Distribution Agreement

Signature:

______________________________________ ____________________

Beau Benjamin Bruce, M.D., M.S. Date

Implementation and Utility of Non-mydriatic Fundus Photography in the Emergency Department

By

Beau Benjamin Bruce, M.D., M.S.
Doctor of Philosophy

Epidemiology

Carolyn D. Drews-Botsch, Ph.D.
Advisor

Mitchel Klein, Ph.D.
Committee Member

William M. McClellan, M.D., M.P.H.
Committee Member

David W. Wright, M.D.
Committee Member

Accepted:

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

Date

Implementation and Utility of Non-mydriatic Fundus Photography in the Emergency Department

By

Beau Benjamin Bruce
B.S., Georgia Institute of Technology, 1998
M.D., Emory University, 2002
M.S., Emory University, 2010

Advisor: Carolyn D. Drews-Botsch, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Epidemiology
2014

Abstract

Implementation and Utility of Non-mydriatic Fundus Photography in the Emergency Department
By Beau Benjamin Bruce

Background

Non-mydriatic ocular fundus photography provides a way to easily and rapidly examine the ocular fundus without pharmacologic pupil dilation. The candidate developed a novel line of research using fundus photography to screen for ocular fundus abnormalities in the emergency department (ED): the Fundus photography vs. Ophthalmoscopy Trial Outcomes in the Emergency Department (FOTO-ED) study.

Objectives

The goal of this dissertation was to assess factors associated with the implementation and utility of fundus photography in the ED. Our objectives were to evaluate (1) whether the reason the patient came to the ED influences (a) if the patient's ocular fundus was examined and (b) if the ED physician considered the photographs helpful, (2) whether patient characteristics influence if a photograph will be misread, and (3) whether an abnormal photograph predicts return ED visits, hospital admission, and mortality.

Methods

Using the 704 patients enrolled in the FOTO-ED study, we employed a variety of epidemiological methods including logistic regression and time-to-event regression (Cox proportional hazards model, including extensions, and recurrent event models).

Results

Men with neurological complaints (OR for men: 0.31; 95%CI:0.14–0.71 vs. women 0.68; 95%CI:0.38–1.23; p=0.08) and blacks with visual complaints were less likely to be examined (OR for blacks: 1.33; 95%CI:9.65–2.71 vs. patients of other/ unknown race: 3.02; 95%CI:1.48–6.13; p=0.08). Lower quality (OR:1.44 per quality unit; 95%CI:1.03–2.08; p=0.03) and older age (OR:1.03; 95%CI:1.00–1.05; p=0.02) were associated with a higher frequency of false positive errors and black race was associated with a higher frequency of false negative errors (OR:7.46; 95%CI:0.73–60.66; p=0.06). Abnormal photographs were associated with a significantly higher rate of hospital admission (HR:1.94; 95%CI:1.27–2.96; p=0.002) and of death from any cause (HR:4.10; 95%CI:1.51–12.42; p<0.01) controlling for age, race, sex, mean arterial pressure, and body mass index, but not with ED revisit.

Conclusions

Disparities in examination frequency were seen in this high-risk population based upon complaint, age, and race. The simplicity of obtaining non-mydriatic fundus photography and its association with a higher rate of hospital admission and death suggests it may represent a "sixth vital sign." Our findings require validation and further exploration in a larger population.

Implementation and Utility of Non-mydriatic Fundus Photography in the Emergency Department

By

Beau Benjamin Bruce
B.S., Georgia Institute of Technology, 1998
M.D., Emory University, 2002
M.S., Emory University, 2010

Advisor: Carolyn D. Drews-Botsch, Ph.D.

A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Epidemiology
2014

Acknowledgements

I would like to express my deepest gratitude to Drs. Nancy J. Newman and Valérie Biousse, my mentors and neuro-ophthalmology colleagues, for their consistent and enthusiastic support of all my academic endeavors. I would also like to thank my dissertation committee for their guidance, especially Dr. Mitchel Klein, whose passion for and knowledge of epidemiology kindled my zeal for the field. I would like to thank everyone who has been involved in FOTO-ED and its related research projects (in chronological order) because none of this would have been possible without you: Nancy J. Newman, Valérie Biousse, David W. Wright, Katherine L. Heilpern, Antoinette Ward, Lee Economy, Cédric Lamirel, Amanda D. Henderson, Daniela Toffoli, Kevin P. Delaney, Matthew T. Keady, Mario A. Pérez, Linda P. Kelly, Praneetha Thulasi, Clare L. Fraser, Emily B. Graubart, Philip S. Garza, Carolyn D. Drews-Botsch, Mitchel Klein, William M. McClellan, Laurel N. Vuong, Samuel S. Bidot, and Rabih Hage. I would also like to thank all the nurse practitioners, nurses, staff, and physicians in the Emory University Emergency Department for their enthusiastic support.

I sincerely appreciate the financial support of the National Institutes of Health's National Eye Institute (K23-EY019341), Atlanta Clinical & Translational Science Institute, Knights Templar Eye Foundation, Research to Prevent Blindness, Emory University's University Research Committee and Courtesy Scholarship, and the American Academy of Neurology Foundation that made this degree and research possible. Finally, I cannot thank my parents, sister, and wife enough for all the sacrifices they have made that have sustained me throughout my lifelong pursuit of knowledge.

Table of Contents

List of Tables

List of Figures

Chapter 1
Background & Aims

1.1 Introduction

When the direct ophthalmoscope was invented in the mid-1800s, it transformed medicine by providing physicians with a way to examine the posterior pole of the ocular fundus. While the posterior pole only measures about one square centimeter, this region is not only affected by countless vision-threatening diseases, but by numerous general medical and neurologic conditions, many with potentially life-threatening consequences. Furthermore, there is no other place on the human body where either a part of the central nervous system or its microvasculature can be directly visualized noninvasively.

Recent developments in non-mydriatic ocular fundus photography have provided an alternative way to easily and rapidly examine the posterior pole without the need for pharmacologic dilation of the pupils. The candidate has developed a novel line of research regarding the diagnostic characteristics of this technology when used in the emergency department (ED) for the screening of ocular findings among patients with primarily non-ophthalmic complaints, the Fundus photography vs. Ophthalmoscopy Trial Outcomes in the Emergency Department (FOTO-ED) study.

The goal of this dissertation is to extend the candidate's research in this field by further assessing factors associated with the implementation and utility of fundus photography in the ED with comparison, where appropriate to direct ophthalmoscopy.

1.2 Background*

1.2.1 Examination of the ocular fundus: important, but neglected

Ophthalmoscopy is a key element of the physical examination. Despite the rapid progress that has been made in various diagnostic medical technologies (e.g., neuroimaging), visualization of the ocular fundus is often the only diagnostic clue to the identification of potentially serious ophthalmic and neuro-ophthalmic diseases. Examination of the fundus is necessary for the diagnosis of various disorders causing acute visual loss that require urgent management (e.g., retinal detachment), the detection of warning signs of impending visual loss and potentially catastrophic neurologic complications (e.g., papilledema, central retinal artery occlusion, anterior ischemic optic neuropathy), and to determine the severity of certain medical conditions (e.g., hypertensive crisis).

Fundus examination should be routine in the detection of vision- and life-threatening signs in patients presenting with headache, focal neurologic deficits, and severely elevated blood pressure and in the evaluation of patients with acute visual changes. Indeed, several life-threatening intracranial disorders, such as intracranial mass, cerebrospinal fluid shunt malfunction, hydrocephalus, meningitis, and cerebral vein thrombosis often present to the ED with headache and associated papilledema,[1,2] which in the absence of ophthalmoscopic examination will go undetected. As an example consider idiopathic intracranial hypertension (IIH), a condition that affects primarily young, obese women and which leads to permanent severe visual loss in up to 10% of cases.[3,4] Headache is the most common presenting symptom in IIH (occurring

* Portions of this section adapted from Bruce BB. Evaluation of mean arterial pressure as a risk factor for missed ophthalmoscopic findings in the emergency department. Master's Thesis, Emory University, 2010.

in over 90% of cases) and the visual loss is typically insidious with patients often becoming severely visually impaired from papilledema before recognizing visual changes.[1,5]

1.2.2 Why focus on the emergency department setting?

Many of these neuro-ophthalmic disorders cannot be easily diagnosed by routine neuroimaging studies and thus require vigilant ED care, including ophthalmoscopic examination. Therefore, failure to correctly examine the ocular fundus in the ED can not only place patients at risk for poor outcomes but expose their caregivers to medicolegal liability.[6] However, examination of the ocular fundus is not consistently performed in patients presenting with these complaints and conditions. For example, two studies of headache management in the ED found documentation of ophthalmoscopy in only 37–48% of cases.[7,8] This disturbingly low frequency of fundus examination may even be an overestimate of their typical performance due to the Hawthorne effect, assuming that the ED physicians knew they were being observed as part of a study. The under-utilization of ophthalmoscopy is likely due to several factors:

1. limited training in use of the ophthalmoscope,[9,10]
2. reluctance to perform pharmacologic pupillary dilation in the ED,
3. limited experience in recognizing important ophthalmoscopic findings, and [10–12]
4. increasing demands on physicians' time.

In addition, lack of adequate specialty care in the ED is an increasingly important healthcare problem in the United States,[13] and poor access to ophthalmologic specialty care in the ED is especially concerning.[14] Although the problem is greater in rural areas, even in urban areas there are significant delays in obtaining emergency ophthalmologic consultations.[15] These issues pose major roadblocks to the acute management of devastating ocular vascular diseases such as central retinal artery occlusion and giant cell arteritis. Because ophthalmology is primarily a specialty where pathology is visible, telemedicine using ocular fundus photography may provide part of the solution to the triage of these patients for further consultation and evaluation. Indeed, many ophthalmologists cover multiple sites while on call. By allowing an on-call ophthalmologist the ability to "examine" the patient without traveling to these various sites, ophthalmic telemedicine can lead to better distribution of limited eye care resources.

Numerous projects, such as Orbis International's Cyber-Sight project, have demonstrated the ability to perform Internet tele-ophthalmologic consultations among local, national, and international physicians and surgeons.[16,17] As of February 2014, over 8,000 consults had been performed using ORBIS's telemedicine program.[18] Although telemedicine has been explored in an ophthalmic ED as a means for resident physicians to consult with their senior physicians overnight,[19] it had not, to our knowledge, been applied to patient care in a large, general ED prior to the FOTO-ED study.

1.2.3 Why use non-mydriatic ocular fundus photography?

The use of non-mydriatic ocular fundus photography overcomes many barriers to an adequate ophthalmoscopic examination in the ED because many physicians are reluctant to perform routine dilation of patients for ophthalmoscopic examination, pupillary dilation takes up to 30 minutes, and most patients prefer not to have their pupils dilated.[12] In addition, neurologic patients represent a unique population in which pupillary reflexes can be critical for monitoring clinical status. Thus, the undilated views of the ocular fundus provided by non-mydriatic ocular fundus photography were expected to be useful in overcoming important obstacles to appropriate patient examination.

From a practical standpoint, we proposed that non-physician staff (e.g., trained nurses, technicians) could obtain clinically useful ocular fundus photography, thus reducing burdens on limited physician time. Digital color photographs can be inserted immediately into the chart or in the electronic medical record, and thus be available to the ED physician during the examination. Several prior studies used ocular fundus photography in population-based studies of vascular disease and to perform systematic screening for diabetic retinopathy in primary care settings and for retinopathy of prematurity in neonatal intensive care units.[20–27] In these studies, trained technicians took photographs of the posterior pole of the eye (which includes the optic nerve, the macula, and the major retinal vessels), often through undilated pupils, showing that it is feasible for non-physician staff to obtain adequate photographs.[28]

Several studies have shown high agreement between dilated ocular fundus examinations by an ophthalmologist and ocular fundus photography for identifying diabetic retinopathy and other ocular conditions that involve the posterior pole of the eye (optic nerve and macula).[29,30] The cost of a non-dilated fundus camera is relatively low and studies have demonstrated its cost effectiveness in screening for diabetic retinopathy.[31] These results were particularly relevant to the FOTO-ED study which aimed primarily to diagnose less subtle ocular findings than early diabetic retinopathy, such as papilledema, and for which the medical morbidities without treatment are often devastating.

Although the provision of adequate fundus photographs alone does not guarantee better recognition of important findings, one small study had previously suggested that internal medicine physicians were considerably better at accurately diagnosing important ocular conditions on photographs compared to examining patients with a direct ophthalmoscope: 71% of the 14 physicians correctly identified papilledema with a ocular fundus photograph while only 21% were able to do so with the direct ophthalmoscope.[12] Furthermore, it is easier to educate

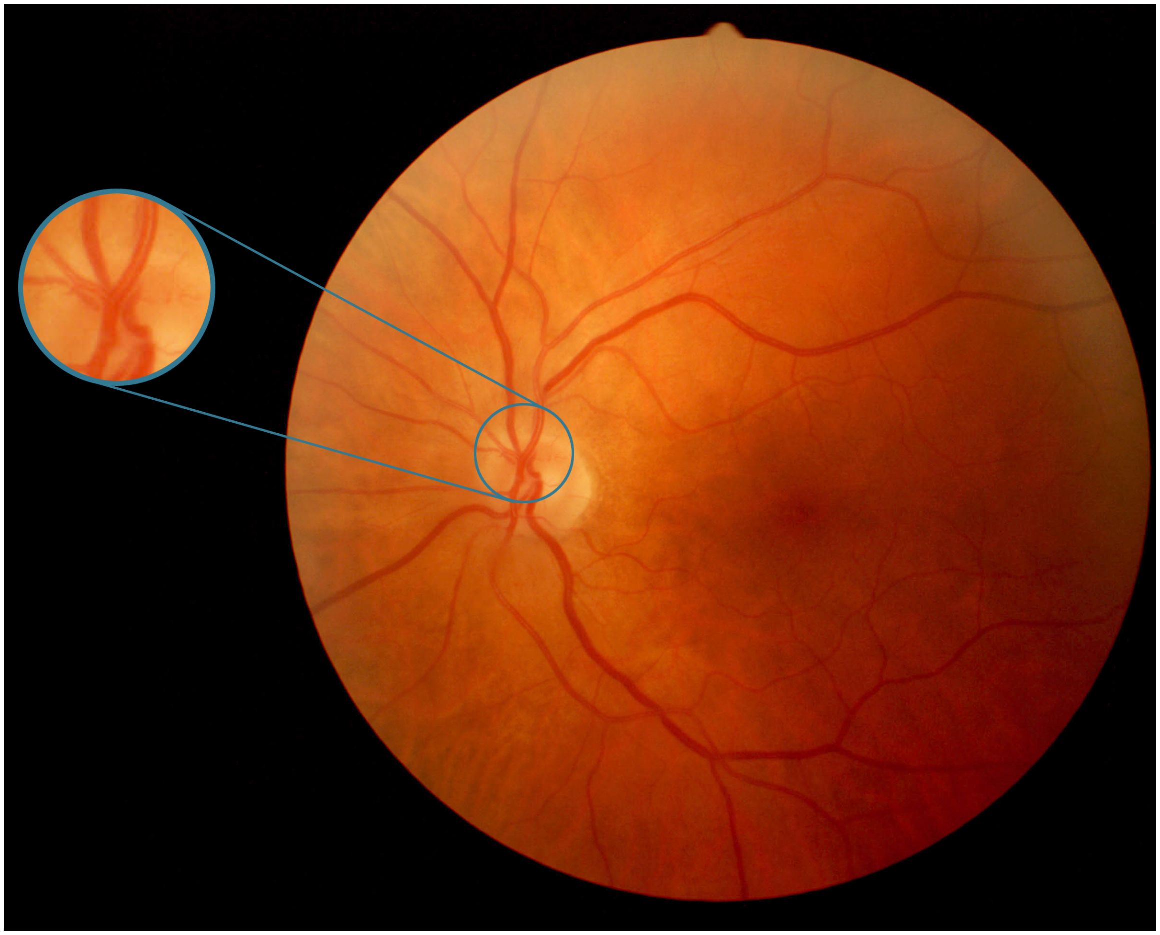


FIGURE 1.1 Comparison of the single field of view for conventional direct ophthalmoscopy (enlarged inset) and non-mydriatic fundus photography (large photo). The most commonly used conventional direct ophthalmoscope only shows part of the optic disc and requires active exploration of the fundus by the examiner, whereas a photograph taken with a non-mydriatic fundus camera allows visualization of the entire posterior pole of the ocular fundus, including the optic nerve, the macula, and the major retinal vessels. From *Academic Emergency Medicine*. Bruce BB, Lamirel C, Biousse V, Ward A, Heilpern KL, Newman NJ, Wright DW. Feasibility of nonmydriatic ocular fundus photography in the emergency department: phase I of the FOTO-ED study. 18:929. Copyright © 2011 Society for Academic Emergency Medicine. Reprinted with permission. Full article available at http://dx.doi.org/10.1111/j.1553-2712.2011.01147.x.

physicians to recognize fundus abnormalities on photographs because the ocular fundus photographs provide a wider field of view than direct ophthalmoscopy and remove the obstacle of simultaneously learning the technical skill of direct ophthalmoscopy (Figure 1.1).

Finally, not only does ocular fundus photography remove the majority of technical barriers to the ophthalmoscopic examination by the ED physician, it has the potential to facilitate consultation with specialty physicians, even those located a great distance away, when interpretation difficulties arise.[32,33] Furthermore, because immediate access to an ophthalmologist is often limited, telemedicine may provide a unique opportunity to provide these specialized services to a broader population of patients in a more timely fashion.

1.3 General Methods of the FOTO-ED Study

Based on our observations, the FOTO-ED study was developed as an interdisciplinary project between neuro-ophthalmology and emergency medicine in order to improve ophthalmologic care in the ED by evaluating whether non-mydriatic fundus photography was a better alternative to direct ophthalmoscopy.

The FOTO-ED study was conducted between April 2009 and August 2011 (clinicaltrials.gov: NCT00873613) and was approved by the Emory University Institutional Review Board. The study was conducted in 2 phases. The first phase evaluated the routine clinical use of direct ophthalmoscopy by ED physicians, whereas the second phase evaluated the routine use of non-mydriatic ocular fundus photography as interpreted by the ED physicians. In both phases, all patients had non-mydriatic ocular fundus photographs obtained.

The inclusion criteria for the FOTO-ED study were adult patients presenting to the ED with a presenting complaint or condition of one or more of the following: headaches, focal neurologic deficits, diastolic blood pressure (DBP) $\geq$120 mmHg, and acute visual changes. The presenting complaints were elicited from the patients in the usual fashion and entered into the electronic medical record (EMR) by the triage staff. Patients were excluded if they were unable to sit up, refused to participate, had altered mental status or were otherwise unable to consent, or were too ill to participate in the study. Nurse practitioners were available to photograph patients from 7 am to 10 pm daily during the first phase and a medical student was similarly available from 8 am to 6 pm on weekdays during the second phase. Patients who presented to the ED outside of these hours could be included if they were still present in the ED during these hours. Additionally, several randomly chosen night and weekend shifts were included during the second phase.

Patients were identified as potentially eligible for enrollment based on the symptoms entered into the EMR at triage. During the first phase, this required active surveillance of the triage log by a study team member, but after the first phase, patients were automatically flagged for consideration for fundus photography by the EMR when their presenting complaint was entered. Active surveillance of the ED's census by study staff identified potentially eligible patients who did not trigger the automated process. Additionally, the log of patients who triggered screening was reviewed for patients who were inadvertently not included.

Patient demographics, including age, gender, race, presenting vital signs, height, and weight, were prospectively collected in the ED. Photographs of the posterior pole of the ocular fundus (optic disc, macula, and major retinal vessels) were obtained from both eyes of enrolled patients at presentation by trained nurse practitioners or a medical student using a commercially available, Food and Drug Administration–approved, non-mydriatic ocular fundus camera (Kowa nonmyd-α-D series cameras; Kowa Optimed, Inc., Torrance, CA).

The images were automatically electronically transferred to a Health Insurance Portability and Accountability Act-compliant database for review by 2 neuro-ophthalmologists who were masked to all patient data, including presenting complaint. These reviewers rated the images for the presence or absence of relevant ocular fundus abnormalities using a standardized case report form. In any case in which there remained diagnostic uncertainty, a third neuro-ophthalmologist made the determination of whether an abnormality was present or absent, masked to patient data but aware of the finding disagreed on by the other 2 reviewers. If the reviewers could not reach a consensus about whether or not an abnormality was present or not, an in-office examination was arranged. This occurred in 10 cases (1.3%) because the potential abnormality was, if even present, extremely mild. In all of these cases, none of the pontential abnormalities were ultimately deemed pathologic. Of note, additional fundus examination alone did not settle suspicion regarding whether an abnormality was present or not. Instead, a combination of history, other physical examination findings, and observation were necessary and sufficient to exclude pathology.

Throughout the FOTO-ED study relevant ocular fundus abnormalities were defined as optic disc edema, isolated intraocular hemorrhage, grade IV hypertensive retinopathy, retinal vascular occlusion, and optic disc pallor (Figure 1.2).

