

Different Risk Factors for Different Stroke Subtypes

Association of Blood Pressure, Cholesterol, and Antioxidants

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Background and Purpose—Blood pressure is an important risk factor for stroke, but the roles of serum total and HDL cholesterol, α -tocopherol, and β -carotene are poorly established. We studied these factors in relation to stroke subtypes.

Methods—Male smokers (n=28 519) aged 50 to 69 years without a history of stroke participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a controlled trial to test the effect of α -tocopherol and β -carotene supplementation on cancer. From 1985 to 1993, a total of 1057 men suffered from primary stroke: 85 had subarachnoid hemorrhage; 112, intracerebral hemorrhage; 807, cerebral infarction; and 53, unspecified stroke.

Results—Systolic blood pressure ≥ 160 mm Hg increased the risk of all stroke subtypes 2.5 to 4-fold. Serum total cholesterol was inversely associated with the risk of intracerebral hemorrhage, whereas the risk of cerebral infarction was raised at concentrations ≥ 7.0 mmol/L. The risks of subarachnoid hemorrhage and cerebral infarction were lowered with serum HDL cholesterol levels ≥ 0.85 mmol/L. Pretrial high serum α -tocopherol decreased the risk of intracerebral hemorrhage by half and cerebral infarction by one third, whereas high serum β -carotene doubled the risk of subarachnoid hemorrhage and decreased that of cerebral infarction by one fifth.

Conclusions—The risk factor profiles of stroke subtypes differ, reflecting different etiopathology. Because reducing atherosclerotic diseases, including ischemic stroke, by lowering high serum cholesterol is one of the main targets in public health care, further studies are needed to distinguish subjects with risk of hemorrhagic stroke. The performance of antioxidants needs confirmation from clinical trials. (*Stroke*. 1999;30:2535-2540.)

Key Words: antioxidants ■ blood pressure ■ cerebral infarction ■ cholesterol
■ intracerebral hemorrhage ■ subarachnoid hemorrhage

High blood pressure is the most important of the known risk factors for all stroke subtypes.¹⁻⁵ Cigarette smoking is also a well-known risk factor for subarachnoid hemorrhage⁴ and cerebral infarction,^{1,2,5,6} but the association with intracerebral hemorrhage is not clear-cut.^{2,3,6-9}

The relations between serum total and HDL cholesterol and stroke risk are not clear, yet there is mounting evidence that serum total cholesterol concentration is inversely associated with the risk of hemorrhagic stroke.^{7,10,11} By contrast, serum total cholesterol concentration >6 mmol/L seems to increase the risk of cerebral infarction.^{7,8,10,12} Data regarding serum HDL cholesterol and the risk of stroke are scant, with high serum HDL cholesterol possibly being protective against cerebral infarction.¹³

α -Tocopherol and β -carotene may act as antioxidants against atherosclerosis and thus prevent cerebrovascular diseases.^{14,15} In addition to antioxidant effects, α -tocopherol and its metabolites have antiplatelet and anticlotting actions,¹⁶⁻¹⁹ but their clinical importance is obscure. High dietary β -carotene intake has been associated with decreased incidence of stroke.^{20,21}

The aim of the present study was to evaluate the association of systolic and diastolic blood pressure, serum total and HDL cholesterol, serum α -tocopherol and β -carotene, and cigarette smoking (measured at the beginning of follow-up) with the risks of subarachnoid and intracerebral hemorrhage and cerebral infarction in middle-aged male smokers.

Subjects and Methods

The present study was carried out within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a randomized, double-blind, placebo-controlled, primary-prevention trial to test the hypothesis that α -tocopherol and β -carotene supplements reduce the incidence of lung and other cancers.^{22,23} Of the 29 133 smokers (≥ 5 cigarettes per day) aged 50 to 69 years who were recruited to the ATBC Study from 1985 to 1988 from the total male population of southwestern Finland (n=290 406), 28 519 were included in the present study. Excluded from the study were 614 men who had reported previous stroke. The median length of follow-up was 6.0 years. The study was approved by the institutional review boards of the National Public Health Institute, Helsinki, Finland, and the National Cancer Institute, Bethesda, Md. All participants gave written informed consent, and their safety was monitored by an outside committee.

