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Estimated Prevalence of Other Ocular Disease Fundus Photography Findings in Non-Referable Diabetic Retinopathy

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Title: Estimated Prevalence of Other Ocular Disease Fundus Photography Findings in Non-Referable Diabetic Retinopathy

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Keywords

Diabetic Retinopathy; Referable Diabetic Retinopathy; Fundus Photography; Automated Screening; Other ocular disease findings

Abstract

Purpose: Automated diabetic retinopathy detection has potential benefits but can disrupt referral pathways for discovering notable other ocular disease findings in those with non-referable diabetic retinopathy. This study identifies other ocular disease finding prevalence and associations in patients with non-referable diabetic retinopathy using National Health and Nutrition Examination Survey (NHANES) data.

Methods: We conducted a cross-sectional study and analyzed NHANES (2005-2008) data from participants with and without diabetes aged ≥40 years with fundus photos with none or mild retinopathy in their worse eye. Other ocular disease findings were determined based on existing NHANES fundus photo labels for any of 12 selected pathologies. We compared demographic and clinical factors in those with and without other ocular disease findings.

Results: In 757 participants with diabetes and non-referable diabetic retinopathy, 44.5% had other ocular disease findings. In 4,053 participants without diabetes, 36.3% had other ocular disease findings ($p<0.01$). Prevalence of glaucomatous changes and hypertensive changes were more common in those with non-referable diabetic retinopathy compared to participants without diabetes. Participants with other ocular disease findings were more prevalent in older, hypertensive, and insured individuals (all $p<0.05$).

Conclusion: Other ocular fundus abnormalities are frequently present among individuals with diabetes undergoing screening despite having non-referable diabetic retinopathy. These findings underscore the potential risk of missed clinically meaningful pathology if automated diabetic retinopathy detection systems focus solely on retinopathy severity. As autonomous screening expands, broader fundus evaluation strategies may be needed to preserve comprehensive ocular disease detection while maintain efficiency.

Introduction

Diabetic retinopathy is a leading cause of blindness among U.S. adults aged 20-74, with its prevalence expected to rise alongside increasing diabetes rates.[1] By 2030, diabetes may affect 14% of the U.S. population, and the number of diagnosed adults is projected to nearly triple by 2060.[2] In 2021, Lundeen et al. estimated that 9.6 million Americans have diabetic retinopathy (DR), with 1.84 million people affected by vision-threatening diabetic retinopathy, classified by severe non-proliferative retinopathy, proliferative retinopathy, panretinal photocoagulation scars, or macular edema.[1]

Given the increasing prevalence of diabetes in the US, primary care providers (PCP) serve a crucial role in timely detection and management of DR. According to the American Diabetes Association (ADA) and American Academy of Ophthalmology (AAO) guidelines, annual dilated eye exams are recommended for patients with type 1 diabetes (T1DM) 5 years after diagnosis, and for patients with type 2 diabetes (T2DM) at the time of diagnosis.[3,4]

Several barriers hinder patient adherence to diabetic retinopathy screening recommendations[5], including limited time during primary care visits, inconsistent provider training, and low patient awareness.[6,7] Additionally, referrals to eyecare providers often pose logistical and financial challenges, especially for underserved population.[7,8] A study by Thomas et al. found that pediatric patients with T1DM cited lack of recommendation for eye exams, time constraints, and transportation as key obstacles.[8] Despite initiatives like Medicare's Merit-based Incentive Payment System (MIPS), screening adherence remains low, estimated at 30-60%.[5]

Fully autonomous artificial intelligence (AI) evaluation for diabetic retinopathy based on fundus photography at the PCP office aims to alleviate the growing demand of diabetic eye examinations on patients, providers, and the medical system. Approved by the FDA in 2018, these tools have demonstrated high sensitivity and specificity for the detection of "referable" DR, defined as more-than-mild diabetic retinopathy (mtmDR) or the presence of diabetic macular edema (DME).[9-11] Autonomous AI detection of mtmDR in primary care can help triage care and improve adherence to screening guidelines. However, there are no formal recommendations for managing less-than-moderate or "non-referable" DR. Current practice avoids referring these patients for in-person eye exams, instead opting for annual fundus photo screening until referable

DR is discovered – ultimately reducing the number of dilated eye exams compared to the traditional approach.

