Metformin Use in Prediabetes Among U.S. Adults, 2005–2012

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OBJECTIVE

To determine the prevalence of and characteristics associated with metformin use among U.S. adults with prediabetes using the National Health and Nutrition Examination Survey (NHANES) 2005–2012.

RESEARCH DESIGN AND METHODS

The American Diabetes Association's guidelines for metformin use in prediabetes have evolved, with 2017 recommendations suggesting metformin be considered in patients with prediabetes and additional risk factors (BMI ≥35 kg/m^2, age <60 years, or prior gestational diabetes mellitus) or rising hemoglobin A_{1c} (HbA_{1c}). We estimated the age-adjusted prevalence of metformin use among individuals with prediabetes (defined by HbA_{1c} 5.7–6.4%, fasting glucose 100–125 mg/dL, 2-h poststimulated glucose 140–199 mg/dL, or self-report) and used multivariate logistic regression to evaluate characteristics associated with metformin use.

RESULTS

Of 22,174 adults, 7,652 had prediabetes. The age-adjusted prevalence of metformin use among those with prediabetes was 0.7%. Metformin use was associated with higher mean BMI (35.1 kg/m^2 vs. 29.6 kg/m^2, $P < 0.01$) and higher glucose (fasting glucose 114 mg/dL vs. 105 mg/dL, $P = 0.03$; 2-h poststimulated glucose 155 mg/dL vs. 128 mg/dL, $P = 0.003$; and HbA_{1c} 6.0% [42 mmol/mmol] vs. 5.6% [38 mmol/mmol], $P < 0.01$). Metformin use was low even among those with BMI ≥35 kg/m^2, a group for whom metformin use is recommended. Metformin use did not vary by race, poverty-to-income ratio, or education.

CONCLUSIONS

Metformin use was <1% among U.S. adults with prediabetes and only slightly more common among those with additional risk factors for diabetes.

Eighty-six million adults in the U.S. have prediabetes, and up to 70% of these individuals will eventually develop diabetes (1,2). In the Diabetes Prevention Program (DPP), the incidence of diabetes in the placebo group was 62% after a mean follow-up of 15 years (3). Considering the number of individuals who will progress from prediabetes to diabetes (2), there is limited evidence on whether patients with prediabetes are being managed with metformin. The American Diabetes Association (ADA) recommends an intensive diet and physical activity behavioral counseling program for all patients with prediabetes and suggests that metformin be considered in patients with additional risk factors (BMI ≥35 kg/m^2, age <60 years, or history of gestational diabetes), largely based on subgroup analyses from the DPP (4,5). In 2017, the ADA also recommended that metformin be considered in those with prediabetes and a rising hemoglobin A_{1c} (HbA_{1c}) despite lifestyle intervention.

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The prevalence of metformin use for prediabetes and the characteristics of patients currently being prescribed metformin for prediabetes are not well described. A prior study using National Health and Nutrition Examination Survey (NHANES) data demonstrated that >96% of identified individuals with impaired fasting glucose and impaired glucose tolerance fulfilled older, broader criteria for metformin consideration (6). Although the majority of people with prediabetes likely qualify for metformin use based on age and BMI (7), recent analyses conducted in selected populations in the U.S. have shown that metformin use in prediabetes is low (3.7% from claims data from UnitedHealthcare and <0.1% from electronic health data from Kaiser Permanente) (8,9).

Using data from NHANES 2005–2012, we evaluated the prevalence of metformin use and the characteristics associated with metformin use among U.S. adults with prediabetes. We hypothesized that the prevalence of metformin use for prediabetes would be low (<5%) and that higher BMI, younger age, comorbid conditions, and higher glucose and HbA_{1c} levels would be associated with use of metformin among adults with prediabetes.

RESEARCH DESIGN AND METHODS

Data Collection

We examined data from four consecutive 2-year cycles (2005–2006, 2007–2008, 2009–2010, and 2011–2012) of NHANES to estimate the prevalence of metformin use in prediabetes. NHANES is a biannual, stratified, multistage probability sample of the U.S. civilian, noninstitutionalized population (10). Participants undergo an in-home interview and a visit to a mobile examination center; nonresponse is accounted for in the sampling weights.

