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The Relationship Between Health Insurance Status and Diabetic Retinopathy Progression

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Objective: To determine if baseline diabetic retinopathy (DR) severity mediates the relationship between health insurance status and DR progression.

Design: Retrospective cohort study.

Subjects: Seven hundred sixteen patients aged ≥ 18 years with a diagnosis of type 1 or 2 diabetes mellitus, and a diagnosis of nonproliferative DR (NPDR) were identified from the electronic health record of a tertiary academic center between June 2012 and February 2022.

Methods: NPDR severity at baseline was the proposed mediator in the relationship between insurance status and proliferative DR (PDR) progression. Logistic regression was used to determine the association between insurance status and NPDR severity at baseline, and Cox proportional hazards regression was used to assess the association between insurance status and time to PDR progression. To analyze the mediation effect of NPDR severity at baseline, a counterfactual approach, which decomposes a total effect into a natural direct effect and a natural indirect effect was applied.

Main Outcome Measures: Time to progression from first NPDR diagnosis to first PDR diagnosis.

Results: Of the 716 patients, 581 (81%) had Medicare or private insurance, 107 (15%) had Medicaid, and 28 (4.0%) were uninsured at their baseline eye visit. Uninsured or Medicaid patients had a higher proportion of moderate or severe NPDR at their baseline eye visit and a higher proportion of progression to PDR. After adjusting for confounders and NPDR severity at baseline, patients who were uninsured had significantly greater risk of progression to PDR compared with that of patients with Medicare/private insurance (hazard ratio [HR]: 2.63; 95% confidence interval [CI]: 1.10−6.25). Patients with Medicaid also had an increased risk of progression to PDR compared with that of patients with Medicare/private insurance, although not statistically significant (HR: 1.53; 95% CI: 0.81−2.89). NPDR severity at baseline mediated 41% of the effect of insurance status (uninsured vs. Medicare/private insurance) on PDR progression.

Conclusions: Patients who were uninsured were more likely to have an advanced stage of NPDR at their baseline eye visit and were at significantly greater risk of progression to PDR compared with patients who had Medicare or were privately insured. Mediation analysis revealed that differences in baseline NPDR severity by insurance explained a significant proportion of the relationship between insurance status and DR progression.

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Diabetic retinopathy (DR) remains a leading cause of vision impairment and blindness worldwide, and its prevalence is expected to increase given rising diabetes mellitus (DM) rates and an aging population.[1] The severe vision-threatening stages of the disease include proliferative DR (PDR) and diabetic macular edema (DME).[2] In many patients, these advanced stages of disease can be prevented with routine screening and appropriate and prompt diagnosis and treatment.[3] Unfortunately, some patients at high risk of DR progression are not receiving adequate eye care.[3,4] Various health disparities exist in DR outcomes by race, ethnicity,[5] and socioeconomic status (SES).[6,7]

In a previous study, we found a strong association between health insurance status and risk of progression from nonproliferative DR (NPDR) to PDR in a tertiary care center in the United States (US).[8] Patients with NPDR with Medicaid or no insurance were at a greater risk of progression to PDR compared with patients with private insurance or Medicare, after adjusting for covariates including age and NPDR severity at baseline.[8] Only a few previous studies have identified disparities in DR outcomes associated with health insurance. One study found that patients with Medicare and private insurance presented with better baseline visual acuity compared with

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patients with Medicaid at the initiation of treatment for DME, suggesting that insurance may play a role in earlier diagnosis and treatment.[9] Another study found that patients with Medicaid had reduced odds of following up with an eye care clinician after an emergency room visit for PDR, pointing to differences in types of health care utilization by insurance type.[10] Another study showed that Medicaid patients were more likely to have vision-threatening forms of DR than those with private insurance.[6]

Although health insurance has been shown to be an important modifiable risk factor for disease progression, previous studies have shown that merely having some level of insurance has not been demonstrated to resolve health disparities.[11] To address health inequalities and improve patient outcomes, it is essential to understand the factors that contribute to the link between insurance status and disease progression. In this study, we investigated the mechanisms underlying the relationship between health insurance and progression from NPDR to PDR. We hypothesized that baseline NPDR severity plays an important role in mediating this relationship, based on results from prior studies.[8,9] We used mediation analysis to gain a more in-depth understanding of this relationship to inform future strategies to improve vision outcomes.