Recent teleophthalmology studies, including the INSIGHT trial, found that 44.2% of patients screened for DR via telemedicine had other ocular condition findings such as age-related macular degeneration (AMD), glaucoma, or cataracts.[12-14] This raises concerns that patients with non-referable DR detected by AI may miss timely diagnosis of other ocular diseases due to reduced referrals.

The purpose of this study is to quantify the incidence of both sight threatening and non-sight threatening "other ocular disease findings" (OODF) in patients with diabetes who would no longer be referred for in-person examination. To further evaluate the risks and implications of the current automated DR examination system and referral guidelines, we used an existing national dataset to determine the prevalence of other ocular disease findings in participants with diabetes classified as non-referable DR. Secondarily, we examine associated socioeconomic and clinical risk factors associated with in participants with non-referable diabetic retinopathy.

Methods

We used the National Health and Nutrition Examination Survey (NHANES) 2005-2006 and 2007-2008 data to determine the prevalence of other ocular disease findings (OODF). NHANES is a nationally representative survey performed annually that includes a variety of clinical, social, economic, and demographic data. The complex survey design allows for estimates of US population prevalences based on census data and application of weights to adjust for the representativeness of survey participants. The 2005-2006 and 2007-2008 survey cohorts in particular included non-mydriatic fundus photographs taken in participants greater than 40 years old that were evaluated by a consensus decision of masked graders from the Wisconsin Ocular Epidemiologic Reading Center for various retinal findings including severity of diabetic retinopathy. In addition, these fundus photographs were re-evaluated in 2013 by graders at the Wilmer Eye Center for findings of glaucomatous changes.

We examined the findings of those participants with a diagnosis of diabetes (self-reported or HbA1c > 6.5%). To classify participants with non-referable diabetic retinopathy, we defined the criteria as having none or mild DR in their worse eye (raw n=757, adjusted n=11.4M). Other ocular disease findings were defined as those with at least one of twelve non-diabetic eye disease

fundus photography findings of either eye, which includes: early or late AMD, subretinal neovascularization, epiretinal membrane, arteriolar embolus, venous occlusion, hypertensive retinopathy, choroidal nevus, macular hole, glaucomatous changes, and/or miscellaneous notable ocular disease. We also determined the prevalence of other ocular disease findings in participants aged greater than 40 years old without diabetes (n=4,053, adjusted n=90.5 M) in these cohorts.

To examine associated risk factors with other ocular disease findings in this population, we compared non-referable participants with other ocular disease findings versus non-referable participants without other ocular disease findings across several demographic and clinical characteristics collected in NHANES including gender, race, education level, birth location, health insurance status, household income, smoking status, average blood pressure (>140/90), subjective visual acuity, and best corrected visual acuity (both eyes >20/40). Considering survey design, we compared continuous variables using a t-test and categorical variables using Rao-Scott Chi Square testing.

We then generated a multivariable model including the significant clinical and demographic characteristics, as well as age, sex, and ethnicity. The model was compared to other candidate models with fewer parameters and was selected based on minimization of Akaike's Information Criterion (AIC) to select the most parsimonious useful model. This final model generated an odds ratio to quantify the effect of the significant variables within the multivariable model.

We performed statistical analysis in R (R version 4.2.1) with the survey library package used for the analysis of complex survey design. Four-year weight estimates and population prevalences were derived using recommended practice from the National Center for Health Statistics.[15]

Results

Among the 757 (adjusted n = 11.4M) participants identified with diabetes and non-referable DR, the median age was 58.8 years (IQR 51.0-66.7). There were (51.2%$\pm$0.8%) female participants and (48.8%$\pm$0.8%) male participants (Table 1). In terms of race, 65.5%$\pm$4.6%), 16.7%$\pm$2.6%), and 7.7%$\pm$1.5% of the participants were non-Hispanic white, non-Hispanic black, and Mexican American, respectively. Most participants reported high school education equivalent or less and having household income less than $55,000 annually. A majority of

participants had health insurance (88%±1.6%), and 65%±2.8% self-reported to be non-smokers. Of participants with non-referable DR, 27.6% (1.7%) also had hypertension, and the median hemoglobin A1c was 6.8% (IQR 6.2-7.6). Self-reported visual acuity was overall good to excellent in most participants, with 76.1%±1.7% having visual acuity better than 20/40 in both eyes.