1.4 Clinical Results of Phase I of the FOTO-ED Study

In the first phase of the FOTO-ED study,[34,35] 350 adult patients were enrolled. Since this phase relied on active surveillance of the patient census by nurse practitioners during their regular clinical care shifts, the number of missed and ineligible patients were not recorded. A review of the ED census logs found 1944 patients with potentially eligible complaints/conditions. Therefore, at least 18% of the eligible patients seen during the period over which Phase I was conducted were enrolled, but this is a lower bound because eligibility cannot be assessed from the census log alone. The median age was 44.5 years (interquartile range [IQR] 31–59 years), and 220 (63%) were women. The presenting complaints and conditions were headache in 228 (65%), acute focal neurologic deficit in 100 (29%), acute visual change in 92 (26%), DBP $\geq$ 120 mm Hg in 21 (6%). Patients could have more than one presenting complaint or condition. The performance of ED physicians and the findings on direct ophthalmoscopy were prospectively recorded, with the physicians unaware of the photography results.

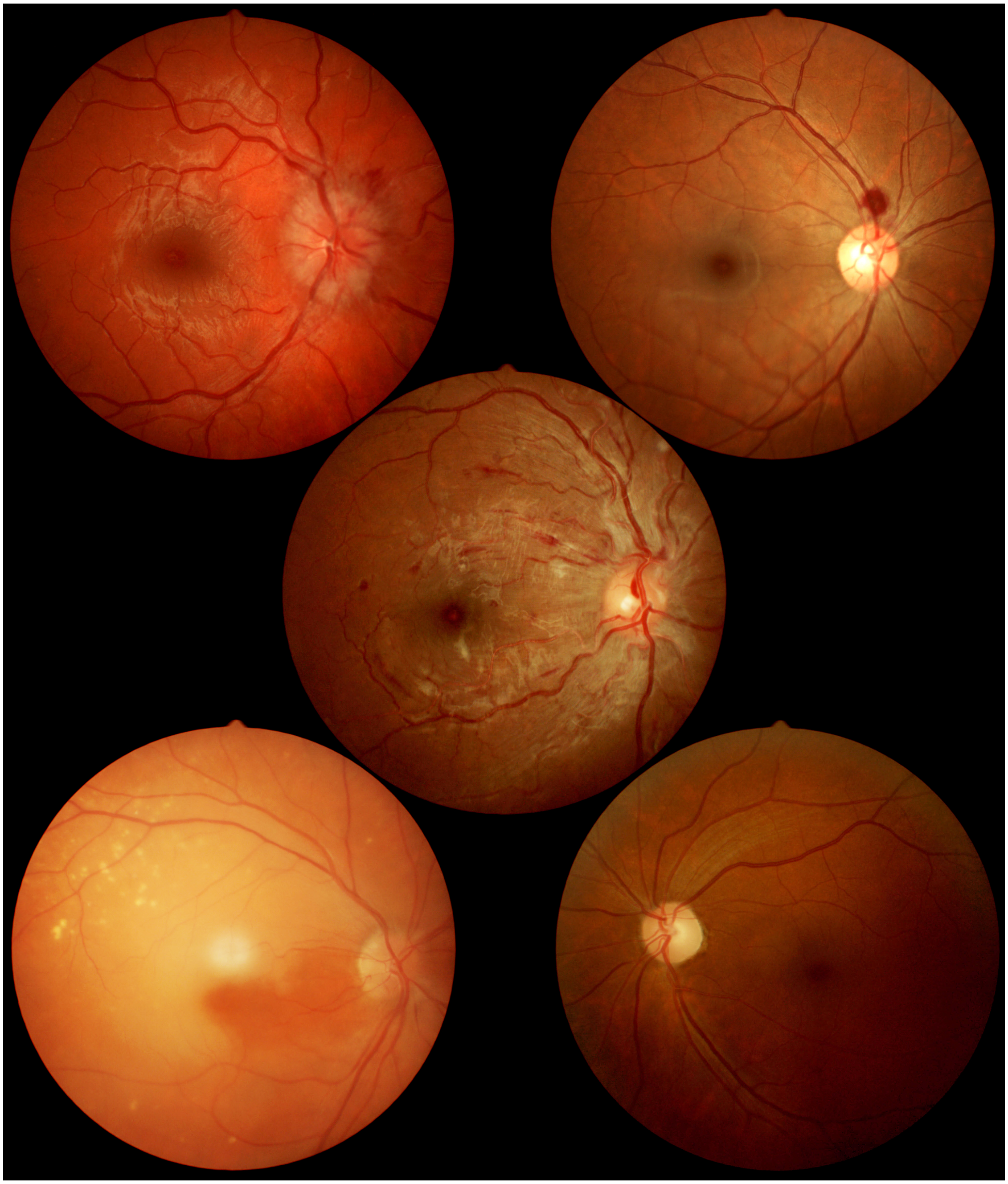


FIGURE 1.2 Examples of non-mydriatic fundus photographs obtained during the FOTO-ED study. Top left: Optic nerve edema from intracranial hypertension. Top right: Intraocular hemorrhage. Center: Grade IV hypertensive retinopathy with optic nerve edema, arterial attenuation, and retinal hemorrhages. Bottom left: Acute retinal ischemia from central retinal artery occlusion. Bottom right: Optic nerve pallor. The black backgrounds of the original images were cropped and the brightness/contrast was adjusted. From *The New England Journal of Medicine*. Bruce BB, Lamirel C, Wright DW, Ward A, Heilpern KL, Biousse V, Newman NJ. Nonmydriatic ocular fundus photography in the emergency department. 364:387. Copyright © 2011 Massachusetts Medical Society. Reprinted with permission. Full article available at http://dx.doi.org/10.1056/NEJMc1009733.

During routine evaluation, ophthalmoscopy was performed by an ED physician for only 48 of the 350 patients (14%; 95% confidence interval [CI]: 10–18%). In 44 enrolled patients, relevant ocular findings (13%; 95% CI: 9–17%) were identified with the use of non-mydriatic fundus photography: 13 cases of optic nerve edema, 13 cases of intraocular hemorrhages, 10 cases of hypertensive retinopathy (grade 3 or 4), 4 cases of arterial vascular occlusion, and 4 cases of optic nerve pallor. Eleven of the findings were known before patients presented to the ED. Of the remaining 33 relevant findings, 6 were identified on ophthalmologic consultation to the ED and 27 solely by means of fundus photography (82%; 95% CI: 65–93%). In only 5 of these 33 patients was ophthalmoscopy performed by an ED physician; results were recorded as normal for all 5 patients. For each photography session the nurse practitioner rated the ease and speed of fundus photography and patients rated the ease, speed, and comfort of non-mydriatic photography on a 10-point Likert scale (10 best; Table 1.1). The quality of the photographs was of some diagnostic value for 97% of enrolled patients (i.e., greater than grade 1, see Figure 3.1). Median photography time was 1.9 minutes (IQR: 1.3–2.9).

TABLE 1.1 Summary of nurse practitioner ratings of ease and speed and patient ratings of ease, speed, and comfort on a 10-point (10 best) Likert scale.

	Mean	**SD**	**% rating = 10**	**% rating ≥ 7**
Nurse practitioners				
Ease	8.7	1.9	55	85
Speed	8.9	1.8	56	86
Patients				
Ease	9.3	1.6	72	92
Speed	9.2	1.6	67	90
Comfort	8.8	1.8	54	87

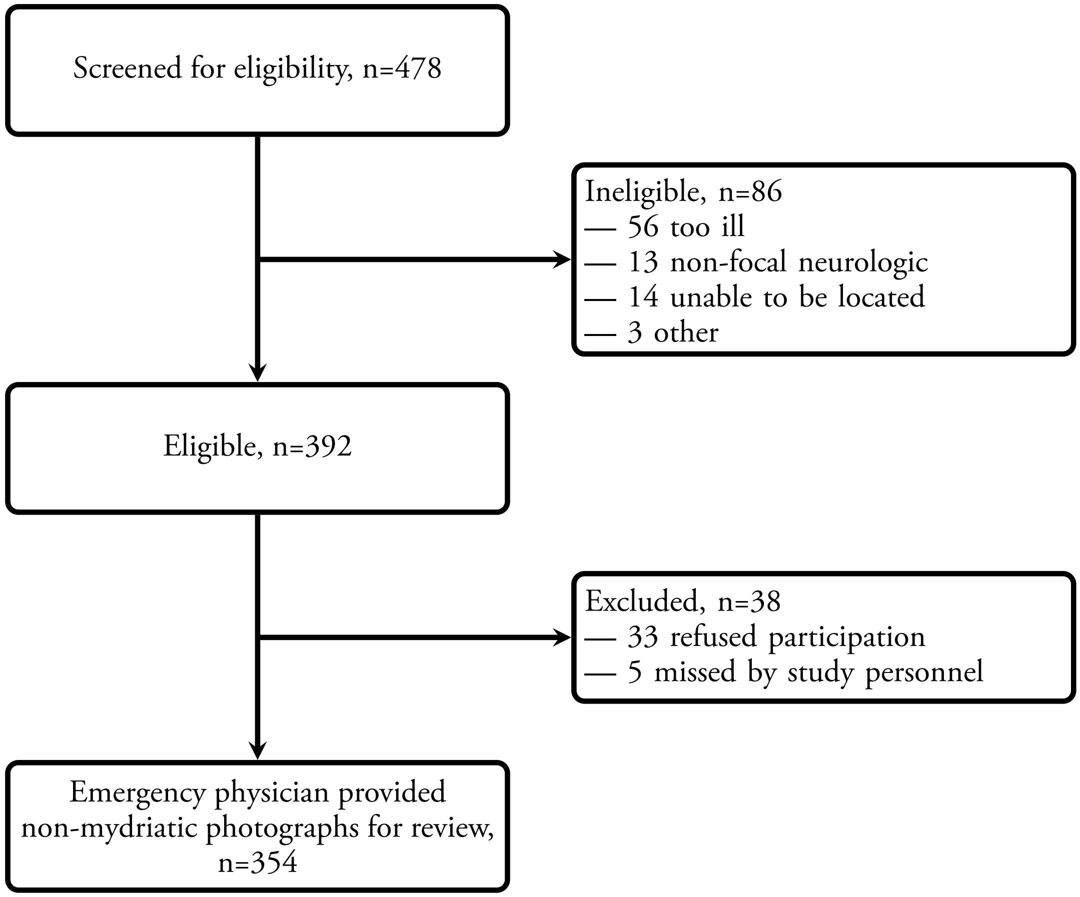


FIGURE 1.3 Patient screening and enrollment in phase II of the FOTO-ED study.

1.5 Clinical Results of Phase II of the FOTO-ED Study

Among 478 patients screened for eligibility, 354 were enrolled in phase II of the FOTO-ED study (Figure 1.3).[36] Eighty-six patients were ineligible (56 too ill, 13 non-focal neurologic complaints, 14 unable to be located, 3 other reasons), and 33 patients refused participation. Using the EMR automated screening process, 345 of the enrolled subjects (97%) were identified, with the remainder identified by active surveillance by study personnel. Five eligible patients (3 headache, 2 focal neurologic) who triggered the automated process were missed by study staff.

The median age was 45.9 years (IQR: 33–57) and 251 (71%) were women. Two hundred six patients (58%) had headache, 123 (35%) had focal neurologic symptoms, 56 (16%) had acute visual changes, and 21 (6%) had DBP ≥ 120 mm Hg (patients were allowed to have more than 1 presenting complaint). Thirty-five patients (10%; 95% CI: 7%–13%) had relevant findings identified by neuro-ophthalmologist review of the photographs, including 6 patients with disc edema, 6 with grade III/IV hypertensive retinopathy, 7 with isolated intraocular hemorrhages, 15 with optic disc pallor, and 1 with a retinal vascular occlusion. Among the 354 enrolled patients, the ED physicians reviewed the photographs of 239 patients (68%) and reported that the photographs were helpful in their evaluation of 125 patients (35%; 95%CI: 30%–41%). The ED physicians identified 16 of the 35 relevant findings (46%) during their review of the fundus photographs.

We concluded that non-mydriatic fundus photographs were used by ED physicians more frequently than they performed direct ophthalmoscopy (Table 1.2), that their detection of relevant abnormalities improved, and that ocular fundus photography often assisted with ED care even when the photographs were normal.

TABLE 1.2 Comparison of FOTO-ED Phases I and II.

	Phase I	**Phase II**
ED examination method	direct ophthalmoscopy	non-mydriatic photography
Number of patients' fundi viewed by ED physician	48/350 (14%)	239/354 (68%)
Number of abnormalities detected by ED physician*	0/44 (0%)	16/35 (46%)

* Absolute difference: 46%; 95%CI: 29–62% (p<0.00001)

1.6 Dissertation Aims

The goal of this dissertation was to extend the candidate's research by further assessing factors associated with the implementation and utility of fundus photography in the ED with comparison, where appropriate, to direct ophthalmoscopy. We approached this overall goal by addressing the following specific aims:

- Assess patient factors associated with
  - whether ED physicians used ocular fundus photographs or performed direct ophthalmoscopy and
  - whether ED physicians reported that ocular fundus photographs were helpful.
- Determine patient and photographic quality factors associated with erroneous (false positives and false negative) readings by ED physicians.
- Determine if abnormal fundus photography is independently predictive of ED revisit, hospital admission, and death after considering other patient factors present at triage: e.g., age, sex, race, blood pressure, and presenting complaint/condition.

1.7 General Dissertation Methods

Additional data on patient ED revisits, admissions, and death were collected. Statistical analysis was performed using R: A language and environment for statistical computing (R Foundation for Statistical Computing, http://www.R-project.org). Medians and IQRs were reported for continuous data and percentages were reported for categorical data. Medians were compared using the Mann-Whitney U test and proportions were compared using χ^2 or Fisher exact tests, as appropriate. Two-tailed p values <0.05 were considered statistically significant. mean arterial pressure (MAP) was calculated for use as a modeling covariate according to the method of Razminia *et al.*:[37]

$$\text{DBP} + (0.33 + [0.0012 \times \text{heart rate}]) \times \text{pulse pressure}$$

.

While we recognize that MAP is collinear with the presenting condition of DBP$\geq$ 120 mmHg, there were only 42 (6%) patients with a DBP $\geq$ 120. This did not appear to cause modeling issues likely due to the low frequency of patients with severely elevated blood pressure and the higher amount of information provided by the continous variable, MAP, than our dichotomized inclusion criteria.

Model selection was performed using the method of Kleinbaum and Klein and confounding was evaluated using the 10% change in estimate rule unless otherwise specified.[38]

Non-linearity was accounted for by use of restricted cubic splines (also called natural splines) using the truncated power basis with five knots unless otherwise noted. Knots were equally spaced on the quantile scale with the outer quantiles of 0.05 and 0.95. Five knots were used based upon Harrell's recommendation of five knots for continuous variables where the sample size is $\geq$100.[39] Knot placements are found in Appendix C.

1.8 Description of Overall Cohort

The overall FOTO-ED cohort consisted of 704 patients. As discussed in Sections 1.4 & 1.5, the patients were enrolled in two phases: 350 (50%) in Phase I and 354 (50%) in Phase II. The median age in years of the cohort was 45.2 (IQR: 32.4–57.9). The race of the patients was 375 (53%) black, 276 (39%) white, 32 (5%) other, and 21 (3%) unknown. The patients were 471 (67%) women. There were 434 (62%) patients with a presenting complaint of headache, 224 (32%) with a presenting complaint of focal neurologic deficit, and 148 (21%) with a presenting complaint of a vision problem (patients were allowed to have more than one presenting complaint/condition). There were 42 (6%) patients with a DBP $\geq$ 120. Regarding the number of presenting complaints and conditions, 574 (82%) patients had one complaint, 116 (16%) two, and 14 (2%) three. There were 79 (11%) ocular fundus abnormalities per the neuro-ophthalmologist reading (i.e., the reference standard).

1.9 Risk of abnormality by patient characteristics

The risk of fundus abnormality based on neuro-ophthalmology review by presenting complaint/condition was 12 (29%) for elevated DBP, 29 (20%) for visual complaint, 38 (9%) for headache, and 18 (8%) for acute focal neurological deficits. There was no association between the number of complaints/conditions and the frequency of fundus abnormality: 61 (10.6%) of the 574 patients with one complaint, 18 (15.5%) of the 116 patients with two complaints, and 0 (0.0%) of the 14 patients with three complaints had abnormal photographs ($p = 0.13$).

Sex was unassociated with frequency of abnormality: 28 (12.0%) of men vs. 51 (10.8%) of women had abnormal photographs ($p = 0.64$). Black race was associated with a higher frequency of abnormal fundus findings (uncontrolled for other variables): 22 (6.7%) of patients of other or unknown race vs. 57 (15.2%) of patients of black race had abnormal photographs ($p < 0.01$). Age was not associated with a higher odds of abnormality (OR per 10 years: 1.00; 95%CI: 0.87–1.14; $p = 0.951$), but higher MAP (OR per 10 mmHg: 1.24; 95%CI: 1.11–1.37 ; $p < 0.001$) and higher BMI (OR per 5 kg/m^2: 1.18; 95%CI: 1.04–1.35; $p = 0.012$) were associated with a higher odds of abnormality.

Chapter 2
Patient Factors Associated with the Use and Perceived Helpfulness of Photographs

2.1 Introduction

Patient characteristics such as age, race, and gender can potentially influence how thoroughly a particular aspect of the physical examination is performed. In a study of 138 second-year medical students' skill assessments on standardized patients, it was found that women received higher scores than men when examining the chest of simulated patients who were women whereas there were no differences between the scores received by men and women students when the simulated patient was a man.[40] However, differences are seen not only on parts of the physical examination that are overtly gender-sensitive, but even on apparently gender-neutral aspects of the examination, such as the lymphatic examination.[41]

While examination of the ocular fundus is not particularly gender-sensitive, the use of the direct ophthalmoscope requires the examiner to get extremely close to the patient, approximately one inch from their face, which can lead to a substantial personal discomfort for both patient and physician.[42] In addition, whether or not a particular component of the physical examination is performed and the thoroughness with which it is performed is expected to vary with the patient's clinical problem and other aspects of the patient's history and physical examination, such as vital signs.[43]

In the first part of this chapter, we explore our hypothesis that the patient's presenting complaint or condition (e.g., headache) was associated with whether the patient's ocular fundus was examined by the ED physician. Because ocular fundus photographs remove the need for the examiner to invade the patient's personal space, we further hypothesized that any association between the patient's presenting complaint and examination would be potentially modified by the whether direct ophthalmoscopy or fundus photography was available.

In the second part of this chapter, we explore our hypothesis that that the patient's presenting complaint or condition was associated with whether the ED physicians reported that the ocular fundus photographs were helpful to the patient's care. In this part, we also examine the presence of ocular fundus abnormalities (determined by neuro-ophthalmologist review) as an effect modifier of this association.

2.2 Part 1: Is patient complaint associated with whether ED physicians examined the ocular fundus?

2.2.1 Methods

The entire cohort of 704 patients was analyzed in this part in order to evaluate whether patient complaint was associated with whether ED physicians examined the ocular fundus. Univariable analysis followed by multivariable logistic regression was the analysis used. For logistic regression modeling, the outcome of interest was whether the ED physician examined the ocular fundus using either direct ophthalmoscopy in the first phase of the study or fundus photography in the second phase. The main exposure of interest was patient complaint, and the main effect modifier of interest was examination technique (operationalized as the phase of the study). Other factors of interest included age, sex, MAP, and BMI. The model took the following general form:

$$\begin{aligned} \text{logit}(\text{P}(\text{exam}|x)) &= \text{complaint} \\ &\quad \pm \text{complaint} \times \text{phase} \end{aligned}$$

$$\pm \sum \text{other factors}$$

$$\pm \sum \text{interactions}$$

Phase (representing the examination technique: direct ophthalmoscopy in Phase I and fundus photography in Phase II), race (black vs. other or unknown race), and sex were coded as indicator variables. Complaint was coded as four indicator variables for each complaint: headache, acute focal neurologic deficit, visual changes, and DBP $\geq$ 120 mmHg. Age, MAP (mmHg), and BMI (kg/m^2) were coded as continuous variables. Non-linearity was accounted for by restricted cubic splines using the truncated power basis with five knots equally spaced on the quantile scale with the outer quantiles of 0.05 and 0.95. Knot placements are found in Appendix C. Non-linear terms were retained only when significant at the 0.05 level. Additional general methods are found in Section 1.7.

2.2.2 Results

The overall frequency of complaints among the 704 patients in the cohort was previously summarized in Section 1.8. There were no univariable associations between whether the patient was examined and any of the enrollment complaints or conditions (Table 2.1).

Considering phase, there was a significantly lower frequency of patients with visual complaints in the second phase (Table 2.2). Although the differences did not reach significance, there also appeared to be fewer patients with headache and more patients with focal neurologic deficits in the second phase compared with the first.

Only the patients with visual complaints were significantly more likely to be examined than patients without visual complaints even after controlling for phase (OR = 2.52; 95%CI:

TABLE 2.1 Univariable associations between whether the patient was examined and the enrollment complaints and conditions.

Complaint or condition	Number (%) examined by whether the complaint or condition was: Present		Absent		$\chi^2_{d.f.=1}$	p-value
Headache	174 / 434	(40.1)	113 / 270	(41.9)	0.21	0.64
Focal neurologic deficit	82 / 224	(36.6)	205 / 480	(42.7)	2.4	0.12
Visual complaint	67 / 148	(45.3)	220 / 556	(39.6)	1.6	0.21
DBP ≥ 120 mmHg	14 / 42	(33.3)	273 / 662	(41.2)	1.0	0.31

TABLE 2.2 Frequency of complaint by phase.

