RESEARCH ARTICLE

Age-Related Differences in the Role of Risk Factors for Ischemic Stroke

George Howard, DrPH, Maciej Banach, MD, PhD, Brett Kissela, MD, MS, Mary Cushman, MD, MSc, Paul Muntner, PhD, Suzanne E. Judd, PhD, and Virginia J. Howard, PhD

Correspondence
Dr. Howard
ghoward@uab.edu

Neurology® 2023;100:e1444-e1453. doi:10.1212/WNL.0000000000206837

MORE ONLINE

Infographic
NPub.org/ig10014

Abstract

Background and Objectives

Reports assessing the association of stroke risk factors with incident stroke have generally assumed a uniform magnitude of associations across the age spectrum, an assumption we assess in this report.

Methods

Participants enrolled 2003–2007 in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study who were stroke free at baseline were followed for incident stroke. Associations of traditional stroke risk factors with incident stroke were assessed using (1) proportional hazards analysis based on the baseline age of the participant and (2) Poisson regression analysis assessing associations based on the changing age of the participant during their follow-up (age at exposure). In each analysis, age strata were selected to have a similar number of strokes in each stratum, specifically 45–64, 65–73, and 74+ years for the proportional hazards analysis and 45–69, 70–79, and 80+ years for Poisson regression.

Results

A total of 1,405 ischemic stroke events occurred among 28,235 participants over a median follow-up of 11.3 years, with a total of 276,074 person-years exposure. For both analytic approaches, the magnitude of the association with stroke was significantly less at older ages for diabetes (hazard or relative risk decreasing from ≈2.0 in younger strata to ≈1.3 in older strata), heart disease (from ≈2.0 to ≈1.3), and hypertension defined at a threshold of 140/90 mm Hg (from ≈1.80 to ≈1.50); however, there was no age-related difference in the magnitude of the association for smoking, atrial fibrillation, or left ventricular hypertrophy.

Discussion

Hypertension and diabetes are 2 of the more important risk factors for stroke; however, their association with stroke risk appears substantially less at older ages. That the magnitude of the association for smoking, atrial fibrillation, and left ventricular hypertrophy does not decrease with age suggests their relative importance in determining stroke risk likely increases with age.

From the Department of Biostatistics (G.H., S.E.J.), UAB School of Public Health, Birmingham, AL; Polish Mother Memorial Hospital Research Institute (M.B.), Lodz, Poland; Department of Neurology and Rehabilitation Medicine (B.K.), University of Cincinnati, OH; Department of Medicine (M.C.), University of Vermont, Burlington, VT; and Department of Epidemiology (P.M., V.J.H.), UAB School of Public Health, Birmingham, AL.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CHS = Cardiovascular Health Study; **LVH** = left ventricular hypertrophy; **REGARDS** = REasons for Geographic And Racial Differences in Stroke.

Risk functions offer the opportunity to identify individuals at high risk for stroke to target interventions and to identify high-risk groups for community-level interventions. Several stroke risk functions have been developed from the Framingham cohort[1,2]; the Cardiovascular Health Study (CHS) of a general population cohort older than 65 years[3]; the Stroke Riskometer in Auckland, Rotterdam, and Russian communities[4]; and the QSTROKE score using administrative data from 676 practices in England and Wales.[5] These risk functions have generally been consistent in findings and have documented the leading stroke risk factors to be hypertension, diabetes, cigarette smoking, atrial fibrillation, left ventricular hypertrophy (LVH), and heart disease.

Most of the stroke risk functions assume that risk factors have a consistent risk association across the age spectrum.[1,3,4] The lack of consideration of a potential age-related differential association with risk factors has also been extended to approaches to monitor cardiovascular health including *Life's Simple 7*,[6] and the updated *Life's Essential 8*,[7] both of which attribute successful health management uniformly across the age spectrum. Exceptions that do reflect differential risk associations at different ages include (1) the update to the Framingham Stroke Risk Function that considered an age-specific differential impact for diabetes (above/below age 65 years)[2] and (2) the QSTROKE risk function that included interaction terms between age and several stroke risk factors.[5] The QSTROKE risk function included interaction terms in the final model, but the description of the magnitude of the age-related effect modification is not described in the manuscript.[5]

Although there are counter examples,[8] there is a considerable literature suggesting a general trend of a smaller estimated relative magnitude of the association for cardiovascular risk factors at older ages.[9-15] An age-related change in the impact of risk factors may represent a true difference (perhaps through competing risks) but also could be due to biases introduced through pathways including sample selection and methods of analysis.[8,16]

With the graying of America, the age distribution of the general population is shifting upward, with an associated anticipated increase in the average age at first stroke.[17,18] In 2010, 23% of strokes in the United States occurred above age 85 years; however, by 2050, this percentage is anticipated to increase to 34%, with over 50% of stroke events after age 75 years.[18] With the exception of the CHS risk function, there were relatively few older participants in the populations used for the development of the risk functions. However, the CHS excluded participants under the age of 65 years and hence cannot assess whether the factors described in their analysis are consistent in the younger population. As such, the potential that age could act as an effect modifier of the impact of risk factors on stroke risk has not been thoroughly investigated.

The goal of this work is to assess the relative impact of the traditional risk factors across the age spectrum. The REasons for Geographic And Racial Differences in Stroke (REGARDS) study recruited a large cohort of Black and White individuals with no upper age limit and offers a unique opportunity to assess age-related differences in the magnitude of the association for stroke risk factors.