Methods

Data Sources and Study Cohort

This was a retrospective cohort study using electronic health record (EHR) data from the University of California, San Francisco, (UCSF), a tertiary academic medical center. Detailed methods have been reported.[8] In brief, patients with a diagnosis of DR based on International Classification of Diseases (ICD)-9 and/or -10 codes who had $\geq$ 1 completed, in-person visit with an eye care clinician (optometrist or ophthalmologist) at UCSF after June 1, 2012 were selected.[8] We included patients who were aged $\geq$ 18 years and had $\geq$ 1 coded diagnosis of type 1 or 2 DM. For this study, we only included patients with a diagnosis of NPDR with severity coded by an eye care clinician. The baseline eye visit refers to the eye care encounter with the first NPDR diagnosis in the EHR. Patients with a prior diagnosis of PDR before the baseline visit were excluded. The UCSF data for mediation analysis were last accessed on August 8, 2022. The UCSF data for insurance types among all patients were last accessed on November 30, 2023. The institutional review board at UCSF approved this study and issued a waiver of informed consent for all subjects. This study followed the tenets of the Declaration of Helsinki.

Variables and Study Outcomes

The primary outcome was time from the baseline eye visit to progression to PDR. The proposed mediator was NPDR severity at baseline based on evidence from prior reports,[8,9] and the proposed mediation pathway is shown in Figure 1. The exposure was primary insurance type at the baseline eye visit and was categorized into private insurance or Medicare (any Medicare with or without other secondary coverage), Medicaid, and uninsured. Medicare and private insurance were grouped together because of their similar association with PDR progression (Table S1, available at www.ophthalmologyscience.org). Because of the limited number of patients in the severe NPDR group (n = 47), we grouped them with moderate NPDR in the analysis.

At the patient level, the confounders included were age, sex, race/ethnicity, and DM type. Because patient-level SES data were largely unavailable in the EHR, we used zip code-level data: Area Deprivation Index (ADI) for socioeconomic disadvantage and Rural-Urban Commuting Area (RUCA) codes for rural-urban residence.[12–14] The ADI is based on the Census Block Group level, which allows for state- or national-level rankings of neighborhoods by socioeconomic disadvantage, with values ranging from 1 (least socioeconomically disadvantaged) to 100 (most socioeconomically disadvantaged).[15] We used the national-level ADI based on patient zip codes from the EHR. Rural-urban residence was determined by the RUCA codes from the Department of Agriculture that classified zip codes into rural or urban.[14]

Mediation Analysis

To perform mediation analysis, the following criteria must be met: (1) significant association of insurance type with PDR progression (exposure-outcome); (2) significant association of insurance type with NPDR severity at baseline (exposure-mediator); and (3) significant association of NPDR severity at baseline with PDR progression (mediator-outcome). If all of these criteria are met, then mediation (indirect effect) can be established (Fig 1).

Logistic regression was used to study the effect of insurance type on NPDR severity at baseline (exposure-mediator model), which was then sequentially adjusted by patient-level confounders of age, sex, race/ethnicity, and DM type and community-level confounders of ADI and rural-urban residence. For the exposure-outcome and mediator-outcome models, univariable and multivariable Cox proportional hazards regression was used. We first conducted univariable Cox regression using insurance type and sequentially added; (1) patient-level confounders; (2) community-level confounders; and (3) the mediator (i.e., NPDR severity at baseline) into the Cox model.

To analyze the causal mediation effect, we used the counterfactual approach described by VanderWeele et al[16,17] for binary outcomes, which was later extended to survival outcomes.[18] The counterfactual framework allows for the decomposition of a total effect into a natural direct effect and a natural indirect effect in the presence of nonlinearities. Because we could only perform mediation analysis on a binary exposure variable, those with Medicaid and those who were uninsured were individually compared with those with Medicare/private insurance. The details of the mediation analysis including the calculation of natural direct effect, natural indirect effect, total effect, and the proportion of mediation are presented in File S1 (available at www.ophthalmologyscience.org).

