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Risk factors for corneal ulcers: a population-based matched case-control study in Nepal

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Abstract

Background/Aims.—We aimed to examine risk factors for corneal ulcer in a rural and peri-urban setting in Nepal.

Methods.—This population-based matched case-control study was nested in a cluster-randomized trial in 24 Village Development Committees in Nepal. Incidence density sampling was used to match incident corneal opacity cases to controls, matching on time of opacity, age,

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sex, and location. Cases and controls were invited to participate in a survey of risk factors for corneal ulcer. Risk factors were evaluated using conditional logistic regression to account for matching.

Results.—Of the 540 participants with incident opacities identified in the trial, 433 were willing to participate in this substudy and matched to a control. Compared to controls, cases had lower odds of having any education vs no education (aOR 0.60, 95% CI 0.39 to 0.94), working in non-manual labor occupations vs manual labor occupations (aOR 0.64, 95% CI 0.42 to 0.95), and preferring medical shops for ocular trauma vs eye care system centers (aOR 0.58, 95% CI 0.37 to 0.92). Cases had higher odds of protective goggle use vs no protection (aOR 3.8, 95% CI 1.3 to 11.0) and having an ocular injury vs none (aOR 7.7, 95% CI 4.3 to 13.6) compared to controls.

Conclusion.—We found ocular injury, manual labor, and lower education to be strongly associated with the development of corneal ulcer. Given the persistent burden of corneal blindness in this area, prevention efforts could target efforts to increase access to care in areas where these factors are common.

INTRODUCTION

Despite global declines in the number of people affected by corneal blindness, corneal opacity remains among the leading causes of blindness and visual impairment worldwide.[1] Low- and middle-income countries bear much of this burden,[1] with corneal opacity in these settings commonly caused by infectious keratitis or corneal ulcer.[2] Corneal ulcer is often avoidable with prevention and early treatment, suggesting that the persistent prevalence of corneal blindness stems in part from a lack of access to appropriate eye care resources.[2, 3]

Groups at high risk for corneal ulcer could be targeted by prevention efforts in order to leverage available resources in settings with a large burden of corneal blindness. Previous studies indicate that common risk factors for corneal ulcer include ocular trauma, male sex, low socioeconomic status, agricultural work and other manual labor, and contact lens wear.[3–12] However, the frequency of these risk factors varies by setting,[4, 13] and thus context-specific evidence is required to inform targeted prevention activities. Here, we aimed to evaluate risk factors for corneal ulcer in a rural and peri-urban setting in Nepal.

MATERIALS AND METHODS

Study Design and Setting.

This population-based matched case-control study was nested in the Village Integrated Eye Worker (VIEW) trial, which randomized 24 Village Development Committees (VDCs) in the Chitwan and Nawalparasi districts in Nepal to receive a corneal ulcer prevention program or no program.[14, 15] At the time of the study, each VDC was in turn subdivided into 9 wards. The trial included an annual population-based census over 3 years to enumerate the study population and photograph the corneas of participants suspected of having an incident corneal ulcer during the study period. Photographs were evaluated by trained graders to determine the presence of an incident corneal ulcer. For the present study, incident cases were pair-matched using incidence density sampling to population-based controls selected from the same round of census data collection. Cases and controls were invited to a study visit that included a questionnaire on risk factors for corneal ulcer.

Ethical approval for the overall trial and this sub-study was obtained before study activities commenced from the Nepal Health Research Council, Nepal Netra Jyoti Sangh, and the University of California San Francisco Committee on Human Research. Participants provided verbal consent for participation in both the trial and the case-control study. Study activities adhered to the guidelines of the Declaration of Helsinki and an independent Data and Safety Monitoring Committee provided oversight during the study period.

Participants and Recruitment.

