Review of cadmium exposure and smoking-independent effects on atherosclerotic cardiovascular disease in the general population

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Abstract

Exposure to cadmium (Cd) via food and smoking is associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). Blood and urine levels of Cd are established biomarkers of exposure. Our aim was to review: 1) the smoking-independent associations between Cd exposure and ASCVD, including the possible presence of a non-linear dose-response relationship with Cd exposure; and 2) the causal effects of Cd exposure on different stages of atherosclerosis.

The results indicate that Cd confers increased risk of ASCVD and asymptomatic atherosclerosis in the carotid and coronary arteries above B-Cd >0.5 μg/L or U-Cd >0.5 μg/g creatinine, but it has not been shown below a threshold of these exposure levels. Adjustment for smoking does not exclude the possibility of residual confounding, but several studies in never-smoking cohorts have shown associations between Cd and ASCVD, and experimental studies have demonstrated pro-atherosclerotic effects of Cd.

Cd accumulates in arterial walls and atherosclerotic plaques, reaching levels shown to have proatherosclerotic effects. Suggested early mechanisms are increased subendothelial retention of atherogenic lipoproteins, which become oxidized; endothelial dysfunction and damage with increased permeability for monocytes, which in the intima turn to macrophages and then to foam cells. Later, Cd may contribute to plaque rupture and erosion by endothelial apoptosis and degradation of the fibrous cap. Finally, by having prothrombotic and antifibrinolytic effects, the CVD risk may be further increased.

In summary, there is strong evidence that Cd causes ASCVD above a suggested exposure level via mechanisms in early, as well as late stages of atherosclerotic disease.

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Introduction

Atherosclerotic cardiovascular diseases (ASCVD) encompass coronary heart disease, cerebrovascular ischemic strokes, aortic aneurysm, and lower limb ischemia. Ischemic coronary heart disease and stroke are the top two causes of death and disability in those above 50 years of age in the world population (1). In affluent countries, the incidences of ischemic heart disease and stroke have been dramatically reduced by preventive measures and improved health care, but these diseases are still major causes of death and disability (2).

Atherosclerosis is a vascular disease, located in the subintimal space at predilection sites in the arterial vascular tree with the atherosclerotic plaque as the key lesion. Age is the predominant risk factor, and the majority of men aged over 60 have atherosclerosis in the coronary and carotid arteries, though the prevalence in women is lower (3). A minority of these plaques will lead to overt clinical disease, mainly by being transformed into vulnerable lesions which may rupture or in some other way cause blood clots with ensuing ischemic damage to the end organ (4). The major risk factors for atherosclerotic heart disease are hyperlipidaemia, hypertension, tobacco smoking, and diabetes, reflecting influences of heredity, socioeconomic factors, and lifestyle.

In the past decade, exposure to cadmium (Cd) has emerged as a candidate risk factor for cardiovascular disease (CVD), as summarized in several previous reviews [5-8]. However, it is still unclear to what extent this is independent of tobacco smoking, as the latter is both an important source of Cd and a potent cardiovascular risk factor.

The aim of this review is two-fold. In Part I we review the smoking-independent associations between Cd, measured in blood or urine, and ASCVD. We also investigate the possibility of a non-linear dose-response relationship, with Cd exposure showing a threshold effect above which there is an increase in risk. In Part II we review human, animal, and experimental studies which have investigated causal effects of Cd exposure on different stages of atherosclerotic disease. Finally, we summarize the evidence for Cd as a risk factor for ASCVD.