Statistical Analysis

Characteristics across insurance groups were compared by the Kruskal–Wallis rank sum test for continuous variables and Pearson's chi-square test or the Fisher exact test for categorical variables. Statistical significance was set as 2-sided $P < 0.05$. The mediation analysis was performed using SAS 9.4. All other statistical analyses were conducted in R version 4.1.0.

Results

Cohort Characteristics

The cohort consisted of 716 patients with NPDR (Table 2). Three hundred fifty-four (49%) were female, and the median age was 65 (interquartile range [IQR], 55–73) years. For primary coverage, 581 (81%) had Medicare/private

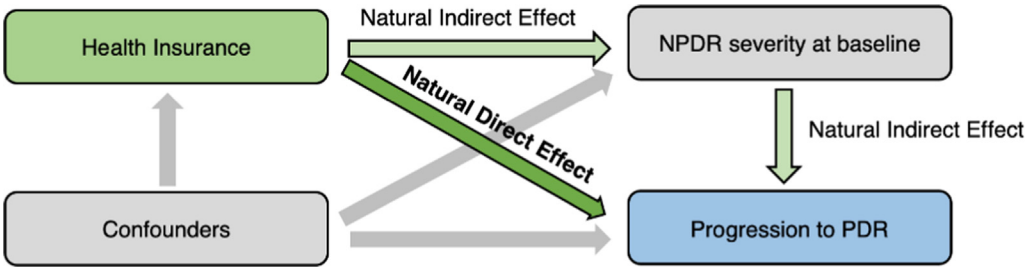

Figure 1. Proposed mediation pathway of the effect of health insurance (exposure) on progression from nonproliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR; outcome) through NPDR severity at baseline (mediator). Confounders include patient-level confounders (age, sex, race/ethnicity, and diabetes mellitus type) and neighborhood-level confounders (area deprivation index and rural-urban residence).

insurance, 107 (15%) had Medicaid, and 28 (4.0%) were uninsured at the baseline eye visit. In our cohort, compared with the general UCSF patient population, there were more patients with Medicare coverage (45% cohort vs. 17% all), fewer patients with private insurance (36% cohort vs. 50% all) and Medicaid (15% cohort vs. 28% all), and similar numbers of patients who were uninsured (4% cohort vs. 5% all), respectively. The higher proportion of patients with Medicare and lower proportion with private insurance and Medicaid coverage is likely due to the older age in our cohort (median 65 years; IQR 55−73). The proportion of patients with progression from NPDR to PDR was higher in patients who had Medicaid (15%) or were uninsured (25%), compared with those who had private insurance/Medicare (6.9%, $P < 0.001$). The proportion of patients with moderate or severe NPDR at baseline in those with no insurance (57%) or Medicaid (34%) was also greater than that of the Medicare/private insurance group (23%, $P < 0.001$). Patients also differed in community-level socioeconomic measures by insurance. Patients with Medicaid had higher ADI (median: 5; IQR: 3−7 vs. median 4; IQR: 2−6) and were more likely to live in rural areas (5.6% vs. 1.4%) than those with Medicare/private insurance.

Mediation Analysis

The logistic regression models investigating the association between insurance and NPDR severity at baseline found that having no insurance at or before the baseline eye visit was associated with worse NPDR severity after adjusting for confounders (odds ratio [OR]: 4.39; 95% confidence interval (CI): 2.00−9.88; Table 3).

In the univariable Cox regression that investigated the relationship between insurance and PDR progression, patients who had Medicaid (hazard ratio [HR]: 2.79; 95% CI: 1.56−4.99) or were uninsured (HR: 3.48; 95% CI: 1.55−7.81) were both at greater risk of PDR progression compared with patients with Medicare/private insurance (Table 4). In the multivariable Cox regression adjusted for confounders, uninsured patients were still at significantly greater risk of progression to PDR (HR: 3.89; 95% CI: 1.69−8.94) compared with patients with Medicare/private insurance. This association was attenuated when the Cox model was further adjusted for the mediator, NPDR severity at baseline, but remained statistically significant (HR: 2.63; 95% CI: 1.10−6.25). In this adjusted Cox model, patients with moderate/severe NPDR at baseline were at significantly greater risk of progression to PDR compared with those with mild NPDR (HR: 2.82; 95% CI: 1.53−5.20; Table S5A, available at www.ophthalmologyscience.org).

