

Trends in Cardiovascular Disease Morbidity and Mortality in American Indians Over 25 Years: The Strong Heart Study

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Background—American Indians experience high rates of cardiovascular disease. We evaluated whether cardiovascular disease incidence, mortality, and prevalence changed over 25 years among American Indians aged 30 to 85.

Methods and Results—The SHS (Strong Heart Study) and SHFS (Strong Heart Family Study) are prospective studies of cardiovascular disease in American Indians. Participants enrolled in 1989 to 1990 or 2000 to 2003 with birth years from 1915 to 1984 were followed for cardiovascular disease events through 2013. We used Poisson regression to analyze data for 5627 individuals aged 30 to 85 years during follow-up. Outcomes reflect change in age-specific cardiovascular disease incidence, mortality, and prevalence, stratified by sex. To illustrate generational change, 5-year relative risk compared most recent birth years for ages 45, 55, 65, and 75 to same-aged counterparts born 1 generation (23–25 years) earlier. At all ages, cardiovascular disease incidence was lower for people with more recent birth years. Cardiovascular disease mortality declined consistently among men, while prevalence declined among women. Generational comparisons were similar for women aged 45 to 75 (relative risk, 0.39–0.46), but among men magnitudes strengthened from age 45 to 75 (relative risk, 0.91–0.39). For cardiovascular disease mortality, risk was lower in the most recent versus the earliest birth years for women (relative risk, 0.56–0.83) and men (relative risk, 0.40–0.54), but results for women were inconclusive.

Conclusions—Cardiovascular disease incidence declined over a generation in an American Indian cohort. Mortality declined more for men, while prevalence declined more for women. These trends might reflect more improvement in case survival among men compared with women. (*J Am Heart Assoc.* 2019;8:e012289. DOI: 10.1161/JAHA.119.012289.)

Key Words: cardiovascular disease • epidemiology • race

American Indians experience high morbidity and mortality from cardiovascular disease (CVD). In 2019, the American Heart Association reported that American Indians and Alaskan Natives in the aggregate had a higher prevalence (12%) of heart disease than Hispanic and non-Hispanic whites, blacks, and Asians

(range, 1%–8%).¹ According to the 2010 US Census, American Indians and Alaskan Natives comprise just 1.7% of the total population (5.2 million people),² and they are often excluded from studies of racial disparities in CVD. The SHS (Strong Heart Study) is a population-based cohort study of CVD in American Indians that began in 1988. In 2000, the SHS recruited participants and their relatives in large multigeneration families, creating the SHFS (Strong Heart Family Study) cohort. Combining the SHS and SHFS cohorts resulted in the largest longitudinal data set available to study CVD in American Indians, one that initially included 7694 unique individuals who were aged 14 to 93 at baseline. The original SHS data showed higher rates of heart disease and stroke than did national data on all other racial and ethnic groups.^{3,4} Sharing SHS findings with the participating communities led to a strong emphasis on CVD prevention, especially among patients with diabetes mellitus. However, it is unknown whether changes in CVD mortality or morbidity have occurred among cohort members over the decades since the inception of SHS.

We analyzed data from the combined SHS and SHFS cohort to evaluate temporal change in CVD (prevalence, incidence, and CVD-related mortality risk) in American Indians. Our goals were to estimate (1) CVD trends by age, year of data collection, and birth

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Clinical Perspective

What Is New?

- The SHS (Strong Heart Study) is the only population-based cohort study that allows longitudinal analysis of age-specific cardiovascular disease outcomes in American Indians.
- Over a 25-year period, cardiovascular disease incidence decreased among American Indian women and men from 3 geographic regions who were aged 30 to 85 during follow-up.
- Over the same period, cardiovascular disease mortality decreased in men but not in women.

What Are the Clinical Implications?

- Cardiovascular disease appears to be declining in the American Indian communities represented in the SHS, but women may have experienced less improvement in cardiovascular disease mortality than men.
- The SHS protocols included medical referral for management of cardiovascular disease risk factors, and so improvement observed in cohort participants may not reflect the experience of other American Indian people across the United States.
- Our findings may support the value of public health programs to improve heart health in American Indian communities.

year cohort; and (2) generational differences in CVD incidence and mortality risk. We focused on differences in age-specific CVD outcomes across generations, hypothesizing that CVD incidence and mortality risk would be lower at the same age in people born more recently.

Methods

Transparency and Openness

The data used for this analysis are subject to oversight from the Publications and Presentations Committee of the SHS (<https://strongheartstudy.org/>), and are subject to tribal sovereignty agreements that require tribal approval before dissemination of data or results to third parties. Because of these constraints, requests from other researchers to access the data used in this analysis must be submitted to the SHS. Upon approval, the data set may be obtained from the corresponding author (Muller).

Human Subject Protections

The Indian Health Service, institutional review boards for each participating institution, and participating communities approved all study protocols. All participants provided informed

consent. All necessary tribal approvals were obtained before this article was submitted for publication.

Study Populations

The SHS is a longitudinal study of CVD and its risk factors among American Indian tribal members in 3 geographic regions.⁵ A total of 4549 enrollees aged 45 to 74 years were examined at baseline in 1989 to 1991. Baseline data collection included personal history and lifestyle questionnaires, a clinical exam, and laboratory measurements. Follow-up efforts (1992–1995, *n*=3638; and 1996–2000, *n*=3197) reexamined 89% and 88% of surviving cohort members, respectively. In 2001 to 2003, the SHFS enrolled 3665 American Indians aged 14 to 93 years at baseline who were members of 94 extended families that centered on original SHS cohort members.⁶ SHFS participants provided data again in 2007 to 2010. Study protocols for both cohorts included education about CVD and its risk factors as well as medical referral for participants found to have medical conditions (eg, hypertension, diabetes mellitus, and heart disease) at any study exam. The pooled sample size for both cohorts was 7694 unique individuals. However, one study community withdrew consent for further research participation in 2016, leaving 5938 unique individuals for the present investigation. Analysis was limited to people with a minimum age of 30 years during follow-up for whom CVD surveillance was completed in 2013 (*n*=5627).

