Title

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Relationship between cooking fuel and lens opacities in South India: a 15-year prospective cohort study

Running head: Cooking fuel and cataract in South India

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Abstract

Purpose. Unclean cooking fuels such as wood and kerosene have been associated with cataract in cross-sectional studies. This study sought to determine whether exposure to unclean cooking fuels was associated with subsequent cataract progression.

Design. Prospective cohort study.

Methods. This is a secondary observational analysis of the community-based Antioxidants in Prevention of Cataracts trial (ClinicalTrials.gov ID NCT01664819). The exposure of interest was cooking fuel type, measured at baseline. Main outcome measures were baseline cataract severity and self-reported cataract surgery at a 15-year visit.

Results. Baseline and 15-year follow-up data were available for 798 and 579 participants, respectively. Wood or kerosene was used by 711/798 (89.1%) baseline participants, including 539/579 (93.1%) participants with complete follow-up. Cooking fuel type was not associated with cataract severity at baseline (p=0.443). Out of 8,334 person-years of follow up, 90 cataract surgeries were observed over 15 years (1.08 surgeries per 100 person-years; 95%CI 0.87-1.32). Use of wood or kerosene was not associated with 15-year incidence of cataract surgery relative to individuals using propane (adjusted p=0.154). Cataract surgery was more common in older individuals (HR 1.1 per year, 95%CI 1.1-1.2, p<0.001), those with baseline myopia (HR 2.1, 95%CI 1.2-3.5, p=0.009) and women (HR 3.5, 95%CI 1.2 to 10.1, p=0.019).

Conclusions. This study found no association between unclean cooking fuels and cataract progression over a 15-year period. No other modifiable risk factors were associated with incident self-reported cataract surgery.

Introduction.

Cataract is the primary cause of blindness worldwide, and unoperated cataract disproportionately affects those in low- and middle-income countries.[1-3] Laboratory studies have shown that cigarette smoke and wood cooking fuel smoke condensates can induce cataract formation in rat models, likely through the formation of reactive oxygen species; however, the available epidemiological evidence for the effects of cooking fuel smoke on human cataract formation is sparse.[4] Cooking fuels can be classified as unclean (i.e., solid fuels [e.g., wood, dung, coal], and kerosene) and clean (e.g., propane, liquified petroleum gas, electricity, and solar), based on the fact that unclean fuels produce harmful chemicals (e.g., carbon monoxide and polycyclic aromatic hydrocarbons) during combustion which can contribute to adverse health outcomes.[5,6] Several studies have found higher odds of cataract in individuals exposed to unclean cooking fuels relative to those using cleaner cooking fuels, but they have been exclusively cross-sectional or case-control studies.[7-12] Thus, a more in-depth analysis of the effects of cooking fuel on cataract severity and surgery is warranted. This is especially relevant in a place like South India given the high number of households using unclean cooking fuels,[13] the high prevalence and early onset of cataract,[14,15] and the high proportion of individuals requiring eye care not using existing eye care services.[16]

The aim of this study was to investigate whether exposure to different types of cooking fuels was related to cataract severity and need for cataract surgery over a 15-year follow-up period. We hypothesized that exposure to unclean cooking fuels (i.e., wood or kerosene) would be associated with (1) the severity of nuclear sclerotic, cortical spoking, and posterior subcapsular (PSC) cataract in a cross-sectional analysis of baseline data, and (2) cataract progression, measured by a proxy of cataract surgery in a longitudinal analysis.

Materials and methods.