The strength of the association between Medicaid and PDR progression decreased after adjusting for confounders and NPDR severity at baseline after adjusting for the mediaton. Although not statistically significant, there was a trend toward an increased risk of progression to PDR in those with Medicaid compared with Medicare/private insurance (HR 1.53; 95% CI 0.81−2.89). In the same adjusted Cox model, the association between moderate/severe NPDR at baseline and PDR progression did remain significant (HR: 2.14; 95% CI: 1.24−3.70; Table S5B).

For uninsured vs. Medicare/private insurance patients, the exposure-outcome, exposure-mediator, and mediator-outcome pathways were all significantly associated. As such, the natural direct effect, natural indirect effect (mediation), and total effect of insurance on the risk of PDR progression were statistically significant (Table 6). The mediator, NPDR severity at baseline, explained 41% of the association between being uninsured at baseline with PDR progression. For Medicaid patients, positive associations were seen in the 3 pathways, although not all were statistically significant. Although the mediation effect through NPDR severity at baseline (natural indirect effect) was not statistically significant for Medicaid patients (HR: 1.07; 95% CI: 0.97−1.18), partial mediation by NPDR severity at baseline was present (17%).

Discussion

In this study, we found that NPDR severity at baseline is an influential factor that mediates a significant proportion of the impact of health insurance type on DR progression for those who are uninsured at their baseline eye visit. The effect was still present but not statistically significant for patients with Medicaid. Our study shows that health insurance is an important risk factor for PDR progression, but having any insurance (i.e., Medicaid) is not enough to eliminate health disparities. Given the range of potential insurance scenarios and their accompanying societal costs, the specific strategies used at a systems level should be guided by a clear understanding of the mechanisms underlying the relationship

Table 2. Study Population Characteristics at Baseline

Characteristic	Total	Insurance Type			
	N = 716	*Medicare/Private n = 581 (81%)*	*Medicaid, n = 107 (15%)*	*Uninsured, n = 28 (4.0%)*	P *Value**
Progression to PDR (n, %)	63 (8.8%)	40 (6.9%)	16 (15%)	7 (25%)	< 0.001
Age, median (IQR), yrs	65 (55–73)	67 (56–75)	59 (52–63)	65 (56–74)	< 0.001
Sex (n, %)					0.15
Female	354 (49%)	282 (49%)	61 (57%)	11 (39%)	
Male	362 (51%)	299 (51%)	46 (43%)	17 (61%)	
Race/ethnicity, n (%)					< 0.001
White or Caucasian	214 (30%)	182 (31%)	22 (21%)	10 (36%)	
Asian	227 (32%)	196 (34%)	27 (25%)	4 (14%)	
Black or African American	78 (11%)	68 (12%)	8 (7.5%)	2 (7.1%)	
Hispanic or Latino	109 (15%)	72 (12%)	30 (28%)	7 (25%)	
Other	88 (12%)	63 (11%)	20 (19%)	5 (18%)	
NPDR severity, n (%)					< 0.001
Mild	533 (74%)	450 (77%)	71 (66%)	12 (43%)	
Moderate/Severe	183 (26%)	131 (23%)	36 (34%)	16 (57%)	
Diabetes mellitus type, n (%)					0.86
Type 1	69 (9.6%)	57 (9.8%)	9 (8.4%)	3 (11%)	
Type 2	647 (90%)	524 (90%)	98 (92%)	25 (89%)	
Area deprivation index, median (IQR)	4 (2–6)	4 (2–6)	5 (3–7)	4 (3–6)	0.03
Rurality, n (%)					0.03
Rural	14 (2.0%)	8 (1.4%)	6 (5.6%)	0 (0%)	
Urban	702 (98%)	573 (99%)	101 (94%)	28 (100%)	

IQR = interquartile range; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.
*Fisher exact test; Kruskal–Wallis rank sum test; Pearson chi-square test.

between insurance and health outcome. This work is an important first step to understand the impact of insurance on diabetic eye disease progression and can help inform future initiatives and directions to promote health equity in eye care.

