertension, dyslipidemia, body mass index (BMI), blood pressure, lipid levels, and use of blood pressure and lipid-lowering agents. BCN applied these models to identify members in the highest three deciles of risk. These individuals received letters informing them of their increased risk of pre-diabetes and type 2 diabetes and encouraging them to follow-up with their primary care physicians for diagnostic testing. In total, 5219 members received strategy 2 letters. Each strategy 2 letter was followed in 90 days by a single reminder letter. If these targeted individuals were subsequently diagnosed as having pre-diabetes or had a qualifying HbA1c level, they received a strategy 1 invitation letter.

Strategy 3 (broad email campaign)

In January 2018, an email was sent to 29 875 employees encouraging them to be screened for pre-diabetes. An online questionnaire was included, with recommendations regarding testing for pre-diabetes and, if found to have pre-diabetes, encouragement to enroll in a NDPP at no out-of-pocket cost.

For this analysis, individuals with pre-diabetes were defined as those identified in strategy 1 plus individuals targeted by strategy 2 or strategy 3 who had a HbA1c or claim in the 1 year after the invitation date that met criteria for pre-diabetes. If discordant information was present, such as a claims diagnosis of type 2 diabetes and a HbA1c in the pre-diabetes range, adjudication was performed. Individuals with a new claims diagnosis of type 2 diabetes were included only if the first HbA1c was in the pre-diabetes range. All individuals with a new claims diagnosis of pre-diabetes were included unless they had both an additional claim for type 2 diabetes and a HbA1c >6.4% (46 mmol/mol).

Metformin

Pharmacologic treatment of pre-diabetes was not mentioned in any of the three outreach strategies. However, it was expected that metformin might also be used by individuals with pre-diabetes. Prevalence of metformin use was assessed using BCN pharmacy claims data for filled metformin prescriptions. Metformin use before the invitation was defined as one or more filled prescription(s) for metformin in the year before the invitation to enroll in a NDPP. Metformin use after the invitation was defined as one or more filled prescription(s) for metformin in the year after the invitation. Ever metformin use included any metformin use before or after the date of the invitation letter. Individuals with pre-diabetes were initially dichotomized as having ever or never used metformin, with comparisons performed with χ^2 tests and t-tests. Next, the timing of metformin use was described as: (1) before the invitation to participate in a NDPP only, (2) before and after the invitation, or (3) after the invitation only. Because NDPP enrollment was only assessed after the invitation but metformin could be used at any time, we categorized members based on metformin use as well as enrollment in a NDPP: (1) metformin use only at any time, (2) NDPP enrollment without any use of metformin at any time, or (3) NDPP enrollment and metformin use at any time (figure 1).

Residential address zip codes were merged with data from the US Census Fact Finder Tool available at https://data.census.gov/cedsci/ (accessed 2 Jun 2020) to describe zip code specific median household income, per cent unemployment, and per cent participation in the Supplemental Nutrition Assistance Program (SNAP) based on 5-year averages derived from the American Community Survey. Study participants were sent an informed consent document, and receipt of a completed survey was considered to imply consent. All analyses were performed using SAS V.9.4 (SAS Institute), and missing

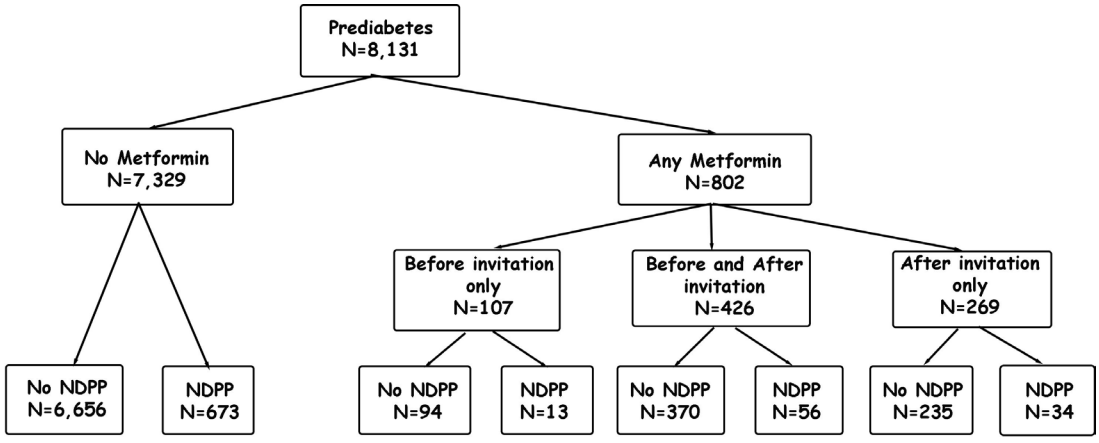

Figure 1 Identification of groups by enrollment in the National Diabetes Prevention Program (NDPP) as well as timing of metformin use.

data were excluded from the analyses. In general, less than 10% of data were missing.