Continuing surveillance has followed CVD morbidity and mortality in the combined cohort.^{4,7,8} CVD events in the current analysis were myocardial infarction; other definite coronary heart disease as documented by coronary angiography, coronary revascularization, and other tests; heart failure; and stroke. Definitions for the CVD outcomes are based on criteria used by the Framingham cohort study and evolved over time to reflect changing diagnostic guidelines. Stroke definition does not include transient ischemic attack. Surveillance protocols rely on a combination of data obtained by self-report; medications data; medical and death records abstraction; and physical exams that included ECG, echocardiogram, and laboratory assays. Abstracted medical records for all potential events identified in this way included medical history and physical examinations, emergency room visits, medical consultations, ECGs, laboratory assays, medical imaging, discharge summaries, operations, and other procedures from the Indian Health Service and other facilities. Potential CVD-related deaths were reviewed by 2 independent physicians, with adjudication by a third physician to resolve disagreement. Mortality surveillance included examination of death certificates from state health departments, records from the Indian Health Service, and autopsy and coroner's reports, as well as key informant interviews

with physicians or family members. The well-enumerated and relatively closed tribal populations represented in the original SHS supported excellent CVD ascertainment, with follow-up rates for mortality and morbidity generally exceeding 99%.

For the current analysis of the combined cohorts, adjudicated CVD data were available through December 31, 2013. Outcomes represent events considered definite by the adjudication process described above.

Measures

We defined birth cohorts in 10-year intervals from 1915 through 1984, and we defined attained age categories in 5-year intervals from 30 through 85. Calendar time period was divided into 5 evenly spaced intervals across all years of CVD event surveillance (1989–1993, 1994–1998, 1999–2003, 2004–2008, and 2009–2013). Demographic data included sex, study site, and age at initial enrollment. We used SHS baseline data for people who participated in both cohorts, which in all cases preceded SHFS enrollment. CVD prevalence at baseline was recorded by subtype (coronary heart disease/myocardial infarction, heart failure, stroke) and as a composite measure reflecting any prevalent CVD. The composite measure was the primary outcome in this analysis. For SHFS participants, we used family-cluster identification variables to account for clustered data. For descriptive purposes we included selected CVD risk factors measured at each participant's first exam: current smoking, body mass index, blood lipids, systolic blood pressure, prevalent hypertension (systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or on antihypertensive medication), fasting blood glucose, prevalent diabetes mellitus (fasting glucose ≥ 126 mg/dL, use of prescribed hypoglycemic therapy, or on renal dialysis with self-reported history of diabetes mellitus), and antihypertensive or lipid-lowering medication. Medication data were collected at every study visit by using a Medication Check List form that included prescription and nonprescription drugs.

Statistical Analysis

Our analysis was based on age-period-cohort (APC) models, a group of statistical methods designed to estimate effects of biological aging (age); external influences that affect the health of all people in a given calendar year (period); and differences specific to birth cohorts, such that younger cohorts have different disease burdens at a given age than older cohorts (cohort).⁹ These models have been applied to analyses of CVD in other populations.^{10–20} We calculated descriptive statistics for baseline variables by sex and birth cohort as mean, range, and SD for continuous variables, and as frequencies for dichotomous variables. We estimated 10-

year risk (incidence and mortality) or 10-year period prevalence with exact 95% CIs for each category of attained age and birth year.

We estimated rates and prevalence based on total person-years (incidence and mortality) and sample size (prevalence) in the relevant age and birth year cohort category; these estimates were used to generate the plots depicted in the Figure. All estimates excluded people who died before the start of the interval and were therefore conditioned on survival to the minimum age or year of each category. Additionally, incidence estimates excluded people with prevalent CVD at the start of the interval. For prevalence, we estimated the percentage of participants who either had prevalent CVD at the start of the interval or experienced incident CVD during that interval. We focused on graphs for the age+birth year combination to address our a priori question of whether age-specific CVD outcomes differed across generations.

For the inferential analysis, we used Poisson regression to estimate annual change in CVD incidence and mortality by attained age, birth year, and calendar year. We used continuous variables for each of these factors to reflect the hypothesized continuous trends. First, we estimated univariate models (age only, birth year only, or calendar year only) with quadratic terms to account for nonlinearity. Second, we fit separate models for each pairwise combination of the 3 factors (age and birth year, age and calendar year, birth year and calendar year) with quadratic terms for the individual factors and an interaction term for the linear coefficients of 2 factors. We did not include an interaction for the quadratic terms, because preliminary analyses suggested that they did not improve model fit. All analyses were conducted separately by sex. We did not estimate models that simultaneously included all 3 factors (age, period, and cohort). This choice was based on the well-established limitation of collinearity among these variables (age+period=cohort), which renders the model with all 3 variables unidentified.^{21–23} Existing methods to allow simultaneous estimation of the effects of all 3 variables typically impose untestable and often unreasonable modeling constraints. Therefore, we restricted our analyses to pairwise combinations and interpreted our results with appropriate caution. Models used robust variance estimation to account for correlation of SHFS cohort members by family unit.

We used marginal standardization^{24,25} to illustrate generational changes in CVD risk at ages 45, 55, 65, and 75 in the combined cohort. For each attained age, we estimated the relative risk (RR) of CVD incidence and mortality in the youngest compared with the oldest birth years represented in the data set. These values corresponded to 25-year differences for ages 45 (people born in 1968 versus people born in 1943), 55 (people born in 1958 versus people born in 1933),

