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The Lifetime Risk of Stroke Estimates From the Framingham Study

Sudha Seshadri, MD; Alexa Beiser, PhD; Margaret Kelly-Hayes, RN, EdD; Carlos S. Kase, MD; Rhoda Au, PhD; William B. Kannel, MD; Philip A. Wolf, MD

Background and Purpose—The lifetime risk (LTR) of stroke has not been reported for the United States population; such data would assist public education and health planning.

Methods—Framingham Original cohort participants (n=4897) who were stroke- and dementia-free at 55 years of age were followed biennially for up to 51 years (115 146 person years). We estimated the sex-specific 10-, 20-, and 30-year risks and LTR of developing a stroke by baseline age and blood pressure (BP) and compared it with the risk of developing Alzheimer disease (AD).

Results—A total of 875 participants (522 women) developed a first-ever stroke; 749 (448 women) had an ischemic stroke. LTR of stroke was high and remained similar at ages 55, 65, and 75 years, approximating 1 in 5 for women and 1 in 6 for men. Participants with a normal BP (<120/80 mm Hg) had approximately half the LTR of stroke compared with those with high BP (≥140/90 mm Hg). The LTR of AD at age 65 (292 participants; 211 women) approximated 1 in 5 for women and 1 in 10 for men. The LTR of developing either stroke or dementia approximated 1 in 3 in both sexes.

Conclusion—The LTR of stroke in middle-aged adults is 1 in 6 or more, which is equal to or greater than the LTR of AD. Women had a higher risk because of longer life expectancy. BP is a significant determinant of the LTR of stroke, and promotion of normal BP levels in the community might be expected to substantially reduce this risk. (*Stroke*. 2006;37:345-350.)

Key Words: stroke ■ epidemiology ■ blood pressure ■ Alzheimer disease

The average life expectancy in the United States today is 77 years,¹ so that most young adults should expect to grow old, and, as an unwelcome corollary, they will face the risk of developing diseases that are increasingly prevalent with age. The lifetime risk (LTR) of developing several of these conditions, such as dementia, coronary artery disease, and hip fractures, have been estimated,²⁻⁴ but the LTR of stroke has not been reported previously for the United States population. Estimation of the LTR of stroke is particularly important because stroke is a leading cause of mortality and the most common cause of neurological disability in older persons. Epidemiological studies have identified blood pressure (BP) as the single most important, modifiable stroke risk factor,⁵ and BP in middle age predicts the risk of stroke in older persons.⁶ Accordingly, we estimated the short- and intermediate-term risks and the LTR of developing stroke in the community-based Framingham cohort overall and also within BP categories defined by the Seventh Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) criteria.⁷ To put the LTR of stroke in perspective, we compared it with the LTR of dementia and Alzheimer's disease (AD). We chose

this comparison because dementia, largely attributable to AD, is the only other neurological condition listed among the 10 leading causes of total disease burden (based on disability, mortality, and societal costs) in developed countries,⁸ and these are the 2 most widely feared aging-related neurological diseases in the public perception.

Methods

Participants

The Framingham Heart Study is an ongoing cohort study that began in 1948 with the enrollment of 5209 participants into the Original cohort.⁹ These participants have been assessed biennially with medical histories, physical examinations, laboratory tests for vascular risk factors, and, at some examinations, by brain imaging studies. The present investigation, approved by the institutional board of Boston Medical Center, used 3 samples from the Framingham Original cohort: (1) 4897 participants who survived stroke-free up to 55 years of age and were followed for up to 51 years (115 146 person years) to estimate the LTR of first-ever stroke. (2) A dementia-free group of participants were identified in 1975 and have been under surveillance for the development of incident dementia.² A total of 2794 persons from this group who reached 65 years of age free of dementia were followed for up to 29 years (42 233 person years) to estimate the LTR of dementia and AD. (3) Finally, 2711 participants

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TABLE 1. Age- and Sex-Specific, Mortality-Adjusted, 10-, 20- and 30-Year and LTR Estimates* for the Development of Stroke (all types) and Ischemic Stroke

