Stroke Disparities and Selection Bias in an American Indian Cohort: the Strong Heart and Strong Heart Stroke Studies

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Dedication

This work is dedicated to my dad.

Abstract

Background. American Indians experience higher stroke morbidity and mortality compared to US general population, but are underrepresented in public health research. Data on incident stroke in American Indians derive mainly from the Strong Heart Study (SHS), a population-based cohort study of cardiovascular disease in 4549 American Indians who were 45-74 years old when baseline exams were conducted from 1988-1990. The SHS had higher stroke rates than reported for Whites and African Americans in external comparisons to other cohorts. These findings suggested similar disparities in covert vascular brain injury (VBI), an often asymptomatic form of cerebrovascular disease that precedes clinical events. Accordingly, from 2010-2013 the Strong Heart Stroke Study (SHSS) used structural cranial magnetic resonance imaging to assess covert VBI in 1033 surviving members of the SHS.

Goals. In this dissertation we addressed three limitations to using SHS and SHSS data for analysis of stroke and covert VBI in American Indians: Manuscript 1) lack of research that directly compares stroke incidence and mortality in American Indians vs. other racial groups, and which limits current knowledge to external comparisons that do not account for differences in stroke risk factors; Manuscript 2) potential selection bias in SHSS data when survival and participation of cohort members depends on both the exposures and outcomes of interest; and Manuscript 3) an inherent limitation in effect measures estimates that condition on categories defined by progressively older age or longer time since exposure, and which leads to observed point estimates that are potentially biased estimates of the true effects.

Manuscript 1. Methods: We pooled data from the SHS and the Atherosclerosis Risk in Communities Study (ARIC) to compare stroke risk and post-stroke mortality in American Indians vs. Blacks and Whites. We used Cox regression to estimate hazard ratios (HR) with attained age as the time scale to account for differences in baseline age at enrollment, and adjusted estimates for baseline factors that included prevalent hypertension and diabetes. Due to effect modification, analyses were stratified by birth year tertile (1914-1930, 1931-1937, and 1938-1947). We used logistic regression to compare 30-day and 1-year post-stroke mortality among participants from both studies

who experienced stroke during follow-up. Results: Stroke risk among American Indians in the SHS was lower than among Blacks for all birth year tertiles (1914-1930: HR = 0.9 (95% CI = 0.7, 1.1); 1931-1937: HR = 0.9 (95% CI = 0.7, 1.2); 1938-1947: HR = 0.9 (95% CI = 0.7, 1.2)), but higher than among Whites (1914-1930: HR = 1.6 (95% CI = 1.3, 2.0); 1931-1937: HR = 2.2 (95% CI = 1.7, 2.8); 1938-1947: HR = 2.7 (95% CI = 2.0, 3.6)) in ARIC. Adjusting for risk factors including prevalent diabetes at baseline resulted in strengthening of associations compared to Blacks (oldest to youngest tertile HR = 0.8 (95% CI = 0.6-1.0); 0.7 (95% CI = 0.5-1.0); and 0.6 (95% CI = 0.4-0.8)), and attenuation of associations compared to Whites (oldest to youngest tertile HR = 1.1 (95% CI = 0.9-1.5); 1.2 (95% CI = 0.9-1.6); and 1.1 (95% CI = 0.8-1.5)). American Indians had higher risk of 30-day and 1-year mortality compared to Blacks (relative risk = 2.2 (95% CI = 1.4-3.0) and 1.4 (95% CI = 1.1-1.8), respectively) and Whites (relative risk = 1.8 (95% CI = 1.2-2.3) and 1.5 (95% CI = 1.1-1.8), respectively). These comparisons persisted after adjusting for risk factors.

Manuscript 2. Methods: We used marginal structural models with inverse probability weighting to adjust for selection bias in the SHSS, applied to the analysis of prevalent hypertension and covert VBI as measured by white matter hyperintensities. Predicted probabilities of survival from 1988-2010 and participation of survivors were estimated and inverted to create weights, and stabilized using conventional methods to reflect the distribution of hypertension in cohort participants. In addition, we computed novel stabilized weights that account for each person's probability of meeting the inclusion criterion of remaining stroke-free up to their SHSS exam. These weights allowed us to avoid over-correcting for attrition of individuals who would have subsequently gone on to experience clinical stroke. We applied these weights to estimate the prevalence difference (PD) for the association of hypertension with a binary indicator of abnormal VBI, as well as the mean difference (MD) for a continuous variable reflecting the ratio of white matter/total intracranial volume; the ratio estimates were multiplied by 1000 to simplify presentation of results. Hypertension was evaluated as both a cross-sectional risk factor and accounting for longitudinal trends in prevalence since baseline. Results: In the cross-sectional analysis, hypertension was associated with

higher prevalence of abnormal VBI in unweighted models (PD = 7.9% (95% CI = -2, 17)). The point estimate increased 13% after selection weighting (PD = 8.9% (95% CI = 0, 18)). Prevalent hypertension was likewise associated with a higher proportion of white matter volume compared to the total intracranial volume in unweighted models (MD = 0.8 (95% CI = -0.4, 2.0)) and after selection weighting (MD = 0.9 (95% CI = -0.3, 2.1)). Adjusting weights to account for the stroke-free inclusion criterion did not change results compared to the conventional stabilized estimates. In the analysis treating hypertension as a longitudinal exposure, prevalent hypertension at all three study exams was associated with higher prevalence of abnormal VBI (PD = 8.0% (95% CI = -6, 22)) and higher ratio of white matter/total intracranial volume (MD = 1.7 (95% CI = 0.0, 3.4)) compared to not having hypertension at any exam. Selection weighting had no appreciable impact on point estimates in the longitudinal analysis.

Manuscript 3. Methods: We used Mathematica software with constrained optimization to identify bounds for the risk difference (RD) when conditioning on event-free survival to some minimum age or time since exposure. Bounds were identified assuming only causative exposure effects in the target population, and allowing for exposure to prevent disease in some individuals so long as the causative effects were proportionally greater in the overall population. We applied these bounds to the analysis of post-stroke survival from Manuscript 1, with follow-up time divided into 0-30 days, 31-180 days, and 181-365 days after the stroke event. Results: The RD attenuated across follow-up periods for American Indians vs. Blacks (0-30 days: RD = 14% (95% CI = 6, 23); 31-180 days: RD = -1% (95% CI = -7, 4); 181-365 days: RD = -3% (95% CI = -7, 2)) and Whites (0-30 days: RD = 12% (95% CI = 3, 21); 31-180 days: RD = 1% (95% CI = -5, 6); 181-365 days: RD = -2% (95% CI = -6, 3)). With assumptions of only causative exposure effects, bounds on the the conditional risk difference for American Indians vs. Blacks were 0-16% for 0-30 days post-stroke event, and 1-13% for 181-365 days post-stroke. For American Indians vs. Whites the bounds were 0-14% for 0-30 days post stroke, and 0-13% for 31-180 days post-stroke. Allowing for preventive effects that were equal to or less than causative effects yielded bounds that were too wide for meaningful interpretation (all lower bounds = 0; all upper bounds $\geq$ 30).

Conclusions. We found that American Indians in the SHS had lower stroke risk than Blacks, but not than Whites, in ARIC after adjusting for risk factors that included prevalent diabetes. These findings suggest that diabetes may be a factor behind stroke disparities in some American Indian communities. American Indians had higher post-stroke mortality than Blacks and Whites especially in the first 30 days after stroke onset, but cumulative risk comparisons and analyses using bounds for conditional effects were consistent with elevated risk persisting for at least 1 year. Among long-term survivors of the SHS who participated in the SHSS assessment of covert VBI, selection bias may be of concern for some analyses. Although adjusting selection weights for the stroke-free inclusion criterion did not change results in this example, other studies with inclusion criteria that result in excluding larger proportions of the study population may wish to include sensitivity analyses with similar adjustments.

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List of Abbreviations

ARIC	Atherosclerosis Risk in Communities Study
CI	Confidence interval
HDL	High-density lipoproteins
HR	Hazard ratio
ICD-9	International Classification of Diseases – 9th Revision
IPW	Inverse probability weighting
LDL	Low-density lipoproteins
MD	Mean difference
PD	Prevalence difference
PR	Prevalence ratio
RD	Risk difference
RR	Risk ratio
SHS	Strong Heart Study
SHSS	Strong Heart Stroke Study
US	United States
VBI	Vascular brain injury
WMH	White matter hyperintensities

A. Introduction

American Indians experience substantial stroke morbidity and mortality but are underrepresented in research on stroke and covert vascular brain injury (VBI), such as white matter hyperintensities (WMH) or silent infarcts that often precede clinical events. Data on incident stroke in American Indians derive mainly from the Strong Heart Study (SHS), a population-based cohort study of cardiovascular disease in 4549 American Indians from three geographic regions who were 45-74 years old at baseline.[1] From 1988-2004 the SHS documented stroke rates in men and women exceeding those for Whites and Blacks in other large cohort studies.[2] Thirty-day and 1-year mortality were also unexpectedly high among SHS participants who experienced incident stroke, though it was unclear whether this finding was driven primarily by disparities in short-term risks that attenuated among longer term survivors. No longitudinal cohorts exist that allow direct comparison of stroke incidence or post-stroke survival in American Indians with other racial groups.

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective cohort study that enrolled 15,792 participants from four locations across the US.[3] Recruitment and baseline exams were conducted from 1987-1989, with cardiovascular events and stroke ascertained through 2011. Analyses documented higher risk in Black participants than in Whites,[4] and ARIC was among the cohorts to which SHS investigators made external comparison of stroke rates for American Indians. ARIC and the SHS shared many similarities in study design and timing of enrollment for baseline exams, and together represent an opportunity for pooling data to include American Indians in racial comparisons of stroke incidence and survival.

High stroke incidence observed in SHS participants suggests similarly elevated burdens of covert VBI. Accordingly, from 2010-2013 the ancillary Strong Heart Stroke Study (SHSS) used cranial magnetic resonance imaging to investigate covert VBI and its risk factors in 1033 SHS members. Because the SHSS comprised long-term survivors of the SHS cohort, selection bias could arise from differential mortality or attrition associated with the exposures and outcomes of interest.[5] In this context, selection bias would likely result in underestimating magnitudes of associations between risk factors

and covert VBI, and analyses to address the SHSS scientific aims may need to adjust for potential selection bias in the data.

The SHSS analytic plan includes estimating effect measures for the cohort as a whole, and separately by age category (65-74, 75-84, and ≥ 85 years old). Age-specific estimates can suffer from a special form of selection bias that renders effects fundamentally unidentifiable, which means they cannot be directly estimated from observed data.[6] This type of selection bias also applies to effect estimates that condition on surviving some minimum time since start of treatment or exposure, such as 1-year survival among people who survive at least 30 days after their stroke event. In older age groups or longer-term survivors this "conditional effects bias" can lead to observing effect estimates that are diminished or even qualitatively reversed compared to the true associations. In randomized controlled trials cumulative effects are estimated without bias, in expectation, but no methods currently exist that guarantee unbiased estimation of conditional effects even for prospective studies with perfect randomization, large sample size, and no missing data or attrition. For scientific questions that necessitate estimating conditional effects measures, methods to place bounds around unobservable parameters would facilitate sensitivity analyses and contextualize interpretation of results.

This dissertation comprises three papers that address the questions described above. In Manuscript 1: *Comparing stroke incidence and survival in American Indians, Blacks, and Whites: the Strong Heart Study and Atherosclerosis Risk in Communities Study*, we pooled longitudinal data from the SHS and ARIC to evaluate racial differences in stroke outcomes with and without adjusting for stroke risk factors. Manuscript 1 expands on previous findings in the SHS, and is the first population-based longitudinal analysis to directly compare stroke incidence and survival in American Indians to any other racial group.

In Manuscript 2: *Inverse probability weighting for selection bias tailored to inclusion criteria in the target population: covert vascular brain injury among American Indians in the Strong Heart Stroke Study,* we used marginal structural models with inverse probability weighting (IPW) to adjust for selection bias in the analysis of prevalent hypertension and covert VBI in the SHSS. Manuscript 2 extends traditional

applications of IPW for selection bias to account for correlation between equations used to predict selection and the probability of meeting inclusion criteria, in this case absence of prevalent stroke.

In Manuscript 3: *A bounding method to for effect estimates conditioned on age or time since exposure*, we expanded on a previous publication[6] to develop a simple bounding method for conditional effects based on identifiable parameters that can be estimated from observed data. Manuscript 3 provides a practical tool that can be applied to conditional effects in analyses using SHS and SHSS data, and which can be more broadly applied to other longitudinal or cross-sectional studies that are focused on quantifying effects conditioned on age or time.

B. Background

B.1 Stroke

Stroke is the general term used to describe clinical symptoms resulting from restriction of blood flow to (ischemic stroke) or bleeding from (hemorrhagic stroke) blood vessels in the brain.[7] Stroke is strongly associated with older age and biological or vascular aging, especially in developed countries but also increasingly in the developing world.[8,9] A conventional, albeit arbitrary, diagnostic criterion requires symptom duration of at least 24 hours to distinguish stroke from transient ischemic attack.[10] In recent years some researchers and clinicians have advocated for the term "brain attack" to reflect mechanistic similarities between ischemic stroke and heart attack, and to emphasize the need for acute emergency treatment as soon as possible after symptom onset, though this terminology is criticized for insufficient focus on post-stroke disability and rehabilitation.[11,12] Stroke has also been called a "cerebrovascular accident," although this terminology has been criticized as implying chance events that are not preventable.

Vascular aging and stroke are caused by deterioration in the health and functioning of vascular endothelial cells that line the walls of blood vessels.[13] Oxidative stress and inflammation contribute to this vascular endothelial dysfunction,[14] which in turn contributes to atherosclerosis and increased risk of ischemic and hemorrhagic strokes via plaque formation, plaque rupture, and weakened blood vessels.[15-19] Relative burdens of stroke subtypes vary between countries.[20] In the US about 85% of strokes are ischemic, and 15% are hemorrhagic.[7] The US also exhibits geographical variation in stroke risk, with the highest burdens found among residents of the "stroke belt" across the Southeastern states.[21]

There are three main causes of ischemic stroke. Cerebrovascular blood flow can be restricted by clots that form in the brain, clots that travel to the brain from other parts of the body, or narrowing of the blood vessels.[22] About 30% of strokes are cryptogenic, with unknown cause.[23] Normal cerebrovascular blood flow in the cortex is approximately 50 ml/100 mg/minute, but reduction by as much as 60% can occur without causing noticeable symptoms.[11] Blockage that reduces blood flow below 10 mL/100 mg/minute causes rapid membrane failure and cell death in an area of affected tissue known as the

infarct core. The core is surrounded by a region of less obstructed blood flow in which neuronal function is impaired but the cells are still intact. This region, known as the ischemic penumbra, is the target for acute thrombolytic treatment and subsequent rehabilitation therapy.[24] In general, treatment within 3 hours of symptom onset is essential for restoring full or partial function to the penumbra. Approximately one-fourth of ischemic stroke victims die within one year of the event.[25]

Hemorrhagic stroke occurs when blood leaks from weakened or damaged blood vessels in the brain. Intracerebral hemorrhage occurs when a diseased blood vessel leaks or bursts within the brain, and accounts for about two-thirds of hemorrhagic stroke.[26] The remaining one-third reflect sub-arachnoid hemorrhage, which is bleeding between the layers of tissue that cover the brain and is usually caused by aneurism rupture or physical trauma. Depending on the location and extent of the lesion, hemorrhagic stroke can result in cell death due to oxygen deprivation downstream from the bleeding, as well as damage to surrounding tissue from the extravascular hematoma. Hemorrhagic stroke can occur in the absence of previous ischemia, or as the so-called "hemorrhagic transformation," in which bleeding occurs at the site of a primary ischemic stroke.[27] Hemorrhagic stroke is more lethal than ischemic stroke; about half of all victims die within one year of the event.[28]

Risk factors for stroke are similar to risk factors for other cardiovascular diseases. In general, risk factors can be subdivided into modifiable and unmodifiable categories, with both informing general assessment of an individual's risk profile while the latter can also serve as targets for preventive intervention.[25] Unmodifiable risk factors include older age; male sex, although females have higher risk for some age categories; Black, American Indian, or Hispanic race/ethnicity; genetic predisposition; and low birth weight, although this may be considered modifiable from a primordial prevention perspective.[29] Major modifiable risk factors include high blood pressure; diabetes; cardiac arrhythmias, especially atrial fibrillation; left ventricular hypertrophy; dyslipidemia; smoking; physical inactivity; depression; and obesity.[25,30-33] Current understanding of stroke risk factors has been largely shaped by US-based cohort studies, including ARIC.[34-41] Unfortunately, the

prevalence of many risk factors is increasing, with ominous implications for public health.[42,43]

For decades stroke was the 3rd leading cause of death in the US after heart disease and cancer, but in the last few years it has dropped to 4th, after chronic lower respiratory disease.[44] This change is generally attributed to improved management of chronic disease risk factors, most notably hypertension and atrial fibrillation,[45] although the decreased mortality could be due in part to improved specificity of stroke diagnosis.[46] Most strokes occur in middle-aged and elderly adults, thus most clinical and epidemiologic research has focused on this population. In recent years the decline in stroke mortality has plateaued,[47,48] however, and evidence increasingly suggests rising stroke incidence among people younger than 45 years old and in some racial minority populations.[49-52]

B.2 Racial Disparities

Stroke incidence and survival varies by race and ethnicity. According to the Centers for Disease Control and Prevention, in 2013 stroke prevalence was higher in people reporting American Indian (4.6%) or Black (4.0%) race than in people identifying as White (2.5%).[7] Black stroke survivors also report more disability than their White counterparts, such as difficulty walking 10 steps without resting (42% vs. 29%), using fingers to grasp small objects (18% vs. 11%), or participating in social activities (24% vs. 16%).[53] People of color die from stroke at younger ages than Whites,[54] and Blacks who experience stroke have higher mortality rates than Whites.[55-57] Not surprisingly, research suggests that disparities in stroke incidence are linked to disproportionate burdens of stroke risk factors, though most research has focused on Blacks and the vast majority of publications do not include American Indians or Alaska Natives.[58-64] Among stroke survivors, Blacks and Hispanics report poorer health-related quality of life and more stroke-related disability than Whites.[65,66]