Cadmium

Cd is a persistent non-essential toxic metal which has adverse health effects at both occupational and environmental exposure levels. The most well-known toxic effects are kidney damage and osteoporosis/osteomalacia [9, 10]. In addition, Cd is carcinogenic [10, 11] and can cause emphysema, at least at occupational exposure [10].
Human exposure to Cd is ubiquitous, and the main exposure sources are food and tobacco smoke. Cd is present in agricultural soil, both as a natural background and increased by phosphate fertilizers. In non-smoking populations, various crops such as rice, wheat, vegetables, and potatoes usually account for the main part of the intake. In Europe and North America, the average intake of Cd is between 10 and 20 µg/day [10, 12]. Intestinal uptake of dietary Cd is about 5–10%, and is typically higher when iron stores are low, since absorption is mediated by divalent metal transporters [10]. Dietary Cd exposure is therefore usually higher in menstruating than in non-menstruating people. Tobacco smoking further increases Cd exposure, as Cd in tobacco smoke is effectively absorbed (about 50%) in the lungs. Smoking of ten cigarettes results in inhalation of 1–2 µg of Cd.

Cd accumulates mainly in the kidneys (about 50%), liver, and muscles. High concentrations are also found in erythrocytes, while concentrations in plasma are very low. There is no efficient excretion mechanism of Cd; only small amounts are excreted in urine. Elimination is therefore very slow, with a half-life of 10–40 years.

Cadmium in blood (B-Cd) and/or urine (U-Cd) is widely used for biological monitoring [10, 13]. Since Cd excretion in urine is proportional to the Cd in the kidney, U-Cd can be used as a biomarker for the body burden of Cd [14]. B-Cd also reflects the body burden at steady state, but changes faster following altered exposure, for example after smoking cessation. Current smokers have about twice as much Cd in the kidney and urine as never-smokers, and 3–4 times as much B-Cd [15-17].

PART I. Epidemiological studies on cadmium and atherosclerotic cardiovascular diseases

Four comprehensive systematic reviews and meta-analyses have been published on Cd exposure as a risk factor for CVD in the general population [5-8]. Some of them also presented separate results for ASCVD, as summarized in Table 1. Another recent review only included US studies [18].

A review of occupational risk factors for CVD [19] included six studies of occupational exposure to Cd [20-25]. None of them adjusted the analyses for smoking habits, and so they are not commented on here.

Since one focus in the present review is on dose-response, we did not include two large studies on dietary exposure [26-27]. The contrast in estimated dietary intake was low, and the partial Pearson correlation coefficient between the dietary Cd estimate and measured U-Cd in a subsample of never-smokers was only 0.1 [28]. Regarding studies based on U-Cd, we only included studies which were able to adjust for diuresis. Therefore a study in Australian women [29] based on very dilute samples not adjusted for creatinine was not considered.

Coronary heart disease

Studies with adjustment for smoking habits

Nine of the studies included in reviews of Cd and CVD in the general population reported associations between Cd exposure and coronary heart disease (CHD). All of them adjusted the risk estimates for smoking habits. Six of the studies were longitudinal [17, 26, 27, 30-32] and three were cross-sectional [33-35]. In the time since the reviews by Tinkov et al. [8] and

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Chowdhury et al. [7] were conducted, one cross-sectional study [36] has been published. The studies are summarized in Table 2.

The previous reviews and meta-analyses additionally included studies with a broader disease concept of CVD, including for example hypertension, heart failure, or cardiac arrhythmia [37-40]. CVD was also investigated in a recent study by Domingo-Relloso et al. [41].

Among the four longitudinal studies, the two studies based on the National Health and Nutrition Examination Survey (NHANES) from the USA showed positive associations between CHD and increasing U-Cd [30, 31], but in one of them [30] only in men. The Strong Heart study [32] reported a significant positive association between U-Cd and CHD incidence. In the Swedish Malmö Diet and Cancer Study (MDCS) data set [17], a significant positive association was found between B-Cd and acute coronary events.

Three of the cross-sectional studies [33-35] found a positive association between blood or urine Cd and CHD, while this was not the case in the study by Jeong et al. [36]. Thus, most studies have shown a positive association with occurrence of CHD, in agreement with the recent meta-analyses [7, 8].