Gender	Age (y)	n: All Strokes (and ischemic strokes)	Initial Stroke, All Types (875 events)				Initial Ischemic Stroke (749 events)			
			Short-term and Intermediate-term Risks				Short-term and Intermediate-term Risks			
			10-Year	20-Year	30-Year	LTR	10-Year	20-Year	30-Year	LTR
Women	55	522 (448)	2.3 (1.7–2.9)	6.5 (5.6–7.5)††	14.3 (13.0–15.6)	21.1 (19.4–22.7)††	1.8 (1.3–2.3)	5.4 (4.5–6.2)††	12.1 (10.9–13.4)	18.1 (16.6–19.7)††
	65	462 (400)	4.6 (3.8–5.5)††	13.2 (11.8–14.5)	19.5 (17.8–21.1)†	20.6 (19.0–22.3)††	3.9 (3.1–4.7)††	11.3 (10.1–12.6)	16.9 (15.4–18.5)†	17.9 (16.2–19.5)††
	75	347 (303)	10.5 (9.1–11.9)	18.3 (16.5–20.1)††		19.7 (17.8–21.6)††	9.1 (7.8–10.4)	16.0 (14.3–17.8)††		17.2 (15.4–19.0)††
	85	140 (123)	13.4 (11.1–15.6)††			15.8 (13.3–18.2)††	11.9 (9.8–14.0)††			13.8 (11.5–16.2)††
Men	55	353 (301)	2.9 (2.2–3.6)	8.7 (7.5–9.9)††	14.7 (13.2–16.2)	16.9 (15.3–18.6)††	2.4 (1.7–3.1)	7.3 (6.2–8.4)††	12.6 (11.2–14.1)	14.5 (12.9–16.0)††
	65	293 (251)	7.0 (5.8–8.2)††	14.1 (12.5–15.8)	16.5 (14.7–18.3)†	16.8 (15.1–18.6)††	5.8 (4.7–6.9)	12.3 (10.7–13.8)	14.1 (12.4–15.7)†	14.4 (12.8–16.1)††
	75	166 (145)	10.4 (8.6–12.1)	13.8 (11.8–15.8)†		14.3 (12.2–16.4)††	9.3 (7.7–11.0)	12.0 (10.1–13.8)††		12.5 (10.6–14.4)††
	85	38 (30)	8.5 (5.7–11.3)††			9.8 (6.7–12.8)††	6.6 (4.1–9.0)††			7.8 (5.0–10.6)††

*Risks expressed in percentages over period of observation; values in parentheses are 95% CIs; † $P<0.05$ and †† $P<0.01$, comparing risks in men and women using a z test.

who reached 65 years of age free of both stroke and dementia were followed for up to 29 years (39 985 person years) to estimate the LTR of developing either stroke or dementia.

Case Definition

Details of our stroke surveillance and protocol for determining the diagnosis and type of stroke have been published.^{5,10} Stroke was defined as an acute-onset focal neurological deficit of vascular etiology, persisting for >24 hours. Both ischemic and hemorrhagic stroke subtypes were included. Stroke subtypes were categorized based on pre-established criteria that include clinical features, imaging studies, and other laboratory criteria, noninvasive vascular studies, cardiac evaluations for a source of embolus, and, when available, information from autopsy studies. Ischemic stroke was diagnosed if a focal neurological deficit was documented and the imaging showed no hemorrhage, the imaging showed an ischemic infarct that correlated with the clinical deficit, or an ischemic infarct was documented at autopsy.

Screening techniques and procedures used to diagnose and categorize dementia have been described previously.^{2,11} *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*, criteria were used to define dementia,¹² but we additionally required that severity be at least “moderate” by Framingham criteria (≥ 1 on the Clinical Dementia Rating Scale)¹³ and that symptoms be present for ≥ 6 months. AD was defined using NINCDS-ADRDA criteria for definite, probable, or possible AD.¹⁴ All deaths were reviewed to assign a cause of death (stroke or an alternative etiology) and to determine whether dementia was present at the time of death.