Variable	No Diabetes				Non-Referable Diabetic Retinopathy				P value
	Unweighted N, *Weighted N, in thousands* **Column %** (SE or IQR)								
Total Population	4053	*90522*	**100%**		757	*11404*	**100%**		
Median Age (years [IQR])	52.6 [46.2, 61.3]				58.8 [51.0, 66.7]				p<0.001*
Gender									p=0.52
Male	1995	*42486*	**46.9%**	(0.8%)	384	*5564*	**48.8%**	(2.7%)	
Female	2058	*48036*	**53.1%**	(0.8%)	373	*5841*	**51.2%**	(2.7%)	
Race									p<0.001*
Mexican American	611	*4646*	**5.1%**	(0.7%)	147	*877*	**7.7%**	(1.5%)	
Non-Hispanic Black	732	*7503*	**8.3%**	(1.1%)	218	*1900*	**16.7%**	(2.6%)	
Non-Hispanic White	2285	*71440*	**78.9%**	(1.9%)	309	*7465*	**65.5%**	(4.6%)	
Other Hispanic	281	*2585*	**2.9%**	(0.6%)	63	*593*	**5.2%**	(1.1%)	
Other Race/Multi-Racial	144	*4348*	**4.8%**	(0.6%)	20	*569*	**5.0%**	(1.5%)	
Education Level									p<0.001*
Less than 9th Grade	488	*5132*	**5.7%**	(1.9%)	154	*1483*	**13.0%**	(2%)	
9-11th Grade	556	*9280*	**10.3%**	(0.9%)	146	*1664*	**14.6%**	(1.1%)	
HS Grad/GED Equivalent	994	*23273*	**25.7%**	(1.1%)	201	*3498*	**30.7%**	(2.8%)	
Some College or AA Degree	1069	*25635*	**28.3%**	(1.2%)	173	*3027*	**26.5%**	(2.1%)	
College Graduate or above	945	*27175*	**30.0%**	(1.9%)	83	*1733*	**15.2%**	(2%)	
Birth Location									p=0.42
Born in Mexico	375	*2869*	**3.2%**	(0.5%)	80	*454*	**4.0%**	(0.8%)	
Born in Other Country	465	*8166*	**9.0%**	(1.2%)	85	*1116*	**9.8%**	(1.9%)	
Born in US	3213	*79488*	**87.8%**	(1.3%)	592	*9834*	**86.2%**	(2.1%)	
Health Insurance									p=0.44
No	718	*12097*	**13.4%**	(1.27%)	121	*1369*	**12.0%**	(1.57%)	
Yes	3334	*78422*	**86.6%**	(1.27%)	635	*10032*	**88.0%**	(1.56%)	
Household Income									p<0.001*
$0 to $24,999	1022	*15273*	**17.8%**	(1.4%)	269	*3098*	**28.6%**	(2.5%)	
$25,000 to $54,999	1227	*25372*	**29.6%**	(1.4%)	247	*3545*	**32.8%**	(2.1%)	
$55,000 to $74,999	476	*12419*	**14.5%**	(0.8%)	64	*1316*	**12.2%**	(2.2%)	
$75,000 and Over	1051	*32536*	**38.0%**	(2.1%)	126	*2857*	**26.4%**	(2.2%)	
Smoking									p=0.10
Every Day	750	*17243*	**37.4%**	(2%)	123	*1889*	**31.4%**	(2.9%)	
Not at all	1240	*26770*	**58.1%**	(2%)	271	*3909*	**65.0%**	(2.8%)	
Some days	107	*2094*	**4.5%**	(0.6%)	20	*214*	**3.6%**	(0.9%)	
Average BP > 140/90									p<0.001*
No	3151	*72085*	**80.7%**	(0.8%)	534	*8155*	**72.4%**	(1.7%)	
Yes	902	*17278*	**19.3%**	(0.8%)	223	*3116*	**27.6%**	(1.7%)	
Median %Hemoglobin A1c [IQR]	5.4 [5.2,5.7]				6.8 [6.2,7.62]				p<0.001*
Self-Reported Visual Acuity									p<0.001*
Excellent	1189	*29995*	**33.2%**	(1%)	142	*2550*	**22.4%**	(2.2%)	
Good	2050	*46956*	**51.9%**	(1.2%)	393	*5969*	**52.3%**	(2.5%)	
Fair	670	*11454*	**12.7%**	(0.8%)	177	*2389*	**21.0%**	(2.3%)	
Poor	118	*1751*	**1.9%**	(0.2%)	38	*435*	**3.8%**	(0.7%)	
Very poor	22	*321*	**0.4%**	(0.1%)	7	*60*	**0.5%**	(0.17%)	
Both Eyes BCVA better than 20/40									p=0.002*
No	867	*15727*	**17.4%**	(0.9%)	204	*2704*	**23.9%**	(1.7%)	
Yes	3186	*74531*	**82.6%**	(0.9%)	553	*8592*	**76.1%**	(1.7%)	