Complaint or condition	Phase I (n=350)		Phase II (n=354)		$\chi^2_{d.f.=1}$	p-value
Headache	228	(65.1)	206	(58.2)	3.6	0.06
Focal neurologic deficit	101	(28.9)	123	(34.7)	2.8	0.09
Visual complaint	92	(26.3)	56	(15.8)	11.6	<0.01
DBP ≥ 120 mmHg	21	(6.0)	21	(5.9)	0.00	0.97

In phase I, the ED physicians had access to direct ophthalmoscopy only.
In phase II, the ED physicians had access to fundus photography.

1.57–4.05) (Tables 2.3 & 2.4). There was a trend toward significance ($p = 0.073$) with respect to effect measure modification by phase for the ORcomparing examination for the complaint of headache vs. not (OR, phase I: 1.40; 95%CI: 0.75–2.61; OR, phase II: 0.69; 95%CI: 0.44–1.09; Table 2.4) which is consistent with the finding of a higher frequency of patients without headache than with headache being examined in the first phase vs. a higher frequency of patients with headache than without headache being examined in the second phase of the study (Table 2.3).

TABLE 2.3 Frequency of examination by complaint stratified by phase.

Complaint or condition	Number (%) examined by whether the complaint or condition was: Present		Absent	
Phase I - examination by direct ophthalmoscopy				
Headache	28 / 228	(12.3)	20 / 122	(16.4)
Focal neurologic deficit	9 / 101	(8.9)	39 / 249	(15.7)
Visual complaint	22 / 92	(23.9)	26 / 258	(10.1)
DBP ≥ 120 mmHg	2 / 21	(9.5)	46 / 329	(14.0)
Phase II - examination by review of fundus photographs				
Headache	146 / 206	(70.9)	93 / 148	(62.8)
Focal neurologic deficit	73 / 123	(59.3)	166 / 231	(71.9)
Visual complaint	45 / 56	(80.4)	194 / 298	(65.1)
DBP ≥ 120 mmHg	12 / 21	(57.1)	227 / 333	(68.2)

We considered age, sex, race, BMI, and MAP as both potential effect modifiers and confounders. All two way interactions between each of these variables and each of the complaints were considered simultaneously in a logistic regression model that retained the potential interaction between a complaint of headache and phase discussed above. Two interaction terms were significant at the 0.10 level in this model and both were retained following backward elimination at the 0.10 significance level: 1) between focal neurological complaint and sex ($p = 0.084$) and 2) between visual complaint and race ($p = 0.085$). The potential interaction between a complaint of headache and phase was not significant in this model ($p = 0.263$), and it was not considered further.

Confounding by phase, age, BMI, and MAP (the variables that were not part of interaction terms) was considered next. Phase could not be removed from the model due to substantial

TABLE 2.4 Odds ratios comparing ocular fundus examination vs. not by individual complaints/conditions with consideration for potential effect measure modification by phase (Phase I: direct ophthalmoscopy, Phase II: fundus photographs).

Complaint or condition	**Crude OR (95% CI)**	**OR, phase I (95% CI)**	**OR, phase II (95% CI)**	***p* for interaction**
Headache	0.93 (0.68–1.27)	0.71 (0.38–1.33)	1.44 (0.92–2.25)	0.07
Focal neurologic deficit	0.77 (0.56–1.07)	0.53 (0.25–1.13)	0.57 (0.36–0.91)	0.86
Visual complaint	1.26 (0.88–1.82)	2.80 (1.50–5.25)	2.19 (1.09–4.42)	0.61
DBP ≥ 120 mmHg	0.71 (0.37–1.38)	0.65 (0.15–2.87)	0.62 (0.25–1.52)	0.96

changes in the ORs for headache and visual complaints. Only severely elevated DBP appeared to be confounded (Table B.1) by at least some of the remaining variables, and all subsets showed that only the combination of age and MAP fully controlled for confounding (Table B.2). Body mass index was dropped from the final model (Tables 2.5 & 2.6). There was no evidence of a non-linear relationship for age or MAP in the model: $\chi^2_{\text{d.f}=6} = 11.5, p = 0.075$. Although neither of the interaction terms were significant individually, total interaction was significant ($\chi^2_{\text{d.f.}=2} = 6.677, p = 0.035$).

TABLE 2.5 Final multivariable logistic model for association between examination by ED physician and complaint/condition.

Variable	**Coefficient**	**Standard Error**	**Wald**	***p*-value**
Headache	−0.20	0.27	−0.7	0.47
Acute focal neurologic complaint (NEURO)	−1.17	0.42	−2.8	<0.01
Visual complaint (VISION)	1.10	0.36	3.1	<0.01
DBP ≥ 120 mmHg	−1.07	0.55	−1.9	0.05
Fundus photography (vs. direct ophthalmoscopy)	2.83	0.22	13.1	<0.01
Woman	−0.09	0.25	−0.4	0.72
Black race	0.24	0.22	1.1	0.27
Age, years	−0.01	0.01	−1.0	0.32
MAP, mmHg	0.01	0.01	1.3	0.20
NEURO × Woman	0.78	0.44	1.8	0.08
VISION × Black race	−0.82	0.47	−1.8	0.08

Intercept: -2.43
Overall model likelihood ratio test: $\chi^2_{d.f.=11} = 258, p = < 0.001$.
le Cessie-van Houwelingen-Copas-Hosmer unweighted sum of squares test for global goodness of fit: $p = 0.69$
Total interaction: $\chi^2_{d.f.=2} = 6.677, p = 0.035$
See Table 2.6 for related ORs and Table B.4 for related ANOVA table

TABLE 2.6 Odds ratios associated with final multivariable logistic model for association between examination by ED physician and complaint/condition.

Variable	OR	95% CI
Headache	1.22	(0.71–2.08)
DBP ≥ 120 mmHg	0.34	(0.12–1.02)
Fundus photography (vs. direct ophthalmoscopy)	16.97	(11.11–25.94)
Age, years	0.99	(0.98–1.01)
MAP, mmHg	1.01	(1.00–1.02)

Part A. Non-interacting effects

ORs (95%CIs)	Man	Woman
Focal neurologic complaint present	0.3 (0.1–0.7)	0.6 (0.3–1.2)
Focal neurologic complaint absent	1.0*	0.9 (0.6–1.5)

Part B. Interaction between focal neurological complaint and sex

ORs (95%CIs)	Other/unknown race	Black race
Visual complaint present	3.0 (1.5–6.1)	1.7 (0.8–3.5)
Visual complaint absent	1.0*	1.3 (0.8–1.9)

Part C. Interaction between visual complaint and race

*reference category

2.3 Part 2: Is patient complaint associated with whether ED physicians considered photographs helpful?

2.3.1 Methods

In this part the primary goal was to assess if patient complaint was associated with whether ED physicians considered photographs *helpful* considering abnormality (based on neuro-ophthalmology review) as an effect modifier. The subset of patients eligible for this part were the 239 (34%) patients who were examined in the second phase because ED physicians were only asked in this phase about the helpfulness of the photographs.

Univariable analysis followed by multivariable logistic regression was the analysis used. For logistic regression modeling, the outcome of interest was whether the ED physician the ocular fundus photography was helpful. The main exposure of interest was again patient complaint, and the main effect modifier of interest was whether the patient's photographs were abnormal per neuro-ophthalmology review. We also considered abnormality per ED physician review as an alternative to abnormality per neuro-ophthalmology review. Other factors of interest included age, sex, MAP, and BMI. The model took the following general form:

$$\begin{aligned}\text{logit}(\text{P}(\text{helpful}|x)) = {} & \text{complaint} \\ & \pm \text{complaint} \times \text{abnormal} \\ & \pm \sum \text{other factors} \\ & \pm \sum \text{interactions}\end{aligned}$$

Variable coding was as per Section 2.2.1 for complaint, sex, race, age, MAP, BMI. Helpfulness and fundus abnormality were coded as indicator variables.

2.3.2 Results

For 14 (5.9%) patients among the 239 eligible for this part, the ED physicians did not report whether the photographs were helpful. Among the remaining 225 patients, the ED physicians reported that they found the photographs helpful in 125 (56%) cases, and 26 (12%) had photographic abnormalities per neuro-ophthalmologist review. The distribution of presenting complaints and conditions in this subpopulation was 136 (60%) headaches, 71 (32%) acute focal neurologic deficits, 43 (19%) visual changes, and 11 (5%) DBPs ≥ 120 mmHg. Photographs were reported helpful significantly more often when a patient did not have an acute focal neurologic deficit vs. when the patient had an acute focal neurological deficit, and when a patient had a visual complaint vs. when the patient did not have a visual complaint (Table 2.7).

There were no significant differences in the frequency of complaints among abnormal vs. normal patients (Table 2.8); however, there was a trend toward significance for a higher

TABLE 2.7 Univariable associations between whether the ED physicians found the photographs helpful and the enrollment complaints and conditions among patients examined in Phase II.

Complaint or condition	Number (%) reported helpful by whether the complaint or condition was: Present		Absent		$\chi^2_{\text{d.f.}=1}$	*p*-value
Headache	76 / 136	(55.9)	49 / 89	(55.1)	0.01	0.9
Focal neurologic deficit	32 / 71	(45.1)	93 / 154	(60.4)	4.6	0.03
Visual complaint	33 / 43	(76.7)	92 / 182	(50.5)	9.7	<0.01
DBP ≥ 120 mmHg	6 / 11	(54.5)	119 / 214	(55.6)	0.00	0.94

TABLE 2.8 Frequency of abnormality on neuro-ophthalmology review by complaint among patients examined in Phase II.

Complaint or condition	Number (%) abnormal by whether the complaint or condition was: Present		Absent		$\chi^2_{\text{d.f.}=1}$	*p*-value
Headache	17 / 136	(12.5)	9 / 89	(10.1)	0.30	0.58
Focal neurologic deficit	7 / 71	(9.9)	19 / 154	(12.3)	0.29	0.59
Visual complaint	6 / 43	(14.0)	20 / 182	(11.0)	0.30	0.58
DBP ≥ 120 mmHg	3 / 11	(27.3)	23 / 214	(10.7)	2.8	0.09

In phase I, the ED physicians had access to direct ophthalmoscopy only.
In phase II, the ED physicians had access to fundus photography.

frequency of abnormality when DBP ≥ 120 mmHg despite the low frequency of this condition overall. There was no evidence of effect measure modification of the OR for helpfulness for any presenting complaint or condition by abnormality (Tables 2.9 & 2.10), although the complete separation seen among patients with abnormal photography for visual complaint and DBP prevented accurate estimation of these stratum specific ORs.

Next, we evaluated age, sex, race, BMI, and MAP as potential effect modifiers and confounders. The chunk test for interaction was non-significant ($p = 0.88$; d.f.=24), and all interaction terms were dropped. All subsets of confounders were evaluated Table B.3. Only models containing age and MAP fully controlled for confounding. There was no evidence of a non-linear relationship for age or MAP in the model: $\chi^2_{\text{d.f}=6} = 2.4, p = 0.876$. Likewise, there was no evidence of effect measure modification by abnormality per ED physician review ($\chi^2_{\text{d.f}=4} = 3.3, p = 0.509$) nor was abnormality per ED physician review associated with helpfulness controlling for the other variables in this model (1.05; 95%CI: 0.50–2.21; $p = 0.896$). Precision was improved by dropping the other variables, resulting in the final

TABLE 2.9 Frequency of reported helpfulness by complaint stratified by abnormality on neuro-ophthalmology review showing no obvious effect measure modification (see also Table 2.10).

Abnormal				
	Helpful			
Complaint or condition	**No (n=11)**		**Yes (n=15)**	
Headache	9	(81.8)	8	(53.3)
Focal neurologic deficit	5	(45.5)	2	(13.3)
Visual complaint	0	(0.0)	6	(40.0)
DBP ≥ 120 mmHg	0	(0.0)	3	(20.0)
Normal				
	Helpful			
Complaint or condition	**No (n=89)**		**Yes (n=110)**	
Headache	51	(57.3)	68	(61.8)
Focal neurologic deficit	34	(38.2)	30	(27.3)
Visual complaint	10	(11.2)	27	(24.5)
DBP ≥ 120 mmHg	5	(5.6)	3	(2.7)

model (Table 2.11). We found that photographic quality was not associated with perceived helpfulness when added to this final model: 1.39; 95%CI: 0.75–2.58; $p = 0.292$.

2.4 Discussion

We found that a patient's presenting complaints and conditions were associated with whether the ocular fundus was examined after controlling for phase of the study (i.e., fundus photography vs. direct ophthalmoscopy), sex, race, age, and MAP. First, patients with focal neurological complaints were significantly less likely to be examined than patients with other complaints, and

TABLE 2.10 Odds ratios comparing helpfulness by complaint/condition with consideration for potential effect measure modification by abnormality.

Complaint or condition	Crude OR (95% CI)	OR, normal (95% CI)	OR, abnormal (95% CI)	p for interaction
Headache	1.03 (0.60–1.77)	1.21 (0.68–2.13)	0.25 (0.04–1.60)	0.11
Focal neurologic deficit	0.54 (0.30–0.95)	0.61 (0.33–1.10)	0.18 (0.03–1.24)	0.24
Visual complaint	3.23 (1.50–6.94)	2.57 (1.17–5.65)	*	0.76
DBP ≥ 120 mmHg	0.96 (0.28–3.24)	0.47 (0.11–2.03)	*	0.71

* unable to be reliably estimated due to complete separation (see Table 2.9)

there was an interaction with the sex of the patient. Men with focal neurological complaints were less likely than women with focal neurological complaints to be examined (the OR for examination for men with neurological complaints vs. other complaints/conditions was 0.31; 95%CI: 0.14–0.71 and for women it was 0.68; 95%CI: 0.38–1.23). Second, patients with visual complaints were significantly more likely to be examined than patients with other complaints, and there was a significant interaction with the race of the patient. Black patients with visual complaints were less likely than patients of other races with visual complaints to be examined (the OR for examination for blacks with visual complaints was 1.33; 95%CI: 0.65–2.71 and for patients of other/unknown race it was 3.02; 95%CI: 1.48–6.13). Finally, there was trend toward patients with elevated DBP being less likely to be examined than patients with other complaints (OR = 0.34; 95%CI: 0.12–1.02).

TABLE 2.11 Final multivariable logistic model for association between helpfulness of examination and presenting complaints/conditions.

Variable	**OR**	**95% CI**	***p*-value**
Headache	1.06	(0.45–2.48)	0.89
Focal neurologic complaint	0.67	(0.29–1.53)	0.34
Vision complaint	2.98	(1.18–7.56)	0.02
DBP $\geq$ 120	1.32	(0.26–6.63)	0.73
Age (per 10 years)	0.82	(0.68–1.00)	0.05
MAP (per 10 mmHg)	0.96	(0.80–1.16)	0.68

Intercept: 1.5093
Overall model likelihood ratio test: $\chi^2_{\mathrm{d.f.}=6} = 18$, $p = 0.007$
le Cessie-van Houwelingen-Copas-Hosmer unweighted sum of squares test for global goodness of fit: $p = 0.24$

The only presenting complaint or condition that was significantly associated with the perceived helpfulness of ocular fundus photography was visual complaints. Photographs taken of patients with visual complaints had about three times the odds of being reported helpful compared to patients with other complaints and conditions (OR = 2.98; 95%CI: 1.18–7.56). Older age was also significantly associated with a lower odds of perceived helpfulness (OR = 0.82; 95%CI: 0.68–1.00).

As discussed in Chapter 1, ideally all patients with the presenting complaints and conditions that we studied would be examined because they are at a relatively high risk of relevant ocular fundus findings. It is unsurprising that ED physicians would tend to examine patients with visual complaints more frequently and more often report ocular fundus photographs as helpful for these patients because visual complaints intuitively raise a high concern for a problem that is directly affecting the eye. Indeed, as discussed in Section 1.9, 29 (20%) of the 148 patients with visual complaints had abnormalities. However, the group with the highest frequency of findings were the 42 patients with DBP $\geq$ 120 of which 12 (29%) had abnormalities. Yet, this was a group that likely had a lower odds of being examined.

It is unclear why men with acute focal neurologic disorders were less likely to be examined compared to women with acute focal neurologic disorders, especially when men and women had similar frequencies of abnormality: 6 (7.1%) of the 84 men vs. 12 (8.6%) of the 140 women had abnormal photographs ($p = 0.7$) among the 224 patients with focal neurologic complaints. However, the most concerning finding was the lower odds of examination among blacks with visual complaints because it runs counter to the higher frequency of abnormalities found among black patients. As discussed in Section 1.9, blacks were at a higher overall risk of ocular fundus abnormalities and this also held true among the 148 patients with visual complaints: 10 (13.0%) of the 77 patients of other or unknown race vs. 19 (26.8%) of the 71 patients of black race had abnormal photographs ($p = 0.03$).

The Institute of Medicine's report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* found that blacks and Hispanics tend to receive lower quality healthcare even after controlling for access-related factors, such as insurance status.[44] Beyond disparities that may result from systematic issues and health care seeking behavior, they reported evidence of racial disparities at the level of the clinical encounter. The report suggested that the typical uncertainty of any clinical encounter, especially when compounded by significant time constraints and high pressure decision making (such as in the ED), combined with patients from different racial and ethnic backgrounds may unconsciously release physicians' biases and stereotypes in a way that affects patient encounters. Both sex and racial differences have been observed in the management of acute myocardial infarction,[45] a condition for which there is significant time pressures involved.

However, we suggest that our results be interpreted with caution since these differences barely reached significance and we do not know additional details about the patient encounters that may have influenced decisions about whether to examine the ocular fundus in a given patient. Nevertheless, these findings suggest that an exploration of sex and racial disparities in the examination of the ocular fundus is warranted and that additional education of ED physicians about the epidemiology of ocular fundus abnormalities may be needed to heighten awareness about which patients are at greatest risk of ocular abnormalities.

Chapter 3
Patient and Photographic Factors Associated with Errors

3.1 Introduction

Just as patient characteristics such as sex and race can influence how throughly a particular aspect of the physical examination is performed,[40,41,44] they can also potentially influence the likelihood that errors are made. In Chapter 2, we addressed one type of error that can occur: failure to examine the patient's ocular fundus when an abnormality is present.

In this chapter, we will address the errors that can occur when photographs are reviewed by ED physicians: false negative and false positive readings. The reading of the neuro-ophthalmologists serves as the reference standard by which these errors are determined.

In the overall FOTO-ED study, we considered sensitivity to be the more important than specificity because of the high risk to patients of missing a relevant ocular fundus finding. On the other hand, a false positive (which would reduce specificity), would typically result in an ophthalmology consult in order to confirm or refute the ED physician's concern. In our calculations we disregarded whether the patient was examined by direct ophthalmoscopy or not in phase I and whether the photographs were reviewed or not in phase II because a failure to examine a patient has a strong impact on the sensitivity. In phase I, the ED physicians did not detect any of the relevant findings on their own using direct ophthalmoscopy (0/44=0%; 95% CI 0%–8%). In phase II, the ED physicians had significantly higher sensitivity for relevant ocular fundus findings using non-mydriatic ocular fundus photography (16/35=46%; 29%–63%; p for absolute difference in sensitivities: <0.0001). To estimate the actual test characteristics of ocular fundus photography performed by ED physicians, we also limited the analysis to the

239 patients whose photographs were reviewed by emergency physicians. Based on these patients, sensitivity was 59% (16/27; 95% CI: 39% to 78%) and specificity was 86% (182/212; 95%CI: 80% to 90%).[36]

One potential cause of error is poor photographic quality. The quality of fundus photographs can be degraded by a number of factors. In the FOTO-ED study, we evaluated factors that were associated with diminished photographic quality using the 1734 photographs taken on the 350 patients enrolled in the first phase of the study.[46] The general quality of each ocular fundus photograph was graded on a 5-point scale: 1, inadequate for any diagnostic purpose; 2, unable to exclude all emergent findings; 3, only able to exclude emergent findings; 4, not ideal but still able to exclude subtle findings; and 5, ideal quality (Figure 3.1).