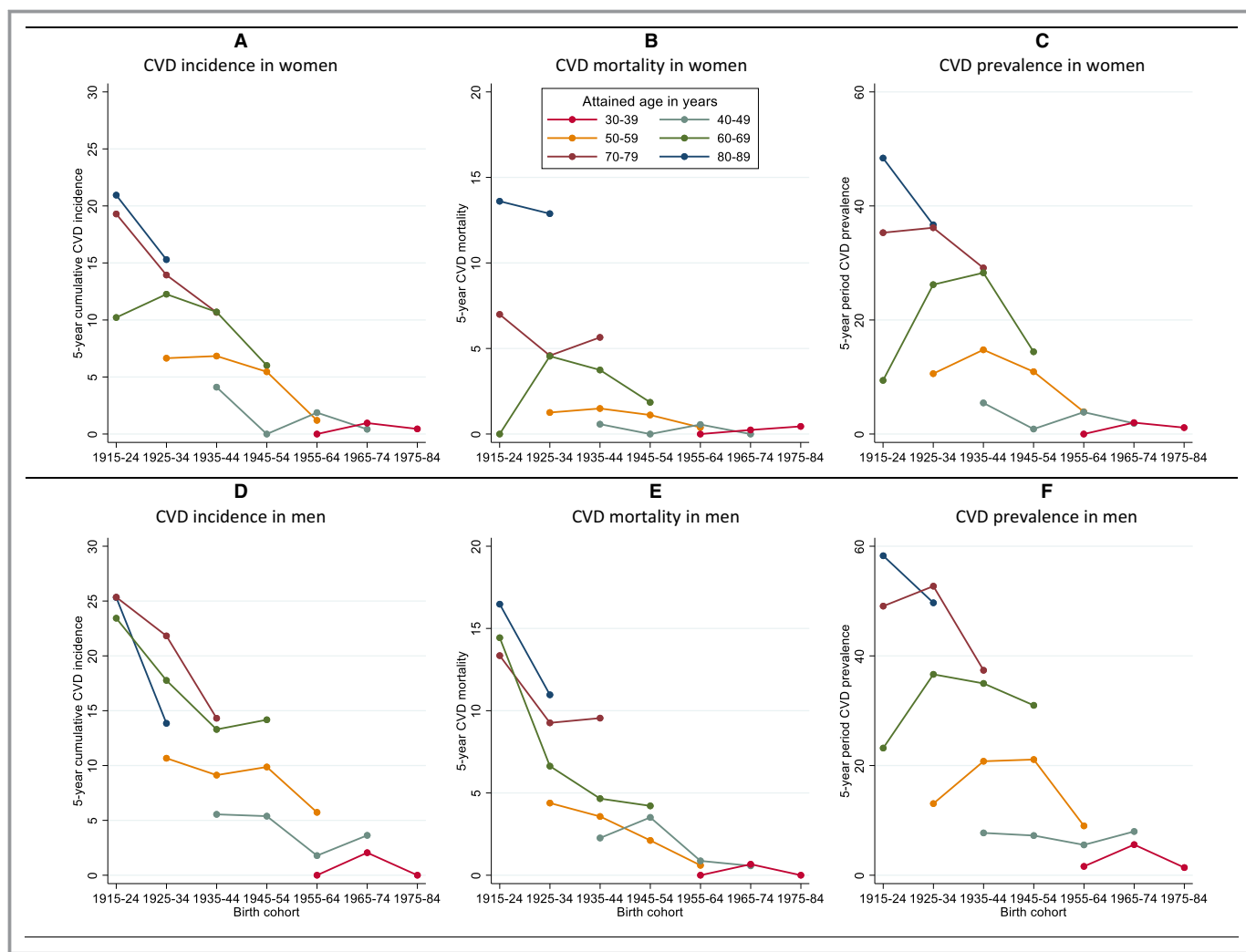


Figure. CVD incidence (A [women], D [men]), mortality (B [women], E [men]), and prevalence (C [women], F [men]) by attained age, birth cohort, and sex for American Indians in the Strong Heart Study. CVD indicates cardiovascular disease.

and 65 (people born in 1948 versus people born in 1923), and a 23-year difference for age 75 (people born in 1938 versus people born in 1915). We excluded ages 35 and 85 from this analysis because data were sparse. We used Stata statistical software (version 14.2; StataCorp LP, College Station, TX) for all data management and analyses, and results are presented as point estimates with 95% CIs.

Results

Our analysis included 5627 participants who met all inclusion criteria. Descriptive statistics for baseline data by sex and birth year cohort appear in Table 1. CVD incidence, mortality, and prevalence by attained age and birth year cohort appear in Tables 2 and 3 for women and men, respectively. For any birth cohort, CVD generally increased with age for both sexes. Reading across attained age rows, trends were consistent, with lower CVD incidence in more recent birth cohorts for

older attained age categories in both women and men. These patterns are also shown in the Figure, with a downward trend in incidence among more recent birth cohorts compared with those born earlier. Similar trends were clearly evident for CVD mortality risk only among men; women did not show consistent improvement in age-specific mortality risk across birth cohorts. Conversely, age-specific CVD prevalence appeared to decline slightly among women in younger birth cohorts, but not among men.

Results from univariate Poisson regression models for CVD incidence and mortality appear in Table 4. These findings are presented to the thousandths' digit so that readers who desire to do so can independently calculate their own estimates for any pairwise combination of the age, period, and cohort factors. Results from bivariate models for women and men appear in Tables 5 and 6, respectively. In general and as expected, CVD incidence and mortality rates increased with older age and declined with more recent birth year and

Table 1. Baseline Characteristics Assessed During the Initial Enrollment Exam for the Pooled Cohorts Stratified by Birth Year

