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LIPID LEVELS AND THE RISK OF ISCHEMIC STROKE IN WOMEN

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Abstract

Objective—To evaluate the association between total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol to HDL-C ratio, and non-HDL-C with the risk of ischemic stroke in a large cohort of apparently healthy women.

Methods—Prospective cohort study among 27,937 US women aged ≥45 years participating in the Women's Health Study who provided baseline blood samples. Stroke occurrence was self-reported

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and confirmed by medical record review. We categorized plasma lipid measurements into quintiles. We used Cox proportional hazards models to evaluate the association between lipids and risk of ischemic stroke.

Results—During 11 years of follow-up, 282 ischemic strokes occurred. All lipid levels were strongly associated with increased risk of ischemic stroke in age-adjusted models. The association attenuated particularly for HDL-C after adjustment for potential confounders. For the comparison of the highest to the lowest quintile, the multivariable-adjusted hazard ratios (95% confidence intervals; *P* for trend across mean quintile values) of ischemic stroke were 2.27 (1.43-3.60; P_{trend}<0.001) for total cholesterol; 1.74 (1.14-2.66; P_{trend}=0.003) for LDL-C; 0.78 (0.52-1.17; P_{trend}=0.27) for HDL-C; 1.65 (1.06-2.58; P_{trend}=0.02) for total cholesterol to HDL-C ratio; and 2.45 (1.54-3.91; P_{trend}<0.001) for non-HDL-C.

Conclusions—In this large cohort of apparently healthy women, total cholesterol, low-density lipoprotein cholesterol, the total cholesterol to high-density lipoprotein cholesterol ratio, and non-high-density lipoprotein cholesterol were significantly associated with increased risk of ischemic stroke.

Results from large trials of cholesterol-lowering statins have shown that these agents decrease the incidence of ischemic stroke among patients with existing strokes or TIAs[1] or at high risk for strokes.[2-4] However, in contrast to the well-established association between various lipid measures and coronary heart disease,[5-7] the epidemiologic evidence associating lipid levels with increased risk of ischemic stroke is less clear. Some studies found increased risk of ischemic stroke associated with increased total cholesterol levels[8-15] while others found no clear association.[16-21] With regard to cholesterol components, an association between low high-density lipoprotein cholesterol (HDL-C) levels and ischemic stroke has been shown in several studies[11, 12, 14, 22-25] but the association between low-density lipoprotein cholesterol (LDL-C) and ischemic stroke is less studied and inconsistent.[12, 21] In addition, most of the studies that evaluated the association between lipid levels and ischemic stroke included patients with pre-existing coronary heart disease, [8, 11, 12, 14, 17, 19] or were performed exclusively in men.[8, 9, 11, 16, 20, 23, 24] In women, a large pooled analysis of 8 cohort studies found an association between increasing total cholesterol and risk of non-hemorrhagic stroke only for women <55 years of age but not for older ages.[26]

We thus aimed to evaluate the association between lipid levels and risk of subsequent ischemic stroke in the Women's Health Study (WHS), a prospective cohort of >27,000 apparently healthy women aged 45 years and above with measured lipid profiles at baseline and a follow-up information during a mean of 11 years.

METHODS

Participants

Study subjects were all participants in the WHS, a completed randomized clinical trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among apparently healthy women. The design, methods, and results of the WHS have been described in detail previously.[27, 28] Briefly, a total of 39,876 women who were all registered health professionals throughout the United States and the Commonwealth of Puerto Rico, aged 45 years or older at study entry (1992-1995), and without a history of cardiovascular disease, cancer, or other major illnesses, were randomly assigned to one of four treatment groups: active aspirin (100 mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both placebos. All participants gave written informed consent and the Institutional Review Board of the Brigham and Women's Hospital approved the study design and procedures. Baseline information was self-reported and was collected by a mailed

questionnaire that asked about a large number of cardiovascular risk factors and life-style variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes (including stroke), personal characteristics, medical history, and health habits during the study period. For this analysis, we included follow-up information from the time of randomization through March 31, 2005.