Dataset, study population, and setting. This study is a secondary, non-pre-specified, observational analysis of data collected for the Antioxidants in Prevention of Cataracts (APC) trial that took place in 5 peri-urban villages surrounding Madurai, India.[17] The original trial was conducted from May 1998 until June 2003 and a 15-year follow-up visit (ClinicalTrials.gov ID NCT01664819) was performed from August 2012 until July 2013. The original aim of the trial was to determine if antioxidant supplementation could slow the 5-year rate of cataract progression among individuals aged 35-50 years of age; the aim of the 15-year follow up was to assess for a long-term effect of antioxidant therapy and to identify risk factors for incident cataract. The inclusion and exclusion criteria, examination techniques, and data collection methods of the trial have been detailed elsewhere.[18] Neither the trial nor the follow-up demonstrated benefits of vitamin supplementation.[17,19] Prospective ethical approval for the clinical trial and 15-year follow-up was obtained from the University of California San Francisco and Aravind Eye Hospital; ethical approval for this secondary analysis was obtained from the London School of Hygiene and Tropical Medicine. Informed consent was obtained from all participants. The study was in accordance with the Health Insurance Portability and Accountability Act (HIPAA) regulations and adhered to the tenets of the Declaration of Helsinki.

Data collection and management. Methods for the baseline study visit have been described in detail previously.[18] Participants underwent a full medical and ophthalmologic examination. Cataract severity was assessed by three masked graders according to the Lens Opacities Classification System III scale (LOCS III).[20] Specifically, nuclear opalescence, cortical opacity, and PSC opacity were each evaluated on a 0.1-unit increment scale, with higher numbers corresponding to more severe cataract. Demographic information, including socioeconomic status (SES) and education, was collected at baseline as was information on cataract risk factors. Participants were asked about their role in cooking (i.e., primary cook or not) and the type of cooking fuel most used in their household. At the 15-year follow-up visit, study workers made household visits for all participants in the trial, documenting vital status (i.e., alive, died, or moved) and asking if and when they had undergone cataract surgery. Vital status of missing participants was determined from household members or neighbors.

Definitions and conventions. Baseline cataract severity on the LOCS III scale was averaged between three graders and treated as a continuous variable. A binary indicator of self-reported cataract surgery in either eye was used as the primary outcome for the 15-year analysis. The categorization of the remaining variables is described in Supplemental File 1.

Statistical methods.

Cataract severity. A complete-case cross-sectional analysis of baseline eye-level data was performed. The outcome of interest was a multivariate indicator for cataract

severity (i.e., LOCS III scores for each of three outcomes: nuclear opalescence, cortical opacity, and PSC). First, univariable associations between each baseline factor and multivariate cataract severity was assessed, then a multivariable model was built to explore the association between cataract severity and cooking fuel type (i.e., wood vs. kerosene oil vs. propane gas). The model was adjusted for age, sex, SES, occupation, smoking status, sunlight exposure, best corrected visual acuity (BCVA), and refractive error *a priori*, given these are risk factors thought to be important for development of one or more type of cataract.[21-23] Additionally, the model was adjusted for the participant’s involvement in cooking as those involved in cooking would theoretically be exposed to more cooking fuel smoke, and for any baseline covariates with a p-value < 0.1 in the univariable analyses. A multivariate generalized least squares regression model was implemented, specifying different variances for each type of cataract severity score and an unstructured correlation matrix to account for correlation of observations from the same study participant (*nlme* package in R statistical software).[24,25] Statistical significance of regression coefficients was assessed with an F-test (i.e., testing the null hypothesis that cataract severity score means were equal across all groups of the independent variable). A sex by cooking fuel interaction term was explored but was not statistically significant and therefore not included in the final model. A sensitivity analysis was performed by fitting a multivariate linear regression model to person-level data with the cataract severity scores in the worst eye as the multivariate outcome and refractive error in the worst eye and BCVA in the better eye as eye-level covariables. As the data came from a completed clinical trial the sample size was fixed. Using a t-test as an approximation, the sample size of 798 would provide 80% power to detect a difference in mean cataract severity score of at least 0.4 between any two exposure groups, given 85% of participants were exposed, a mean cataract severity score of 2.2 in the unexposed group, equal standard deviations of 0.5 in both groups, and a two-sided alpha of 0.05. In practice, the significance level was set to 0.001 to account for multiple comparisons.