Overall, the abovementioned studies provide strong support for associations between Cd exposure and risk of CHD after adjustment for smoking status. However, adjustment for smoking status (never, former, or current smoking) is not perfect. Within the categories of current smokers and former smokers who had recently given up smoking, those with a high consumption of cigarettes could be expected to have both higher levels of Cd in blood and urine and a higher risk of CHD than those with a low consumption. On the other hand, adjustment for smoking might assign part of the risk of inhaled Cd to smoking. Recent reports using mediation analysis suggest that Cd in cigarette smoke can explain a substantial part of the risk of ASCVD from smoking [42, 43].

### Studies in never-smokers

One way of avoiding residual confounding from smoking is to perform stratified analyses in never-smokers. This was the chosen method in four of the studies reviewed above using Cd in blood or urine [17, 32, 33, 35], and in a recent large Danish study including only never-smokers [44]. In three of the studies, the risk of CHD in never-smokers was increased in the highest exposure categories (Table 2).

### Dose-response

Taken together, the dose-response data based on Cd in blood or urine provide no support for an association between Cd exposure and risk of CHD at low-level exposure (B-Cd <0.5 µg/L or U-Cd <0.5 µg/g creatinine (µg/gC)). This was based mainly on the large Danish study in never-smokers [44] and the lack of an association at lower B-Cd categories reported in two studies [17, 35].

When comparing somewhat higher levels of Cd in blood and urine (B-Cd >0.5 µg/L or U-Cd >0.5 µg/gC) with low-level reference categories, there was strong support for a positive association in all studies [17, 31-33, 35]. This includes both the smoking-adjusted studies and the studies in never-smokers, with the exception of the study by Menke et al. [30], which showed an association only in men. A limitation is the relatively low numbers of never-smokers in the high exposure categories. The two Korean studies [34, 36] reported...
overall high B-Cd. The study by Lee et al. [34] had a GM of 1.5 µg/L, but very few individuals with B-Cd <0.5 µg/L. The reference category in the study by Jeong et al. [36] included all individuals with B-Cd below the 90th percentile, which was 1.9 µg/L. Therefore, these two studies, which showed conflicting results, cannot be used in the assessment of dose-response.

Stroke

Studies with adjustment for smoking habits

The abovementioned systematic reviews and meta-analyses on Cd and CVD [5-8] included six studies on stroke which were adjusted for smoking habits and based on B-Cd or U-Cd. Three of the studies were cross-sectional [34,35, 38] and three were longitudinal [17, 32, 37]. In the time since the reviews by Tinkov et al. and Chowdhury et al. [7-8] were conducted, one more cross-sectional study [36] has been published. The studies are summarized in Table 3.

Among the longitudinal studies, the Strong Heart study [32] and the Swedish MDCS study [17] found significant positive associations between U-Cd or B-Cd and stroke, while this was not the case in the CadmiBel study [37]. However, the latter was very small (21 cases). Three of four cross-sectional studies [35-36, 38] found positive associations between blood or urine Cd and stroke, while one study [34] found no association.

Considering that the Belgian study was very small, the studies based on Cd in blood and urine generally show a positive association with occurrence of stroke, in agreement with the recent meta-analyses [7-8]. Overall, the abovementioned studies provide strong support for associations between Cd exposure and risk of stroke after adjustment for smoking status.

Studies in never-smokers

In never-smokers (Table 3), only one of the longitudinal studies [17] showed an association between Cd exposure and stroke, while the Strong Heart study [32], and the large Danish study [45] showed no such association. The two cross-sectional studies [35, 38] did not provide substantial support for an association. Overall, these studies provide little support for associations between Cd exposure and risk of stroke in never-smokers.

Ischemic stroke versus cerebral haemorrhage

In studies where ischemic and haemorrhagic stroke were separated [17, 45], the risk estimates were very similar for ischemic stroke and total stroke. This is to be expected, since a large majority of stroke cases are ischemic.