Prior to randomization, women were asked whether they would be willing to provide a fasting venous blood sample. Women who answered affirmatively were mailed a blood collection kit containing EDTA tubes. Blood samples were received from 28,345 of which 27,937 of these samples could be assayed for a full lipid panel. Levels of total cholesterol and HDL-C were measured enzymatically on a Hitachi 911 autoanalyzer (Roche diagnostics, Basel, Switzerland) while LDL-C was determined directly (Genzyme, Cambridge, Mass.). Non-HDL-C was calculated by subtracting HDL-C from total cholesterol. We categorized all lipid values into quintiles. We further evaluated the association between total cholesterol, LDL-C, and HDL-C based on the Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (ATP III)[29] categories and as continuous terms (in mmol/L).

Ascertainment of stroke

Participants who reported a stroke on a follow-up questionnaire were asked for permission to review their medical records. A diagnosis of stroke was confirmed only after review of the medical records by an Endpoints Committee of physicians, including a Board certified vascular neurologist. A nonfatal stroke was defined as a new focal-neurological deficit of sudden onset and vascular mechanism that lasted >24 hours. Cases of fatal stroke were documented by evidence of a cerebrovascular mechanism obtained from all available sources, including death certificates, autopsy reports, hospital records, family members, or next of kin. Clinical information and results from diagnostic tests including brain imaging were used to distinguish between ischemic, hemorrhagic, and unknown stroke subtype. Furthermore, ischemic stroke were subcategorized into its potential etiologic cause. The inter-observer agreement of the classification of stroke and its major subtypes in the WHS was excellent.[30]

Statistical Analyses

We compared baseline characteristics of participants according to total cholesterol categories. To compare mean response among total cholesterol quintiles, we used analyses of covariance (ANCOVA) adjusting for age. We compared categorical variables adjusting for age using direct standardization. We used Cox proportional hazards models to evaluate the association between the various lipid measures and the risk of ischemic stroke. We calculated age- and multiple-adjusted hazard ratios (HRs) and their corresponding 95% CIs. We made a distinction between two multivariable models: Model 1 controlled for the potential confounding factors age (quadratic term), alcohol consumption (rarely/never, 1-3 drinks/month, 1-6 drinks/week, ≥1 drinks/day), exercise (rarely/never, <1 times/week, 1-3 times/week, ≥4 times/week), smoking (never, past, current <15 cigarettes, current ≥15 cigarettes), body mass index (quartiles), family history of myocardial infarction prior to age 60, current postmenopausal hormone use, history of diabetes, migraine status, and, in addition, for cholesterol lowering medication use and randomized treatment assignments. Because lipid levels have been associated with risk of subsequent risk of hypertension,[31] and thus, hypertension may be a potential biological mediator of the lipid-ischemic stroke association, we additionally controlled for systolic blood pressure categories (10 mm Hg increments) as well as for antihypertensive medication use in a second multivariable model.

We evaluated whether the association between total cholesterol and stroke was modified by age (<55, 55-64, ≥65 years), history of hypertension (yes, no), body mass index (<25, 25-29.9, ≥30 kg/m^2), smoking status (never, past, current), current postmenopausal hormone use (yes,

no), or randomized aspirin assignment that has been shown to reduce the risk of ischemic stroke in the WHS.[27]

We performed all analyses by using SAS statistical software (SAS Institute Inc, version 9.1, Cary, NC) and we calculated *P* for trend across mean values of the lipid quintile categories (P_{trend}). All tests are two-tailed and we considered a $P<0.05$ as significant.

RESULTS

The mean age (SD) of the 27,937 participating women was 54.7 (7.1) years, 94.5% were white, 1.8% black, and 3.7% of other ethnicity. All participants were health care professionals of whom 12.3% had education in licensed practical or vocational nursing, 11.0% had a completed 2-year and 31.6% a 3-year associate registered nursing training, 23.2% had bachelor degrees, 14.8% master degrees, and 5.4% had doctoral degrees.

In Table 1, we summarize the association between total cholesterol quintiles and various baseline characteristics. Compared to women in the lowest total cholesterol quintile (<179 mg/dL [<4.60 mmol/L]), women in the highest quintile (≥244 mg/dL [≥6.31 mmol/L]) had a higher body mass index, higher systolic blood pressure values, were more likely to report a history of hypertension, a history of migraine, a history of diabetes, to be a current smoker, to exercise less, reported more often to have a family history of premature myocardial infarction, were less likely to currently use postmenopausal hormones and more likely to use cholesterol lowering medication.