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At baseline, the participants completed a questionnaire about their general background, smoking, and medical history, including a question about physician-diagnosed stroke. Blood pressure levels were assessed by nurses who were trained to obtain standardized and coherent measurements. Height and weight were measured, and body mass index was calculated as weight divided by height squared. Serum total and HDL cholesterol levels were determined enzymatically (CHOD-PAP method, Boehringer-Mannheim). HDL cholesterol was measured after precipitation of VLDL and LDL cholesterol with dextran sulfate and magnesium chloride. Serum α -tocopherol and β -carotene were determined by high-performance liquid chromatography.²⁴ Alcohol consumption during the previous year was assessed with a detailed dietary history questionnaire.²⁵

The end points were incident subarachnoid and intracerebral hemorrhage and cerebral infarction. Strokes were identified by record linkage to the National Hospital Discharge Register and the National Register of Causes of Death, which used 2 editions of the *International Classification of Diseases* (ICD): up to the end of 1986, the 8th edition (ICD-8) was used; thereafter, the 9th edition (ICD-9) was used.^{26,27} ICD codes 430 to 434 and 436 were included in the present study, but ICD-8 codes 431.01 and 431.91 and ICD-9 code 432 denoting subdural hematoma and ICD-9 codes 4330X, 4331X, 4339X, and 4349X representing occlusion or stenosis of a precerebral or cerebral artery without infarction were excluded. In a reviewed sample, the diagnoses of subarachnoid and intracerebral hemorrhage and cerebral infarction proved correct by strict preset criteria in 79%, 82%, and 90% of the discharge diagnoses and in 95%, 91%, and 92% of the causes of death.²⁸ Of men with stroke, 77% had been examined with computed tomography, 4% had been examined with MRI, 17% had been examined with angiography, 7% had had brain surgery, 7% were examined at autopsy, and 14% had clinical evaluation only.

Baseline systolic and diastolic blood pressures were divided into 3 categories: ≤ 139 , 140 to 159, and ≥ 160 mm Hg and ≤ 89 , 90 to 99, and ≥ 100 mm Hg for systolic and diastolic, respectively. Serum total cholesterol was categorized as ≤ 4.9 , 5.0 to 5.9, 6.0 to 6.9, and ≥ 7.0 mmol/L, and HDL cholesterol was categorized as ≤ 0.84 , 0.85 to 1.14, 1.15 to 1.44, and ≥ 1.45 mmol/L. Smoking was determined as the number of cigarettes smoked per day, and men were divided into 3 groups (5 to 15, 16 to 20, and ≥ 21 cigarettes per day). Serum α -tocopherol and β -carotene were divided into quartiles. Information on diabetes and heart disease (coronary heart disease, myocardial infarction, valvular disease, arrhythmia, cardiac enlargement, and congestive heart failure) was based on medical history reported before the follow-up. The level of education was categorized as primary school (< 7 years), secondary school (7 to 12 years), and university or other higher education (> 12 years). Leisure-time physical activity was categorized as sedentary or active (strenuous exercise at least once a week).

When calculating person-years for incidence rates, the follow-up ended at any stroke end point of interest, at death, or at April 30, 1993, the end of follow-up. Crude incidence rates were calculated per 10 000 person-years. Relative risks were computed by using Cox proportional hazards models adjusted for age, systolic blood pressure, body mass index, serum total and HDL cholesterol, diabetes, previous heart disease, alcohol consumption, number of cigarettes smoked per day, education, physical activity, and α -tocopherol and β -carotene trial supplementation. Baseline values of blood pressure were missing for 5 men; weight or height, for 17 men; serum total cholesterol, for 33 men; serum HDL cholesterol, for 37 men; and serum α -tocopherol and β -carotene, for 27 men. Men with a missing value for the specific variable under study were excluded from respective multivariate analyses, whereas missing values of covariates were replaced with group-specific mean values. When the effect of a specific variable was examined, the examined variable was categorized, but the covariates were in their continuous forms in the models. When risk factor profiles were compared, variables were in their continuous forms in the models, their effects were evaluated concurrently, and men with missing values were all excluded. All analyses were repeated in the trial placebo group only. Because the

findings were similar, only the results based on the total study population are reported in detail.