	Birth Year						
	1915–1924 (n=602)	1925–1934 (n=1152)	1935–1944 (n=1636)	1945–1954 (n=630)	1955–1964 (n=601)	1965–1974 (n=516)	1975–1984* (n=490)
Age at enrollment, mean (SD)	70.0 (3.3)	60.6 (3.6)	51.2 (4.0)	49.0 (3.7)	42.1 (2.9)	32.5 (3.1)	22.3 (2.8)
Female, N (%)	369 (61.3)	699 (60.7)	920 (56.2)	379 (60.2)	366 (60.9)	301 (58.3)	271 (55.3)
Prevalent CVD							
Myocardial infarction, N (%)	27 (4.5)	36 (3.1)	35 (2.1)	10 (1.6)	5 (0.8)	7 (1.4)	0 (0.0)
Heart disease, N (%) [†]	40 (6.6)	59 (5.1)	52 (3.2)	12 (1.9)	5 (0.8)	7 (1.4)	0 (0.0)
Heart failure, N (%)	28 (4.7)	66 (5.7)	42 (2.6)	12 (1.9)	6 (1.0)	1 (0.2)	1 (0.2)
Stroke, N (%)	10 (1.7)	10 (0.9)	10 (0.6)	2 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Any, N (%)	67 (11.1)	114 (9.9)	93 (5.7)	23 (3.7)	11 (1.8)	8 (1.6)	1 (0.2)
Current smoking, N (%)	165 (27.4)	399 (34.7)	680 (41.6)	273 (43.3)	253 (42.2)	204 (39.6)	226 (46.1)
Body mass index (kg/m ²), mean (SD)	29.3 (5.6)	30.5 (6.0)	30.8 (6.1)	31.3 (6.5)	32.2 (7.4)	33.1 (8.3)	30.1 (7.9)
Blood lipids (all mg/dL)							
Total cholesterol, mean (SD)	191.5 (37.2)	196.1 (38.3)	196.8 (40.6)	194.7 (37.1)	190.3 (41)	184.2 (34.3)	170.5 (33.2)
LDL, mean (SD)	116.8 (31.8)	120.5 (33.4)	121.0 (33.7)	113.2 (33.0)	103.5 (29.7)	102.4 (30.2)	92.8 (26.6)
HDL, mean (SD)	46.7 (13.9)	47.2 (14.6)	46.1 (14.1)	49.9 (15.5)	53.6 (15.8)	49.8 (13.5)	50.6 (13)
Triglycerides, median (IQR) [‡]	120 (84, 172)	121 (84, 172)	122 (85, 177)	136 (93, 195)	140 (102, 198)	130 (95, 193)	115 (84, 159)
Systolic blood pressure (mm Hg), mean (SD)	135.1 (21.0)	128.8 (20.0)	123.7 (17.4)	124.9 (17.3)	121.8 (14.2)	119.5 (14)	117 (13)
Prevalent hypertension, N (%) [§]	330 (55.0)	486 (42.4)	532 (32.7)	228 (36.4)	187 (31.4)	103 (20.0)	47 (9.6)
Fasting blood glucose (mg/dL), mean (SD)	139.2 (61.2)	145.4 (71.3)	140.7 (72.1)	123.2 (59.3)	114.1 (51.4)	106.0 (46.7)	92.6 (22)
Prevalent diabetes mellitus, N (%)	268 (45.8)	496 (44.3)	582 (36.2)	159 (25.7)	111 (18.6)	68 (13.2)	14 (2.9)
Antihypertensive medication, N (%) [¶]	198 (32.9)	319 (27.7)	329 (20.1)	152 (24.1)	107 (17.8)	36 (7.0)	6 (1.2)
Cholesterol-lowering medication, N (%) [#]	4 (0.7)	8 (0.7)	25 (1.5)	26 (4.1)	9 (1.5)	9 (1.7)	0 (0)

Participants in both cohort studies are represented in descriptive statistics only by their initial Strong Heart Study exam. CVD indicates cardiovascular disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SHFS, Strong Heart Family Study, baseline exams conducted 2000–2003; SHS, Strong Heart Study, baseline exams conducted 1988–1990.

*Included only in the analysis for attained ages of 30 and older.

[†]Includes myocardial infarction and coronary heart disease.

[‡]Median and interquartile range are reported for triglyceride given positively skewed distribution.

[§]Hypertension is defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current use of antihypertensive medication.

^{||}Diabetes mellitus is defined as a fasting glucose level ≥ 126 mg/dL or the use of insulin or oral hypoglycemic medication. Participants on renal dialysis or with a kidney transplant who responded positively to the question, “Has a medical person ever told you that you had diabetes mellitus?” were also classified as having diabetes mellitus.

[¶]Antihypertensive medication use is defined as taking an angiotensin-converting enzyme inhibitor, α -blocker, angiotensin receptor blocker, β -blocker, calcium channel blocker, hydrochlorothiazide, vasodilator, or other hypertension medication.

[#]Cholesterol-lowering medication use is defined as any indication of bile acid sequestrants or statin usage.

more recent calendar year. Quadratic terms reflect the curvilinear trends seen in the Figure.

Age-specific risk ratios for CVD incidence and mortality appear in Table 7. For all comparisons, people with more recent birth year had lower CVD risks relative to their same-aged counterparts in earlier birth years. CIs around point estimates tended to be wider among younger than older ages,

and wider among women than men. For CVD incidence the RR magnitude was fairly stable for women, with no clear increasing or decreasing trend across the ages represented (range, 0.39–0.50). Among men, RR declined steadily from age 35 (RR, 0.91; 95% CI, 0.40–2.05) to 75 (RR, 0.39; 95% CI, 0.25–0.61). For mortality, RR increased from age 35 to 75 for women (95% CI, 0.56–0.83) and men (95% CI, 0.40–0.54),

Table 2. CVD Incidence and Mortality (Both Reflect 5-Year Risk Calculated From Rates) and Prevalence (5-Year Period) by Attained Age and Birth Year Cohort From 1989 to 2013 Among American Indian Women in the SHS and SHFS