During a mean of 11 years of follow-up (307,769 person years), a total of 282 ischemic strokes were confirmed, which translates to an incidence rate of ischemic stroke of 9.2 (95% CI, 8.2-10.3) per 10,000 women per year. In age-adjusted analyses, we found strong associations between all lipid level quintiles and risk of subsequent ischemic stroke (Table 2). After additional adjustment for potential confounders and randomized treatment assignments, the effect estimates were attenuated. Compared to women in the lowest quintile, those in the highest quintile had (model 1)-adjusted HRs (95% CIs; *P* for trend across mean values of quintile categories) of ischemic stroke of 2.27 (1.43-3.60; $P_{trend}<0.001$) for total cholesterol; 1.74 (1.14-2.66, $P_{trend}=0.003$) for LDL-C; 0.78 (0.52-1.17, $P_{trend}=0.27$) for HDL-C; 1.65 (1.06-2.58, $P_{trend}=0.02$) for total cholesterol to HDL-C ratio; and 2.45 (1.54-3.91, $P_{trend}<0.001$) for non-HDL-C. Further control for markers of the potential biological mediator hypertension slightly attenuated these risk estimates (Table 2), still leaving significant trends across mean total cholesterol, LDL-C, and non-HDL-C quintiles. We tested for significant deviation from linearity across mean values of cholesterol quintiles and found no violation.

When we categorized lipid values based on the ATP III recommendations,[29] the model 1-adjusted HRs (95% CIs, P for trend across mean values of categories) of ischemic stroke were 1.70 (1.24-2.33; $P_{trend}=0.001$) for total cholesterol ≥240 mg/dL (>6.21 mmol/L) (when compared to total cholesterol <200 mg/dL [<5.17 mmol/L]); 1.59 (1.06-2.39, $P_{trend}=0.003$) for LDL-C ≥160 mg/dL (≥4.14 mmol/L) (when compared to LDL-C <100 mg/dL [<2.59 mmol/L]); and 0.78 (0.54-1.13, $P_{trend}=0.23$) for HDL-C ≥60 mg/dL (≥1.55 mmol/L) (when compared to HDL-C <40 mg/dL [<1.03 mmol/L]). As with quintile categories, additional control for systolic blood pressure and antihypertensive medication use attenuated these estimates, still leaving significant trends across mean ATP III categories for total cholesterol and LDL-C.

When we evaluated lipid levels as continuous measure, a one millimole per liter-unit increase of cholesterol measures (38.7 mg/dL) was associated with a model 1-adjusted HR for ischemic stroke of 1.17 (95% CI, 1.06-1.30; $P=0.003$) for total cholesterol, 1.15 (95% CI, 1.01-1.31; $P=0.029$) for LDL-C, 0.91 (95% CI, 0.64-1.28; $P=0.58$) for HDL-C, and 1.19 (95% CI, 1.07-1.32; $P=0.001$) for non-HDL-C. While there was a significant linear trend for all

continuous cholesterol measures, the association between continuous total cholesterol and ischemic stroke appeared to be curve-linear (*P* value for quadratic term = 0.03), indicating exponentially increasing risk particularly for high total cholesterol values.

We furthermore evaluated which lipid measure is the best statistical predictor of ischemic stroke risk by contrasting a multivariable model (model 1) to a model that additionally included indicator variables for the various lipid measure quintiles, using a 4-degree of freedom likelihood ratio test. The strongest predictive model for ischemic stroke was the model that included non-HDL-C (chi square=24.3, $P<0.001$) followed by the model that included total cholesterol (chi square=15.7, $P=0.004$), and the model that included LDL-C (chi square=14.6, $P=0.006$). All other lipid measures did not significantly improve the prediction of stroke when added to the multivariable model that also included non-HDL-C.

The association between total cholesterol ATP III categories and ischemic stroke was not modified by age ($P_{interaction}=0.43$), smoking status ($P_{interaction}=0.32$), body mass index ($P_{interaction}=0.15$), history of hypertension ($P_{interaction}=0.59$), or randomized aspirin assignment ($P_{interaction}=0.21$). We found effect modification by current postmenopausal hormone use ($P_{interaction}=0.020$), suggesting that women who used postmenopausal hormones did not have increased risk of ischemic stroke with increasing total cholesterol categories.