Several large cohort studies have directly compared stroke incidence in Black and White participants. In ARIC from 1987-1995 stroke rates were higher in Black men (53 per 10,000 person-years (95% CI = 41, 69)) and women (40 per 10,000 person-years (95% CI = 31, 51)) than in White men (20 per 10,000 person-years (95% CI = 16, 26))

and women (15 per 10,000 person-years (95% CI = 12, 19)).[4] Thirty-day case fatality rates were also higher among Black than White stroke victims (13% vs. 9%), although the smaller number of fatalities did not allow for precise point estimates. In the Cardiovascular Health Study, Black women had higher 5- and 10-year stroke rates (15.7 and 16.3 per 10,000 person years, respectively) than White men (15.4 and 15.2, respectively) or women (9.7 and 13.2, respectively), but interpretation of rates for Blacks of both sexes is limited due to relatively small numbers of events.[34] Of 390 Cardiovascular Health Study participants who experienced incident stroke from 1989-1997, fatalities were 2.9 times higher in Blacks than in Whites.[67]

B.3 Covert Vascular Brain Injury

Covert VBI typically precedes clinical events, manifesting as WMH, hemorrhages, infarcts, or atrophy in the absence of stroke. These conditions have been linked to behavioral changes, cognitive impairment, dementia, and subsequent stroke and death.[68-72] Small vessel disease is implicated in the etiology of covert VBI,[73] as are older age, hypertension, and diabetes.[74-77] Large cohort studies, including ARIC, that used magnetic resonance imaging to quantify covert VBI documented high prevalence of brain abnormalities in middle-aged and elderly populations without a history of stroke or transient ischemic attack.[78-80] Data also suggest that defining cerebrovascular disease only by clinical symptoms of transient ischemic attack or stroke dramatically underestimates the burden of covert disease.[81]

B.4 Stroke in American Indians

American Indians and Alaska Natives comprise 1.7% of the US population (5.2 million people),[82] and approximately 45% live on rural reservations. Until recently it was widely believed that American Indians experienced less stroke-related morbidity and mortality than the general population,[83] despite disproportionate burdens from many chronic diseases and other stroke risk factors, including hypertension, obesity, type 2 diabetes and cardiovascular disease.[84] In an analysis of longitudinal changes 4 years after enrollment, the SHS reported unfavorable results for hypertension, blood lipids, diabetes, and albuminuria.[85] Even among modifiable risk factors that did not show longitudinal

differences, the SHS cohort still exhibited disproportionate levels of low physical activity, obesity, and smoking compared to the general population. The Indian Health Service states that American Indians and Alaska Natives in their service population are 60% more likely than Whites to experience a stroke, and self-reported stroke is higher for American Indians and Alaska Natives than other US racial groups.[44] American Indians have been excluded or underrepresented from the vast majority of stroke research, however, and a 2011 statement from the American Heart Association/American Stroke Association concluded that stroke among Native people has not been thoroughly examined.[52]

The only rigorous data on stroke incidence and mortality in American Indians comes from the SHS. Using meticulous community surveillance, 306 strokes were prospectively ascertained from 1989-2004 among 4549 participants. In the seminal publication on stroke incidence in American Indians, age-adjusted rates in the SHS were 71 and 65 per 10,000 person-years for men and women, respectively, with 7% cumulative incidence from 1988-2004.[2] No direct racial comparisons were possible, but the SHS incidence rates were higher than for Blacks or Whites of similar ages in the Framingham Heart Study,[36] Cardiovascular Health Study,[34] and ARIC.[4] Age-specific incidence rates were also consistently higher in the SHS cohort than age-matched rates in Whites from Rochester, Minnesota from 1985-1989[86] and in Blacks in the Greater Cincinnati/Northern Kentucky Stroke Study in 1993.[87] Stroke mortality in American Indians has been reported as being both lower[54] and higher[55] than Whites. These inconsistencies may in part reflect data quality issues, including underestimation of disease due to racial misclassification.[88,89] Among American Indians in the SHS who experienced stroke, 1-year case-fatality was 31% for men and 33% for women, compared to 21% for men and 24% for women in pooled data from multiple cohorts.[2] Similarly, in Montana from 1991-2000, higher proportions of deaths in people younger than 65 years old were due to stroke in American Indians compared to Whites for both men (36% vs. 11%) and women (28% vs. 7%).[90]

B.5 Covert Vascular Brain Injury in American Indians

The American Heart Association has cited research suggesting a large, mostly unrecognized burden of cerebrovascular disease among the US Native population.[91] Other than the recently completed SHSS for which results are not yet available, however, we could find no published research that has evaluated covert VBI in American Indians or Alaska Natives.

C. Manuscript 1. Comparing stroke incidence and survival in American Indians, Blacks, and Whites: the Strong Heart Study and Atherosclerosis Risk in Communities Study

Clemma J. Muller, Alvaro Alonso, Jean Forster, David Vock, Rebecca Gottesman, Wayne Rosamond, W.T. Longstreth, Jr., Richard F. MacLehose

C.1 Overview

Background and Purpose. Stroke incidence and post-stroke mortality have been reported as being higher in American Indians than other US racial groups, but previous cross-study comparisons have been unable to account for risk factors or underlying trends. We pooled data from the Strong Heart Study, a longitudinal study of cardiovascular disease in American Indians, and the Atherosclerosis Risk in Communities Study, a longitudinal study that included both Blacks and Whites, to compare stroke incidence and post-stroke survival in these three groups.

Methods. Both studies launched in the late 1980s, with similarities in study design that facilitated pooled analysis. We used Cox regression to compare stroke hazards in American Indians (n = 4111) vs. Blacks (n = 3765) and Whites (n = 10,413), with attained age as the time scale and stratified by birth year tertile (1914-1930, 1931-1937, and 1938-1947) to accommodate effect modification. Among the subset of participants who experienced incident stroke during follow-up, we used logistic regression to estimate differences in 30-day and 1-year post-stroke mortality for American Indians (n = 310) vs. Blacks (n = 416) and Whites (n = 613). All effect estimates are presented before and after adjusting for confounding by demographic and risk factor variables.

Results. In the unadjusted analysis of stroke incidence American Indians had lower hazard ratios (HR) than Blacks across all birth cohorts (1914-1930: HR = 0.9 (95% CI = 0.7, 1.1); 1931-1937: HR = 0.9 (95% CI = 0.7, 1.2); 1938-1947: HR = 0.9 (95% CI = 0.7, 1.2)). In adjusted models, magnitude of associations increased across tertile (oldest to youngest cohort HR = 0.8 (95% CI = 0.6, 1.0); 0.7 (95% CI = 0.5, 1.0); and 0.6 (95% CI = 0.4, 0.8)). In the unadjusted analysis American Indians had higher stroke incidence than

Whites, with increasing magnitude across tertile (1914-1930: HR = 1.6 (95% CI = 1.3, 2.0); 1931-1937: HR = 2.2 (95% CI = 1.7, 2.8); 1938-1947: HR = 2.7 (95% CI = 2.0, 3.6)). Magnitude of associations greatly attenuated after confounder adjustment (oldest to youngest tertile HR = 1.1 (95% CI = 0.9, 1.5); 1.2 (95% CI = 0.9, 1.6); and 1.1 (95% CI = 0.8, 1.5)), with differences in diabetes prevalence accounting for most of the change. Among people who experienced stroke during follow-up, American Indians had higher 30-day mortality than Blacks and Whites (21% vs. 9% and 12%, respectively). After confounder adjustment, American Indians had higher risk ratios (RR) compared to Blacks (RR = 2.6 (95% CI = 1.4, 3.9)) and Whites (RR = 2.0 (95% CI = 1.1, 3.0)). American Indians had higher 1-year mortality compared to Blacks and Whites (31% vs. 22% and 21%, respectively), with RRs after confounder adjustment in comparison to Blacks (RR = 1.4 (95% CI = 0.9, 1.8)) and Whites (RR = 1.4 (95% CI = 0.9, 1.9)) that were attenuated compared to the 30-day mortality comparisons.

Conclusions. In this pooled analysis American Indians had lower stroke risk than Blacks and only slightly higher stroke risk than Whites after adjusting for confounders that included prevalent diabetes. Post-stroke mortality was substantially higher in American Indians than Blacks or Whites, especially within 30 days after the stroke event. American Indians are underrepresented in research on stroke incidence and post-stroke survival; the latter may be a particularly important focus for future studies to address stroke disparities in this population.

C.2 Introduction

Approximately 800,000 strokes occur annually in the US.[92,93] Compared to other racial groups, American Indians and Alaska Natives have among the highest burdens of many stroke risk factors, including hypertension, diabetes, obesity, and smoking.[42,85,94] Data collected in 2013 by the Behavioral Risk Factor Surveillance System showed higher self-reported prevalent stroke for American Indians and Alaska Natives ≥ 18 years old (4.6%) than for all other racial groups, including Blacks (4.0%) and Whites (2.5%).[7] Stroke mortality for American Indians is generally reported as lower than for other racial groups and Hispanics,[95,96] but racial misclassification often leads to underestimating disease-specific mortality rates in American Indians and Alaska Natives.[88,89,97,98] Although American Indians and Alaska Natives are conventionally treated as a single group when reporting national health statistics, heterogeneity in stroke morbidity and mortality is evident within the US Native population.[83] In spite of these statistics, American Indians are underrepresented in public health research on stroke incidence and mortality.[52,99,100]

Information on stroke incidence in American Indians derives mainly from the Strong Heart Study (SHS), a population-based cohort study of cardiovascular disease in 4549 American Indians from three geographic regions. Data from the SHS suggested that American Indians have higher stroke incidence than Whites and Blacks in other prospective studies,[2] but no longitudinal cohorts exist that allow direct comparison to other racial groups. Population-based estimates of stroke disparities in American Indians have therefore been restricted to external comparisons between the SHS and other studies. Comparison of stroke incidence in this context is difficult, however, due to different durations of follow-up and different distributions of other risk factors across cohorts.

The Atherosclerosis Risk in Communities Study (ARIC) is a large, population-based prospective cohort study that recruited participants from four sites across the US.[3] ARIC enrolled both Blacks and Whites to allow direct comparison of stroke outcomes in these two groups.[4,101-103] The SHS and ARIC share many similarities in study design and

timelines: baseline exams began in 1988 for SHS participants who were then 45-74 years old, and in 1987 for ARIC participants who were then 45-64 years old. In this analysis we pooled SHS and ARIC data to compare stroke morbidity and mortality in American Indians vs. Blacks and Whites. Our aims were to estimate racial differences in stroke incidence among people who were free of stroke at baseline, and in post-stroke survival among people who experienced stroke during follow-up. Our *a priori* hypotheses were that American Indians in the SHS would have higher stroke incidence and poorer survival than their Black and White counterparts in ARIC, even after accounting for age, sex, and other influential stroke risk factors.

C.3 Methods

Human Subjects Protections

The Institutional Review Board at the University of Minnesota and publications committees for the SHS and ARIC approved these analyses. We obtained all necessary tribal approvals prior to submission of the manuscript for publication.

Study Populations

The SHS was launched in 1988, funded by the National Heart, Lung, and Blood Institute to study longitudinal risk factors for cardiovascular disease in American Indians.[1] The SHS comprised 13 tribes in three regions: Southwest, Southern Plains, and the Northern Plains. All tribal members aged 45-74 years were invited to participate, with a total baseline enrollment of 4549 people. Data collection included detailed personal history and lifestyle questionnaires, a clinical exam, and laboratory measurements with blood samples. The SHS conducted follow-up and community surveillance to adjudicate cardiovascular disease events and mortality, most recently through December 31, 2008.

The ARIC Study was funded by National Heart, Lung, and Blood Institute to investigate patterns and causes of atherosclerosis and cardiovascular disease in a cohort comprising Black and White adults who were 45-64 years old at the baseline exam (1987-1989).[3] ARIC included four field sites (Washington County, MD; Forsyth County, NC; Jackson, MS; Minneapolis suburbs, MN). Each site used tailored probability-sampling methods to recruit a population-representative cohort. The final cohort (*n* =

15,792) was 55% female and 27% Black.[104] Semi-annual telephone interviews were conducted to assess hospitalizations, self-reported events, and overall health status. Adjudicated events and mortality are available for ARIC participants through December 31, 2011.

Stroke Ascertainment

The SHS established a rigorous surveillance and adjudication process for stroke, with diagnostic criteria based on international standards.[1,105] Mortality surveillance was conducted by examination of State Health Department death certificate data; Indian Health Service, autopsy, or coroner's report records; and key informant interviews with physicians or family members. Morbidity surveillance was based on hospital chart abstraction and personal interview of participants. A nosologist reviewed putative events for ICD-9 criteria (codes 431-437). Two independent physicians reviewed potential fatal and nonfatal strokes, and adjudication by the full SHS Mortality Committee resolved disagreements. Two neurologists further reviewed stroke-related events for a final diagnosis (not a stroke; possible stroke; definite stroke) and confirmation of ICD-9 classification. This surveillance protocol may have failed to capture some strokes, especially nonfatal events that occurred in cohort members who migrated out of the participating SHS communities. Nevertheless, the well-enumerated and relatively closed tribal populations in the SHS led to mortality and morbidity follow-up rates generally exceeding 99%.[2,106,107]

The ARIC protocol for stroke adjudication was conducted in two phases.[4] First, putative stroke-related hospitalizations or deaths were identified in annual telephone contacts with participants or next of kin, or by review of local hospital discharge records and death certificates. Hospitalizations were flagged for abstraction if records contained ICD-9 codes (430-438) or keywords relevant to cerebrovascular disease. Putative events were also identified based on reference to diagnostic magnetic resonance imaging, other cerebral imaging, or time spent in a neurovascular intensive care unit. Second, formal adjudication began with standardized abstraction of death and hospital records by a single trained nurse. Abstracted information was then classified by computer algorithm as ischemic stroke (thrombotic or lacunar infarcts, cardioembolic), hemorrhagic stroke

(subarachnoid or intracerebral hemorrhage), possible cryptogenic stroke, out-of-hospital fatal stroke, or non-stroke using National Stroke Survey criteria.[108] Information was independently reviewed and classified by an ARIC neurologist or study physician, with final event status determined by computer-physician agreement. Disagreement was resolved by a second independent physician reviewer.

Measures

Cohort and Demographics

Race (American Indian; Black; White) and cohort (SHS; ARIC) were each defined using categorical variables. Other demographic variables included baseline age, sex, and years of education.

Stroke Incidence and Survival

We classified each person according to his or her first incident stroke (none, any) and calculated a variable reflecting age at stroke, death, loss to follow-up, or administrative censoring. For each person who experienced incident stroke, we calculated binary indicators of 30-day and 1-year post-stroke survival.

Covariates

Covariates for the pooled analysis reflect stroke risk factors measured at the baseline exams that were assessed similarly enough or could be standardized *post hoc* to minimize study-specific differences across cohorts. Current alcohol consumption in the SHS was identified by positive endorsement of drinking at least 12 alcoholic beverages in one's life, drinking alcohol in the past month, and usually drinking ≥ 1 beverage per week;[109] current alcohol consumption in ARIC was identified by positive endorsement of presently drinking alcoholic beverages and of usually drinking ≥ 1 alcoholic beverage (wine, beer, or hard liquor) per week.[110] Current smoking in the SHS was identified by positive endorsement of smoking at least 100 cigarettes in one's life and smoking cigarettes at the time of the exam;[109] current smoking in ARIC was identified by positive endorsement of smoking at least 400 cigarettes in one's life and smoking cigarettes at the time of the exam.[111] Body mass index (kg/m^2) was measured during the clinical exams for both cohorts. We included blood lipids in the analysis (LDL, HDL) even though they have been inconsistently associated with incident stroke in the two cohorts.[2,102,112-114]

Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. Borderline hypertension was defined as systolic or diastolic blood pressure = 120-139 or 80-89 mmHg, respectively, without prevalent hypertension. We calculated a variable indicating good blood pressure control (≤ 140/90 mmHg) measured at the baseline exam. The SHS defined prevalent diabetes as fasting glucose ≥ 126 mg/dL, 2-hour glucose tolerance test blood glucose ≥ 200 mg/dL, previous physician diagnosis of diabetes, or use of insulin or hypoglycemic oral medication. Diabetes was defined similarly in ARIC except that the 2-hour glucose tolerance tests were not performed, therefore we standardized prevalent diabetes by removing cases in the SHS that were indicated only by glucose tolerance test results. Impaired glucose metabolism was defined as fasting glucose = 110-125 mg/dL without prevalent diabetes,[2] and for all participants we created a variable indicating fasting glucose ≤ 125 mg/dL at the baseline exam. Both cohorts assessed prevalent coronary heart disease and myocardial infarction, and congestive heart failure at the baseline exam.

Analysis

Stroke Incidence

To create the pooled data set we excluded ARIC participants with race other than Black or White (n = 48), participants with prevalent stroke in SHS (n = 36) or ARIC (n = 286), and ARIC participants with unknown baseline stroke status (n = 362). We then excluded participants with missing data for any variable used in the analysis (402 American Indians, 399 Blacks, 519 Whites). We estimated race- and sex-specific stroke rates in two ways. First, we estimated stratified rates per 10,000 person-years, with years since baseline as the time scale and with baseline age standardized to the 1990 US Census as was done for the previous analysis in the SHS.[2] Second, we estimated stratified rates per 10,000 person years for successive attained age thresholds (≥ 45, ≥ 55, ≥ 65, and ≥ 75 years old). Cox regression was used to compare stroke hazards with attained age as the time scale, so that each participant entered the model at his or her baseline age. We truncated attained age at 90 years old, which was the maximum attained age in ARIC. Only 44 SHS participants were older than 90 as of the most recent adjudication ending December 31, 2008. Cox regression models were specified in three ways: 1) unadjusted,

2) adjusting for sex and birth year, and 3) additionally adjusting for lifestyle and health factors measured at baseline (education, alcohol consumption, smoking, body mass index, hypertension, diabetes, and cardiovascular disease). Because study site was colinear with race for all SHS and most ARIC locations, this variable was not included as a covariate in the pooled analysis. Models adjusting for health factors treated hypertension as a 3-category ordinal variable and included an indicator of poor blood pressure control. Diabetes was similarly modeled as an ordinal variable including an indicator of high fasting glucose. We tested for effect measure modification between race and sex as well as race and birth year. Analyses were stratified if effect measure modification was present. Results are presented as point estimates with 95% confidence intervals, and we tested the proportional hazards assumption for all models.