Results

A total of 1057 men with no history of stroke suffered from incident stroke during the follow-up: 85 men had subarachnoid hemorrhage, 112 had intracerebral hemorrhage, 807 men had cerebral infarction, and 53 men had unspecified stroke. Table 1 shows the baseline characteristics by outcome.

Subarachnoid Hemorrhage

There was a steady increase of adjusted relative risk with increasing systolic and diastolic blood pressure, and serum HDL cholesterol levels ≥ 0.85 mmol/L seemed to decrease and smoking ≥ 16 cigarettes per day seemed to increase the risk (Table 2). Serum β -carotene levels ≥ 0.26 mg/L increased the adjusted relative risk (Table 3).

Intracerebral Hemorrhage

The risk of intracerebral hemorrhage increased with increasing systolic and diastolic blood pressures (Table 2). The adjusted relative risk decreased unvaryingly to 0.20 at serum total cholesterol levels ≥ 7.0 mmol/L compared with the lowest levels (< 5.0 mmol/L). An interesting finding was that the adjusted relative risk dropped to ≈ 0.50 in all 3 upper serum α -tocopherol quartiles compared with the lowest quartile (< 9.8 mg/L) (Table 3).

Cerebral Infarction

The adjusted relative risk of cerebral infarction was increased with increasing systolic and diastolic blood pressures (Table 2). A marginally increased risk associated with serum total cholesterol was evident in only the highest concentrations (≥ 7.0 mmol/L), but the decrease in the risk with increasing serum HDL cholesterol was already evident in concentrations ≥ 0.85 mmol/L. The higher the levels of both serum α -tocopherol and β -carotene, the smaller was the adjusted relative risk, being statistically significant at the highest levels (≥ 13.6 mg/L and ≥ 0.26 mg/L, respectively) (Table 3).

Risk Factor Profiles in Comparison

The multivariate adjusted risk factor profile of subarachnoid hemorrhage had little in common with those of intracerebral hemorrhage and cerebral infarction, whereas the latter ones resembled each other. High systolic and diastolic blood pressure increased the risk of all stroke subtypes. Only smoking increased and serum HDL cholesterol decreased the risk of subarachnoid hemorrhage. High serum total cholesterol seemed to decrease the risk of intracerebral hemorrhage but to increase the risk of cerebral infarction. By contrast, low serum HDL cholesterol increased the risk of cerebral infarction but not of intracerebral hemorrhage. In addition, age significantly increased the risks of both intracerebral hemorrhage and cerebral infarction. Diabetes and heart disease marginally increased the risk of intracerebral hemorrhage and significantly increased the risk of cerebral infarction. On the other hand, physical activity marginally decreased the risk of intracerebral hemorrhage and significantly decreased the risk of cerebral infarction. Body mass index had no effect on any

TABLE 1. Participant Characteristics at Beginning of Follow-Up by Outcome

Characteristics	Subarachnoid Hemorrhage	Intracerebral Hemorrhage	Cerebral Infarction	Unspecified Stroke	No Stroke
No. of cases	85	112	807	53	27 462
Age, y	57.2	59.7	59.8	61.5	57.6
Blood pressure, mm Hg					
Systolic	153.1	154.7	150.8	154.4	141.5
Diastolic	94.6	93.4	91.1	92.0	87.5
Body mass index, kg/m ²	26.6	26.5	26.7	26.6	26.3
Serum cholesterol, mmol/L					
Total	6.10	5.69	6.33	6.18	6.23
HDL	1.15	1.23	1.15	1.16	1.20
Alcohol consumption, g/d	22.5	19.0	20.2	18.4	18.0
Smoking, cigarettes/d	23.0	19.4	20.3	18.6	20.4
Previous diseases, %					
Heart disease	24.7	34.8	38.5	39.6	24.2
Diabetes	2.4	6.3	11.0	11.3	3.9
Education, %					
Primary school	83.5	82.2	80.7	73.6	78.8
Secondary school	10.6	9.8	13.1	20.7	13.6
University level	5.9	8.0	6.2	5.7	7.6
Leisure-time physical activity, %					
Sedentary	36.5	46.8	49.3	60.4	41.3
Active	63.5	53.2	50.7	39.6	58.7
Serum α -tocopherol, mg/L	11.8	10.4	12.0	11.8	11.9
Serum β -carotene, mg/L	0.22	0.17	0.19	0.18	0.21

Mean values and proportions are shown.

type of stroke. The main findings remained unchanged when evaluated in the trial placebo group only.

