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**Access and cost-related non-adherence to prescription medications among lupus cases and controls: the Michigan Lupus Epidemiology & Surveillance (MILES) Program**

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## Cost-related prescription non-adherence in lupus

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### ABSTRACT

**Background:** Medication access and adherence are important determinants of health outcomes. We investigated factors associated with access and cost-related non-adherence to prescriptions in a population-based cohort of systemic lupus erythematosus (SLE) patients and controls.

**Methods:** Detailed sociodemographic and prescription data were collected by structured interview in 2014-2015 from participants in the Michigan Lupus Epidemiology & Surveillance (MILES) Cohort. We compared access between cases and frequency-matched controls and examined associated factors in separate multivariable logistic regression models.

**Results:** 654 participants (462 SLE cases, 192 controls) completed the baseline visit; 584 (89%) were female, 285 (44%) black, and mean age was 53 years. SLE cases and controls reported similar frequencies of being unable to access prescribed medications (12.1% vs 9.4%,

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respectively;  $p=NS$ ). SLE patients were twice as likely as controls to report cost-related prescription non-adherence in the preceding 12 months to save money (21.7% vs 10.4%;  $p=0.001$ ), but also more likely to ask their doctor for lower cost alternatives (23.8% vs 15.6%,  $p=0.02$ ). Disparities were found in association with income, race and health insurance status, but main findings persisted after adjusting for these and other variables in multivariable models.

**Conclusion:** SLE patients were more likely than controls from the general population to report cost-related prescription non-adherence, including skipping doses, taking less medicine and delaying filling prescriptions, yet less than 1 in 4 patients asked providers for lower cost medications. Consideration of medication costs in patient decision-making could provide a meaningful avenue for improving access and adherence to medications.

### SIGNIFICANCE AND INNOVATION

- Inability to access prescriptions a doctor felt necessary was reported in approximately 10% of SLE cases and controls.
- Cost-related non-adherence to prescriptions is significantly higher in SLE patients compared with frequency-matched controls from the general population, with over one fifth of SLE patients deviating from taking medication as prescribed for cost reasons.
- Though SLE cases were more likely than controls to ask providers for lower cost medications, inquiries about lower cost medications were infrequent in both groups.
- Consideration of medication costs as part of shared decision making between patients and providers is a potential avenue for intervention.

## INTRODUCTION

Systemic lupus erythematosus (SLE), or lupus, is a chronic autoimmune disease that disproportionately affects women and minorities (1). SLE disease manifestations are heterogeneous and can affect many organ systems, resulting in one of the highest mortality rates among the rheumatic diseases (2). Medical treatments for SLE place significant financial burden on patients and the healthcare system. The mean annual direct costs per patient are estimated to range from USD \$2,214 to \$16,875, with mean annual pharmacy costs ranging between \$1,572–13,138, and accounting for 19–23% of total direct costs (3,4). The mean annual indirect costs (*e.g.*, sick leave, unemployment, housework) are estimated from USD \$2,239 to \$35,540 (year 2010 values), with increased costs associated with accumulated lupus damage (5).

Poor outcomes such as increased flares, emergency department visits, hospitalizations, and renal disease have been noted in association with non-adherence in SLE, making it essential to improve understanding of factors that compromise adherence (6–11). Several studies have documented non-adherence in SLE, and a review by Costedoat-Chalumeau found the most common cause of non-adherence was fear of side effects (12). However, cost-related aspects of non-adherence have not been a central focus in the existing studies.

We utilized the Michigan Lupus Epidemiology & Surveillance (MILES) Cohort to characterize access and cost-related non-adherence to prescription medications and associated disparities in SLE cases and frequency-matched controls from the general population.

## METHODS

The MILES Cohort is a population-based cohort of SLE patients and controls from southeastern Michigan created in 2014-2015. The precursor to the MILES Cohort was the MILES Surveillance

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Registry, one of the National US Lupus Registries supported by the Centers for Disease Control & Prevention (CDC), described elsewhere (1,13). In brief, the MILES Registry included residents of Wayne or Washtenaw Counties in Michigan during 2002-2005, with a new or existing diagnosis of SLE during this calendar period. The two counties comprising the source population for the Registry encompass the cities of Detroit and Ann Arbor, and a population of approximately 2.4 million persons (roughly 25% of the Michigan population). Population-based controls for the MILES Cohort were recruited from a random sample of households in the same source population, and were frequency-matched based on sex, race, age and geography. Due to the rarity of SLE in males, an equivalent number of male controls to male SLE cases were recruited. Prospective controls were excluded if they had a history of lupus or a lupus-like condition.