Cataract progression. A complete-case longitudinal analysis of participant-level data was performed. The outcome of interest was a binary indicator of cataract progression (i.e., self-reported cataract surgery in either eye). A Cox-proportional hazards model was implemented in R statistical software, first with univariable analyses of baseline factors, and then with a multivariable analysis whose exposure of interest was cooking fuel type.[26] Refractive error for the worse eye and BCVA for the better eye was used for each participant. Start time was defined as the date enrolled in the trial and censor time was defined as the date of cataract surgery, the date deceased, or the time of 15-year follow up. In the case of loss to follow up, censor time was assumed to occur at the study midpoint, with a sensitivity analysis conducted on only those with complete follow up. The model was adjusted for baseline age, sex, SES, occupation, smoking status, sunlight exposure, BCVA, and refractive error *a priori*. Additional baseline risk factors with a p-value ≤ 0.1 in univariable analysis were added to the final model. A sex by cooking fuel interaction term was explored but was not statistically significant and therefore not included in the final model. The sample size was fixed according to the underlying trial, with 579 individuals having completed follow up at 15 years. The available sample provided 80% power to detect a difference in proportions of 0.46 between any two exposure groups, assuming 85% of participants were exposed, 20% of controls experienced the outcome, and a two-sided alpha 0.05, though as mentioned above, the significance level was set to 0.001 to account for multiple comparisons.

Given neither the clinical trial nor 15-year follow-up found any benefit of antioxidant supplementation, trial arm was not adjusted for in the Cox regression analysis.[17,19]

Results.

A total of 798 participants (1,596 study eyes) were enrolled. At the baseline visit 1,156 (72.4%) eyes had nuclear opalescence at the ≥2 LOCS III threshold; 161 (10.1%) eye had cortical changes at the ≥1 threshold; and 21 (1.3%) eyes had PSC changes at the ≥1 threshold (Supplemental Table 1). Mean LOCS III scores were 2.3 (SD 0.5), 0.5 (SD 0.5), and 0.1 (SD 0.2) for nuclear, cortical, and PSC cataracts, respectively. Many eyes had more than one type of cataract, with positive correlation of severity scores between the different types of cataract ($p < 0.001$ for each pairwise comparison; Supplemental Figure 1). Of the 798 participants at baseline, 579 (72.6%) completed follow up at 15 years while 68 (8.5%) had died, and 151 (18.9%) were lost to follow up. There was a total of 8,334 person-years of follow up and 90 cataract surgeries in 579 individuals for an overall rate of 1.08 cataract surgeries per 100 person-years (95%CI 0.87 to 1.32).

Characteristics of participants enrolled at baseline (i.e., the cross-sectional sample) as well as those participating in the 15-year study visit (i.e., the longitudinal sample) are summarized in Table 1. The mean age at baseline was 40.8 (SD 5.1) and the majority were female (N=489, 61.3%). Wood or kerosene cooking fuel was used by 711 (89.1%) participants in the cross-sectional sample and 539 (93.1%) participants in the longitudinal sample. The distribution of most baseline variables was similar between participants at baseline and 15-year follow up (Table 1 for person-level statistics and Supplemental Table 1 for eye-level statistics). Participants and non-participants of the 15-year study visit had similar baseline characteristics except non-participants were more likely to have been overweight, less likely to have been employed in agricultural work, and less likely to have been exposed to large amounts of sunlight. Non-participants were also more likely to have missing baseline data (Table 1).

Univariable cross-sectional associations between each variable and baseline cataract severity are shown in Supplemental Table 2, and the results of the adjusted model are shown in Table 2. After adjustment, there was little evidence of an association between cooking fuel and cataract ($p = 0.443$). Variables that were associated with cataract severity in the multivariable analysis included age, female sex, myopia, and BCVA worse than 20/20, each of which were associated with more severe cataract, and higher SES which was associated with less severe cataract ($p < 0.001$ for each, Table 2). Results of the person-level sensitivity analysis to predict cataract severity in the worse eye were largely the same except that sunlight exposure and BMI were more strongly associated with cataract severity (Supplemental Table 4).

