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

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Abstract

Introduction: 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 mmHg (from ≈1.80 to ≈1.50); however, there

was no age-related difference in the magnitude of association for smoking, atrial fibrillation or left ventricular hypertrophy.

Discussion: Hypertension and diabetes are two of the more "important" risk factors for stroke; however, their association with stroke risk appears substantially less at older ages. That the magnitude of association for smoking, atrial fibrillation and LVH do not decrease with age suggests their relative importance in determining stroke risk likely increases with age.

Introduction

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) a general population cohort over age 65,[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 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 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),[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 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 US occurred above age 85; however, by 2050, this percent is anticipated to increase to 34%, with over 50% of stroke events after age 75.[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, CHS excluded participants under the age of 65, 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) recruited a large cohort of black and white individuals with no upper age limit, and offers a unique opportunity to assess age-related difference in the magnitude of association for stroke risk factors.

Methods

REGARDS is a population-based study of 30,239 community-dwelling Black or White participants, aged 45+, 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 physiological variables (including blood pressure), performing an electrocardiogram (ECG), and collecting blood and urine samples. Participants have been contacted at 6-month intervals (through September 30th, 2019 for this analysis) for 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 two different analytic approaches, facilitating comparisons between the analytic approaches. The age strata were specified prior to 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 two thresholds: 1) a systolic blood pressure of ≥140 mmHg, diastolic of ≥90 mmHg, or self-reported use of antihypertensive medications, or 2) a systolic blood pressure of ≥130 mmHg, diastolic of ≥80 mmHg, or use of antihypertensive medications. Diabetes was defined by 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 by ECG evidence or self-report of a physician diagnosis. LVH was defined using ECG evidence using the Sokolow criteria.[22] Heart disease was defined by baseline ECG evidence of a myocardial infarction, self-reported physician diagnosis of MI, or previous CABG, angioplasty or coronary stenting.

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

- *Analysis based on 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 to 64, 65 to 73, and 74 and over (oldest age 98 years). The association for risk factors within each age stratum were assessed in: 1) univariate models, 2) "full" multivariable models containing all risk factors, and 3) in "parsimonious" models where statistically non-significant ($p > 0.05$) 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 backwards stepwise process was estimated using bootstrap methods with 1000 replications.

- *Analysis based on the age at exposure:* Individuals were followed for incident stroke for up to 16 years (2003 to 2019), and this analysis allowed the estimated magnitude of the risk factor association to 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 relative risk per person-year exposure was used to estimate 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 exposure to the young stratum, 10 years exposure to the middle stratum, and 4 years 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 276,074 person-years of exposure (see Table 2). With the strata defined by age-at-baseline, there was a generally similar number of stroke events (ranging from 455 to 514), while 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%), to 8.6% (7.9% - 9.4%). For the age-at-exposure analysis, there was 134,955 person-years of 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), while the stroke event rate per 100,000 person-years increased from 273 (95% CI: 246 – 302), to 615 (95% CI: 567 – 688), 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 in the bottom panel for the age-at-exposure analysis. The numerical estimates for the multivariable portion of these figures are provided in eTable 1. For both diabetes and heart disease, the magnitude of association with stroke risk was smaller at older age for both analytic approaches in both the univariate and multivariable analysis ($p < 0.05$ 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.

In contrast, for both atrial fibrillation and LVH, the magnitude of the multivariable estimated increased risk was relatively constant across the three 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 mmHg and 130/80 mmHg). There was a similar pattern for the age-at-baseline analysis; however, these differences between age strata were significant for the 140/90 mmHg threshold ($p = 0.0016$), but only approached statistical significance for the 130/80 mmHg threshold ($p = 0.067$). In the multivariable analysis, for both the age-at-baseline and age-at-exposure analysis, adjustment for the other risk factors attenuated the magnitude of the association for the youngest age stratum, but had little attenuating impact in the two older age strata. As a product of the attenuation, the age-related differences in the magnitude of the association became non-significant for both blood pressure thresholds for the age-at-baseline analysis, and for the 130/80 mmHg threshold for the age-of-exposure analysis ($p > 0.16$); however, the age-related differences for the age-at-exposure analysis remained significant for the 140/90 mmHg 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 to White participants, with higher risk for younger Black compared to 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 two 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 age-at-exposure univariate analysis, there was an age-related difference in the association with smoking, with higher risk for smokers in the young stratum, but no evidence of higher risk for smokers in the oldest stratum ($p = 0.017$). This pattern visually persisted with multivariable adjustment; however, the age-related differences became statistically non-significant ($p = 0.12$).