In a multivariable ordinal logistic regression model, we found that older age (OR 0.76 per 10 years per quality rating unit increase; 95%CI: 0.69–0.85) and black race (OR 0.42 per quality rating unit increase; 95%CI: 0.28–0.63) were associated with poorer quality photography. The influence of these factors on photographic quality was not surprising. Age is associated with smaller pupils, which make it more difficult to obtain photography,[47] and an increase in the frequency of cataract, which obstructs the view of ocular fundus. Indeed, in a population-based 10-year incidence study of cataract and cataract surgery in an Australian population 49 years or older, 72% of the participants were affected by cataract or had cataract surgery over the 10-year follow-up period.[48] Black race is associated with increased retinal pigmentation on average, which causes decreased reflectance of the ocular fundus.[49]

In the second phase of the FOTO-ED study,[36] there were 41 reading errors made among the 239 patients whose photographs were reviewed by the ED physicians. There were eleven false negative errors who had findings on neuro-ophthalmology review but whose photographs were reported as "likely normal, but unsure" (7 patients) and "normal" (4 patients). These 11 abnormal findings included 6 optic disc pallor, 3 isolated flame-shaped hemorrhages, 1 grade

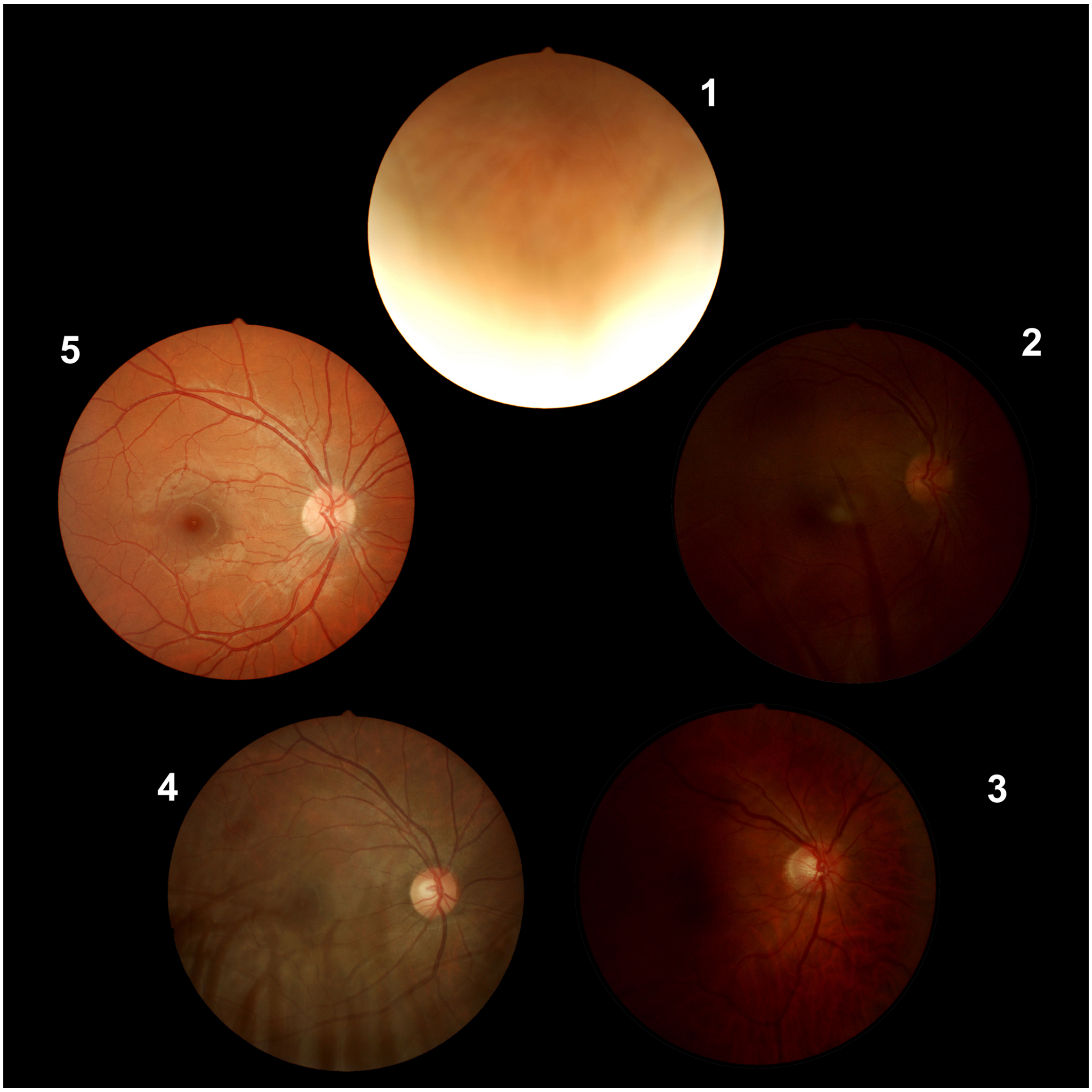


FIGURE 3.1 Example images for each level of the five-point scale used for general quality assessment: 1) The quality is inadequate for any diagnostic purpose. 2) Graders are unable to exclude all emergent findings. 3) Graders are only able to exclude emergent findings. 4) The quality is not ideal, but graders are able to exclude subtle findings. 5) Ideal quality. From *Ophthalmology*. Lamirel C, Bruce BB, Wright DW, Delaney KP, Newman NJ, Biousse V. Quality of nonmydriatic digital fundus photography obtained by nurse practitioners in the emergency department: the FOTO-ED study. 119:619. Copyright © 2012 American Academy of Ophthalmology. Reprinted with permission. Full article available at http://dx.doi.org/10.1016/j.ophtha.2011.09.013.

III/IV hypertensive retinopathy, and 1 disc edema. All of these findings occurred in patients with a complaint of headache (6 of 11 patients; 1 also with visual changes and 1 with severely elevated blood pressure), focal neurologic deficit (2 patients), or both (3 patients). We also reported that all these patients had photographs of good quality (ie, images of grade 3 quality for both eyes) suggesting that other factors were relevant in these misreadings. The other thirty patients were false positive reads who the ED physicians reported as having "likely abnormal, but unsure" or "abnormal" photographs but who did not have relevant findings based on neuro-ophthalmologist review. Twenty-five of these 30 image sets (83%) were either of poor quality (9 patients) or represented the misidentification of a camera artifact as pathology (16 patients). The artifacts were either smudges on the camera lens or reflections from ocular structures. All of the 5 misreadings of high-quality image sets incorrectly indicated optic nerve pathology in patients with normal results. Overall, these findings suggested that photographic quality was important in false positive readings. We previously reported these findings in a qualitative fashion,[36] and in this chapter we seek to quantitatively evaluate the effect of photographic quality and the influence of other patient factors on errors.

In the first part of this chapter, we focus on whether the effect of poor photographic quality as a cause of photographic reading errors by ED physicians is confounded by patient characteristics (particularly age and race as suggested by our prior studies). In the second part of this chapter, we consider an alternative perspective on the same three factors where the effect of patient characteristics on misreads by the ED physicians are potentially mediated by the quality of the photographs.

3.2 Part 1: Is photographic quality associated with erroneous readings?

3.2.1 Methods

In this first part, our goal was to determine if photographic quality rating is associated with erroneous (false positives and false negatives) readings by emergency department physicians, controlling for patient factors, particularly age and race (Figure 3.2).

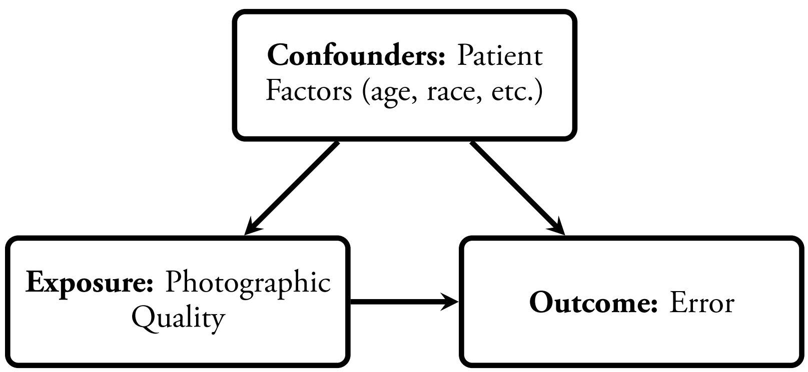


FIGURE 3.2 Directed acyclic diagram describing the relationship between variables considering photographic quality as the exposure of interest.

The subset of patients eligible for this part were the 239 (34%) patients who were examined in the second phase because fundus photography was used by the emergency department physicians only in this phase.

Univariable analysis followed by multivariable logistic regression and multinomial logistic regression were the analyses used. For logistic regression modeling, the outcome of interest was whether an error had occurred. Errors were defined as disagreements between the neuro-ophthalmologist's reading of the patient's photographs (serving as a reference standard) and the emergency department physician's reading of the patient's photographs. For multinomial logistic regression, the outcome was divided into no error, false positive, and false negative.

Ideally, we could leverage the fact that some fundus abnormalities are unilateral, and limit the analysis only to patients with unilateral abnormalities. We could then perform conditional logisitic regression of $\text{logit}(P(\text{error}|x))$ against photographic quality at the eye unit of analysis conditioning on the patient pairs.

However, we suspected we did not have adequate data for this analysis and also planned an analysis where the main exposure of interest was the quality of the photographs at the patient level. This was operationalized as the average of the maximum quality photograph taken of each eye and treated as a quasi-continuous value. The primary confounders of interest were age and race, but other factors of interest included sex, MAP, and BMI. Other variables were coded as in Section 2.2.1. The model took the following general form:

$$\begin{aligned}\text{logit}(P(\text{error}|x)) = {} & \text{quality} \\ & \pm \text{age} + \text{race} \\ & \pm \sum \text{other factors} \\ & \pm \sum \text{interactions}\end{aligned}$$

3.2.2 Results

There were 10 patients with unilateral disease who had erroneous readings by the ED physicians. Only four of the eyes' photographs had discordant quality, insufficient for conditional logistic regression (would not converge). However, for all 4 patients the abnormality occured in the photograph with the lower quality rating: three were one quality level worse than the fellow eye, and the other one was two quality levels worse than the fellow eye (Wilcoxon signed rank test, $p = 0.089$).

There were 239 (34%) patients eligible for the remainder of this analysis, including binary logistic regression, from among the 704 patients in the entire cohort. The median quality for these patients was 4.0 (IQR: 3.0–4.8). Their median age was 47.5 years (IQR: 34.0–57.3), and 141 (59%) were black.

Quality was significantly linearly associated with erroronous readings by ED physicians (OR for an error occurring per quality unit increase: 0.72; 95%CI: 0.53–0.97; $p = 0.03$; test for non-linearity using 5-knot spline: $\chi^2_{\text{d.f}=3} = 2.9, p = 0.403$). There were no significant second-order interactions between quality and age, race, sex, MAP, or BMI (p for interaction: 0.462). Controlling for age and race, there was evidence of confounding (OR for an error occurring per quality unit increasing to 0.83; 95%CI: 0.59–1.16; $p = 0.269$), although this OR was no longer significant (Table 3.1). There was no evidence of additional confounding by sex, MAP, or BMI (OR for error an occurring per quality unit increase: 0.85; 95%CI: 0.60–1.20; $p = 0.346$).

For multinomial logistic regression with false positive vs. false negative vs. no error as the outcome, quality was only significantly associated with false positive errors, OR = 0.69 (95% CI: 0.48–0.97; $p = 0.03$) and not false negative errors OR = 0.80 (95% CI: 0.44–1.38; $p = 0.42$). There was evidence of confounding by age for the association between false positive

TABLE 3.1 Final model regarding association between examination by ED physician and complaint.

Variable	**OR**	**95% CI**	***p*-value**
Mean maximum quality	0.83	(0.59–1.20)	0.27
Age, per year	1.02	(1.00–1.05)	0.09
Black race	0.93	(0.45–2.03)	0.83

Intercept: -1.87
Overall model likelihood ratio test: $\chi^2_{\text{d.f.}=3} = 8, p = 0.048$.
le Cessie-van Houwelingen-Copas-Hosmer unweighted sum of squares test for global goodness of fit: $p = 0.37$

errors and quality [OR for false positives per quality unit controlling for age = 0.82 (95% CI: 0.54–1.19; $p = 0.3$)], but not race [OR for false positives per quality unit controlling for race = 0.68 (95% CI: 0.47–0.95; $p = 0.02$)].

3.3 Part 2: Are patient characteristics associated with erroneous readings and is this association mediated by photographic quality?

3.3.1 Methods

In this second part, our goal was to determine if there is an effect of patient factors (particularly age and race) on quality rating, and if so, whether there is evidence that the effect of those factors on error is mediated by photographic quality (Figure 3.3).

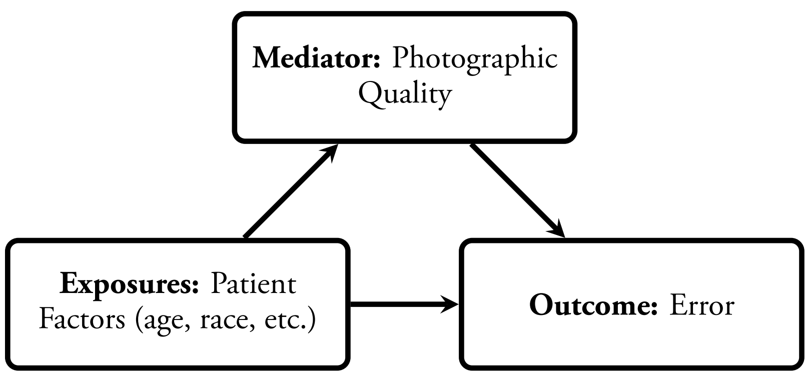


FIGURE 3.3 Directed acyclic diagram describing the relationship between variables considering photographic quality as a mediator.

The subset of patients eligible for this part was again the 239 (34%) patients who were examined in the second phase.

Univariable analysis followed by multivariable logistic regression and multinomial logistic regression were the analyses used. For logistic regression modeling, the outcome of interest was whether an error had occurred. Errors were defined as in Section 3.2.1.

The primary exposures of interest were age and race, and other factors of interest included sex, MAP, and BMI. Quality of the photographs at the patient level was now considered as a possible mediator. Models excluding and including quality were compared in an attempt to evaluate the direct (mediated by quality) and indirect effects (independent of quality) of other patient factors of interest. Variables were coded as described in Sections 2.2.1 & 3.2.1. The model took the following general form:

$$\begin{aligned} \text{logit}(\text{P}(\text{error}|x)) = {} & \text{age} + \text{race} \\ & \pm \sum \text{other patient factors} \\ & \pm \text{quality} \\ & \pm \sum \text{interactions} \end{aligned}$$

3.3.2 Results

The patients used in this aim are described Section 3.2.2. Age was significantly associated with erroronous readings by ED physicians (OR for error occuring per 10 year increase in age was 1.32; 95%CI: 1.06–1.64; $p = 0.012$). Race was not significantly associated with an error (Table 3.2). Sex, MAP, and BMI were also not significantly associated with errors. Comparing the model containing only age and race to the full model (Table 3.1), but now from the perspective of quality being a potential mediator of the effect of age and race, one can see that the OR for age is very similar (OR per 10 year increase in age: 1.24; 95%CI: 0.97–1.58; $p = 0.085$) suggesting that the effect of age is not strongly intermediated by quality, even though the effect of age no longer reached significance.

TABLE 3.2 Effect of patient factors on erroneous photographic readings.

Variable	OR	95% CI	p-value
Age, per year	1.03	(1.01–1.05)	0.01
Black race	0.98	(0.49–2.12)	0.95

Intercept: -2.94
Overall model likelihood ratio test: $\chi^2_{d.f.=2} = 7, p = 0.035$.
le Cessie-van Houwelingen-Copas-Hosmer unweighted sum of squares test for global goodness of fit: $p = 0.99$

For multinomial logistic regression, older age was only significantly associated with false positive errors, OR = 1.03 (95% CI: 1.00–1.05; $p = 0.02$) and not false negative errors OR = 1.02 (95% CI: 0.98–1.07; $p = 0.28$) even though the ORs were extremely similar. Black race was nearly significantly associated with false negative errors only, OR = 7.46 (95% CI: 0.73–60.66; $p = 0.06$) and not false positive errors OR = 0.59 (95% CI: 0.24–1.31; $p = 0.19$).

After considering quality, there was little change in any of the OR estimates, suggesting little, if any, mediation of the effect of age and race through differences in quality. The OR for age was 1.02 (95% CI: 0.99–1.05; $p = 0.14$) per year for false positive errors and 1.02 (95% CI: 0.97–1.07; $p = 0.35$) per year for false negative errors. The OR for black (vs. other/unknown race) was 7.35 (95% CI: 0.72–60.29; $p = 0.06$) for false negative errors and 0.55 (95% CI: 0.22–1.23; $p = 0.14$) for false positive errors.

3.3.3 Discussion

Similar to our preliminary observations, our data generally support no common features that explain all errors, and instead suggest that there are different mechanisms of false positive and false negative errors. We confirmed that higher quality was significantly associated with a lower odds of false positive error (i.e., false positives were more likely to occur in images of poor quality as we had previously observed). We found that age appeared to confound the association between poor photographic quality and false positive errors, suggesting that age is both a cause of poor quality (suggested by previous quality analyses) as well as a cause of false positive errors (supported by our analysis considering age as an exposure of interest in the second part of the chapter). Despite support for a causal path from age through quality to false positive errors, comparing the model including quality to the model that did not, the ORs for age were similar suggesting that other effects of age than its contribution to poor photographic quality are likely to primarily explain the greater odds of false positive photographs seen with increasing age.

We also found the odds of a false negative errors occurring in black patients to be over 7 times that of one occurring in patients of other or unknown race. While black race was associated with poor quality on average, all of the false negative readings occurred in photographs of generally good quality,[36] and we did not find any association between quality and false negative readings in our quantitative analysis. However, it is possible that the darker retinal pigmentation on average seen in blacks compared to whites may have made it more difficult to see and interpret the abnormal fundus findings, several of which were subtle. In addition, given that the majority of false negative findings were optic disc pallor, the expectation of a sharper contrast between a darker retina and the normal optic disc, which is typically unpigmented, may have raised the examiner's threshold for calling optic disc pallor. On the other hand, one could claim that it is possible that this same effect made it more likely for the neuro-ophthalmologist examiners to overdiagnose optic disc pallor. However, this is less likely since several other features are used by neuro-ophthalmologists to diagnose optic disc pallor (comparison with the contralateral side, loss of small disc capillaries, etc.). This racial difference again raises questions about potential racial and ethnic disparities that deserves further exploration.

There are several limitations of this chapter's analysis. First, it is unlikely that our directed acyclic diagrams represent the true causal mechanisms, and there are likely unmeasured and unknown confounders influencing the relationships between our variables of interest. Second, there were only a small number of false negative readings leading to considerable inprecision in our estimates of the association between race and false negative readings, and thereby increasing the possibility that this association occurred by chance.

Chapter 4
Fundus Abnormalities as Predictor of ED Revisit, Hospital Admission, and Death

4.1 Introduction

The ocular fundus consists of:

- central nervous system tissues, i.e., the optic nerve and retina, and
- the retinal vasculature, which contains both large and small vessel components supplied by the anterior cerebral circulation like the majority of the brain.

The retinal and cerebral microvasculatures share embryological origins and are very similar anatomically and physiologically.[50] Both are barrier circulations sharing mechanical (luminal tight junctions) and metabolic components (e.g., transport proteins: GLUT-1, P-glycoprotein, and transferrin). Both circulations also have autoregulatory mechanisms to maintain constant blood flow in the face of changes in systemic blood pressure.[51] As blood pressure increases, vasoconstriction (arteriolar narrowing) occurs. As retinal autoregulatory mechanisms fail, blood and fluid leak from vessels (hemorrhages and exudates) and ischemia ensues (cotton wool spots). In addition, retinal thromboembolic events can be directly visualized as emboli and vascular occlusions.[52] Hypertension and diabetes are important risk factors for stroke, and both conditions lead to changes in the retinal microvasculature.[51] Ocular fundus photography provides an excellent tool to observe and measure these changes in patients presenting to the ED.

Therefore, it should not be surprising that there is substantial epidemiologic evidence that abnormalities of the ocular fundus are associated with the long-term risk of neurologic disease and cardiovascular disease. Numerous studies have related retinal microvascular abnormalities to the long-term risk of stroke.[50,53] Indeed, the Atherosclerosis Risk in Communities study found that retinal microvascular abnormalities, particularly microaneurysms and soft exudates, predicted subclinical strokes independent of the patient's hypertensive and diabetic status.[54] Other investigators have also found a similar relationship between hypertensive retinopathy and silent brain infarction in patients without a history of stroke or transient ischemic attack, independent of the patient's current hypertensive status.[55] Likewise, multiple population-based studies have similarly found a relationship between retinal microvascular changes and stroke, after controlling for traditional stroke risk factors.[56–58] In particular, retinal microvascular changes that are more reflective of acute blood pressure changes (i.e., focal arteriolar narrowing, retinal hemorrhages, microaneurysms, and cotton-wool spots) tend to portend a higher risk of incident stroke than those that appear to be markers of cumulative long-term hypertension damage (i.e., generalized retinal arteriolar narrowing and arteriovenous nicking).[50,58,59]

Retinal microvascular changes have also been associated with the long-term risk of cardiovascular disease. Retinal microvascular changes have been associated with twice the risk of incident congestive heart failure, even among otherwise low-risk individuals,[60] and sub-analyses of the Beaver Dam Eye Study have found that individuals with retinal microaneurysms and retinal hemorrhages are twice as likely to die from cardiovascular events as those without these signs.[61] Furthermore, there is an increased risk of ischemic heart disease mortality related to arteriolar narrowing.[62]

Based upon the association of ocular fundus findings with neuro- and cerebrovascular disease, common causes of morbidity and mortality, we hypothesized that ocular fundus abnormalities would be predictive of future visits to the ED, hospital admission, and all-cause mortality.

4.2 Methods

The entire cohort of 704 patients previously described Section 1.8 was eligible for the analyses in this chapter. Univariable followed by time-to-event analyses were performed. Kaplan-Meier survival estimates were used to evaluate the association between fundus photography results and each of the outcomes. Cox proportional hazards regression models, with extensions if needed, were used to model the incidence rates for the different end points: ED revisits, hospital admissions, and all-cause mortality.

The number of knots was reduced to four for mortality because of instability in the model estimates from inadequate outcome frequency in each spline term when our usual choice of five knots was used (see Section 1.7). Knot placements are found in Appendix C. Non-linear terms were retained only for the variables significant at the 0.05 level. An Andersen-Gill (counting process) regression model with robust variance estimator was used for the recurrent event analyses of ED visits and hospital admissions. Follow-up was censored at a maximum of 5 events for recurrent event analyses. Median follow-up time was 1.7–1.9 years depending on outcome.