Methods

REGARDS is a population-based study of 30,239 community-dwelling Black or White participants, aged 45+ years, residing in the 48 contiguous US states or the District of Columbia. These randomly selected individuals were recruited between 2003 and 2007 using a combination of mail and telephone contact. An initial telephone interview conducted by trained staff assessed demographic and cardiovascular risk factors. An in-home assessment was performed approximately 2–3 weeks afterward collecting data on physiologic variables (including blood pressure), performing an ECG, and collecting blood and urine samples. Participants have been contacted at 6-month intervals (through September 30th, 2019, for this analysis) for the surveillance of potential stroke events, assessment of cognitive function, and other health-related outcomes. Medical records for suspected strokes have been retrieved and adjudicated by a physician panel.[19]

The threshold age values defining the age strata were selected with the competing goals of having (1) approximately the same number of incident strokes (and, hence, approximately the same statistical power to establish associations with risk factors) in each stratum and (2) similar age thresholds for the 2 different analytic approaches, facilitating comparisons between the analytic approaches. The age strata were specified before the assessment of any associations with stroke risk factors.

The traditional stroke risk factors were assessed at baseline: hypertension, diabetes, cigarette smoking, atrial fibrillation, LVH, and heart disease. Because of the well-recognized higher stroke risk in the Black population,[19-21] Black race was also considered as part of the traditional risk factor group. Hypertension was defined using 2 thresholds: (1) a systolic

blood pressure of ≥140 mm Hg, diastolic of ≥90 mm Hg, or self-reported use of antihypertensive medications; or (2) a systolic blood pressure of ≥130 mm Hg, diastolic of ≥80 mm Hg, or use of antihypertensive medications. Diabetes was defined as a fasting glucose of ≥126 mL/dL (or ≥200 mL/dL among participants failing to fast) or self-reported use of medications to control glucose levels. Cigarette smoking was defined as self-report of current smoking. Atrial fibrillation was defined using ECG evidence or self-report of a physician diagnosis. LVH was defined using ECG evidence using the Sokolow criteria.[22] Heart disease was defined using baseline ECG evidence of a myocardial infarction, self-reported physician diagnosis of myocardial infarction, or previous coronary artery bypass graft, angioplasty, or coronary stenting.

Two analytic approaches were used to assess the potential differential impact of risk factors across the age spectrum.

- Analysis based on the age at baseline: Proportional hazards analysis was used to estimate the hazard ratio for risk factors within age stratum. Defining strata with approximately the same number of stroke events resulted in strata of 45–64, 65–73, and 74 and over (oldest age 98 years). The association for risk factors within each age stratum was assessed in (1) univariate models, (2) full multivariable models containing all risk factors, and (3) parsimonious models where statistically nonsignificant ($p > 0.05$) factors were incrementally removed using backward stepwise methods. Differences in the magnitude of the association between the age strata were assessed using a 2-degree-of-freedom test for any differences between strata. Finally, in recognition that the list of risk factors selected by the backward stepwise method is a random variable (i.e., the individual factors being retained in a backward selection process will likely differ should the same study be duplicated), the probability that a factor would be retained in the backward stepwise process was estimated using bootstrap methods with 1,000 replications.
- Analysis based on the age at exposure: Individuals were followed for incident stroke for up to 16 years (2003–2019), and this analysis allowed the estimated magnitude of the risk factor association with change as the participant aged during the follow-up period (a.k.a. an age-at-exposure analysis). Specifically, each person's contribution to years at risk within each age stratum was calculated, and Poisson regression providing the relative risk per person-year exposure was used to estimate the association of risk factors with stroke events. Again, the strata were defined to provide approximately the same number of stroke events, resulting in a slightly different age thresholds of 45–69, 70–79, and 80+ years. As individuals aged, their contribution to the risk for specific age stratum could shift. For example, an individual aged 68 years and followed for 16 years would contribute 2 years of exposure to the young stratum, 10 years of exposure to the middle stratum, and 4 years of exposure to the older stratum.

Standard Protocol Approvals, Registrations, and Patient Consents

The institutional review boards of participating institutions approved the study methods, and written informed consent was obtained from all participants.

Data Availability

Investigators are welcomed to access the REGARDS data and documentation under a data use agreement process by contacting the REGARDS study at regardsadmin@uab.edu.

Results

Among the 30,239 REGARDS participants, 28,235 (93%) were stroke free at baseline and followed for subsequent stroke events. Table 1 provides a description of the study population by baseline age, with older participants being more likely to be White and to have a higher prevalence of hypertension, atrial fibrillation, LVH, and heart disease but less likely to be actively smoking. A total of 1,405 incident ischemic stroke events occurred over a median of 11.3 years of follow-up (ranging from 8.7 to 11.6 among the age strata), with a total of 276,074 person-years of exposure (Table 2). With the strata defined by age at baseline, there were a generally similar number of stroke events (ranging from 455 to 514), whereas the crude proportion with stroke increased across the age strata from 3.1% (95% CI 2.8%–3.4%) to 6.2% (95% CI 5.7%–6.8%) or to 8.6% (7.9%–9.4%). For the age-at-exposure analysis, there were 134,955 person-years of