The results of the backwards stepwise analysis to select the most parsimonious model is shown in Table 3. For both the age-at-baseline and the age-at-exposure analysis, hypertension defined with a threshold of 140/90 mmHg was retained in the younger and middle age strata, while hypertension defined with a threshold of 130/80 mmHg was retained in the older age strata. In the bootstrap analysis, hypertension defined as 140/90 mmHg 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 mmHg was retained only 33% and 23% of the replications in the younger and middle age stratum, 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 was selected 86% of the replications in the oldest age stratum).

For the age-at-baseline analysis, smoking was retained in all three 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 three 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 in only 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 age should be considered in 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 the whether the focus of clinical attention on specific risk factors should shift with 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 left ventricular hypertrophy in the elderly. However, this observation should be interpreted with substantial caution. We are not proposing that treatment of hypertension in the elderly for stroke prevention

become unimportant, to do so would be discordant with the evidence from the Hypertension in the Very Elderly (HYVET) trial,[24] which assessed the impact of antihypertension medications in patients 85+ years old with systolic blood pressures 160+ mmHg. 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 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 increased risk of other conditions such as falls, and the benefit of reduced stroke risk could be offset by 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 impacted may be larger at older ages. The approximate event rate in those with, and without, a risk factor can 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 mmHg criteria), 3.1% of the overall population had a stroke, the prevalence of hypertension 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

to 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, implies 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 versus 1.50), hypertension resulted in a larger absolute risk difference in the older strata (3.1% versus 1.6%). It is always important 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 (Men: 3.87; 95% CI: 1.97 – 7.61 and Women: 2.92; 95% CI: 0.95 – 9.89) than for those aged 65 and over (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 significant effect modification for hypertension, diabetes, 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 mmHg to 130/80 mmHg.[26] Perhaps the most intriguing finding in our report is that the 140/90 mmHg threshold seems more closely related with incident stroke risk for the two younger age strata, while the 130/80

mmHg threshold appears more predictive for the oldest age stratum. Potential reasons for the age-related differential strength of association between the two 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; in 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 mmHg while those with lower risk may not be (i.e., confounding by treatment).

We employed two analytic approaches, with each approach providing different-but-valuable insights. Importantly, the findings of the two approaches were generally concordant, with similar magnitude of association for both univariate and multivariable analysis shown in Figure 1. Perhaps the greatest benefit of the age-of-exposure analysis is accounting for changing age of the study participants over the multi-year follow-up. Conversely, perhaps the greatest benefit of the age-at-baseline analysis is the ability 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 two 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 competing risk of death is minimized in both analytic approaches employed in this report. Austin, et al. provides a thoughtful review of the two approaches to account for competing risks.[27] The first of these approaches employs “cause-specific models,” and is appropriate where the analysis is 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 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 methods.[28] It is critical to carefully consider the goal of the analysis in selecting between these approaches, as there is wide-spread confusion in the literature regarding the appropriate approach.[29] As the focus of the current report is on the etiological 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 employed censor participants at the time of death, both approaches have employed the cause-specific approach, reducing the potential impact of competing risk from death.

There were several substantial strengths to this report, most notably is the cohort size, long follow up, and age-span provided by the REGARDS study, allowing stratification of the participants into three age strata spanning the entire adult age range where each strata 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 proportion to the square root of the sample size (number of events), these differences introduced in the precision of the estimates is relatively small ($\sqrt{368}$ = 19.2 and $\sqrt{579}$ = 24.1, respectively). For a risk factor that is 50% prevalent, these number 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 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 underway 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 three-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 implies 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 mmHg criteria appears more closely related to stroke risk in those under age 75, while defining hypertension using the 130/80 mmHg criteria appears more closely related for those above this age. While there were sparse data examining age-related changes in the magnitude of association for stroke risk factors, these findings suggest that markers of stroke risk may differ at older ages, and raises the need for additional studies assessing predictors of stroke risk across the age spectrum.

