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 8,131 individuals with pre-diabetes were identified. Of these, 7,766 (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, 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.

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%.\(^2\)\(^3\) 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 revision (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 pre-diabetes or had a qualifying HbA1c level, they received a strategy 1 invitation letter.
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 prediabetes who never used metformin (table 1).

Women comprised the majority of individuals with prediabetes 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 lowering medication for diabetes who never used metformin (table 1). Like-wise, 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. Rates of obesity and smoking were not significantly different among groups.

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).

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.4-4 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
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 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 | | | | |
| Women | 4649 (57) | 549 (68) | 4100 (56) | <0.0001 |
| 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/m²) | 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 | 6.1±0.9 | 5.8±0.4 | <0.0001 |
| n=4876 (60) | n=625 (78) | n=4251 (58) | |
| 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.
of prescribing was twofold higher in women or individuals with obesity.\textsuperscript{13} Additionally, metformin prescriptions were 1.5 times more common in those with two or more comorbidities.\textsuperscript{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 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 (66) | 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/m²) | 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 | 6.2±1.0 | 6.1±0.8 | n=80 (74) n=367 (86) 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.
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/m² showed a 53% risk reduction, while individuals with BMI values in the overweight categories (22–30 kg/m²) had a 3% risk reduction. 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).

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.

Our analysis showed that individuals with biochemical

| 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 ($) | 71319          | 68100           | 71081          | 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/m²)    | 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)          | 0.0084         |
| 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.
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. A recent single-center analysis has shown that low-income non-Hispanic white participants have less weight loss than their non-low income counterparts. 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. 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. 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. In the DPP Outcomes Study, coronary calcium score severity was less in men receiving metformin versus placebo, an effect not seen in women. 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. 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. 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. 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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