

Cadmium, Carotid Atherosclerosis, and Incidence of Ischemic Stroke

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Background—Exposure to cadmium has been associated with carotid plaques, inflammation in carotid plaques, and increased risk of ischemic stroke. This study examined the separate and interacting effects of blood cadmium levels and carotid plaques on the risk of incident ischemic stroke.

Methods and Results—Cadmium levels were measured in 4156 subjects (39.2% men; mean±SD age 57.3±5.9 years) without history of stroke, from the Malmö Diet and Cancer cohort. The right carotid artery was examined using B-mode ultrasound examination at baseline. Incidence of ischemic stroke was monitored over a mean follow-up of 16.7 years. Carotid plaque was present in 34.5% of participants. Cadmium was significantly higher in subjects with plaque (mean±SD: 0.53±0.58 µg/L versus 0.42±0.49 µg/L; $P<0.001$). A total of 221 subjects had ischemic stroke during the follow-up. Incidence of ischemic stroke was associated both with carotid plaque (hazard ratio 1.44, 95% confidence interval, 1.09–1.90, $P=0.009$) and cadmium (hazard ratio for quartile [Q] 4 versus Q1–3: 1.95, confidence interval, 1.33–2.85, $P=0.001$), after adjustment for risk factors. There was a significant interaction between cadmium and plaque with respect to risk of ischemic stroke ($P=0.011$). Adjusted for risk factors, subjects with plaque and cadmium in Q4 had a hazard ratio of 2.88 (confidence interval, 1.79–4.63) for ischemic stroke, compared with those without plaque and cadmium in Q1 to Q3.

Conclusions—Cadmium was associated with incidence of ischemic stroke, both independently and in synergistic interaction with carotid plaques. This supports the hypothesis that cadmium promotes vulnerability of carotid plaques, thereby increasing the risk of rupture and ischemic stroke. (*J Am Heart Assoc.* 2017;6:e006415. DOI: 10.1161/JAHA.117.006415.)

Key Words: arteriosclerosis • cadmium • incidence • ischemic stroke • plaque

Cadmium is a nonessential metal with toxic, proinflammatory, and carcinogenic effects. The general population is exposed to cadmium through food such as rice, wheat, and potatoes from contaminated agricultural soil; tobacco smoking further increases cadmium exposure.¹ Cadmium has many adverse health effects, including increased risk of cardiovascular disease.^{2,3} A recent study from the population-based Malmö Diet and Cancer study (MDC) reported that cadmium in blood was associated with incidence of cardiovascular diseases, including ischemic stroke. The hazard ratio (HR) for

ischemic stroke in quartile (Q) 4 (≥ 0.50 µg/L) was 2-fold increased.⁴ A study from the United States (the Strong Heart Study) also showed a nonlinear relationship between urinary cadmium and incident stroke, with a HR in Q4 of 1.87 (95% confidence interval [CI], 1.22–2.86), while the risk was not significantly increased in Q2 or Q3.⁵ In addition, another study from the United States reported that blood cadmium level in Q4 (≥ 0.61 mg/L) was significantly associated with prevalence of cardiovascular disease, odds ratio 1.44 (1.07–1.95).⁶

High concentration of blood cadmium is associated with increased prevalence of carotid plaque.^{7,8} A study of 64-year-old women reported relationships between cadmium in blood and urine, respectively, and increased plaque burden, both in cross-sectional and longitudinal analyses.⁷ A relationship between blood cadmium and prevalence of carotid plaque was also observed in the MDC, with significantly increased prevalence of plaque for individuals in the fourth quartile.⁸

The arterial wall is a target organ for cadmium accumulation.⁹ It was shown that cadmium concentration is 50 times higher in symptomatic carotid plaque compared with blood, and concentrations are highest in the plaque areas where ruptures usually occur.¹⁰ Moreover, cadmium has been associated with increased macrophage content in

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Clinical Perspective

What Is New?

- Blood cadmium is a risk factor for incidence of ischemic stroke, and the risk of stroke increases synergistically in the presence of carotid plaque.

What Are the Clinical Implications?

- Cadmium is a toxic element that accumulates in the human body and the impact on public health could be important since many individuals are exposed.
- Exposure to cadmium through diet and smoking should be minimized.
- Blood cadmium could be a marker of plaque vulnerability and risk of stroke.

symptomatic carotid plaque,¹¹ which is a common characteristic of vulnerable carotid plaque.¹² Based on previous research, we hypothesized that high levels of blood cadmium (ie, in the top Q of the distribution), could contribute to ischemic stroke by promoting development of plaques and plaque vulnerability. Our aim was to examine the separate and interacting effects of cadmium and carotid plaques on the risk of incident ischemic stroke.