Dose-response

Taken together, the dose-response data based on Cd in blood or urine provided no support for an association between Cd exposure and risk of stroke at low-level exposure (B-Cd <0.5 µg/L or U-Cd <0.5 µg/gC). This was based mainly on the large Danish study in never-smokers [45] and the lack of an association at lower B-Cd categories in the studies by Barregard et al. [17] and Hecht et al. [35].

When comparing somewhat higher levels of Cd in blood and urine (B-Cd >0.5 µg/L or U-Cd >0.5 µg/gC) with low-level reference categories, there was strong support for a positive association in the smoking-adjusted studies [17, 32, 35, 38] and the studies of never-smokers, with the exception of the study by Tellez-Plaza et al. [32]. A limitation is that there

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were relatively few never-smokers in the high exposure categories. For reasons mentioned in the section on CHD, the two Korean studies [34, 36] could not be used in the assessment of dose-response.

**Peripheral artery disease**

**Studies with adjustment for smoking habits**

The review by Tinkov et al. [8] included three studies of peripheral artery disease (PAD) based on the US NHANES 1999–2004 [46], the Strong Heart Study [47], and a study in Swedish women [48]. The findings from NHANES 1999–2004 have also been presented by Zhuang et al. [49] and in part (NHANES 1999–2000) by Navas-Acien et al. [50, 51]. In addition, a letter by Ujueta et al. [52] reports that in 43 clinical patients with CHD, U-Cd was higher in the 22 patients with PAD than in the 21 patients without PAD.

Overall, the abovementioned studies, which are summarized in Table 4, provide strong support for an association between Cd exposure and risk of PAD after adjustment for smoking status.

**Studies in never-smokers**

In never-smokers, only the two US studies [46, 47] had enough cases of PAD to allow separate analyses of never-smokers. The odds ratios were above 1, but with very wide confidence intervals. We conclude that the data in never-smokers are insufficient for an assessment of a possible association between Cd exposure and risk of PAD.

**Dose-response**

Taken together, the dose-response data based on Cd in blood or urine provided no support for an association between Cd exposure and risk of PAD at low-level exposure (B-Cd <0.5 µg/L or U-Cd <0.5 µg/gC), given the lack of associations in the lower B-Cd or U-Cd categories in the abovementioned studies. At levels of B-Cd >0.5 µg/L or U-Cd >0.5 µg/gC, the comparison with lower reference categories showed relatively strong support for associations with the risk of PAD.

**Aortic aneurysm**

We found only one study examining the association between Cd exposure and aortic aneurysm [53]. In a Swedish case-control study with 297 cases of abdominal aortic aneurysm (AAA) and 594 controls, after adjustment for smoking and other risk factors the OR for AAA was 2.5 (95% CI 1.3–5.0) in the upper tertile of B-Cd (>0.3 µg/L) compared with the first tertile (<0.17 µg/L). There were only 24 cases of AAA in never-smokers and no association with B-Cd. This single study does not provide sufficient information for conclusions on Cd and aortic aneurysm.

**Asymptomatic atherosclerosis in carotid or coronary arteries**

The review by Tinkov et al. [8] included one study on carotid artery intima-media thickness (cIMT) [54], two studies from Sweden of carotid artery plaque [55-56], and another Swedish study of both plaque and cIMT [57]. After this review was conducted, Lin et al. [58] published a study on cIMT in young (12–30 years) Taiwanese individuals. In addition, the first study of coronary artery atherosclerosis (estimated as coronary artery calcium score [CACS]) was published recently [59].
Studies with adjustment for smoking habits

Most of the studies with adjustment for smoking habits showed significant associations with carotid artery plaque or cIMT. Since a large cIMT may have explanations other than atherosclerosis [60], we focused on the studies which measured plaque – the hallmark of atherosclerotic disease. Two of them showed positive associations with B-Cd [55, 56] while one of them did not [57]. The coronary arteries were only investigated (using CACS) in one study, which showed a significant association with B-Cd in smoking-adjusted analyses [59].