DISCUSSION

In this prospective cohort of more than 27,000 women free of cardiovascular disease at baseline, all lipid levels were strongly associated with subsequent risk of ischemic stroke after adjusting for age. After additional adjustment for a large number of potential confounders, total cholesterol, LDL-C, the total cholesterol to HDL-C ratio, and non-HDL-C remained significantly associated with increased risk of ischemic stroke. HDL-C was not significantly associated with risk of ischemic stroke after multivariable adjustment, although the point estimate suggested a protective association. We did not find significant effect modification by age, smoking status, history of hypertension, body mass index, or randomized aspirin assignment. On the other hand, the association between total cholesterol and ischemic stroke was modified by postmenopausal hormone use, indicating that the association between total cholesterol and ischemic stroke was only apparent among non-postmenopausal hormone users.

The association between all lipid levels and risk of stroke were attenuated after adjustment for factors that affect lipid levels such as exercise,[32] alcohol consumption,[33] smoking habits,[34] and body mass index.[34] Since these behavioral factors are also risk factors for ischemic stroke,[35] our data may indicate that lipid levels are part of the mechanism by which these factors may increase the risk of stroke. The strong influence of these behavioral factors on HDL-C levels[32-34] may be part of the reason why HDL-C was not strongly associated with the risk of ischemic stroke after multivariable adjustment. Indeed, after excluding these behavioral factors from the multivariable model, HDL-C was significantly associated wit risk of ischemic stroke (data not shown). In addition, postmenopausal hormone use is increasing HDL-C levels[36] and since women who use postmenopausal hormones tend to live a healthier lifestyle[35] this confounding effect may have been further aggravated.

While, with the exception of HDL-C, all lipid measures were associated with risk of ischemic stroke, non-HDL-C was the strongest statistical predictor of ischemic stroke followed by total cholesterol. This is in agreement with two recent studies that have identified non-HDL-C as a strong predictor for coronary heart disease[5] and overall cardiovascular disease.[37] It has been previously shown in the WHS that non-HDL-C is highly correlated ($r=0.87$) with apolipoprotein B_{100}, and both are of equally strength in prediction vascular events.[37] However, with regard to risk detection, non-HDL-C may be preferred since it can be easily calculated by subtracting HDL-C from total cholesterol.

Strengths of our study include the large number of participants and outcome events, long follow-up period and high participation rate, detailed standardized information on many lifestyle factors, validated stroke cases with high interobserver agreement,[30] the reliability of our laboratory assays, as well as the homogenous nature of the cohort which reduces confounding. Furthermore, our analyses were controlled for a large number of confounding factors including migraine that has recently been associated with unfavorable lipid levels[38] and is a risk factor for ischemic stroke.[39]

Several limitations should be considered when interpreting our findings. First, all lipid levels were only measured once and thus intra-individual variability of lipid levels is possible. However, such non-differential misclassification would likely yield to an underestimation of the lipid-ischemic stroke association in this prospective study. Second, although we controlled for cholesterol lowering medication use at baseline, we did not incorporate subsequent use of such medications during follow-up. Third, women who participated in the WHS were all health professionals and mostly white. Thus, generalizability to other populations may be limited. However, we have no reason to believe that the biological mechanisms by which unfavorable lipid profiles may affect ischemic stroke risk differs in other populations. Fourth, despite adjustment for a large number of potential confounding factors, residual and unmeasured confounding remains an alternative explanation because our study is observational.

The association between total cholesterol and risk of ischemic stroke has been investigated in several prior observational studies, of which some found increased risk with increasing cholesterol levels[8-10, 12, 14, 15] and some no clear associations.[11, 18, 20, 25] In a prospective study of over 787,000 Korean civil servants, total cholesterol was strongly associated with increased risk of ischemic stroke. For a 1 mmol (38.7 mg/dL) increase of total cholesterol, the relative risk of ischemic stroke was 1.41 (95% CI, 1.37-1.45) and total cholesterol levels of >4.14 mmol (>160.1 mg/dL) were significantly associated with stroke risk.[15] The Asia Pacific Cohort Studies Collaboration pooled data from 29 cohorts from the Asia-Pacific region and found a 25% increase in the risk of ischemic stroke for every 1 mmol/L (38.7 mg/dL) increase in total cholesterol.[13] The Women's Pooling Project pooled data from 8 cohort studies and found a 23% increase in the relative risk of ischemic stroke for every 1 mmol/L (38.7 mg/dL) increase in total cholesterol among women aged <55 years.[26] In older age groups, however, there was no apparent association between total cholesterol and ischemic stroke. Other studies did not find an association between total cholesterol and ischemic stroke risk.[18-20, 24] This lack of association may be partly explained by evaluating only stroke mortality[18, 19, 24] and by controlling for markers of hypertension,[18, 20, 24] a potential biological mediator by which cholesterol increase ischemic stroke risk.[31]