Age, race, sex, education level, health insurance coverage, smoking status, comorbid conditions (hypertension, coronary heart disease, and/or heart attack), and family history of diabetes were obtained through the household questionnaire. We used the poverty-to-income ratio, the ratio of a family's income to the poverty threshold, to assess income level (11).

During the household interviews, interviewers asked the survey participants if they had taken prescription medications in the past month (12). If yes, the participant was asked to show the interviewer all medication containers. Medication names were entered and automatically matched to a prescription drug database. If a medication container was not available, the participant was asked to verbally list the medication name. The interviewer's original entry and matched database drug name were saved under separate variables for quality control purposes (12). Participants were asked if they had ever been told by a doctor or health professional that they have "diabetes or sugar diabetes" with possible responses of "yes," "no," or "borderline." If they answered "no," then they were asked if they had ever been told any of the following: that they had "prediabetes, impaired fasting glucose, impaired glucose tolerance, borderline diabetes or that your blood sugar is higher than normal but not high enough to be called diabetes or sugar diabetes."

For each mobile examination, participants were randomly selected to attend a morning, afternoon, or evening session at which height, weight, and systolic blood pressure were measured. HbA_{1c} levels were measured at all sessions. Fasting triglycerides, LDL cholesterol, and fasting and 2-h plasma glucose from an oral glucose tolerance test were measured at the morning sessions only.

All study participants provided written informed consent. Study protocols were approved by the research ethics board of the National Center for Health Statistics.

Population

Participants were considered to have prediabetes based on *1*) laboratory values (HbA_{1c} 5.7–6.4% [39–46 mmol/mmol], fasting plasma glucose 100–125 mg/dL, or 2-h poststimulated plasma glucose 140–199 mg/dL) (13) without meeting any laboratory criteria for diabetes or *2*) self-reported "borderline" diabetes or prediabetes as described above. We excluded persons younger than 20 years of age, those with self-reported diabetes, pregnant women, and persons who were on diabetes medications besides just metformin (Fig. 1).

Statistical Analysis

Our primary outcome of interest was the prevalence of metformin use among people with prediabetes. We estimated the age-adjusted prevalence of prediabetes in the overall population and the age-adjusted prevalence of metformin use among individuals with prediabetes using the 2000 Census population as the standard population structure (14). Sample weights from NHANES were used to represent the total civilian, noninstitutionalized U.S. population and to account for the complex survey design: we used the household interview weights for self-reported prediabetes, the mobile examination center weights for HbA_{1c}, and the fasting plasma glucose and oral glucose tolerance test weights for fasting glucose and 2-h stimulated glucose, respectively (7). We used Taylor series linearization methods for variance estimation. We compared means and proportions using linear and logistic regression, respectively, in bivariate models. In the multivariate model, we adjusted for variables that were significantly associated with metformin use in bivariate analyses (insurance status, hypertension, overweight, HbA_{1c}, and BMI).

Additionally, we examined the percentage of individuals who were on metformin based on different criteria for metformin use (Table 3). We also looked at metformin use by survey cycle and used survey-weighted logistic regression to calculate a *P* trend across survey cycles (15).

We performed a sensitivity analysis estimating the prevalence of metformin use among individuals with prediabetes defined by HbA_{1c} criteria only. We also conducted two subgroup analyses of individuals with prediabetes who were on metformin stratified by BMI (≥35 and <35 kg/m^2) and age (<60 and ≥60 years). Statistical analyses were performed using STATA software (version 13.1; StataCorp, College Station, TX) survey modules. All tests of significance were two tailed, with α-levels of 0.05.