CVD Outcome and Attained Age, y	Birth Year Cohort						
	1915–1924	1925–1934	1935–1944	1945–1954	1955–1964	1965–1974	1975–1984
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Incidence							
30–34						2.0 (0.4–5.8)	0.0 (0.0–2.0)
35–39					0.0 (0.0–10.8)	0.4 (0.1–2.1)	2.4 (0.1–12.6)
40–44			0.0 (0.0–100)	0.0 (0.0–100)	1.5 (0.3–4.3)	0.5 (0.01–2.9)	
45–49			4.1 (1.7–8.3)	0.0 (0.0–2.4)	2.1 (0.9–4.3)	0.0 (0.0–7.4)	
50–54		0.0 (0.0–100)	5.6 (3.9–7.8)	5.0 (2.8–8.3)	1.4 (0.3–4.2)		
55–59		6.7 (3.2–11.9)	7.8 (6.0–9.9)	5.8 (3.6–9.0)	0.0 (0.0–8.4)		
60–64	0.0 (0.0–100)	8.4 (6.0–11.4)	10.2 (8.1–12.7)	4.5 (2.2–8.1)			
65–69	10.2 (4.8–18.6)	15.5 (12.5–18.9)	11.3 (8.8–14.2)	10.3 (4.6–19.3)			
70–74	17.7 (13.1–23.1)	17.7 (14.2–21.7)	10.7 (7.5–14.8)				
75–79	20.9 (16.0–26.4)	9.0 (6.0–12.7)	10.2 (3.9–21.0)				
80–84	23.5 (17.4–30.5)	15.6 (10.4–22.1)					
85–89	16.9 (10.4–25.4)	13.7 (3.9–31.5)					
Mortality							
30–34						0.7 (0.02–3.6)	0.0 (0.0–2.0)
35–39					0.0 (0.0–10.8)	0.0 (0.0–1.4)	2.4 (0.1–12.5)
40–44			0.0 (0.0–100)	0.0 (0.0–100)	0.0 (0.0–1.8)	0.0 (0.0–1.9)	
45–49			0.6 (0.01–3.2)	0.0 (0.0–2.4)	0.9 (0.2–2.6)	0.0 (0.0–7.3)	
50–54		0.0 (0.0–100)	1.0 (0.4–2.2)	1.1 (0.2–3.1)	0.0 (0.0–1.7)		
55–59		1.3 (0.2–4.5)	1.8 (1.0–3.0)	1.2 (0.3–2.9)	2.2 (0.1–11.8)		
60–64	0.0 (0.0–100)	2.8 (1.5–4.7)	3.4 (2.2–4.9)	2.1 (0.7–4.8)			
65–69	0.0 (0.0–4.0)	6.0 (4.2–8.3)	4.2 (2.8–5.9)	1.2 (0.03–6.4)			
70–74	6.8 (4.1–10.5)	4.4 (2.8–6.6)	5.3 (3.3–7.9)				
75–79	7.2 (4.5–10.9)	4.8 (2.9–7.3)	7.6 (2.8–15.7)				
80–84	13.7 (9.5–19.0)	12.9 (8.7–18.1)					
85–89	13.4 (8.4–20.0)	13.0 (4.4–27.7)					
Prevalence							
30–34						2.3 (0.7–5.2)	0.8 (0.09–2.7)
35–39					0.0 (0.0–3.2)	1.7 (0.5–3.9)	1.8 (0.2–6.4)
40–44			0.0 (0.0–97.5)	0.0 (0.0–14.8)	1.7 (0.6–3.9)	1.9 (0.6–4.3)	
45–49			5.5 (3.5–8.1)	0.9 (0.1–3.1)	3.9 (2.1–6.4)	0.8 (0.02–4.6)	
50–54		0.0 (0.0–70.6)	8.1 (6.3–10.2)	6.4 (4.1–10.0)	3.9 (2.0–6.7)		
55–59		10.6 (7.5–14.4)	14.1 (11.9–16.7)	10.6 (7.6–14.2)	5.1 (1.9–10.8)		
60–64	0.0 (0.0–52.2)	14.1 (11.5–17.0)	20.5 (17.8–23.5)	11.9 (8.5–16.0)			
65–69	9.4 (5.8–14.3)	24.5 (21.1–28.1)	26.0 (22.8–29.3)	13.9 (9.0–20.1)			
70–74	20.8 (16.7–25.5)	31.3 (27.4–35.5)	28.1 (24.5–31.9)				
75–79	30.5 (25.4–36.0)	33.1 (28.8–37.6)	30.2 (24.2–36.8)				
80–84	40.9 (34.7–47.3)	35.5 (30.3–40.9)					
85–89	41.2 (33.7–49.0)	28.6 (20.2–38.2)					

CVD indicates cardiovascular disease; SHFS, Strong Heart Family Study; SHS, Strong Heart Study.

Table 3. CVD Incidence and Mortality (Both Reflect 5-Year Risk Calculated From Rates) and Prevalence (5-Year Period) by Attained Age and Birth Year Cohort From 1989 to 2013 Among American Indian Men in the SHS and SHFS