Our study used a novel mediation analysis approach to determine the direct and indirect contribution of insurance type on DR progression. We found that NPDR severity at baseline explains 17% to 41% of the effect of insurance status on DR progression. We found that patients with Medicaid or no insurance presented to eye care visits at more advanced DR stages compared with those with Medicare/private insurance, leading to greater risk of progression to PDR. This disparity may be due to less access to preventive screening or eye care for patients with Medicaid and those who are uninsured. Previous studies have shown that adults who were uninsured were less likely to receive preventive eye care, such as dilated eye examinations, compared to those with insurance.[19–21] Similarly, patients with Medicaid have been found to have fewer diabetic eye examinations and reduced access to eye care than those with private insurance.[22,23] Routine eye screening is essential for detecting and intervening on DR at an early

Table 3. Exposure-Mediator Model: Univariable and Multivariable Logistic Regression of NPDR Severity on Insurance Status

Insurance Type	Probability of Moderate/Severe NPDR (vs. Mild NPDR)					
	Univariable		*Multivariable**		*Multivariable*†	
	OR (95% CI)	P *Value*	*OR (95% CI)*	P *Value*	*OR (95% CI)*	P *Value*
Medicare/Private (Reference)	-	-	-	-	-	-
Uninsured	4.58 (2.12–10.14)	< 0.001	4.27 (1.95–9.58)	< 0.001	4.39 (2.00–9.88)	< 0.001
Medicaid	1.74 (1.11–2.71)	0.02	1.52 (0.95–2.42)	0.08	1.51 (0.93–2.41)	0.09

ADI = area deprivation index; CI = confidence interval; DM = diabetes mellitus; NPDR = nonproliferative diabetic retinopathy; OR = odds ratio.
*Insurance + Age + Sex + Race/Ethnicity + DM Type.
†Insurance + Age + Sex + Race/Ethnicity + DM Type + ADI + Rural-urban residence.

Table 4. Exposure-Outcome Model: Univariable and Multivariable Cox Proportional Hazards Regression of Insurance Status on Time to Progression to PDR

Insurance Type	Time to PDR							
	Univariable		*Multivariable**		*Multivariable†*		*Multivariable† + Mediator (NPDR Severity)*	
	HR (95% CI)	*P Value*	*HR (95% CI)*	*P Value*	*HR (95% CI)*	*P Value*	*HR (95% CI)*	*P Value*
Medicare/private (reference)	-	-	-	-	-	-	-	-
Uninsured	3.48 (1.55–7.81)	0.002	3.82 (1.67–8.74)	0.002	3.89 (1.69–8.94)	0.001	2.63 (1.10–6.25)	0.03
Medicaid	2.79 (1.56–4.99)	< 0.001	1.90 (1.04–3.48)	0.04	1.79 (0.96–3.36)	0.07	1.53 (0.81–2.89)	0.19

ADI = area deprivation index; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.
*Insurance + Age + Sex + Race/Ethnicity + DM Type.
†Insurance + Age + Sex + Race/Ethnicity + DM Type + ADI + Rural-urban residence.

stage.[24,25] Without timely preventive screening and eye care, patients with Medicaid or no insurance may present to an eye care clinician only when they are symptomatic with vision changes or pain from DME or complications of severe NPDR or PDR. Malhotra et al[9] demonstrated this finding in their study, which found that patients with Medicare and private insurance presented with better baseline visual acuity compared with patients with Medicaid at the initiation of treatment for DME. These findings underscore the importance of addressing disparities in access to preventive screening and eye care for the uninsured and underinsured. More work is needed to understand the existing barriers to eye care and, subsequently, how to improve eye care access. Future directions may include targeted public health initiatives aimed at increasing the availability of eye screenings and preventive care for this population.

Although our study revealed that NPDR severity at baseline plays an important mediating role on the impact of insurance status on PDR progression, the mediation is only partial. For the Medicaid group especially, baseline NPDR severity only explains 17% of the total insurance effect, indicating that there may be other mediators in the pathway yet to be investigated. We considered other potential mediators, such as presence or number of dilated eye examinations or primary care visits before the baseline eye visit, because previous studies have shown that insurance impacts access to preventive eye screening or care.[19–23] However, one of the intrinsic limitations of EHR data is not knowing what occurs outside of the health care system. We had missing data regarding primary care visits for approximately 40% of patients. We were not able to determine if these patients did not have a primary care provider or if they had one outside of the UCSF health care system, and we ran into similar issues for prior dilated eye examinations. Consequently, we could not reliably test either as potential mediators. One approach to address this is to supplement EHR data with external data sources, such as insurance claims data, although this approach would only apply to a subset of patients with a specific type of insurance (e.g., Medicare or Medicaid) and would not apply to those who lack insurance.[26]