Appendix. Authors

Name	Location	Contribution
George Howard, DrPH	Department of Biostatistics, UAB School of Public Health, Birmingham AL	Primary author and statistical analysis
Maciej Banach, MD**,** PhD	Polish Mother Memorial Hospital Research Institute, Lodz, Poland	Contributor to the development of the concept for the paper, and substantial editorial input
Brett Kissela, MD, MS	Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH	Neurological expertise, providing adjudication of endpoints, and substantial editorial input
Mary Cushman, MD, Msc	Department of Medicine, University of Vermont, Burlington, VT	Director of central laboratory, epidemiological expertise, and substantial editorial input
Paul Muntner, PhD	Department of Epidemiology, UAB School of Public Health, Birmingham, AL	Expertise in hypertension assessment and epidemiological expertise, and substantial editorial input
Suzanne E. Judd, PhD	Department of Biostatistics, UAB School of Public Health, Birmingham AL	Epidemiological expertise and substantial editorial input
Virginia J. Howard, PhD	Department of Biostatistics, UAB School of Public Health, Birmingham AL	Epidemiological expertise and substantial editorial input

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	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
Left ventricular hypertrophy (%)	8	10	13
Heart disease (%)	12	20	27

Table 1: Description of study population on the traditional risk factors. Percentages are provided among participants where the risk factors were observed, and data were missing on diabetes for 4% of participants; heart disease, atrial fibrillation and left ventricular hypertrophy in 2% of participants; and hypertension and smoking on <1% of participants.

		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 to 302)	615 (567 to 668)	974 (889 to 1,067)

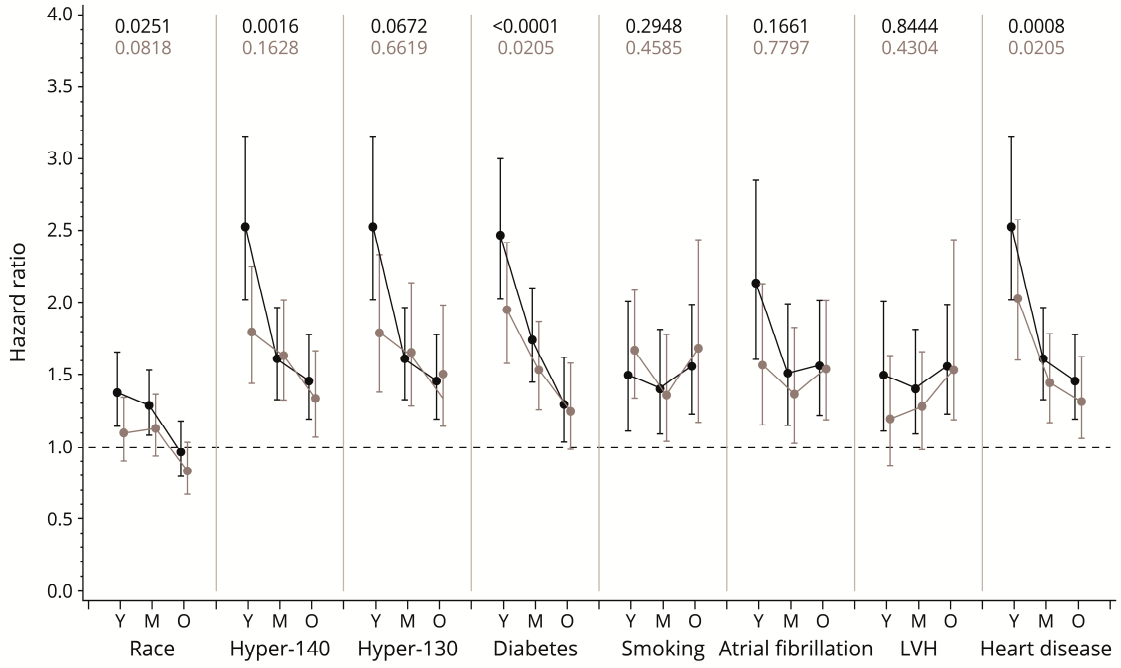
Table 2: Description of the number of patients, years of exposure, number of stroke event and crude stroke rates within each age stratum for both analyses. For the age-at-baseline analysis, data are provided for the number of patients, median follow-up, and number and percent (with 95% confidence intervals) 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% confidence intervals). Each person's contribution to years-at-risk within each age stratum was calculated as the participant potentially ages between age strata.