Table 1 Description of the Study Population on the Traditional Risk Factors

	Age at baseline		
	45–64	**65–73**	**74+**
N	14,603	8,239	5,393
Age at baseline (mean ± SD)	57 ± 5	69 ± 3	79 ± 4
Male (%)	42	47	47
Black (%)	44	39	35
Hypertension 140/90 (%)	52	63	67
Hypertension 130/80 (%)	69	77	79
Diabetes (%)	19	24	21
Smoking (%)	19	12	6
Atrial fibrillation (%)	7	9	13
LVH (%)	8	10	13
Heart disease (%)	12	20	27

Abbreviation: LVH = left ventricular hypertrophy.
Percentages are provided among participants in whom the risk factors were observed, and data were missing on diabetes for 4% of participants; heart disease, atrial fibrillation, and LVH in 2% of participants; and hypertension and smoking on <1% of participants.

Table 2 Description of the Number of Patients, Years of Exposure, Number of Stroke Events, and Crude Stroke Rates Within Each Age Stratum for Both Analyses

		Analysis relative to age at baseline			Analysis relative to age at exposure		
		45–64	65–73	74+	45–69	70–79	80+
Participants (N)		14,603	8,239	5,393	N/A		
Median follow-up		11.6	11.3	8.7			
Strokes	N	455	514	446			
	%	3.1 (2.8–3.4)	6.2 (5.7–6.8)	8.6 (7.9–9.4)			
Person-years of follow-up		N/A			134,955	94,093	47,026
Stroke events					368	579	458
Event rate per 100,000 (95% CI)					273 (246–302)	615 (567–668)	974 (889–1,067)

For the age-at-baseline analysis, data are provided for the number of patients, median follow-up, and number and percentage (with 95% CIs) of stroke events. For the age-at-exposure analysis, data are provided for the number of person-years exposure, number of stroke events, and event rate per 100,000 (with 95% CIs). Each person's contribution to years at risk within each age stratum was calculated as the participant potentially ages between age strata.

exposure in the youngest stratum, 94,093 person-years in the middle stratum, and 47,026 person-years in the oldest stratum. The number of stroke events was generally similar across age strata (ranging from 368 to 579), whereas the stroke event rate per 100,000 person-years increased from 273 (95% CI 246–302) to 615 (95% CI 567–688) or to 974 (95% CI 889–1,067).

Figure 1 shows the differences in the association of the risk factors with stroke risk across age strata, with the top panel showing the univariate and multivariable hazard ratio from the age-at-baseline analysis and similarly the bottom panel for the age-at-exposure analysis. The numerical estimates for the multivariable portion of these figures are provided in eTable 1, links.lww.com/WNL/C600. For both diabetes and heart disease, the magnitude of the association with stroke risk was smaller at older age for both analytic approaches in both the univariate and multivariable analyses ($p < 0.05$ in all analyses). For both of these risk factors, the multivariable risk (i.e., either hazard ratio or risk ratio, as appropriate) in the young age stratum was approximately 2.0 times greater for those with the risk factor prevalent but only approximately 1.3 times greater in the oldest stratum.

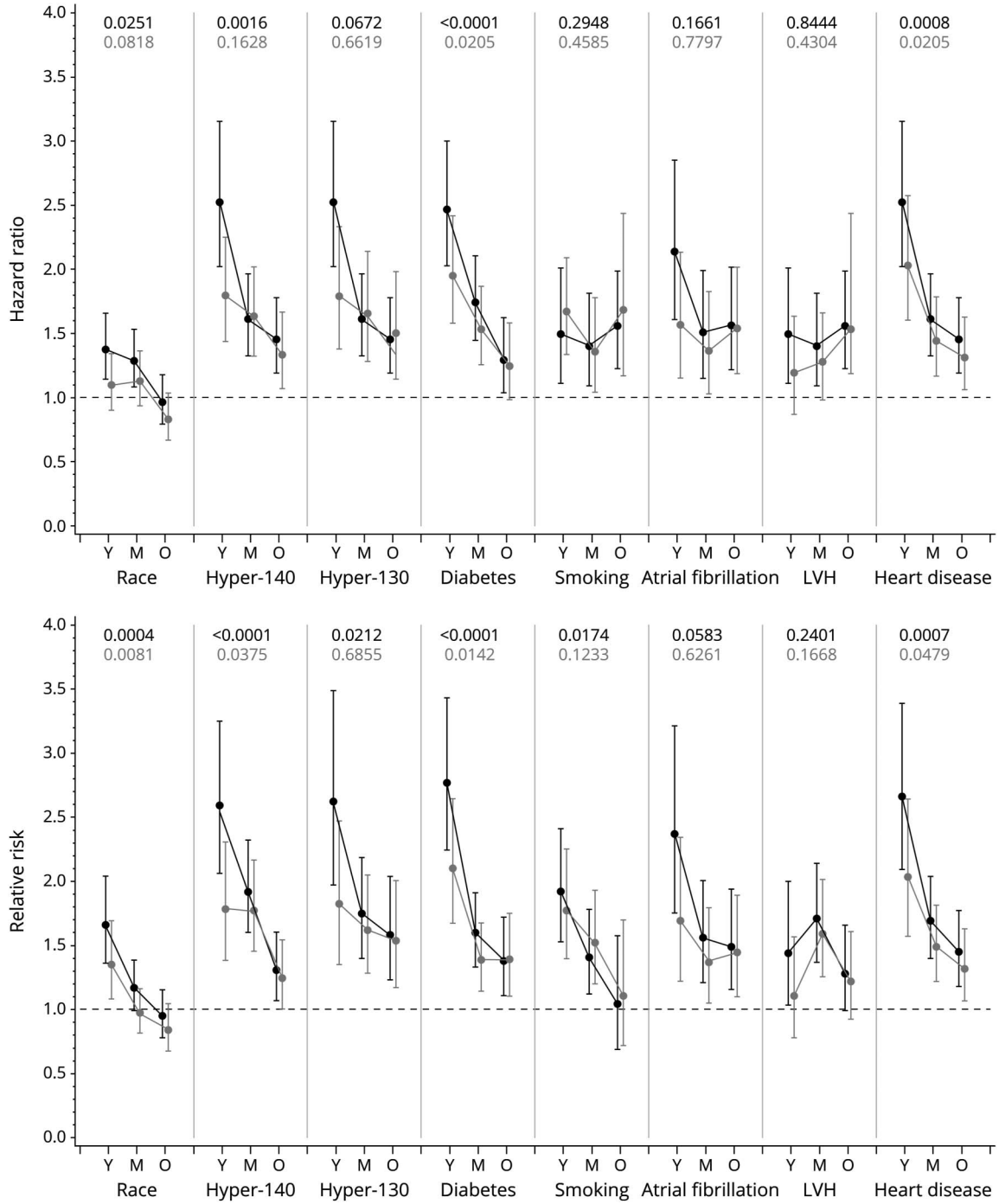
By contrast, for both atrial fibrillation and LVH, the magnitude of the multivariable estimated increased risk was relatively constant across the 3 age strata using both analysis approaches ($p > 0.17$ for all analyses). There was also no evidence of age-related differences in the univariate associations ($p > 0.05$); however, the association approached being significant for atrial fibrillation in the age-at-exposure analysis ($p = 0.058$).