Overall, these studies, which are summarized in Table 5, provide relatively strong support for associations between Cd exposure and risk of atherosclerosis in carotid and coronary arteries after adjustment for smoking status.

Studies in never-smokers

None of the studies of carotid artery plaque showed any association with B-Cd in never-smokers [55-56]. The single study of coronary arteries showed an association between B-Cd and high calcium score in never-smokers, but this was based on relatively few individuals. Therefore, studies in never-smokers provide only limited support for associations between Cd and asymptomatic atherosclerosis.

Dose-response

Taken together, the dose-response data based on Cd in blood or urine provided no support for an association between Cd exposure and risk of carotid or coronary artery atherosclerosis at low-level exposure (B-Cd <0.5 µg/L), based on the lack of associations in the lower B-Cd categories in the abovementioned studies.

At levels of B-Cd >0.5 µg/L or U-Cd >0.5 µg/g C, the comparison with lower reference categories showed relatively strong support for associations with the risk of carotid or coronary artery atherosclerosis (Table 5).

Chelation of toxic metals

The excretion of metals can be increased by various chelating agents, and has been tested long ago as a treatment for lead poisoning. A review by Lamas et al. [61] included an interesting randomized clinical trial among patients with previous myocardial infarction, in which treatment with edetate disodium for about two years reduced the incidence of cardiovascular events, including myocardial infarction and stroke, especially in patients with diabetes. This reduction may have been caused by chelation of lead and/or Cd, or by other constituents of the chelator.

Part II. Cadmium and atherosclerotic cardiovascular diseases: underlying mechanisms

ASCVD is preceded by the gradual development of atherosclerosis from early to complicated lesions (See Supplement: Atherosclerosis, Box 1 Early atherosclerosis, lipid retention for background).

Cadmium in initiation and progression of atherosclerosis

Cadmium toxicity
Cadmium inactivates sulphhydryl groups of enzymes, causes oxidative stress, epigenetic changes, damages to DNA and mitochondria leading to cell death and interferes with calcium signaling (See Supplement for details).

Cadmium and hyperlipidaemia

The response-to-retention hypothesis, which conjectures that the key initiating event in atherosclerosis is the retention of cholesterol-rich apoB-containing lipoproteins within the arterial wall, is also linked to hyperlipidaemia as a source of an excess of lipoprotein particles [62]. Data from human studies of general populations and cohorts with high exposures to Cd, in combination with results from animal and experimental studies support the hypothesis that Cd exposure can contribute to hyperlipidaemia with increased concentrations of triglycerides, total and low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol. Cd has direct and indirect effects on cholesterologenic enzymes and hepatic lipogenesis in animal studies (See Supplement and Table S2). The close relationship between smoking and Cd-exposure makes it difficult to clarify the association between higher Cd doses and lipid levels because of residual confounding. But animal studies clearly show how Cd exposure is accompanied by hyperlipidaemia.

Cadmium and lipid retention

ApoB-rich lipoproteins are bound to proteoglycans in the arterial subintimal matrix (See Supplement Box 2 for background).

When cultured bovine vascular smooth muscle cells were exposed to Cd chloride at noncytotoxic levels (0.2 µM or less), there was an increased accumulation of the small proteoglycans biglycan and decorin in vascular smooth muscle cells [63]. Moreover, cultured bovine aortic endothelial cells showed increased numbers of heparin sulphate proteoglycan molecules after addition of Cd chloride at 2.0 µM [64]. In apoB100 transgenic mice, intimal hyperplasia in the carotid arteries was surgically induced and a Cd-containing gel was applied at non-toxic concentration [65]. In comparison with controls, gene expression analysis of the carotid arteries after two weeks showed that Cd treatment increased expression of genes encoding the proteoglycan perlecan and a proteoglycan modifying enzyme. Importantly, apoB staining was significantly increased in carotid arteries from the mice exposed to Cd compared to controls. These results provide direct experimental evidence that Cd promotes subendothelial retention of atherogenic lipoproteins.