The Institutional Review Boards of the University of Michigan and Michigan Department of Health and Human Services Ethics provided ethics approval; cohort participants signed written, informed consent. This study utilizes baseline data from the Cohort, and these visits were conducted between February 2014 to September 2015.

### **Data collection**

Detailed clinical, sociodemographic and healthcare access and utilization data were collected through structured interviews at the MILES baseline visit. This included questions related to prescription medication access and adherence in the preceding 12 months, modeled after a subset of questions from the 2015 US National Health Interview Survey (NHIS) for adults (14) (see **Supplementary Material**). To assess prescription access, participants were asked whether they had been unable to obtain prescription medicines they or a doctor believed necessary in the preceding 12 months, and if affirmative, the main reason why. Cost-related prescription non-adherence was a composite measure based on participant report of at least one of the following: skipping medication doses, taking less medicine, or delay in filling a prescription.

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Race and ethnicity were based on self-report. Income was based on household pretax income in the previous calendar year. Health insurance coverage in the past 12 months was based on participant response, with the following categories as options: private insurance, Medicare, Medigap (supplemental Medicare coverage), Medicaid, military, Indian Health Service, a state-sponsored health plan, other government program, or none. Persons with both private and public (e.g., Medicaid) coverage were classified as having private coverage. Patient-reported outcomes for health-related quality of life and co-existing symptom complexes included the RAND Medical Outcomes Study 36-Item Short-Form Survey Instrument (MOS SF-36) (15), the PROMIS-Depression Short Form v1.0 (16), and the Survey Criteria for Fibromyalgia (FM Scale) (17).

### Statistical analysis

Chi-square tests of independence were used to test whether there were differences in proportions between cases and controls by study characteristics. Logistic regression was used to model the association between the variables and outcomes of interest. Separate logistic regression models were used for each of the outcomes. Multivariable models were used to adjust for covariates that were determined to be potential confounders *a priori*. Data management was performed using REDCap electronic data capture tools hosted at the University of Michigan (18). Statistical analyses were performed using Stata (StataCorp, College Station, TX) and R (R Foundation) software packages.

## RESULTS

654 participants (462 SLE cases, 192 controls) completed the study visit. Mean age of the cohort was 53.4 years (SD 12.8); 584 (89.3%) of participants were female, and 285 (44%) self-reported as black race. Baseline characteristics for the cases and controls are presented in

### Table 1.

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### *Prescription access*

A similar proportion of SLE cases and controls reported that in the last 12 months they were unable to get prescription medicines they or a doctor believed necessary: 56 (12.1%) of SLE cases and 18 (9.4%) of controls ( $p=0.3$ ). The main reasons reported for being unable to get such prescriptions were similar among both cases and controls: “insurance company wouldn’t approve, cover or pay for medicine” (34.8%) and “couldn’t afford medicine” (34.8%). Among SLE cases, after adjusting for potential confounders in multivariable models, patients with Medicaid or no insurance were 3 to 7 times more likely than those with private insurance to report being unable to obtain medications [Medicaid OR 3.6 (95% CI 1.5, 8.6),  $p=0.005$ ; no insurance 7.2 (95% CI 1.6, 33.2),  $p=0.011$ ].

### *Cost-related prescription non-adherence*

SLE cases were significantly more likely than controls to report the following in the preceding 12 months to save money: skipping doses, taking less medicine, delaying filling prescriptions and asking their doctor for a lower cost medication (**Table 2**). Among the SLE cases, there were pronounced differences in cost-related prescription non-adherence across types of health insurance coverage: approximately 60% of persons with no insurance deviated from taking medication as prescribed, compared to approximately 25% of persons with Medicaid or Medicare, and 16% of persons with private or another type of insurance ( $p=0.002$ ). Strategies used by participants to reduce costs according to health insurance type are presented in **Figure 1**.