RESULTS

In total, 8131 individuals with pre-diabetes were identified. Of these, 802 (9.9%) filled at least one prescription for metformin, and 7329 individuals (90.1%) never filled a prescription for metformin. Seven-hundred seventy-six individuals (9.5%) enrolled in a NDPP with or without use of metformin.

Metformin ever users versus never users

Metformin users were younger than those with pre-diabetes who never used metformin (table 1).

Women comprised the majority of individuals with pre-diabetes who were identified, and women were more likely than men to use metformin. White individuals were more likely than Asian individuals to use metformin, with no difference in metformin use between whites and blacks. At least one visit to a primary care physician or specialist in the prior year increased the likelihood of metformin use. Individuals with non-U-M primary care physicians were more likely to be prescribed metformin than those with U-M primary care physicians (10.8% vs 9.4%, p value=0.05). Among U-M primary care physicians, there was no difference in rate of metformin use by patients treated by internal medicine or family medicine physicians. In areas where individuals who used metformin resided, the median income was lower. There were no differences in neighborhood unemployment rates. The per cent of individuals using SNAP was slightly higher in areas where individuals who used metformin resided. BMI was significantly higher in those who used metformin, as was the baseline blood pressure. Lipid panels revealed higher baseline triglycerides but lower total cholesterol, low density lipoprotein (LDL), and high density lipoprotein (HDL) in those who used metformin. Baseline HbA1c levels were higher in individuals who used metformin. In review of available claims data, metformin users more commonly carried diagnoses of obesity and hypertension. Antihypertensive and lipid-lowering medication use were more common in those using metformin. Smoking rates and cardiovascular disease prevalence were similar in metformin users and nonusers.

Timing of metformin use

Of those who used metformin, 107 individuals (13.3%) used the medication only in the year before the invitation to participate in a NDPP, 426 individuals (53.1%) used metformin before and after the invitation, and 269 individuals (33.5%) used it only after the invitation. Members who used metformin only before invitation were the youngest, followed by those who used metformin both before and after the invitation (table 2).

In all three groups, women were most likely to use metformin, although more men tended to use metformin after the invitation. The differences in metformin use by race were statistically significant, with increased use of metformin after the invitation by individuals who identify themselves as non-white. There was a lower rate of primary care physician visits within the preceding year, but no difference in specialist physician visits among those who used metformin. Median neighborhood income was lowest, and percentage of individuals using SNAP were highest in those who used metformin after the invitation. BMI was similar in all metformin user groups. However, BMI was significantly higher in those who used metformin than in those who did not use metformin (table 1). Likewise, systolic and diastolic blood pressure were similar in all metformin user groups but higher than in metformin non-users (table 1). HbA1c was highest in those who used metformin before and after the invitation, followed by those who used metformin only after the invitation. Claims data showed higher rates of hypertension and cardiovascular disease and greater use of antihypertensive and lipid-lowering medications among metformin users after the invitation. Rates of obesity and smoking were not significantly different among groups.

Utilization of both NDPP and metformin

Of the 8131 individuals with pre-diabetes, 6656 (81.9%) did not participate in a NDPP or ever use metformin. An NDPP only without metformin was used by 673 (8.3%) individuals. Metformin only was used by 699 (8.6%) individuals, and 103 (1.3%) individuals both used metformin and enrolled in an NDPP. Of the 699 who used metformin only, 94 (13%) discontinued, 370 (53%) continued, and 235 (34%) initiated metformin after their invitation to enroll in a NDPP. Older age was associated with enrollment in an NDPP, while any metformin use was associated with younger age (table 3).

Men were more likely to use metformin than to enroll in an NDPP. Median neighborhood income was highest for those who enrolled in an NDPP, either with or without metformin, and lowest for those who elected to use metformin only. Neighborhood mean per cent of SNAP utilization was highest in those using metformin only. Metformin users had higher BMIs than those who chose lifestyle only. HbA1c values and blood pressures levels were highest in those who took metformin alone. Those who took metformin had higher rates of obesity than those who enrolled in a NDPP. Hypertension was more prevalent in those using metformin as was the prevalence of antihypertensive medication use. Those who used metformin only had higher rates of smoking. Rates of cardiovascular disease were the same across groups.