Corneal photographs taken during the census were used to identify cases and controls. Photographs were taken of both corneas of all study area residents at the baseline visit. At annual follow-up census visits at months 12, 24, and 36, photographs were taken of both corneas for those participants reporting ocular trauma, ocular pain, a sudden decrease in vision, or ocular infection in the past year, and also for participants with an obvious corneal opacity. As described in detail elsewhere,[14, 15] corneal photographs were taken using a smartphone camera enhanced with the Ocular CellScope attachment (Development Impact Lab, Berkeley, CA USA), which includes a +25 diopter lens and external illumination to produce high quality cornea photographs.[16] Trained masked graders evaluated each photograph from a follow-up census for the presence of corneal opacity. If an opacity was present, photographs from earlier censuses were also graded to determine whether the corneal opacity was new or existing. Images from participants judged to have a new opacity during this initial round of grading were forwarded to a team of masked ophthalmologists for confirmation; the ophthalmologist's assessment was used as the final grade.[14]

Cases were defined as those participants with a new corneal opacity or a corneal opacity with unknown status of the cornea on a previous exam. Controls were selected from among the participants not suspected of having an incident corneal opacity in the past year or those with photographs graded as not having an incident corneal ulcer. Controls were pair-matched to cases using age (± 2 years), sex, and ward of residence and were selected from among those without incident corneal opacity during the same census as cases.

Cases were contacted by phone to determine when they experienced the corneal ulcer. A follow-up visit was scheduled at Bharatpur Eye Hospital, Kawaswoti Eye Care Center, or Parsa Eye Care Center approximately 12 months (−3 months, + 9 months) after the onset of the ulcer. Matched controls were also contacted by phone and similarly scheduled for a follow-up visit in the same window. Visits were conducted by mobile teams at the residence of cases and controls if hospital or eye care center visits were not possible. Cases and controls were contacted by phone and/or in person a maximum of 3 times to schedule a visit. A corneal ulcer risk factor questionnaire was administered at a follow-up visit performed specifically for this case-control study, including questions about education, occupation, use of eye protection, health care-seeking behavior, and details of ocular trauma, if experienced. Data were collected on a REDCap mobile application, and stored on servers hosted at the University of California, San Francisco.[17, 18] Data collectors were trained on use of the instrument and were masked to case status as well as trial arm.

Sample size and statistical considerations.

Given the study design, the sample size for this case-control study was fixed by the number of incident corneal ulcers identified during the trial, with controls matched in a 1:1 ratio. The effect size detectable with the sample size depends on the proportion exposed to each risk factor. For example, for risk factors in which 25% of controls were exposed, 433 cases matched to 433 controls provides 80% power to detect an odds ratio of 1.5, whereas for risk factors in which 95% of controls were exposed, the detectable effect size would be an odds ratio of 3.0, assuming an alpha of 0.05. Demographic characteristics and risk factors were summarized by case status with frequency and percentage for categorical variables and median and inter-quartile range for continuous variables. Ocular injury characteristics were also summarized by case status, though as there were only 10 case-control pairs with data on ocular injuries because few controls experienced an injury, formal paired comparisons were not possible. To examine loss to follow-up, demographic characteristics of included corneal ulcer cases were compared to excluded cases using Fisher exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Conditional logistical regression was used to estimate odds ratios (ORs) for each risk factor, accounting for the matching variables (age, sex, ward). Multi-level categorical variables were collapsed or dichotomized when cell sizes were small (< 10%). Univariable models were examined first to explore individual risk factors, and final adjusted models included risk factors with P-values < 0.05 in univariable comparisons. Analyses were repeated in a non-prespecified exploratory subgroup analysis, with subgroups defined according to population density assessed from household-level GPS data from the baseline census. Population density was calculated for each household as the average distance to its 10 nearest neighbors, and then subsequently summarized as a ward-level mean. The median ward-level density was used to classify wards as low- or high-density. As cases and controls were matched on ward and therefore population density, tests of statistical interaction were not pursued and stratified results are presented instead.