Post-Stroke Survival

This analysis was restricted to the subset of participants who experienced incident stroke during follow-up. We used logistic regression to estimate racial differences in 30-day and 1-year post-stroke mortality. Similar to the analysis of incident stroke, we estimated three specifications: 1) unadjusted; 2) adjusted for sex, birth year, and age at stroke event; and 3) additionally adjusted for lifestyle factors and prevalent disease. We tested for effect measure modification between race and sex, and between race and birth year. We used marginal standardization to report risk differences (RD) and risk ratios (RR) for American Indians compared to Blacks and Whites.[115] We used Stata version 13.1 (StataCorp, College Station, TX) for all analyses.

C.4 Results

Table C.1 gives descriptive statistics for the 18,289 stroke-free participants of the SHS and ARIC who were included in the analysis. American Indians in the SHS had far lower percentages of people with post-secondary education than Blacks and Whites in ARIC, and higher percentages with self-reported current smoking. American Indians and Whites had lower prevalence of hypertension than Blacks, but American Indians had the highest prevalence of borderline hypertension. American Indians also had much higher percentage of people with prevalent diabetes.

Although American Indians in the SHS had lower prevalence of hypertension than Blacks in ARIC, among people with hypertension American Indians had higher mean systolic blood pressure than both Blacks and Whites (Table C.2, top). Hypertensive American Indians were also less likely than their Black and White counterparts to be medicated and in good control at the baseline study exam. Among participants with diabetes, American Indians had higher mean fasting glucose and lower percentages of people with fasting glucose ≤ 126 mg/dL than their Black and White counterparts in ARIC (Table C.2, bottom).

American Indians had fewer mean years elapsed between the baseline exam and stroke onset than Blacks and Whites (Table C.3). American Indians and Blacks had similar mean age at stroke onset and both had younger mean age than Whites; however, American Indians had younger mean age than Blacks when SHS data were restricted to the baseline ages represented in ARIC. When baseline age data were standardized to the 1990 US Census and with years since baseline exam as the time scale, American Indians had lower stroke rates than Blacks and higher rates than Whites for both women and men. Using attained age as the time scale, stroke rates were generally lower for American Indian women and men compared to Blacks, though differences were smaller among people with older attained age. Rates for both American Indians and Blacks were consistently higher than for Whites regardless of attained age.

In the Cox regression analysis for the total sample (Table C.4), American Indians had similar stroke risk compared to Blacks (unadjusted HR = 0.9 (95% CI = 0.8, 1.1)) and higher stroke risk than Whites (unadjusted HR = 2.0 (95% CI = 1.8, 2.3)). Covariate adjustment resulted in larger magnitude of effect estimates for the former comparison and smaller magnitude for the latter. Models that were unadjusted or adjusted only for sex and birth year showed violation of proportional hazards between American Indians and Whites, and both covariate-adjusted models indicated significant interaction between race and birth year ($p < 0.001$). We estimated all subsequent stroke incidence models separately by birth year tertile (1914-1930; 1931-1937; and 1938-1947) and verified no residual interactions or violations of the proportional hazards assumption. In the stratified models American Indians had lower stroke risk than Blacks before and after covariate

adjustment in all three birth cohorts, with highest magnitude of difference in the youngest birth cohort after accounting for prevalent hypertension and diabetes. American Indians had higher stroke risk compared to Whites in all unadjusted models, with differences of larger magnitudes in younger birth cohorts. HRs attenuated dramatically after full covariate adjustment, however, with nearly equal incidence when accounting for prevalent hypertension and diabetes regardless of birth year. HRs for covariates are shown in the Appendix.

Univariate confounder adjustment (results not shown) revealed that the change in HRs after adjusting for confounding by lifestyle and health factors was almost entirely driven by the higher prevalence of diabetes in American Indians than in Blacks and Whites, though the impact for comparisons to Blacks was slightly offset by the higher prevalence of hypertension in the latter. Diabetes prevalence declined from oldest to youngest birth cohorts for all three racial groups (data not shown), but the relative prevalence increased across tertiles for American Indians vs. both Blacks (prevalence ratios = 2.0, 2.4, and 2.9 from oldest to youngest tertile) and Whites (prevalence ratios = 4.1, 6.3, and 7.4 from oldest to youngest tertile).

Among the 1339 people who experienced incident stroke during follow-up, cumulative mortality and mean age at death in American Indians were similar to Blacks and higher than Whites (Table C.5). Compared to both Blacks and Whites, however, American Indians had fewer mean years from stroke to death as well as higher 30-day and 1-year mortality. In fact, 30-day mortality in American Indians was strikingly similar to 1-year mortality estimates in Blacks and Whites. Mortality RDs persisted after covariate adjustment (Table C.6). Differences attenuated for 1-year mortality comparisons, although American Indians continued to show higher risk on the absolute and multiplicative scales. Covariate adjustment had little impact on comparisons for 1-year mortality.

C.5 Discussion

We found that American Indians in the SHS had slightly lower stroke risk than Blacks, and higher risk than Whites in ARIC before adjusting for lifestyle and health

covariates. When stratified by birth year tertile, HRs for American Indians vs. Whites increased substantially from the oldest to youngest birth year tertiles. This finding is congruent with research showing that Whites benefitted more than other racial groups from recent declines in stroke morbidity and mortality.[95] Among people who experienced incident stroke, American Indians in the SHS had higher 30-day mortality than Blacks or Whites in ARIC. Differences were less striking for 1-year mortality, although American Indians still showed higher risk than Blacks or Whites.

In the only previous publication on incident stroke in American Indians using SHS data through 2004, the authors reported rates for women (653 per 100,000 person years) and men (707 per 100,000 person years) that were higher than rates for Blacks and Whites in other studies.[2] In our analysis, age-standardized rates for American Indian men and women using stroke events through 2008 were lower than in the previous publication, but were still higher than rates for Blacks and Whites (288 and 179 per 100,000 person-years, respectively) used for external comparisons by the previous study's authors.[87] Rates from both analyses of SHS data were also higher than previously reported for Blacks and Whites in ARIC,[4] but the latter were not age-standardized and external comparisons are problematic given the differences in baseline ages between the two cohorts. By specifying attained age as the time scale for the Cox regression analysis of incident stroke, we attempted to minimize concerns of bias from the older baseline age range for American Indians in the SHS. Our analysis also expanded previous comparisons to include direct estimation of HRs and standardization of definitions for key risk factors such as diabetes and hypertension.

Not surprisingly, research suggests that racial disparities in stroke incidence are linked to disproportionate burdens of stroke risk factors, though most studies have focused exclusively on Blacks and very few publications include American Indians or Alaska Natives.[59,61,62,116,117] After adjusting for covariates including diabetes and hypertension, HRs were greatly attenuated for comparisons between American Indians and Whites but were magnified for comparisons between American Indians and Blacks. Also notable was the larger impact of covariate adjustment in younger birth cohorts for comparisons to both Blacks and Whites, patterns which mirrored the steep increase in

diabetes prevalence ratios across birth year tertiles—especially for comparisons between American Indians and Whites. To some extent, then, trends we observed across birth cohorts may reflect the emerging diabetes epidemic among American Indians during the 20th Century.

Declining stroke incidence since the 1960s also coincided with declining mortality, leading to stroke being downgraded from 3rd to 4th most common cause of death in the US.[47] In recent years the decline in stroke mortality has plateaued,[47,48] and as with stroke incidence racial and ethnic minorities may have not experienced the same improvements as Whites. In our analysis 30-day mortality in American Indians resembled 1-year estimates in Blacks and Whites, clearly showing that American Indians in the SHS who experienced stroke tended to die much sooner than their Black and White counterparts in ARIC. This striking disparity could reflect barriers to timely access of acute healthcare services in the primarily rural, reservation communities of the SHS; greater stroke severity or poorer underlying health status in American Indian stroke patients; disparities in healthcare quality or rehabilitation services; or some combination of these and other explanations. Among people who survived at least 30 days, however, the difference in death rates was markedly lower as shown by the smaller racial differences in 1-year mortality.

The inferential implications of adjusting for risk factors depend on one's view of race as an exposure for disease.[118] Two opposing perspectives have historically been pitted against each other with strong proponents and detractors on both sides.[119] In one, race is an innate biological construct that directly acts to cause disease, such as genetic differences in response to certain medications. In the other, race is an externally imposed label that affects other people's decisions or actions, such as physicians providing differential treatment to patients based on race. Although some debate persists,[120-125] race as a biological construct has been debunked in the genetic, clinical, and epidemiologic literature.[126-131] If race is viewed as an innate cause of stroke, adjusting for other health conditions can be viewed as conditioning on intermediate factors.[132] If race is viewed as a socially invented caste system, then adjusting for other health conditions can be viewed as appropriately controlling for confounding due to discrimination directed at certain

racial groups that in itself causes higher burdens of stroke risk factors.[133] In either scenario, adjusting for mediating factors requires assumptions of no uncontrolled confounding between the mediators and the outcome. Some epidemiologists have recently proposed a causal model within which racial "effects" can be identified by articulating interventions on factors such as socioeconomic status that overlap with race,[134] or an etiologic model in which a temporal cascade of causes and effects could bring about associations between two factors (race and stroke) that may not by themselves satisfy conventional criteria for causal inference.[135] The latter especially facilitates placing epidemiologic study of racial disparities in a social justice context.[136] In this analysis, we opted to present results both with and without covariate adjustment. The raw data are useful for demonstrating disparities in the lived experience of American Indians, while covariate adjustment may help elucidate targets for intervention to reduce disproportionate burdens of stroke morbidity and mortality, such as diabetes prevention or improved access to emergency healthcare, even while acknowledging unresolved questions about exact causal relationships.

C.6 Limitations

This analysis has several limitations. First, because American Indian race is colinear with the SHS we cannot know with certainty the extent to which comparisons to Blacks and Whites in ARIC are influenced by differences in study design. By restricting the pooled analysis to the SHS and ARIC cohorts, however, we attempted to mitigate this limitation by combining data sets with similar designs, timelines, and ages of participants. Although the SHS enrolled older participants (45-74 years old at baseline) than ARIC (45-64 years old at baseline), setting attained age as the time scale allowed comparisons between all participants who reached any given age during follow-up. Nevertheless, differences in stroke ascertainment cannot be ruled out as a partial explanation for differences in stroke outcomes between SHS and ARIC participants, especially since ARIC adjudication did not include out-of-hospital fatal strokes. Second, it is unclear to what extent our results can generalize to broader statements about stroke incidence or post-stroke mortality in the larger populations of American Indians, Blacks,

and Whites across the US. Nearly all of the Black participants in ARIC were enrolled at the Mississipi (89%) or North Carolina (10%) field sites; both states are located in the so-called "stroke belt" of the US,[21] and we cannot evaluate stroke incidence in Blacks from outside this region. Similarly, our study should not be interpreted as reflecting stroke disparities in Alaska Natives, although American Indians and Alaska Natives are frequently grouped together in public health research. Third, as described in the previous section the covariate-adjusted analysis must be interpreted as potentially adjusting for intermediates between race and stroke incidence or post-stroke mortality. Fourth and relatedly, the inferential analysis relies on untestable assumptions of no uncontrolled confounding; no bias from sparse data in some combinations of covariates; correct specification of the Cox and logistic regression models; and consistency of exposure, meaning that any given race label confers the same health effects on everyone to whom it is applied. Under the sociocultural cause model of racial disparities this assumption is unlikely to be met. Instead, the meaning of race and its impact on health likely varies across culture, geography, and time. In this paper, racial disparities must be interpreted as reflecting overall associations while acknowledging the likelihood that the population-level differences may not apply equally to all individuals.

C.7 Summary and Conclusion

American Indians in the SHS had lower stroke risk than Blacks and higher risk than Whites in ARIC. After adjusting for confounders including hypertension and diabetes, differences were strengthened for comparisons to Blacks and attenuated for comparisons to Whites. The strongest impact of covariate adjustment was observed in the youngest birth years tertile. American Indians who experienced stroke had at least 2-fold higher risk of 30-day post-stroke morality than both Blacks and Whites, with elevated risks of smaller magnitude for 1-year post-stroke mortality.

American Indians and Alaska Natives comprise 1.7% of the US population, or 5.2 million people.[137] American Indians have higher stroke prevalence than any other racial or ethnic group;[51] die from stroke at younger ages than Whites;[90] and have among the highest burdens of stroke risk factors.[42,83] Nevertheless, multiple reports have concluded

that Native people are underrepresented in stroke research.[52,99,100,138] Our analysis suggests that the diabetes epidemic in American Indians may be a strong factor in the high stroke rates among SHS participants, and that targeting diabetes prevention and treatment is critical to reducing stroke disparities in this population. Our analysis also highlights profound disparities in post-stroke survival, especially in the month immediately following the event. Further epidemiologic and experimental studies are needed to understand and intervene on the causes for earlier post-stroke death risk in American Indians.

Table C.1. Baseline characteristics by age, study, and race among cohort participants who were stroke-free at baseline.

	SHS	**ARIC**	
	American Indian (*n* = 4111)	**Black (*n* = 3765)**	**White (*n* = 10,413)**
Age:			
45-54	50%	58%	51%
55-64	33%	41%	48%
65-74	18%	1%*	1%*
Female	60%	61%	53%
Education:			
0-11	47%	41%	17%
12-16	50%	28%	46%
17+	3%	31%	38%
Current alcohol consumption	42%	32%	65%
Current smoking	34%	30%	25%
Body mass index, kg/m^2	31 (6)	30 (6)	27 (5)
Waist:Hip ratio	0.95 (0.07)	0.92 (0.08)	0.93 (0.08)
Blood lipids:			
LDL, *mg/dL*	117 (34)	137 (43)	137 (38)
HDL, *mg/dL*	46 (13)	55 (18)	51 (17)
Congestive heart failure	3%	7%	4%
Coronary heart disease (includes myocardial infarction)	3%	4%	5%
Systolic blood pressure, *mmHg*	127 (19)	129 (21)	118 (17)
Diastolic blood pressure, *mmHg*	77 (10)	80 (12)	72 (10)
Hypertension:			
None	29%	21%	45%
Borderline	32%	22%	23%
Hypertensive	39%	57%	32%
Fasting glucose, *mg/dL*	148 (73)	117 (55)	104 (28)
Diabetes:			
None	43%	69%	81%
Impaired fasting glucose	16%	13%	11%
Diabetic	41%	18%	8%

SHS = Strong Heart Study; ARIC = Atherosclerosis Risk in Communities Study

* 97 ARIC participants were 65-66 years old at baseline

Table C.2. Blood pressure measured at the baseline exam and antihypertensive medication among hypertensive cohort members (top), and fasting glucose among diabetic cohort members (bottom).

	American Indian	**Black**	**White**
People with hypertension	**(*n* = 1583)**	**(*n* = 2155)**	**(*n* = 3298)**
Blood pressure at exam:			
Systolic, *mean mmHg (SD)*	142 (20)	137 (23)	130 (20)
Diastolic, *mean mmHg (SD)*	82 (11)	84 (13)	76 (11)
Medication and control:**			
No medication	40%	25%	22%
Medicated, poor control	27%	28%	17%
Medicated, good control	33%	47%	61%
People with diabetes	**(*n* = 1703)**	**(*n* = 680)**	**(*n* = 811)**
Fasting glucose at exam, *mean mg/dL (SD)*	211 (76)	200 (87)	172 (66)
Fasting glucose ≤ 125 mg/dL	3%	10%	11%

** Medication = antihypertensive drugs; good control = blood pressure < 140/90 mmHg at baseline exam; poor control = blood pressure ≥ 140/90 at baseline exam

Table C.3. Descriptive statistics for incident stroke by race for American Indians in the Strong Heart Study and Blacks and Whites in the Atherosclerosis Risk in Communities Study

	American Indians		**Blacks**		**Whites**	
	Women (n = 2447)	**Men (n = 1664)**	**Women (n = 2309)**	**Men (n = 1456)**	**Women (n = 5532)**	**Men (n = 4881)**
Number of strokes	189	121	243	173	280	333
Age at stroke[*], *mean (SD)*	69 (9)	67 (9)	68 (8)	66 (8)	71 (8)	70 (7)
Years from baseline to stroke, *mean (SD)*	10 (5)	8 (5)	12 (6)	11 (6)	14 (7)	13 (6)
Stroke incidence[**] (95% CI)						
Age-standardized[†]	58 (43, 88)	60 (41, 102)	61 (45, 73)	76 (50, 92)	30 (20, 31)	41 (27, 41)
Attained age[‡]						
≥ 45 years old	30 (21, 42)	23 (15, 37)	36 (28, 47)	52 (39, 69)	10 (7, 14)	16 (12, 22)
≥ 55 years old	48 (39, 59)	42 (32, 56)	54 (47, 63)	70 (58, 84)	22 (19, 25)	30 (26, 34)
≥ 65 years old	72 (59, 88)	77 (60, 100)	75 (64, 88)	85 (70, 104)	38 (33, 43)	52 (46, 59)
≥ 75 years old	105 (79, 139)	113 (76, 169)	107 (81, 142)	99 (66, 148)	65 (53, 79)	71 (58, 87)

[*] Mean age for American Indians with same baseline ages (45-64 years old) as Blacks and Whites = 65 (7) for both women and men

[**] Per 10,000 person-years

[†] Using 1990 US Census; time scale = years elapsed since baseline exam

[‡] Time scale = attained age up to 90 years old

Table C.4. Hazard ratios from Cox regression of incident stroke by race and birth cohort tertile.