The association between LDL-C and risk of ischemic stroke has only been evaluated in few studies. A large study of over 11,000 patients with coronary heart disease showed a 14% increase in the relative risk of verified ischemic stroke or transient ischemic attack per 40 mg/dL (1.03 mmol/L) increase in LDL-C.[12] In contrast, a large cohort study of over 14,000 middle-aged men and women found no consistent association between LDL-C and ischemic stroke during 10 years of follow-up.[21]

With regard to HDL-C, several studies found a significant association between HDL-C and ischemic stroke after adjustment for potential confounders.[11, 12, 14, 24, 25] In a large prospective cohort of 7735 men, men in the top fifth percentile of HDL-C (>1.33 mmol/L) had a significant 40% reduction in risk of nonfatal stroke when compared to the lowest fifth percentile.[24] A multiethnic case-control study of elderly individuals showed significant associations between HDL-C and risk of ischemic stroke after confounder adjustment.[25] Compared to participants with HDL-C values of <35 mg/dL (<91 mmol/L), participants with >50 mg/dL (>1.29 mmol/L) had odds ratio of 0.31 (95% CI, 0.21-0.46). The association was

not modified by gender or ethnicity. Overall, the published data strongly suggest that lower HDL-C levels are associated with increased risk of ischemic stroke.

Some studies have suggested that the association between lipid levels and ischemic stroke differs within the ischemic stroke subtypes.[9, 14, 25] In a health insurance-based case-control study, total cholesterol was stronger associated with ischemic strokes of the atherosclerotic and lacunar subtypes.[14] Furthermore, in that study[14] and the previously mentioned case-control study,[25] high HDL-C levels were more strongly associated with the atherosclerotic subtype. In the WHS, total cholesterol appeared also to be more strongly associated with the atherosclerotic and lacunar ischemic stroke subtype (data not shown). However, since the number of outcome events in the ischemic stroke subtype categories was small and the interrater agreement for ischemic stroke subtypes was only moderate,[30] our ability to assess this issue is limited.

Several large randomized trials among individuals with existing or at high risk for cardiovascular disease have shown that lipid lowering therapy with statins results in reduced risk of ischemic stroke.[1-4] The data of the randomized trials, the data of others, and our data strongly support the notion that lipids are a biological risk factor for ischemic stroke and that avoiding unfavorable cholesterol levels may help to prevent ischemic stroke as recommended the primary prevention guidelines of the American Heart Association/American Stroke Association.[40] Our results further underscore the importance of unfavorable lipid levels as risk factor for first ischemic stroke among apparently healthy individuals without prior vascular disease.

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REFERENCES

1. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549–559. [PubMed: 16899775]
2. White HD, Simes RJ, Anderson NE, et al. Pravastatin therapy and the risk of stroke. N Engl J Med 2000;343:317–326. [PubMed: 10922421]
3. Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004;363:757–767. [PubMed: 15016485]
4. Amarenco P, Labreuche J, Lavallee P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke 2004;35:2902–2909. [PubMed: 15514180]
5. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 2005;112:3375–3383. [PubMed: 16316964]
6. Shai I, Rimm EB, Hankinson SE, et al. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women: potential implications for clinical guidelines. Circulation 2004;110:2824–2830. [PubMed: 15492318]
7. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2001;104:1108–1113. [PubMed: 11535564]