Statistical Analysis

Participants were followed until they developed the outcome of interest (first-ever stroke or dementia), died, or until their most recent Framingham Study evaluation before December 2003. The estimation of cumulative incidence of diseases of the elderly is complicated by the competing risk of death. Subjects who die during the observation period are treated as censored observations in traditional survival analytic techniques, and their potential contribution to the probability of disease is distributed among subjects still at risk. However, the potential contribution of a subject who has died should be 0. Treating such subjects as censored inflates the estimate of cumulative incidence. We used a modified double-decrement survival analysis technique described previously,^{2,11} which adjusts the cumulative incidence for the competing risk of death, thereby providing an estimate of the actual risk of one developing the disease during his or her lifetime.

Sex-specific 10-, 20-, and 30-year risks, and the LTR of developing a first-ever stroke were defined for stroke-free participants at

baseline ages 55, 65, 75, and 85 years (referred to as “index” ages) for all stroke, and specifically for ischemic stroke. Sex-specific 10-, 20-, and 30-year risks and the LTR of developing dementia and AD were estimated at ages 65, 75, and 85 years. In these event-specific analyses (considering either stroke or dementia), subjects were not censored when they developed the alternative event because the development of stroke did not preclude the development of dementia and vice versa. The combined risk of developing “either stroke or dementia” was also estimated, and for this analysis, only the first event (either stroke or dementia) was considered.

We further examined the risk of stroke and AD within BP categories defined using JNC 7 cut points (with the modification that we used actual BP levels, disregarding treatment). Participants were stratified by BP recorded at the last available examination before the index age (≤ 2 years earlier). We defined 4 categories using systolic BP (SBP) and diastolic BP (DBP) measured in mm Hg: SBP <120 and DBP <80; 120 \leq SBP <140 or 80 \leq DBP <90; 140 \leq SBP <160 or 90 \leq DBP <100 and SBP ≥ 160 or DBP ≥ 100 . If categorization by SBP and DBP varied, participants were placed in the higher category; in >90%, classification into a higher category was based on SBP. In separate analyses, participants on antihypertensive therapy at index age were excluded. All statistical analyses were performed using SAS software (SAS Institute).

Results

Description of Participants

During a 51-year follow-up period, 18% (875 participants; 522 women) developed a first-ever stroke. Of these, 86% (749 participants; 448 women) developed an ischemic stroke. Over a 29-year follow-up period, 14% (400 participants; 270 women) developed dementia, and 73% of these (292 participants; 211 women) had AD.

LTR of Stroke

Table 1 displays the LTR of stroke, which remained relatively constant until 75 years of age, at 1 in 5 for women (20% to 21%) and approximately 1 in 6 for men (14% to 17%). The LTR at 85 years of age was lower (16% for women and 10% for men; $P<0.05$ compared with participants 55 to 75 years of age). Although the incidence rate of stroke increased with age, this was counterbalanced by a decreasing residual life expectancy (data not presented).