	American Indians vs. Blacks	**American Indians vs. Whites**
	Hazard Ratio (95% CI)	*Hazard Ratio (95% CI)*
Total Sample		
Unadjusted	0.92 (0.78, 1.06)	2.01 (1.76, 2.31)
Adjusted for sex and birth year	0.88 (0.76, 1.02)	2.01 (1.75, 2.31)
All covariates*	0.75 (0.64, 0.88)	1.15 (0.98, 1.35)
Stratified by Birth Cohort Tertile		
Birth years 1914-1930		
Unadjusted	0.86 (0.69, 1.08)	1.60 (1.32, 1.95)
Adjusted for sex and birth year	0.84 (0.66, 1.07)	1.60 (1.30, 1.98)
All covariates*	0.79 (0.61, 1.01)	1.14 (0.90, 1.45)
Birth years 1931-1937		
Unadjusted	0.89 (0.68, 1.18)	2.15 (1.65, 2.80)
Adjusted for sex and birth year	0.89 (0.67, 1.17)	2.22 (1.70, 2.90)
All covariates*	0.73 (0.54, 0.98)	1.15 (0.85, 1.55)
Birth years 1938-1947		
Unadjusted	0.90 (0.68, 1.20)	2.66 (1.97, 3.60)
Adjusted for sex and birth year	0.94 (0.70, 1.26)	2.83 (2.08, 3.86)
All covariates*	0.60 (0.44, 0.84)	1.08 (0.76, 1.53)

* Adjusted for sex, birth year, education, alcohol consumption, current smoking, body mass index, and prevalent cardiovascular disease, hypertension, diabetes.

Table C.5. Post-stroke mortality by race.

	American Indian (*n* = 310)	**Black (*n* = 416)**	**White (*n* = 613)**
Cumulative mortality	63%	62%	54%
Age at death, *mean (SD)*	70 (9)	71 (8)	75 (7)
Years to death, *mean (SD)*	2.9 (4)	3.8 (4)	4.1 (5)
30-day mortality	21%	9%	12%
1-year mortality	31%	22%	21%

Table C.6. Racial differences in 30-day and 1-year mortality after primary stroke.

	Unadjusted		**Fully adjusted***	
	RD (95% CI)	**RR (95% CI)**	**RD (95% CI)**	**RR (95% CI)**
30-day mortality				
American Indians vs. Blacks	11 (6, 17)	2.2 (1.4, 3.0)	14 (6, 23)	2.6 (1.4, 3.9)
American Indians vs. Whites	9 (4, 14)	1.8 (1.2, 2.3)	12 (3, 21)	2.0 (1.1, 3.0)
1-year mortality				
American Indians vs. Blacks	9 (3, 16)	1.4 (1.1, 1.8)	8 (-1, 17)	1.4 (0.9, 1.8)
American Indians vs. Whites	10 (4, 16)	1.5 (1.1, 1.8)	8 (-1, 17)	1.4 (0.9, 1.9)

RD = Risk difference; RR = Risk ratio; CI = confidence interval

* Adjusted for sex, age at stroke event, birth year, education, alcohol consumption, smoking, body mass index, and prevalent cardiovascular disease, hypertension, and diabetes.

D. Manuscript 2: Inverse probability weighting for selection bias tailored to inclusion criteria in the target population: covert vascular brain injury among American Indians in the Strong Heart Stroke Study

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D.1 Overview

Background and Purpose. Covert vascular brain injury (VBI) is a risk factor for stroke and cognitive dysfunction. The Strong Heart Stroke Study used structural cranial magnetic resonance imaging to assess VBI and its risk factors in 1033 surviving members of the Strong Heart Study, a longitudinal cohort study of cardiovascular disease in American Indians. All participants were ≥ 62 years old, and data may be affected by selection bias if exposures and outcomes are both correlated with differential survival over time. Marginal structural models with inverse probability weighting (IPW) are commonly used to adjust for selection bias, but may inadvertently introduce bias when weights are correlated with presence of inclusion criteria that require excluding a subgroup from the analysis. In this case, evaluating covert VBI requires excluding participants with clinical stroke. We describe a modification of traditional IPW methods that tailors weights to account for correlation with inclusion criteria, with analysis of hypertension and covert VBI (white matter hyperintensities grade and volume) presented as an example.

Methods. We used logistic regression to estimate the association between prevalent hypertension and a binary indicator of VBI (white matter hyperintensity grade ≥ 3), and linear regression to estimate the same association for white matter hyperintensity volume as a proportion of total intracranial volume (ratio multiplied by 1000 to simplify presentation of results). Estimates reflected cross-sectional associations and longitudinal trends in hypertension from previous Strong Heart Study visits, with IPW to adjust for confounding and selection bias. Weights were stabilized to reflect the distribution of

prevalent hypertension in the target population. In addition, we tailored weights to account for each participant's probability of meeting the stroke-free inclusion criterion.

Results. After covariate adjustment the cross-sectional prevalence difference was 7.9% (95% CI = -2, 17) for the unweighted analysis, and 8.9% (95% CI = 0, 18) using IPW for selection bias with stabilized weights and for weights tailored to probability of being stroke-free. Estimates for the mean difference in white matter hyperintensity volume were 0.8 (95% CI = -0.4, 2.0) for the unweighted analysis; 0.9 (95% CI = -0.2, 2.1) with stabilized selection weights; and 0.9 (95% CI = -0.3, 2.1) with selection weights tailored to the stroke-free target population. In the analysis using longitudinal hypertension patterns, being hypertensive at all previous study visits was positively associated with covert VBI, but there was no apparent impact of using IPW to adjust for selection bias.

Conclusions. Among elderly American Indians in the SHSS, hypertension was positively associated with covert VBI as measured by abnormal WMH grade and higher white matter/intracranial volume ratio. By tailoring selection weights proportional to stroke risk in the cohort, our point estimates relate to a target population aligned with SHSS inclusion criteria.

D.2 Introduction

Covert vascular brain injury (VBI) is pathology in the brain characterized by white matter hyperintensities (WMH), asymptomatic hemorrhages or infarcts, and cerebral tissue atrophy in the absence of overt clinical symptoms.[68] Covert VBI is typically diagnosed via magnetic resonance imaging, although it is increasingly recognized as comorbid with detectable changes in cognition, physical function, and mood.[73,139-141] Covert VBI predicts high risk of future stroke,[142,143] and is understudied in most racial and ethnic minority groups. American Indians are particularly underrepresented in magnetic resonance imaging studies, despite notable disparities including higher stroke incidence and prevalence, younger age at onset and death from stroke, and higher burdens of VBI risk factors such as hypertension and diabetes compared to the general US population.[2,51,83,94,144-148]

The Strong Heart Stroke Study (SHSS) was funded to evaluate covert VBI and its comorbidities in American Indians,[149] with exams conducted from 2010-2013. The SHSS examined 1033 surviving members of the Strong Heart Study, a longitudinal population-based cohort study of American Indians from three geographic regions who were 45-74 years old when baseline exams were conducted in 1988-1990.[1] The SHSS goals include identifying correlates of prevalent covert VBI using cross-sectional data collected at SHSS exams and longitudinal data previously collected by the Strong Heart Study. Because the SHSS comprises elderly long-term survivors of the original cohort who were healthy enough to undergo magnetic resonance imaging, study results could be affected by selection bias.[150] Specifically, if covert VBI and a potential risk factor are each associated with lower probability of survival or participation in the SHSS, the observed point estimate could be biased towards showing a null or even a negative association between the two conditions.[5]

Marginal structural models with inverse probability weighting (IPW) were originally used by epidemiologists to adjust for time-varying confounding in longitudinal data,[151,152] but are commonly applied to adjust for selection bias.[153-155] IPW functions by weighting observations based on the inverse of their predicted probabilities of being in the study to generate a data set in which there is no statistical association between

exposure and selection. The default target population usually reflects the covariate distribution in the total study population, but weights can be tailored for inference to the exposed, unexposed, or other specialized target populations.[156] When studies involve inclusion criteria that may themselves correlate with prediction equations for constructing weights, such as SHSS analyses that require absence of prevalent clinical stroke, special care should be taken to ensure appropriate statistical inference. We constructed weights for IPW models to adjust for selection bias in the SHSS and tailored weights to a stroke-free inclusion criterion. We demonstrate the method for evaluating the association between hypertension and covert VBI as manifested by WMH. Our aims were to 1) evaluate the cross-sectional association between hypertension and covert VBI measured by the SHSS, and 2) evaluate the association for longitudinal patterns of hypertension measured from 1988-2013 by the Strong Heart Study and the SHSS. Our second aim also included use of IPW to adjust for time-varying confounding between hypertension and other VBI risk factors.

D.3 Methods

Human Subjects Protections

The Institutional Review Board at the University of Minnesota and publications committees for the Strong Heart Study and SHSS approved these analyses. We obtained all necessary tribal approvals prior to submission of the manuscript for publication.

Study Population

The Strong Heart Study was launched in 1988, funded by the National Heart, Lung, and Blood Institute to study longitudinal risk factors for cardiovascular disease in American Indians.[1] Investigators partnered with 13 tribes in three geographic regions: Southwest, Southern Plains, and Northern Plains. All tribal members aged 45-74 years were invited to participate, and 4549 people were ultimately enrolled. The Strong Heart Study collected data in three phases over 12 years: 1988-1991 (baseline), 1993-1995, and 1998-2000. Study visits included extensive clinical exams with electrocardiogram assessment of cardiac function, and laboratory analysis of blood and urine samples. At

each phase, follow-up was conducted to track cardiovascular disease events and mortality.

Also funded by the National Heart, Lung, and Blood Institute, the SHSS was launched in 2010 to examine covert VBI and its correlates in all surviving members of the Strong Heart Study cohort.[149] The SHSS was a cross-sectional study, although participants were drawn from the longitudinal cohort and previously collected data could be included in analyses of prevalent covert VBI at the SHSS exam. Exclusion criteria were prior surgery for cerebral aneurysm; implanted cardiac pacemaker, defibrillator, or artificial heart; contraindicating metal prostheses; internal electrical device such as cochlear implant; history of employment as a metal worker; weight exceeding 350 pounds; and physical or cognitive inability to complete study procedures. Of the 1664 Strong Heart Study members who were still alive at the start of SHSS recruitment, 201 were ineligible, 261 died or were otherwise incapacitated before they could be recruited, and 169 chose not to participate. Data collection on the remaining 1033 participants was completed in December, 2013. SHSS clinic visits comprised an extensive physical exam and personal interview, fasting blood and urine collection, neurocognitive and neuropsychological testing, physical performance assessment, and structural cranial magnetic resonance imaging. Of the 1033 enrolled participants, 998 completed all components of the study visit. For SHSS analyses focused on covert VBI in the absence of clinical events, an additional inclusion criterion requires analyzing data only for the 934 participants who did not have prevalent stroke.

Measures

Demographic data collected at the Strong Heart Study and SHSS exams included field site (Southwest, Southern Plains, Northern Plains), date of exam, age, sex, education, marital status, percentage of one's life lived on a federal reservation, and self-rated fluency in one's Native language (fluent, speaks some but not fluent, none). Cigarette smoking was assessed by the following questions: "During your lifetime have you smoked 100 cigarettes or more total?", "Do you smoke cigarettes now?", and "On the average, how many cigarettes do/did you usually smoke per day?" Alcohol consumption was similarly assessed: "Have you ever consumed alcoholic beverages?",

"If yes, when was your last drink?", "How many alcoholic drinks do you have in a typical week?" and "How many days in a typical month do you have at least one drink?" Based on answers to these questions, smoking and alcohol use were classified as current, former, or never. Body mass index (kg/m^2) was calculated based on measurements taken at the exam; obesity was defined as body mass index ≥ 30 kg/m^2. High and low density lipoproteins (mg/dL) were measured after overnight fasting. Systolic and diastolic blood pressure (mmHg) reflected the average of the second and third measurements taken during the clinic exam. Urine samples were assayed to quantify the albumin-creatine ratio and categorized to indicate microalbuminuria (30-299 mg/g) or macroalbuminuria ($\geq$ 300 mg/g). Prevalent diabetes was defined as fasting plasma glucose $\geq$ 126 mg/dL, 2-hour glucose challenge plasma glucose $\geq$ 200 mg/dL (this criterion was not assessed by the SHSS), or use of insulin or hypoglycemic oral medication. Prevalent transient ischemic attack was assessed by self-report using a form developed by the Atherosclerosis Risk in Communities Study.[157] Formal adjudication protocols were used to identify prevalent and incident stroke and cardiovascular disease (myocardial infarction, coronary heart disease, congestive heart failure).[1,105] Prevalent atherosclerosis was assessed by carotid ultrasound during the Strong Heart Study phase 3 exams.[158]

At each Strong Heart Study and SHSS exam, continuous blood pressure measures were combined with medical history information to create binary indicators of prevalent hypertension based on systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or use of antihypertensive medication (ACE inhibitor, alpha 2 agonist, angiotensin II receptor agonist, beta blocker, calcium channel blocker, vasodilator, thiazide diuretic, or dihydropyradine). For the cross-sectional analysis, the exposure of interest was prevalent hypertension at the SHSS exam. For the longitudinal analysis, we created a multi-category variable for each combination of prevalent hypertension status across baseline, 10-year follow-up, and the SHSS (eight categories total).

In the SHSS, cranial magnetic resonance imaging scans were conducted using General Electric 1.5T Signa scanners at the Southwest and Southern Plains sites, and a Siemens 1.5T Symphony scanner in the Northern Plains.[149] For each participant, investigators obtained six series of images: a sagittal T1-weighted localizer, coregistered

5mm axial T1, T2, and T2* (susceptibility)-weighted images in the anterior commissure/posterior commissure plane, 3mm axial FLAIR images, and 1.5mm sagittal T1-weighted volumetric gradient echo images. Scans were read at the University of Washington by two trained neuroradiologists using established scoring criteria.[78,159] Volumetric measures included gray matter (total brain, intracranial, left and right hippocampus) and white matter as a proportion of total intracranial volume. For this analysis we multiplied the white matter volume/intracranial volume ratio by 1000 to simplify presentation of results. For WMH, grade was quantified on a 10-point scale by SHSS neuroradiologists, with covert VBI defined as abnormal WMH grade ≥ 3.

Missing Data

Even small amounts of missing data in variables used to estimate inverse probability weights can lead to large numbers of observations dropped from a complete-case analysis, especially when predicted probabilities are measured for two selection mechanisms (death and non-participation) over multiple phases of data collection. To preserve sample size, we used multiple imputation by chained equations with 100 repetitions to impute missing values for all variables used in the IPW analysis.[160] Missing values for variables from the 10-year follow-up exam were only imputed for people who participated in the 10-year follow-up, and missing values for the SHSS exam were only imputed for SHSS participants. We used all 100 imputed data sets to estimate predicted probabilities for the IPW analysis, with each person's average value retained to calculate weights in the final data set. For descriptive statistics of individual variables in the SHSS we used the mean values of each variable across all 100 imputed data sets, rounded to the nearest integer for ordered categorical factors (education and albuminuria).

Inverse Probability Weighting for Confounding

As outlined in a recent overview,[161] IPW for control of time-varying confounders is accomplished in four steps: 1) for each time point at which data were collected, fit a model to predict exposure given current and past covariates; 2) for each time point, use the model to estimate each individual's predicted probability of experiencing his or her observed exposure status; 3) for each individual, create a weight that is proportional to

the inverse of the product of his or her predicted probabilities from step 2; and 4) use the product of estimates from step 3 as probability weights in the inferential analysis. Step 4 creates a pseudopopulation in which there is no association between confounders and exposure. IPW models can become unstable when very large weights arise from very low predicted probabilities, so weights are typically stabilized by replacing the numerator with the predicted probability of each individual having their observed exposure status conditioned on previous exposure. Final effect measures estimate the overall difference in the outcome that would be observed if the entire target population were exposed compared to if the entire target population were unexposed. In its simplest application, IPW can be used to control for confounding at a single time point using cross-sectional data.[162]

We used IPW to adjust for confounding in the analysis of hypertension and covert VBI in the SHSS. For the cross-sectional analysis we estimated unstabilized weights as the inverse of the predicted probability of each SHSS participant's observed hypertension status, conditioned on potential confounders (study site, age, sex, baseline education, marital status, body mass index, smoking status, high- and low-density lipoproteins, prevalent diabetes, and prevalent cardiovascular disease) measured during the SHSS exam. These weights were stabilized by replacing the numerators with the overall prevalence of each person's observed hypertension status:

$$c\_wt_{XS} = \frac{\Pr(H_{SHSS} = h_{SHSS})}{\Pr(H_{SHSS} = h_{SHSS} | C_{SHSS})} \quad [1]$$

Where $\Pr(H_{SHSS} = h_{SHSS})$ is the mean predicted probability of observed hypertension status using imputed data for the SHSS. Because we restricted the cross-sectional analysis to data collected during the SHSS exams, stabilized numerators did not condition on previous hypertension status.