RESULTS

Between February 2014 and August 2017, 540 participants with incident corneal ulcers were identified from photographs taken during the annual census conducted as part of the VIEW trial (Figure 1). The final sample included 433 cases pair-matched to 433 controls without a corneal opacity identified during the same census (Figure 1). Of the 107 cases not included in the final sample, 45 (42%) scheduled a study visit but were lost to follow-up, 37 (35%) had died, been hospitalized, or had moved, 18 (17%) were unreachable by the study team or did not have a potential matched control, and 7 (7%) refused. Age and sex were similar among participating and non-participating cases, but a greater proportion of non-participants were from rural wards (25% vs 15%, $P = 0.02$, Supplementary Table 1).

Table 1 summarizes characteristics of study participants and risk factors by case status. Among both cases and controls, the median age was 41 years (IQR 27 to 54) and 264 pairs (61%) were female. The majority of cases and controls resided in peri-urban wards (76%) and 238 (55%) resided in a Village Development Committee receiving the active intervention in the VIEW trial. Most study visits were conducted by mobile teams at the residence of participants. Two hundred five cases (51%) and 180 controls (43%) reported having no formal education. Manual labor occupations were common among both cases (46%) and controls (37%), with most participants in both groups reporting agricultural work. When asked where they would seek care for ocular trauma, common responses included centers with an eye care provider (33% of cases and 31% of controls) and medical shops (9% of cases and 12% of controls). Among those reporting an ocular injury (29% of cases and 6% of controls), the most common object of injury was plant matter (61% of cases and 36% of controls). Farming and other outdoor activities were most common at the time of injury (36% of cases and 32% of controls). The majority of both cases and controls sought treatment after injury (80% of cases and 72% of controls), with 43% of cases taking more than 48 hours to present for treatment compared to 29% of controls.

Table 2 displays odds ratios (ORs) for each risk factor in unadjusted and adjusted models. Compared to controls, cases had lower odds of having any education vs no education (aOR 0.60, 95% CI 0.39 to 0.94), working in non-manual labor occupations vs manual labor occupations (aOR 0.64, 95% CI 0.42 to 0.95), and preferring medical shops for care for ocular trauma vs eye care system centers (aOR 0.58, 95% CI 0.37 to 0.92). Cases had higher odds of wearing protective goggles while working vs wearing no protection (aOR 3.8, 95% CI 1.3 to 11.0) and having experienced an ocular injury vs no injury (aOR 7.7, 95% CI 4.3 to 13.6) compared to controls. No differences were identified in salary or use of spectacles or contacts among cases and controls. In a non-prespecified exploratory subgroup analysis, the magnitude of association was more extreme in communities with lower population density as opposed to those with higher population density for most risk factors (Figure 2).

DISCUSSION

Prevention and early treatment efforts targeted to high-risk populations may alleviate the persistent burden of blindness from corneal ulcer in low- and middle-income settings. In this population-based matched case-control study nested within a trial, we aimed to identify risk factors for corneal ulcer in a rural and peri-urban setting in Nepal. Ocular injury, manual labor, and no education were associated with a greater odds of corneal ulcer in this setting. Exploratory subgroup analyses suggested the strength of these associations may be greater in more rural areas.

Ocular trauma has been identified as a leading risk factor for corneal ulcer in numerous studies, particularly in rural settings with a high prevalence of agricultural work.[3–7, 9–12, 19, 20] In these settings, plant matter is often implicated as the object of injury, as was seen here.[4–7, 9, 11, 12, 20] Similarly, another common risk factor identified in other studies is having a manual labor occupation like agricultural work that presents more opportunity for injury.[3, 5, 7, 9–12] Education and socioeconomic status have also been associated with corneal ulcer risk in other studies.[3, 10, 11] This study did not directly measure socio-economic status. Although cases and controls had similar salaries and were matched on location, we did find that approximately 40% of this population had no education and that no education was associated with a higher odds of corneal ulcer. This association with education is likely a proxy for broader access to care associated with awareness, location, and resources. Other studies have also identified male sex as a risk factor. As case-control pairs were matched on sex, we were unable to examine sex as a risk factor. Our study population included more females (62%) than males, in line with overall population demographics in this part of Nepal.[15]