RESULTS

We identified 91 participants with prediabetes who were taking only metformin and 7,561 participants with prediabetes who were not taking any diabetes medications (age-adjusted prevalence of metformin use 0.7%) (Fig. 1). The age-adjusted prevalence of metformin use among individuals with prediabetes defined by HbA_{1c} only was 1.0%. Metformin use for prediabetes

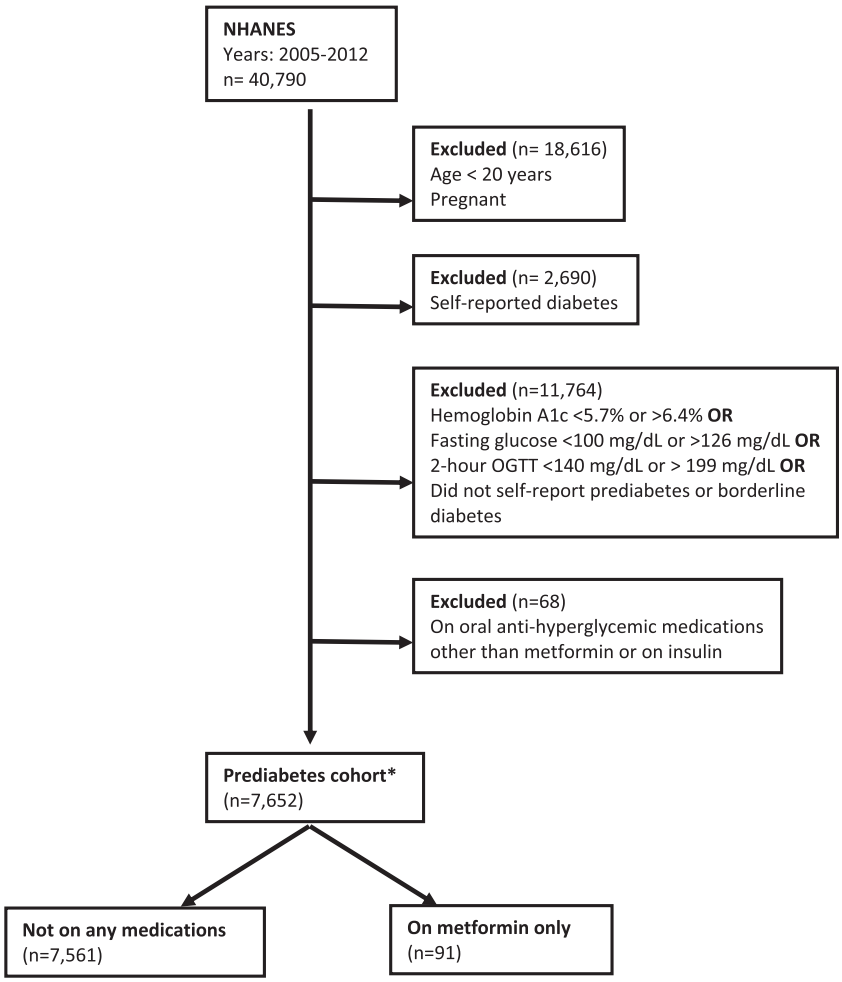

Figure 1—Study flow diagram. *Age-adjusted prevalence of prediabetes among adults was 40.8% (undiagnosed prediabetes, 36.4%; self-reported prediabetes, 4.6%). OGTT, oral glucose tolerance test.

was not associated with younger age but was associated with higher mean BMI (35.1 vs. 29.6 kg/m^2, $P < 0.01$) and higher glucose (fasting glucose 114 vs. 105 mg/dL, $P = 0.03$; HbA_{1c} 6.0% [42 mmol/mmol] vs. 5.6% [38 mmol/mmol], $P < 0.01$; 2-h poststimulated glucose 155 vs. 128 mg/dL, $P = 0.003$). More people with prediabetes who were on metformin had an HbA_{1c} ≥6% compared with those not on metformin (51.0 vs. 14.5%; $P < 0.001$). In the multivariable model, adults with prediabetes on metformin had significantly higher odds of having an HbA_{1c} ≥6 vs. <6% (adjusted odds ratio [OR] 4.56 [95% CI 2.48, 8.37]) and being informed of overweight status by a doctor (adjusted OR 3.27 [95% CI 1.68, 6.37]) (Table 2).

In our additional analyses, we found that the majority of people with prediabetes on metformin met more than one laboratory criterion for prediabetes (fasting glucose, HbA_{1c}, or 2-h poststimulation plasma glucose) (Supplementary Table 1). While the additional risk factors delineated in the 2007 and 2017 ADA recommendations for metformin use were more common among those on metformin (Table 1), most people with those risk factors were not on metformin (Table 3).