Table 1. Comparison of the number of survey participants (unweighted and weighted) without diabetes and with non-referable diabetic retinopathy across demographic and clinical variables.

Of participants with non-referable DR, 44.5% of (adjusted n=5.1M) had other ocular disease findings (Table 2). Comparatively, 36.3% of 4,053 participants aged greater than 40 without diabetes (adjusted n=90.5M) had other ocular disease findings. The socioeconomic factors associated with non-referable DR participants having other ocular disease findings were increased age, health insurance, and lower household income. Compared to participants with non-referable DR without other ocular disease findings, participants with non-referable DR and other ocular disease findings were significantly older (median age 63.9 versus 54.8 years), had a lower household income, and were more likely to have health insurance (91% vs 85%). The clinical factor significantly associated with participants with non-referable DR having other ocular disease findings was increased blood pressure. Participants with non-referable DR and other ocular disease findings had a higher prevalence of elevated average blood pressure (34% vs 22%) compared to participants with non-referable DR without other ocular disease findings. There were no other significant differences between the two groups.

Variable	No Other Ocular Disease Findings				Any Other Ocular Disease Findings				P value
	Unweighted N, *Weighted N, in thousands* **Column %** (SE or IQR)								
Total Population	387	*6329*	**100%**		370	*5075*	**100%**		
Median Age (years [IQR])	54.8 (12.0)				63.9 (15.6)				p<0.001*
Gender									p=0.06
Male	178	*2833*	**44.8%**	(3.5%)	206	*2731*	**53.8%**	(3.5%)	
Female	209	*3497*	**55.2%**	(3.5%)	164	*2344*	**46.2%**	(3.5%)	
Race									p=0.31
Mexican American	75	*473*	**7.5%**	(1.6%)	72	*405*	**8.0%**	(1.9%)	
Non-Hispanic Black	119	*1152*	**18.2%**	(3.3%)	99	*748*	**14.7%**	(2.1%)	
Non-Hispanic White	147	*3984*	**62.9%**	(5.4%)	162	*3481*	**68.6%**	(4.3%)	
Other Hispanic	39	*412*	**6.5%**	(1.5%)	24	*181*	**3.6%**	(1.3%)	
Other Race/Multi-Racial	7	*309*	**4.9%**	(2%)	13	*260*	**5.1%**	(2%)	
Education Level									p=0.29
Less than 9th Grade	74	*734*	**11.6%**	(2.1%)	80	*749*	**14.8%**	(2.5%)	
9-11th Grade	77	*953*	**15.1%**	(1.4%)	69	*711*	**14.0%**	(1.5%)	
HS Grad/GED Equivalent	95	*1805*	**28.5%**	(3.7%)	106	*1693*	**33.4%**	(3.7%)	
Some College or AA Degree	99	*1973*	**31.2%**	(3.4%)	74	*1053*	**20.8%**	(3%)	
College Graduate or above	42	*864*	**13.7%**	(2.4%)	41	*868*	**17.1%**	(2.7%)	
Birth Location									p=0.90
Born in Mexico	41	*258*	**4.1%**	(1%)	39	*197*	**3.9%**	(0.9%)	
Born in Other Country	47	*642*	**10.1%**	(2.3%)	38	*474*	**9.3%**	(2%)	
Born in US	299	*5430*	**85.8%**	(2.5%)	293	*4404*	**86.8%**	(2.2%)	
Health Insurance									p=0.04*
No	78	*923*	**14.6%**	(2.4%)	43	*446*	**8.8%**	(1.8%)	
Yes	308	*5404*	**85.4%**	(2.4%)	327	*4629*	**91.2%**	(1.8%)	
Household Income									p=0.01*
$0 to $24,999	122	*1492*	**25.0%**	(3.4%)	147	*1605*	**33.1%**	(2.3%)	
$25,000 to $54,999	120	*1724*	**28.9%**	(2.3%)	127	*1821*	**37.6%**	(3.5%)	
$55,000 to $74,999	35	*843*	**14.1%**	(3%)	29	*473*	**9.8%**	(2.3%)	
$75,000 and Over	82	*1909*	**32.0%**	(3.7%)	44	*948*	**19.6%**	(2.9%)	
Smoking									p=0.06
Every Day	75	*1263*	**37.6%**	(4.5%)	48	*627*	**23.6%**	(3.5%)	
Not at all	122	*1954*	**58.1%**	(4.4%)	149	*1955*	**73.8%**	(3.7%)	
Some days	12	*145*	**4.3%**	(1.5%)	8	*68*	**2.6%**	(1.1%)	
Average BP > 140/90									p<0.001*
No	291	*4871*	**77.6%**	(2.5%)	243	*3284*	**65.7%**	(1.9%)	
Yes	96	*1405*	**22.4%**	(2.5%)	127	*1712*	**34.3%**	(1.9%)	
Median %Hemoglobin A1c [IQR]	6.80 [1.40]				6.70 [1.60]				p=0.48
Self-Reported Visual Acuity									p=0.61
Excellent	74	*1469*	**23.2%**	(2.7%)	68	*1082*	**21.3%**	(2.8%)	
Good	195	*3194*	**50.5%**	(3.5%)	198	*2774*	**54.7%**	(3.2%)	
Fair	100	*1449*	**22.9%**	(2.8%)	77	*940*	**18.5%**	(3.3%)	
Poor	14	*178*	**2.8%**	(1.1%)	24	*258*	**5.1%**	(1.3%)	
Very poor	4	*39*	**0.6%**	(0.2%)	3	*21*	**0.4%**	(0.3%)	
Both Eyes BCVA better than 20/40									p=0.15
No	83	*1303*	**20.7%**	(3%)	121	*1402*	**28.1%**	(3.4%)	
Yes	304	*5000*	**79.3%**	(3%)	249	*3592*	**71.9%**	(3.4%)	

