Metformin Use Linked to Lower Osteoarthritis Prevalence in U.S. Adults with Type 2 Diabetes

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INTRODUCTION: Beyond its established role in managing type 2 diabetes (T2DM), metformin has shown potential protective effects on cartilage health. Previous studies have demonstrated metformin's anti-inflammatory and chondroprotective properties [1], with some reporting reduced knee pain [2] and delayed need for joint replacement [3]. However, population-level evidence linking metformin use to osteoarthritis (OA) remains limited. Using nationally representative data from the U.S. National Health and Nutrition Examination Survey (NHANES), this study aimed to investigate the association between metformin use and OA prevalence among adults with T2DM.

METHODS: Data were pooled from 10 NHANES cycles (1999-2020). The analytic sample included adults aged ≥30 years with T2DM, defined as physician-diagnosed diabetes at ≥30 years old and not currently using insulin (Fig 1). Metformin use and OA were identified from self-reported prescription and physician diagnosis, respectively. Covariates were selected a priori [1,3-5] and grouped as demographic (age, sex, and race/ethnicity), socioeconomic (poverty-income ratio and insurance status), lifestyle (smoking and physical activity), and clinical (body mass index, chronic kidney disease, and number of prescription medications) factors. Survey cycles were included to adjust for secular trends. All analyses account for NHANES' complex sampling design to ensure nationally representative estimates. Weighted descriptive statistics were reported overall and by metformin status (Table 1). Associations between metformin use and OA were estimated using survey-weighted multivariable logistic regression (Tables 2-3, Fig 2). Analyses were performed in Stata 18.

RESULTS: The final analytic sample included 3,665 adults with T2DM (unweighted N_{Female}=1,786 and N_{Male}= 1,879; M_{Age}=61 years), representing 12.2 million U.S. adults (Fig 1). Metformin users were more often men (52.97% vs 47.03%, p=0.014), had higher mean poverty-income ratio (2.92 vs 2.64, p<0.001) and body mass index (32.92 vs 32.12 kg/m², p=0.027), had lower prevalence of chronic kidney disease (3.38% vs 10.93%, p<0.001), and took more medications (4.12 vs 3.78, p<0.001). Survey-weighted logistic regression models showed that metformin use was associated with lower odds of OA in both crude and adjusted models (Table 2). In the unadjusted model, metformin users had 29% lower odds of OA compared to non-users (OR=0.71, 95% CI: 0.54-0.93, p=0.014). After adjustment for covariates, the association strengthened, with metformin use associated with 38% lower odds of OA (OR=0.62, 95% CI: 0.46-0.84, p=0.002). Older age (≥ 55, OR=2.08, 95% CI: 1.42-3.04, p<0.001) and women (OR=2.30, 95% CI: 1.81-2.93, p<0.001) had higher odds of OA. Hispanic (OR=0.44, 95% CI: 0.31-0.62, p<0.001) and non-Hispanic Black (OR=0.45, 95% CI: 0.34-0.60, p<0.001) adults had significantly lower odds compared with non-Hispanic White adults. Higher BMI (OR=1.04, 95% CI: 1.02-1.06, p<0.001) and a greater number of medications (OR=1.34, 95% CI: 1.20-1.50, p<0.001) were associated with higher odds of OA. Adjusted predicted OA prevalence was 25.75% among non-users and 18.50% among metformin users, corresponding to a -7.25% absolute difference (p=0.003) (Table 3). Stratified analyses showed the prevalence of OA was significantly lower among users aged 30-54 years compared with non-users (-13.07%, p=0.014). Among adults aged ≥55 years, the reduction was non-significantly smaller (-5.29%, p=0.070). For women, the adjusted prevalence difference was 10.5% lower (p=0.007), whereas among males it was 3.9% lower (p=0.073). Sex- and age-interactions were not statistically significant (Table 3), *i.e.*, the trend between subgroups requires confirmation in larger cohorts.