Based on multivariable models (**Figure 2**), the odds of cost-related prescription non-adherence were nearly three times higher among cases versus controls, after adjusting for sex, race, age, insurance status, and household income [OR 2.9 (95% CI 1.6, 5.1);  $p=0.000$ ]. The odds of cost-related non-adherence remained significantly higher among cases when models were further adjusted for six of the eight MOS SF-36 domains, PROMIS depression score, or fibromyalgia (OR range 1.9-2.5). SLE cases were 2-3 times as likely as controls to report the following forms of non-adherence to save money, after adjusting for potential confounders: skipping medications

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[OR 2.9 (95% CI 1.4,6.0); p=0.004], taking less medicine [OR 3.7 (95% CI 1.7,7.8); p=0.001], and delaying filling a prescription [OR 2.1 (95% CI 1.1,4.0); p=0.017] (**Supplemental Figure 1**).

Among SLE cases, increasing age was significantly associated with lower odds of skipping medications [OR 0.97 (95% CI 0.95, 1.0); p=0.022], taking less medication [OR 0.98 (95% CI 0.96, 1.0); p=0.048], and delaying medication [OR 0.96 (95% CI 0.94, 0.98); p=0.000], after adjusting for all covariates, whereas no association with age was found among controls.

Among SLE cases, those identifying as black were half as likely as whites to ask for cheaper medications [OR 0.5 (95% CI 0.3, 0.8); p=0.008], while those of “other” (non-black, non-white) or unknown race were three times more likely than white persons to delay medication [OR 3.1 (95% CI 1.1, 9.0) p=0.036] and over six times as likely to use alternative therapies [OR 6.5 (95% CI 2.0, 21.0); p=0.002], accounting for covariates. SLE cases reporting household income below the US median were significantly more likely to deviate from taking medication as prescribed for all three approaches, compared to those with household income above the US median: skip medications [OR 3.3 (95% CI 1.5, 7.1); p=0.002], take less medication to save money [OR 2.8 (95% CI 1.4,5.5); p=0.003], delay filling prescriptions to save money [OR 2.5 (95% CI 1.3,4.9); p=0.009], again adjusting for covariates.

## DISCUSSION

In this sociodemographically diverse study that included well-characterized SLE cases and frequency-matched population controls from Southeastern Michigan, we found that SLE patients were more likely than controls to report cost-related prescription non-adherence, as assessed by activities such as skipping medications, taking less medicine, or delaying filling a prescription. Overall, fewer than 1 in 4 participants asked their providers for lower cost medications. Disparities in cost-related adherence were found in association with household income and health insurance type.

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In a recent review of 11 studies, the majority reported that over half of SLE patients were non-adherent to therapy (19). Another review found that factors associated with non-adherence included low socioeconomic and educational status, depression, disease severity, polypharmacy and the quality of the patient-doctor relationship (12). Our study builds on prior work by examining cost-related aspects of non-adherence in SLE, and enables comparison to population controls from the same region, as well as adults from the general US population, given that our assessment of prescription drug access included data elements in common with the National Health Interview Survey (NHIS) (14). SLE cases in our study were over twice as likely to deviate from taking medications as prescribed compared to the MILES controls or US adults from NHIS over the same calendar period (20) (SLE 21.7%; MILES controls 10.4%, NHIS 8%). SLE cases more commonly reported asking a doctor for lower cost medication (23.8%) compared to our controls (15.6%) or the NHIS adults (15.1%) (20); and yet only one-fourth do so. Black participants in our study were less likely to ask their doctor for lower cost alternatives compared to white participants. These findings, coupled with the fact that many physicians routinely overestimate costs of inexpensive medications but underestimate costs of expensive ones (21), highlight a potential opportunity to not only educate patients about medication costs but to address a knowledge gap among rheumatologists.

Cost-related non-adherence in other patient populations has been shown to be associated with population-level prescription drug coverage, with non-adherence rates lowest in Scandinavian and Western European countries and highest in the US (22). One study found cost-related non-adherence to be 43.3% for working-age adults in the United States who lacked health insurance (23). A review has shown that medication costs rather than drug coverage was the more influential factor for cost-related non-adherence (24). There is a paucity of treatment options in lupus; the newest FDA approved medication, belimumab, following a weight-based dosing regimen can cost approximately \$35,000 per year (25). The study findings and previous literature in other chronic diseases finding cost-related non-adherence is linked to worse outcomes (26–29) support that medication management efforts aimed at improving adherence

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would benefit from including cost considerations. In diabetes, where cost-related non-adherence has been found to be 16-19% (30,31), different factors contribute based on age. A study utilizing data from the Behavioral Risk Factor Surveillance System showed that household income and lack of health insurance were the most important factors in explaining cost-related non-adherence for diabetics <65 years of age, while depression was the predominant factor for those >65 years of age (32). Such nuances will need to be evaluated further in lupus.