For the univariate age-at-exposure analysis of hypertension, there was a significant difference ($p < 0.02$) in the magnitude of the association with stroke for both blood pressure thresholds (i.e., 140/90 and 130/80 mm Hg). There was a similar pattern for the age-at-baseline analysis; however, these differences between age strata were significant for the 140/90 mm Hg threshold ($p = 0.0016$) but only approached statistical significance for the 130/80 mm Hg threshold ($p = 0.067$). In the multivariable analysis, for both the age-at-baseline and age-at-exposure analyses, adjustment for the other risk factors attenuated the magnitude of the association for the youngest age stratum but had little attenuating impact in the 2 older age strata. As a product of the attenuation, the age-related differences in the magnitude of the association became nonsignificant for both blood pressure thresholds for the age-at-baseline analysis and for the 130/80 mm Hg threshold for the age-at-exposure analysis ($p > 0.16$); however, the age-related differences for the age-at-exposure analysis remained significant for the 140/90 mm Hg blood pressure threshold ($p = 0.038$).

For both analyses (age at baseline and age at exposure), there was univariate evidence of age-related differences in the risk of stroke for Black compared with White participants, with a higher risk for younger Black compared with White participants ($p < 0.025$). This racial difference decreased in the older age strata. With multivariable adjustment, this pattern persisted for the age-at-exposure analysis ($p = 0.0081$), but the difference was only marginally significant in the age-at-baseline analysis ($p = 0.082$).

Smoking was the only traditional risk factor with an apparent difference in the age-related pattern between the 2 analyses. For the age-at-baseline analysis, there was little evidence of an age-related difference in the impact of smoking in either the univariate ($p = 0.24$) or multivariable ($p = 0.48$) analysis. However, for the age-at-exposure univariate analysis, there was an age-related difference in the association with smoking, with a higher risk for smokers in the young stratum but no evidence of a higher risk for smokers in the oldest stratum ($p = 0.017$). This pattern visually persisted with multivariable

Figure 1 Univariate (Black Line) and Multivariable (Gray Line) Hazard Ratio (Top Panel: For Age-at-Baseline Analysis) and Relative Risk (Bottom Panel: For Age-at-Exposure Analysis) for the Traditional Risk Factors (With 95% CI) in the Younger (Y), Middle (M), or Older (O) Age Strata



For the age-at-baseline analysis (upper panel), young included those aged 45–64 years at baseline, middle aged 65–73 years, and older 74+ years. For the age-at-exposure analysis (lower panel), young included exposure between the ages of 45–69 years, middle from 70 to 79 years, and older 80+ years. The numbers at the top of the figure are the *p* values for univariate (black) and multivariable (gray) differences in the relative impact of the risk factor between the age strata (2-degree-of-freedom test of any differences). LVH = left ventricular hypertrophy.

adjustment; however, the age-related differences became statistically nonsignificant ($p = 0.12$).