In this setting, we found a low prevalence of use of contact lenses, spectacles, and protective goggles. Contact lens use is a common risk factor for corneal ulcer in higher income settings where their use is more prevalent.[3, 4, 19, 21, 22] Use of either spectacles or goggles could theoretically be preventative if commonly used. Here, we found that use of protective goggles was associated with an increased odds of corneal ulcer, a likely spurious finding which may be due to recall bias and the challenge of temporal ordering with self-reported past exposures. It is possible that after experiencing a corneal ulcer, cases were more likely to use or recall eye protection than controls. Similarly, the protective association seen with the intention to seek care for ocular trauma at a medical shop compared to eye care centers may be reflective of a form of recall bias and timing issues. In this setting, medical shop owners complete a 3-year pharmacy training program but do not receive focused training in eye care,[23] whereas eye care centers like eye hospitals, private eye clinics, and vision centers are staffed with various levels of trained eye care personnel, including ophthalmic assistants, optometrists, and ophthalmologists. Given the severity of the condition they experienced after ocular injury, cases may have been more likely to indicate the need to present to an eye care center for ocular trauma than controls who did not have that experience. On the other hand, these results may also indicate greater access to and awareness of convenient health care resources like medical shops among the controls. A recent survey in the same setting in Nepal found that even though less than half of medical shop owners could correctly identify corneal abrasions and infections, the majority would appropriately provide topical antibiotics for corneal abrasions and ulcers.[23]

The population-based design using incidence density sampling is a strength of this study, as we expect controls to represent the experience of the source population that gave rise to cases, with less potential for selection bias compared to other case-control designs. The study also benefited from a rigorous approach to data collection involving masked data collectors and standardized data collection forms. In addition, our approach to outreach ensured relatively high follow-up of cases despite the lapse of time between the experience of corneal ulcer and the study visit. Limitations of this study include the possibility of selection bias related to the proportion of cases from rural wards that did not participate in this study. It is possible that, had we been able to include these rural cases, some of the risk factors associated with rural, low population density locations like manual labor or education would have had stronger associations with case status. As previously mentioned, the possibility of recall bias and the challenge of temporal ordering with self-reported past exposures must be considered in the interpretation of these results. It is also possible that the case definition, which included a screening question about the experience of ocular trauma, could have led to an overrepresentation of trauma-related corneal opacities among the cases, although the associations seen here were similar to those reported in other settings. Although overmatching is a risk with this study design, we matched on variables known to be associated with both the exposures in question and the outcome. We also chose matching variables that we did not anticipate to be intermediates on the causal pathway. Given these considerations, we do not think matching impacted validity or precision in our results related to these forms of overmatching.[24] However, there may be residual confounding not accounted for by matching given the observational design. Finally, as this study took place in a rural and peri-urban setting in lowland Nepal, the generalizability of these is limited to similar agricultural settings.

In this population-based matched case-control study in a rural and peri-urban setting in Nepal, we found ocular trauma, manual labor, and lower education to be strongly associated with the development of corneal ulcer. Given the continued burden of corneal blindness in this area, prevention efforts could consider increasing awareness of available eye care resources and access to prompt eye care in areas where these factors are particularly common.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement.

De-identified data associated with these analyses will be made available upon reasonable request to the corresponding author.

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KEY MESSAGES

What is already known on this topic.

Despite being avoidable with prevention and early treatment, corneal opacity remains a leading cause of visual impairment and blindness globally. Population subgroups at high risk for corneal ulcer and opacity could be targeted by prevention efforts. Previous studies show that common risk factors for corneal ulcer include ocular trauma, male sex, low socioeconomic status, agricultural work and other manual labor, and contact lens wear. However, the frequency of these risk factors varies by setting. Context-specific evidence is required to inform targeted prevention activities.

What this study adds.

This population-based matched case-control study provides information on risk factors for corneal ulcer relevant for this rural and peri-urban setting in Nepal with a high burden of corneal ulcer.

How this study might affect research, practice, or policy.

These results may guide prevention efforts to consider increasing awareness of available eye care resources and access to prompt eye care in this setting and similar settings where these factors are particularly common.