Discussion

The advantages of the present study are manifold. This study was population-based, and the number of participants was large. The accuracy of stroke diagnoses was good. The diagnostic practice of stroke remained apparently stable during the follow-up, even though the ICD coding system changed in the beginning of follow-up. The main findings remained unchanged when examined in the trial placebo group only, indicating that controlling the trial supplementation by mathematical modeling in the total study group was successful. Risk factors for different stroke subtypes have also been evaluated in the MRFIT Study¹ but only for fatal strokes, and follow-up for that study started in the 1970s, when computed tomography was not yet diagnostic practice.

The risks of all subtypes of stroke increased with increasing systolic and diastolic blood pressures, which is in accord with the literature.¹⁻⁵ Similar to earlier studies,^{7,8,10,11} a trend of inverse association was found between serum total cholesterol and the risk of subarachnoid hemorrhage. The inverse association of serum total cholesterol with the risk of intracerebral hemorrhage was significant despite the relatively high upper limit of the lowest quartile (4.9 mmol/L); in other studies, the highest incidences have been observed in lower concentrations (<4.14 mmol/L).¹¹ The risk of cerebral infarc-

tion was increased in men with serum cholesterol at least 7.0 mmol/L, a level similar to that reported by others.^{7,10,12} Serum HDL cholesterol was inversely associated with the risks of subarachnoid hemorrhage and cerebral infarction but not with the risk of intracerebral hemorrhage; there appeared to be a threshold for the lowered risks at ≥ 0.85 mmol/L for subarachnoid hemorrhage and cerebral infarction. Woo et al²⁹ reported decreased odds ratios for all strokes combined at serum HDL cholesterol levels ≥ 0.97 mmol/L. In their study, subarachnoid hemorrhages were excluded, 21% of the strokes were intracerebral hemorrhages and 79% were ischemic events, and lipid concentrations were measured after the stroke occurred.

All men in the present study were cigarette smokers; nonsmoking controls were not available. Nevertheless, the number of cigarettes smoked increased the risk of subarachnoid hemorrhage but not the risk of intracerebral hemorrhage and cerebral infarction. This emphasizes the importance of smoking as a risk factor for subarachnoid hemorrhage and its comparatively lesser role in the other stroke subtypes, even though the apparent weak association of cigarette smoking with the latter ones relates to the study design and lack of variability in smoking exposure among the participants. Similar findings have been reported in other studies.^{2,3,5,9,30,31}

Subarachnoid hemorrhage is commonly caused by rupture of an arterial aneurysm. An aneurysm may be due to a congenital defect in the wall of an artery or, more probably,

TABLE 2. Crude Incidence per 10 000 Person-Years and Adjusted Relative Risk (95% CI) of Stroke Subtypes by Systolic and Diastolic Blood Pressure, Serum Total and HDL Cholesterol, and Smoking at Beginning of Follow-Up