The results of the backward stepwise analysis to select the most parsimonious model are shown in Table 3. For both the age-at-baseline and the age-at-exposure analyses, hypertension defined with a threshold of 140/90 mm Hg was retained in the younger and middle age strata, whereas hypertension defined with a threshold of 130/80 mm Hg was retained in the older age strata. In the bootstrap analysis, hypertension

Table 3 Description of the Magnitude of the Association Between Risk Factor Prevalence and Stroke Risk for the Most Parsimonious Model

	Age-at-baseline exposure						Age-at-exposure RR (95% CI)		
	HR (95% CI)			% inclusions in models					
	Younger	Middle	Older	Younger	Middle	Older	Younger	Middle	Older
Black				12	22	39	1.34 (1.07–1.67)		
Hypertension (140/90)	1.85 (1.49–2.31)	1.66 (1.35–2.05)		87	83	25	1.79 (1.39–2.31)	1.76 (1.44–2.14)	
Hypertension (130/80)			1.49 (1.13–1.95)	33	23	65			1.51 (1.16–1.97)
Diabetes	1.89 (1.53–2.34)	1.52 (1.25–1.85)		100	97	39	2.01 (1.60–2.54)	1.32 (1.09–1.60)	1.35 (1.08–1.68)
Smoking	1.68 (1.35–2.10)	1.39 (1.06–1.82)	1.63 (1.13–2.36)	99	63	68	1.76 (1.39–2.23)	1.52 (1.20–1.93)	
Atrial fibrillation	1.53 (1.13–2.09)	1.35 (1.01–1.80)	1.56 (1.19–2.03)	74	52	86	1.66 (1.20–2.30)	1.35 (1.03–1.76)	1.44 (1.10–1.88)
LVH		1.30 (1.00–1.69)	1.48 (1.15–1.91)	16	46	83		1.55 (1.23–1.95)	
Heart disease	1.98 (1.56–2.50)	1.40 (1.13–1.72)	1.33 (1.07–1.64)	100	90	69	1.99 (1.54–2.58)	1.45 (1.19–1.77)	1.34 (1.09–1.66)

Multivariable models with selection by backward stepwise methods for the traditional risk factors. For the age-at-baseline analysis (6 left columns), young included those aged 45–64 years at baseline, middle aged 65–73 years, and older 74+ years. The first 3 columns show the hazard ratios from the most parsimonious model. The next 3 columns show the % of the replications where the factor was selected in backward stepwise models from 1,000 bootstrap samples of the dataset. For the age-at-exposure analysis (3 right columns), young included exposure between the ages of 45–69 years, middle from 70 to 79 years, and older 80+ years. Values show the relative risk (with 95% confidence bounds).

defined as 140/90 mm Hg was included 87% of the replications in the young age stratum and 83% in the middle age stratum but only 25% in the oldest age stratum. Conversely, hypertension defined as 130/80 mm Hg was retained only 33% and 23% of the replications in the younger and middle age stratum, respectively, but 65% in the oldest age stratum.

Both atrial fibrillation and heart disease were included in the most parsimonious model for all age strata for both analytic approaches and were included in greater than 50% of the replications (and were selected 86% of the replications in the oldest age stratum).

For the age-at-baseline analysis, smoking was retained in all 3 age strata and was selected in over 99% of the replications in the young age stratum, 63% in the middle age stratum, and 68% in the oldest age stratum. For the age-at-exposure analysis, smoking was selected in the younger and middle age stratum, but not in the oldest age stratum.

For the age-at-baseline analysis, diabetes was retained in the younger and middle age stratum, but not in the older age stratum. In the analysis of the probability of being retained, diabetes was retained in 100% of the replications for the youngest age stratum and 97% for the middle age stratum; however, it was retained in only 39% of the oldest age stratum. In the age-at-exposure analysis, diabetes was retained in all 3 age strata.

In the age-at-baseline analysis, LVH was retained in the middle and older age stratum, but not in the younger. In the analysis of the probability of being retained, for the youngest age stratum, it was only retained in 16% of the replications but 46% of the replications in the middle age stratum and 83% of the replications in the older age stratum. For the age-at-exposure analysis, it was retained only in the middle age stratum.

Discussion

These findings suggest that there are substantial age-related differences in the magnitude of the association for several risk factors for stroke. Specifically, prevalent diabetes or heart disease has a greater impact on stroke risk for younger than for older individuals, even approaching having no impact in the oldest age stratum. Likewise, there is some evidence that the association of smoking on stroke may decrease at older age when assessed by age at the time of exposure. The association of atrial fibrillation and stroke risk appears relatively consistent across the age spectrum. The association of LVH and stroke risk is also constant in the multivariable analysis but appears larger in the elderly in the analysis of the likelihood of being retained in parsimonious models. In summary, these findings suggest that age should be considered in the interpretation of which risk factors are most strongly related to stroke risk, potentially implying an age-related difference in

the attention focused on specific risk stroke factors during screening evaluations.

We hope to raise the issue of whether the focus of clinical attention on specific risk factors should shift with an increasing age. For example, hypertension has long been acknowledged as the risk factor with the largest population attributable risk for stroke,[23] and as such, most clinicians have appropriately placed their attention on this risk factor for primary stroke prevention. However, this report shows that the relative impact of hypertension becomes smaller than other risk factors at older ages, and as such, it may be appropriate to shift the focus to atrial fibrillation, smoking, and LVH in the elderly. However, this observation should be interpreted with substantial caution. We are not proposing that the treatment of hypertension in the elderly for stroke prevention becomes unimportant, and to do so would be discordant with the evidence from the Hypertension in the Very Elderly Trial,[24] which assessed the impact of antihypertensive medications in patients aged 85+ years with systolic blood pressures 160+ mm Hg. This trial was stopped early for an efficacy benefit in favor of antihypertensive treatment, although with the addition of the run-over data resulted in a marginally significant treatment difference (p = 0.06). We are not suggesting that the treatment of hypertension (and diabetes) becomes unimportant, only that it may be wise for the relative attention of the clinicians shift to the management of risk factors including atrial fibrillation, smoking, and LVH that seem to be associated with stroke risk in the elderly.