Methods

During 1991 to 1996, a total of 28 449 men and women from the general population, aged 45 to 73 years, participated in the screening examination of the MDC (participation rate: 41%).^{4,13} The MDC included self-administered questionnaires, physical examination, and blood sampling. A random 50% (n=6103) of those who participated between October 1991 and April 1994 were examined with ultrasound of the right carotid artery. After excluding subjects with history of stroke, and missing information on ultrasound-assessed plaque status in the carotid artery, blood cadmium concentration, and other covariates, a total of 4156 subjects were included in this study. The MDC was approved by the Ethics Committee of Lund University, Lund, Sweden (MDC LU 51-90). All participants gave written informed consent.

As previously reported, participants underwent B-mode ultrasonography (Acuson 128 CT system, Mountain View, CA) of the right carotid artery according to a standardized protocol by trained certified sonographers.^{8,14} In short, the bifurcation area of the right common carotid artery was scanned within a predefined “window” comprising 3 cm of the distal common carotid artery, the bifurcation, and 1 cm of the internal and external carotid arteries, respectively.^{15,16} The presence of carotid plaque was defined as a focal thickening of the intima–media layer >1.2 mm and a plaque area >10 mm².^{8,16}

Intra- and interobserver variation analyses were performed regularly; the mean absolute difference for carotid intimal medial thickness between 2 measurements for the same observer was 9.0% (SD 7.2; $r=0.77$) and between 2 observers was 8.7% (SD 6.2, $r=0.85$).¹⁶

Cadmium was analyzed in erythrocytes using inductively coupled plasma mass spectrometry operating in the helium collision cell mode, as described previously.^{4,8} The imprecision was 9.6%, calculated as the coefficient of variation for 50 duplicate samples (mean 0.43 µg/L). The detection limit was 0.02 µg/L. An interlaboratory comparison on biobanked erythrocytes analyzed at the laboratories of Sahlgrenska and the Department of Occupational and Environmental Medicine, Lund University showed very good agreement (N=20, range 0.20–0.96 µg/L, Pearson’s correlation coefficient=0.99, slope 1.04, SEM 0.04). Cadmium in whole blood was estimated by multiplying Ery-Cadmium with hematocrit.

Follow-Up

All participants were followed up from the baseline examination until first onset of stroke, emigration from Sweden, death, or end of follow-up at December 31, 2010. Incidence of ischemic stroke was ascertained by linkage to the Swedish Hospital Discharge Register and the Stroke Register of Malmö.¹⁷ The diagnosis was validated by review of medical records in 94% of the cases. Information about pathogenetic subtypes of ischemic stroke was available up to 2008. The pathogenetic subtypes were determined by an experienced neurologist.¹⁸

Statistical Analyses

Mann–Whitney *U* test was used to assess the association between plaque and cadmium.

Subjects were categorized into sex-specific quartiles of cadmium (Q1–Q4). Cox proportional hazards regression was used to estimate the HR and 95% CI of incident ischemic stroke in relation to cadmium concentrations, with adjustments for (1) age and sex (model 1); (2) age, sex, waist circumference, smoking status, diabetes mellitus, systolic blood pressure (BP), BP-lowering drugs, low-density lipoprotein, high-density lipoprotein, lipid-lowering drugs, and C-reactive protein (model 2). In addition, we evaluated the joint effect of cadmium and carotid plaque by dividing the cohort into 4 groups according to cadmium (Q4 versus Q1–3) and plaque (yes versus no). The fourth quartile was chosen as cut-off, based on previous population-based studies of cadmium exposure and cardiovascular disease.^{4–6,8} Interactions between cadmium (Q4 versus Q1–3) and carotid plaque were analyzed using a multiplicative interaction term in model 2. An additive model of interaction was also assessed by calculating

relative excess risk because of interaction (RERI) with CIs as described by Andersson et al.¹⁹ RERI is defined as

$$\text{RERI} = \text{RR}_{ab} - \text{RR}_a - \text{RR}_b + 1,$$

where RR denote the relative risks for those with risk factor a, b, or both risk factors. If RERI=0 this indicates no additive interaction.