We estimated weights for the longitudinal analysis using the same variables in a similar manner as described for the cross-sectional analysis, except that weights were estimated separately for baseline, 10-year follow-up, and the SHSS. We calculated the predicted probability of each person's observed hypertension status at phase *i* conditioned

on selection into phase *i*, time-varying covariates at phase *i*, hypertension and time-varying covariates at the previous phase (phase *i* – 1) for 10-year follow-up and the SHSS only, and time-invariant covariates (field site, sex, baseline education) measured at baseline. The inverse of these predicted probabilities generated unstabilized confounding weights for that phase. We stabilized the confounding weights by replacing the numerator with the overall probability of observed hypertension status (for baseline) or the predicted probability of observed hypertension status at phase *i* conditioned on hypertension at phase *i* – 1 (for 10-year follow-up and the SHSS):

$$\mathrm{c\_wt}_i = \frac{\Pr(\mathrm{H}_i = h_i | \mathrm{Sel}_i = 1, \mathrm{H}_{i-1})}{\Pr(\mathrm{H}_i = h | \mathrm{Sel}_i = 1, \mathrm{C}_i, \mathrm{H}_{i-1}, \mathrm{C}_{i-1}, \mathrm{C}_B)} \quad [2]$$

where $\Pr(\mathrm{H}_i = h_i | \mathrm{Sel} = 1, \mathrm{H}_{i-1})$ is the probability of observed hypertension status at phase *i* conditioned on participation in phase *i* and hypertension at phase *i* – 1, if applicable. In the denominator of equation 2 C_i, C_{i-1} and C_B are confounders measured at phase *i*, phase *i* – 1 if applicable, and at baseline, respectively. The product of phase-specific confounding weights comprised the final time-varying confounding weight for longitudinal analysis:

$$\mathrm{c\_wt}_{\mathrm{long}} = \mathrm{c\_wt}_{\mathrm{B}} \times \mathrm{c\_wt}_{10} \times \mathrm{c\_wt}_{\mathrm{SHSS}} \quad [3]$$

Inverse Probability Weighting for Selection Bias

IPW can be used to adjust for selection bias when sufficient data are available to estimate predicted probabilities of attrition over time.[155] Statistical models are weighted so individuals contribute information proportional to their predicted probability of being in the study, creating a pseudopopulation in which there is no association between exposure and selection. Predicted probabilities for IPW can be structured to separately account for attrition by death and non-participation of survivors; these estimates are then inverted and multiplied to generate weights in which final selection probabilities are balanced within each covariate stratum. As with IPW for confounding, selection weights are typically stabilized by setting the numerator equal to the predicted probability of selection conditioned only on exposure status.

We used data from the baseline and 10-year follow-up exams to predict survival and participation of survivors in the SHSS. The 10-year follow-up was approximately midway between baseline and the SHSS, and we chose this approach as a compromise between only using baseline data to estimate selection weights (simpler, but more prone to bias from time-varying confounding) and using all available Strong Heart Study data including the 5-year follow-up exams (less risk of bias from time-varying confounding, but more risk of bias from model misspecification and heavier reliance on imputation). With the exception of magnetic resonance imaging outcomes collected at the SHSS exam, all variables listed in Measures were considered for models predicting survival and participation of survivors.

For the 10-year follow-up and the SHSS visits we first used imputed data to estimate the mean predicted probability of survival to that phase, conditioned on observed hypertension status, time-varying predictors at the previous phase (C_{i-1}), and fixed predictors measured at baseline (C_B): $\Pr(Surv_i = 1|H_{i-1}, C_{i-1}, C_B)$. Note that C_B was only included as a vector separate from C_{i-1} for the SHSS visit. Next we restricted the data to survivors at phase *i* and used imputed data to estimate the mean predicted probability of participation in phase *i*, conditioned the same factors as for survival probabilities: $\Pr(Part_i = 1| Surv_i = 1, H_{i-1}, C_{i-1}, C_B)$. Each person's unstabilized weight for selection at phase *i* was calculated as the product of the inverse of predicted probabilities for survival and participation, stabilized by replacing numerators with the predicted probabilities of selection conditioned on previous exposure and a subset of baseline predictors (field site, sex, age, prevalent diabetes, and prevalent cardiovascular disease):

$$s\_wt_i = \frac{\Pr(Sel_i = 1|H_B, C_B^*)}{\Pr(Surv_i = 1|Part_{i-1} = 1, H_{i-1}, C_{i-1}, C_B) \times \Pr(Part_i = 1|S_i = 1, H_{i-1}, C_{i-1}, C_B)} \quad [4]$$

The product of these interval-specific weights (baseline to phase 3, phase 3 to the SHSS) constituted the final stabilized selection weights from baseline through the SHSS:

$$s\_wt_{final} = s\_wt_{10} \times s\_wt_{SHSS} \quad [5]$$

Tailoring weights for inclusion criteria

The population of interest for studies of covert VBI is often limited to people who have not experienced overt clinical events, namely strokes, but who may have asymptomatic pathology that could benefit from medical intervention. Therefore, although all living Strong Heart Study cohort members were invited to participate, analysis of covert VBI in the SHSS will often require excluding observations with prevalent stroke. We were concerned about the potential for correlation between predicted probability of attrition and risk of experiencing stroke prior to the SHSS. If covariate profiles associated with low probability of selection into the SHSS were also associated with high risk of stroke, then the resulting large selection weights could over-correct for the missing observations people with these combinations of risk factors are assumed to represent. Conceptually, in this scenario the pseudopopulation generated by IPW would not reflect the desired stroke-free target population. We therefore tailored the numerators of selection weights from equation 5 to jointly account for each person's predicted probability of selection and of being stroke-free at their SHSS exam.[156]

If selection probability and stroke risk were independent of each other, then their joint probability in the numerator of stabilized weights could be easily estimated as the product of the individual probabilities: Pr(Sel = 1, Stk = 0) = Pr(Sel = 1) × Pr(Stk = 0). Because people with higher stroke risk are likely to have low probability of survival, however, the probabilities are not independent and so instead we modeled their joint association. For all 1031 SHSS participants who were stroke-free at baseline, we used imputed baseline data to estimate the predicted probability of remaining stroke-free until their SHSS exam, conditioned on the same variables (field site, sex, age, prevalent diabetes, prevalent cardiovascular disease) as used to estimate the predicted probability of selection for stabilized weights in equation 4. Selection weights tailored to the stroke-free target population were then estimated as follows:

$$t\_wt_{final} = [\Pr(Stroke_{SHSS} = 0 | Sel_{SHSS} = 1, H_B, C_B^*) \times \Pr(Sel_{SHSS} = 1 | H_B, C_B^*)] \times s\_wt_{final} \quad [6]$$

The tailored weights reduced each person's influence on the final data analysis in proportion to his or her estimated stroke risk, creating a pseudopopulation better aligned with inclusion criteria for studying covert VBI.

Statistical Analysis

We analyzed the cross-sectional association between hypertension and covert VBI using logistic regression models with the binary indicator of WMH score ≥ 3 as the outcome. Marginal risk differences were estimated from the fitted logistic models.[163] Mean differences in the continuous measure of white matter volume were estimated using linear regression. In both regression models, exposure was the binary indicator of prevalent hypertension in the SHSS.

For the longitudinal analysis, exposure was measured using the multi-category variable reflecting each combination of prevalent hypertension status across the all three exams (baseline, 10-year follow-up, and SHSS). Because of sparse data for non-monotonic "recovery" patterns in which people changed from being classified as hypertensive at baseline and/or 10-year follow-up to being classified as not having hypertension and one or more subsequent exams, we dropped participants in these categories (n = 59) from the longitudinal analysis and only considered monotonic exposure patterns for which people who were: 1) normotensive at all three exams (reference group), 2) normotensive at baseline and 10-year follow-up but hypertensive at the SHSS exam, 3) normotensive at baseline and hypertensive at both the 10-year follow-up and SHSS exams, or 4) were hypertensive at all three exams. For each analysis we estimated unweighted crude associations, associations weighted for covariate confounding, and associations simultaneously weighted for covariate confounding and selection bias. The latter used "master" weights calculated as the product of individual weights for confounding and selection.[164] Table D.1 summarizes the combination of weights for each analysis. Point estimates are reported with 95% confidence intervals. We used Stata version 13 (StataCorp, College Station, TX) for all analyses.

D.4 Results

Of the 4549 cohort members who enrolled in the Strong Heart Study from 1988-1991, 36 had prevalent stroke at baseline and were excluded from this analysis. Of the 4513 cohort members without prevalent stroke at baseline, 1031 survived and participated in the SHSS from 2010-2013. On average SHSS participants were younger, better educated, more likely to be female, more likely to be obese, and either healthier than or similar to Strong Heart Study cohort members who did not participate (Table D.2). In particular, fewer SHSS participants than non-participants had prevalent hypertension, diabetes, cardiovascular disease, and albuminuria at baseline.

Of the 1031 SHSS participants with no stroke at baseline, 934 were also stroke-free at the SHSS exam. Before multiple imputation, WMH grade and white matter volume were missing for 34 and 59 of these individuals, respectively. After imputation (Table D.3), people with abnormal WMH grade tended to be older, have lower educational attainment and were less likely to be currently married than people with normal WMH grade. Although body mass index on the continuous scale appeared similar between groups, people with abnormal WMH had lower prevalence of obesity. People with abnormal WMH also tended to have higher prevalence of microalbuminuria, self-reported myocardial infarction, and self-reported congestive heart failure. As expected, people with abnormal WMH grade had more white matter expressed both as total volume and as proportion of intracranial volume. Prevalent hypertension at the SHSS exam was only slightly more common in people with abnormal WMH. Descriptive statistics for the longitudinal hypertension variable was restricted to the subset of 878 participants who attended all three study visits (Strong Heart Study baseline and 10-year follow-up, and the SHSS). Of these, a lower percentage of people with severe WMH had no hypertension or hypertension only at the SHSS, and a higher percentage had hypertension at all three study visits.

Table D.4 shows descriptive statistics for confounding and selection weights by hypertension and WMH grade. Among the 934 stroke-free SHSS participants, 81% (n = 756) had prevalent hypertension and 36% (n = 336) had abnormal WMH grade. Only 56 (6%) were normotensive and had abnormal WMH. Mean values for stabilized weights

centered slightly below 1.0, reflecting the lower average weights for SHSS participants vs. non-participants. Weights tailored to the stroke-free population were smaller than stabilized weights, with differences approximately proportional to the 91% overall probability of remaining stroke free from baseline to the SHSS.

Approximately one-third of participants without hypertension had abnormal WMH grade. Prevalence difference estimates increased after incorporating confounding weights regardless of adjustment for differential selection (Table D.5). As expected, point estimates also increased in models incorporating selection weights, with similar results for stabilized and tailored target populations. In the analysis for the ratio of white matter and intracranial volume, covariate adjustment resulted in substantially higher point estimates regardless of selection weighting. Selection weighting had little or no impact on unadjusted models, but led to approximately 20% higher point estimates in covariate-adjusted models.

Table D.6 shows results for the longitudinal analysis comparing prevalence of abnormal WMH by the joint distribution of hypertension status at the Strong Heart Study baseline and 10-year follow-up exams, and the SHSS exam among cohort members who completed all three visits. Due to sparse data for categories in which 59 people with hypertension at baseline or 10-year follow-up were classified as normotensive at a subsequent visit (Table D.3), these categories were dropped from the analysis (final n = 819). Having hypertension at all three study visits was consistently associated with higher prevalence differences compared to people with no hypertension at any study visit, though the magnitude of point estimates decreased in models weighted for time-varying confounding. Table D.7 shows results for the longitudinal analysis comparing white matter volume as a proportion of intracranial volume. People with hypertension at all three study visits consistently showed higher mean values compared to people with no hypertension at any visit. In contrast to the binary outcome, magnitude of point estimates increased after covariate adjustment. Selection weighting had no apparent impact on analyses for the longitudinal analysis.

D.5 Discussion

We found that hypertension correlated with more severe VBI among elderly American Indians in the cross-sectional SHSS analysis. In the longitudinal analysis, joint patterns of hypertension over 20 years suggested that people with the longest duration of hypertension were more likely to have prevalent covert VBI in the SHSS than people without hypertension at any exam. After covariate adjustment there was little or no difference between people who developed hypertension after the Strong Heart Study baseline exam compared to cohort members who remained free of hypertension at all visits. These findings are consistent with biological models that view covert VBI as arising from cumulative effects of long-term vascular disease,[165] and with research in other populations.[75,77,166-170] Cross-study comparisons are complicated, however, by other studies' reliance on odds ratios for binary outcomes and log-transformation for continuous outcomes. We opted for prevalence-based effect measures because prevalence is more interpretable than odds and because odds ratios overestimate prevalence ratios when outcomes are common,[171] as was the case for abnormal WMH. For the continuous volume ratio we were interested in overall mean differences at the population level for each longitudinal hypertension comparison. These estimates are more easily interpreted when adhering to the original scale, and the SHSS sample size was sufficiently large to invoke the Central Limit Theorem for unbiased inference.[172] In spite of these limitations to external comparisons, our results contribute to the growing body of evidence supporting a vascular etiology of covert VBI, evidence which is strengthened by the similar qualitative conclusions across studies despite variation in design and analytic methods.

In the cross-sectional analysis point estimates increased in models incorporating selection weights, as expected if selection bias is affecting SHSS data. In reality the assumptions behind IPW models are unlikely to be perfectly satisfied, and so our analysis should be interpreted as mitigating, rather than eliminating, selection bias for the cross-sectional association between hypertension and severe WMH in the SHSS. Contrary to our expectations, however, there was no strong evidence that IPW adjusted for selection bias in the longitudinal analysis. A possible explanation pertains to the two additional

exclusions of participants compared to the cross-sectional models. First, we dropped people who did not participate in the 10-year follow-up. Because this subgroup went on to enroll in the SHSS, it might comprise disproportionately younger, healthier individuals who had temporarily migrated out of the Strong Heart Study communities or who did not participate due to work or other obligations as opposed to people who did not participate for reasons related to subsequent poor health or mortality. Second, we dropped 59 people who had hypertension at the Strong Heart Study baseline and/or 10-year follow-up but who did not have hypertension at one or more subsequent exams, and it is highly likely this group comprised people with less severe disease and lower risk of hypertension-related morbidity or mortality compared to their counterparts with monotonic hypertension prevalence.

Tailoring weights to account for inclusion criteria is an important strength of our IPW analysis, and departs from conventional applications that stabilize weights to the exposure distribution observed in the study cohort. By further tailoring numerators to account for stroke risk, we estimated results for a target population aligned with SHSS inclusion criteria. This is needed for valid inference because many variables predicting higher mortality risk in the selection models (e.g., male sex, higher blood pressure, prevalent diabetes and cardiovascular disease) are also well-established risk factors for clinical events. Stroke-free SHSS participants with low predicted probabilities of selection—and therefore large selection weights—due to the presence of these risk factors would simultaneously have high predicted probabilities of clinical stroke. Upweighting these individuals without further adjustment could then overcorrect for missing observations who would have experienced subsequent stroke. The extent to which failing to account for inclusion or exclusion criteria would bias an IPW analysis depends on the magnitude of stroke risk in people with high selection weights, and the prevalence of stroke in the target population. In our case fewer than 10% of SHSS participants had prevalent stroke and it is possible that bias would be less problematic than if a more highly prevalent condition were cause for exclusion.

For investigators who are comfortable estimating stabilized weights, modeling the predicted probability of being in a specific target population conditioned on selection and

exposure status is a straightforward extension of a familiar method.[156] If inclusion criteria correlate with selection, it is important to appropriately model their joint distribution rather than estimating separate predicted probabilities as if each factor were independent of the other(s). The main caveat is that care must be taken to ensure appropriate temporality in the conditional model, $\Pr(\text{Factor}_1 = f_1 | \text{Factor}_2 = f_2)$, if one factor is potentially a downstream effect of the other. Flexible specification of the target population can facilitate sensitivity analyses, for example by weighting to a population that is free of comorbidities or in which no one is taking certain medications. This could allow for more nuanced interpretation of effect measure estimates compared to the frequent practice of dropping sick or medicated individuals from a data set.

D.6 Limitations

Our analysis has limitations that should also be considered when interpreting weighted point estimates. First, due to limitations in the SHSS data we adjusted the target population based on self-reported prevalent stroke rather than a more rigorous adjudicated determination as was available for previous phases of the Strong Heart Study. Adjudication for the SHSS is currently underway, however, and it will be a trivial matter to adjust the relevant predicted probability estimates once this information is available. Furthermore, self-reported stroke has been shown to be a reasonable surrogate for adjudicated stroke in other populations.[173-178] No publication has specifically compared self-reported vs. adjudicated stroke in elderly American Indians, but these studies provide some support for the internal validity of our analysis. Second, currently available Strong Heart Study data only include adjudicated clinical events and mortality through December, 2008. Therefore our prediction models conflate attrition from death and non-participation of survivors beginning in January, 2009. However, proportionally more attrition was due to death as the cohort aged and became less mobile, and SHSS field staff have reported that the majority of non-participation was due to excessive frailty or other health problems that correlate with mortality. Therefore we are likewise confident that selection weights and IPW results will not change dramatically when fully adjudicated mortality data become available. Third, we did not use data collected at the 5-

year follow-up of the Strong Heart Study for estimating time-varying confounding or selection weights. Estimates using all available data might be more accurate, but the tradeoff is additional complexity and potential for bias to increase exponentially due to repeated misspecification of the imputation or prediction models. We therefore compromised by estimating weights for two intervals of approximately equal (10 years) duration.

D.7 Summary and Conclusion

Among elderly American Indians in the SHSS, covert VBI as measured by abnormal WMH grade and higher white matter/intracranial volume ratio was correlated with prevalent hypertension and with being hypertensive at three study exams conducted over 20 years. People with hypertension first detected at the 10-year follow-up or SHSS exam did not have substantially worse outcomes than their normotensive peers, suggesting a dose-response model with covert VBI developing after long-term exposure to hypertension and other vascular diseases. By tailoring selection weights proportional to stroke risk in the cohort, our results relate to a target population aligned with SHSS inclusion criteria. When variables predicting selection into an analysis also correlate with eligibility, investigators might want to consider using tailored weights, especially when a large proportion of the study population fails to qualify for inclusion.