4.3 Results

4.3.1 ED Revisits

There were 313 (44%) patients who visited the ED at least once after their index visit (Figure 4.1).

Kaplan-Meier analysis did not show a significantly greater hazard of return to the ED for patients with abnormal fundus photography compared to those with normal fundus photography when only the first revisit was considered (Figure 4.2).

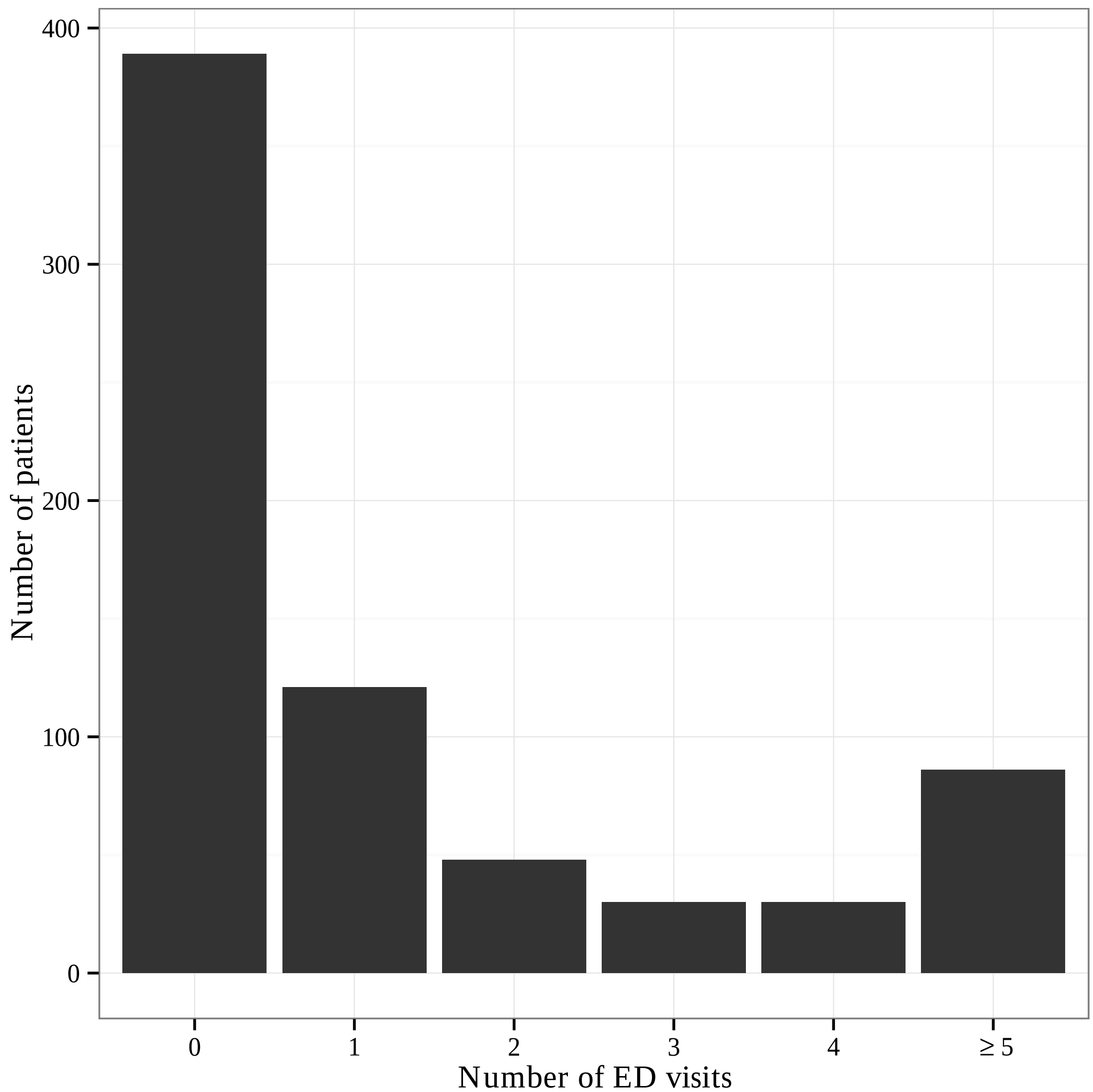
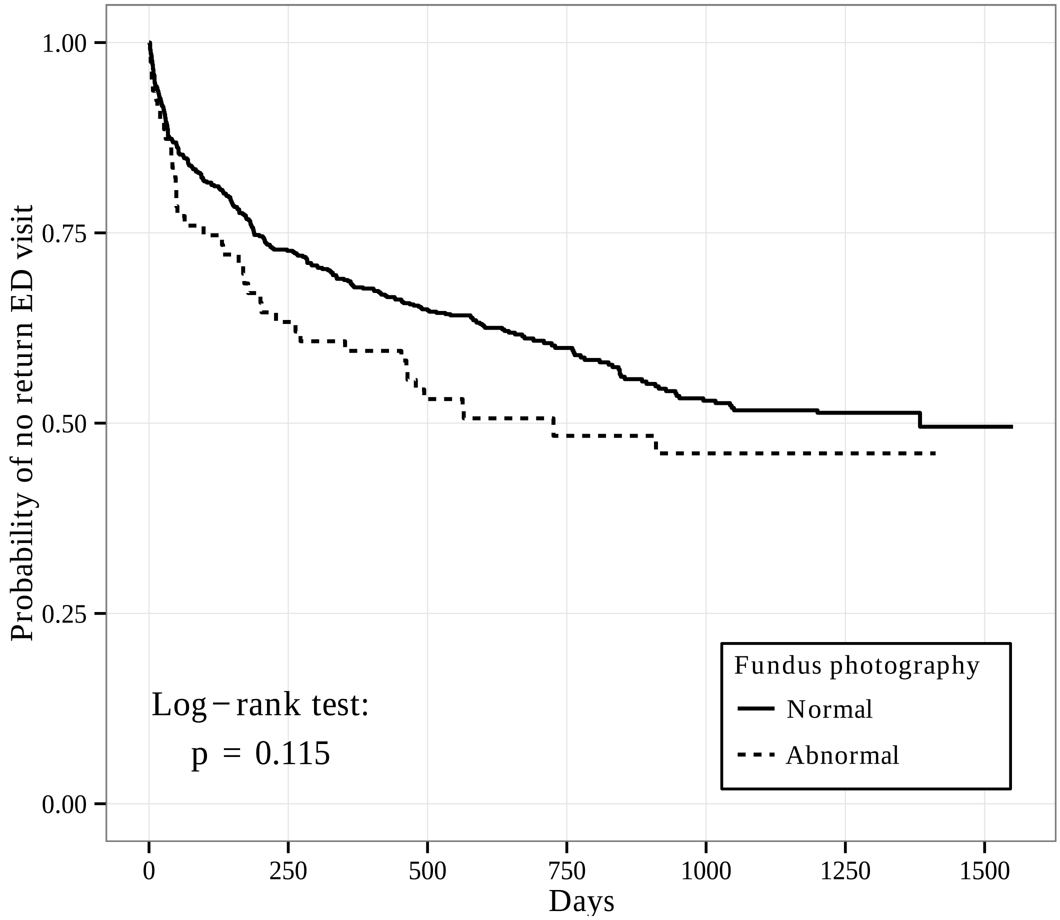


FIGURE 4.1 Number of repeat ED visits between presentation and April 2013.

Linearity for each continous variable was assessed by including five-knot restricted cubic splines (see Section 4.2 for additional details) for each continuous variable included in the Cox model of ED revisits. There was evidence of possible non-linearity for age, but not for MAP or BMI (Table D.1).

Schoenfeld residuals showed no evidence that the proportional hazards assumption was violated by any individual variable or by the full model containing all variables of interest (Table D.2 & Figure D.1).



Normal	625	454	406	190	168	128	2
Abnormal	79	50	42	21	20	18	0

Numbers at risk

FIGURE 4.2 Kaplan-Meier curve for 1st ED visit.

Confounding of the association between abnormal fundus photographs and ED revisits was accessed using all subsets of covariates (Table D.3). The only variables that appeared to confound the association were race and BMI. This is best seen by comparing the hazard ratios for the full model and the model containing only race and BMI and by comparing the model with none of the covariates with those that only control individually for race and BMI. Since neither age nor MAP were significant predictors and because precision for our estimate of the effect of abnormal fundus photography slightly improved when they were not included in the

TABLE 4.1 Final model of time to first ED visit.

Variable	HR	95% CI	p-value
Abnormal fundus photograph	1.17	(0.84–1.63)	0.35
Black race	1.49	(1.17–1.89)	<0.01
BMI, per kg/m^2	1.02	(1.00–1.03)	0.04

model, age and MAP were dropped from the final model; race and BMI were retained since they were significantly associated with a return to the ED (Table 4.1).

There was no difference in the median number of return ED visits between patients with abnormal vs. normal ocular fundus photography (abnormal: 1.0 (IQR: 0.0–3.0); normal: 0.0 (IQR: 0.0–2.0); $p = 0.14$). We also evaluated a *recurrent* event model for return ED visits, and there was no association between recurrent return ED visits and abnormality on fundus photography: OR = 1.25; 95%CI: 0.92–1.69; $p = 0.156$.

4.3.2 Hospital Admissions

There were 240 (34%) patients who were admitted to the hosptial on or after their index visit (Figure 4.3). Kaplan-Meier analysis showed a significantly greater hazard of hospital admission for patients with abnormal fundus photography compared to those with normal fundus photography (Figure 4.4).

Linearity was assessed by including five-knot restricted cubic splines (see Section 4.2 for additional details) for continuous variables that were included in the Cox models of first hospital admission. There was evidence of significant non-linearity for age, but not MAP or BMI (Table D.4).

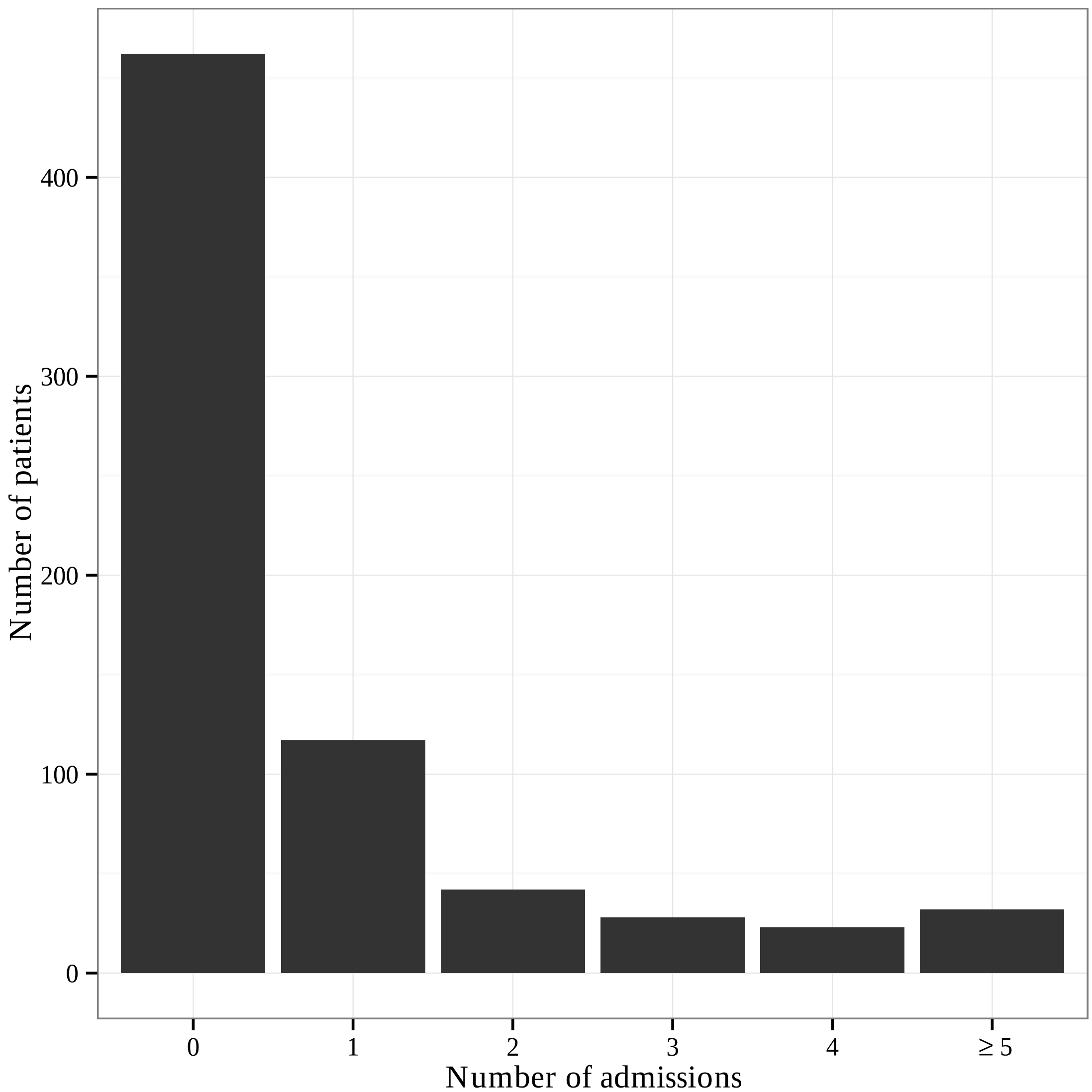


FIGURE 4.3 Number of admissions between presentation and April 2013.

Schoenfeld residuals showed evidence that the proportional hazards assumption was violated only by race and BMI (Table D.5 & Figure D.2). After stratifying the Cox model by race and BMI ≥30 (based on the World Health Organization definition of obesity), the proportional hazards assumption was no longer violated (Table D.6 & Figure D.3).

Confounding of the association between abnormal fundus photographs and hospital admission was accessed using all model subsets (Table D.7). There was no evidence of confounding.

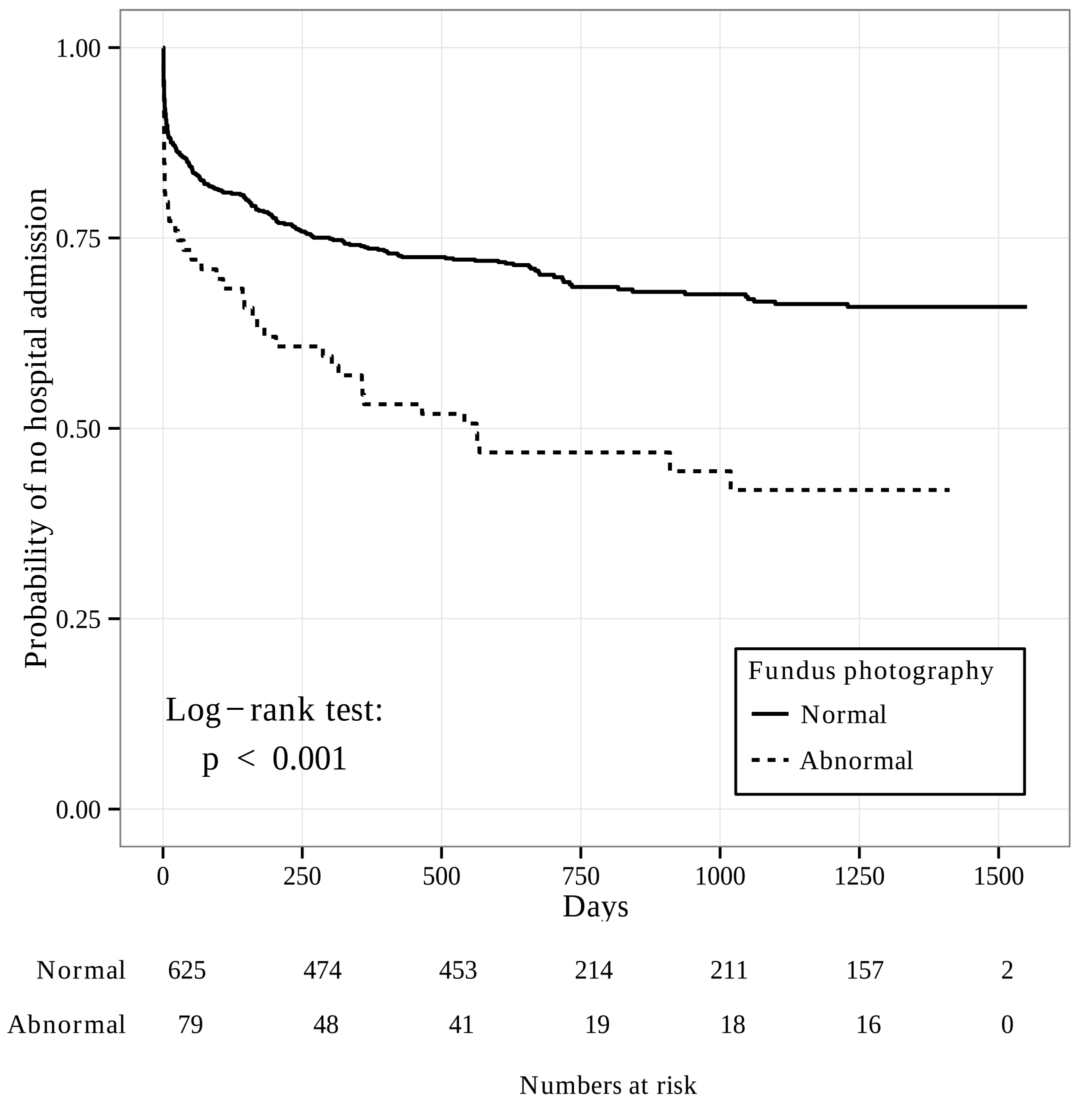


FIGURE 4.4 Kaplan-Meier curve for 1st hospital admission.

Stepwise elimination was performed. MAP was the least significant ($p = 0.305$) and was removed from the model. All remaining variables were significant and retained in the final model (Table 4.2).

There was a difference in the median number of hospital admissions between patients with abnormal vs. normal ocular fundus photography (abnormal: 1.0 (IQR: 0.0–1.0); normal: 0.0 (IQR: 0.0–1.0); p <0.001), but unlike first hospital admission, there was no association

TABLE 4.2 Final Cox proportional hazards model of time to first hospital admission stratified by race.