Table 2. Comparison of the number of survey participants (unweighted and weighted) with non-referable diabetic retinopathy with or without any other eye disease findings across demographic and clinical variables.

The most prevalent other ocular disease finding in participants with non-referable DR was epiretinal membrane (17.3% (±1.4%), followed by hypertensive retinopathy (14.7%±2%),

followed by hard drusen greater than 125 microns (9.4%±1%), followed by glaucomatous changes (6.1%±1%), followed by choroidal nevus (4.4%±0.8%), which was found in 17.2% (weighted n=1.7M) of participants (Figure 1). Comparatively, the most prevalent other ocular disease finding in participants without diabetes was epiretinal membrane (14.7%±0.7%), followed by hypertensive retinopathy (9.2%±0.5%), followed by hard drusen greater than 125 microns (6.1%±0.6%), followed by glaucomatous changes (3.8%±0.4%), followed by choroidal nevus (4.9%±0.4%). Differences in prevalence of any other ocular disease finding ($p < 0.001$), hypertensive changes ($p=0.026$), and glaucomatous changes ($p = 0.031$) between participants with non-referable diabetic retinopathy and those without diabetes were statistically significant, while all other disease finding prevalences were not significantly different (Table 3).

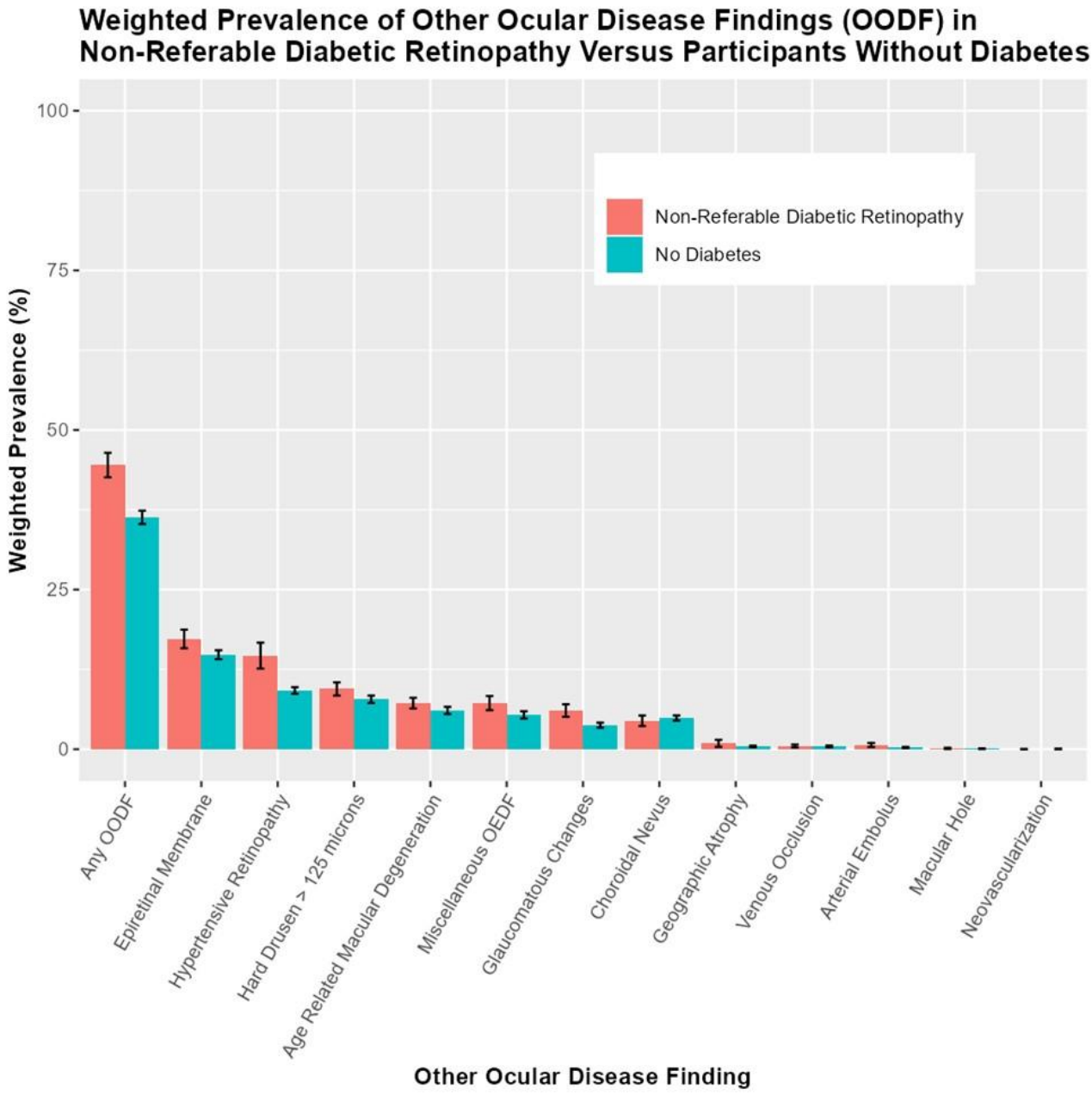


Figure 1. Weighted prevalence of incidental eye disease findings (OODF) in participants with non-referable diabetic retinopathy versus participants without diabetes.

Other Ocular Disease Finding	No Diabetes		Non-Referable Diabetic Retinopathy		P value
	Prevalence	Standard Error	Prevalence	Standard Error	
Age Related Macular Degeneration	6.07%	0.56%	7.21%	0.83%	0.156
Hard Drusen > 125 microns	7.82%	0.58%	9.43%	1.03%	0.085
Geographic Atrophy	0.43%	0.12%	0.91%	0.55%	0.323
Neovascularization	0.04%	0.03%	0.00%	0.00%	0.174
Epiretinal Membrane	14.80%	0.70%	17.27%	1.45%	0.061
Arterial Embolus	0.25%	0.10%	0.67%	0.31%	0.210
Venous occlusion	0.43%	0.14%	0.50%	0.23%	0.833
Hypertensive Changes	9.20%	0.51%	14.65%	2.03%	0.026
Choroidal Nevus	4.88%	0.41%	4.45%	0.83%	0.673
Miscellaneous Eye Disease	5.37%	0.57%	7.22%	1.10%	0.096
Macular Hole	0.08%	0.04%	0.12%	0.09%	0.679
Glaucomatous Changes	3.76%	0.39%	6.05%	0.98%	0.032
Any Other Ocular Disease Finding	36.31%	1.04%	44.50%	1.92%	0.0002

Table 3. Prevalence of other ocular disease findings in participants without diabetes and with non-referable diabetic retinopathy.