Hence, there is clear support for the hypothesis that Cd exposure has proatherosclerotic effects on proteoglycans and retention of LDL cholesterol, but more studies are warranted.

Cadmium and oxidation of LDL cholesterol

A key driver of inflammation in atherosclerosis is oxidized LDL cholesterol and oxidative stress is a key mechanism in Cd toxicity. The question is whether Cd can contribute to oxidative modifications of lipoproteins.

Wistar rats exposed for six months to Cd in drinking water at doses corresponding to those in human exposure showed dose-dependent increases in oxidized LDL [66]. Concomitant antioxidant treatment with zinc prevented this oxidation. Similar results were obtained in another study of Wistar rats exposed to Cd, resulting in a proatherosclerotic serum lipid profile, reduced levels of antioxidant enzymes, and an increase of malondialdehyde as a
measure of lipid peroxidation. Added antioxidant polyphenols attenuated the Cd-induced dyslipidaemia and indicators of oxidative stress [67].

Supporting data also exist in humans. Women with high levels of B-Cd (>5µg/L vs. <5µg/L) showed clear indication of oxidative stress in terms of increased plasma levels of malondialdehyde [68]. In a population study, U-Cd was associated with the same and other markers of oxidative stress [69]. Hence, these data support an association between Cd exposure and oxidation of LDL cholesterol.

A tentative mechanistic link is paraoxonase 1 (PON1). This is a Ca^{2+}-dependent HDL-associated enzyme that protects low-density lipoprotein (LDL) from oxidation through hydrolysis of lipid peroxides [70-71]. A meta-analysis showed that coronary heart disease is associated with 19 percent lower serum PON1 activity than in controls [72]. PON1-null mice were more susceptible to atherosclerosis than wild-type littermates and had LDL that was highly susceptible to oxidation [73]. PON1 is inhibited by oxidative stress, and in vitro studies as well as human studies have shown that Cd, as a cause of oxidative stress, is associated with lower PON1 activity [74-76].

**Cadmium accumulation in arterial wall and effects on the endothelial cell viability**

As shown in Table 6, the content of Cd in the human abdominal aorta at upper-middle-age and above ranges from 1.78 to 7 µM [77, 78]. In symptomatic carotid plaques, Cd levels were 0.34 µM on average, and correlated with blood Cd [79]. Thus, B-Cd accumulates in lesion-prone arterial walls and in atherosclerotic plaques, reaching concentrations similar to those found to be associated with proatherosclerotic mechanisms in experimental studies [80, 81].

Cd is known to injure vascular endothelial cells and alter vascular permeability. One underlying mechanism is that at non-cytotoxic concentrations of 10–100 nM, Cd can inhibit chemotaxis and tube formation in vascular endothelial cells. These effects on repair and angiogenesis seem to be mediated through disruption of vascular endothelial cadherin, a Ca^{2+}-dependent cell adhesion molecule [82, 83]. The disruption of vascular endothelial cadherin-cadherin bonds leads to opening of gaps between endothelial cells, leading to immune cells having direct access to the subintimal space as shown in a mouse model [84]. Cd also induces cell death by several mechanisms, ranging from apoptosis and necrosis to autophagy, which have different causes and pathways such as DNA damage and mitochondrial dysfunction [83]. Apoptosis has been observed in human endothelial cells at a Cd concentration of 61 nM, which is found in humans at high exposure levels [85]. Hence, Cd may cause endothelial damage and cell death, thereby ameliorating the passage of immune cells into the subintimal space and atherosclerotic disease.

**Cadmium and endothelial dysfunction**

Endothelial dysfunction of the normal functional phenotype is of great importance for the development of atherosclerosis (See Supplement Box 3 for background).