SYNOPSIS/PRECIS

This population-based matched case-control study in Nepal evaluated risk factors for corneal ulcer. We found that ocular injury, manual labor, and lower education were associated with the development of corneal ulcer in this setting.

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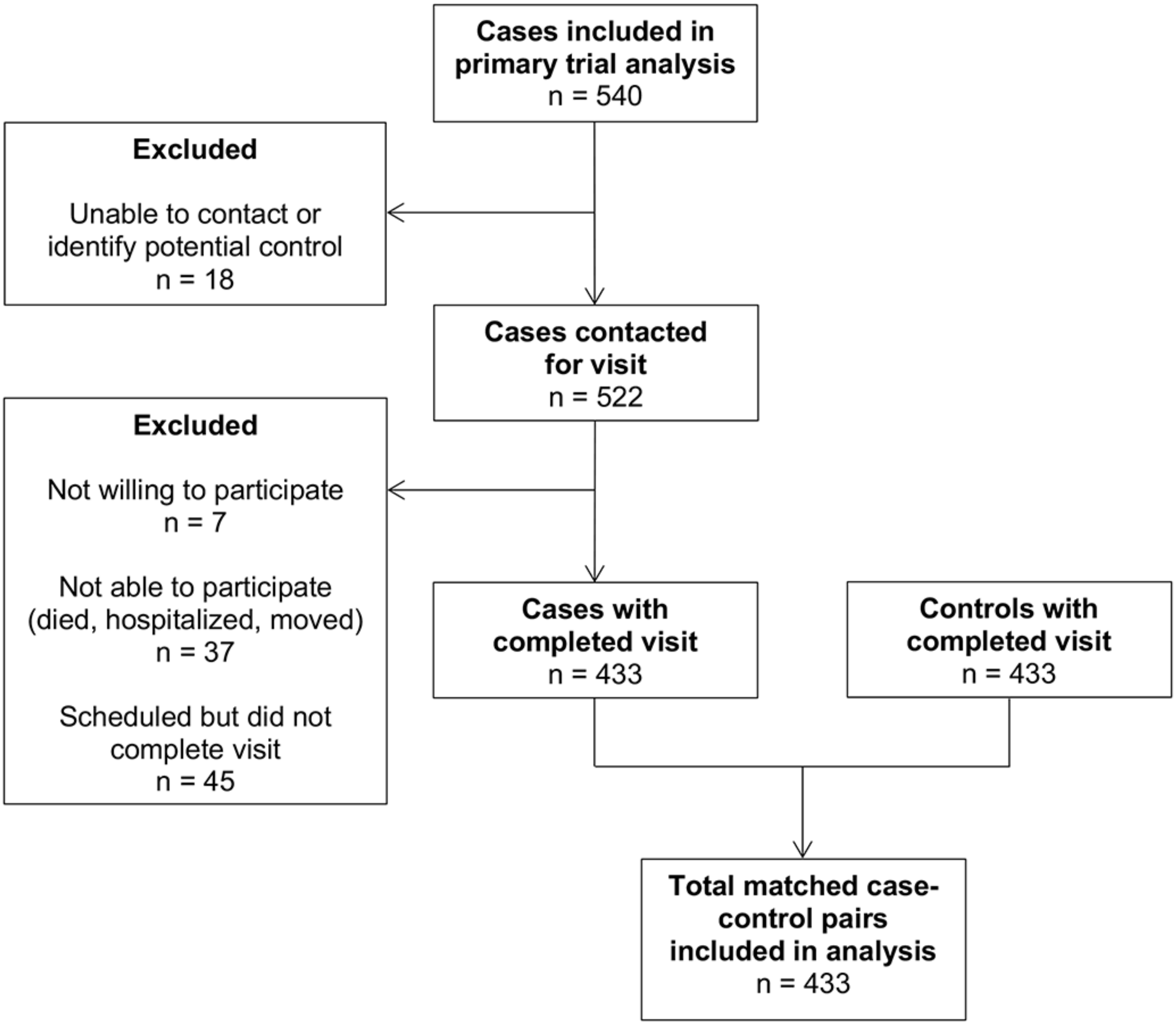

Figure 1.
Eligible cases were participants with incident corneal ulcers identified from corneal photographs taken during the main trial. Cases were contacted by phone or in-person visits up to 3 times to complete a study visit for the case-control study. Controls were matched to cases on age (± 2 years), sex, and ward of residence from among trial participants still at risk for corneal ulcer within the same census period as cases.