Non-adherence in lupus has been shown to be independently associated with worse outcomes in SLE, including increased all-cause and SLE-related emergency department visits (33) and hospitalizations (7,11). Renal disease, often asymptomatic, can insidiously progress without diligent adherence to immunosuppressive and anti-hypertensive medications. As expected, renal disease and particularly end stage renal disease (ESRD), is more common in non-adherent SLE patients (6,10). While in the US, both ESRD and mortality in lupus have been associated with race and socioeconomic status (34,35), such disparities in lupus are less prominent in other countries. In a British inception cohort with 21 years of follow-up, race was predictive of neither lupus damage accrual nor death (36); the authors point to the equitable access within the national UK health care system as a potential explanation for the lack of association between ethnicity and damage accrual. A US-based study by Mosley-Williams *et al.* found that barriers to medication adherence differed between black and white women with SLE; for instance, black women were more likely to rely on religion and reported greater concern about long-term side effects (37). Our novel finding that persons of “other” race (mostly Asian in our study) were more likely to use alternative medications to save money further suggests that cultural influences may affect adherence in lupus and warrant further study. The variable ‘race’ should be considered a contextual variable and crude proxy for a variety of social, cultural and biological constructs, and not interpreted simply as a risk factor or intrinsic biological factor *per se* (38–41). Furthermore, it is increasingly recognized that accumulated and pervasive effects of structural racism contribute to race-associated disparities in health outcomes (42,43). Vigorous investigations will be needed to unravel the complexity of ‘race’ in lupus.

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This study has several strengths. It is one of the largest population-based, epidemiologic studies of a well-characterized, racially diverse, control-matched lupus population in the US. The lupus cases are therefore not restricted to patients from the tertiary care setting. Further, the comparison group is also population-based and not restricted to “healthy” (usually employed) controls, which increases generalizability to the underlying population.

Our study also has several limitations. First, the majority of our study population self-reported race as white or black, which reflects regional demographics but limits generalizability of our results beyond these racial groups. Only a small percentage reported Hispanic ethnicity so that ethnicity could not be examined. Second, many of the coverage provisions of the Affordable Care Act (ACA) took effect January 1<sup>st</sup> 2014 (44), the month prior to the start of our baseline visits that formed the basis of this study. For example, lupus patients without insurance may have purchased private coverage through the newly-created Health Insurance Marketplace, yet, the 12-month period addressed in the interview questions would encompass time before such insurance took effect in January 2014. The passage of the ACA is complicated by the acceleration of cost-sharing and expansion of tiered medications systems raising costs and increasing hurdles for patient medication access (45). In light of this juxtaposition, it will be important to monitor the issue of prescription drug access and adherence as the healthcare landscape continues to change. In our study, questions about medication access were related to prescriptions in general, not to specific medications such as immunosuppressives, antimalarials or anti-hypertensives. It is unclear how much of the lack of access and non-adherence was related specifically to medications treating underlying lupus, rather than for other, comorbid conditions. However, lupus-specific medication questions would have precluded comparisons to controls. Finally, the degree to which self-reported non-adherence reflects actual non-adherence is unclear.

Our data from this epidemiologic study reveal that SLE patients were more likely than controls from the general population to report cost-related non-adherence to prescriptions. Disparities were found in association with income and health insurance status. Racial disparities were noted in strategies to reduce costs. Overall, fewer than one in four patients asked providers for

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lower cost medications. These findings point to the importance of physicians trying to ascertain adherence and being aware of medication costs to individual patients when planning treatment changes and prescribing medications, which could provide a meaningful avenue for improving medication access and adherence through shared decision-making.

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**Table 1. Baseline characteristics of the systemic lupus erythematosus (SLE) cases and frequency-matched\* controls, 2014-2015.**