DISCUSSION: In the U.S., approximately 29.4 million adults are diagnosed with diabetes [7], and 20.4 million are prescribed metformin [8], making it one of the most widely used treatments with substantial public health relevance. In this study, metformin use was associated with significantly lower odds of OA among non-insulin dependent adults with T2DM. In the adjusted model, metformin users had 38% lower odds of OA compared to non-users, corresponding to a 7.25% absolute reduction in predicted prevalence. Stratified analyses suggested stronger reductions among younger adults and females. Although interaction tests did not show statistical difference in metformin use and OA association by age or sex, the observed trends align with prior evidence of demographic differences in OA pathophysiology [5,6]. The relatively small T2DM subpopulation in NHANES may limit subgroup precision, emphasizing the need for a larger cohort to clarify potential differential benefits. Additionally, because NHANES data are cross-sectional, causal relationships cannot be established. Despite these limitations, this study contributes to evidence that metformin may protect against OA and emphasizes the need for prospective longitudinal studies to better assess causality. **SIGNIFICANCE:** Metformin, a widely used and low-cost T2DM treatment, was associated with lower OA prevalence in this study. Given OA's major burden and the lack of disease-modifying therapies, metformin may offer a promising preventative strategy. Subgroup trends suggest greater benefit in younger adults and females, but confirmation in larger, prospective studies is needed.

REFERENCES: [1] Baker+ 2023. [2] Pan+ 2025. [3] Ye+ 2025. [4] Zhu+ 2021. [5] Tschons+ 2021. [6] Loeser+ 2016. [7] CDC National Diabetes Statistics Report 2024. [8] ClinCalc DrugStats Database 2023.

Table 1 Characteristics of adults with type 2 diabetes by metformin use

	Overall (N=3,665)	Non-User (N=1,358)	User (N=2,307)	p-value
Sex (%)				**0.014**
Male	50.76	46.80	52.97	
Female	49.24	53.21	47.03	
Age (years, %)				0.071
30-54	29.46	26.60	31.05	
55+	70.54	73.40	68.95	
Race/Ethnicity (%)				0.728
NH White	62.80	64.19	62.03	
NH Black	14.14	13.61	14.43	
Hispanic	13.64	13.15	13.91	
Other	9.43	9.06	9.63	
PIR (mean ± SE)	2.82 ± 0.04	2.64 ± 0.06	2.92 ± 0.05	**<0.001**
Insurance Status (%)				0.847
Uninsured	7.93	8.08	7.85	
Insured	92.07	91.92	92.15	
Smoking Status (%)				0.572
Non-Smoker	84.50	83.88	84.85	
Smoker	15.49	16.12	15.15	
Physical Activity (%)				0.994
Not Active	57.05	57.06	57.04	
Active	42.95	42.94	42.96	
BMI (kg/m², mean ± SE)	32.65 ± 0.16	32.16 ± 0.26	32.92 ± 0.21	**0.027**
CKD (%)				**<0.001**
No CKD	93.92	89.07	96.62	
CKD Present	6.08	10.93	3.38	
Number of RXs (mean ± SE)	4.00 ± 0.03	3.78 ± 0.05	4.12 ± 0.04	**<0.001**

Unweighted sample sizes are reported. Categorical variables are presented as weighted percentages and continuous variables as weighted means ± SEs. Abbreviations: NH, Non-Hispanic; PIR, Poverty–Income Ratio; BMI, Body Mass Index, CKD, Chronic Kidney Disease; RXs, Medications. Bolded p-values indicate p<0.05.

Fig 1. Flow diagram of study participant selection from NHANES 1999-2020.

Table 2 Odds ratios for OA by metformin use

Model	Odds Ratio [95% CI]	p-value
Crude (unadjusted)	0.71 [0.54, 0.93]	0.014
Adjusted*	0.62 [0.46, 0.84]	0.002

* Adjusted for demographic, socioeconomic, lifestyle, and clinical factors.

Fig 2. Odds ratios from adjusted model shows the relationship between metformin use and OA after considering covariates. Red points indicate p<0.05.

Table 3 Predicted probabilities of OA by metformin use: overall and stratified

	Users (%)	Non-Users (%)	Marginal Effect [95% CI]	p-value	Interaction p-value
Overall	18.50	25.75	-7.25 [-11.98, -2.52]	0.003	NA
Sex					0.299
Male	13.52	17.44	-3.91 [-8.21, 0.38]	0.073	
Female	23.53	34.03	-10.50 [-18.12, 2.89]	0.007	
Age (years)					0.078
30-54	9.65	22.72	-13.07 [-23.52, -2.63]	0.014	
55+	21.84	27.13	-5.29 [-11.03, 0.45]	0.070	

Predicted probabilities (%) from survey-weighted logistic regression adjusted for covariates. Marginal effects represent the difference in OA probability between metformin users and non-users. Negative marginal effect values indicate a lower predicted probability of OA among metformin users. The p-values correspond to within-group comparisons. Interaction p-values test whether metformin effect varies by subgroup.