8. Iso H, Jacobs DR Jr. 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. [PubMed: 2619783]
9. Benfante R, Yano K, Hwang LJ, Curb JD, Kagan A, Ross W. Elevated serum cholesterol is a risk factor for both coronary heart disease and thromboembolic stroke in Hawaiian Japanese men. Implications of shared risk. Stroke 1994;25:814–820. [PubMed: 8160226]
10. Di Mascio R, Marchioli R, Vitullo F, Di Pasquale A, Cavasinni L, Tognoni G. Serum cholesterol and risk of ischemic stroke: results of a case-control study. On behalf of PROGETTO 3A Investigators. Prev Med 1995;24:128–133. [PubMed: 7597014]
11. Leppala JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP. Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. Stroke 1999;30:2535–2540. [PubMed: 10582974]
12. Koren-Morag N, Tanne D, Graff E, Goldbourt U. Low- and high-density lipoprotein cholesterol and ischemic cerebrovascular disease: the bezafibrate infarction prevention registry. Arch Intern Med 2002;162:993–999. [PubMed: 11996608]
13. Zhang X, Patel A, Horibe H, et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. Int J Epidemiol 2003;32:563–572. [PubMed: 12913030]
14. Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT Jr. Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Neurology 2004;63:1868–1875. [PubMed: 15557504]
15. Ebrahim S, Sung J, Song YM, Ferrer RL, Lawlor DA, Davey Smith G. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. Br Med J 2006;333:22. [PubMed: 16757495]
16. Kagan A, Popper JS, Rhoads GG. Factors related to stroke incidence in Hawaii Japanese men. The Honolulu Heart Study. Stroke 1980;11:14–21. [PubMed: 6444469]
17. Prospective studies collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Lancet 1995;346:1647–1653. [PubMed: 8551820]
18. Blood pressure, cholesterol, and stroke in eastern Asia. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Lancet 1998;352:1801–1807. [PubMed: 9851379]
19. Hart CL, Hole DJ, Smith GD. Risk factors and 20-year stroke mortality in men and women in the Renfrew/Paisley study in Scotland. Stroke 1999;30:1999–2007. [PubMed: 10512898]
20. Bowman TS, Sesso HD, Ma J, et al. Cholesterol and the risk of ischemic stroke. Stroke 2003;34:2930–2934. [PubMed: 14615618]
21. Shahar E, Chambless LE, Rosamond WD, et al. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Stroke 2003;34:623–631. [PubMed: 12624282]
22. Lindenstrom 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. [PubMed: 8044059]
23. Tanne D, Yaari S, Goldbourt U. High-density lipoprotein cholesterol and risk of ischemic stroke mortality. A 21-year follow-up of 8586 men from the Israeli Ischemic Heart Disease Study. Stroke 1997;28:83–87. [PubMed: 8996494]
24. Wannamethee SG, Shaper AG, Ebrahim S. HDL-Cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. Stroke 2000;31:1882–1888. [PubMed: 10926951]
25. Sacco RL, Benson RT, Kargman DE, et al. High-density lipoprotein cholesterol and ischemic stroke in the elderly: the Northern Manhattan Stroke Study. JAMA 2001;285:2729–2735. [PubMed: 11386928]
26. Horenstein RB, Smith DE, Mosca L. Cholesterol predicts stroke mortality in the Women's Pooling Project. Stroke 2002;33:1863–1868. [PubMed: 12105367]
27. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293–1304. [PubMed: 15753114]
28. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294:56–65. [PubMed: 15998891]

29. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497. [PubMed: 11368702]
30. Atiya M, Kurth T, Berger K, Buring JE, Kase CS. Interobserver agreement in the classification of stroke in the Women's Health Study. Stroke 2003;34:565–567. [PubMed: 12574576]
31. Sesso HD, Buring JE, Chown MJ, Ridker PM, Gaziano JM. A prospective study of plasma lipid levels and hypertension in women. Arch Intern Med 2005;165:2420–2427. [PubMed: 16287773]
32. Sagiv M, Goldbourt U. Influence of physical work on high density lipoprotein cholesterol: implications for the risk of coronary heart disease. Int J Sports Med 1994;15:261–266. [PubMed: 7960321]
33. Gaziano JM, Buring JE, Breslow JL, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. N Engl J Med 1993;329:1829–1834. [PubMed: 8247033]
34. Connelly PW, Petrasovits A, Stachenko S, MacLean DR, Little JA, Chockalingam A, Canadian Heart Health Surveys Research Group. Prevalence of high plasma triglyceride combined with low HDL-C levels and its association with smoking, hypertension, obesity, diabetes, sedentariness and LDL-C levels in the Canadian population. Can J Cardiol 1999;15:428–433. [PubMed: 10322252]
35. Kurth T, Moore SC, Gaziano JM, et al. Healthy lifestyle and the risk of stroke in women. Arch Intern Med 2006;166:1403–1409. [PubMed: 16832006]
36. Mackey RH, Kuller LH, Sutton-Tyrrell K, Evans RW, Holubkov R, Matthews KA. Hormone therapy, lipoprotein subclasses, and coronary calcification: the Healthy Women Study. Arch Intern Med 2005;165:510–515. [PubMed: 15767525]
37. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA 2005;294:326–333. [PubMed: 16030277]
38. Scher AI, Terwindt GM, Picavet HS, Verschuren WM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: the GEM population-based study. Neurology 2005;64:614–620. [PubMed: 15728281]
39. Kurth T, Slomke MA, Kase CS, et al. Migraine, headache, and the risk of stroke in women: a prospective study. Neurology 2005;64:1020–1026. [PubMed: 15781820]
40. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37:1583–1633. [PubMed: 16675728]