CONCLUSIONS

Despite compelling evidence to support the use of either a NDPP or metformin for prevention of type 2 diabetes in those with pre-diabetes, uptake has been historically poor.[2–4] In this analysis, we found that metformin use for diabetes prevention was substantially more common than previously reported (9.9% vs 4%) even without targeted recommendations for its use. We also showed that following invitation to enroll in an NDPP, different populations favored proceeding with a lifestyle intervention

Table 1 Baseline characteristics of premier care members ≥18 years of age with pre-diabetes, stratified by metformin use

	Total	Any metformin use	No metformin use	P value
Number (%)	8131	802 (10)	7329 (90)	–
Age (years)	50±12	48±12	51±12	<0.0001
Sex				<0.0001
Women	4649 (57)	549 (68)	4100 (56)	
Men	3482 (43)	253 (32)	3229 (44)	
Race				0.0124
Asian	634 (10)	43 (7)	591 (10)	
Black	532 (8)	51 (8)	481 (8)	
White	5254 (81)	520 (83)	4734 (81)	
Other	85 (1)	14 (2)	71 (1)	
At least one primary care visit in prior year	6789 (84)	691 (86)	6098 (83)	0.0299
At least one specialist visit in prior year	5323 (66)	569 (71)	4754 (65)	0.0005
Geocoded indicators				
Median neighborhood income ($)	$69 751	$68 487	$69 888	0.0386
Per cent unemployment	35.0±4.7	34.7±4.7	35.0±4.7	0.0847
Per cent Supplemental Nutrition Assistance Program	8.7±6.5	9.2±6.3	8.6±6.5	0.0125
BMI (kg/m^2)	32.3±7.3	36.7±7.8	31.8±7.1	<0.0001
Blood pressure (mm Hg)				
Systolic	125±15	127±15	125±15	0.0017
Diastolic	75±10	77±10	75±10	<0.0001
Lipids (mg/dL)				
Total cholesterol	194±39	190±40	195±39	0.0062
HDL cholesterol	52±15	49±13	52±15	<0.0001
Women	57±15	52±13	58±16	<0.0001
Men	46±12	42±10	46±12	<0.0001
Triglycerides	147±94	160±116	145±91	0.0049
LDL cholesterol	114±33	111±34	114±33	0.0206
HbA1c (%)	5.8±0.5 n=4876 (60)	6.1±0.9 n=625 (78)	5.8±0.4 n=4251 (58)	<0.0001
Claims diagnosis of …				
Overweight/obesity	2817 (35)	418 (52)	2399 (33)	<0.0001
Hypertension	3064 (38)	371 (46)	2693 (37)	<0.0001
Any antihypertensive medication	2865 (35)	376 (47)	2489 (34)	<0.0001
Dyslipidemia	2733 (34)	290 (36)	2443 (33)	0.1077
Any lipid-lowering medication	1636 (20)	206 (26)	1430 (20)	<0.0001
Smoking	530 (7)	48 (6)	482 (7)	0.5194
Women	256 (6)	24 (4)	232 (6)	0.2144
Men	274 (8)	24 (10)	250 (8)	0.3212
Cardiovascular disease	800 (10)	81 (10)	719 (10)	0.7939

Data are number (%) or mean±SD.
BMI, body mass index; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein.

versus pursuing therapy with metformin. Individuals who used metformin therapy were generally younger, had a higher BMI, and had more medical comorbidities. Interestingly, these subgroups are the ones who have been identified as being most likely to respond to metformin for diabetes prevention.[3 6 7] An approach to tailor interventions to those most likely to benefit has identified this very subset of individuals with pre-diabetes, as they appear to be at the highest risk for progression to type 2 diabetes.[7] Prior analysis of metformin prescriptions for pre-diabetes in a national private insurance database likewise showed that the predicted probability

Table 2 Baseline characteristics of premier care members ≥18 years of age with pre-diabetes, stratified by the timing of metformin use