We generated a multivariable logistic regression model including age, health insurance status, household income, elevated blood pressure, as well as gender and race/ethnicity. After feature removal to minimize the AIC, our most parsimonious model included age, gender, income, but not ethnicity/race or health insurance status. In our final model, we found significant effects for age where a participant with non-referable diabetes was 6.5% more likely to have other ocular disease findings for each year over 40 (OR 1.065, 95% CI: 1.035 - 1.097, $p < 0.001$), and that women were little over half as likely as men to have other ocular disease findings (OR 0.571, 95% CI: 0.366 - 0.890, $p = 0.015$).

Variable	Odds Ratio (95% Confidence Interval)	P value
Intercept	0.151 (0.042 - 0.539)	0.005
Age	1.065 (1.035-1.097)	<0.001
Female Sex	0.571 (0.366 - 0.890)	0.015
Elevated Blood Pressure	1.380 (0.890 - 2.138)	0.143
Household Income $25,000 to $54,999	1.044 (0.675 -1.613)	0.842
Household Income $55,000 to $74,999	0.787 (0.414 -1.494)	0.448
Household Income $75,000 and Over	0.679 (0.343 - 1.346)	0.255

Table 4. Odds ratios from multivariable logistic regression model including factors of age (in years), sex, elevated blood pressure, household income strata (as an ordinal categorical variable).

Discussion

Implementation of fully autonomous diabetic retinopathy detection would introduce a notable shift in healthcare delivery. Of the 9.6 million diagnosed patients with diabetes in the US, 21.37% (2.05 million individuals) are projected to have non-referable diabetic retinopathy.[1] If screened autonomously, these patients would be reassured that their diabetic eye disease is mild enough to not warrant referral by an eye specialist, compared to the existing screening guidelines where patients would have been recommended to be evaluated in person, sometimes for the first time, at which point other ocular disease would potentially be identified. Based on the results of this study, up to 44.5%, estimated at 5.1 million individuals, will have some other ocular disease findings, of which 17.3% would have ERM (2.3M), 14.7% hypertensive retinopathy (0.75M), 9.4% non-exudative AMD (0.48M), 6.1% glaucomatous changes (0.31M), and 4.4% choroidal nevus (0.22M).

We evaluated risk factors to identify those with other ocular disease findings within the non-referable DR population. We found that increased age, having health insurance, and lower household income were significantly associated with the presence of other ocular disease

findings. Although the relationship between the status of health insurance and presence of other eye disease findings is unclear, having health insurance potentially facilitates regular access to eye care and routine exams. Individuals with insurance are more likely to visit eyecare providers for comprehensive exams which may often reveal unrelated, asymptomatic eye diseases such as diabetic retinopathy.[16] Furthermore, insurance coverage often reduces the financial burden, allowing more people to seek preventative care rather than waiting until symptom onset. Coverage through Medicaid has been linked with greater use of vision services, and expanding insurance coverage for comprehensive eye exams has the potential to reduce vision impairment and related economic burdens associated with delayed care.[16]

Patients undergoing evaluation for DR are a notable population for several reasons. Firstly, diabetes disproportionately affects those with greater socioeconomic barriers and who may have challenges accessing subspecialty care.[7,8] Exams for DR provide a systematic "nudge" for these patients and establishes a pathway for them to receive regular eye care. Secondly, there is greater awareness from a primary care standpoint for referral to an eye care specialist in the management of diabetes compared to other indications.[5,6] The AAO Preferred Practice Pattern guidelines recommend that the general population receives an eye examination starting from age 40 every five years[4]; however, in a study surveyed primary care providers in both rural and urban centers, under 50% would refer an asymptomatic 42-year-old patient for an eye exam who had never seen an eye doctor before.[17] In the same study, over 90% of surveyed primary care providers would refer patients with newly diagnosed diabetes, regardless of ocular complaints. Lastly, diabetes is a well-established risk factor for multiple ocular conditions, including glaucoma, cataracts, and ocular surface disease.[18] As a result, individuals with diabetes may represent an ideal target population for enhanced screening efforts to detect these eye diseases early. In our data, this is reflected in the higher incidence of glaucomatous findings and hypertensive retinopathy within the non-referable DR population compared to patients without diabetes.