Table 1

Age-adjusted baseline characteristics according to total cholesterol quintiles in the Women's Health Study (N=27,937).

	Total Cholesterol Quintiles					
	Quintile 1 N=5725	Quintile 2 N=5600	Quintile 3 N=5529	Quintile 4 N=5681	Quintile 5 N=5402	P*
Mean (cut offs), mg/dL†	**159 (<179)**	**190 (179-199)**	**209 (200-218)**	**230 (219-243)**	**274 (≥244)**	
Characteristics						
Mean LDL-C, mg/dL† (SE)	85.4 (0.25)	107.0 (0.25)	122.1 (0.25)	138.3 (0.25)	170.2 (0.26)	<0.001
Mean HDL-C, mg/dL† (SE)	49.1 (0.20)	53.1 (0.20)	54.0 (0.20)	55.2 (0.20)	57.5 (0.20)	<0.001
Mean total cholesterol:HDL-C ratio (SE)	3.5 (0.02)	3.8 (0.02)	4.1 (0.02)	4.5 (0.02)	5.2 (0.02)	<0.001
Mean non-HDL-C, mg/dL† (SE)	110.4 (0.27)	136.5 (0.27)	154.7 (0.27)	175.0 (0.27)	216.4 (0.28)	<0.001
Mean age, years (SE)	52.5 (0.09)	53.8 (0.09)	54.8 (0.09)	56.0 (0.09)	56.5 (0.09)	<0.001
Mean body mass index, kg/m^2 (SE)	25.4 (0.07)	25.7 (0.07)	26.0 (0.07)	26.2 (0.07)	26.4 (0.07)	<0.001
Body mass index ≥30 kg/m^2, %	17.0	16.7	17.4	19.0	20.0	<0.001
Systolic blood pressure, mm Hg (SE)	122.1 (0.18)	122.7 (0.18)	123.9 (0.18)	124.6 (0.18)	125.3 (0.18)	<0.001
Hypertension, %	22.4	22.5	25.3	27.8	28.4	<0.001
Diabetes, %	2.3	2.3	2.6	2.4	3.1	0.005
Smoking, %						<0.001
Never	52.9	52.7	52.5	51.0	48.7	
Past	37.7	36.3	36.1	36.5	36.5	
Current <15 cigarettes	3.8	4.2	4.3	4.6	5.2	
Current ≥15 cigarettes	5.6	6.7	7.1	7.9	9.6	
Alcohol consumption, %						0.13
<1/week	57.9	56.8	57.3	57.5	58.9	
1-6/week	32.2	32.6	32.0	32.6	30.5	
≥1/day	10.0	10.6	10.7	10.0	10.6	
Physical activity, %						<0.001
<1/week	54.6	55.6	57.6	58.0	59.5	
2-3/week	32.4	32.2	31.7	31.6	30.5	
≥4/week	13.0	12.2	10.8	10.4	10.0	
Migraine, %	17.8	17.7	18.4	18.8	19.9	0.001
Family history of MI prior age 60	10.3	12.9	13.0	13.5	15.1	<0.001
Current postmenopausal hormone use, %	51.2	48.3	47.0	46.2	45.8	<0.001
Cholesterol lowering medication use, %	1.6	2.2	3.0	4.1	5.1	<0.001
Randomized aspirin, %	50.4	49.1	49.4	50.9	50.6	0.32

Abbreviations: SE, standard error; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MI, myocardial infarction.

*P values from ANCOVA for continuous or Mantel-Haenszel test for categorical variables.

†To convert cholesterol values to millimoles per liter, multiply by 0.02586.