Furthermore, the pathogenetic subtypes of ischemic stroke were studied in relation to cadmium and carotid plaque. The association between incident ischemic stroke and cadmium level was also assessed using restricted cubic splines with 4 knots of blood cadmium, adjusted for sex and age, for those with plaque and those without plaque. An additional cubic spline was made to explore cadmium level and plaque. $P < 0.05$ was considered statistically significant. SPSS Statistics version 23.0 was used.

Results

Carotid plaque was present in 34.5% of participants. Cadmium was significantly higher in subjects with carotid plaques (mean±SD 0.53±0.58 µg/L) compared with those without plaques (0.42±0.49 µg/L, $P < 0.001$). The prevalence of plaque was 30.1%, 30.6%, 34.6%, and 42.8%, respectively, for subjects with cadmium in the first (lowest), second, third, and fourth quartiles. The restricted cubic spline model of plaque across cadmium levels, adjusted for age and sex, is shown in Figure 1A.

A total of 221 subjects were diagnosed with ischemic stroke during a mean follow-up of 16.7±3.5 years. Cadmium was significantly associated with ischemic stroke adjusted for age and sex. This association remained significant (HR: 1.66; 95% CI, 1.01–2.72) after adjustment for risk factors (Table 1). The restricted cubic spline model of incident ischemic stroke across cadmium levels, adjusted for age and sex is shown in

Figure 1B and 1C. Incidence of ischemic stroke was not linear across the cadmium level. Especially for individuals with carotid plaque, those in the fourth quartile of blood cadmium showed an increase risk of ischemic stroke. Plaque was also associated with ischemic stroke, after adjustments for risk factors (model 2) (HR: 1.47; 95% CI, 1.12–1.94, $P = 0.006$). When cadmium and plaque were simultaneously adjusted in model 2, both of them were significantly associated with ischemic stroke (cadmium [Q4 versus Q1–3]: HR: 1.95; 95% CI, 1.33–2.85, $P = 0.001$; plaque: HR: 1.44; 95% CI, 1.09–1.90, $P = 0.009$). Subjects with plaque and cadmium in the top quartile had the highest risk of ischemic stroke (HR: 2.88; 95% CI, 1.79–4.63, $P < 0.001$), compared with those without plaque and cadmium in Q1 to Q3, after adjustment for risk factors (Table 2, Figure 2).

The interaction between carotid plaque and high cadmium (Q4) was tested by a multiplicative interaction term in the Cox model. The interaction term was significant ($P = 0.011$), indicating a stronger effect of cadmium in subjects with plaque, with respect to incidence of ischemic stroke. RERI was calculated to assess interaction based on assumptions of additive risks. The risk associated with carotid plaque and high cadmium was significantly higher than expected from risk addition (adjusted for age and sex; RERI: 1.78; 95% CI, 0.78–2.77; adjusted in model 2; RERI: 1.49, 95% CI, 0.33–2.65).

Information on subtypes of ischemic stroke was available for 165 cases; large-artery atherosclerosis ($n = 27$), cardioembolism ($n = 37$), small-artery occlusion ($n = 59$), and undetermined ($n = 42$). After adjustment for age, sex, and smoking status, subjects with plaque and cadmium in Q4 had a HR of 4.94 (95% CI, 1.38–17.72, $P = 0.014$) for the large-artery atherosclerosis subtype, compared with those without plaque and cadmium in Q1 to Q3. The corresponding HRs for the small-artery occlusion and cardioembolic subtypes were 2.26