A study from Thailand included three groups of women with different exposure levels to Cd (B-Cd geometric means of 1.31, 3.97, and 8.48 µg/L, respectively). Plasma and erythrocyte nitrite concentrations as measures of nitric oxide (NO) production of endothelial cells were
found to be reduced in groups with higher Cd exposure, whereas plasma concentrations of asymmetric dimethylarginine (ADMA), an eNOS inhibitor, were increased. Plasma levels of thrombomodulin were also elevated in the exposed groups, indicating endothelial injury. Markers of lipid and protein oxidation were increased and the antioxidant glutathione was reduced in the Cd-exposed groups. Tobacco smoking as a potential confounder was not considered, but the Cd gradient was far above that caused by smoking [68]. An increase of ADMA as a measure of eNOS inhibition has also been reported from an occupationally exposed group in comparison with controls [86].

Studies in rats using oral exposure to Cd, reflecting relatively high human exposure to Cd in heavily contaminated areas and/or in occupational conditions, support that Cd impairs NO-related vascular relaxation. In one study, circulating levels of NO were reduced whereas lipid peroxidation increased, indicating oxidative stress and reduced NO production by the endothelium [87]. In another study, Cd exposure was associated with both a reduced relaxation of aortic rings after acetylcholine stimulation and a reduction in eNOS expression. The likely explanation is a decrease of muscarinic receptor responses to acetylcholine caused by interaction of Cd with the thiol groups of muscarinic receptors [88]. In ApoE -/- mice, Cd exposure caused reduced NO bioavailability and endothelial dysfunction [89].

These data strongly indicate that Cd exposure causes reduced NO bioavailability and endothelial dysfunction via oxidative stress.

**Cadmium, endothelium, and proinflammatory changes**

Activated endothelium is characterized by expression of adhesion molecules and prothrombotic factors. In a study of middle-aged women, circulating intercellular adhesion molecule-1 (ICAM-1) was associated with both blood and urine Cd and the occurrence and extent of ultrasound-assessed plaques in the carotid arteries [55]. However, experimental studies of human aterial, endothelial cells do not support a proinflammatory effect of Cd initiated by activation of vascular cell adhesion molecule-1 (VCAM-1), ICAM-1, or proinflammatory genes (Table 7). In the three studies of human arterial endothelial cells there were no, or even down-regulation of proinflamator genes [48, 90, 91]. Admittedly, cadmium induced expression of adhesion molecules in HUVECs [92], but these are venous cells with questionable relevance for atherosclerosis.

On the other hand, studies of rodent and bovine endothelial cells have reported proinflammatory effects of Cd exposure as well as expression of adhesion molecules [84, 93-95]. Conversely, Cd may also inhibit the proinflammatory effect of lipopolysaccharides on endothelial cells [95].

When interpreting these data in the perspective of human atherosclerosis, it is important to keep in mind the extreme diversity of endothelial cells and their functional state in relation to anatomical location and types of blood vessels, and the extensive differences between arteries and veins, as well as large arteries and microvasculature. [96].

**Cadmium and animal models of atherosclerosis**

Studies of cholesterol-fed rabbits exposed to Cd showed both an increase and a dose-dependent reduction in atherosclerotic lesions. In studies of ApoE knock-out mice, Cd exposure was consistently associated with progress of atherosclerosis (Table 8). Atherogenic alterations of the circulating lipid profile, oxidative stress, endothelial dysfunction and immunostaining for VCAM-1 and heat-shock protein-1 were also observed [54, 82, 84].
In summary, Cd causes atherosclerosis in established mouse models of this disease. In human, animal, and experimental studies, Cd exposure causes oxidative stress and endothelial dysfunction. However, none of the studies in human arterial endothelial cells showed that Cd exposure upregulated the expression of proinflammatory genes or adhesion molecules. Hence, the role of Cd in inflammation in the early stage of atherosclerosis is unclear.