	SLE Cases (n=462)	Controls (n=192)	p-value
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	mean (SD) or frequency (%)	mean (SD) or frequency (%)	
Age (years) SD	53.3 (12.3)	53.6 (14.0)	NS
Sex <sup>a</sup>			<0.001
Female	430 (93.1)	154 (80.2)	
Male	32 (6.9)	38 (19.8)	
Race			NS
White	233 (50.4)	107 (55.7)	
Black	208 (45)	77 (40.1)	
Other/unspecified <sup>b</sup>	21 (4.5)	8 (4.2)	
Median Income			NS
Below US Median	198 (45.5)	70 (38.0)	
Above US Median	237 (54.5)	114 (62.0)	
Poverty	87 (18.8)	45 (23.4)	NS
Insurance			NS
None	10 (2.2)	7 (3.6)	
Medicaid <sup>c</sup>	112 (24.2)	47 (24.5)	
Medicare/age <65 yrs	68 (14.7)	13 (6.8)	
Medicare/age ≥65 yrs	66 (14.3)	29 (15.1)	
Private	198 (42.9)	90 (46.9)	
Other	8 (1.7)	6 (3.1)	
Number of prescriptions (at time of visit) <sup>d</sup>			
Prescription medications	7 (3, 11)	2 (0, 5)	<0.001

## Cost-related prescription non-adherence in lupus

Chronic prescription medications <sup>e</sup>	5 (2, 9)	1 (0, 4)	<0.001
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\*Frequency-matched by sex, race, age, and geography; NS=not significant (at 0.05 level)

<sup>a</sup> given the rarity of SLE in males, an equivalent number of male controls to cases was recruited, thus the female to male ratio within controls differs compared to cases

<sup>b</sup> Other/unspecified races include: American Indian and Alaska Native (AIAN) (n=8), Asian (n=6), other/unknown (n=15).

<sup>c</sup> Participants with dual Medicaid/Medicare coverage (73 SLE and 16 controls) were included in the Medicaid category

<sup>d</sup> number of prescribed medications reported by participant as “currently taking” at the time of study visit [reported as median (interquartile range)]

<sup>e</sup> chronic medication use defined as ≥3 months

**Table 2. Self-reported prescription access, cost-related non-adherence, and participant strategies used to reduce prescription drug costs within the preceding 12 months in SLE cases compared to frequency-matched controls.**

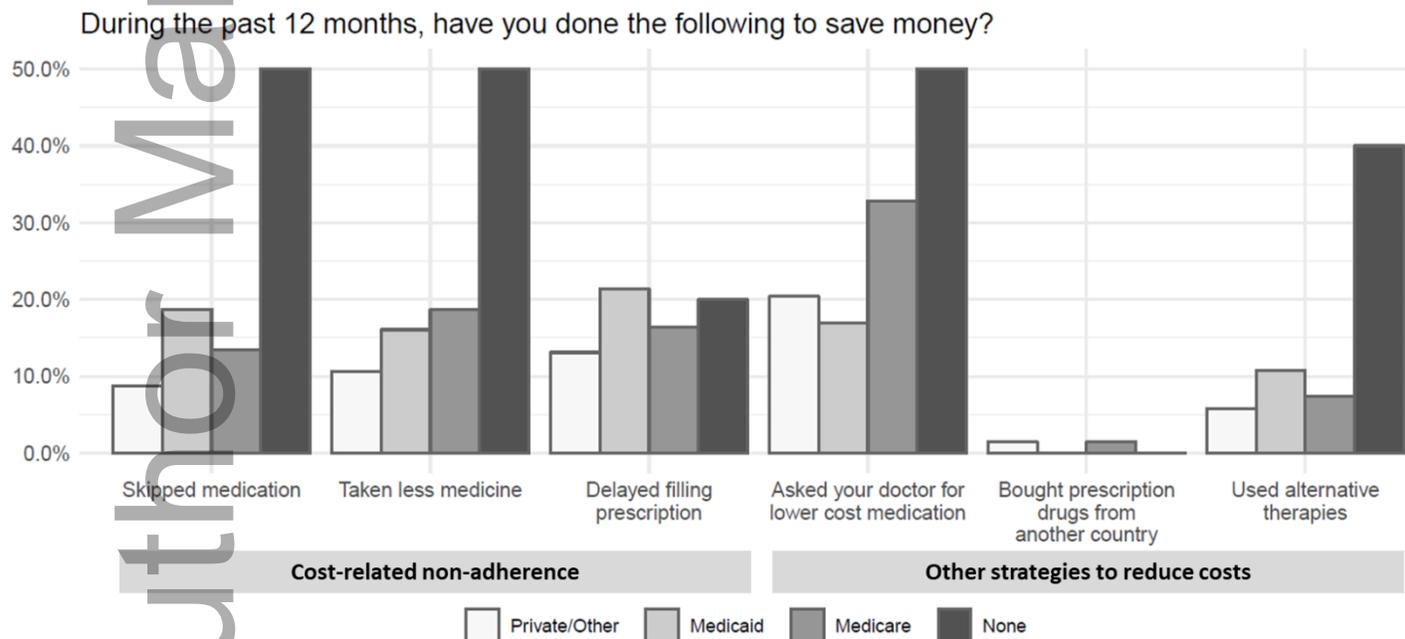
Interview item	SLE cases (n=462) frequency (%)	Controls (n=192) frequency (%)	p- value
<b>Prescription access</b>			
Unable to get prescriptions doctor felt necessary	56 (12.1)	18 (9.4)	0.3
<b>Cost-related non-adherence: <sup>a</sup></b>			
a. Skipped medication doses to save money	62 (13.4)	12 (6.3)	0.008
b. Taken less medicine to save money	70 (15.2)	11 (5.7)	0.001
c. Delayed filling a prescription to save money	75 (16.2)	17 (8.9)	0.013
<b>Other strategies to reduce prescription costs</b>			