CVD Outcome and Attained Age, y	Birth Year Cohort						
	1915–1924	1925–1934	1935–1944	1945–1954	1955–1964	1965–1974	1975–1984
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Incidence							
30–34						0.0 (0.0, 3.4)	0.0 (0.0– 2.6)
35–39					0.0 (0– 22.8)	3.2 (1.2– 6.9)	0.0 (0.0– 11.9)
40–44			0.0 (0.0– 100)	0.0 (0.0– 100)	1.6 (0.2– 5.5)	3.1 (0.9– 7.9)	
45–49			5.6 (2.3– 11.1)	5.4 (2.0– 11.4)	1.9 (0.5– 4.9)	5.3 (0.7– 17.8)	
50–54		0.0 (0.0– 100)	7.4 (5.1– 10.4)	7.3 (3.8– 12.4)	6.2 (2.7– 11.8)		
55–59		10.7 (5.0– 19.3)	10.5 (8.0– 13.4)	12.1 (7.8– 17.6)	3.7 (0.1– 19.0)		
60–64		18.8 (14.4– 24.0)	13.6 (10.6– 17.0)	10.1 (5.5– 16.6)			
65–69	23.4 (13.3– 36.7)	16.8 (12.7– 21.6)	13.0 (9.7– 16.8)	25.3 (14.0– 39.9)			
70–74	20.9 (14.4– 28.7)	23.7 (18.3– 29.9)	13.5 (8.9– 19.2)				
75–79	30.6 (22.5– 39.8)	18.8 (12.7– 26.3)	19.5 (7.7– 37.7)				
80–84	28.2 (17.2– 41.6)	14.2 (6.4– 26.1)					
85–89	19.1 (6.6– 39.0)	11.4 (0.3– 48.9)					
Mortality							
30–34						0.0 (540)	0.0 (712)
35–39					0.0 (72)	1.0 (953)	0.0 (146)
40–44			0.0 (0.0– 100)	0.0 (0.0– 100)	0.8 (646)	0.7 (672)	
45–49			2.3 (0.5– 6.5)	3.5 (557)	0.9 (1067)	0.0 (196)	
50–54		0.0 (0.0– 100)	2.7 (1.4– 4.6)	2.3 (845)	0.7 (670)		
55–59		4.4 (1.2– 10.9)	4.2 (2.8– 6.2)	1.9 (1024)	0.0 (158)		
60–64		6.4 (3.9– 9.8)	4.2 (2.7– 6.2)	2.0 (761)			
65–69	14.4 (6.9– 25.6)	6.8 (4.5– 9.9)	5.2 (3.4– 7.6)	10.0 (284)			
70–74	10.3 (6.1– 16.0)	8.9 (5.9– 12.7)	9.3 (6.1– 13.5)				
75–79	16.6 (11.2– 23.3)	9.8 (6.2– 14.4)	10.8 (3.6– 23.3)				
80–84	17.9 (10.9– 27.1)	11.5 (5.9– 19.7)					
85–89	13.7 (5.8– 26.5)	7.1 (0.2– 33.8)					
Prevalence							
30–34						2.7 (0.7– 6.7)	1.4 (0.3– 4.0)
35–39					1.6 (0.04– 8.7)	5.7 (3.0– 9.7)	0.0 (0.0– 4.4)
40–44			0.0 (0.0– 97.5)	0.0 (0.0– 28.5)	2.7 (0.9– 6.3)	6.9 (3.7– 11.5)	
45–49			7.7 (5.1– 11.2)	7.2 (3.7– 12.6)	5.2 (2.7– 8.9)	10.3 (4.8– 18.7)	
50–54		0.0 (0.0– 70.8)	13.0 (10.4– 16.0)	11.0 (7.1– 15.9)	8.5 (0.5– 13.3)		
55–59		13.1 (8.7– 18.6)	19.8 (16.7– 23.1)	19.8 (14.7– 25.7)	12.0 (5.6– 21.6)		
60–64		25.2 (21.0– 29.7)	26.7 (23.1– 30.5)	24.5 (18.4– 31.3)			
65–69	23.2 (16.4– 31.1)	33.6 (28.9– 38.5)	32.6 (28.5– 36.8)	31.9 (23.6– 41.2)			
70–74	33.0 (26.7– 39.8)	45.0 (40.0– 50.6)	35.8 (31.0– 40.8)				
75–79	48.3 (40.8– 55.9)	48.0 (41.7– 54.4)	39.1 (30.8– 47.9)				
80–84	53.9 (44.4– 63.2)	49.0 (40.9– 57.2)					
85–89	59.4 (46.4– 71.5)	47.5 (31.5– 63.9)					

CVD indicates cardiovascular disease; SHFS, Strong Heart Family Study; SHS, Strong Heart Study.

Table 4. Univariate Poisson Regression Models for CVD Incidence, Mortality, and Prevalence

	Factor		Constant
	Linear (95% CI)	Quadratic (95% CI)	Estimate (95% CI)
Women			
Incidence			
Age	0.070 (0.060 to 0.080)	−0.002 (−0.002 to −0.001)	−4.072 (−4.171 to −3.974)
Birth year	−0.067 (−0.079 to −0.056)	−0.001 (−0.001 to −0.0002)	−4.397 (−4.507 to −4.288)
Calendar year	−0.007 (−0.020 to 0.006)	−0.006 (−0.009 to −0.004)	−3.711 (−3.820 to −3.603)
Mortality			
Age	0.089 (0.070 to 0.107)	−0.001 (−0.001 to 0.0003)	−5.432 (−5.595 to −5.269)
Birth year	−0.080 (−0.102 to −0.058)	−0.0005 (−0.001 to 0.0004)	−5.620 (−5.798 to −5.443)
Calendar year	0.034 (0.014 to 0.054)	−0.005 (−0.007 to −0.002)	−4.818 (−4.982 to −4.654)
Men			
Incidence			
Age	0.063 (0.052 to 0.073)	−0.002 (−0.002 to −0.001)	−3.629 (−3.734 to −3.524)
Birth year	−0.056 (−0.067 to −0.045)	−0.0004 (−0.0009 to 0.0001)	−3.967 (−4.090 to −3.845)
Calendar year	−0.013 (−0.027 to 0.001)	−0.004 (−0.006 to −0.002)	−3.496 (−3.611 to −3.381)
Mortality			
Age	0.076 (0.060 to 0.093)	−0.001 (−0.002 to 0.0004)	−4.745 (−4.899 to −4.591)
Birth year	−0.071 (−0.090 to −0.051)	−0.0004 (−0.001 to 0.0004)	−5.033 (−5.215 to −4.851)
Calendar year	−0.008 (−0.026 to 0.011)	−0.0009 (−0.004 to 0.002)	−4.471 (−4.641 to −4.300)

P value for sex interaction term for **incidence** models: age, *P*=0.14; birth year, *P*=0.24; calendar year, *P*=0.91. *P* value for sex interaction term for **mortality** model: age, *P*=0.06; birth year, *P*=0.37; calendar year, *P*=0.02. Age centered at 60 years; birth year centered at 1945; calendar year centered at 2000. CVD indicates cardiovascular disease.

with men showing consistently higher magnitude of generational improvement compared with their same-aged female counterparts.

Discussion

Our analysis focused on intergenerational, age-specific CVD trends among American Indians in the SHS and SHFS cohorts. Three findings were especially notable. First, more recent birth years were associated with lower CVD incidence among women and men alike, especially for older ages. Second, more recent birth years were associated with lower risk of CVD-related mortality among men, although results for women were inconclusive. Third, age-specific CVD prevalence was generally lower among women in more recent birth years, but little or no change was observed among men.