Results of the univariable Cox models exploring associations between baseline factors and subsequent self-reported cataract surgery are summarized in Supplemental Table 3 and results from adjusted models in Table 3. Individuals reporting use of wood cooking fuel at baseline had a higher rate of subsequent cataract surgery compared with propane-users (HR 2.0, 95%CI 0.3 to 11.1), as did kerosene-users (HR 3.8, 95%CI 0.8 to 19.0)—a weak association that did not approach statistical significance when assessing for differences between the three groups separately ($p = 0.154$) or when comparing the wood and kerosene groups versus the propane group ($p = 0.142$). Age was strongly associated with higher rates of cataract surgery (HR 1.2, 95%CI 1.1 to 1.2); myopia (HR 2.1, 95%CI 1.2 to 3.5) and female sex (HR 3.5, 95%CI 1.2 to 10.1) had weaker associations that did not meet the predetermined level of statistical significance. The results of the sensitivity analyses including only those with complete follow up led to similar results (Table 4).

Discussion.

The present study failed to find a significant association between exposure to unclean cooking fuel and the severity of nuclear, cortical, or PSC cataract or cataract surgery over 15 years. In a multivariable analysis of cross-sectional data, cataract severity was associated with age, myopia, BCVA worse than 20/20, female sex and low SES. In a multivariable analysis of longitudinal data, incident cataract surgery was associated with increasing age and had weaker non-significant associations with myopia and female sex.

The results from the present study add to the conflicting body of literature regarding the effects of cooking fuel on cataract. Several case control and cross-sectional studies have found increased odds of cataract,[11] although many of these did not adjust for confounders and lacked information on case selection.[8-10,12] More recent studies have addressed some of the methodological concerns. Ravilla and colleagues found that lifetime years of biomass cooking fuel use were associated with increased odds of nuclear cataract in women, but not men, in an Indian population that primarily used non-ventilated cook-stoves.[11] Pokhrel's case-control study found that use of an unventilated solid fuel stove was associated with higher odds of cataract while use of a ventilated stove was not.[8] Krishnaiah found no increased odds of cataract among individuals using unclean fuels (e.g., wood, leaves, or cow dung) after adjustment for extensive confounders and risk factors in the Andhra Pradesh Eye Disease Study.[27] A large, six-country study found a strong association between solid fuels and kerosene and cataract in India and China but not in other countries; however, the study did not adjust for confounders such as sun exposure.[28] No longitudinal studies of cooking fuel exposure and cataract risk have yet been published to the knowledge of the authors. Our point estimates for the longitudinal analysis are consistent with the hypothesis that unclean cooking fuels such as kerosene and wood increase the risk of cataract (i.e., higher rates of cataract surgery for wood and kerosene, and lower rates for propane); however, the confidence intervals were wide, and the association was not statistically significant. It is possible that factors interacting with cooking fuel (e.g., amount of kitchen ventilation, which can influence concentration of combustion products) could be important for cataract formation, but also possible that cooking fuel is not a risk factor for cataract severity or surgery.

The prevalence of baseline opacities was similar to that of individuals aged 40-49 in another study conducted in the same region of India.[15] As has been reported in numerous other studies, age was strongly associated with nuclear, cortical, and PSC cataract severity and cataract surgery over 15 years.[29-32] Female sex was associated with more severe nuclear and cortical cataract, in agreement with previous studies,[27,30,33] including a 2004 study conducted in the same study area.[15] Females also had a higher rate of cataract surgery than men, in contrast with what has been reported elsewhere;[33] however, this association was weak. Being in charge of cooking—a task typically done by women in this part of India—was also associated with less severe cataract in the cross-sectional analyses, although not in the longitudinal analyses. The relationship between sex and cataract is likely complex and may depend on numerous other risk factors, such as whether those in charge of cooking are using ventilated stoves.[8]

Sun exposure was associated with more severe nuclear cataract in the cross-sectional analysis, in line with previous studies;[34] however, the p-value for this association did not meet the predetermined threshold for significance. Sun exposure was not associated with the rate of cataract surgery over 15 years, in contrast to a 2018 cohort study which found higher rates of cataract surgery in the highest quintile of sunlight exposure.[35] This discrepancy may be explained by measurement error as sunlight exposure was assessed through self-response, did not take protective gear or meteorological data into account,[36] and was assumed to be constant for the 15 years of follow up.