## Cost-related prescription non-adherence in lupus

Asked doctor for lower cost medication to save money	110 (23.8)	30 (15.6)	0.02
Bought prescription from another country to save money	5 (1.08)	2 (1.04)	0.9
Used alternative therapies to save money	38 (8.2)	11 (5.7)	0.3

\*Composite measure including: “skipped medication doses”, “taken less medicine” and/or “delayed filling a prescription”. Persons could use more than one strategy to reduce prescription drug costs.

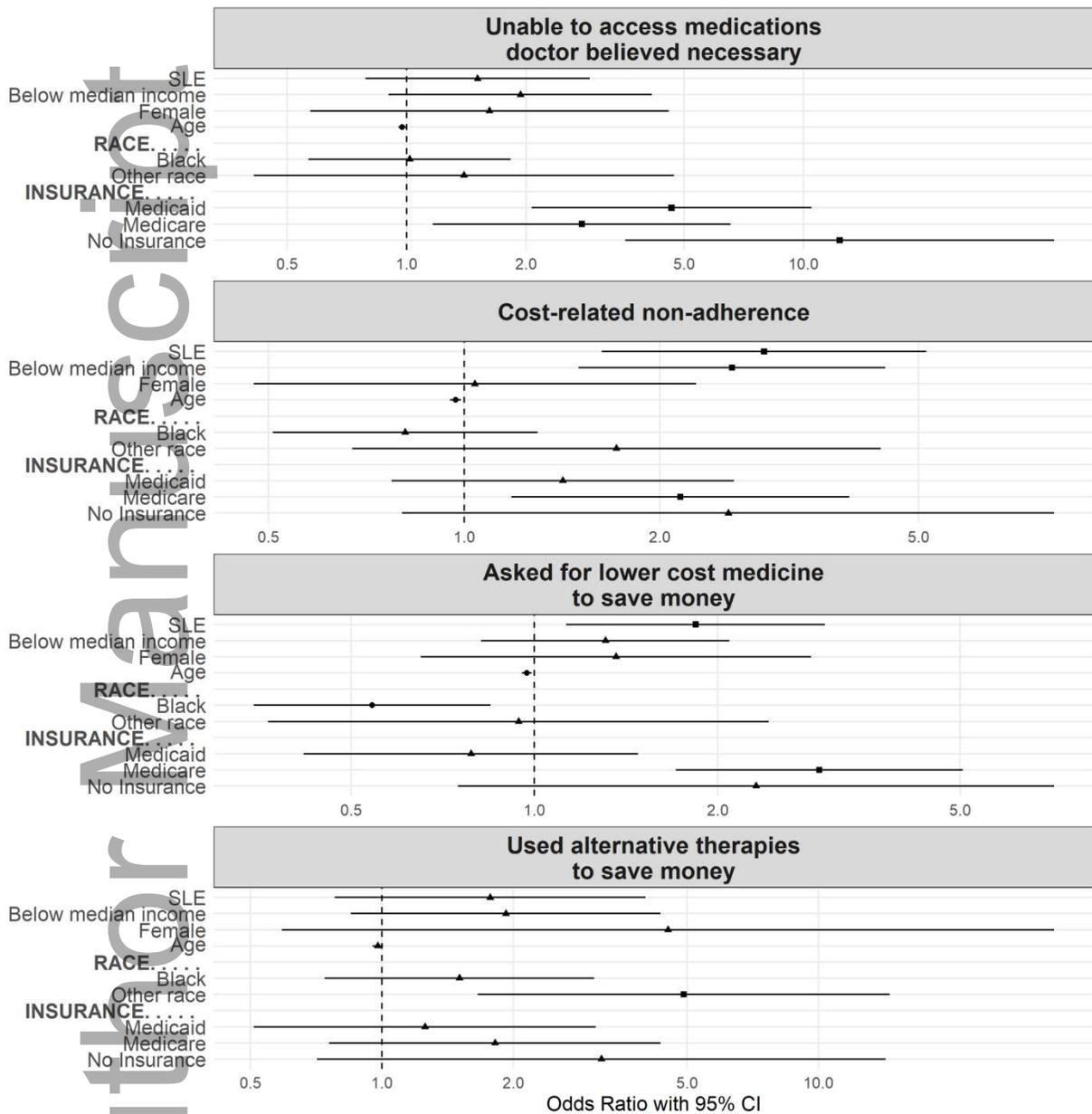
**Figure 1. Participant strategies used by SLE cases in the MILES Cohort to reduce prescription drug costs, according to health insurance status.**