These results indicate that, in general, CVD rates are declining among American Indians in the SHS and SHFS, despite inconclusive findings on mortality risk in women. The observed trends in our analysis could reflect improvements in healthcare access, quality of care, or medication adherence; positive lifestyle changes; or a combination of these and other factors.²⁶ For example, significant shifts in diet and lifestyle

occurred in many American Indian communities during and shortly after World War II, which could have differentially influenced the future cardiovascular health of children born in the 1940s and 1950s compared with those born in later decades. Additional secular influences might include more aggressive therapy for people with CVD risk factors such as dyslipidemia, hypertension, and type 2 diabetes mellitus; new treatment options or changes in healthcare guidelines (eg, widespread use of statins) that affect everyone, regardless of age; or factors such as attitudes toward smoking and alcohol use among youth that change across generations. Analyses are in progress to examine changes in biological and lifestyle risk factors among SHS and SHFS cohort members. High-level social, political, or environmental changes that affect entire populations simultaneously—period effects in the APC framework—are also potential influences on CVD that should be considered. These external factors are unlikely explanations for our findings, however, as social and economic conditions such as unemployment or funding for the Indian Health Service have not improved consistently over time, nor at levels that would account for the trends observed in the SHS and SHFS.

The difference in results for CVD mortality observed between women and men underscores an important limitation

Table 5. Bivariate Poisson Regression Models for CVD Incidence and Mortality Among Women

	Factor		Interaction*	Constant
	Linear (95% CI)	Quadratic (95% CI)	Linear (95% CI)	Estimate (95% CI)
Age, birth year				
Incidence				
Age	−0.003 (−0.028 to 0.021)	−0.006 (−0.008 to −0.004)	−0.010 (−0.014 to −0.006)	−4.149 (−4.281 to −4.018)
Birth year	−0.076 (−0.099 to −0.052)	−0.005 (−0.007 to −0.003)		
Mortality				
Age	0.049 (0.012 to 0.086)	−0.003 (−0.006 to −0.0003)	−0.006 (−0.012 to −0.0004)	−5.422 (−5.627 to −5.217)
Birth year	−0.043 (−0.079 to −0.006)	−0.003 (−0.006 to −0.0003)		
Age, calendar year				
Incidence				
Age	0.070 (0.059 to 0.080)	−0.001 (−0.002 to −0.0005)	0.0004 (−0.0009 to 0.002)	−3.881 (−4.005 to −3.757)
Calendar year	−0.020 (−0.035 to −0.005)	−0.005 (−0.007 to −0.003)		
Mortality				
Age	0.087 (0.067 to 0.107)	−0.001 (−0.002 to 0.001)	0.001 (−0.001 to 0.003)	−5.273 (−5.485 to −5.061)
Calendar year	−0.005 (−0.029 to 0.020)	−0.004 (−0.007 to −0.001)		
Birth year, calendar year				
Incidence				
Birth year	−0.082 (−0.098 to −0.066)	−0.001 (−0.002 to −0.001)	0.002 (0.0003 to 0.003)	−4.297 (−4.444 to −4.150)
Calendar year	0.060 (0.036 to 0.083)	−0.006 (−0.008 to −0.004)		
Mortality				
Birth year	−0.093 (−0.122 to −0.064)	−0.001 (−0.002 to 0.001)	0.0003 (−0.002 to 0.003)	−5.767 (−6.039 to −5.495)
Calendar year	0.084 (0.045 to 0.123)	−0.004 (−0.006 to −0.001)		

Coefficients can be exponentiated to estimate relative risk. Interaction estimated for linear terms; age centered at 60 years; birth year centered at 1945; calendar year centered at 2000. CVD indicates cardiovascular disease.

*Interaction between the 2 linear terms (eg, age and birth year).

in studies that use prevalence to estimate population-level change in CVD. In our analysis, age-specific CVD prevalence was lower in women from more recent birth cohorts but was relatively consistent across birth cohorts for men. Prevalence data alone might therefore indicate a decline in CVD among American Indian women in our study communities, but not among their male counterparts. However, with the broader perspective offered by incidence and mortality data, a very different conclusion is warranted: the absence of reduction in prevalence for men likely reflects the fact that men experienced a greater decline than women in CVD mortality. In other words, longer survival of people with CVD can cancel out concurrent reductions in incidence, resulting in little or no change in prevalence even when incidence and mortality are improving. Results from our Poisson analysis of incidence and mortality rates are consistent with this explanation. Our study lacked sufficient power to formally evaluate effect measure modification by sex, and future research is needed to confirm this finding.

The present study used APC models designed to distinguish among effects of biological aging that apply to everyone, regardless of birth year; external influences that affect the health of all people in a given calendar year; and differences specific to birth cohorts.⁹ Ours was the first study to apply APC models to an analysis of generational differences in CVD for a geographically diverse sample of American Indians. Within the conventional APC framework, we focused our analysis on the age+cohort pair of factors. A major limitation of this approach is that excluding the period construct prevented us from determining whether underlying trends regarding calendar time were partly responsible for cohort differences. This conundrum reflects the well-established problem of collinearity among age, period, and cohort.^{21,27} Various analytic solutions have been proposed, but each imposes its own additional assumptions, and results are heavily dependent on the model chosen.^{28–31} We therefore decided to forgo modeling all 3 factors simultaneously, and instead focused on age+cohort as most relevant to

Table 6. Bivariate Poisson Regression Models for CVD Incidence and Mortality Among Men

	Factor		Interaction*	Constant
	Linear (95% CI)	Quadratic (95% CI)	Linear (95% CI)	Estimate (95% CI)
Age, birth year				
Incidence				
Age	0.022 (−0.003 to 0.046)	−0.004 (−0.007 to −0.002)	−0.005 (−0.009 to −0.001)	−3.706 (−3.854 to −3.557)
Birth year	−0.039 (−0.065 to −0.014)	−0.002 (−0.004 to −0.00003)		
Mortality				
Age	0.054 (0.020 to 0.088)	0.0003 (−0.002 to 0.003)	0.002 (−0.004 to 0.007)	−4.940 (−5.153 to −4.727)
Birth year	−0.027 (−0.061 to 0.007)	0.0006 (−0.002 to 0.003)		
Age, calendar year				
Incidence				
Age	0.067 (0.056 to 0.077)	−0.001 (−0.002 to −0.001)	−0.001 (−0.003 to 0.0004)	−3.551 (−3.680 to −3.421)
Calendar year	−0.016 (−0.032 to 0.001)	−0.002 (−0.004 to −0.0001)		
Mortality				
Age	0.079 (0.061 to 0.098)	−0.001 (−0.002 to 0.0004)	0.0003 (−0.002 to 0.002)	−4.765 (−4.963 to −4.567)
Calendar year	−0.033 (−0.056 to −0.010)	0.0004 (−0.002 to 0.003)		
Birth year, calendar year				
Incidence				
Birth year	−0.080 (−0.095 to −0.064)	−0.001 (−0.002 to −0.001)	0.003 (0.001 to 0.005)	−3.955 (−4.107 to −3.804)
Calendar year	0.070 (0.043 to 0.096)	−0.004 (−0.007 to −0.002)		
Mortality				
Birth year	−0.087 (−0.113 to −0.060)	−0.001 (−0.002 to 0.0003)	0.001 (−0.001 to 0.003)	−5.219 (−5.477 to −4.962)
Calendar year	0.053 (0.016 to 0.089)	0.0000 (−0.003 to 0.003)		