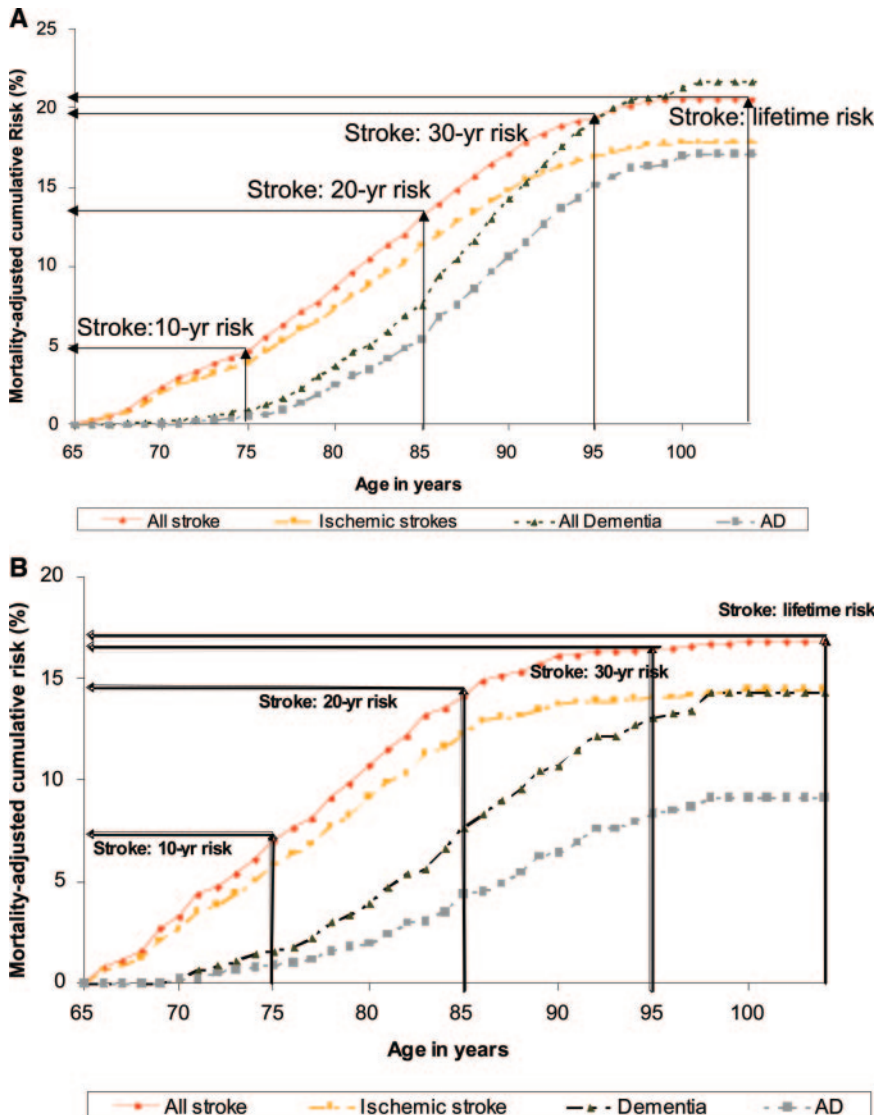


Figure 1. A, Women, 65 years of age: 10-, 20-, 30-year, and LTRs of first-ever stroke and dementia (LTR of stroke, ischemic stroke, all-dementia, and AD in participants followed over their lifespan). B, Men, 65 years of age: 10-, 20-, 30-year, and LTRs of first-ever stroke and dementia (LTR of stroke, ischemic stroke, all-dementia, and AD in participants followed over their lifespan).

Short- and Intermediate-Term Risks of Stroke

Figure 1a and 1b plot the 10-, 20-, 30-year, and the LTR of stroke in women and men 65 years of age. Table 1 presents these risks for each index age. At 65 years of age, the 10-year risk was lower in women; by 75 years of age, women and men were at equal risk. At 85 years of age, the pattern was reversed, and 10-year risks were higher in women.

LTR, Short-Term, and Intermediate-Term Risks for Ischemic Stroke (Table 1; Figure 1a and 1b)

The LTR of ischemic stroke at 55 or 65 years of age was higher in women (18%) than in men (14% to 15%; $P < 0.01$). As with overall stroke risk, the 10-year risk of ischemic stroke was lower in women than in men at < 75 years of age but higher thereafter.

LTR, Short-Term, and Intermediate-Term Risks for Stroke by BP Category

There was a graded increase in stroke risk with increasing BP (Table 2; Figure 2). Participants with a normal BP (SBP < 120 and DBP < 80 mm Hg) had a significantly lower LTR

of stroke than participants with a high BP (SBP ≥ 140 or DBP ≥ 90 mm Hg; $P < 0.01$). In women, these risks were 1 in 6 (15%) and 1 in 4 (26%), respectively, whereas in men, they were 1 in 10 (10%) and 1 in 5 (21%). A similar risk gradient across the 4 BP categories was noted in younger (55 years of age) and in older participants (75 and 85 years of age), and the graded increase in risk with higher BP persisted when people on antihypertensive drugs were excluded (data not presented).

LTR of Dementia

The short-term, intermediate-term, and the LTR of dementia and AD are presented in Table 3 and Figure 1a and 1b. We observed a higher risk of dementia and AD in women (22% to 24% and 17% to 20%, respectively) compared with men (14% to 17% and 9% to 12%, respectively; $P < 0.01$). Thus, > 1 in 5 women and 1 in 6 men who reached 65 years of age developed dementia; ≈ 1 in 5 women and 1 in 10 men developed AD. These risks did not vary across BP categories (data not shown).