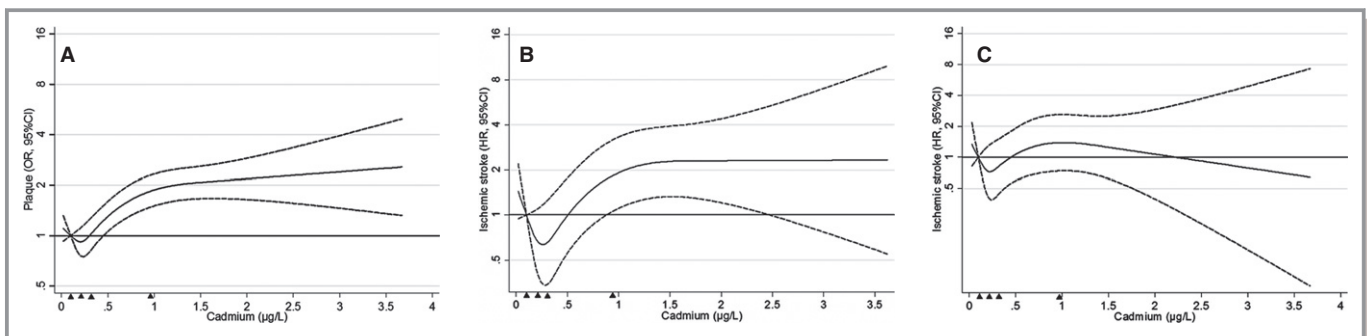


Figure 1. A, Restricted cubic spline model for prevalence of plaque across cadmium levels, Odds ratio adjusted for age and sex. B, Restricted cubic spline model of incident ischemic stroke across cadmium levels, Hazard ratio adjusted for age and sex among those with plaque. C, Restricted cubic spline model of incident ischemic stroke across cadmium levels, Hazard ratio adjusted for age and sex among those without plaque. Triangles indicate median cadmium concentrations for Q1 to Q4 (Q1: 0.13 µg/L; Q2: 0.21 µg/L; Q3: 0.33 µg/L; Q4: 0.97 µg/L). CI indicates confidence interval; HR, hazard ratio; OR, odds ratio; Q, quartile.

Table 1. HR (95% CI) of Incident Ischemic Stroke in Relation to Cadmium in Q (n=4156)

	Q1	Q2	Q3	Q4	P Value, Q4 vs Q1
N	1038	1040	1040	1038	
Cadmium, $\mu\text{g/L}$ (men/women)	0.04 to 0.15/0.02 to 0.18	0.15 to 0.23/0.18 to 0.27	0.24 to 0.47/0.27 to 0.49	0.47 to 5.07/0.49 to 4.83	
Ischemic stroke n (n/1000 py)*	47 (2.66)	46 (2.61)	48 (2.73)	80 (4.84)	
Model 1	1.00	0.86 (0.57–1.30)	0.87 (0.58–1.30)	1.91 (1.33–2.74)	<0.001
Model 2	1.00	0.91 (0.60–1.37)	0.84 (0.56–1.28)	1.66 (1.01–2.72)	0.040

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, waist circumference, smoking status, diabetes mellitus, blood pressure (BP), BP-lowering drugs, low-density lipoprotein, high-density lipoprotein, lipid-lowering drugs, and C-reactive protein. CI indicates confidence interval; HR, hazard ratio; Q, quartile.

*Number of cases (incidence per 1000 person-years).

(95% CI, 1.01–5.07, $P=0.048$) and 2.41 (95% CI, 0.81–7.17, $P=0.114$), respectively.

Sensitivity Analysis

In a sensitivity analysis, we excluded 25 subjects who had been diagnosed with atrial fibrillation before the baseline examinations. The results were essentially identical and there was still a significant multiplicative interaction term between cadmium and plaque with respect to incidence of ischemic stroke ($P=0.008$).

Discussion

Cadmium has proatherogenic effects as shown in experimental and clinical studies.^{7,8,11,20, 21} Atherosclerotic plaque is a known risk factor for ischemic stroke, and inflammation in the plaque is a critical mechanism for plaque rupture.^{7,8,22} Previous studies from the MDC and other cohorts have reported relationships between cadmium in blood and cardiovascular disease, including carotid plaque.^{4–6,8} The

present results show that cadmium and carotid plaque were associated with risk of future ischemic stroke in a synergistic manner. Since the whole population is exposed to cadmium through the diet and cadmium is eliminated very slowly from the human body, this observation could have important implications for public health.

The blood vessels have been identified as a target organ for cadmium accumulation.⁹ Cadmium has been associated with pro-inflammatory effects, both in experimental and human studies.²³ An in vitro study showed increased necrosis and apoptosis in macrophages exposed to cadmium, even at low environmental concentration.²⁴ It has been shown that cadmium inhibits fibroblast proliferation and collagen synthesis in vascular muscle cells.²⁵ These effects could potentially reduce the stability of carotid plaque. Experimental studies have also shown that cadmium can impair the endothelial function at cadmium concentrations that are below the reference values.²⁶ Even though causality cannot be proven in this study, there are several adverse effects of cadmium that potentially could increase the risk of stroke.