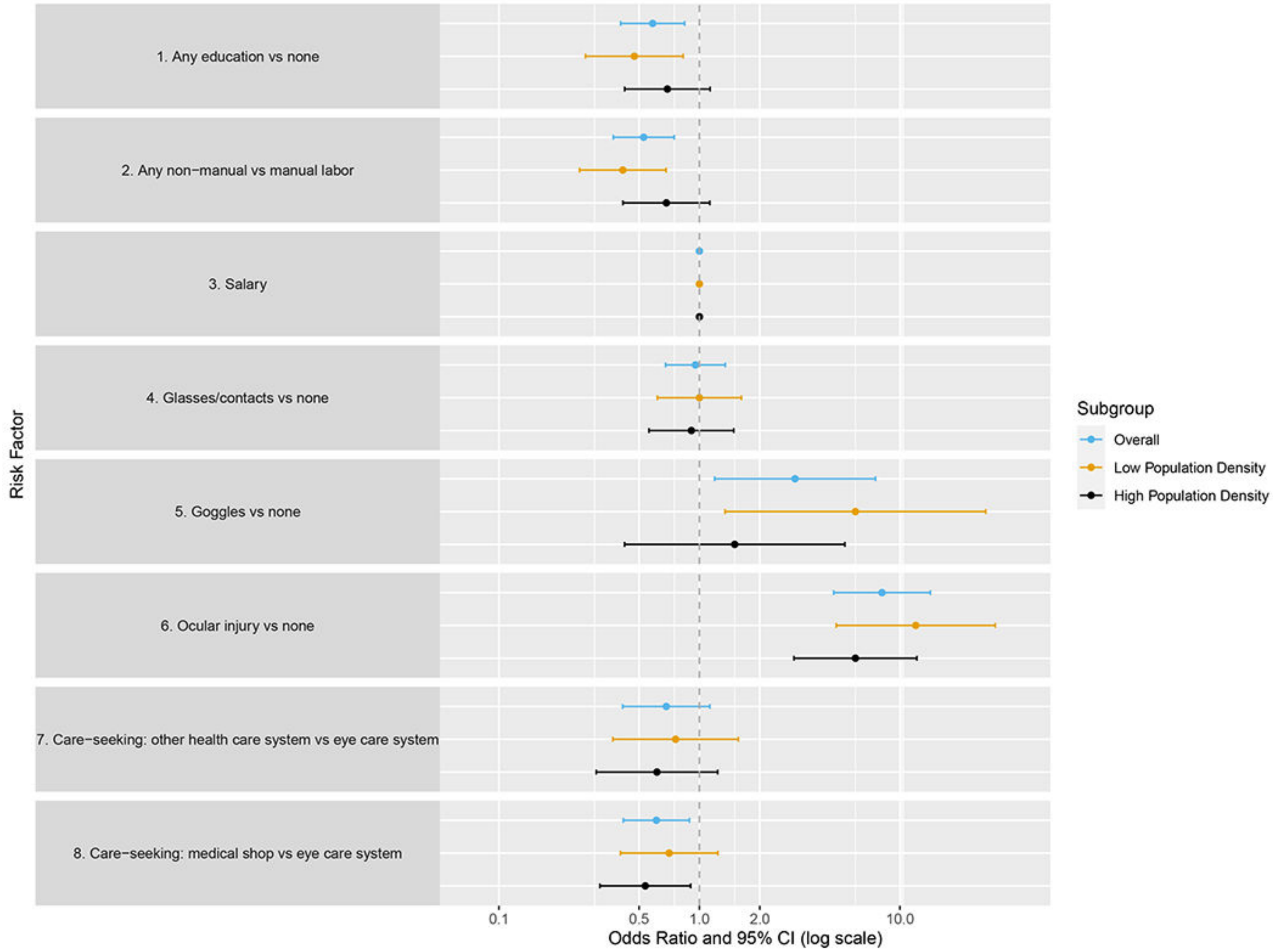

Figure 2.