Variable	HR	95% CI	*p*-value
Abnormal fundus photograph	2.04	(1.46–2.97)	<0.01
Age, 3rd (57.8 years) vs. 1st (32.4) quartile	1.51	(1.05–2.18)	*

* Age is represented by a 5-knot restricted cubic spline (see Figure 4.5)
Overall p for age: <0.001
p for non-linear terms of age: 0.007

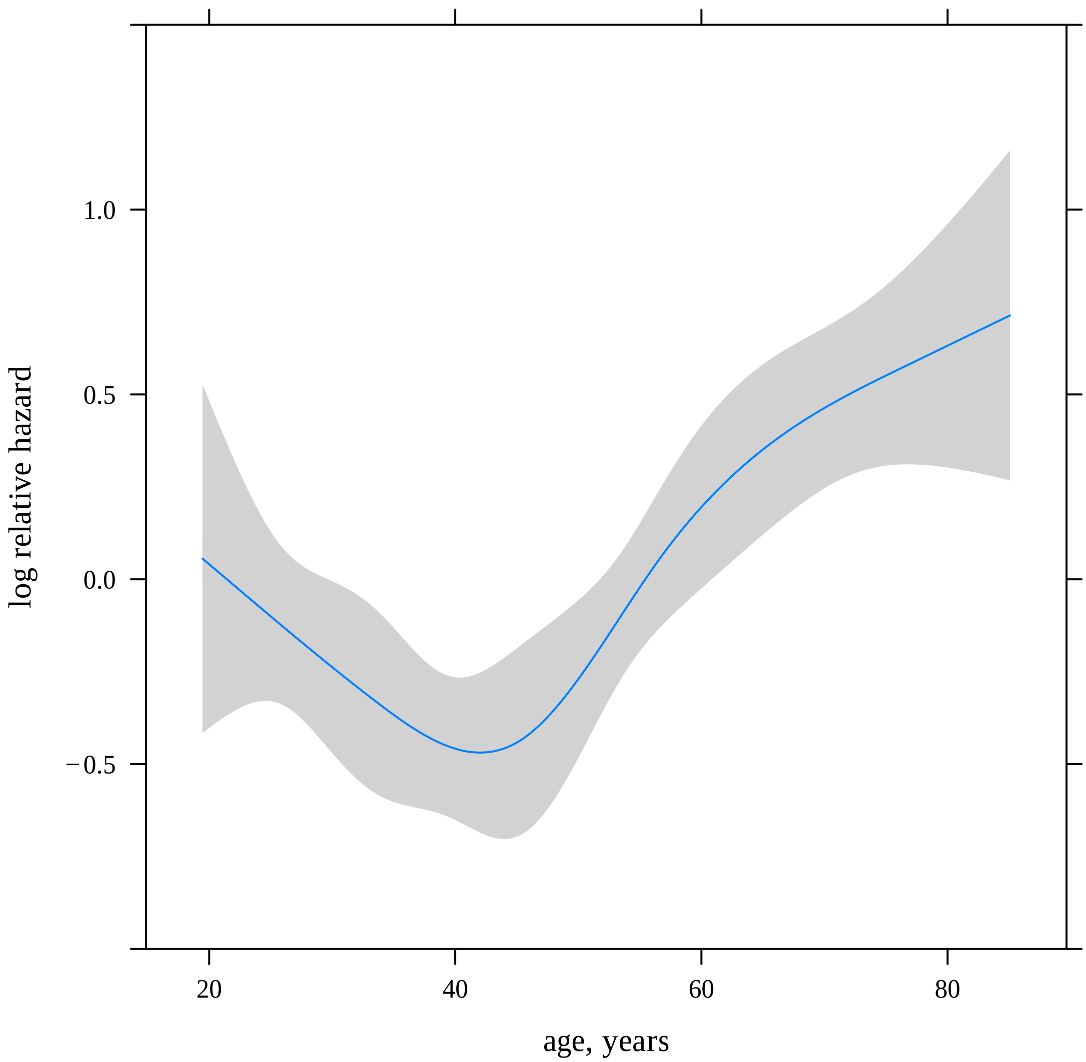


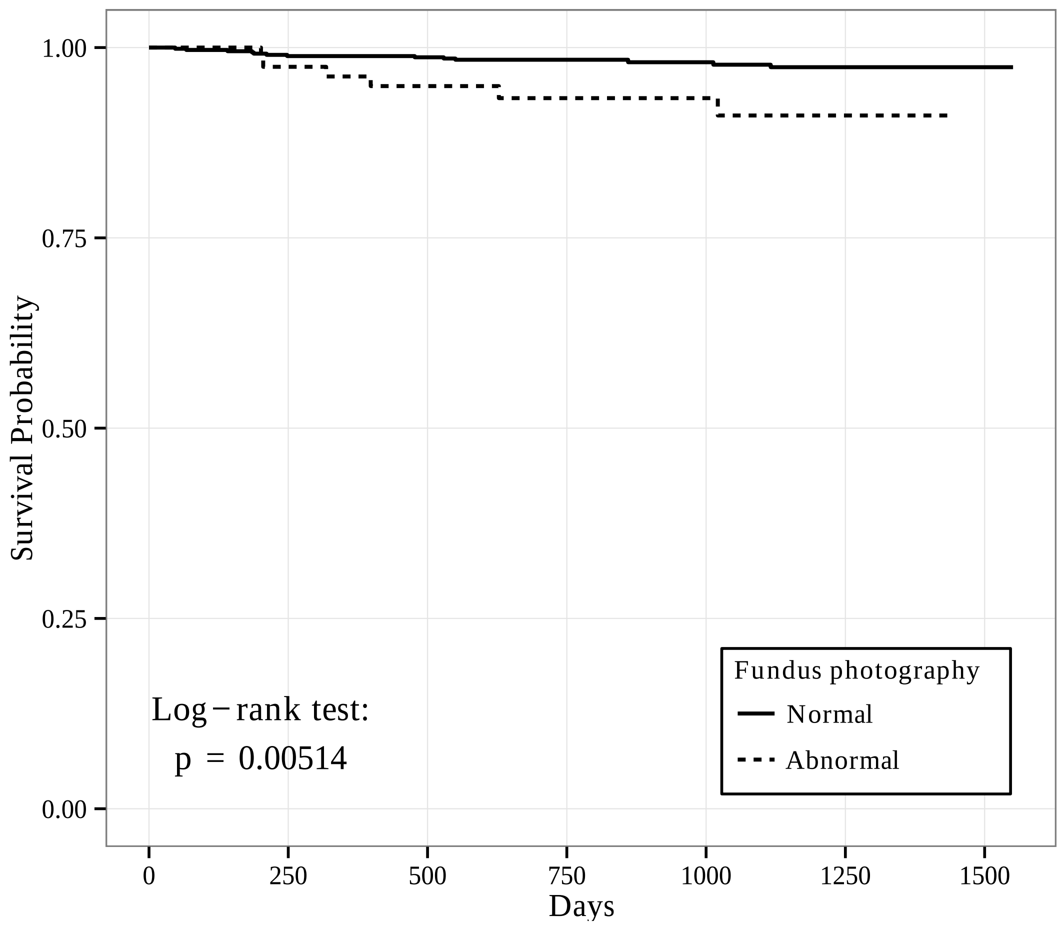
FIGURE 4.5 Five-knot restricted cubic spline with 95% CI for log relative hazard of hospital admission vs. age in years adjusted to reference categories for categorical variables and to the mean values of other continuous variables.

between *recurrent* hospital admissions and abnormalities on fundus photography: OR = 1.26; 95%CI: 0.93–1.71; $p = 0.13$.

Because admissions that are a direct consequence of the initial hospital visit can occur on or within a few days of the initial ED visit, we performed a sensitivity analysis excluding patients admitted within 7 days of their index visit controling for age and continued to find a significantly increased rate of hospital admission among patients with abnormal fundus photography: HR = 1.94; 95%CI: 1.27–2.96; $p = 0.002$. There 28 patients with ocular fundus abnormalities who were admitted more than 7 days after their index visit at least one time, 13 (46%) were considered to be definitely related to the ocular fundus findings (Table 4.3). Continuing to exclude patients admitted within 7 days of their index visit and controlling for age, patients with fundus abnormalites considered related to their subsequent reason for admission had a significantly higher rate of admission: HR = 8.00; 95%CI: 4.36–14.67 ; $p < 0.001$. If instead, the patients with fundus abnormalities considered related to their subsequent reason for admission were excluded, there was no association between abnormality and time to first admission: HR = 1.15; 95%CI: 0.67–1.99; $p = 0.608$.

4.3.3 All-cause mortality

Nineteen (2.7%) of the 704 patients died during follow-up. Eight had a complaint of headache only, 4 had focal neurologic complaint only, 3 had visual complaint only, 2 had elevated DBP only, 1 had a focal neurologic complaint and visual changes, and 1 had a headache and focal neurological complaints. Kaplan-Meier analysis showed a significantly greater hazard of all-cause mortality with abnormal fundus photography compared to those with normal fundus photography (Figure 4.6).



Normal	625	618	617	302	301	231	2
Abnormal	79	77	75	41	41	35	0

Numbers at risk

FIGURE 4.6 Kaplan-Meier curve for all-cause mortality.

TABLE 4.3 Relationship of ocular fundus findings to the 28 initial hospital admissions occurring at least 7 days after ED visit.

Finding & admission related	Ocular fundus finding	Reasons for admission
Yes (n=13)	optic disc edema	CSF shunt malfunction (2), CSF shunt placement, neurosarcoidosis
	optic disc pallor	optic neuritis, pituitary macroadenoma, temporal arteritis
	isolated intraocular hemorrhage	congestive heart failure (3)
	grade III/IV hypertensive retinopathy	cardiac arrest, renal failure
No (n=15)	optic disc edema	head trauma, conversion disorder, unruptured cerebral aneurysm
	optic disc pallor	hypernatremia, cholangitis, ovarian cyst rupture, colon cancer, chest pain
	isolated intraocular hemorrhage	pancreatic mass, menorrhagia, gastroparesis, epilepsy
	grade III/IV hypertensive retinopathy	hepatocellular carcinoma, menorrhagia, altered mental status

CSF = cerebrospinal fluid

TABLE 4.4 Final Cox model of time to death from any cause.

Variable	**Hazard ratio**	**95% CI**	***p*-value**
Abnormal fundus photograph	4.10	(1.51–12.42)	<0.01
Age, 3^{rd} (57.8 years) vs. 1^{st} (32.4) quartile	2.56	(1.35–4.85)	<0.01
Black race	0.98	(0.36–2.99)	0.97
MAP, 3^{rd} (116.6 mmHg) vs. 1^{st} (94.7) quartile	0.22	(0.06–0.87)	*
BMI, 3^{rd} (32.9 kg/m^2) vs. 1^{st} (24.0) quartile	0.84	(0.46–1.55)	0.58

* MAP is represented by a 4-knot restricted cubic spline (see Figure 4.7)
Overall p for MAP: 0.02
p for non-linear terms of MAP: 0.008

Linearity was assessed by including four-knot restricted cubic splines (see Section 4.2 for additional details) for continuous variables that were included in the Cox models of all-cause mortality. There was evidence of significant non-linearity for MAP, but not for age or BMI (Table D.8). Age and BMI were subsequently included without non-linear terms.

Schoenfeld residuals were used to assess the proportional hazards assumption. There was no evidence that the proportional hazards assumption was violated (Table D.9 & Figure D.4).

Confounding of the association between abnormal fundus photographs and hospital admission was accessed using all model subsets (Table D.10). No variables were confounders by the 10% rule. However, because age was significantly associated with mortality and because of concerns about residual confounding, all variables were retained in the final model (Table 4.4).

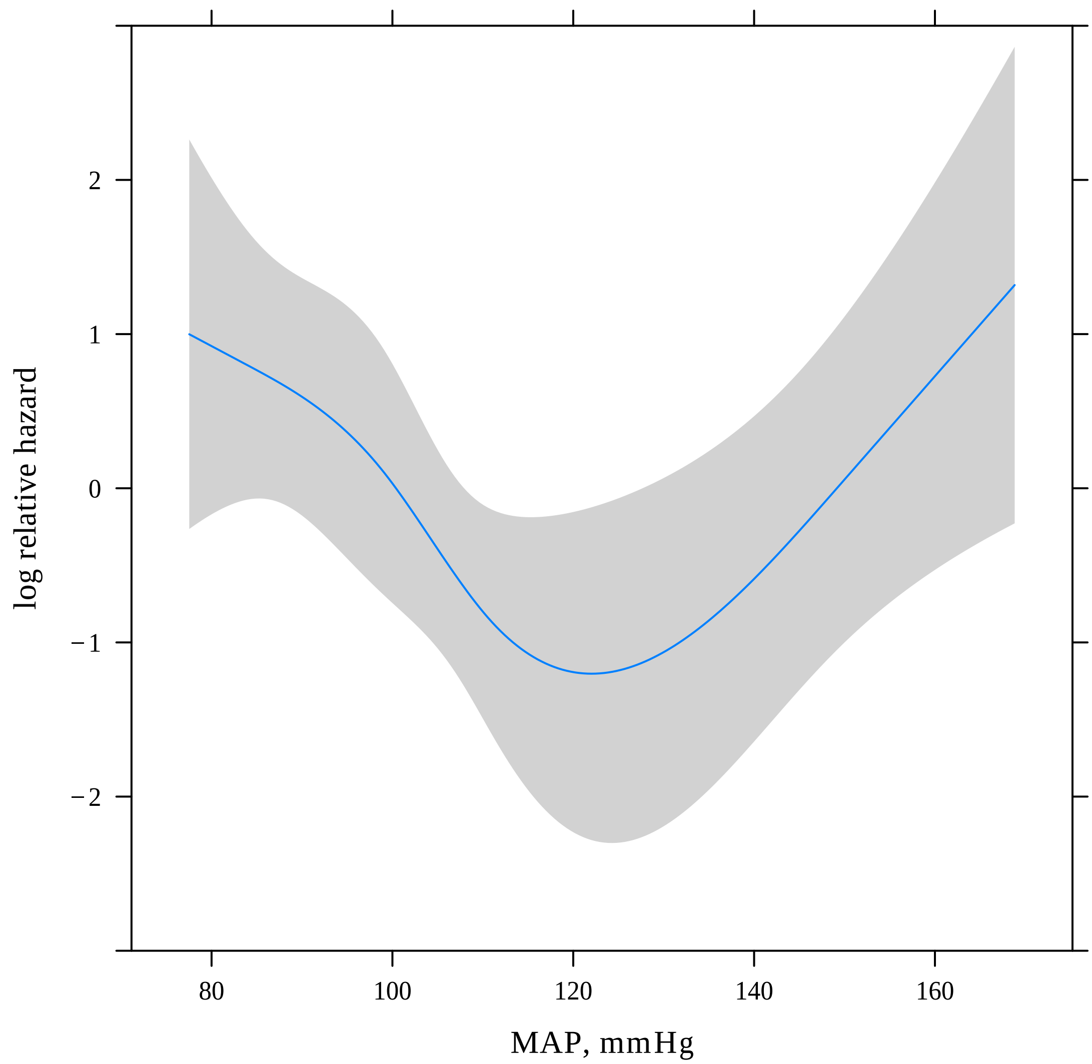


FIGURE 4.7 Four-knot restricted cubic spline with 95% CI for log relative hazard of death vs. MAP adjusted to reference categories for categorical variables and to the mean values of other continuous variables.

4.4 Discussion

We found that abnormal fundus photographs were associated with a significantly higher rate of hospital admission (about 2 times higher) and of death from any cause (about 4 times higher), but not with ED revisit, controlling for age, race, sex, MAP, and BMI. In the case of ED revisits, black race increased the rate by about 1.5 times while an increase in BMI by 10 kg/m^2 increased it by about 1.2 times. Older age was also significantly associated with hospital admission and mortality as would be expected.

While ocular fundus findings could lead to initial hospital admission (e.g., newly diagnosed papilledema, which is swelling of the optic nerves related to increased intracranial pressure), it is not expected that these findings would directly cause future admissions that did not occur within the first few days after the initial ED visit. However, we found that even after excluding admissions within a week of the index visit, fundus abnormalities continued to double the rate of admission. Outside of the early period, we do not suspect that abnormalities of the ocular fundus are direct causes of death, but rather serve as a biomarker of overall neuro- and cardiovascular health, which does have direct effects on the future risk of hospitalization and death. Based on the Kaplan-Meier curves of all-cause mortality, there appears to be several months before substantial separation occurs between patients with normal and abnormal fundus photography suggesting there is a window of opportunity for interventions that may be able to prolong patient's lives.

Although there was a higher frequency of hospital admission among the patients with abnormal fundus photography, there was no significant association between recurrent hospital admissions and the results of fundus photography. This is likely partially related to statistical power because we only recorded the first 5 hospital admission dates and because we appropriately used the robust sandwich variance estimator for the recurrent event analysis (which generally increases the estimate of the variance). However, the lower hazard ratio in the recurrent events model compared with the hazard ratio for first hospital admission is not necessarily unexpected, since we would expect that admissions subsequent to the first would be less associated with the findings at the index visit.

One limitation of our data is that the underlying causes of death are unknown and therefore it is difficult to establish that the ocular findings are indeed theoretically related to excess cardio- and neurovascular disease. Another limitation is that we do not have clinical information about the patients' other medical problems and ED discharge diagnoses. It is therefore possible that the association of fundus photography with hospital admission and death could be fully explained by this information. Another limitation of our data is our very heterogenous group of patients from a single, university-based ED, with conclusions in some cases based on a relatively small number of events (e.g., mortality). Finally, even if we are able to validate our findings regarding the value of ocular fundus abnormalities for risk stratification in a larger multicenter investigation, it is unclear that we will necessarily be able to impact the patient's outcomes with targeted interventions based solely upon the presence of fundus abnormalities.

Chapter 5
Conclusion & Future Directions

5.1 Summary of dissertation-related findings

We found that patients with focal neurologic deficits and elevated DBP were less likely to be examined compared to patients with other complaints while patients with visual complaints were more likely to be examined. We found that men with neurological complaints and blacks with visual complaints were less likely to be examined which was concerning because these groups were at equal or greater risk of ocular fundus abnormalities than their counterparts.

We found that lower quality and older age were associated with a higher frequency of false positive errors and that black race was associated with a higher frequency of false negative errors. We also found that neither the effects of older age nor of race on errors appeared to be primarily mediated by photographic quality.

Finally, we found that abnormal fundus photography was associated with a higher hazard of hospital admission and of all-cause mortality independent of other factors that were controlled.

5.2 Limitations

The FOTO-ED study, and therefore our present studies, had several notable limitations. First, our study was limited to patients considered to be at high risk for ocular findings and we had no subjects without these complaints in order to compare their frequency of ocular fundus abnormalities and their subsequent clinical course. However, in a community-wide survey of 842 persons, 23 (2.7%) had potentially serious undiagnosed ocular fundus findings, but only two of these were of the type requiring urgent management (0.2%),[63] suggesting that our academic ED setting and inclusion criteria contribute to the very high risk of acutely relevant ocular fundus abnormalities (11%).

Second, patient identification in the first phase required substantially more vigilance by the nurse practitioners during their already busy clinical shifts. Thus, the patients included in the first phase likely had somewhat more severe disease and had a higher frequency of visual complaints than the patients in the second phase when the automated identification system was in place. Because no details regarding which patients were screened but excluded were recorded in the first phase it is difficult to assess the potential impact this selection bias may have had on our results.

Third, there were convenience aspects of our sample because of the limited availability of study staff. However, even if we were to assume that patients presenting during the nights and weekends were substantially different from patients presenting during weekdays, our findings would still have important implications for the care of patients in the ED during the periods studied.

Fourth, in the second phase of the study, the ED physicians were notified that photographs were available for their review both by case report forms and by a notification on the ED census screen in the electronic medical record. In the first phase of the study, the ED physicians had no stimulus to examine the ocular fundus beyond being aware that a study on the topic was ongoing in the ED. This may have been partially responsible for the more frequent use of fundus photography in the second phase compared to direct ophthalmoscopy in the first phase. However, it seems unlikely that notification alone accounts for the ED physicians using photographs 5 times more frequently than direct ophthalmoscopy. Furthermore, because 32% of the patients did not have their photographs reviewed by ED physicians, despite notification alerts, including 23% of patients with relevant abnormalities, it appears clear that our method of notification alone does not lead to consistent examination of the fundus.[36]

Fifth, some of our subgroup analyses are limited by small cell sizes. This was particularly seen in Section 2.3.2 where the small number of patients with DBP $\geq$ 120 mmHg led to complete separation. However, these small cell sizes likely caused some of our analyses to be underpowered.

Finally, it is important to note that our findings are based on a single, university-based ED. It is unclear whether the higher patient acuity expected in our center will allow our results to be generalized to other EDs, particularly in the community.

5.3 Conclusion

Overall, our work is in the spirit of consequential or consequentialist epidemiology, which calls upon our field to refocus our rigorous scientific methods from primarily studying etiology to making healthcare more effective, equitable, and efficient.[64,65] Indeed, combining our present work with that of the overall FOTO-ED study, it is clear that substantial efforts are required to reach a goal of 100% examination of the ocular fundus in the patients at highest risk of underlying ocular findings. The studies in Chapters 2 & 3 show that there are possible gender and race disparities in the frequency of ocular fundus examination that require further exploration. If these findings are confirmed, it is likely that a broader approach than simply appealing to the high frequency of relevant findings for appropriate patient care will be required to overcome all the barriers to ideal fundus examination in the ED.

While we recognize that abnormal ocular findings are not usually, if ever, the primary motivation for hospital admission or the cause of death, we did find that nearly half of the ocular fundus findings had a clear relationship to the patient's future admission to the hospital. However, further work is needed to identify which half of the patients with ocular fundus findings will need more aggressive diagnostic and therapeutic intervention in hopes of preventing these poor outcomes at the time they are in the ED. Regardless, the simplicity with which fundus photography can be obtained and its strong association with mortality among patients presenting to the ED with an important subset of complaints and conditions (including headache the fourth most common presenting complaint and most common neurological complaint in the ED[66]) suggests that fundus photography may represent a "sixth vital sign" for these patients (temperature, heart rate, blood pressure, respiratory rate, and pain are usually considered the five vital signs).

However, it is important not to overemphasize the importance of our results at this early stage in our investigation. As we have already pointed out, our findings are based upon a relatively small sample from a single, university-based ED and should be interpreted within the context of the limitations of our study (see Section 5.2). However, we feel that our results, particularly with respect to hospital admission and mortality, justify confirmation in a larger, multicenter study. Ideally, future studies of non-mydriatic fundus photography in the ED will focus not only risk stratification, but on targeted, early intervention in patients with abnormal photographs to prevent poor outcomes.

5.3.1 Education

With regards to improving ocular fundus examination in the emergency department, we recognize that education will be an important component. Toward that end, we are currently conducting a quality improvement project in the Emory University ED, which will include an web-based educational component, to help ED physicians learn to read fundus photographs for abnormalities and correctly interpret common artifacts.

We have also been evaluating the use of fundus photography as an alternative to direct ophthalmoscopy in the education of medical students. We studied 138 first-year medical students,[67] 119 (86%) of whom completed all required elements. For learning ophthalmoscopy, 85 (71%) preferred humans to patient simulators. For learning relevant features of the ocular fundus, 92 (77%) preferred photographs to ophthalmoscopy on simulators or humans. The students' accuracy was better when interpreting fundus photographs than when performing ophthalmoscopy on simulators, and their performance improved after specific teaching about assessing fundus photographs before testing ($P = 0.02$). Examination of the ocular fundus was found easier and less frustrating when using photographs than when using ophthalmoscopy on simulators or humans. Eighty-four students (70%) said they would prefer to have fundus photographs instead of using the ophthalmoscope during upcoming clinical rotations.

In a one-year follow-up study of the same students,[68] 107 (90%) of which participated, the students' self-reported median frequency of fundus examination over the preceding year was <10% (interquartile range: 0%-20%). Of 107 students, 85 (79%) felt uncomfortable with ophthalmoscopy, 47 (44%) stated they would not perform ophthalmoscopy during general physical examinations, and 81 (76%) stated they would prefer using photographs over ophthalmoscopy for fundus examination. Students continued to be more accurate using photographs than ophthalmoscopy and still preferred photographs for examining the ocular fundus. Although both groups performed significantly worse in identifying relevant fundus features than 1 year prior, the difference was equal in the 2 groups and likely related to a lack of fundus examination skill reinforcement in the interim. Most students felt uncomfortable with ophthalmoscopy, which may cause avoidance of ocular fundus examination in clinically appropriate situations. Of concern, 20% of students cited discouragement by their clinical preceptor as their primary reason for not performing ophthalmoscopy, which suggests that postgraduate education may be needed to create a long-term change in the use and performance of fundus examination.