In addition, other studies have demonstrated that insurance status often reflects SES and facilitates access to health care services, thus serving as a strong surrogate marker for social determinants of health.[27–29] A report from the US Census Bureau on health insurance coverage in 2022 found associations between higher private insurance coverage with full time employment, higher household income, and higher levels of education.[29] Because Medicaid eligibility is largely based on household income, the rates of Medicaid coverage have been shown to increase in patients living in poverty.[29] Furthermore, the proportion of uninsured adult noncitizens have been reported to be higher than native-born adult citizens, likely due to residency requirements for government health plans such as Medicare and Medicaid.[29]

In our study, although patient-level SES data were not available, we tried to account for SES by using ADI for socioeconomic disadvantage and RUCA for rural-urban residence derived from zip code-level data in our analysis.

Table 6. Mediation Model: Direct and Indirect Effect of Insurance Status on Time to Progression to Proliferative Diabetic Retinopathy

Effect Types	Mediator: NPDR Severity (Moderate/Severe vs. Mild)			
	Uninsured		*Medicaid*	
	HR (95% CI)	*P Value*	*HR (95% CI)*	*P Value*
Natural direct effect	2.62 (1.11–6.23)	0.03	1.53 (0.81–2.89)	0.19
Natural indirect effect	1.43 (1.09–1.88)	0.009	1.07 (0.97–1.18)	0.17
Total effect	3.75 (1.59–8.88)	0.003	1.64 (0.87–3.09)	0.13
Proportion mediated	0.412		0.172	

CI = confidence interval; HR = hazard ratio; NPDR = nonproliferative diabetic retinopathy.

Our mediation analysis found that NPDR severity at baseline explains only 17% to 41% of the effect of insurance status on DR progression. This finding aligns with prior research theorizing that SES affects health outcomes through a sustained lack of access to diverse resources, thereby increasing risk factors for multiple diseases and chronic conditions.[28,30] In our study, the relationship between insurance status and DR progression is likely multifactorial, with more advanced NPDR severity at baseline representing just one aspect of resource limitation among many. Our study offers an initial understanding of the role of insurance status on PDR progression. Future investigation aided by comprehensive data sources can further elucidate the mechanisms that underlie the relationship between insurance status, SES, and DR outcomes.

Patients who were uninsured at their baseline eye visit had a 2.6-fold increase in the risk of developing PDR compared with those with Medicare/private insurance. The group with Medicaid, although not statistically significant, still possessed a nonnegligible 1.5-fold increase in the risk of progression compared with the Medicare/private insurance group. We attribute this lack of statistical power in the Medicaid group to the limited sample size of our study cohort. Although the sample size in the Medicaid group was greater than the uninsured group, the effect size of Medicaid versus that of Medicare/private insurance may be smaller than that of the uninsured group and thus may need a larger sample size than present in our study. These initial findings motivate additional research on the effect of insurance status on PDR progression using larger databases such as the IRIS Registry (Intelligent Research in Sight) and All of Us Registry to improve statistical power for studying these subgroups.[31,32]

There are several limitations of this study. First, health care utilization variables, such as prior dilated eye examinations and primary care visits were missing, which is unfortunately intrinsic to EHR data because of the fragmented US health care system. Because of this missing information, we were unable to definitively determine whether our baseline eye visit corresponded to the incident visit for NPDR because we only had access to EHR data from a single institution. In studies utilizing claims data, it is customary to utilize a look-back period to validate the occurrence of incident disease. However, even with the implementation of a look-back period when using EHR data, it is not possible to ascertain whether a patient received care outside of the health care system. Consequently, we opted not to employ a look-back period in our study because it would not definitely determine incident disease and it would severely decrease our sample size. Using comprehensive data sources that link EHR to claims data is a potential future solution but unfortunately is time-intensive and costly and only limited to those with insurance. An alternative future solution is to access clinical notes, which can offer more comprehensive information about patients' health care encounters and additional details that could contribute to a more accurate understanding of incident disease.