Our findings align with results from other screening initiatives, such as the MI-SIGHT telemedicine study, which effectively identified high rates of vision-threatening disease in underserved communities, including glaucoma (24%), diabetic retinopathy (7.3%), visual impairment (10.3%), and macular degeneration (2.0%).[19] In a comparable study conducted in underserved communities in New Jersey, 31% of 341 participants screened at urban soup

kitchens were found to have vision-threatening eye diseases.[20] The most common findings included other retinal abnormalities (41%), glaucoma (32%), significant cataract (21%), and diabetic retinopathy (5%). These studies provide a model for how population-based screening can reveal substantial hidden disease burden and inform future policy around autonomous AI implementation.

Our study has limitations. Retrospective data collected from 2005–2006 and 2007–2008 may not necessarily reflect current incidences of disease. Additionally, the labels for disease states were based solely off fundus photography, rather than a comprehensive eye examination. Therefore, an in-person visit may have higher sensitivity for other ocular diseases, such as cataracts or peripheral retinal findings not well visualized on standard fundus photography. For instance, while ultra-widefield (UWF) imaging is commonly used in eyecare providers' office as a screening tool for retinal pathology, studies show that nearly half of peripheral horseshoe tears were missed by fundus photography alone compared to scleral depressed retinal examinations, demonstrating fundus photography's limitations in detecting all retinal pathologies.[21] However, the use of data labels solely based on fundus photography has increasingly been shown to serve as a promising alternative and/or in adjunct to ophthalmic telemedicine and AI testing.[22,23]

Additionally, our study offers an estimate of threatened missed detections of other eye diseases that should be interpreted in the context of real-world outcomes. Many patients could already be under the care of an eye care provider who would identify these other ocular disease findings without the need for a referral related to their diabetes. Other patients with non-referable DR may not attend their recommended annual eye examination due to the many barriers discussed above. Even then, some patients who do attend their referral examination may not necessarily have their other ocular disease findings detected at their in-office examination based on the sensitivity of the examination. Alternatively, a comprehensive dilated examination conducted by a trained eye clinician may detect pathology not able to be identified by fundus photography alone.[24] Therefore, we consider the 5.1 million potential individuals with other ocular disease findings who would no longer be referred for in-person exams as a rough upper limit estimate of how many patients could be missed if policy shifted from in-person referrals to an autonomous AI-based system focused only on referable DR.

Many of the other disease findings included in this study would typically be managed with monitoring without intervention. Some may require intervention, in the case of glaucoma or

AMD, or an investigation of other systemic health conditions, as in the case of hypertensive retinopathy or arterial embolus. The true healthcare and systems impact of delayed detection of these disease findings is a complex, but pertinent unknown as the ophthalmologic field faces an aging population and increased patient demand. Thus, more data on other ocular disease findings in patients that would be deferred in-person examination, such as the aforementioned MI-SIGHT study, should be acquired as real-world trials of fully autonomous diabetic eye examinations are undertaken to obtain better estimates.[19] Future work to identify these alternative pathologies using fundus photography may complement autonomous diabetic retinopathy detection infrastructure and help minimize risks of undetected disease.

Our study has several key strengths. Our study utilizes a nationally representative dataset, which improves the generalizability of our findings to a broad and diverse population. The large samples size identified from this database increases the statistical power of our analysis and enhances the generalizability of our results across various groups, including different age ranges, socioeconomic backgrounds, and various demographic patterns. Additionally, expert consensus graders labeled disease findings, ensuring standardization in accurate and consistent identification of ocular findings on fundus photographs.

Conclusion

Among adults aged 40 years and older with non-referable diabetic retinopathy, other ocular disease findings were common, affectingly nearly half of participants. These additional fundus abnormalities were associated with demographic and systemic factors including age, blood pressure, and insurance status, underscoring their clinical and public health relevance. As automated diabetic retinopathy detection systems are increasingly adopted, there is potential risk that clinically meaningful non-diabetic ocular pathology may go unrecognized if screening focuses solely on retinopathy severity. Screening models that incorporate broader fundus evaluation may help preserve comprehensive disease detection while maintaining efficiency. Further investigation is warranted to better define the clinical consequence of these findings and to inform the implementation of fully autonomous screening pathways.

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Competing Interests

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by CL, EL, and KN. The first draft of the manuscript was written by CL and EL, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This is an observational study. The Yale Research Ethics Committee has confirmed that no ethical approval is required.

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