5.3.2 Expansion & New Directions

We plan expansions of our study to other local sites (e.g., Grady Memorial Hospital and Emory University Hospital Midtown) and to international sites over the coming years which will allow us to validate our results in other settings and further explore the large-scale feasibility and cost-benefit of the telemedical evaluations that this technique provides.

We are planning to evaluate the role of ocular fundus findings in the diagnosis and prognosis of patients with TIA and minor stroke. New portable, handheld cameras are expanding the patient population to which we can apply non-mydriatic photography, and we plan to evaluate their use in patients who are too ill to sit-up in the ED and in the neurosciences intensive care unit. Non-mydriatic photography will also likely have applications in other settings, such as headache clinics, general neurology clinics, and pediatric EDs. Fundus photography also provides the potential for automatic photographic reading to assist frontline clinicians, another area which we hope to evaluate further.[69]

Our long-term goals specifically include the study of early therapeutic interventions for acute neuro-ophthalmic vascular diseases, such as anterior ischemic optic neuropathy and central retinal artery occlusion, disorders that cause severe visual loss in thousands of Americans each year. As exhibited by clinical trials in stroke using intravenous tissue plasminogen activator, there is a narrow therapeutic window for preserving and healing neural tissues, including the optic nerve and retina. However, within existing clinical frameworks the diagnosis of these disorders is often delayed because specialized expertise is not readily available in the ED of most medical centers. Non-mydriatic photography and telemedicine may provide the method needed to provide this specialized expertise to patients and advance patient care and clinical research. The advantages of telemedicine have already been demonstrated in the process of administering emergent therapies in stroke, and given my background, I hope to apply advances in tele-ophthalmology and non-mydriatic fundus photography in the ED, to the management of acute neuro-ophthalmic patients. Ultimately, establishing an ED tele-ophthalmology medical network could open a door to evaluating novel therapies such as neuro-protective agents for acute neuropathies and provide improved patient care for patients with these emergent diseases.

Chapter 6
References

1. Miller NR, Newman NJ, Biousse V, Kerrison JB, eds. *Walsh and Hoyt's clinical neuro-ophthalmology*. Philadelphia: Lippincott Williams & Wilkins; 2005.
2. Biousse V, Ameri A, Bousser MG. Isolated intracranial hypertension as the only sign of cerebral venous thrombosis. *Neurology*. 1999; 53: 1537–42.
3. Ball AK, Clarke CE. Idiopathic intracranial hypertension. *Lancet Neurol*. 2006; 5: 433–442.
4. Corbett JJ, Savino PJ, Thompson HS, Kansu T, Schatz NJ, Orr LS, Hopson D. Visual loss in pseudotumor cerebri. follow-up of 57 patients from five to 41 years and a profile of 14 patients with permanent severe visual loss. *Arch Neurol*. 1982; 39: 461–474.
5. Thambisetty M, Lavin PJ, Newman NJ, Biousse V. Fulminant idiopathic intracranial hypertension. *Neurology*. 2007; 68: 229–232.
6. Schliep *v.* Providence Yakima Med. Ctr.. In *Wash. App.*, 2005.
7. Breen DP, Duncan CW, Pope AE, Gray AJ, Al-Shahi Salman R. Emergency department evaluation of sudden, severe headache. *QJM*. 2008; 101: 435–443.
8. Maizels M. Headache evaluation and treatment by primary care physicians in an emergency department in the era of triptans. *Arch Intern Med*. 2001; 161: 1969–1973.
9. Cordeiro MF, Jolly BC, Dacre JE. The effect of formal instruction in ophthalmoscopy on medical student performance. *Med Teach*. 1993; 15: 321–325.
10. Morad Y, Barkana Y, Avni I, Kozer E. Fundus anomalies: what the pediatrician's eye can't see. *Int J Qual Health Care*. 2004; 16: 363–365.
11. Ang GS, Dhillon B. Do junior house officers routinely test visual acuity and perform ophthalmoscopy? *Scott Med J*. 2002; 47: 60–63.
12. Roberts E, Morgan R, King D, Clerkin L. Funduscopy: a forgotten art? *Postgrad Med J*. 1999; 75: 282–284.
13. Committee on the Future of Emergency Care in the United States Health System Board on Health Care Services. The emergency care workforce. In *Hospital-based emergency care: at the breaking point*. Washington, DC: National Academies Press; 2007: 209–258.
14. Rudkin SE, Oman J, Langdorf MI, Hill M, Bauche J, Kivela P, Johnson L. The state of ED on-call coverage in California. *Am J Emerg Med*. 2004; 22: 575–581.
15. Mohanty SA, Washington DL, Lambe S, Fink A, Asch SM. Predictors of on-call specialist response times in California emergency departments. *Acad Emerg Med*. 2006; 13: 505–512.
16. Solberg KE. Telemedicine set to grow in india over the next 5 years. *Lancet*. 2008; 371: 17–18.
17. ORBIS. Cyber-sight [online], available at: http://www.orbis.org. Accessed on 25 Apr 2014.
18. ORBIS Canada. ORBIS Canada Twitter Feed [online], available at: http://twitter.com/ORBISCA/status/433620212517048320. Accessed on 25 Apr 2014.
19. Bar-Sela SM, Glovinsky Y. A feasibility study of an internet-based telemedicine system for consultation in an ophthalmic emergency room. *J Telemed Telecare*. 2007; 13: 119–124.
20. Baker ML, Larsen EK, Kuller LH, Klein R, Klein BE, Siscovick DS, Bernick C, Manolio TA, Wong TY. Retinal microvascular signs, cognitive function, and dementia in older persons. the cardiovascular health study. *Stroke*. 2007; 38: 2041–2047.

21. Cheung N, Rogers S, Couper DJ, Klein R, Sharrett AR, Wong TY. Is diabetic retinopathy an independent risk factor for ischemic stroke? *Stroke*. 2007; 38: 398–401.
22. Cheung N, Wang JJ, Klein R, Couper DJ, Richey Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease: The atherosclerosis risk in communities study. *Diabetes Care*. 2007; 30: 1742–1746.
23. Liew G, Mitchell P, Wang JJ, Wong TY. Fundoscopy: to dilate or not to dilate? *BMJ*. 2006; 332: 3.
24. Wong T, Mitchell P. The eye in hypertension. *Lancet*. 2007; 369: 425–435.
25. Wong TY. Fred hollows lecture: hypertensive retinopathy - a journey from fundoscopy to digital imaging. *Clin Experiment Ophthalmol*. 2006; 34: 397–400.
26. Wong TY, Klein R, Amirul Islam FM, Cotch MF, Couper DJ, Klein BE, Hubbard LD, Sharrett AR. Three-year incidence and cumulative prevalence of retinopathy: the atherosclerosis risk in communities study. *Am J Ophthalmol*. 2007; 143: 970–976.
27. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med*. 2004; 351: 2310–2317.
28. Hubbard LD, Brothers RJ, King WN, Clegg LX, Klein R, Cooper LS, Sharrett AR, Davis MD, Cai J. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the atherosclerosis risk in communities study. *Ophthalmology*. 1999; 106: 2269–2280.
29. Lin DY, Blumenkranz MS, Brothers RJ, Grosvenor DM. The sensitivity and specificity of single-field nonmydriatic monochromatic digital fundus photography with remote image interpretation for diabetic retinopathy screening: a comparison with ophthalmoscopy and standardized mydriatic color photography. *Am J Ophthalmol*. 2002; 134: 204–213.
30. Chow SP, Aiello LM, Cavallerano JD, Katalinic P, Hock K, Tolson A, Kirby R, Bursell SE, Aiello LP. Comparison of nonmydriatic digital retinal imaging versus dilated ophthalmic examination for nondiabetic eye disease in persons with diabetes. *Ophthalmology*. 2006; 113: 833–840.
31. Maberley D, Walker H, Koushik A, Cruess A. Screening for diabetic retinopathy in james bay, ontario: a cost-effectiveness analysis. *CMAJ*. 2003; 168: 160–164.
32. Ells AL, Holmes JM, Astle WF, Williams G, Leske DA, Fielden M, Uphill B, Jennett P, Hebert M. Telemedicine approach to screening for severe retinopathy of prematurity: a pilot study. *Ophthalmology*. 2003; 110: 2113–2117.
33. Lamirel C, Bruce BB, Wright DW, Newman NJ, Biousse V. Nonmydriatic digital ocular fundus photography on the iPhone 3G: the FOTO-ED study. *Arch Ophthalmol*. 2012; 130: 939–940.
34. Bruce BB, Lamirel C, Wright DW, Ward A, Heilpern KL, Biousse V, Newman NJ. Nonmydriatic ocular fundus photography in the emergency department. *N Engl J Med*. 2011; 364: 387–389.
35. Bruce BB, Lamirel C, Biousse V, Ward A, Heilpern KL, Newman NJ, Wright DW. Feasibility of nonmydriatic ocular fundus photography in the emergency department: Phase I of the FOTO-ED study. *Acad Emerg Med*. 2011; 18: 928–933.
36. Bruce BB, Thulasi P, Fraser CL, Keadey MT, Ward A, Heilpern KL, Wright DW, Newman NJ, Biousse V. Diagnostic accuracy and use of nonmydriatic ocular fundus photography by emergency physicians: phase II of the FOTO-ED study. *Ann Emerg Med*. 2013; 62: 28–33.e1.
37. Razminia M, Trivedi A, Molnar J, Elbzour M, Guerrero M, Salem Y, Ahmed A, Khosla S, Lubell DL. Validation of a new formula for mean arterial pressure calculation: the new formula is superior to the standard formula.. *Catheter Cardiovasc Interv*. 2004; 63: 419–425.
38. Kleinbaum DG, Klein M. *Logistic Regression: A Self-Learning Text*. New York: Springer-Verlag; 2002.

39. Harrell FE. *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*, pages 23–24. New York: Springer-Verlag; 2001.
40. Carson JA, Peets A, Grant V, McLaughlin KS. The effect of gender interactions on students' physical examination ratings in objective structured clinical examination stations. *Acad Med*. 2010; 85: 1772–1776.
41. Humphrey-Murto S, Touchie C, Wood TJ, Smee S. Does the gender of the standardised patient influence candidate performance in an objective structured clinical examination? *Med Educ*. 2009; 43: 521–525.
42. Digre KB, Corbett JJ. *Practical Viewing of the Optic Disc*. Burlington, MA: Butterworth-Heinemann; 2003.
43. Enelow AJ. *Interviewing and Patient Care*. New York: Oxford University Press; 1996.
44. "Smedley BD, Stith AY, Nelson AR", eds. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*. Washington: National Academies Press; 2003.
45. Vaccarino V, Rathore SS, Wenger NK, Frederick PD, Abramson JL, Barron HV, Manhapra A, Mallik S, Krumholz HM. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. *N Engl J of Med*. 2005; 353: 671–682.
46. Lamirel C, Bruce BB, Wright DW., Delaney KP, Newman NJ, Biousse V. Quality of non-mydriatic digital fundus photography obtained by nurse practitioners in the emergency department: The FOTO-ED study. *Ophthalmology*. 2012; 119: 617–624.
47. Winn B, Whitaker D, Elliott DB, Phillips NJ. Factors affecting light-adapted pupil size in normal human subjects. *Invest Ophthalmol Vis Sci*. 1994; 35: 1132–1137.
48. Kanthan GL, Wang JJ, Rochtchina E, Tan AG, Lee A, Chia EM, Mitchell P. Ten-year incidence of age-related cataract and cataract surgery in an older Australian population. The Blue Mountains Eye Study. *Ophthalmology*. 2008; 115: 808–814.
49. Delori FC, Pflibsen KP. Spectral reflectance of the human ocular fundus. *Appl Opt*. 1989; 28: 1061–1077.
50. Baker ML, Hand PJ, Wang JJ, Wong TY. Retinal signs and stroke: revisiting the link between the eye and brain. *Stroke*. 2008; 39: 1371–1379.
51. Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat*. 2005; 206: 319–348.
52. Wong TY, Klein R, Klein BE, Tielsch JM, Hubbard L, Nieto FJ. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. *Surv Ophthalmol*. 2001; 46: 59–80.
53. Henderson AD, Bruce BB, Newman NJ, Biousse V. Hypertension-related eye abnormalities and the risk of stroke. *Rev Neurol Dis*. 2011; 8: 1–9.
54. Cooper LS, Wong TY, Klein R, Sharrett AR, Bryan RN, Hubbard LD, Couper DJ, Heiss G, Sorlie PD. Retinal microvascular abnormalities and MRI-defined subclinical cerebral infarction: the Atherosclerosis Risk in Communities Study. *Stroke*. 2006; 37: 82–86.
55. Kwon HM, Kim BJ, Oh JY, Kim SJ, Lee SH, Oh BH, Yoon BW. Retinopathy as an indicator of silent brain infarction in asymptomatic hypertensive subjects. *J Neurol Sci*. 2007; 252: 159–162.
56. Wong TY, Klein R, Nieto FJ, Klein BE, Sharrett AR, Meuer SM, Hubbard LD, Tielsch JM. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. *Ophthalmology*. 2003; 110: 933–940.
57. Wong TY. Is retinal photography useful in the measurement of stroke risk? *Lancet Neurol*. 2004; 3: 179–183.
58. Wong TY, McIntosh R. Systemic associations of retinal microvascular signs: a review of recent population-based studies. *Ophthalmic Physiol Opt*. 2005; 25: 195–204.

59. Sharrett AR, Hubbard LD, Cooper LS, Sorlie PD, Brothers RJ, Nieto FJ, Pinsky JL, Klein R. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1999; 150: 263–270.
60. Wong TY, Rosamond W, Chang PP, Couper DJ, Sharrett AR, Hubbard LD, Folsom A. R., Klein R.. Retinopathy and risk of congestive heart failure. *JAMA*. 2005; 293: 63–69.
61. Mimoun L, Massin P, Steg G. Retinal microvascularisation abnormalities and cardiovascular risk. *Arch Cardiovasc Dis*. 2009; 102: 449–456.
62. Witt N, Wong TY, Hughes AD, Chaturvedi N, Klein BE, Evans R, McNamara M, Thom SA, Klein R. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. *Hypertension*. 2006; 47: 975–981.
63. Smith RE, Ganley JP. Ophthalmic survey of a community. 1. Abnormalities of the ocular fundus. *Am J Ophthalmol*. 1972; 74: 1126–1130.
64. Cates W. Invited commentary: consequential(ist) epidemiology: let's seize the day. *Am J Epidemiol*. 2013; 178: 1192–1194.
65. Galea S. An argument for a consequentialist epidemiology. *Am J Epidemiol*. 2013; 178: 1185–1191.
66. Pitts SR, Niska RW, Xu J, Burt CW. National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. *Natl Health Stat Report*, pages 1–38, 2008.
67. Kelly LP, Garza PS, Bruce BB, Graubart EB, Newman NJ, Biousse V. Teaching ophthalmoscopy to medical students (the TOTeMS study). *Am J Ophthalmol*. 2013; 156: 1056–1061.
68. Mackay DD, Garza PS, Bruce BB, Bidot S, Graubart EB, Newman NJ, Biousse V, Kelly LP. Teaching Ophthalmoscopy to Medical Students (TOTeMS) II: A One-Year Retention Study. *Am J Ophthalmol*. 2014; 157: 747–748.
69. Fleming AD, Philip S, Goatman KA., Prescott GJ, Sharp PF, Olson JA. The evidence for automated grading in diabetic retinopathy screening. *Curr Diabetes Rev*. 2011; 7: 246–252.

Appendix A
Abbreviations Used

BMI	body mass index
CI	confidence interval
CSF	cerebrospinal fluid
DBP	diastolic blood pressure
ED	emergency department
EMR	electronic medical record
FOTO-ED	Fundus photography vs. Ophthalmoscopy Trial Outcomes in the Emergency Department
IIH	idiopathic intracranial hypertension
IQR	interquartile range
MAP	mean arterial pressure
OR	odds ratio

Appendix B
Assessment of confounding for logistic models

TABLE B.1 Assessment of confounding of the association between examination and complaint by age, BMI, and MAP.

Complaint or condition	Crude or stratum specific OR (95% CI)	Adjusted OR (95%CI)
Headache	0.86 (0.51–1.46)	0.83 (0.48–1.42)
Focal neurological complaint, men	0.30 (0.13–0.69)	0.31 (0.14–0.71)
Focal neurological complaint, women	0.69 (0.38–1.25)	0.68 (0.38–1.24)
Visual complaint, black race	1.36 (0.67–2.76)	1.33 (0.65–2.72)
Visual complaint, other/unknown race	2.97 (1.46–6.02)	2.99 (1.47–6.08)
DBP ≥ 120 mmHg	0.52 (0.21–1.27)	0.35 (0.12–1.02)

TABLE B.2 Assessment of confounding of the association between examination and presentation with DBP $\geq$ 120 mmHg by all subsets of age, BMI, and MAP.

Terms	OR
age, BMI, MAP	0.35 (0.12–1.02)
age, MAP	0.34 (0.12–1.02)
BMI, MAP	0.38 (0.13–1.11)
MAP, age	0.51 (0.21–1.26)
MAP	0.38 (0.13–1.11)
age	0.51 (0.21–1.25)
BMI	0.52 (0.21–1.27)
none	0.52 (0.21–1.27)

TABLE B.3A Assessment of confounding of the association between helpfulness and complaints/conditions by all subsets of abnormal fundus photography (abnormal), age, race, BMI, and MAP.

	OR			
Terms	**headache**	**neuro**	**vision**	**DBP**
none	1.12*	0.67	3.13	1.07*
abnormal	1.12*	0.67	3.12	1.06*
age	0.94	0.67	3.00	1.12*
sex	1.07*	0.64	3.13	1.04*
race	1.12*	0.65	3.16	1.03*
BMI	1.08*	0.67	3.16	1.00*
MAP	1.11*	0.66	3.09	1.56*
abnormal, age	0.94	0.67	3.00	1.11*
abnormal, sex	1.07*	0.64	3.12	1.03*
abnormal, race	1.12*	0.65	3.16	1.04*
abnormal, BMI	1.08*	0.67	3.16	1.00*
abnormal, MAP	1.10*	0.65	3.07	1.54*
age, sex	0.92	0.66	3.00	1.09*
age, race	0.94	0.66	3.02	1.09*
age, BMI	0.90	0.68	3.05	1.04*
age, MAP	0.94	0.67	2.98	1.32
sex, race	1.08*	0.63	3.16	1.01*
sex, BMI	1.05*	0.66	3.16	0.98*
sex, MAP	1.08*	0.64	3.10	1.49*

TABLE B.3B Assessment of confounding of the association between helpfulness and complaints/conditions by all subsets of abnormal fundus photography (abnormal), age, race, BMI, and MAP.

Terms	OR			
	headache	**neuro**	**vision**	**DBP**
race, BMI	1.08*	0.66	3.18	0.99*
race, MAP	1.11*	0.64	3.12	1.54*
BMI, MAP	1.07*	0.66	3.13	1.52*
abnormal, age, sex	0.92	0.66	3.00	1.09*
abnormal, age, race	0.94	0.66	3.02	1.10*
abnormal, age, BMI	0.90	0.68	3.06	1.05*
abnormal, age, MAP	0.94	0.67	2.97	1.32
abnormal, sex, race	1.08*	0.63	3.17	1.02*
abnormal, sex, BMI	1.05*	0.66	3.17	0.99*
abnormal, sex, MAP	1.07*	0.64	3.08	1.48*
abnormal, race, BMI	1.08*	0.66	3.19	0.99*
abnormal, race, MAP	1.11*	0.64	3.11	1.54*
abnormal, BMI, MAP	1.06*	0.66	3.12	1.51*
age, sex, race	0.92	0.65	3.02	1.08*
age, sex, BMI	0.89	0.67	3.05	1.03*
age, sex, MAP	0.92	0.66	2.99	1.29
age, race, BMI	0.90	0.68	3.06	1.04*
age, race, MAP	0.95	0.66	3.00	1.33
age, BMI, MAP	0.91	0.67	3.04	1.30

TABLE B.3C Assessment of confounding of the association between helpfulness and complaints/conditions by all subsets of abnormal fundus photography (abnormal), age, race, BMI, and MAP.

Terms	**OR** headache	neuro	vision	DBP
sex, race, BMI	1.05*	0.65	3.18	0.97*
sex, race, MAP	1.08*	0.62	3.12	1.49*
sex, BMI, MAP	1.05*	0.65	3.13	1.48*
race, BMI, MAP	1.07*	0.65	3.15	1.52*
abnormal, age, sex, race	0.92	0.65	3.03	1.08*
abnormal, age, sex, BMI	0.89	0.67	3.06	1.04*
abnormal, age, sex, MAP	0.92	0.65	2.98	1.28
abnormal, age, race, BMI	0.91	0.68	3.06	1.05*
abnormal, age, race, MAP	0.95	0.66	3.00	1.33
abnormal, age, BMI, MAP	0.91	0.67	3.03	1.30
abnormal, sex, race, BMI	1.06*	0.65	3.19	0.98*
abnormal, sex, race, MAP	1.08*	0.62	3.12	1.49*
abnormal, sex, BMI, MAP	1.05*	0.65	3.12	1.48*
abnormal, race, BMI, MAP	1.07*	0.65	3.15	1.51*
age, sex, race, BMI	0.89	0.67	3.06	1.03*
age, sex, race, MAP	0.93	0.65	3.01	1.29
age, sex, BMI, MAP	0.90	0.67	3.04	1.28
age, race, BMI, MAP	0.91	0.67	3.04	1.30
sex, race, BMI, MAP	1.05*	0.64	3.15	1.48*

TABLE B.3D Assessment of confounding of the association between helpfulness and complaints/conditions by all subsets of abnormal fundus photography (abnormal), age, race, BMI, and MAP.