Table 2

Hazard ratios (HR) and 95% confidence interval (CI) for ischemic strokes (N=282) according to lipid level quintiles in the Women's Health Study (N=27,937)

	No. of events	Incidence rate*	Age-adjusted HR (95% CI)	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
Total Cholesterol (mg/dL)§					
<179	24	3.8	1.00 (referent)	1.00 (referent)	1.00 (referent)
179-199	46	7.5	1.69 (1.03-2.77)	1.69 (1.03-2.77)	1.69 (1.03-2.77)
200-218	53	8.7	1.78 (1.09-2.88)	1.78 (1.10-2.88)	1.74 (1.07-2.82)
219-243	76	12.2	2.20 (1.38-3.49)	2.13 (1.34-3.39)	2.06 (1.29-3.27)
≥244	83	13.9	2.40 (1.52-3.80)	2.27 (1.43-3.60)	2.13 (1.34-3.38)
P for trend//			<0.001	<0.001	0.002
LDL Cholesterol (mg/dL)§					
<96	31	5.0	1.00 (referent)	1.00 (referent)	1.00 (referent)
96-113	45	7.3	1.36 (0.86-2.14)	1.33 (0.84-2.10)	1.33 (0.84-2.11)
114-129	45	7.3	1.19 (0.75-1.89)	1.18 (0.74-1.87)	1.17 (0.74-1.86)
130-150	79	12.9	1.97 (1.30-2.98)	1.92 (1.26-2.92)	1.89 (1.24-2.88)
≥151	82	13.3	1.85 (1.22-2.80)	1.74 (1.14-2.66)	1.68 (1.10-2.57)
P for trend//			<0.001	0.003	0.006
HDL Cholesterol (mg/dL)§					
<41	81	13.2	1.00 (referent)	1.00 (referent)	1.00 (referent)
41-48	53	8.6	0.66 (0.47-0.93)	0.78 (0.55-1.10)	0.79 (0.55-1.13)
49-55	52	8.5	0.66 (0.47-0.94)	0.88 (0.62-1.27)	0.93 (0.64-1.33)
56-64	48	7.8	0.58 (0.41-0.84)	0.78 (0.53-1.14)	0.82 (0.56-1.21)
≥65	48	7.7	0.56 (0.40-0.81)	0.78 (0.52-1.17)	0.82 (0.55-1.23)
P for trend//			0.002	0.27	0.41
Total to HDL cholesterol ratio					
<3.1	32	5.2	1.00 (referent)	1.00 (referent)	1.00 (referent)
3.1-3.6	43	6.9	1.23 (0.78-1.94)	1.22 (0.77-1.94)	1.17 (0.74-1.85)
3.7-4.2	53	8.6	1.42 (0.92-2.21)	1.32 (0.84-2.07)	1.26 (0.80-1.97)
4.3-5.1	67	10.9	1.74 (1.14-2.65)	1.50 (0.96-2.33)	1.42 (0.92-2.22)
≥5.2	87	14.3	2.17 (1.44-3.26)	1.65 (1.06-2.58)	1.49 (0.95-2.33)
P for trend//			<0.001	0.02	0.071
Non-HDL cholesterol (mg/dL)§					
<123	23	3.7	1.00 (referent)	1.00 (referent)	1.00 (referent)
123-144	33	5.3	1.23 (0.72-2.09)	1.18 (0.69-2.02)	1.17 (0.68-1.99)
145-164	65	10.6	2.16 (1.34-3.48)	2.04 (1.26-3.30)	1.97 (1.22-3.18)
165-189	62	10.1	1.92 (1.19-3.12)	1.75 (1.07-2.84)	1.65 (1.01-2.68)
≥190	99	16.2	2.89 (1.83-4.57)	2.45 (1.54-3.91)	2.26 (1.42-3.62)
P for trend//			<0.001	<0.001	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

*Unadjusted incidence rate per 10,000 women per year.

†Model 1 adjusted for age, body mass index, alcohol consumption, exercise, smoking, history of diabetes, family history of myocardial infarction <60 years, treatment for elevated cholesterol, postmenopausal hormone use, migraine status, and randomized treatment assignments.

‡Model 2 adjusts for all variables in model 1 and additionally for systolic blood pressure and antihypertensive treatment.

§To convert cholesterol values to millimoles per liter, multiply by 0.02586.

//P for trend across mean values of quintile categories.