	Metformin use before invitation only	Metformin use before and after invitation	Metformin use after invitation only	Overall p value
Number (%)	107 (1)	426 (5)	269 (3)	–
Age (years)	43±12	48±12	49±11	<0.0001
Sex				0.3257
Women	78 (73)	295 (69)	176 (65)	
Men	29 (27)	131 (31)	93 (35)	
Race				0.0367
Asian	3 (4)	25 (7)	15 (7)	
Black	10 (13)	19 (5)	22 (11)	
White	62 (83)	296 (86)	162 (78)	
Other	0 (0)	6 (2)	8 (4)	
At least one primary care visit in prior year	90 (84)	384 (90)	217 (81)	0.0023
At least one specialist visit in prior year	82 (77)	304 (71)	183 (68)	0.2672
Geocoded Indicators				
Median neighborhood income ($)	$68 163	$70 130	$66 040	0.0103
Per cent unemployment	34.8±5.1	34.6±4.4	34.8±4.9	0.7363
Per cent Supplemental Nutrition Assistance Program	9.3±6.4	8.7±5.7	10.0±7.1	0.0217
BMI (kg/m^2)	36.1±7.2	36.9±7.9	36.6±7.8	0.5938
Blood pressure (mm Hg)				
Systolic	126±13	127±14	127±16	0.6425
Diastolic	77±10	76±10	77±11	0.9817
Lipids (mg/dL)				
Total cholesterol	190±40	189±39	191±41	0.9502
HDL cholesterol	47±14	49±13	49±13	0.6366
Women	51±16	53±12	52±13	0.6491
Men	40±8	42±11	41±9	0.7108
Triglycerides	146±72	165±138	159±88	0.4733
LDL cholesterol	114±32	110±34	111±35	0.6747
HbA1c (%)	5.9±0.5 n=80 (74)	6.2±1.0 n=367 (86)	6.1±0.8 n=178 (66)	0.0525
Claims diagnosis of …				
Overweight/obesity	55 (51)	228 (54)	135 (50)	0.6837
Hypertension	38 (36)	214 (50)	119 (44)	0.0173
Any antihypertensive medication	41 (38)	225 (53)	110 (41)	0.0015
Dyslipidemia	40 (37)	161 (38)	89 (33)	0.4353
Any lipid-lowering medication	16 (15)	128 (30)	62 (23)	0.0029
Smoking	4 (4)	25 (6)	19 (7)	0.4663
Women	0 (0)	14 (5)	10 (6)	0.1115
Men	4 (14)	11 (8)	9 (10)	0.6665
Cardiovascular disease	10 (9)	34 (8)	37 (14)	0.0466

Data are number (%) or mean±SD.
BMI, body mass index; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein.

of prescribing was twofold higher in women or individuals with obesity.[13] Additionally, metformin prescriptions were 1.5 times more common in those with two or more comorbidities.[13]

Although not powered to assess the impact of metformin use on reduction in incidence of type 2 diabetes in specific subgroups, the DPP showed heterogeneity of metformin treatment effect. Younger individuals achieved larger

Table 3 Baseline characteristics of premier care members ≥18 years of age with pre-diabetes, stratified by metformin use and engagement in a NDPP

	NDPP only	Metformin only	Metformin+NDPP	P value
Number	673 (46)	699 (47)	103 (7)	–
Age (years)	53±10	48±12	48±12	<0.0001
Sex				0.0064
Female	473 (70)	465 (67)	84 (82)	
Male	200 (30)	234 (33)	19 (18)	
Race				0.8160
Asian	50 (9)	39 (7)	4 (5)	
Black	41 (7)	43 (8)	8 (9)	
White	466 (82)	448 (83)	72 (84)	
Other	10 (2)	12 (2)	2 (2)	
Geocoded indicators				
Median neighborhood income ($)	71 319	68 100	71 081	0.0031
Per cent unemployment	34.4±4.6	34.8±4.8	34.0±4.2	0.1632
Per cent Supplemental Nutrition Assistance Program	8.2±6.0	9.4±6.4	8.2±5.6	0.0010
BMI (kg/m^2)	33.4±6.8	36.7±7.9	37.0±6.7	<0.0001
Blood pressure (mm Hg)				
Systolic	125±15	127±15	126±14	0.1894
Diastolic	74±10	77±10	76±10	<0.0001
Cholesterol (mg/dL)				
Total cholesterol	198±39	189±41	194±31	0.0073
HDL cholesterol	54±14	49±13	48±10	<0.0001
Female	58±14	52±13	50±10	<0.0001
Male	45±11	42±10	39±6	0.0045
Triglycerides	146±80	161±121	157±74	0.1019
LDL cholesterol	116±33	110±35	114±28	0.0384
HbA1c (%)	5.8±0.3	6.2±0.9	5.9±0.4	<0.0001
Claims diagnosis of …				
Overweight/obesity	294 (44)	357 (51)	61 (59)	0.0016
Hypertension	240 (36)	326 (47)	45 (44)	0.0002
Any antihypertensive medication	222 (33)	333 (48)	43 (42)	<0.0001
Dyslipidemia	242 (36)	250 (36)	40 (39)	0.8298
Any lipid-lowering medication	147 (22)	185 (26)	21 (20)	0.0911
Smoking	14 (2)	45 (6%)	3 (3)	0.0002
Female	8 (2)	23 (5)	1 (1)	0.0094
Male	6 (3)	22 (9)	2 (11)	0.0220
Cardiovascular disease	50 (7)	70 (10)	11 (11)	0.1946