TABLE 2. Age- and Sex-Specific, Mortality-Adjusted, 10-, 20-, and 30-Year and LTR Estimates* for the Development of Stroke (all types) for Subjects 65 Years of Age, Described Within Subgroups Defined by BP at 65 Years of Age

Gender	JNC VII Category†	First-Ever Stroke, All Types			
		Short- and Intermediate-Term Risks			LTR
		10-Year	20-Year	30-Year	
Women	Normal	1.6 (0.0–3.2)	5.7 (2.8–8.6)	9.9 (5.9–14.0)	14.6 (9.2–20.4)
	Prehypertension	3.0 (1.7–4.3)	10.8 (8.5–13.1)	17.3 (14.3–20.2)	18.2 (15.1–21.3)
	Stage 1 hypertension	4.1 (2.4–5.7)	15.8 (12.7–18.9)	24.7 (20.9–28.5)	25.8 (21.9–29.7)
	Stage 2 hypertension	9.9 (7.3–12.6)	19.9 (16.3–23.5)	25.3 (21.3–29.3)	25.6 (21.6–29.6)
Men	Normal	2.1 (0.1–4.2)	8.2 (4.2–12.1)	10.4 (6.0–14.9)	10.4 (6.0–14.9)
	Prehypertension	6.2 (4.2–8.2)	12.3 (9.6–15.0)	14.9 (12.0–17.9)	14.9 (12.0–17.9)
	Stage 1 hypertension	7.2 (4.6–9.7)	16.3 (12.6–20.0)	20.0 (16.0–24.1)	20.5 (16.3–24.6)
	Stage 2 hypertension	10.8 (7.0–14.7)	19.9 (14.9–24.9)	22.1 (16.8–27.4)	22.1 (16.8–27.4)

*Risks expressed in percentages over period of observation; values in parentheses are 95% CIs. †BP categories, all values in mm Hg, if categorization by SBP and DBP varied, the higher value was used: normal SBP <120 and DBP <80; prehypertension 120≤SBP<140 or 80≤DBP<90; stage 1 hypertension 140≤SBP<160 or 90≤DBP<100; stage 2 hypertension SBP ≥160 or DBP ≥100.

Combined Risk of Stroke or Dementia

Table 4 shows that the LTR of developing either stroke or dementia at age 65, 75, or 85 years is >1 in 3 (39% at 65 years and 38% at 85 years) for women and ≈1 in 4 for men (28% at 65 years and 24% at 85 years).

Comparison of Stroke and AD Risks

Figure 1a and 1b show that in 65-year-old participants, the 10- and 20-year risks of developing stroke were higher than the corresponding risk of AD. Men 65 to 75 years of age also had a higher LTR of stroke (1 in 6 for stroke; 1 in 10 for AD), whereas women at this age had an LTR of stroke approximately equal to their LTR of AD (1 in 5). At 85 years of age, the LTR of stroke was lower than the corresponding risk of AD in both sexes, but this difference was statistically significant only in women. The flattening of the LTR curves for stroke and AD in very old subjects (as shown in Figure 1a and

1b) is based on relatively small numbers and may, therefore, be attributable to chance.

Discussion

We observed that the LTR of stroke for middle-aged and “young-old” adults (55 to 75 years of age) was substantial at 1 in 6 or higher. This risk was higher in women (1 in 5) compared with men, largely because of the greater life expectancy in women, which increased their period at risk. For the oldest-old participants (>85 years of age), the LTR of stroke decreased, despite a continued rise in stroke incidence, because the remaining life expectancy decreased more rapidly than the risk of stroke increased.