Risk Factor	Subarachnoid Hemorrhage				Intracerebral Hemorrhage				Cerebral Infarction			
	N	I	RR	(95% CI)	N	I	RR	(95% CI)	N	I	RR	(95% CI)
Systolic blood pressure												
≤139 mm Hg	21	2.7	1.00	...	26	3.3	1.00	...	243	30.8	1.00	...
140–159 mm Hg	36	6.5	2.57	(1.49–4.44)	43	7.8	2.20	(1.34–3.61)	292	52.7	1.54	(1.29–1.83)
≥160 mm Hg	28	9.4	3.86	(2.14–6.94)	43	14.4	3.78	(2.28–6.25)	272	91.2	2.38	(1.99–2.85)
Diastolic blood pressure												
≤89 mm Hg	30	3.3	1.00	...	37	4.0	1.00	...	339	37.0	1.00	...
90–99 mm Hg	30	6.0	1.89	(1.13–3.16)	40	8.0	2.10	(1.34–3.31)	282	56.3	1.54	(1.31–1.81)
≥100 mm Hg	25	11.1	3.54	(2.04–6.17)	35	15.6	4.17	(2.58–6.74)	186	82.6	2.27	(1.88–2.73)
Serum total cholesterol												
≤4.9 mmol/L	12	5.7	1.00	...	25	11.9	1.00	...	104	49.4	1.00	...
5.0–5.9 mmol/L	35	7.0	1.20	(0.62–2.32)	47	9.3	0.77	(0.47–1.26)	235	46.7	1.00	(0.79–1.26)
6.0–6.9 mmol/L	19	3.6	0.60	(0.29–1.24)	30	5.6	0.46	(0.27–0.78)	241	45.2	0.97	(0.77–1.22)
≥7.0 mmol/L	19	4.8	0.78	(0.38–1.62)	10	2.5	0.20	(0.10–0.42)	226	57.3	1.25	(0.99–1.57)
Serum HDL cholesterol												
≤0.84 mmol/L	14	8.3	1.00	...	11	6.6	1.00	...	127	75.6	1.00	...
0.85–1.14 mmol/L	29	4.4	0.50	(0.26–0.95)	47	7.2	1.24	(0.64–2.41)	341	52.2	0.75	(0.61–0.93)
1.15–1.44 mmol/L	33	6.5	0.69	(0.36–1.33)	30	5.9	1.05	(0.52–2.15)	205	40.3	0.59	(0.46–0.74)
≥1.45 mmol/L	9	2.9	0.26	(0.11–0.62)	24	7.7	1.33	(0.62–2.85)	133	42.9	0.59	(0.45–0.77)
Smoking												
5–15 cigarettes/d	20	3.7	1.00	...	42	7.8	1.00	...	273	50.4	1.00	...
16–20 cigarettes/d	31	5.6	1.42	(0.81–2.51)	31	5.6	0.74	(0.46–1.18)	267	48.2	0.99	(0.83–1.17)
≥21 cigarettes/d	34	6.2	1.55	(0.87–2.74)	39	7.1	0.98	(0.62–1.55)	267	48.8	1.04	(0.87–1.24)

N indicates number of incident strokes; I, incidence per 10,000 person-years; and RR, relative risk adjusted for age, body mass index, systolic blood pressure, serum total and HDL cholesterol, smoking, alcohol consumption, diabetes, heart disease, education, physical activity, and α -tocopherol and β -carotene supplementation.

to an acquired lesion related to degenerative changes of the vessel wall later in life.³² Hypertension alone or in connection with atherosclerosis, combined with hemodynamic action and natural weak points in the cerebral vessel wall, is thought to be important in causing the degenerative changes.³² It is still unclear how the effect of smoking is mediated in subarachnoid hemorrhage and what roles the hemodynamic and

rheological changes caused by smoking play in the pathogenesis, but the increased serum proteolytic activity of cigarette smokers may be one explanation.³³

The etiopathology of intracerebral hemorrhage is poorly understood.³⁴ The most popular current theory of “microaneurysms” has been challenged lately, and it has been postulated that fibrinoid necrosis of small arteries and arterioles

TABLE 3. Crude Incidence per 10 000 Person-Years and Adjusted Relative Risk (95% CI) of Stroke Subtypes by Serum α -Tocopherol and β -Carotene at Beginning of Follow-Up