**Figure 2. Forest plots from a series of multivariable models of factors associated with aspects of prescription medication access and adherence.**

## Cost-related prescription non-adherence in lupus

Squares represent positive odds ratios (ORs), circles negative ORs, and triangles non-significant ORs; horizontal lines represent 95% CIs.



\*The referent category for race is white, and for insurance is private.

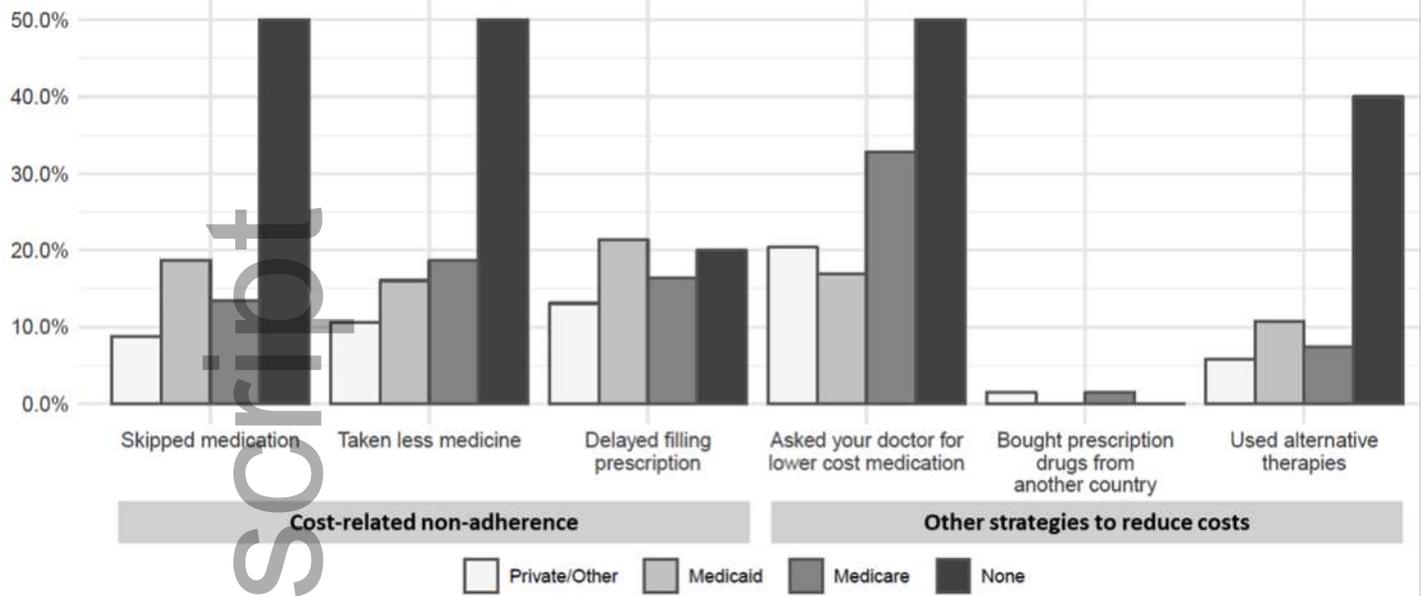
\*\*Axes denoting the odds ratio are truncated from 0.35 to 10 for visualization purposes. The OR for “No Insurance” on “Unable to access medications doctors believed necessary” is approximately 12 and thus falls outside of this range. Additionally, the upper 95 interval mark is higher than 10 for the effect of “No Insurance”