The treatment to prevent any disease in the elderly is complicated by an increasing frailty at older ages. In the elderly, effective stroke prevention may be associated with an increased risk of other conditions such as falls, and the benefit of reduced stroke risk could be offset by an increased risk of other serious negative outcomes. We commend Richard Lindley's thoughtful review of this issue, who noted that the elderly are frequently excluded from clinical trials by design,[25] requiring treatment decisions to be made based on observational data (such as this report) where associations may be more subject to bias.

The impact of risk factors is traditionally described on a relative scale, and we suggest that this is appropriate for this report. However, it could be argued that even with the relative impact of risk factors decreasing with age, increases in the incidence of stroke at older ages may imply that the absolute number of individuals affected may be larger at older ages. The approximate event rate in those with, and without, a risk factor can be estimated given an overall event rate, the prevalence of the risk factor, and the estimated relative risk for that factor. For example, in the younger age stratum for hypertension (defined using the 130/80 mm Hg criteria), 3.1% of the overall population had a stroke, the prevalence of hypertension was 69%, and the multivariable risk ratio was 1.79. Given the parameters, calculations suggest that approximately 2.0% of the normotensive participants had a stroke, compared with approximately 3.6% of the hypertensive participants, resulting in an absolute risk difference of 1.6%. Similar calculations for the older age strata, where 8.6% of participants had a stroke, the prevalence of hypertension was 79%, and the relative risk was 1.50, imply that approximately 6.2% of normotensive and 9.3% of hypertensive participants suffered a stroke, for an absolute risk difference of 3.1%. Hence, despite the larger relative risk for the young than old age strata (1.79 vs 1.50), hypertension resulted in a larger absolute risk difference in the older strata (3.1% vs 1.6%). It is always important to remember that smaller relative risks in older cohorts may still be associated with larger absolute differences in stroke risk.

Our findings show a smaller magnitude of the association of diabetes with stroke risk at older ages. This is consistent with the revised Framingham Stroke Risk Function that reported a larger association for diabetes under age 65 years (men: 3.87; 95% CI 1.97–7.61 and women: 2.92; 95% CI 0.95–9.89) than for those aged 65 years and older (men: 1.41; 95% CI 0.87–2.30 and women: 1.07; 95% CI 0.58–1.96). Like our findings, diabetes was not significantly associated with stroke risk in the older population for either men or women. The QSTROKE risk function report noted that there were significant interactions between age and systolic blood pressure, coronary heart disease, type 2 diabetes, and smoking; however, the report failed to describe the magnitude of the effect modification.[5] Of these, we also showed a significant effect modification for hypertension, diabetes, and heart disease; however, the effect of smoking did not differ significantly by age in the REGARDS cohort. The QSTROKE analysis did include atrial fibrillation, but like the finding in REGARDS there was no apparent interaction with age.[5] Under the presumption that the effect modification in the QSTROKE cohort was for smaller associations with risk factors at older ages, our findings are also largely concordant with their findings.

Recent guidelines changed the blood pressure level criteria for hypertension from 140/90 to 130/80 mm Hg.[26] Perhaps the most intriguing finding in our report is that the 140/90 mm Hg threshold seems more closely related with incident stroke risk for the 2 younger age strata, whereas the 130/80 mm Hg threshold appears more predictive for the oldest age stratum. Potential reasons for the age-related differential strength of the association between the 2 definitions for hypertension are not clear, but we speculate that it may be related to a cumulative burden of elevated blood pressure. In younger ages, to accumulate a high exposure to high BP, one would need to have very high blood pressure levels; by contrast, an accumulation of exposure could be accrued at older ages by a more modestly elevated blood pressure for a longer period. Alternatively, the differential impact could be related to the intensity of treatment, where (perhaps) older people with high stroke risk are treated to 130–139 mm Hg whereas those with lower risk may not be (i.e., confounding by treatment).

We used 2 analytic approaches, with each approach providing different-but-valuable insights. Notably, the findings of the 2 approaches were generally concordant, with a similar magnitude of the association for both univariate and multivariable analyses shown in Figure 1. Perhaps the greatest benefit of the age-at-exposure analysis is accounting for changing age of the study participants over the multiyear follow-up. Conversely, perhaps the greatest benefit of the age-at-baseline analysis is the ability to implement a bootstrap assessment of the probability of selection of the individual risk factors in developing the most parsimonious model. These advantages underpin the decision to provide results based on the 2 different approaches in the report; however, perhaps the greatest gain is the assurance provided by the concordance of results using different analytic approaches.