Table D.1. Weighting scheme for marginal structural models with inverse probability weighting

	Selection Bias		
Confounding	Unweighted	Stabilized selection[*]	Tailored selection[**]
Crude association:	None	s_wt_{final}	t_wt_{final}
Covariate adjusted[†] cross-sectional:	c_wt_{XS}	$c\_wt_{XS} \times s\_wt_{final}$	$c\_wt_{XS} \times t\_wt_{final}$
Covariate adjusted[†] longitudinal:	c_wt_{long}	$c\_wt_{long} \times s\_wt_{final}$	$c\_wt_{long} \times t\_wt_{final}$

[*] s_wt_{final} = stabilized to the predicted probability of selection conditioned on previous hypertension status and baseline covariates (field site, sex, age, prevalent diabetes, prevalent cardiovascular disease)

[**] t_wt_{final} = tailored to the predicted probability of being stroke-free in the Strong Heart Stroke Study conditioned on selection, baseline hypertension status, and the same baseline covariates as for stabilized weights

[†] Adjusted for field site, age, sex, baseline education, marital status, body mass index, current smoking, current alcohol consumption, high and low density lipoproteins, prevalent diabetes, and prevalent cardiovascular disease

Table D.2. Strong Heart Study cohort members who did and did not participate in the Strong Heart Stroke Study. All variables were measured at baseline exams from 1988-1991; results exclude 36 participants with prevalent stroke.

	Did not participate in SHSS (n = 3482) *Mean (SD) or %*	Participated in SHSS (n = 1033) *Mean (SD) or %*
SHS site:		
Southwest	34%	30%
Southern Plains	34%	34%
Northern Plains	33%	36%
Age, *years*	58 (8)	52 (6)
Female	57%	69%
Married	47%	56%
Education:		
11th grade or less	52%	34%
High school graduate	25%	29%
Any post-secondary	23%	37%
Percent of life spent on a reservation	85 (20)	82 (22)
Current smoking	34%	34%
Current alcohol consumption	41%	43%
Body mass index, *kg/m^2*	31 (6)	31 (6)
Blood lipids:*		
HDL	46 (14)	46 (13)
LDL	116 (33)	121 (32)
Blood pressure:		
Systolic, *mmHg*	130 (21)	122 (15)
Diatolic, *mmHg*	77 (10)	77 (10)
Prevalent hypertension	43%	26%
Diagnosed diabetes	54%	33%
Prevalent cardiovascular disease:		
Myocardial infarction	3%	1%
Coronary heart disease*	4%	1%
Congestive heart failure	5%	1%
Albuminuria:		
None	66%	86%
Micro (30-299 mg/g)	21%	13%
Macro (≥ 300 mg/g)	13%	1%

SHSS = Strong Heart Stroke Study

* Coronary heart disease includes myocardial infarction

Table D.3. Variables collected at the SHSS exam and selected baseline factors for 934 stroke-free SHSS participants, stratified by the binary indicator of abnormal white matter hyperintensities.

	White Matter Hyperintesities	
	Normal: grade 0-2 (*n* = 598) *Mean (SD) or %*	**Abnormal: grade 3-8 (*n* = 336)** *Mean (SD) or %*
SHS site:		
Southwest	31%	30%
Southern Plains	35%	31%
Northern Plains	34%	39%
Age, *years*	71 (5)	75 (6)
Female	68%	69%
Education:*		
11th grade or less	28%	41%
High school graduate	31%	28%
Any post-secondary	41%	31%
Married	37%	26%
Percent of life spent on a reservation*	81 (23)	83 (21)
Body mass index, *kg/m²*	32 (7)	31 (7)
Obese (BMI ≥ 30 kg/m²)	63%	46%
Blood lipids:		
HDL	50 (13)	52 (16)
LDL	98 (35)	91 (32)
Prevalent diabetes	57%	59%
Current smoking	19%	18%
Current alcohol consumption	24%	21%
Blood pressure:		
Systolic, *mmHg*	135 (20)	138 (23)
Diatolic, *mmHg*	69 (11)	68 (12)
Prevalent cardiovascular disease:**		
Myocardial infarction	9%	15%
Congestive heart failure	5%	8%
Albuminuria:		
Micro (30-299 mg/g)	15%	22%
Macro (≥ 300 mg/g)	7%	8%
Brain volume		
White matter, cm³	4.1 (3)	12.1 (8)
Intracranial, cm³	1204 (128)	1205 (140)
White matter / Intracranial	0.0033 (0.002)	0.0099 (0.007)
Cross-sectional exposure		
Prevalent hypertension	80%	83%
Longitudinal exposure	**(*n* = 557)**†	**(*n* = 321)** †
No hypertension at any visit	17%	15%
Hypertensive at SHSS only	36%	32%
Hypertensive at 10-year follow-up and SHSS	22%	22%

Hypertensive at all three visits	17%	26%
Hypertensive at 10-year follow-up only	2%	2%
Hypertensive at baseline only	< 1%	< 1%
Hypertensive at baseline and 10-year follow-up	< 1%	0%
Hypertensive at baseline and SHSS only	5%	3%

* Baseline variable collected by Strong Heart Study (1988-1990)

** Self-report (adjudication in progress)

† Only evaluated for participants who attended all three exams

Table D.4. Selection weights by hypertension and white matter hyperintensities grade for 934* stroke-free Strong Heart Stroke Study participants.

	No hypertension		**Hypertension**	
	WMH grade 0-2 (n = 122) *Mean (SD)*	**WMH grade 3-8** (n = 56) *Mean (SD)*	**WMH grade 0-2** (n = 476) *Mean (SD)*	**WMH grade 3-8** (n = 280) *Mean (SD)*
Confounding weights:				
Cross-sectional	1.09 (1.4)	0.99 (0.7)	1.00 (0.1)	1.00 (0.2)
Longitudinal*	0.90 (1.1)	1.03 (0.9)	1.03 (0.5)	1.07 (0.7)
Selection weights:**				
Stabilized	0.96 (0.2)	0.98 (0.4)	0.96 (0.6)	0.99 (0.5)
Stabilized and tailored	0.89 (0.2)	0.88 (0.3)	0.88 (0.5)	0.88 (0.5)

WMH = white matter hyperintensities; SD = standard deviation

* Longitudinal weights restricted to 878 cohort members who attended all three exams (baseline, 10-year follow-up, and Strong Heart Stroke Study)

** Stabilized to overall hypertension distribution and tailored to the stroke-free target population

Table D.5. Cross-sectional effect estimates comparing white matter hyperintensity measures in people with vs. without prevalent hypertension among 934 stroke-free Strong Heart Stroke Study participants.

	Selection Weighting		
	Unweighted	**Stabilized**	**Stabilized + Tailored**
	Estimate (95% CI)	***Estimate (95% CI)***	***Estimate (95% CI)***
Prevalence difference[*]			
Unadjusted	5.6 (-2, 13)	6.0 (-2, 14)	6.0 (-2, 14)
Covariate-adjusted[†]	7.9 (-2, 17)	8.9 (0, 18)	8.9 (0, 18)
Prevalence ratio[*]			
Unadjusted	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)
Covariate-adjusted[†]	1.3 (0.9, 1.7)	1.3 (0.9, 1.7)	1.3 (0.9, 1.7)
Mean difference[**]			
Unadjusted	0.25 (-0.7, 1.2)	0.23 (-0.9, 1.4)	0.24 (-0.9, 1.4)
Covariate-adjusted[†]	0.80 (-0.4, 2.0)	0.87 (-0.4, 2.1)	0.87 (-0.3, 2.1)

Stabilized = overall hypertension distribution; Tailored = stroke-free target population; CI = confidence interval

[*] Prevalence of white matter hyperintensity grade ≥ 3

[**] Mean difference of white matter volume/intracranial volume, multiplied by 1000 to simplify presentation of results

[†] Adjusted using inverse probability weighting for confounding by field site, age, sex, education at baseline exam, marital status, body mass index, current smoking and alcohol consumption at each exam, high and low density lipoproteins, prevalent diabetes, prevalent cardiovascular disease

Table D.6. Longitudinal effect estimates comparing prevalence of white matter hyperintensity grade ≥ 3 across categories defined by the joint distribution of hypertension at baseline, 10-year follow-up, and the SHSS. Reference group for all comparisons is participants who were normotensive at all three visits. Analysis was restricted to participants who participated all three exams, and 60 participants with "recovery" patterns depicted by gray rows in Table 1 were dropped from the analysis due to sparse data. Final *n* = 819.

		Selection Weighting	
	Unweighted	**Stabilized**	**Tailored**
WMH grade ≥ 3	***Estimate (95% CI)***	***Estimate (95% CI)***	***Estimate (95% CI)***
Prevalence difference, unadjusted			
Not hypertensive	Ref	Ref	Ref
Hypertensive at SHSS	-0.2 (-10, 9)	-0.2 (-10, 10)	0.0 (-10, 10)
Hypertensive at 10 years & SHSS	2.4 (-8, 13)	5.2 (-6, 17)	5.4 (-6, 17)
Hypertensive at all exams	12.6 (2, 23)	11.6 (0, 23)	11.4 (0, 23)
Prevalence difference, covariate-adjusted*			
Not hypertensive	Ref	Ref	Ref
Hypertensive at SHSS	0.3 (-13, 14)	0.4 (-12, 13)	0.7 (-11, 13)
Hypertensive at 10 years & SHSS	-2.1 (-16, 12)	0.5 (-13, 14)	0.9 (-12, 14)
Hypertensive at all exams	8.0 (-6, 22)	7.8 (-6, 22)	8.1 (-6, 22)
Prevalence ratio, unadjusted			
Not hypertensive	Ref	Ref	Ref
Hypertensive at SHSS	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)
Hypertensive at 10 years & SHSS	1.1 (0.8, 1.4)	1.2 (0.8, 1.5)	1.2 (0.8, 1.5)
Hypertensive at all exams	1.4 (1.0, 1.8)	1.3 (0.9, 1.7)	1.3 (0.9, 1.7)
Prevalence ratio, covariate-adjusted*			
Not hypertensive	Ref	Ref	Ref
Hypertensive at SHSS	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)
Hypertensive at 10 years & SHSS	0.9 (0.6, 1.3)	1.0 (0.6, 1.4)	1.0 (0.6, 1.4)
Hypertensive at all exams	1.2 (0.8, 1.7)	1.2 (0.8, 1.6)	1.2 (0.8, 1.7)

WMH = white matter hyperintensity; Stabilized = overall hypertension distribution; Tailored = stroke-free target population; CI = confidence interval

* Adjusted using inverse probability weighting for confounding by field site, age, sex, education at baseline exam, marital status, body mass index, current smoking and alcohol consumption at each exam, high and low density lipoproteins, prevalent diabetes, prevalent cardiovascular disease

Table D.7. Longitudinal effect estimates comparing white matter volume/total intracranial volume across categories defined by the joint distribution of hypertension at baseline, 10-year follow-up, and the SHSS. Reference group for all comparisons is participants who were normotensive at all three visits. Analysis was restricted to participants who participated all three exams, and 60 participants with "recovery" patterns depicted by gray rows in Table 1 were dropped from the analysis due to sparse data. Final n = 818. Results are presented as ratio x 1000.

	Selection Weighting		
WMH volume/Intracranial volume	**Unweighted** ***Estimate (95% CI)***	**Stabilized** ***Estimate (95% CI)***	**Tailored** ***Estimate (95% CI)***
Mean difference, unadjusted			
Not hypertensive	Ref	Ref	Ref
Hypertensive at SHSS	0.07 (-1.0, 1.2)	-0.07 (-1.5, 1.3)	-0.05 (-1.4, 1.3)
Hypertensive at 10 years & SHSS	0.11 (-1.1, 1.3)	0.01 (-1.4, 1.5)	0.04 (-1.4, 1.5)
Hypertensive at all exams	1.16 (0.0, 2.4)	1.02 (-0.6, 2.6)	1.06 (-0.6, 2.7)
Mean difference, covariate-adjusted*			
Not hypertensive	Ref	Ref	Ref
Hypertensive at SHSS	0.68 (-0.7, 2.0)	0.49 (-0.9, 1.9)	0.54 (-0.9, 1.9)
Hypertensive at 10 years & SHSS	0.30 (-1.0, 1.6)	0.10 (-1.3, 1.5)	0.16 (-1.2, 1.6)
Hypertensive at all exams	1.69 (0.0, 3.4)	1.57 (-0.2, 3.3)	1.65 (-0.2, 3.4)

WMH = white matter hyperintensity; Stabilized = overall hypertension distribution; Tailored = stroke-free target population; CI = confidence interval

* Adjusted using inverse probability weighting for confounding by field site, age, sex, education at baseline exam, marital status, body mass index, current smoking and alcohol consumption at each exam, high and low density lipoproteins, prevalent diabetes, prevalent cardiovascular disease

E. Manuscript 3: A bounding method for effect estimates conditioned on age or time since exposure

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E.1 Overview

Background and Purpose. Effect estimates that are calculated separately for categories conditioned on age (e.g., 45-54, 55-64, or 65-74 years old) or time since exposure (e.g., < 1 year, 1-2 years, and > 2 years after starting treatment) can suffer from a type of selection bias which leads to observing effects that are diminished or even qualitatively reversed compared to the true effect in the target population. This "conditional effects bias" cannot be avoided by study design, nor can it be fixed by statistical analysis. We present a method for estimating bounds around the conditional risk difference (RD) based on observed data. Formulae are presented for bounds assuming that exposure can only have causative effects on the outcome, and allowing for the possibility of both preventive and causative effects in the target population. We demonstrate the bounding method for analysis of racial differences in post-stroke survival.

Methods. Using population response types and potential outcomes theory, we explain conditional effects bias in the context of RD. We used constrained optimization to derive bounds around the true conditional RD, first assuming only causal effects (monotonicity) and then relaxing monotonicity to allow for the possibility that exposure could prevent the outcome in some people while causing it in others. We applied the bounds to an analysis of post-stroke mortality in American Indians vs. Blacks and Whites. We estimated the RD for three time periods: 0-30 days, 31-180 days, and 181-365 days after the stroke event. Estimates for the later two periods were conditioned on survival to the end of the preceding period.

Results. Under the assumption of monotonic causal exposure effect, we identified bounds around the conditional RD based on observed data. We were unable to identify bounds when we allowed for unrestricted magnitude of preventive effects relative to

causative effects in the target population. Instead, we identified bounds for the partial constraints in which preventive effects were assumed to be equal to or less than causative effects. In the example, observed RDs for American Indians vs. Blacks were 14% (95% CI = 6, 23) for 0-30 days; -1% (95% CI = -7, 4) for 31-180 days; and -3% (95% CI = -7, 2) for 181-365 days after stroke onset, respectively. For American Indians vs. Whites, analogous observed RDs were 12% (95% CI = -6, 3); 1% (95% CI = -5, 6); and -2% (95% CI = -6, 3). Applying the equation for monotonic causal effects for comparisons to Blacks yielded bounds of 0%-16% and 0%-13% for 31-180 and 181-365 days after the stroke event, respectively. Analogous bounds for comparisons to Whites were 0%-14% and 0%-13%.

Conclusions. Conditional effects suffer from a type of selection bias that can compromise the scientific integrity of public health and clinical trials research. We describe simple formulae to estimate bounds when conditional comparisons are either unavoidable or are of primary interest to investigators. Failure to consider conditional effects bias could lead to reporting effects that are attenuated or even reversed across categories defined by age or time, when in fact those trends are not conclusively supported by the data.

E.2 Introduction

In observational studies and randomized trials, effects are often calculated separately for categories defined by participant age (e.g, 45-54, 55-64, and 65-74 years old) or time since exposure (e.g., < 1 year, 1-2 years, and > 2 years after initiating treatment). In both scenarios the goal is to estimate effects for the age or time period represented in each category, conditional on having survived to that age or time period. This is accomplished by restricting analyses to the subset of people who have not yet experienced the outcome as of the start of the category. Effects conditioned on remaining event-free for successively older ages or longer time intervals are widespread in the literature and have generated conclusions that are entrenched in public health and clinical practice. For example, studies have found that the higher risk of death associated with obesity appears to diminish among older people in analyses stratified by age category.[179,180] This is a conditional effect comparison because subgroups only include people who survived to the minimum age for each category, which may be years after a person becomes obese. Analyses of racial health disparities frequently condition on age, with decreasing magnitudes of effect commonly observed in older groups. In an analysis using data from the National Health Interview Survey, hazard ratios comparing mortality in Black versus White respondents tended to attenuate among older age categories, ranging from 1.3 and 1.5 among women 35-44 and 45-54 years old, respectively, to 0.9 among women 85 and older.[181] Similar patterns were observed in men.

It is not widely recognized that conditional effect estimates are prone to a type of selection bias which can make them unestimable. In one example, observational studies repeatedly showed cardiovascular benefits associated with post-menopausal hormone replacement therapy,[182-185] but a large randomized controlled trial found that hormone replacement therapy actually led to increased incidence of coronary heart disease.[186] Conditional effects bias may have contributed to the discrepancy because women in observational cohorts typically started using hormone replacement therapy months or years before enrolling in the study, whereas women in the randomized trial were under observation from the beginning of treatment.[187]

Unfortunately, conditional effects bias cannot be accounted for by study design or statistical analysis; even large clinical trials with perfect randomization and no loss to follow up are susceptible to the problem.[188] If treatment or exposure (used interchangeably throughout) causes some people to experience the outcome in earlier age categories or time periods than if they had been unexposed, then these more susceptible individuals will drop out of the target population but will still be present in the control population for subsequent conditional comparisons. This means the control population can progress to having higher underlying disease risk than the target population, which in turn can lead to observing apparently protective conditional effects even if the exposure never prevents disease.[6] Although some exposure effects may truly diminish over time, conditional effects bias can also obscure the magnitude of change.

Some authors have advocated avoiding the conditional effects conundrum by instead estimating unconditional alternatives such as cumulative effect measures, in which comparisons reflect all events occurring since the start of exposure for an age or time interval and for which all members of the target population are at risk for the outcome. In practice, however, data may not be available to implement this solution or the scientific question of interest may require estimating conditional effects. The latter scenario, for example, could occur if an insurance company wanted to know whether a medication benefit persisted beyond some fixed duration of treatment, or when clinicians want to know whether female sex becomes a risk factor for cardiovascular disease after some age threshold. In this manuscript we expand on a previous description of conditional effects bias[6] to derive formulae for estimating bounds around the conditional risk difference (RD). Bounds are defined using unconditional risk and RD estimates that can be identified from observed data, and generate an interval of possible true RD values. We demonstrate the bounds with an applied example.