Second, we did not have enough power to detect an association between Medicaid and PDR progression. Our HR of 1.5 is consistent with increased PDR progression with Medicaid insurance, but a larger sample size is needed to rule out that this was due to chance. To address this, we plan to repeat our study using larger national EHR registries. Third, this study uses EHR data from a single academic institution, which is important to note because it may limit the generalizability of findings to different study populations. As an academic tertiary institution, UCSF often attracts patients with more advanced or complex conditions. Our comparison of insurance coverage rates among all patients seen at UCSF Health to national averages, based on 2022 census numbers, reveals some distinctions. Specifically, UCSF took care of more patients with Medicaid coverage (27.7% at UCSF vs. 18.8% nationally) and fewer patients with private insurance (50% at UCSF vs. 65.6% nationally). The rates of Medicare and self-pay were comparable.[29] We do not believe these differences have a significant impact on selection bias.

Lastly, the potential for unmeasured confounding is a common issue in mediation analysis. Although we used community-level ADI and RUCA by zip code, we were unable to control for patient-level SES because social determinants of health data at the patient level were unavailable for most patients in the EHR. Patient-level SES may be able to help control for employment and education, which have been shown to be associated with health insurance status. By accounting for patient-level SES, we can better discern the nuanced relationship between insurance status and SES. There are active measures to increase access to these data fields in the EHR and to use natural language processing to more easily access this data from clinical notes, because studies have shown that inclusion of this information increases patient care and improves outcomes in clinical models.[26,33]

In conclusion, we found that patients with Medicaid or no insurance at the baseline eye visit were more likely to present with an initial more severe stage of NPDR, which increases their risk of progression to PDR. For those with no insurance, NPDR severity at baseline is an influential factor that mediates 41% of the impact of health insurance status on risk of PDR progression. This work is an important first step to understand the impact of insurance status on DR progression and can help inform future initiatives and directions to promote health equity in eye care.

Footnotes and Disclosures

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No animal subjects were used in this study.

Author Contributions:

Conception and design: Guo, Arnold, McCulloch, Sun

Data collection: Guo, Copado, Yonamine, Sun

Analysis and interpretation: Guo, Ma, McLeod, Arnold, McCulloch, Sun

Obtained funding: Sun

Overall responsibility: Guo, Copado, Yonamine, Ma, McLeod, Arnold, McCulloch, Sun

Abbreviations and Acronyms:
ADI = Area Deprivation Index; **CI** = confidence interval; **DM** = diabetes mellitus; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **EHR** = electronic health record; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **IQR** = interquartile range; **NPDR** = nonproliferative diabetic retinopathy; **OR** = odds ratio; **PDR** = proliferative diabetic retinopathy; **RUCA** = Rural-Urban Community Area; **SES** = socioeconomic status; **UCSF** = University of California, San Francisco; **US** = United States.