Risk Factor	Subarachnoid Hemorrhage				Intracerebral Hemorrhage				Cerebral Infarction			
	N	I	RR	(95% CI)	N	I	RR	(95% CI)	N	I	RR	(95% CI)
Serum α -tocopherol												
≤9.7 mg/L	24	5.9	1.00	...	56	13.8	1.00	...	209	51.4	1.00	...
9.8–11.4 mg/L	25	6.2	1.15	(0.64–2.06)	20	5.0	0.45	(0.26–0.77)	186	46.1	0.87	(0.71–1.07)
11.5–13.5 mg/L	13	3.1	0.61	(0.29–1.27)	20	4.8	0.50	(0.28–0.88)	213	51.1	0.92	(0.74–1.13)
≥13.6 mg/L	23	5.6	1.10	(0.53–2.31)	16	3.9	0.47	(0.23–0.93)	198	47.8	0.70	(0.55–0.89)
Serum β -carotene												
≤0.10 mg/L	19	4.7	1.00	...	39	9.7	1.00	...	244	60.8	1.00	...
0.11–0.16 mg/L	22	5.5	1.47	(0.78–2.75)	29	7.3	0.96	(0.58–1.57)	215	54.1	0.97	(0.80–1.17)
0.17–0.25 mg/L	17	4.1	1.25	(0.63–2.49)	24	5.8	0.91	(0.53–1.56)	179	43.1	0.83	(0.67–1.01)
≥0.26 mg/L	27	6.3	2.30	(1.20–4.40)	20	4.7	0.85	(0.47–1.54)	168	39.4	0.78	(0.63–0.97)

RR was adjusted for age, body mass index, systolic blood pressure, serum total and HDL cholesterol, smoking, alcohol consumption, diabetes, heart disease, education, physical activity, and α -tocopherol and β -carotene supplementation.

caused by hypertension might lead directly to cerebral hemorrhage. The etiopathology of cerebral infarction is better understood, and its causes can be grossly divided into thrombosis and embolism or large artery and lacunar disease, both associated with atherosclerosis.^{35,36}

Hypertension seems to be the most important determinant in both intracerebral hemorrhage and cerebral infarction and is known to lead to atherosclerosis, with predilection for precerebral and large cerebral arteries.³⁷ On the other hand, the small intraparenchymal cerebral arteries develop hyaline degeneration and fibrinoid necroses associated with lacunar infarcts and hemorrhages; however, the body of evidence is much weaker for this explanation than for the association between hypertension and atherosclerosis.³⁸

The only risk factors examined in the present study that had opposite effects on the risks of intracerebral hemorrhage and cerebral infarction were serum total and HDL cholesterol levels. The harmful effect of high serum total cholesterol and the protective effect of high serum HDL cholesterol on the risk of cerebral infarction were in accord with the general concepts of atherosclerosis. It has been postulated that low serum cholesterol levels could cause weakening of the endothelium of small intracerebral arteries, which, in connection with hypertension, could lead to hemorrhagic stroke.³⁹ Because intracerebral hemorrhage and cerebral infarction seem to share the risk factors for stroke, there must be some yet-unknown mechanism (which may well be connected to lipid metabolism) that determines whether the degenerative process leads to intracerebral hemorrhage or cerebral infarction.

The protective effect of both serum α -tocopherol and β -carotene on the risk of cerebral infarction is consistent with previous studies.^{20,21,40} The possible beneficial effect of α -tocopherol and β -carotene on both intracerebral hemorrhage and cerebral infarction could be mediated by their antioxidant actions in preventing atherosclerosis. On the other hand, the effect of α -tocopherol could also be mediated by its antiplatelet and anticoagulant actions,^{16–19} which would prevent the thrombotic consequences of atherosclerosis. α -Tocopherol supplementation increased the risk of subarachnoid hemorrhage and decreased the risk of cerebral infarction, whereas β -carotene supplementation increased the risk of intracerebral hemorrhage in our controlled trial.⁴¹ There may be a limited physiological range within which compounds such as α -tocopherol and β -carotene act beneficially, with lower or higher concentrations bringing no additional benefit and possibly even being harmful. In epidemiological studies, serum α -tocopherol and β -carotene may also be markers of lifestyles relevant to stroke risks.

Overall, the risk factor profiles differed among the stroke subtypes, and the risk profile of intracerebral hemorrhage resembled that of cerebral infarction more than that of subarachnoid hemorrhage. On the other hand, the risk profile of all strokes combined reflected, for the most part, the heavy weight of cerebral infarction with the largest incidence. This implies that studies ignoring stroke subtyping might give misleading weights for various risk factors and might not detect true associations. Given that the etiopathology differs

in each stroke subtype, it is important that future studies of stroke classify events properly by subtypes.