Table 2. Incidence of Ischemic Stroke in Relation to Categories of Cadmium (Q4 vs Q1–3) and Prevalence of Carotid Plaque (No Plaque or Plaque) (n=4156)

	Q1 to Q3/No Plaque	Q4/No Plaque	Q1 to Q3/Plaque	Q4/Plaque
N	2127	595	990	444
Ischemic stroke n (n/1000 py)*	80 (2.20)	23 (2.32)	61 (3.68)	57 (8.62)
Model 1 [†]	1.00	1.35 (0.85–2.13)	1.26 (0.90–1.76)	3.39 (2.40–4.76)
Model 2 [†]	1.00	1.25 (0.72–2.17)	1.14 (0.81–1.60)	2.88 (1.79–4.63)
Model 1 [‡]	1.00	2.62 (1.83–3.77)
Model 2 [‡]	1.00	2.41 (1.37–4.23)

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, waist circumference, smoking status, diabetes mellitus, blood pressure (BP), BP-lowering drug, low-density lipoprotein, high-density lipoprotein, lipid-lowering drug, and C-reactive protein. CI indicates confidence interval; HR, hazard ratio; Q, quartile.

*Number of cases (incidence per 1000 person-years).

[†]HR (95% CI) for incident ischemic stroke using Q1 to Q3 and no plaque as a reference in a comparison to all other combinations of Q1 to Q3, Q4, and plaque prevalence.

[‡]HR (95% CI) for incident ischemic stroke comparing cadmium in Q4 vs Q1 to Q3 in individuals with plaque.

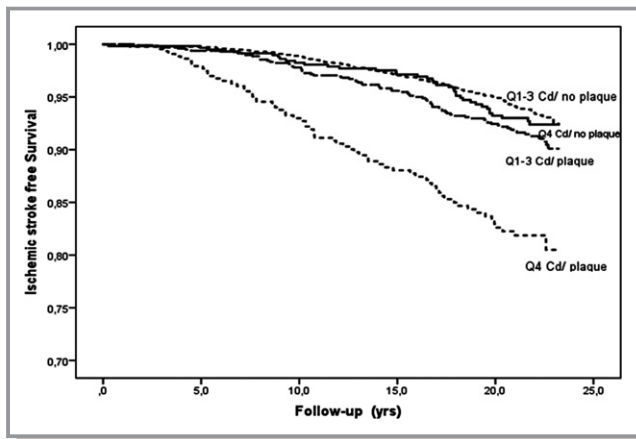


Figure 2. Incident ischemic stroke in relation to cadmium (Q4 vs Q1–3) and carotid plaque (yes/no) (n=4156).

The cohort was followed over a long time period by linkage with local and national registers. Ninety-four percent of the stroke cases were confirmed by review of hospital records. The numbers for the pathogenetic subtypes were small and the results for specific subtypes must be interpreted with caution. However, both large-artery atherosclerosis and small-artery occlusion seem to be associated with presence of plaque and high cadmium. The result for cardioembolic stroke tended to be higher for subjects with plaque and cadmium in Q4. This was a nonsignificant finding that should be interpreted with caution. However, cadmium is a risk factor for heart failure,²⁷ which is a possible cause for cardioembolic stroke. Also, it has been shown that plaque and intima-media thickness are risk factors for atrial fibrillation.²⁸

The association between cadmium and risk of ischemic stroke was only found in the highest cadmium Q (blood cadmium >0.5 µg/L), indicating that there is a threshold. This is consistent with previous studies showing no increased risk of ischemic stroke below this cadmium level.⁶

The ultrasound measurements were performed during 1991 to 1994 as part of a large population-based cohort study according to standardized protocol by trained certified sonographers. Only the right carotid artery was examined, which is a limitation. However, since the number of end points is crucial for prospective studies, the number of participants was prioritized during the screening examination. The relationship with incidence of stroke is largely the same in this cohort, compared with studies with ultrasound assessment of both carotid arteries.²⁹ Carotid plaque was defined as an intima-media thickness protrusion of at least 1.2 mm, which is somewhat less than the definition that later was proposed by the Mannheim consensus group (ie, ≥1.5 mm).³⁰

Some risk factors could have changed during the long follow-up period. Smoking is known to increase cadmium exposure and even though we adjusted for smoking status, it

is important to acknowledge that there could still be residual confounding. We did not have complete information on pack-years, which is a limitation. Cadmium is eliminated very slowly from the human body, with a half time of decades.³ However, even though blood cadmium is a valid measure of the body burden and long-term exposure as long as dietary and smoking habits are stable, blood cadmium is reduced after, for example, smoking cessation.

Conclusions

Cadmium was associated with incidence of ischemic stroke, both independently of and in synergistic interaction with carotid plaques. This finding supports the hypothesis that cadmium promotes vulnerability of carotid plaques, thereby increasing the risk of rupture and ischemic stroke.

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Disclosures

None.

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