Our estimates are based on simultaneously gathered data on both stroke incidence and mortality attributable to competing causes (the 2 key determinants of the LTR) in the same

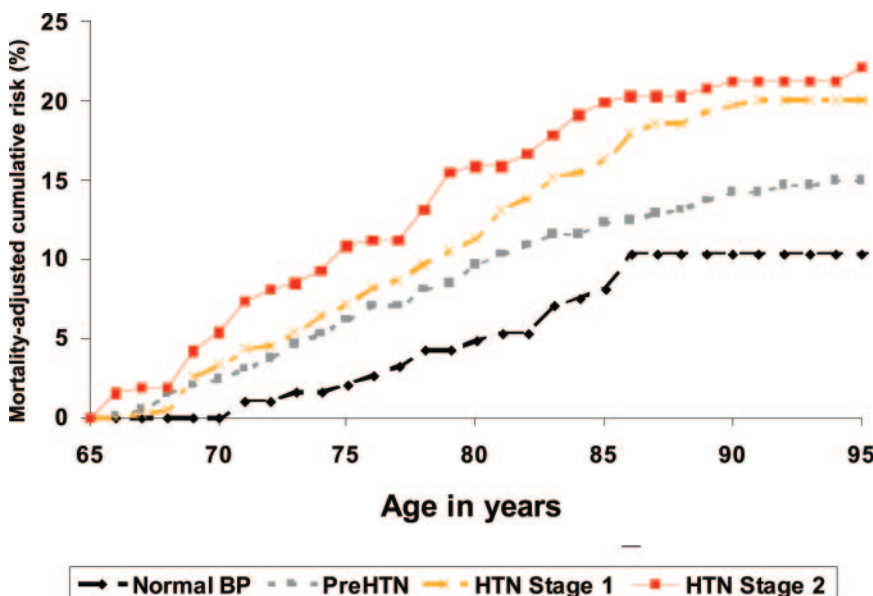


Figure 2. Men, 65 years of age: risk of first-ever stroke by baseline BP; LTR of all-stroke within 4 BP categories defined using SBP and DBP; subjects categorized using higher of 2 values: (1) normal BP: SBP <120 and DBP <80; (2) prehypertension (PreHTN): 120≤SBP<140 or 80≤DBP<90; (3) stage 1 hypertension (HTN Stage 1): 140≤SBP<160 or 90≤DBP<100; (4) stage 2 hypertension (HTN Stage 2): SBP ≥160 or DBP ≥100.

TABLE 3. Age- and Sex-Specific, Mortality-Adjusted, 10-, 20-, and 30-Year and LTR Estimates* for the Development of Dementia and AD at Index Ages 65, 75, and 85 Years

Gender	Age (y)	Dementia, All Types (400 events)				AD (292 events)			
		Short-term and Intermediate-term Risks				Short-term and Intermediate-term Risks			
		10-Year	20-Year	30-Year	LTR	10-Year	20-Year	30-Year	LTR
Women	65	1.0 (0.4–1.5)	7.6 (6.3–9.0)	19.4 (17.2–21.6)	21.7 (19.3–24.0)	0.6 (0.1–1.0)††	5.4 (4.3–6.6)††	15.2 (13.2–7.2)††	17.2 (15.0–19.4)†
	75	7.4 (6.0–8.8)	20.6 (18.2–22.9)		23.1 (20.5–25.7)	5.4 (4.2–6.6)††	16.3 (14.2–18.5)	...	18.5 (16.2–20.9)
	85	20.3 (17.2–23.5)			24.3 (20.7–27.8)	16.9 (13.9–19.8)	20.3 (17.0–23.6)†
Men	65	1.6 (0.8–2.4)	7.7 (6.1–9.3)	13.1 (10.9–15.3)	14.3 (12.0–16.7)	0.9 (0.3–1.5)††	4.4 (3.2–5.7)††	8.3 (6.5–10.2)††	9.1 (7.2–11.1)††
	75	7.6 (5.8–9.3)	14.2 (11.7–16.8)		15.8 (13.0–18.5)	4.4 (3.0–5.7)††	9.2 (7.1–11.3)††	...	10.2 (7.9–12.5)††
	85	13.8 (9.9–17.7)			16.9 (12.5–21.4)	10.0 (6.6–13.4)	12.1 (8.2–15.9)

*Risks expressed in percentages over period of observation; values in parentheses are 95% CIs; † $P<0.05$ and †† $P<0.01$, comparing risks of stroke from Table 1 with risk of AD in corresponding age-, sex-category, comparisons made using z test.

community-based cohort followed >5 decades. Estimates that combine stroke incidence collected in 1 population or time period with mortality data collected in another sample may yield biased estimates of LTR because a variety of risk factors that influence stroke risk (most notably hypertension) can also affect the risk of dying from other causes. There has been only 1 previous published report on the LTR of stroke; those estimates were based on a much shorter (6-year) follow-up of the Rotterdam Study sample and were similar to ours (21% for both men and women 55 years of age).¹⁵