We found that adults with prediabetes on metformin and BMI ≥35 kg/m^2 tended to be white, have a smaller poverty-to-income ratio, and have lower mean HbA_{1c} and fasting glucose compared with their counterparts with BMI <35 kg/m^2 (Supplementary Table 2). In stratified analyses by age, individuals on metformin and age <60 years tended to have a higher mean BMI, higher HbA_{1c}, and 2-h poststimulation plasma glucose; lower systolic blood pressure; and less insurance coverage and were less likely to have a history of heart disease or heart attack (Supplementary Table 3).

Compared with individuals not on any medications, adults with prediabetes on metformin were more likely to have health insurance coverage (92.0 vs. 81.1%; $P < 0.01$) and have comorbid conditions (self-reported hypertension 56.0 vs. 36.2%, $P = 0.02$) (Table 1), but these risk factors were not significantly associated with metformin use after multivariate adjustment (Table 2). Metformin use did not vary based on race, poverty-to-income ratio, or education level (Table 1). When examined by individual survey cycle year, metformin use was lowest during 2005–2006, with 0.4%, compared with subsequent cycles but did not vary significantly across cycles (P for trend = 0.17) (Supplementary Table 4).

CONCLUSIONS

Using nationally representative data from NHANES 2005–2012, we found that metformin use was uncommon, with <1% of U.S. adults with prediabetes reporting metformin use. Our findings are well below the expected usage of metformin in prediabetes based on risk factors (of those with prediabetes and not on metformin, 69% were younger than 60 years and 17% had a BMI ≥35 kg/m^2). We did not find a significant secular trend in the prevalence of metformin use by NHANES cycle (Supplementary Table 4). The small number of people with prediabetes who were treated with metformin tended to have a higher HbA_{1c} and have been informed of overweight status by a doctor. We did not identify disparities in metformin use based on race, poverty-to-income ratio, or education. Although people with prediabetes on metformin had a higher BMI compared with those not on metformin, having a BMI ≥35 kg/m^2 was not independently associated with a higher prevalence of metformin use despite the ADA recommendations (4). Metformin use was not much more common among those with clear risk factors for progression to diabetes (as evident in Table 3), highlighting a missed opportunity for diabetes prevention.

Our findings add to the two prior studies published by Schmittdiel et al. (8)

Table 1—Characteristics of U.S. adults with prediabetes on metformin compared with those not on diabetes preventive medication