Conditional logistic regression was used to estimate exposure odds ratios for each risk factor, accounting for the matching variables (age, sex, ward). Results are presented overall as well as by subgroups defined by population density.

Table 1.

Characteristics of study participants and risk factors by case-control status.[1]

Characteristic	Cases (n = 433)	Controls (n = 433)
Age, median (IQR)[2]	42 (27, 54)	42 (27, 54)
Female sex, n (%)[2]	264 (61%)	264 (61%)
Intervention arm, n (%)[2]	238 (55%)	238 (55%)
Ward type, n (%)[2]		
Rural	68 (16%)	68 (16%)
Peri-urban	327 (76%)	327 (76%)
Urban	38 (9%)	38 (9%)
Location of visit, n (%)		
Eye Hospital	30 (7%)	17 (4%)
Primary Eye Care Center	50 (12%)	24 (6%)
Mobile	326 (75%)	478 (87%)
Missing	27 (6%)	14 (3%)
Education, n (%)		
None	205 (47%)	180 (42%)
Any	200 (46%)	239 (55%)
Missing	28 (7%)	14 (3%)
Occupation,[3] n (%)		
Manual labor	198 (46%)	158 (37%)
Non-manual labor	209 (48%)	261 (60%)
Missing	26 (6%)	14 (3%)
Salary (NPR), median (IQR)	200 (0, 325)	200 (0, 300)
Wore spectacles or contacts, n (%)	96 (22%)	100 (23%)
Wore protective goggles while working, n (%)	18 (4%)	6 (1%)
Ocular injury, n (%)	126 (29%)	25 (6%)
Care-seeking preference for ocular trauma,[3] n (%)		
Eye care provider	289 (33%)	266 (31%)
Other health care provider	41 (5%)	49 (6%)
Medical shop	77 (9%)	105 (12%)
Missing	26 (3%)	13 (2%)

IQR, inter-quartile range

[1] Percentages may not sum to 100% due to rounding.

[2] Matching variables included age (± 2 years), sex, and ward of residence.

[3] Manual labor includes agricultural work and other labor; non-manual labor includes office and other professional work, domestic work, and those identifying as students or unemployed/retired

[4] Eye care provider includes eye hospitals, primary eye care centers, and private eye clinics; other health care provider includes Female Community Health Volunteers and health posts, traditional healers, and private clinics

Table 2.

Unadjusted and adjusted odds ratios of risk factors for corneal ulcer (N=430 case-control pairs).[1]

Risk Factor	Unadjusted OR	Unadjusted 95% CI	Adjusted OR[2]	Adjusted 95 % CI[2]
Education (any vs none)	0.58	0.40 to 0.84	0.60	0.39 to 0.94
Occupation (non-manual vs manual labor)	0.53	0.37 to 0.75	0.64	0.42 to 0.95
Salary	1.00	1.00 to 1.00	NA	NA
Spectacles/contacts vs none	0.96	0.68 to 1.35	NA	NA
Protective goggles vs none	3.00	1.19 to 7.56	3.75	1.28 to 10.95
Ocular injury vs none	8.14	4.67 to 14.19	7.68	4.33 to 13.62
Care-seeking (other health care vs eye care system	0.68	0.41 to 1.13	0.73	0.40 to 1.33
Care-seeking (medical shop vs eye care system	0.61	0.42 to 0.89	0.58	0.37 to 0.92

[1] Estimated using conditional logistic regression to account for matching on age, sex, and ward of residence

[2] Final adjusted model included variables for education, occupation, use of protective goggles, ocular injury, and care-seeking preferences for ocular trauma.