We note that the concern for a change in the magnitude of the association with risk factors from the competing risk of death is minimized in both analytic approaches used in this report. A recent thoughtful review describes the 2 approaches to account for competing risks.[27] The first of these approaches uses cause-specific models and is appropriate where the analysis focuses on etiologic questions including the magnitude of the relative risk. This approach is implemented by censoring individuals at the time of the occurrence of the competing cause. The second approach is appropriate for estimating the incidence or predicting prognosis commonly shown as a cumulative incidence function, such as the Framingham Risk Function estimation of the 10-year risk of stroke.[1] This second approach is implemented by the use of the Fine and Gray[28] methods. It is critical to carefully consider the goal of the analysis in selecting between these approaches because there is widespread confusion in the literature regarding the appropriate approach.[29] As the focus of the current report is on the etiologic question of changes in the magnitude of the relative risk with age, the cause-specific approach is appropriate for this report. As both analytic approaches we used censor participants at the time of death, both approaches have used the cause-specific approach, reducing the potential impact of competing risk from death.

There were several substantial strengths to this report, most notably the cohort size, long follow-up, and age span provided by the REGARDS study, allowing stratification of the participants into 3 age strata spanning the entire adult age range where each stratum included approximately 500 incident stroke events (and, hence, approximately the same statistical power to establish associations with risk factors). The largest difference in the number of stroke events among the strata existed for the age-at-risk analysis, where the youngest age strata had 368 events and the middle age strata had 579 events. Because the precision of estimates is proportional to the square root of the sample size (number of events), these differences introduced in the precision of the estimates are relatively small ($\sqrt{368} = 19.2$ and $\sqrt{579} = 24.1$, respectively). For a risk factor that is 50% prevalent, these numbers of events provide 90% power to detect a hazard ratio of 1.40 for the youngest age strata and 1.31 for the middle age strata.[30] Other strengths include the physician-adjudication of suspected stroke events. There was also a high retention rate of the cohort, with an annual retention rate of 97.4%. Finally, the risk factors were objectively assessed at baseline, including direct measurement of blood pressure, serum levels of glucose, and ECG assessment for atrial fibrillation and LVH. Finally, both analytic approaches model the relative risk, an estimate that is not affected by the increasing prevalence at older ages for factors including hypertension and diabetes. However, there are also weaknesses, most importantly that the risk factors were assessed only at baseline but are subject to change over the follow-up period extending up to 16 years. Because of the complexity of analysis, the focus was only on the impact of traditional stroke risk factors. Relatively few studies have assessed risk factors in the oldest old, and novel risk factors that play a smaller role in the middle-age cohorts may be playing a major role in the elderly. Additional work is under way in REGARDS to examine the impact of novel risk factors across that age spectrum, including psychosocial factors, inflammation, social determinates of health, and other biomarker-based risk factors. Finally, the potential remains that there could be sex or race differences in the magnitude of the age-related effect modification. The assessment of these 3-way interactions requires even larger cohorts (or pooling of multiple cohorts) with a larger number of stroke events.

In conclusion, we observed a substantially smaller magnitude of associations of hypertension, diabetes, and heart disease with stroke risk at older ages, with little or no evidence of an age-related change of the associations for smoking, atrial fibrillation, and LVH with stroke risk. These differences in the relative magnitude of the risk factors imply that considerations to determine whether an individual is at high risk for stroke may differ depending on the age of the individual. In addition, we documented an unanticipated finding where defining hypertension using the 140/90 mm Hg criteria appears more closely related to stroke risk in those under age 75 years, whereas defining hypertension using the 130/80 mm Hg criteria appears more closely related for those above this age. Although there were sparse data examining age-related changes in the magnitude of the association for stroke risk factors, these findings suggest that markers of stroke risk may differ at older ages and raise the need for additional studies assessing predictors of stroke risk across the age spectrum.[31]

Acknowledgment

The authors thank the investigators, staff, and participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at regardsstudy.org. George Howard had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study Funding

This research project was supported by cooperative agreement U01-NS041588 cofunded by the National Institute of

Neurological Disorders and Stroke and National Institute on Aging, NIH.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* September 6, 2022. Accepted in final form December 6, 2022. Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.

Appendix Authors

Name	Location	Contribution
George Howard, DrPH	Department of Biostatistics, UAB School of Public Health, Birmingham, AL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Maciej Banach, MD, PhD	Polish Mother Memorial Hospital Research Institute, Lodz, Poland	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Brett Kissela, MD, MS	Department of Neurology and Rehabilitation Medicine, University of Cincinnati, OH	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Mary Cushman, MD, MSc	Department of Medicine, University of Vermont, Burlington, VT	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Paul Muntner, PhD	Department of Epidemiology, UAB School of Public Health, Birmingham, AL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Suzanne E. Judd, PhD	Department of Biostatistics, UAB School of Public Health, Birmingham, AL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Virginia J. Howard, PhD	Department of Biostatistics, UAB School of Public Health, Birmingham, AL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