Comparison of the LTR of Stroke With the LTR of AD

Our investigation presents the first available comparison of the LTR of stroke and AD in the same cohort. These estimates of the LTR of AD are higher than our previously published figure² because they are based on extended observation of the same cohort with accrual of additional cases. We found that the LTR of stroke either equaled or was greater than the LTR of AD for most participants. Only in the oldest-old (>85 years of age) women was the LTR of stroke significantly lower than the LTR of AD. The combined LTR of developing either stroke or dementia was <30% in men but was nearly 40% in women (exceeding their LTR of developing symptomatic coronary artery disease).³

Strengths and Limitations

The strengths of our study include the use of a population-based cohort, the prospective ascertainment of end points

using rigorous standardized and previously validated clinical diagnostic criteria that have not varied significantly over the 5 decades of follow-up, and the completeness of stroke and mortality ascertainment. These LTR estimates are population based, and therefore, although they serve as general guidelines, they have limited prognostic utility in a given individual in whom the LTR would depend on his or her own estimated life expectancy and level of exposure to various risk factors for stroke and dementia. The Framingham Original cohort is overwhelmingly white, so racial and ethnic differences need to be explored in other cohorts. Time period and birth cohort effects could limit the external validity of our results. We did not find a secular trend in the incidence of stroke in our population,¹⁰ but this issue needs to be addressed in additional studies. Temporal trends in life expectancy, risk factor prevalence and control, in disease awareness, and in the sensitivity of diagnostic tests could alter the LTR of stroke and dementia. Finally, these estimates describe the risk of overt stroke but do not address the risk of silent (covert) stroke, which may be substantial.¹⁶ Therefore, the stroke risks that we report, although high, are likely to be conservative estimates of the true population burden of cerebral vascular disease.

Public Health Significance

These LTR estimates are useful for public education because they are easier to comprehend than measures such as incidence, prevalence, or relative risk. A recent study using focus

TABLE 4. Age- and Sex-Specific, Mortality-Adjusted, 10-, 20-, and 30-Year, and LTR Estimates* for the Development of Either Stroke or Dementia

Gender	Age (y)	First-Ever Stroke or Dementia			
		Risk Period			
		10-Year	20-Year	30-Year	LTR
Women	65	4.0 (2.9–5.2)	18.1 (16.0–20.1)	34.6 (31.9–37.2)	38.6 (35.7–41.4)
	75	15.9 (13.9–17.9)	34.6 (31.7–37.4)	...	39.1 (36.0–42.1)
	85	30.7 (26.9–34.6)	38.1 (33.8–42.5)
Men	65	7.3 (5.5–9.1)	19.4 (16.8–21.9)	26.6 (23.6–29.5)	28.0 (25.0–31.1)
	75	15.5 (13.0–18.0)	24.8 (21.6–28.0)	...	26.7 (23.3–30.1)
	85	20.0 (15.2–24.8)	24.0 (18.7–29.4)

*Risks expressed in percentages over specified period of observation; values in parentheses are 95% CIs.

group discussions concluded that “patients preferred health risks to be framed in absolute terms, using bar graphs, and calculated over their expected lifetime.”¹⁷ Health educators have also emphasized that while raising awareness of a health hazard, it is important to simultaneously provide data on modifiable risk factors because this increases receptivity and minimizes psychological distress.¹⁸ Our data can be used to generate simple bar graphs (supplemental Figure I, available online at <http://stroke.ahajournals.org>) showing, for example, that the LTR of stroke in a 65-year-old woman with BP <120/80 mm Hg is half that of a 65-year old woman with BP \geq 140/90 mm Hg. Currently, two thirds of all hypertension remains undetected or inadequately treated.¹⁹ Although we cannot directly address the benefits of intervention in our observational data, education of middle-aged and older adults regarding their high LTR of stroke and the key contribution of high BP to this risk may be expected to motivate lifestyle modifications, thereby reducing mean population BP levels²⁰ and, ultimately, the population burden of stroke.

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