E.3 Potential Outcomes, Response Types, and Exchangeability

Conditional effects bias can be explained using a potential outcomes framework.[189,190] With a binary exposure and binary outcome, for any given individual there is an outcome that would be observed if the person were exposed, and another—

possibly different—outcome that would be observed if she or he were unexposed. A difference between the two potential outcomes reflects a causal effect of exposure for that individual. In reality, only one exposure status per person is possible at any given time, and only one potential outcome can be observed. The hypothetical outcome for the other exposure status is labeled counterfactual. Within this framework, a population can be divided into four different groups depending on response to exposure: 1) "doomed" people who will experience the outcome regardless of exposure status, 2) "causative" people in whom the exposure causes the outcome, 3) "preventive" people in whom the exposure prevents the outcome, and 4) "immune" people who will not experience the outcome regardless of exposure status. Proportions of each response type in a target population can be written as P_D (doomed), P_C (causative), P_P (preventive), and P_I (immune).[191,192] In this population the proportion of people who would experience disease if exposed is $P_D + P_C$, while the proportion that would experience disease if not exposed is $P_D + P_P$. Thus, the RD of exposure is $(P_D + P_C) - (P_D + P_P) = P_C - P_P$.

For any given target population, the counterfactual response types that do not correspond to actual exposure status must be estimated from a substitute population. We will denote the proportions of people with each response type in the substitute population as Q_D, Q_C, Q_P, and Q_I. The substitute population can provide unbiased information to estimate a causal effect if we assume it is exchangeable with the target population. Exchangeability implies the two groups could have swapped exposure status and we would still have observed the same average causal effect. Full exchangeability, meaning that all $P_j = Q_j$, satisfies this condition and allows unbiased estimation of causal effects.[193] Full exchangeability is guaranteed for a randomized trial, but must be assumed in observational studies after controlling for confounding.[194] In some scenarios weaker exchangeability assumptions are also sufficient to estimate unbiased effects.[195]

Potential outcomes are more complicated when there are multiple time periods during which an outcome could occur. In these scenarios, we want to know whether exposure leads to some people getting the disease in earlier or later periods than if they had been unexposed. Table E.1 summarizes potential outcomes response types for a target population in a study with age or follow up time divided into two periods. For all

population proportions $P_{k,l}$ and $Q_{k,l}$, subscript k indicates in which period the outcome would occur with no exposure, and subscript l indicates in which period the outcome would occur with exposure. Omega (Ω) denotes people for whom the outcome does not occur during any study period. Thus, there is only one immune response type ($P_{\Omega,\Omega}$) reflecting people who would not experience the outcome during the study period regardless of exposure status. Whether or not these individuals would eventually experience the outcome after period 2 is not relevant to estimating the effect of exposure during periods 1 and 2. Other response types are subdivided according to when the outcome would occur for each exposure condition. Doomed people would experience the outcome in the same period regardless of exposure status ($P_{1,1} + P_{2,2} = P_D$). Proportions for the three causative response types reflect all people for whom exposure causes the outcome to occur earlier than if they had instead been unexposed ($P_{2,1} + P_{\Omega,1} + P_{\Omega,2} = P_C$), and similarly for preventive types ($P_{1,2} + P_{1,\Omega} + P_{2,\Omega} = P_P$). Analogous proportions in the unexposed population that provide substitute information for counterfactual data can be denoted by $Q_{\Omega,\Omega}$, $Q_{1,1}$, $Q_{2,2}$, and so on.

In the sections that follow we explain conditional effects bias and develop bounds for the conditional risk difference that can be estimated from observed data. For these sections, the exposed group is the target population for all comparisons. We begin by assuming causative monotonicity of exposure effect: that exposure cannot prevent the outcome for anyone in the target population ($P_P = 0$). For the two-period scenario shown in Table E.1, causative monotonicity means that only the first six response types are relevant for estimating causal effects. We relax the monotonicity restriction later in this manuscript.

E.4 Unconditional Effects

Unconditional effects do not require outcome-free survival to any minimum age or time since exposure. Cumulative effects are the most common unconditional comparisons used in epidemiology and clinical trials research, with comparisons reflecting overall disease risk in exposed vs. unexposed groups (because our target population is people who were exposed) for some interval beginning at the time when exposure status was

initially experienced, chosen, or assigned. Using the population proportions in Table E.1 and the causative monotonicity assumption, the desired cumulative RD for period 1 is $(P_{1,1} + P_{2,1} + P_{\Omega,1}) - (P_{1,1}) = P_{2,1} + P_{\Omega,1}$. Because we cannot identify $P_{1,1}$ from the exposed target population, we invoke the exchangeability assumption and substitute the risk in period 1 ($Q_{1,1}$) from the unexposed population to estimate the cumulative RD:

$$\widehat{RD}_{cumulative,1} = (P_{1,1} + P_{2,1} + P_{\Omega,1}) - (Q_{1,1}) = P_{2,1} + P_{\Omega,1} \quad [1]$$

Note that the individual population proportions $P_{2,1}$ and $P_{\Omega,1}$ cannot be individually estimated. The cumulative RD for period 2 compares the sum of all proportions in the exposed target population that experience the outcome in periods 1 or 2 to the sum of all proportions that experience the outcome in the unexposed substitute population:

$$\widehat{RD}_{cumulative,2} = (P_{1,1} + P_{2,1} + P_{\Omega,1} + P_{2,2} + P_{\Omega,2}) - (Q_{1,1} + Q_{2,2} + Q_{2,1}) = P_{\Omega,1} + P_{\Omega,2} \quad [2]$$

A less common specification for the unconditional RD focuses on risk within a given period for the entire target population, without conditioning on remaining event-free to the start of the period. Thus all members of the population are represented in the risk calculations, but people who already experienced the outcome in a previous period are not counted as events. For period 1, the period-specific unconditional RD and cumulative RD are identical, and hereafter we use RD_1 for these period 1 effects. For period 2, the period-specific unconditional RD reflects only population proportions that would experience disease in period 2, with substitute information used for the counterfactual unexposed condition:

$$\widehat{RD}_{unconditional,2} = (P_{2,2} + P_{\Omega,2}) - (Q_{2,2} + Q_{2,1}) = P_{\Omega,2} - P_{2,1} \quad [3]$$

Although the RD depicted in equation 3 is not frequently reported in public health research, it is used in the bounding method described below. The key feature of all unconditional risk comparisons is that they can be directly estimated from observed data, with the assumption that exchangeability between the target and substitute populations is achieved by randomization or covariate adjustment.

E.5 Conditional Effects

Conditional effects are estimated when the RD for period 2 is restricted to people who survived event-free to the end of period 1.[6,188] Conditional effects could be of interest in a randomized trial, for example, if investigators want to know whether preventive benefits persist beyond some minimum duration of treatment. Conditional effects are also estimated in observational studies that enroll people after they were initially exposed, such as a cohort study that enrolls people starting at age 55 but wishes to evaluate exposures that began prior to study enrollment.

Depicting conditional effects using potential outcomes response types requires defining the population at risk as people who have not yet experienced the outcome at the start of the period. With the notation in Table E.1, the proportion of people in the exposed target population who survive past period 1 is $P_{\Omega,\Omega} + P_{2,2} + P_{\Omega,2}$. The subgroup of these individuals who will experience the outcome in period 2 is $P_{2,2} + P_{\Omega,2}$, whereas the subgroup that would experience the outcome if they had instead been unexposed is $P_{2,2}$. Therefore, the desired counterfactual RD for the surviving exposed population in period 2 is:

$$\mathrm{RD}_{\mathbf{conditional,2}} = \left(\frac{P_{2,2} + P_{\Omega,2}}{P_{\Omega,\Omega} + P_{2,2} + P_{\Omega,2}}\right) - \left(\frac{P_{2,2}}{P_{\Omega,\Omega} + P_{2,2} + P_{\Omega,2}}\right) = \frac{P_{\Omega,2}}{P_{\Omega,\Omega} + P_{2,2} + P_{\Omega,2}} \qquad [4]$$

When we rely on the substitute population to provide counterfactual information for equation 4, the analogous proportion of people surviving past period 1 is $Q_{\Omega,\Omega} + Q_{2,2} + Q_{2,1} + Q_{\Omega,1} + Q_{\Omega,2}$ and the proportion who experience the outcome in period 2 is $Q_{2,2} + Q_{2,1}$. Therefore, the observed conditional risk difference is:

$$\widetilde{\mathrm{RD}}_{\mathbf{conditional,2}} = \left(\frac{P_{2,2} + P_{\Omega,2}}{P_{\Omega,\Omega} + P_{2,2} + P_{\Omega,2}}\right) - \left(\frac{Q_{2,2} + Q_{2,1}}{Q_{\Omega,\Omega} + Q_{2,2} + Q_{2,1} + Q_{\Omega,1} + Q_{\Omega,2}}\right) \qquad [5]$$

Clearly, the observed conditional RD in equation 5 does not match the desired conditional RD from equation 4. Because we cannot isolate $Q_{2,1}$ from the numerator or $(Q_{2,1} + Q_{\Omega,1})$ from the denominator of the substitute population, it is not possible to directly estimate the desired RD in equation 4 without imposing additional assumptions.

E6 Conditional Effects Bias

The inequality between equations 4 and 5 arises from fundamental differences in who survives past period 1 among the target and substitute populations. The surviving exposed subgroup in period 2 is likely to be inherently less susceptible to the outcome than the original exposed population, because people with an underlying susceptibility for whom exposure caused disease to occur in period 1 ($P_{2,1} + P_{\Omega,1}$) are no longer considered at risk. The desired conditional RD in period 2, therefore, pertains to possible delayed exposure effects among these more resilient individuals who were not susceptible to exposure in period 1. The surviving unexposed subgroup, on the other hand, still contains the people for whom exposure would have caused disease to occur in period 1 ($Q_{2,1} + Q_{\Omega,1}$) and who should not be included in the resilient subgroup of interest for estimating the conditional RD.

Conditional effects bias means the desired conditional effect measure cannot be estimated from observed data. The unexposed population cannot provide unbiased substitute information for the counterfactual data in equation 4 unless we impose additional assumptions, such as no exposure effect in period 1 ($Q_{2,1} + Q_{\Omega,1} = 0$). This assumption is also known as a lag effect and may be reasonable for some scenarios, such as the multiple years that elapse between asbestos exposure and developing cancer,[196] but it is not believable for many others. Over long enough time and with ongoing attrition of susceptible people from the exposed group, higher underlying disease risk in unexposed survivors can lead to observing a diminished or apparently preventive effect of exposure in later periods, even when only neutral or causative response types are present in the population. Unfortunately, conditional effects bias cannot be avoided even with infinite sample size, perfect exchangeability between groups at baseline, and complete follow up for the entire population. The problem is that we cannot conclusively distinguish $P_{2,1}$ from $P_{\Omega,2}$,[6] and there will always be multiple combinations of response type proportions that could explain any observed conditional RD.

E.7 Bounding Conditional Effects

When desired effects cannot be identified, an alternative option is to articulate a range of possible true values given the observed data.[197] A previous publication describing conditional effects bias gave bounds for the unobservable proportion $P_{\Omega,2}$, but bounds around response types are not very useful for applied analyses estimating conditional effects.[6] In this section we describe bounds around the conditional RD for period 2, first assuming monotonic exposure effects and only two periods in the study. Next we relax the monotonicity assumption, and discuss implications for studies with age or follow up time divided into three or more periods.

We used Wolfram Mathematica software (version 10.3)[198] to implement constrained optimization for identifying bounds around conditional effects. Mathematica has been previously used for bounding effects with uncontrolled confounding, mediation analysis, and imperfect treatment compliance,[199-207] and can be used to define minimum and maximum possible values for the conditional RD, subject to a list of constraints expressed as equations (e.g., $0 \leq x \leq 1$). Mathematica translates these constraints to matrix notation that reflects a multi-dimensional space of possible true values for the unidentified parameter. Conceptually, Mathematica then uses the simplex algorithm[208] to "move" along the outer edges of the multi-dimensional shape until it identifies the global minimum or maximum value that satisfies all constraints. For the six response types present in a population with monotonic causative exposure effects (Table E.1), we specified that each population proportion, the sum of all proportions, and the cumulative risk difference through period 2 must all lie between [0,1]; $RD_{unconditional,2}$ between [-1,1]; and that RD_1 and the conditional surviving exposed population $P_{\Omega,\Omega} + P_{2,2} + P_{\Omega,2}$ must be greater than 0. The non-zero constraints are necessary because $RD_1 = 0$ implies no exposure effect in period 1, and $P_{\Omega,\Omega} + P_{2,2} + P_{\Omega,2} = 0$ implies that no exposed individuals survived to the start of period 2. Within these constraints, we the following bounds for the conditional RD:

$$\max\left(0, \frac{\widehat{RD}_{unconditional,2}}{1-\widehat{R}_{E,1}}\right) \leq RD_{conditional,2} \leq \frac{\widehat{RD}_{cumulative,2}}{1-\widehat{R}_{E,1}} \qquad [6]$$

where $\widehat{R}_{E,1}$ is the unconditional risk observed in period 1 for the exposed population. Note that equation 6 is also a reformulation of previously described bounds around response type $P_{\Omega,2}$.[6]

E.8 Relaxing Monotonicity

Many exposures can harm some individuals while benefitting others, and conditional effects in these contexts can have important public health or clinical relevance. Allowing for all preventive and causative response types in Table E.1, the RD for period 1 in the exposed target population is $RD^*_1 = (P_{1,1} + P_{2,1} + P_{\Omega,1}) - (P_{1,1} + P_{1,2} + P_{1,\Omega})$, where the asterisk indicates risk estimates allowing for non-monotonic exposure effects. The RD^*_1 is the population proportion in which exposure causes disease minus the proportion in which exposure prevents disease that would otherwise have occurred in period 1. With an exchangeable unexposed substitute population providing the counterfactual data ($Q_{1,1} + Q_{1,2} + Q_{1,\Omega}$), RD^*_1 can be estimated without bias. The same is true for the unconditional RD* in period 2, written as $RD^*_{\text{unconditional},2} = (P_{2,2} + P_{\Omega,2} + P_{1,2}) - (P_{2,2} + P_{2,1} + P_{2,\Omega})$.

Allowing for non-monotonic exposure effects adds an additional layer of complexity to the conditional RD. If exposure delays some events that would have occurred in period 1 ($P_{1,2} + P_{1,\Omega} > 0$), then the surviving target population in period 2 is $P_{2,2} + P_{\Omega,\Omega} + P_{\Omega,2} + P_{1,2} + P_{1,\Omega} + P_{2,\Omega}$, and conditional disease risk for this subgroup in period 2 is $(P_{2,2} + P_{\Omega,2} + P_{1,2})/(P_{2,2} + P_{\Omega,\Omega} + P_{\Omega,2} + P_{1,2} + P_{1,\Omega} + P_{2,\Omega})$. The counterfactual disease risk in period 2 for this same subgroup if they had instead been unexposed is metaphysical, however, because the proportions $P_{1,2}$ and $P_{1,\Omega}$ would have already experienced disease in period 1 and therefore would not be included in the counterfactual denominator. The same phenomenon prevents defining an appropriate counterfactual comparison for estimating the conditional RD with an unexposed target population under assumptions of causative monotonicity.[6] Instead, defining conditional effects with non-monotonic exposures requires more restrictive conditions: among the subset of the target population *who would have survived to the end of period 1 regardless of exposure status*, what is the effect of exposure in period 2? This restriction conceptually eliminates $P_{1,2}$

and $P_{1,\Omega}$ from the target population so that the desired conditional effect can be defined as:

$$RD^{*}_{conditional,2} = \frac{(P_{2,2} + P_{\Omega,2}) - (P_{2,2} + P_{2,\Omega})}{P_{2,2} + P_{\Omega,\Omega} + P_{\Omega,2} + P_{2,\Omega}} = \frac{P_{\Omega,2} - P_{2,\Omega}}{P_{2,2} + P_{\Omega,\Omega} + P_{\Omega,2} + P_{2,\Omega}} \quad [7]$$

The observed conditional RD* in the absence of monotonic exposure effects is defined using population response types as:

$$\widehat{RD}^{*}_{conditional,2} = \left(\frac{P_{2,2} + P_{\Omega,2} + P_{1,2}}{P_{2,2} + P_{\Omega,\Omega} + P_{\Omega,2} + P_{1,2} + P_{1,\Omega} + P_{2,\Omega}}\right) - \left(\frac{Q_{2,2} + Q_{2,1} + Q_{2,\Omega}}{Q_{2,1} + Q_{\Omega,1} + Q_{2,2} + Q_{\Omega,\Omega} + Q_{\Omega,2} + Q_{2,\Omega}}\right) \quad [8]$$

The observed RD* in equation 8 does not pertain to any real-world counterfactual effect measure. Furthermore, without monotonicity assumptions it not possible to estimate the restricted RD* in equation 7.[6,209]

Fortunately, many scientific questions in public health are focused on overall outcomes in the target population, with some *a priori* expectation about directionality of the net exposure effect. In these cases it may be sufficient to adopt weaker monotonicity assumptions than mutual exclusivity of causation and prevention, by instead assuming "marginal monotonicity" of exposure effects at the population level.[206] For causative marginal monotonicity this means the population proportion of each causative type is equal to or greater than the proportion of the preventive type for the same two periods. Specifically, causative marginal monotonicity assumes the three inequalities ($P_{2,1} > P_{1,2}$), ($P_{\Omega,1} > P_{1,\Omega}$), and ($P_{\Omega,2} > P_{2,\Omega}$) are true. With these weaker assumptions, bounds around the conditional RD* restricted to the subset of people who would survive past period 1 regardless of exposure status are defined as follows:

$$Max[0, \frac{\widehat{RD}_{unconditional,2}}{1 - \widehat{R}_{E,1}}] \leq RD^{*}_{C} \leq \frac{2(\widehat{RD}^{*}_{1} + \widehat{RD}^{*}_{unconditional,2})}{1 - \widehat{R}^{*}_{E,1} - \widehat{R}^{*}_{N,1}} \quad [9]$$

where $\widehat{R}^{*}_{N,1}$ is the unconditional risk in period 1 observed in the substitute population. These bounds are wider than estimates assuming no preventive response types, because

the relative magnitudes of causative and preventive response types for RD_1^* are unrestricted within the other linear programming parameters, whereas for the bounds in preventive types $P_{1,2}$ and $P_{1,3}$ are implicitly set to 0.