	Prediabetes, on metformin (n = 91)*		Prediabetes, not on any diabetes preventive medication (n = 7,561)†		
Characteristic	Mean; SE or % (SE)§	N‖	Mean; SE or % (SE)§	N‖	P‡
Age (years)	54.5; 1.9		50.8; 0.4		0.06
Age <60 years	63.3 (6.0)	40	69.4 (9.2)	4,372	0.30
Female	55.7 (7.7)	47	45.9 (7.0)	3,570	0.22
Race					
White	69.0 (5.3)	38	70.2 (1.9)	3,443	
Black	10.5 (2.7)	20	10.4 (0.9)	1,657	
Other/multiracial	7.8 (3.5)	6	6.4 (0.6)	562	0.66
Mexican American	7.5 (2.5)	16	8.3 (0.9)	1,198	
Other Hispanic	5.1 (1.7)	11	4.7 (0.6)	701	
Have health insurance coverage	92.0 (3.3)	82	81.1 (0.9)	5,837	0.008
Education					
More than high school	57.7 (7.0)	36	55.7 (1.1)	3,465	
High school grad/GED or equivalent	23.5 (6.1)	23	24.6 (0.8)	1,852	0.76
Less than high school	18.8 (4.1)	32	19.6 (0.8)	2,233	
Income					
>200% of poverty level	61.3 (7.3)	41	62.1 (1.3)	3,598	
100–200% of poverty level	22.6 (6.1)	26	19.6 (0.8)	1,952	0.38
Lower than poverty level	13.4 (4.2)	20	12.1 (0.6)	1,371	
BMI (kg/m^2)	35.1; 1.4		29.6; 0.1		0.005
BMI (kg/m^2)					
<35	53.6 (7.7)	53	82.9 (0.7)	6,115	<0.001
≥35	46.4 (7.7)	34	17.1 (0.7)	1,330	
Systolic blood pressure (mmHg)	126.3; 2.4		124.1; 0.3		0.38
Cholesterol (mg/dL)					
Total	190.6; 6.7		201.0; 0.8		0.14
HDL	49.0; 2.2		52.0; 0.3		0.20
LDL¶	116.5; 6.5		120.2; 0.8		0.56
Triglycerides¶	171.1; 26.6		140.7; 2.3		0.33
HbA_{1c}, % (mean in mmol/mol)	6.0; 0.07 (42)		5.6; 0.009 (38)		<0.001
HbA_{1c} ≥6%	51.0 (6.7)	56	14.5 (0.6)	1,879	<0.001
Fasting plasma glucose (mg/dL)¶	114.2; 4.0		105.1; 0.2		0.01
2-h poststimulation plasma glucose (mg/dL)¶	155.4; 8.7		127.7; 1.0		0.003
Smoking					
Current smoker	14.4 (5.7)	12	21.1 (0.8)	1,617	
Ever smoker	41.0 (6.7)	36	27.4 (0.9)	2,092	0.70
Never smoker	44.5 (7.4)	43	51.5 (1.1)	3,848	
History of hypertension	56.0 (8.0)	61	36.2 (0.8)	3,118	0.02
History of heart disease and/or heart attack	11.7 (4.8)	9	6.0 (0.4)	549	0.26
Identified as overweight by doctor	74.3 (5.5)	61	36.3 (0.9)	2,768	<0.001
Family history of diabetes	41.3 (7.0)	47	38.3 (0.7)	3,006	0.67

GED, General Educational Development. *N for subjects on metformin by variable: income, BMI, and systolic blood pressure, n = 87; HDL/total cholesterol, n = 84; history of heart attack, n = 89; family history of diabetes, n = 90. †N for subjects not on metformin by variable: insurance, n = 7,554; education, n = 7,550; income, n = 6,921; BMI, n = 7,445; systolic blood pressure, n = 7,217; HDL/total cholesterol, n = 7,422; smoking, n = 7,557; hypertension, n = 7,548; history of heart attack, n = 7,523; overweight, n = 7,555; family history of diabetes, n = 7,392. ‡P value for comparison of means or proportions using linear or logistic regression, respectively, accounting for sampling weights. §Represents weighted means or percentage. ‖Represents unweighted n. ¶Fasting laboratories available only for subjects who attended morning session: fasting glucose, n = 47 for metformin and n = 4,752 for no metformin; 2-h poststimulation plasma glucose, n = 5 for metformin and n = 4,192 for no metformin; for triglycerides, n = 46 for metformin and n = 4,725 for no metformin; for LDL cholesterol, n = 46 for metformin and n = 4,623 for no metformin.

and Moin et al. (9), which used electronic health data (Kaiser) and health insurance claims data (UnitedHealthcare), respectively, to examine a similar question (8,9). Both studies showed that metformin use was low (<0.1–3.7%), but their findings were only generalizable to specific insured populations. Moin et al. (9) demonstrated that female sex, obesity, and a higher number of comorbid conditions were associated with metformin use. Additional factors were not evaluated given the limitations of claims data. In our study, we used a nationally representative database that includes prescription medication data that was confirmed during the in-person interview. Therefore, we avoided misclassification of metformin use, a limitation highlighted in one of the prior studies (9). Similar to prior

Table 2—Adjusted ORs for characteristics associated with metformin use (versus nonuse of metformin) in prediabetes (*n* = 7,464)

Characteristic	OR (95% CI)*	*P*
HbA_{1c} ≥6% (ref. HbA_{1c} <6%)	4.56 (2.48, 8.37)	<0.001
Have health insurance (ref. no health insurance)	2.28 (0.85, 6.14)	0.10
History of hypertension (ref. no history of hypertension)	1.22 (0.57, 2.59)	0.61
Identified as overweight by doctor (ref. not identified as overweight by doctor)	3.27 (1.68, 6.37)	0.001
BMI ≥35 kg/m^2 (ref. BMI <35 kg/m^2)	1.63 (0.78, 3.42)	0.19

*Each OR adjusted for additional covariates: HbA_{1c} ≥6%, health insurance status, history of hypertension, informed of overweight status by doctor, and BMI ≥35 kg/m^2.

analyses of NHANES, awareness of prediabetes status was low (16).