References

1. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22(3):312-318. doi: 10.1161/01.str.22.3.312
2. Dufouil C, Beiser A, McLure LA, et al. Revised Framingham stroke risk profile to reflect temporal trends. *Circulation*. 2017;135(12):1145-1159. doi: 10.1161/CIRCULATIONAHA.115.021275
3. Manolio TA, Kronmal RA, Burke GL, O'Leary DH, Price TR. Short-term predictors of incident stroke in older adults. The Cardiovascular Health Study. *Stroke*. 1996;27(9):1479-1486. doi: 10.1161/01.str.27.9.1479
4. Parmar P, Krishnamurthi R, Ikram MA, et al. The stroke Riskometer™ app: validation of a data collection tool and stroke risk predictor. *Int J Stroke*. 2015;10(2):231-244. doi: 10.1111/ijs.12411
5. Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. *BMJ*. 2013;346:f2573. doi: 10.1136/bmj.f2573
6. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121(4):586-613. doi: 10.1161/CIRCULATIONAHA.109.192703
7. Lloyd-Jones DM, Allen NB, Anderson CAM, et al; American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146(5):e18-e43. doi: 10.1161/CIR.0000000000001078
8. Kaplan GA, Haan MN, Wallace RB. Understanding changing risk factor associations with increasing age in adults. *Annu Rev Public Health*. 1999;20(1):89-108. doi: 10.1146/annurev.publhealth.20.1.89
9. Manolio TA, Pearson TA, Wenger NK, Barrett-Connor E, Payne GH, Harlan WR. Cholesterol and heart disease in older persons and women. Review of an NHLBI workshop. *Ann Epidemiol*. 1992;2(1-2):161-176. doi: 10.1016/1047-2797(92)90051-q
10. Whisnant JP, Wiebers DO, O'Fallon WM, Sicks JD, Frye RL. A population-based model of risk factors for ischemic stroke: Rochester, Minnesota. *Neurology*. 1996;47(6):1420-1428. doi: 10.1212/wnl.47.6.1420
11. Langer RD, Ganiats TG, Barrett-Connor E. Paradoxical survival of elderly men with high blood pressure. *BMJ*. 1989;298(6684):1356-1357. doi: 10.1136/bmj.298.6684.1356
12. Tate RB, Manfreda J, Cuddy TE. The effect of age on risk factors for ischemic heart disease: the Manitoba Follow-Up Study, 1948-1993. *Ann Epidemiol*. 1998;8(7):415-421. doi: 10.1016/s1047-2797(98)00011-8
13. Lind L, Sundstrom J, Arnlov J, Lampa E. Impact of aging on the strength of cardiovascular risk factors: a longitudinal study over 40 years. *J Am Heart Assoc*. 2018;7(1):e007061. doi: 10.1161/JAHA.117.007061
14. Abbott RD, Curb JD, Rodriguez BL, et al. Age-related changes in risk factor effects on the incidence of thromboembolic and hemorrhagic stroke. *J Clin Epidemiol*. 2003;56(5):479-486. doi: 10.1016/s0895-4356(02)00611-x
15. Abbott RD, Curb JD, Rodriguez BL, et al. Age-related changes in risk factor effects on the incidence of coronary heart disease. *Ann Epidemiol*. 2002;12(3):173-181. doi: 10.1016/s1047-2797(01)00309-x
16. Howard G, Goff DC Jr. A call for caution in the interpretation of the observed smaller relative importance of risk factors in the elderly. *Ann Epidemiol*. 1998;8(7):411-414. doi: 10.1016/s1047-2797(98)00041-6
17. Ovbiagele B, Goldstein LB, Higashida RT, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. *Stroke*. 2013;44(8):2361-2375. doi: 10.1161/STR.0b013e31829734f2
18. Howard G, Goff DC. Population shifts and the future of stroke: forecasts of the future burden of stroke. *Ann New York Acad Sci*. 2012;1268(1):14-20. doi: 10.1111/j.1749-6632.2012.06665.x
19. Howard VJ, Kleindorfer DO, Judd SE, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. *Ann Neurol*. 2011;69(4):619-627. doi: 10.1002/ana.22385
20. Sacco RL, Boden-Albala B, Gan R, et al. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. *Am J Epidemiol*. 1998;147(3):259-268. doi: 10.1093/oxfordjournals.aje.a009445
21. Kleindorfer DO, Khoury J, Moomaw CJ, et al. Stroke incidence is decreasing in whites but not in blacks: a population-based estimate of temporal trends in stroke incidence from the Greater Cincinnati/Northern Kentucky Stroke Study. *Stroke*. 2010;41(7):1326-1331. doi: 10.1161/STROKEAHA.109.575043
22. Sokolow M, Lyon TP. American Heart Journal. *Ann Noninvasive Electrocardiol*. 2001;6(4):343-368. doi: 10.1111/j.1542-474x.2001.tb00129.x
23. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH Jr., Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. *Stroke* 2006;37(10):2493-2498. doi: 10.1161/01.STR.0000239694.19359.88
24. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *New Engl J Med*. 2008;358(18):1887-1898. doi: 10.1056/NEJMoa0801369
25. Lindley RI. Stroke prevention in the very elderly. *Stroke*. 2018;49(3):796-802. doi: 10.1161/strokeaha.117.017952
26. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71(19):e127–e248. doi: 10.1016/

j.jacc.2017.11.006./ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines
27. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133(6):601-609. doi: 10.1161/CIRCULATIONAHA.115.017719
28. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509. doi: 10.1080/01621459.1999.10474144
29. Howard G, Long LD. "Trending" statistical methods. *Res Pract Thromb Haemost*. 2018;2:186-187. doi: 10.1002/rth2.12075
30. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics*. 1983;39(2):499-503. doi: 10.2307/2531021
31. *REGARDS Study*. Accessed November 4, 2022. regardsstudy.org.

Age-Related Differences in the Role of Risk Factors for Ischemic Stroke

George Howard, Maciej Banach, Brett Kissela, et al.

Neurology 2023;100;e1444-e1453 Published Online before print January 18, 2023
DOI 10.1212/WNL.0000000000206837