## Cost-related prescription non-adherence in lupus

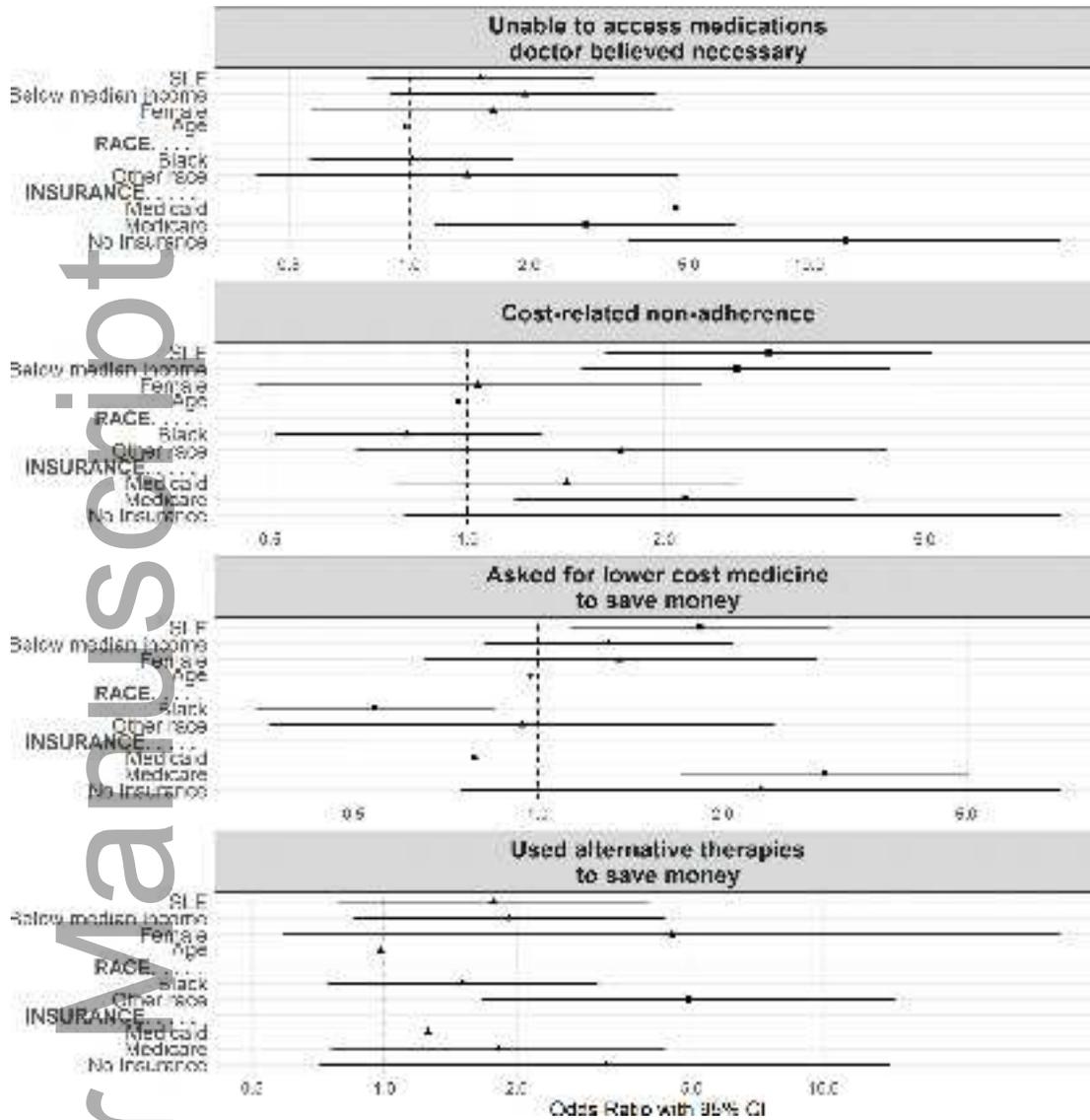
on “Unable to access medications doctors believed necessary”; “No Insurance” on “Skipped medications to save money”; and “Female”, “Other Race”, and “No Insurance” on “Used alternative therapies to save money.

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During the past 12 months, have you done the following to save money?



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acr\_24397\_f2.tif