ADA recommendations for the consideration of pharmacotherapy for the prevention of diabetes have evolved over the past 10 years. In 2005, the ADA did not recommend metformin use for diabetes prevention because it was unclear that it was cost-effective (17). In 2007, the ADA convened an expert panel that concluded that metformin could be considered for people with impaired fasting glucose and impaired glucose tolerance with an additional risk factor, specifically, age <60 years, BMI ≥35 kg/m^2, diabetes in first-degree relatives, elevated triglycerides, low HDL cholesterol, hypertension, or HbA1c ≥6.0% (18). Since 2012, the ADA has recommended that metformin be considered in those with impaired fasting glucose, impaired glucose tolerance, or a HbA_{1c} of 5.7–6.4%, especially in individuals age <60 years, with BMI ≥35 kg/m^2, or with a history of gestational diabetes mellitus (4). Clinicians may also be considering metformin based on a patient's response to lifestyle intervention and may start metformin if a patient is not successful in lowering weight or fasting glucose with lifestyle change. Some evidence supports this strategy: a prior analysis of the DPP showed that it may be reasonable to consider metformin based on the amount of weight loss after 6 months of lifestyle change (19). As of 2017, the ADA added that metformin should be considered in those with rising HbA_{1c} who are not responding to initial lifestyle change (4). It is important to note that the evidence on diabetes prevention underlying the ADA's recommendations is based mainly on the DPP, which required participants to have elevated fasting glucose (95–125 mg/dL) and impaired glucose tolerance; therefore, the benefits of the lifestyle intervention and metformin may both be different for the population meeting criteria for prediabetes based on one abnormal test that is usually not a glucose tolerance test. In particular, while HbA_{1c} was not used as an inclusion criterion for the DPP, it is likely that HbA_{1c} is now being used to screen for prediabetes given the availability of diagnostic categories for prediabetes and diabetes based on HbA_{1c} since 2010 (20). HbA_{1c} does have some limitations in defining hyperglycemia in certain situations (e.g., anemia, specific medication use, different racial groups) and has high specificity but low sensitivity for diagnosing prediabetes and diabetes; this should also be considered in the interpretation of our results and in future work (21,22).

Table 3—Percentage of individuals with prediabetes reporting metformin use by criteria for metformin use

Risk factors for prediabetes	*n**	*N*†	% (SE) on metformin‡
Prediabetes by IFG, IGT, HbA_{1c}, or self-report	91	7,652	0.8 (0.8)
Prediabetes based on IGT alone	1	285	0.8 (0.8)
Prediabetes based on IFG alone	0	1,577	0
Prediabetes based on HbA_{1c} 5.7–6.4% alone	18	3,065	0.6 (0.2)
Prediabetes based on HbA_{1c} 6.0–6.4% alone	13	1,411	0.9 (0.3)
Self-reported prediabetes alone	0	0	0
BMI ≥35 kg/m^2	33	1,316	1.9 (0.5)
IFG and IGT + risk factor§	0	0	0
IGT + risk factor‖	1	190	1.1 (1.0)
IFG + risk factor‖	0	1,178	0
HbA_{1c} 5.7–6.4% + risk factor‖	13	2,101	0.7 (0.2)
Self-reported prediabetes + risk factor‖	0	0	0
IFG and IGT + risk factor‖ + HbA_{1c} 6.0–6.4%	0	179	0