Snuff or betel use was not associated with more severe cataract at baseline, but individuals who reported high use had a higher rate of cataract surgery over 15-years (HR 1.9, 95%CI 1.0 to 3.4). These findings are consistent with a cross-sectional study that found an increased odds of cataract in smokeless tobacco users after adjusting for age and sex.[37] The association between smoking and subsequent cataract has not been consistent in prior reports.[38,39] In the present study, smoking was not a significant risk factor for subsequent cataract surgery. The study did not stratify analyses on type of tobacco, but it is worth noting that the smaller cigarettes (i.e., beedis) widely used in India have a lower daily inhalation dose compared to cigarettes and have not been associated with cataract in other cross sectional analyses.[27]

In line with previous studies, myopes had more severe nuclear cataracts in cross-sectional analysis.[40-42] The cross-sectional relationship may be due to nuclear sclerosis causing a myopic shift, but it is less clear whether myopia itself is a risk factor for subsequent cataract progression.[41,42] In the present study, myopes had increased rates of cataract surgery in the longitudinal analysis, though results did not reach predetermined statistical significance.

The present study's main novelty is its longitudinal analysis of cooking fuel as a risk factor for cataract. Strengths of the study are its inclusion of a broad set of risk factors, analysis stratified by cataract type, and evaluation of risk factors over a long follow-up period. The study also has limitations. Cataract surgery was self-reported, which could have resulted in misclassification, although this would be expected to be non-differential and bias the effect towards the null. It was not logistically or financially feasible to verify self-reported surgery or assess pre-operative cataract severity from medical records. Cooking fuel exposure ascertainment did not include data about combinations of fuels, daily number of meals cooked, length of time spent near the stove, ventilation of the stove or in the home, and other sources of indoor air pollution, which could have led to measurement error and information bias. Moreover, baseline cooking fuel exposure did not account for change in use over time.[11] This would likely have biased the estimated effect of cooking fuel on cataract surgery towards the null, since economic development over 15 years would likely have led to cleaner fuel sources among all participants, reducing differences in exposure. The generalizability of the study results to areas outside South India is uncertain, given potential differences in cooking fuel practices and other risk factors. The generalizability of the results even to similar areas of South India should be viewed with caution since the cohort met relatively strict criteria for participation in the clinical trial.

In conclusion, this study did not find strong evidence that unclean cooking fuel was related to cataract severity or need for cataract surgery over 15 years in this South Indian population. Our study confirmed several risk factors for cataract, strengthening confidence in the data. Future studies of this relationship should employ comprehensive questionnaires to determine years exposed to cooking fuel, other indoor pollutants, and ventilation and periodic follow up to generate time-updated exposure variables. Alternatively, the use of personal monitors or more complex statistical methods could be employed to more accurately measure exposure to products of biomass fuel combustion, as has been reported elsewhere.[43]

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Tables and Figures Captions.

Table 1. Characteristics of the study population at baseline. Data shown for total trial population and stratified by those who completed a 15-year follow-up visit versus those who were lost to follow-up (LTFU) or died.

Table 2. Results of eye-level multivariable multivariate regression model exploring the association between cook fuel exposure and cataract severity. Cross-sectional baseline data was modeled for 1,454 eyes with complete data; the model was adjusted for all the variables listed in the table. Clustering of eye-level variables within the same individual was accounted for using a generalized least squares model.

Table 3. Results of multivariable, person-level Cox models exploring the association between cooking fuel exposure and cataract surgery over 15 years. The estimates presented are hazard ratios for cataract surgery in either eye over 15 years of follow up and include 729 people with complete data at baseline.

Table 4. Results of multivariable person-level sensitivity Cox model exploring the association between cooking fuel exposure and cataract surgery over 15 years. The estimates presented are hazard

ratios for cataract surgery in either eye over 15 years of follow up and include 545 people with complete data at follow up.