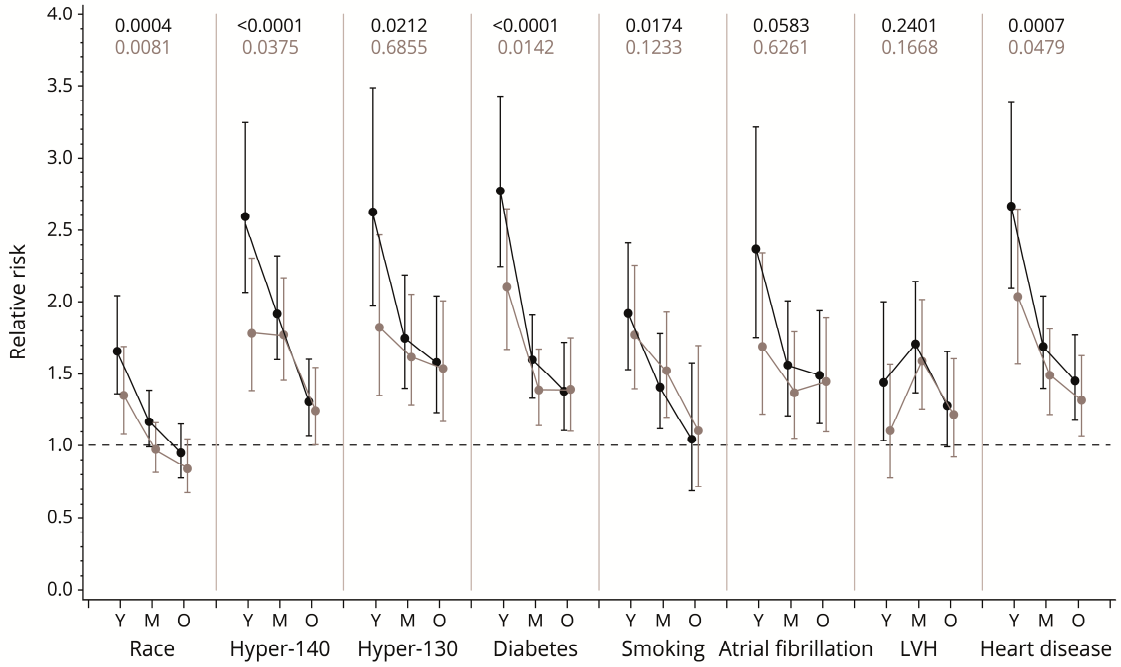
	Age-at-Baseline Exposure						Age-at-Exposure RR (95% CI)		
	HR (95% CI)			% Inclusions in Models			Younger	Middle	Older
	Younger	Middle	Older	Younger	Middle	Older			
Black				12	22	39	1.34 (1.07 – 1.67)		
Hypertension (140/90)	1.85 (1.49 – 2.31)	1.66 (1.35 – 2.05)		87	83	25	1.79 (1.39 – 2.31)	1.76 (1.44 – 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)

Table 3: Description of the magnitude of association between risk factor prevalence and stroke risk for the most parsimonious model. 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 to 64 at baseline, middle aged 65 to 73, and older 74+. The first three columns show the hazard ratios from the most parsimonious model. The next three columns show the % of the replications where the factor was selected in backwards stepwise models from 1000 bootstrap samples of the dataset. For age-at-exposure analysis (3 right columns), young included exposure between the ages of 45 to 69, middle from 70 to 79, and older 80+ years of age. Values show the relative risk (with 95% confidence bounds).

Figure Legends

Figure 1: Univariate (black with solid line) and multivariable (gray with dashed 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, young included those aged 45 to 64 at baseline, middle aged 65 to 73, and older 74+. For the age-at-exposure analysis (upper panel), young included exposure between the ages of 45 to 69, middle from 70 to 79, and older 80+ years of age. 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).





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