IFG, impaired fasting glucose; IGT, impaired glucose tolerance. *Represents unweighted *n* for those treated with metformin. †Represents unweighted *n* for those treated or not treated with metformin. ‡Represents weighted percentage. §2007 guidelines risk factors: age <60 years, BMI ≥35 kg/m^2, family history of diabetes, elevated triglycerides, low HDL cholesterol, hypertension, or HbA_{1c} ≥6%. We defined elevated triglycerides as ≥150 mg/dL and low HDL cholesterol as <40 mg/dL based on Adult Treatment Panel III guidelines (30). ‖2017 guidelines risk factors: age <60 years, BMI ≥35 kg/m^2, or history of gestational diabetes mellitus (not available in this data set) and rising HbA_{1c} despite lifestyle intervention (not available in this data set).

The argument that often has been raised against metformin therapy for prediabetes is that we are putting patients who are at risk for diabetes on a medication that treats diabetes and exposing them to a drug (and its potential side effects) for more time than is necessary. Furthermore, we know there is clinical inertia in treating and advancing therapy in diabetes (23,24), and we expect for this clinical inertia to be even greater with preventive therapy for prediabetes. However, first, prediabetes is associated with premature mortality (25) and autonomic neuropathy and idiopathic polyneuropathy (2). Second, the recommended initial management of both patients with diabetes and prediabetes is lifestyle change. Lifestyle change, irrespective of weight loss, has been shown to decrease the risk of developing diabetes (26). However, in the DPP, 35% of participants in the intensive lifestyle intervention arm were unable to achieve at least 5% weight loss in the first 6 months of the trial (5). If we apply that failure rate to the population of 86 million adults in the U.S. who have prediabetes, then there are roughly 30 million adults who might fail to achieve the prevention target for weight

loss and could potentially benefit from metformin. Third, metformin has been widely studied and has a limited side effect profile, most commonly diarrhea, flatulence, nausea, and vomiting (average 28 vs. 16% in placebo arm, $P = 0.01$, during the DPP) (27). No cases of lactic acidosis were reported in the DPP Outcomes Study (27). Fourth, the 15-year follow-up of the DPP demonstrated that metformin reduced the incidence of diabetes significantly compared with placebo (hazard ratio 0.82 [95% CI 0.72, 0.93]; $P = 0.001$) (3). Fifth, the DPP Outcomes Study demonstrated that achieving a normal glucose level at least once, even if not sustained, can decrease the risk of developing diabetes compared with individuals who consistently had prediabetes (28). It is important to note that in the DPP Outcomes Study, while persons who did not develop diabetes had a lower risk of microvascular complications than those who did develop diabetes, to date, data are still lacking on whether diabetes prevention lowers the risk of macrovascular complications (3).

There are several limitations to this study. Using a single laboratory test to define prediabetes may overestimate the prevalence of prediabetes (and therefore underestimate the prevalence of metformin use in prediabetes); this would be of most concern with fasting and stimulated glucoses given their known variability (29). However, we also incorporated HbA_{1c} data into our definition, which does not have significant variability. In our sensitivity analysis, we found that the prevalence of metformin use remained low (1.0%) even when we defined prediabetes by HbA_{1c} only. History of gestational diabetes mellitus was not available for the entire cohort so was not included in this analysis. We were also unable to examine behavioral factors such as participation in a weight loss program, physical activity, or weight loss attempts. We included self-reported prediabetes in our definition of prediabetes, so it is possible that some of these people may have progressed to diabetes based on their laboratory results. However, all of the people with self-reported prediabetes had at least one laboratory result consistent with prediabetes (Supplementary Table 1). Finally, NHANES data may not be completely reflective of actual clinical practice, and the risk of diabetes in clinical populations may differ. However, using NHANES data allows for nationally representative estimates.

Overall, we found that the vast majority of U.S. adults with prediabetes, including those at high risk of developing diabetes, do not report use of metformin as preventive pharmacotherapy. Metformin is an effective, safe, and low-cost preventive pharmacotherapy option for patients with prediabetes. Ongoing efforts to reduce the risk of type 2 diabetes through intensive lifestyle change are important but must be augmented by other approaches. Further study on how to implement metformin as a preventive intervention for type 2 diabetes is needed to truly stem the tide of the diabetes epidemic.

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