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References

1. Sabanayagam C, Banu R, Chee ML, et al. Incidence and progression of diabetic retinopathy: a systematic review. *Lancet Diabetes Endocrinol*. 2019;7:140−149.
2. Yau JWY, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35:556−564.
3. Stefánsson E. Prevention of diabetic blindness. *Br J Ophthalmol*. 2006;90:2−3.
4. Fathy C, Patel S, Sternberg Jr P, Kohanim S. Disparities in adherence to screening guidelines for diabetic retinopathy in the United States: a comprehensive review and guide for future directions. *Semin Ophthalmol*. 2016;31:364−377.
5. Coney JM, Scott AW. Racial disparities in the screening and treatment of diabetic retinopathy. *J Natl Med Assoc*. 2022;114:171−181.
6. Nguyen CTN, Yosef M, Khalatbari S, Shah AR. Sociodemographic variables associated with risk for diabetic retinopathy. *Clin Diabetes Endocrinol*. 2022;8:7.
7. Patel D, Ananthakrishnan A, Lin T, et al. Social determinants of health and impact on screening, prevalence, and management of diabetic retinopathy in adults: a narrative review. *J Clin Med*. 2022:11.
8. Guo Y, Yonamine S, Ma CJ, et al. Developing and validating models to predict progression to proliferative diabetic retinopathy. *Ophthalmol Sci*. 2023;3:100276.
9. Malhotra NA, Greenlee TE, Iyer AI, et al. Racial, ethnic, and insurance-based disparities upon initiation of anti-vascular endothelial growth factor therapy for diabetic macular edema in the US. *Ophthalmology*. 2021;128:1438−1447.
10. Hinkle JW, Flynn HW, Banta JT, Vanner EA. Patients presenting emergently with proliferative diabetic retinopathy: follow-up and factors associated with compliance. *Retina*. 2020;40:928−935.
11. Call KT, McAlpine DD, Garcia CM, et al. Barriers to care in an ethnically diverse publicly insured population: is health care reform enough? *Med Care*. 2014;52:720−727.
12. Kind AJH, Buckingham WR. Making neighborhood-disadvantage metrics accessible — the neighborhood atlas. *N Engl J Med*. 2018;378:2456−2458.
13. University of Wisconsin School of Medicine and Public Health. 2020 Area Deprivation Index, v.3.2. https://www.neighborhoodatlas.medicine.wisc.edu. Accessed September 1, 2022.
14. Economic Research Service. U.S. Department of Agriculture. *Rural-Urban Commuting Area Codes*. https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes.asp. Accessed September 1, 2022.
15. Kind AJ, Jencks S, Brock J, et al. Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort study. *Ann Intern Med*. 2014;161:765−774.
16. VanderWeele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am J Epidemiol*. 2010;172:1339−1348.
17. Valeri L, VanderWeele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods*. 2013;18:137−150.
18. Valeri L, VanderWeele TJ. SAS Macro for causal mediation analysis with survival data. *Epidemiology*. 2015;26:E23−E24.

19. Zhang X, Saaddine JB, Lee PP, et al. Eye care in the United States: do we deliver to high-risk people who can benefit most from it? *Arch Ophthalmol*. 2007;125:411–418.
20. Ross JS, Bradley EH, Busch SH. Use of health care services by lower-income and higher-income uninsured adults. *JAMA*. 2006;295:2027–2036.
21. Shi Q, Zhao YN, Fonseca V, et al. Racial disparity of eye examinations among the U. S. working-age population with diabetes: 2002-2009. *Diabetes Care*. 2014;37:1321–1328.
22. Thomas CG, Channa R, Prichett L, et al. Racial/ethnic disparities and barriers to diabetic retinopathy screening in youths. *JAMA Ophthalmol*. 2021;139:791–795.
23. Lee YH, Chen AX, Varadaraj V, et al. Comparison of access to eye care appointments between patients with Medicaid and those with private health care insurance. *JAMA Ophthalmol*. 2018;136:622–629.
24. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2013;37:S14–S80.
25. Forster AS, Forbes A, Dodhia H, et al. Changes in detection of retinopathy in type 2 diabetes in the first 4 years of a population-based diabetic eye screening program: retrospective cohort study. *Diabetes Care*. 2013;36:2663–2669.
26. Gianfrancesco MA, Goldstein ND. A narrative review on the validity of electronic health record-based research in epidemiology. *BMC Med Res Methodol*. 2021;21:234.
27. Snyder RA, Chang GJ. Insurance status as a surrogate for social determinants of health in cancer clinical trials. *JAMA Netw Open*. 2020;3:e203890.
28. Unger JM, Blanke CD, LeBlanc M, et al. Association of patient demographic characteristics and insurance status with survival in cancer randomized clinical trials with positive findings. *JAMA Netw Open*. 2020;3:e203842.
29. Keisler-Starkey K, Bunch LN, Lindstrom RA. US Government Printing Office. Health insurance in the United States: 2022. https://www.census.gov/library/publications/2023/demo/p60-281.html. Accessed November 30, 2023.
30. Phelan JC, Link BG, Tehranifar P. Social conditions as fundamental causes of health inequalities: theory, evidence, and policy implications. *J Health Soc Behav*. 2010;51:S28–S40.
31. Parke Ii DW, Lum F, Rich WL. The IRIS® Registry: purpose and perspectives. *Ophthalmologe*. 2017;114:1–6.
32. All of US Research Program Investigators, Denny JC, Rutter JL. The "All of Us" research program. *N Engl J Med*. 2019;381:668–676.
33. Adler NE, Stead WW. Patients in context—EHR capture of social and behavioral determinants of health. *N Engl J Med*. 2015;372:698–701.