Terms	**OR**			
	headache	**neuro**	**vision**	**DBP**
abnormal, age, sex, race, BMI	0.90	0.67	3.07	1.04*
abnormal, age, sex, race, MAP	0.93	0.65	3.01	1.29
abnormal, age, sex, BMI, MAP	0.90	0.67	3.04	1.28
abnormal, age, race, BMI, MAP	0.91	0.67	3.05	1.30
abnormal, sex, race, BMI, MAP	1.05*	0.64	3.15	1.48*
age, sex, race, BMI, MAP	0.90	0.66	3.05	1.29
abnormal, age, sex, race, BMI, MAP	0.90	0.66	3.05	1.29

TABLE B.4 ANOVA table for final multivariable logistic model of the association between examination by ED physician and complaint/condition.

Variable	χ^2	**d.f.**	p**-value**
Headache	0.51	1	0.475
Acute focal neurologic complaint (NEURO)	7.88	2	0.019
—Related interactions	3.16	1	0.075
Visual complaint	9.39	2	<0.01
—Related interactions	3.08	1	0.079
DBP ≥ 120 mmHg	3.72	1	0.054
Fundus photography (vs. direct ophthalmoscopy)	171.25	1	<0.01
Woman	3.78	2	0.151
—Related interactions	3.16	1	0.075
Black race	3.21	2	0.201
—Related interactions	3.08	1	0.079
Age, years	0.97	1	0.324
Mean arterial blood pressure, mmHg	1.65	1	0.199
NEURO × Woman	3.16	1	0.075
VISION × Black race	3.08	1	0.079
TOTAL INTERACTION	6.68	2	0.035
TOTAL	179.40	11	<0.01

Appendix C
Knot placement for non-linearity assessments

TABLE C.1 Placement of 5 knots for evaluation of non-linearity.

Variable	Knot 1	Knot 2	Knot 3	Knot 4	Knot 5
Age (years)	21.6	33.5	45.2	56.6	76.6
BMI (kg/m^2)	19.5	24.3	27.5	32.1	45.4
MAP (mmHg)	83.4	95.7	104.9	114.4	149.6

TABLE C.2 Placement of 4 knots for evaluation of non-linearity.

Variable	Knot 1	Knot 2	Knot 3	Knot 4
Age (years)	21.6	37.2	52.7	76.6
BMI (kg/m^2)	19.5	25.1	30.6	45.4
MAP (mmHg)	83.4	98.9	110.9	149.6

Appendix D

Assessment of confounding, nonlinearity, and proportional hazard assumptions for Cox models

TABLE D.1 Assessment of non-linearity in a Cox proportional hazards model of first ED revisit.

Variable	χ^2	d.f.	p-value
Abnormal fundus photograph	0.63	1	0.426
Age (years)	8.41	4	0.078
—Nonlinear	7.33	3	0.062
Black race	13.00	1	<0.01
Mean arterial pressure (mmHg)	3.06	4	0.547
—Nonlinear	3.04	3	0.385
Body mass index (kg/m^2)	10.26	4	0.036
—Nonlinear	3.22	3	0.359
TOTAL NONLINEAR	14.16	9	0.117
TOTAL	36.50	14	<0.01

TABLE D.2 Assessment of the proportional hazards assumption (score test) in the Cox proportional hazards model of first ED revisit.

Variable	ρ	χ^2	p**-value**
Abnormal fundus photograph	–0.036	0.392	0.531
Age, first term	–0.007	0.015	0.901
Age, second term	0.050	0.748	0.387
Age, third term	–0.054	0.895	0.344
Age, fourth term	0.052	0.843	0.358
Black race	0.035	0.390	0.532
Mean arterial pressure	0.005	0.008	0.927
Body mass index	–0.060	1.343	0.247
GLOBAL	NA	8.918	0.349

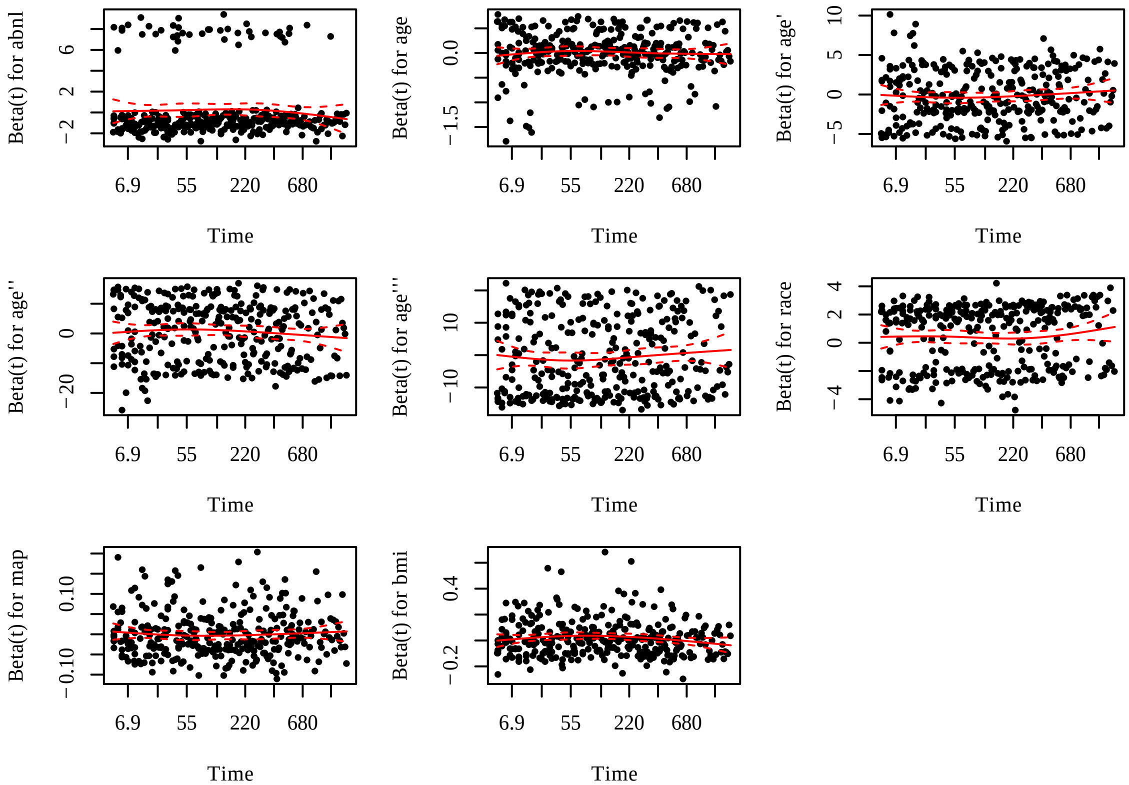


FIGURE D.1 Plot of Schoenfeld residuals (black points) with a fitted natural spline (solid red line, four degrees of freedom) and its 95% confidence intervals (dotted red lines) of Cox proportional hazards model of first ED revisit. abnl=abnormal fundus fundus photography, map=mean arterial blood pressure, bmi=body mass index, '=second spline term, ''=third spline term, '''=fourth spline term

TABLE D.3 Assessment of confounding of the association between abnormal fundus photographs and ED revisits by all subsets of age, race, body mass index (BMI), and mean arterial blood pressure (MAP).

Terms	HR
age, race, MAP, BMI	1.15 (0.82–1.61)
race, MAP, BMI	1.17 (0.83–1.64)
age, MAP, BMI	1.22 (0.87–1.71)
age, race, BMI	1.13 (0.81–1.58)
age, race, MAP	1.19 (0.85–1.66)
age, race	1.18 (0.85–1.64)
age, MAP	1.29 (0.92–1.80)
age, BMI	1.21 (0.87–1.68)
race, MAP	1.21 (0.86–1.69)
race, BMI	1.15 (0.83–1.61)
MAP, BMI	1.23 (0.88–1.72)
age	1.30 (0.94–1.81)
race	1.20 (0.86–1.67)
MAP	1.30 (0.93–1.82)
BMI	1.22 (0.87–1.69)
none	1.30 (0.94–1.81)

TABLE D.4 Assessment of non-linearity in a Cox proportional hazards model of first hospital admissions.

Variable	χ^2	**d.f.**	p**-value**
Abnormal fundus photograph	15.36	1	<0.01
Age (years)	35.66	4	<0.01
—Nonlinear	13.94	3	<0.01
Black race	0.50	1	0.480
Mean arterial pressure (mmHg)	7.34	4	0.119
—Nonlinear	6.24	3	0.101
Body mass index (kg/m^2)	8.71	4	0.069
—Nonlinear	2.80	3	0.423
TOTAL NONLINEAR	24.72	9	<0.01
TOTAL	64.88	14	<0.01

TABLE D.5 Assessment of the proportional hazards assumption (score test) in the Cox proportional hazards model of hospital admissions.

Variable	ρ	χ^2	***p*-value**
Abnormal fundus photograph	−0.011	0.028	0.867
Age, first term	0.001	0.001	0.982
Age, second term	−0.007	0.010	0.920
Age, third term	0.010	0.022	0.882
Age, fourth term	−0.013	0.036	0.849
Black race	0.154	5.588	0.018
Mean arterial pressure	0.042	0.540	0.462
Body mass index	0.123	4.590	0.032
GLOBAL	NA	15.478	0.050

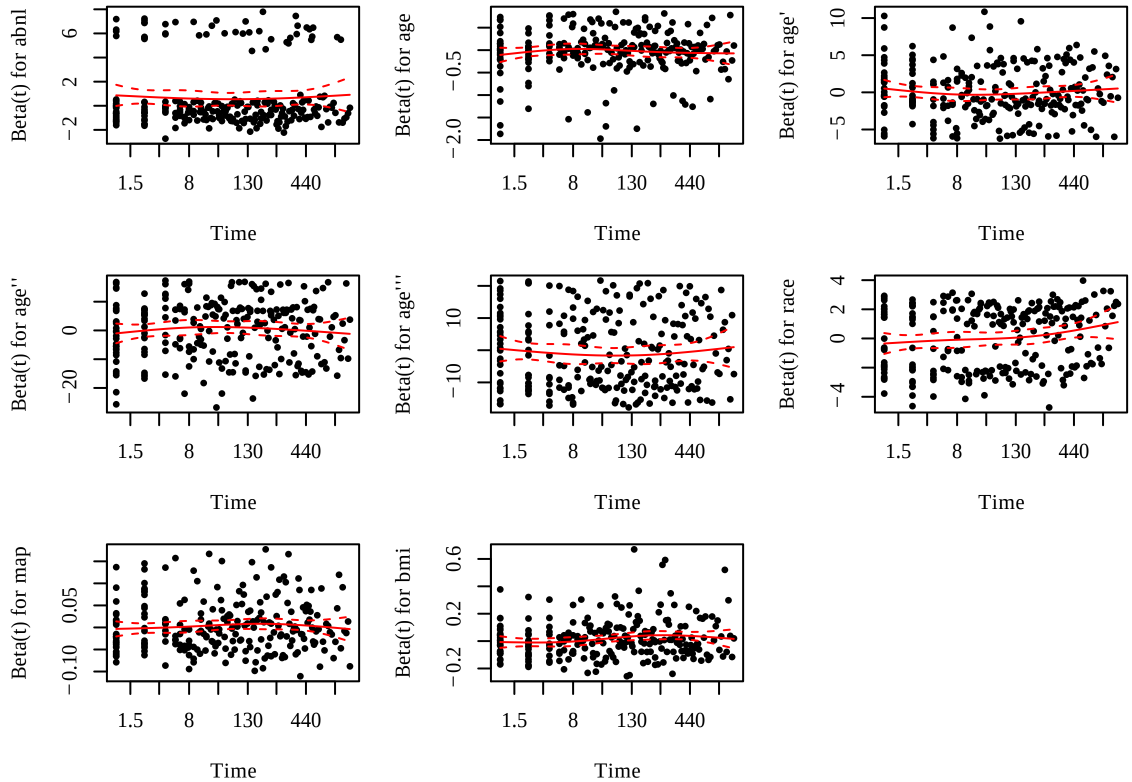


FIGURE D.2 Plot of Schoenfeld residuals (black points) with a fitted natural spline (solid red line, four degrees of freedom) and its 95% confidence intervals (dotted red lines) of Cox proportional hazards model of first hospital admission. abnl=abnormal fundus fundus photography, map=mean arterial blood pressure, bmi=body mass index, '=second spline term, ''=third spline term, '''=fourth spline term

TABLE D.6 Assessment of the proportional hazards assumption (score test) in the Cox proportional hazards model of hospital admissions stratified by race and body mass index 30 or greater.

Variable	ρ	χ^2	p**-value**
Abnormal fundus photograph	0.008	0.015	0.901
Age, first term	0.003	0.002	0.964
Age, second term	–0.001	0.000	0.984
Age, third term	0.002	0.001	0.972
Age, fourth term	–0.004	0.003	0.954
Mean arterial pressure	0.051	0.790	0.374
GLOBAL	NA	1.267	0.973

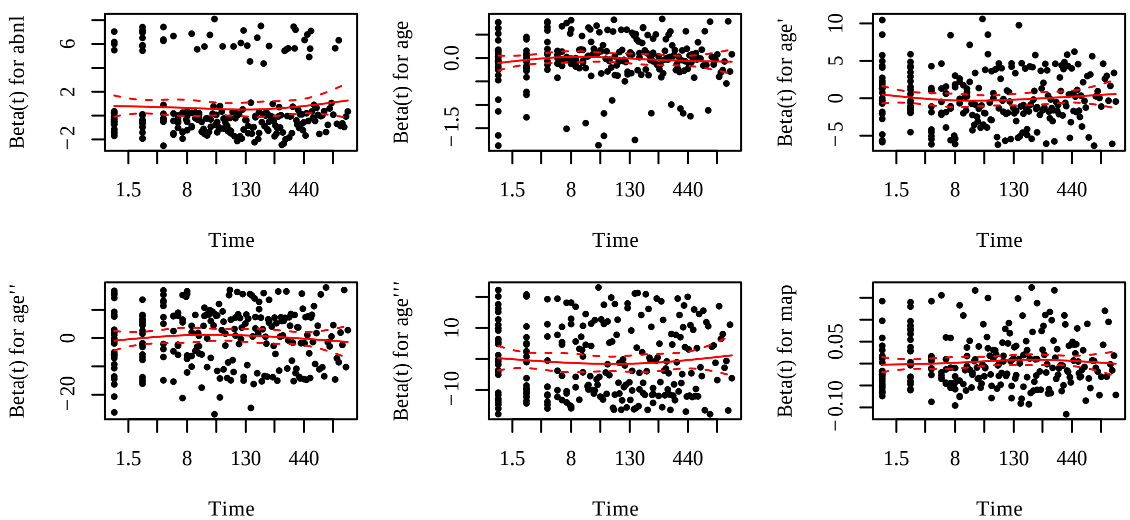


FIGURE D.3 Plot of Schoenfeld residuals (black points) with a fitted natural spline (solid red line, four degrees of freedom) and its 95% confidence intervals (dotted red lines) of Cox proportional hazards model of first hospital admission stratified by race and body mass index 30 or greater. abnl=abnormal fundus fundus photography, map=mean arterial blood pressure, bmi=body mass index, '=second spline term, "=third spline term, '"=fourth spline term

TABLE D.7 Assessment of confounding in a Cox proportional hazards model stratified by race of the association between abnormal fundus photographs and hospital admission by all subsets of age, race, BMI, and MAP.

Terms	**HR**
age, MAP	2.00 (1.42–2.81)
age	2.12 (1.53–2.95)
MAP	1.98 (1.42–2.77)
none	2.10 (1.51–2.91)

TABLE D.8 Assessment of non-linearity in a Cox proportional hazards model of mortality.

Variable	χ^2	**d.f.**	***p*-value**
Abnormal fundus photograph	7.73	1	<0.01
Age (years)	9.27	3	0.026
—Nonlinear	2.85	2	0.240
Black race	0.05	1	0.821
Mean arterial pressure (mmHg)	9.43	3	0.024
—Nonlinear	9.34	2	<0.01
Body mass index (kg/m^2)	1.61	3	0.657
—Nonlinear	1.45	2	0.484
TOTAL NONLINEAR	13.49	6	0.036
TOTAL	29.11	11	<0.01

TABLE D.9 Assessment of the proportional hazards assumption (score test) in the Cox proportional hazards model of mortality.

Variable	ρ	χ^2	p**-value**
Abnormal fundus photograph	0.084	0.145	0.704
Age	0.200	0.557	0.455
Black race	–0.067	0.113	0.737
MAP, first term	–0.018	0.003	0.956
MAP, second term	0.169	0.262	0.609
MAP, third term	–0.187	0.336	0.562
BMI	0.323	2.446	0.118
GLOBAL	NA	5.012	0.658

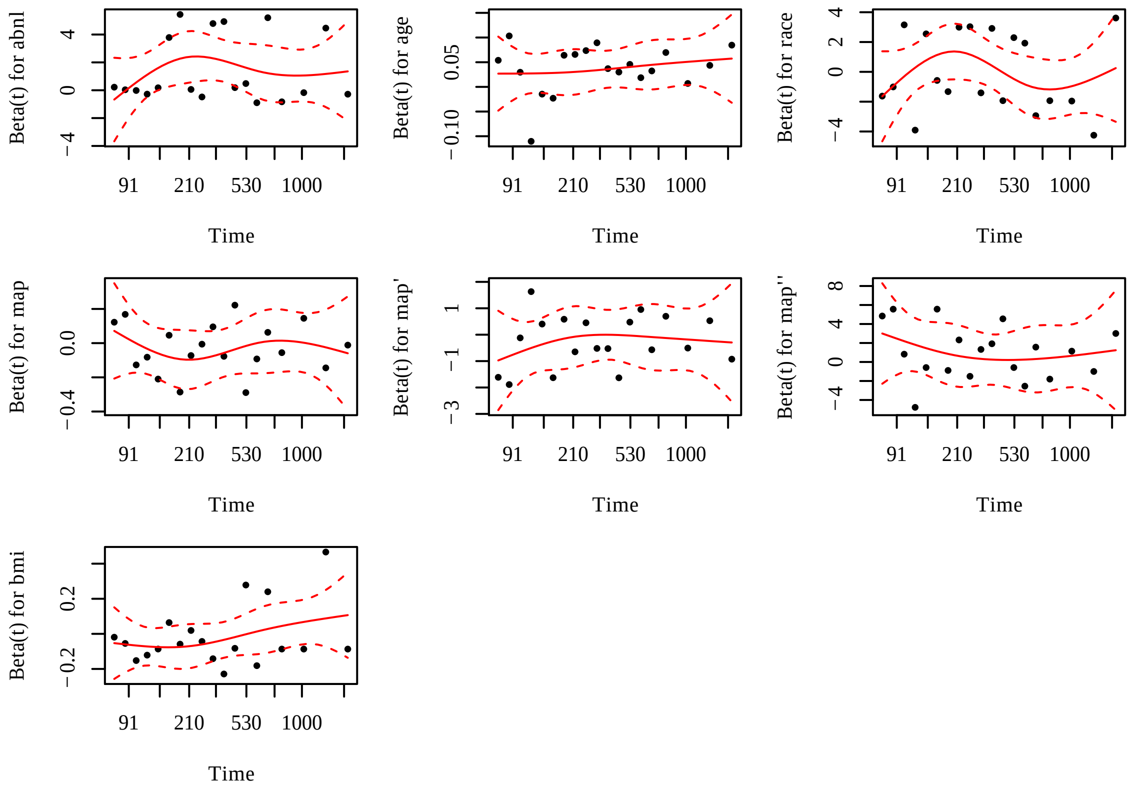


FIGURE D.4 Plot of Schoenfeld residuals (black points) with a fitted natural spline (solid red line, four degrees of freedom) and its 95% confidence intervals (dotted red lines) of Cox proportional hazards model of mortality. abnl=abnormal fundus fundus photography, map=mean arterial blood pressure, bmi=body mass index, '=second spline term, "=third spline term

TABLE D.10 Assessment of confounding of the association between abnormal fundus photographs and all-cause mortality by all subsets of age, race, BMI, and MAP.

Terms	HR
age, race, MAP, BMI	4.10 (1.51–11.15)
race, MAP, BMI	4.12 (1.47–11.54)
age, MAP, BMI	4.09 (1.51–11.08)
age, race, BMI	4.10 (1.51–11.15)
age, race, MAP	4.14 (1.53–11.25)
age, race	4.14 (1.53–11.25)
age, MAP	4.12 (1.52–11.14)
age, BMI	4.09 (1.51–11.08)
race, MAP	4.18 (1.50–11.64)
race, BMI	4.12 (1.47–11.54)
MAP, BMI	3.89 (1.41–10.74)
age	3.67 (1.39–9.65)
race	3.94 (1.47–10.59)
MAP	3.91 (1.42–10.77)
BMI	3.94 (1.49–10.43)
none	3.63 (1.38–9.56)