In conclusion, elevated blood pressure increases the risk of all subtypes of stroke. By contrast, the associations of serum total and HDL cholesterol are different for different strokes. Reducing the burden of atherosclerotic cardiovascular diseases, including cerebral infarction, by lowering high cholesterol is one of the main targets in public health care. Further study is needed to distinguish subjects who benefit from lowering cholesterol without risk of hemorrhagic stroke. The different associations of serum α -tocopherol and β -carotene with the risks of stroke subtypes call for further research to clarify their potential role in stroke prevention. Subarachnoid and intracerebral hemorrhage and cerebral infarction are separate entities, each having an individual risk factor profile. In studies involving the epidemiology of stroke, subtypes of stroke must be dealt with separately.

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References

1. Neaton JD, Wentworth DN, Cutler J, Stamler J, Kuller L. Risk factors for death from different types of stroke: Multiple Risk Factor Intervention Trial Research Group. *Ann Epidemiol.* 1993;3:493–499.
2. Jamrozik K, Broadhurst RJ, Anderson CS, Stewart-Wynne EG. The role of lifestyle factors in the etiology of stroke: a population-based case-control study in Perth, Western Australia. *Stroke.* 1994;25:51–59.
3. Juvela S, Hillbom M, Palomäki H. Risk factors for spontaneous intracerebral hemorrhage. *Stroke.* 1995;26:1558–1564.
4. Teunissen LL, Rinkel GJE, Algra A, van Gijn J. Risk factors for subarachnoid hemorrhage: a systematic review. *Stroke.* 1996;27:544–549.
5. Haapaniemi H, Hillbom M, Juvela S. Lifestyle-associated risk factors for acute brain infarction among persons of working age. *Stroke.* 1997;28:26–30.
6. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *Br Med J.* 1989;298:789–794.
7. Iso H, Jacobs DR, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the Multiple Risk Factor Intervention Trial. *N Engl J Med.* 1989;320:904–910.
8. Reed DM. The paradox of high risk of stroke in populations with low risk of coronary heart disease. *Am J Epidemiol.* 1990;131:579–588.
9. Fogelholm R, Murros K. Cigarette smoking and risk of primary intracerebral haemorrhage: a population-based case-control study. *Acta Neurol Scand.* 1993;87:367–370.
10. Kagan A, Popper JS, Rhoads GG, Yano K. Dietary and other risk factors for stroke in Hawaiian Japanese men. *Stroke.* 1985;16:390–396.
11. Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. *Stroke.* 1989;20:1460–1465.
12. Lindstrom E, Boysen G, Nyboe J. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen city heart study. *Br Med J.* 1994;309:11–15.
13. Gordon T, Kannel WB, Castelli WP, Dawber TR. Lipoproteins, cardiovascular disease, and death: the Framingham Study. *Arch Intern Med.* 1981;141:1128–1131.
14. Kritchevsky SB, Shimakawa T, Tell GS, Dennis B, Carpenter M, Eckfeldt JH, Peacher-Ryan H, Heiss G. Dietary antioxidants and carotid artery wall thickness: the ARIC Study: Atherosclerosis Risk in Communities Study. *Circulation.* 1995;92:2142–2150.
15. Hensrud DD, Heimburger DC, Chen J, Parpia B. Antioxidant status, erythrocyte fatty acids, and mortality from cardiovascular disease and Keshan disease in China. *Eur J Clin Nutr.* 1994;48:455–464.
16. Steiner M. Influence of vitamin E on platelet function in humans. *J Am Coll Nutr.* 1991;10:466–473.
17. de Lorgeril M, Boissonnat P, Salen P, Monjaud I, Monnez C, Guidollet J, Ferrera R, Dureau G, Ninet J, Reanud S. The beneficial effect of dietary