Data are number (%) or mean±SD.
BMI, body mass index; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein; NDPP, National Diabetes Prevention Program.

reductions in progression to type 2 diabetes, with 44% risk reduction in individuals 25–44 years of age and 11% for those ≥60 years old. Individuals with a BMI ≥35 kg/m^2 showed a 53% risk reduction, while individuals with BMI values in the overweight categories (22–30 kg/m^2) had a 3% risk reduction.[19] Metformin has been further shown to produce more sustained weight loss in individuals with pre-diabetes who have greater initial weight loss (>5% of baseline weight loss in the first year).[20]

The metabolic syndrome is associated with impaired fasting glucose, lower HDL cholesterol, elevated triglycerides, abdominal adiposity, and hypertension leading to increased cardiovascular and glycemic risk.[21] Our analysis showed that individuals with biochemical

patterns most consistent with the metabolic syndrome were more likely to be prescribed metformin and less likely to initiate enrollment in the NDPP. In prior analyses of the DPP, the metabolic syndrome has been found to be highly prevalent, affecting nearly half of all participants, and both lifestyle and metformin interventions compared with placebo have been shown to prevent metabolic syndrome.[22] However, for individuals with the metabolic syndrome at the time of enrollment, only the lifestyle intervention was shown to lead to a significant resolution in specific components of the metabolic syndrome. In dedicated analyses of hypertension and lipid profiles in those enrolled in the DPP, lifestyle intervention has been shown to be superior in decreasing the prevalence of hypertension, increasing HDL, and reducing triglycerides, while metformin has been shown to produce modest reductions in triglycerides.[23]

Although the DPP showed the interventions to be effective in all racial and ethnic subgroups,[3] there are known racial and ethnic disparities in the effectiveness of the NDPP, with non-Hispanic whites experiencing greater weight loss in comparison with Hispanic and non-Hispanic black participants.[5] A recent single-center analysis has shown that low-income non-Hispanic white participants have less weight loss than their non-low income counterparts.[24] In the DPP, black women were noted to have significantly less weight loss in the lifestyle intervention arm, while there were no race or sex differences apparent in the metformin arm.[25] Numerous translations of the DPP have been conducted, tailored to the needs of members of ethnic minority communities in the USA, often with improved outcomes.[26] Our results show similar uptake of lifestyle and metformin among races, although with a less diverse sample than the DPP.

Uptake of the NDPP by men has been consistently low. Similarly, we found that uptake of both the NDPP and metformin were much lower in men. Although equivalent weight loss yielded greater reduction in risk factors for type 2 diabetes for men than their women counterparts,[27] women are over three times as likely to enroll in the NDPP lifestyle change program.[28] In the DPP Outcomes Study, coronary calcium score severity was less in men receiving metformin versus placebo, an effect not seen in women.[29] In a meta-analysis, no sex-specific differences in the reduction in incidence of type 2 diabetes was appreciated in both lifestyle and pharmacological interventions.[30] Little is known regarding uptake of metformin by men in a population-based analysis.

Few individuals in our study elected to enroll in a NDPP and to use metformin. In the Indian DPP, it appears that there was little benefit to combination therapy.[11] Interestingly, metformin therapy had a similar effect size to lifestyle changes in the Indian population.

Strengths of our work include the level of detail of the available data for this privately insured population, including lab data, demographics, utilization, and diagnoses. Limitations include the retrospective, observational nature of this work. Pharmacy claims data were used as a surrogate for metformin use without any knowledge of adherence or continuation of the therapy. Additionally, some individuals prescribed metformin may have in fact progressed to type 2 diabetes. Attempts were made to exclude individuals with type 2 diabetes by reviewing A1c values and diagnosis codes.

Several recent editorials have presented compelling arguments for and against metformin use in individuals with pre-diabetes.[31–33] Our study shows that despite no direct recommendation to use metformin for the treatment of pre-diabetes, uptake of metformin was similar to the rate of enrollment in an NDPP. In particular, uptake appears to be higher for individuals who are at higher risk and who are most likely to respond to metformin including those with younger age, higher baseline BMI, increased number of comorbidities, and higher A1c. Uptake among men remained low, but metformin appeared to appeal to men more than a lifestyle intervention. With increasing data supporting the cost-effectiveness of metformin in pre-diabetes, more targeted strategies to increase uptake of metformin in individuals with pre-diabetes not willing to enroll in lifestyle interventions are needed.

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