Coefficients can be exponentiated to estimate relative risk. Interaction estimated for linear terms; age centered at 60 years; birth year centered at 1945; calendar year centered at 2000. CVD indicates cardiovascular disease.

*Interaction between the 2 linear terms (eg, age and birth year).

our scientific question: whether American Indian people born more recently experience different CVD burdens compared with their same-aged counterparts in the previous generation.

Most previous APC studies on CVD have been conducted in other countries and show declining CVD incidence attributable to period and cohort effects, despite aging populations.^{10,14,17,19,20,32–36} Findings on CVD-related mortality have been less consistent, with less improvement reported among women than men by some but not all analyses. In the United States, an APC study published in 2018 used county-level data to demonstrate that recent increases in CVD mortality may be consequences of the obesity and diabetes mellitus epidemics.³⁷

Studies using other analytic methods have also showed declining CVD morbidity and mortality in recent decades among the US general population and for selected racial and ethnic minorities.^{38–42} The extent to which these patterns are mirrored in American Indians, however, has not been conclusively established because the population is either not

included in analyses of racial differences in CVD trends or they are combined with Alaskan Native people into a single category that ignores heterogeneity across US indigenous populations who are in fact characterized by profound variation in culture, healthcare access, socioeconomic status, rurality, lifestyle, and genetic backgrounds. Furthermore, many analyses of CVD trends rely on national data sets that are subject to racial misclassification and underreporting of CVD mortality that typically result in underestimating disease burdens and disparities in American Indians.^{43–48} Our results agree with a previous study that reported decreasing CVD mortality among American Indian and Alaskan Native people from 1950 to about 1980, when declines appeared to plateau.⁴⁹ This analysis was subject to limitations including those described above. Our analysis overcomes some of the limitations affecting other studies by using cohort data from the SHS and SHFS to estimate CVD trends without racial misclassification, and by estimating CVD incidence and mortality with a well-enumerated cohort that allows inference

Table 7. Age-Specific Comparisons of CVD by Birth Year and Sex Among Participants in the SHS and SHFS

Women	Incidence* (PY=41 852)	Mortality* (PY=47 824)
	RR (95% CI)	RR (95% CI)
Age [†] adjusted for birth year		
45 y, 1968 vs. 1943	0.39 (0.19–0.82)	0.56 (0.16–1.91)
55 y, 1958 vs. 1933	0.44 (0.28–0.70)	0.67 (0.31–1.45)
65 y, 1948 vs. 1923	0.50 (0.36–0.68)	0.81 (0.49–1.31)
75 y, 1938 vs. 1915	0.46 (0.31–0.69)	0.83 (0.48–1.45)
Men	Incidence* (PY=25 164)	Mortality* (PY=30 719)
	RR (95% CI)	RR (95% CI)
Age [†] adjusted for birth year		
45 y, 1968 vs. 1943	0.91 (0.40–2.05)	0.40 (0.13–1.25)
55 y, 1958 vs. 1933	0.69 (0.42–1.15)	0.43 (0.21–0.88)
65 y, 1948 vs. 1923	0.53 (0.37–0.75)	0.46 (0.29–0.73)
75 y, 1938 vs. 1915	0.39 (0.25–0.61)	0.54 (0.32–0.92)

Each comparison reflects youngest vs. oldest birth years with CVD surveillance for the relevant age. CVD indicates cardiovascular disease; PY, total person years; RR, relative risk; SHFS, Strong Heart Family Study; SHS, Strong Heart Study.

*Coefficients from regression models are provided in the online supplement.

[†]Ages 35 and 85 years are excluded because of sparse data.

to a population of primarily rural-dwelling American Indians. It also benefits from excellent ascertainment of CVD-related events.

Our study is subject to several additional limitations. First, given concerns of sparse data and participant confidentiality, we did not estimate CVD trends separately across the 3 geographic regions in the combined cohort. Instead, our results reflect overall patterns in a heterogeneous sample of American Indians. Second, given concerns about sample size, we did not evaluate individual types of CVD as separate entities. Such analyses will become possible if more CVD-related events accrue as cohort members age, particularly among the younger SHFS participants. Third, although our findings are representative of the population of our study communities, they may not generalize to American Indians in other parts of the United States because the study communities likely benefited from their participation in longitudinal health research. SHS and SHFS protocols included referral and follow-up to encourage appropriate treatment for participants with newly diagnosed or insufficiently managed chronic conditions or risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, and smoking. These efforts might have contributed to the improvement in CVD observed among cohort members. However, such efforts cannot easily explain the differential decline in mortality risk that we observed in men versus women.

This was the first population-representative cohort study of birth cohort and age-specific CVD trends among American Indians aged 30 years and older. Our findings suggest that age-specific CVD incidence and mortality are declining for women and men, but that women have experienced a smaller decline in mortality than men. These results call for concerted efforts to identify and treat American Indians at high risk of CVD beginning in young adulthood, when American Indians experience substantial health disparities for many CVD risk factors relative to other racial and ethnic groups. Further studies are needed to confirm these trends and examine possible factors associated with the observed decline. Future research using SHS and SHFS data can also extend our findings to include wider generational gaps as the combined cohort ages, and future analyses may have sufficient power to formally evaluate sex-based differences in trends for CVD incidence and mortality.

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