E.9 Three or More Study Periods

When age or follow up time is divided into more than two periods, the same formulae can be used for bounding conditional effects by simply adjusting the definitions of periods 1 and 2. "Period 2" will always be the period in which a conditional RD or RD* is being estimated, and "period 1" is always the aggregate of all preceding periods. This approach is demonstrated in the applied example that follows.

E.10 Example: Racial Differences in Post-Stroke Mortality

The Strong Heart Study (SHS) is a prospective cohort study of cardiovascular disease and its risk factors in American Indians.[1] At baseline exams from 1988-1990 the SHS enrolled 4549 participants ages 45-74 years old, representing 13 tribes from three geographic regions. A 2004 publication reported higher stroke rates and post-stroke mortality for American Indians compared with Blacks and Whites in other cohort studies.[2] Recently we pooled data from the SHS and the Atherosclerosis Risk in Communities Study (ARIC), a large population-based cohort study that enrolled Black and White participants from four geographic sites across the US,[3] to compare stroke incidence and post-stroke mortality for American Indians vs. Blacks and Whites. The statistical analysis used logistic regression with marginal standardization to estimate risk differences adjusting for sex; age at stroke event; birth year; education; alcohol consumption; smoking; and prevalent hypertension, diabetes, and cardiovascular disease. We found that American Indians who experienced stroke had substantially higher risk of 30-day mortality than their Black or White counterparts (Table E.2), but that the magnitude of difference attenuated in the analysis of cumulative risk through 1 year after stroke onset. One question with clinical and public health relevance is whether the smaller RD for cumulative 1-year mortality reflects temporal change in the magnitude or direction of racial differences in survival, for example if American Indians experience early barriers to receiving acute stroke-related healthcare but have better access to

rehabilitation and other long-term services. This question is best answered by estimating conditional effects.

For this example we divided the first year of post-stroke follow up time into three periods (0-30 days, 31-180 days, 181-365 days). We estimated the cumulative RD for each period, and the conditional RD for 31-180 and 181-365 days after stroke onset. The population at risk for each conditional comparison was restricted to the subset of people who survived to the end of the preceding period. Cumulative risks were higher for American Indians than for Blacks or Whites in all three periods (Table 2), but magnitudes of difference decreased over time. Among the subset of people who survived at least 30 days, there was no apparent difference in survival from 31-180 days after stroke onset. Among the subset of people who survived at least 180 days, American Indians appeared to have slightly lower mortality than Blacks and Whites.

We theorized that although American Indian race could confer long-term survival benefits for some individuals, considerations such as the disproportionate burdens of many stroke risk factors among American Indians, well-documented barriers to accessing high quality healthcare, and chronic underfunding of the Indian Health Service—the major healthcare source for most Strong Heart Study communities—suggested causative marginal monotonicity for post-stroke mortality at the population level. Note that in this context causation reflects indirect effects on mortality from the same sociocultural factors that gave rise to modern racial categories, such as the stipulation that only enrolled members of federally recognized American Indian tribes are allowed to receive care from the Indian Health Service. As shown in Table E.2, using equation 6 with assumptions of individual-level causative monotonicity led to bounds around the conditional RDs that were consistent with long-term differences of similar magnitude as observed for the first 30 days following a stroke event. Using equation 9 with assumptions of marginal causative monotonicity resulted in substantially elevated upper bounds for the true conditional RDs, and would require additional user-specified restrictions, such as limiting the relative magnitude of causative and preventive response types in RD_1^*, to provide meaningful context for interpreting the conditional effect.

E.11 Discussion

Conditional effects suffer from a type of selection bias that can compromise the scientific integrity of public health and clinical trials research. Previous publications described the problem[6,188] and advised estimating alternative effects, such as cumulative risk comparisons, that can be identified from observed data. We have described simple formulae to estimate bounds for the true effect measure when conditional comparisons are either unavoidable or are of primary interest to investigators. As demonstrated in the example, failure to consider conditional effects bias could lead to reporting diminishing effects or reversal of directionality beyond some threshold in age or time, when in fact those trends are not conclusively supported by the data.

It can be difficult to understand the difference between conditional effects bias and other types of selection bias, the latter of which could theoretically be avoided by eliminating loss to follow up or other mechanisms for informative missing data. Conditional effects bias, in contrast, is a fundamental identification problem that persists even with infinite sample size and no missing data. Conditional effects bias cannot be fixed by study design or statistical analysis without imposing additional assumptions such as no effect of exposure in specific periods. Conditional effects bounds as described here can be used by analysts as a sensitivity analysis to contextualize findings. These bounds can also be estimated by consumers of published research, when investigators report sufficient descriptive information for estimating period-specific conditional and unconditional risks. Such information at minimum would comprise unconditional denominators for the target and substitute populations, and event counts for each population in each age category or time period. With loss to follow-up or attrition for reasons other than experiencing the outcome, this information should also be provided to allow accurate enumeration of the conditional denominators.

Data do not always exist to allow estimation of the unconditional risks needed for the bounding equations described above. This problem is common in observational data if the original target population cannot be enumerated to calculate denominators for unconditional risks, or when follow up begins some length of time after exposure and the RD cannot be estimated for period 1. For example, in cohort studies that enroll middle-

aged adults but evaluate exposures predating enrollment, period 1 risks are not directly observable and follow up should be viewed as starting in period 2. Bounding conditional effects in these scenarios requires substituting external information for the missing unconditional risk values. External information can reflect empirical estimates from other studies if such data are available, or the investigator's best guess based on expert knowledge. Alternatively, it might be possible to identify values for unconditional effect measures that would lead to qualitative reversal of observed conditional risk comparisons. Other analytic methods could also be considered, such as Bayesian models that specify prior distributions on unobserved parameters. We hope the bounding method described here will increase awareness of conditional effects bias and provide a practical tool for quantifying its magnitude in applied research.

Table E.1. Potential outcomes response types for binary exposure and binary outcome with age or follow-up time divided into two periods.

	Period in which outcome would occur…		Population proportions*	
Response type	**If not exposed**	**If exposed**	**Target**	**Substitute**
Immune	Ω**	Ω	$P_{\Omega,\Omega}$	$Q_{\Omega,\Omega}$
Doomed	1	1	$P_{1,1}$	$Q_{1,1}$
Doomed	2	2	$P_{2,2}$	$Q_{2,2}$
Causative	2	1	$P_{2,1}$	$Q_{2,1}$
Causative	Ω	1	$P_{\Omega,1}$	$Q_{\Omega,1}$
Causative	Ω	2	$P_{\Omega,2}$	$Q_{\Omega,2}$
Preventive	1	2	$P_{1,2}$	$Q_{1,2}$
Preventive	1	Ω	$P_{1,\Omega}$	$Q_{1,\Omega}$
Preventive	2	Ω	$P_{2,\Omega}$	$Q_{2,\Omega}$

* Target population = exposed; Substitute population = unexposed.
**Ω = Outcome will not occur in either age category or follow-up period

Table E.2. Post-stroke mortality among participants of the Strong Heart Study and Atherosclerosis Risk in Communities study.

	Counts		Observed Risk Difference*		Conditional Effects Bounds	
	Deaths	**At risk**	**Cumulative**	**Conditional**	**Monotonic**	**Relaxed**
0-30 days						
AI	64	310				
Black	39	416	14 (6, 23)			
White	71	613	12 (3, 21)			
31-180 days						
AI	21	246				
Black	33	377	11 (2, 20)	-1 (-7, 4)	0, 16	0, 35
White	35	542	11 (1, 20)	1 (-5, 6)	0, 14	0, 31
181-365 days						
AI	11	225				
Black	18	344	8 (-1, 17)	-3 (-7, 2)	0, 13	0, 20
White	24	507	8 (-1, 17)	-2 (-6, 3)	0, 13	0, 33

* Risk difference comparing American Indians to Blacks and Whites, adjusted for sex, age at stroke event, birth year, education, alcohol consumption, smoking, and prevalent disease (cardiovascular disease, hypertension, diabetes).

F. Contribution and Future Directions

This dissertation addressed three issues relevant to evaluating clinical and preclinical cerebrovascular disease in American Indians. In **Manuscript 1** we found that the higher stroke incidence reported in a previous analysis of American Indians in the SHS persisted in a direct comparison to White, but not to Black, participants of ARIC. After adjusting for risk factors including prevalent hypertension and diabetes, stroke incidence in American Indians was only slightly elevated compared to Whites, whereas differences increased in magnitude compared to Blacks. Taken together, these findings suggest that diabetes-related disparities in American Indians may be important factors for understanding stroke disparities in this population, at least compared to Whites from communities represented in ARIC. In contrast to results for stroke incidence, our analysis not only supported the previous finding of higher 30-day and 1-year post-stroke mortality in American Indians, but suggested larger magnitudes of disparities after covariate adjustment compared to both Blacks and Whites. Interpretation of these results is limited by the fact that Black race in ARIC was highly correlated with residence in the stroke belt region of the US, and it is possible that stroke risk in American Indians would be closer to risk in Blacks from similar geographic regions.

This analysis underscores the need for studies of stroke incidence and survival that include American Indians in sufficient numbers to allow for more nuanced evaluation of interracial stroke disparities across place and time. Unfortunately, the high costs and amount of resources needed to enroll cohorts of sufficient size and with long enough follow-up to evaluate stroke outcomes are insurmountable barriers to launching new studies in today's funding environment. Instead, existing cohorts can be combined as shown here to expand the literature on multi-racial comparisons of stroke and other cardiovascular disease events that includes American Indians. Candidate cohorts could include the Cardiovascular Health Study (Blacks and Whites from four locations across the US),[210] the Multi-Ethnic Study of Atherosclerosis (Blacks, Whites, Chinese-Americans, and Mexican-Americans),[211] or the Reasons for Geographic and Racial Differences in Stroke Study (Blacks and Whites).[212] The Strong Heart Family Study, which recruited and examined about 3800 extended family members of 94 index

participants from the SHS, is another potential resource for analyzing stroke outcomes in AIs once adjudicated events are available with sufficient follow-up time to evaluate stroke incidence and fatality. Lastly, smaller hospital-based studies could feasibly be designed and funded to better understand post-stroke survival in Native populations, and to identify appropriate targets for public health intervention.

In **Manuscript 2** we addressed the need for a standardized protocol to adjust for selection bias in the SHSS. Comprising elderly surviving members of the SHS cohort, the SHSS is the only large sample of community-dwelling American Indians with brain magnetic resonance imaging, cognitive testing, and longitudinal data on risk factors for and incidence of cardiovascular disease. The SHSS therefore represents a unique and important opportunity to study not only cerebrovascular disease, but also other aging-related conditions—such as Alzheimer's Disease—that require access to brain scans and data on cognitive function and which have not been adequately studied in American Indians. Many analyses using SHSS data will potentially suffer from selection bias due to differential survival associated with exposures and outcomes.

Marginal structural models using IPW are one method of adjusting for selection bias, and we propose a protocol that can be used as a guide for uniform application of IPW. Importantly, our approach strikes a balance between capitalizing on the breadth and depth of longitudinal data collection and minimizing the potential for introducing bias from model misspecification. Furthermore, we propose a slight adjustment to conventional stabilized weights that ensure appropriate inference to the desired target population when inclusion criteria correlate with predicted probabilities of selection. This adjustment is relevant not only to SHSS analyses that require excluding participants with prevalent stroke, but to other studies whose designs entail a similar combination of inclusion criteria and IPW adjustment for selection bias. In our example, stroke prevalence was low (< 10%), and it is not surprising that tailoring weights to account for stroke risk did not result in substantially different results than obtained by conventional stabilization methods. The proposed tailoring method could be more informative, however, when inclusion criteria lead to dropping a larger proportion of observations from analysis and if observations that are included in the analysis despite low predicted

probabilities of selection (and therefore large weights) simultaneously have high probability of failing to meet inclusion criteria.

The relatively minor impact of IPW weighting for selection bias, however, also raises considerations about the relative benefit of this method given the time-intensive nature of its application. Designing the modeling approach, imputing data, and conducting appropriate analyses are not simple nor are they quickly implemented, and unless investigators anticipate strong selection bias in their data it could be more expedient and sufficiently informative to use other methods for sensitivity analysis. For example, spreadsheet-based adjustments in which investigators can specify possible magnitudes of differential selection probabilities take far less time and can quickly demonstrate approximately what level of selection bias would be necessary to qualitatively alter conclusions.[213] Ultimately, a tiered protocol in which investigators only proceed to the more complicated IPW analysis if simpler methods indicate that such an approach is warranted may be preferable.

In **Manuscript 3** we addressed a pervasive identification problem that is not widely appreciated by applied researchers. Our goals were to provide an accessible description of conditional effects bias, and to present simple bounding formulae that reflect potential magnitude of the bias without requiring additional time-consuming or sophisticated statistical analyses. One limitation of Manuscript 3 is the problematic nature of bounds allowing for non-monotonic exposure effects in the target population. First, simply defining a real-world conditional population requires conceptually excluding individuals in whom exposure prevents the outcome from occurring in period 1. In a public health setting where overall average effects are of interest, this contortion may still yield meaningful results. Because it is impossible to conclusively identify which individuals would be excluded from the surviving target population, however, the constrained definition would not yield effect estimates that could readily be applied to any given individual in a clinical setting. Additional research or analysis would be required to predict a given person's likelihood of being among the population proportions corresponding to preventive response types. Second, even if one accepts the conditional target population as presented, requiring no restrictions in relative magnitude of

preventive vs. causative response types beyond marginal monotonicity resulted in bounds that were too wide for useful interpretation. Future research could focus on narrowing bounds by directly inputting observed risk data into optimization algorithms, or by identifying bounds for a menu of additional user-specified constraints based on subject matter knowledge. Presenting a range of subjective, but minimally restrictive, constraints could facilitate more meaningful sensitivity analysis without requiring the assumption of individual-level monotonicity.

Another important limitation of Paper 3 is that it only presents formulae for bounding RD comparisons on the absolute scale, whereas bounds are not provided for the more ubiquitous multiplicative effect measure of relative risk. This choice was partly driven by our inability to derive bounds for the relative risk that allow for non-monotonic exposure effects in the target population without requiring additional assumptions that are not necessarily supported by the data. Future research should explore the use of weak assumptions that allow derivation of bounds for the relative risk, for example specifying an upper limit that exceeds any value which would reasonably be expected in clinical trials or public health research (e.g., less than 10-fold difference). With this approach the challenge may be to find a balance between assumptions that aren't too restrictive but still yield bounds are narrow enough to provide a useful estimate of potential conditional effects bias. Similarly, future research could focus on Bayesian methods that specify weak prior distributions around unidentified parameters and allow for evaluation of conditional effects bias under a range of transparent specifications.

Taken together, these three papers contribute to the scant public health literature on stroke and cerebrovascular disease in American Indians, and more generally to the methodological toolbox for unbiased identification of effect measures in which estimates are conditioned on survival to some threshold defined by age or time since exposure. We hope this work will be accessible to applied researchers working to understand and remediate public health disparities defined by race and in other underserved populations.

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G. APPENDIX

Hazard ratios for all covariates in the fully adjusted Cox regression model of incident stroke by race and birth cohort tertile.

	Birth Years 1914-1930	**Birth Years 1931-1937**	**Birth Years 1938-1947**
	Hazard Ratio (95% CI)	***Hazard Ratio (95% CI)***	***Hazard Ratio (95% CI)***
Race:			
American Indians vs. Blacks	0.79 (0.61, 1.01)	0.73 (0.54, 0.98)	0.60 (0.44, 0.84)
American Indians vs. Whites	1.14 (0.90, 1.45)	1.15 (0.85, 1.55)	1.08 (0.76, 1.53)
Birth year	1.00 (0.97, 1.03)	0.99 (0.94, 1.04)	0.99 (0.93, 1.06)
Female	0.80 (0.68, 0.94)	0.79 (0.64, 0.97)	0.85 (0.67, 1.08)
Education (ordinal categories)	0.98 (0.88, 1.09)	0.78 (0.68, 0.90)	0.73 (0.62, 0.87)
Current alcohol consumption	0.92 (0.78, 1.10)	0.86 (0.69, 1.06)	0.90 (0.70, 1.15)
Current smoking	1.76 (1.47, 2.10)	1.99 (1.61, 2.45)	2.01 (1.58, 2.57)
Body mass index	1.00 (0.98, 1.01)	0.99 (0.97, 1.01)	1.01 (0.99, 1.03)
Congestive heart failure	1.37 (1.01, 1.85)	1.13 (0.75, 1.70)	1.34 (0.81, 2.22)
Coronary heart disease	1.54 (1.15, 2.05)	2.27 (1.57, 3.27)	1.84 (0.99, 3.42)
Hypertension*	1.30 (1.14, 1.47)	1.29 (1.11, 1.49)	1.33 (1.11, 1.60)
Blood pressure ≥ 140/90 mmHg at baseline	1.30 (1.07, 1.58)	1.35 (1.04, 1.74)	1.61 (1.17, 2.20)
Diabetes**	1.19 (0.98, 1.44)	1.13 (0.87, 1.47)	1.39 (1.01, 1.90)
Fasting glucose ≥ 126 mg/dL at baseline	1.27 (0.87, 1.85)	2.01 (1.20, 3.35)	1.63 (0.89, 2.96)

CI = Confidence interval

* Ordinal categories (normal, borderline, hypertensive)

** Ordinal categories (none, impaired fasting glucose, diabetic)