- antioxidant supplementation on platelet aggregation and cyclosporine treatment on heart transplant recipients. *Transplantation*. 1994;58:193–195.
18. Dowd P, Zheng ZB. On the mechanism of the anticlotting action of vitamin E quinone. *Proc Natl Acad Sci U S A*. 1995;92:8171–8175.
 19. Calzada C, Bruckdorfer KR, Rice-Evans CA. The influence of antioxidant nutrients on platelet function in healthy volunteers. *Atherosclerosis*. 1997;128:97–105.
 20. Daviglus ML, Orenca AJ, Dyer AR, Liu K, Morris DK, Persky V, Chavez N, Goldberg J, Drum M, Shekelle RB, Stamler J. Dietary vitamin C, beta-carotene and 30-year risk of stroke: results from the Western Electric Study. *Neuroepidemiology*. 1997;16:69–77.
 21. Keli SO, Hertog MGL, Feskens EJM, Kromhout D. Dietary flavonoids, antioxidant vitamins, and incidence of stroke: the Zutphen study. *Arch Intern Med*. 1996;154:637–642.
 22. The ATBC Cancer Prevention Study Group. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. *Ann Epidemiol*. 1994;4:1–10.
 23. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 1994;330:1029–1035.
 24. Milne DB, Botnen J. Retinol, alpha-tocopherol, lycopene, and alpha- and beta-carotene simultaneously determined in plasma by isocratic liquid chromatography. *Clin Chem*. 1986;32:874–876.
 25. Pietinen P, Hartman AM, Haapa E, Räsänen L, Haapakoski J, Palmgren J, Albanes D, Virtamo J, Huttunen JK. Reproducibility and validity of dietary assessment instruments, I: self-administered food use questionnaire with a portion size picture booklet. *Am J Epidemiol*. 1988;128:655–666.
 26. World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*. Vol I. 8th revision. Geneva, Switzerland: World Health Organization; 1967.
 27. World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*. Vol I. 9th revision. Geneva, Switzerland: World Health Organization; 1977.
 28. Leppälä JM, Virtamo J, Heinonen OP. Validation of stroke diagnosis in the National Hospital Discharge Register and the Register of Causes of Death in Finland. *Eur J Epidemiol*. 1999;15:155–160.
 29. Woo J, Lau E, Lam CWK, Kay R, Teoh R, Wong HY, Prall WY, Kreef L, Nicholls MG. Hypertension, lipoprotein(a), and apolipoprotein A-I as risk factors for stroke in the Chinese. *Stroke*. 1991;22:203–208.
 30. Longstreth WT Jr, Nelson LM, Koepsell TD, van Belle G. Cigarette smoking, alcohol use, and subarachnoid hemorrhage. *Stroke*. 1992;23:1242–1249.
 31. Juvela S, Hillbom M, Numminen H, Koskinen P. Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage. *Stroke*. 1993;24:639–646.
 32. Lee RMKW. Morphology of cerebral arteries. *Pharmacol Ther*. 1995;66:149–173.
 33. Fogelholm R, Murros K. Cigarette smoking and subarachnoid haemorrhage: a population-based case-control study. *J Neurol Neurosurg Psychiatry*. 1987;50:78–80.
 34. MacKenzie JM. Intracerebral haemorrhage. *J Clin Pathol*. 1996;49:360–364.
 35. Mohr JP. Natural history and pathophysiology of brain infarction. *Circulation*. 1991;83(suppl I):I-172–I-175.
 36. Bamford JM, Warlow CP. Evolution and testing of the lacunar hypothesis. *Stroke*. 1988;19:1074–1082.
 37. Grady PA. Pathophysiology of extracranial cerebral arterial stenosis: a critical review. *Stroke*. 1984;15:224–236.
 38. Johansson BB, Fredriksson K. Cerebral arteries in hypertension: structural and hemodynamic aspects. *J Cardiovasc Pharmacol*. 1985;7(suppl 2):S90–S93.
 39. Bronner LL, Kanter DS, Manson JE. Primary prevention of stroke. *N Engl J Med*. 1995;333:1392–1400.
 40. Chang CY, Lai YC, Cheng TJ, Lau MT, Hu ML. Plasma levels of antioxidant vitamins, selenium, total sulfhydryl groups and oxidative products in ischemic-stroke patients as compared to matched controls in Taiwan. *Free Radic Res*. 1998;28:15–24.
 41. Leppälä JM, Virtamo J, Fogelholm R, Huttunen JK, Albanes D, Taylor PR, Heinonen OP. Controlled trial of alpha-tocopherol and beta-carotene supplements on stroke incidence and mortality in male smokers. *Arterioscler Thromb Vasc Biol*. In press.