**Cadmium and monocytes/macrophages**

Treatment of human macrophages with low concentrations of Cd (5–200 nM) resulted in significant reduction in the levels of several fatty acids, affecting macrophage behaviour and inflammatory state [99]. In human monocytes, Cd at micromolar doses increased MAPK phosphorylation and induced secretion of TNF-α, a prime inducer of inflammation [100]. Conversely, studies of occupationally-exposed young men with B-Cd concentrations in the nanomolar range (but still very high compared with population values in Sweden) showed no increase in TNF-α, but decreases in IL-1β and γ-IFN levels, and thus anti-inflammatory effects [101].

One unresolved issue is that Cd exposure induces expression of the metal binding protein metallothionein in several cell types. Given the high affinity for metallothionein, a large proportion of the Cd content in tissues may not be available [100]. Hence, the effects of Cd on monocyte/macrophage function in atherosclerosis are unclear.

**Cadmium and vascular smooth muscle cells**

Vascular smooth muscle cells (VSMCs) adopt different phenotypes which participate in different phases of atherosclerosis (See Supplement Box 4 for background).

In an experimental study, low levels of Cd (≤100 nM) promoted the proliferation of VSMCs through an intracellular calcium-dependent signalling pathway [102]. This may support a role for Cd in early atherosclerosis with diffuse intimal thickening. Higher Cd levels (1 µM) induce VSMC cell death [80].

The proliferation of arterial smooth muscle cells is dependent on the surrounding extracellular matrix, which includes collagen (types I, III, and IV) and laminin [103]. Interactions of the smooth muscle cells with the underlying matrix regulate cell proliferation. The effects of Cd on DNA synthesis and the proliferation of human aortic smooth muscle cells were studied during culture on fibrillar collagen type I. The results showed that Cd reduced the procollagen synthesis of aortic smooth muscle cells at concentration of 7 µmol/kg, a concentration that is found in the human aortic media of smokers [77].

Hence, low Cd exposure may promote VSMC proliferation in early atherosclerosis, induce cell death at higher doses, and adversely affect the ability of VSMCs to synthesize collagen, thereby reducing plaque stability.

**Cadmium and innate immune response**

Normally, the immune system in a concerted action between its innate (See Supplement Box 5 for background) and adaptive responses handles infections and other threats to the organism. Atherosclerosis is one example of an inappropriate and uncontrolled response
that leads to chronic inflammation and increasing tissue damage. IL-6, as a link in the NLRP3 inflammasome, and part of the innate immune system has been shown to be a causal factor in ASCVD.

Cd exposure may affect different aspects of the rapid and unspecific innate immune system. As recently reviewed, individual studies in various cell types have suggested different pathways which may be activated by Cd [104]: 1) Up-regulation of important pro-inflammatory cytokines and chemokines and transcription factor genes in swine enterocytes; 2) stimulation of IL-6 and IL-8 production in astrocytes; 3) stimulation of biosynthesis of PGE2 in mouse osteoblastic cell by different pathways; 4) Cd induction of COX-2 expression which was associated with ICAM-1 expression in mouse brain endothelial cells; 5) activation of IL-8 in lung epithelial cells by an NF-κB-independent pathway. Again, Cd exposure may also show anti-inflammatory effects.

In general, available data as described above, suggest that Cd in micromolar concentrations causes upregulation of the mediators and markers of inflammation, and appears to have pro-inflammatory properties [81]. However, the data are not consistent. Cd has both pro-inflammatory and anti-inflammatory effects due to dose and exposure duration. More importantly, the effects of Cd may differ not only between species but also between organs and cell types [81, 104, 105]. Most studies have used exposure levels of Cd clearly above those observed in humans [81].

Another approach is to examine if Cd exposure is associated with C-reactive protein (CRP), which is the end product of the NLRP3 inflammasome corresponding to the interleukin (IL)-1β, IL-18, IL-6, and CRP signalling pathway. In three cohorts from the NHANES project and a large cohort of middle-aged Swedish men and women, U-Cd and B-Cd were both associated with CRP after adjustment for smoking and other confounders [106-109]. The latter study also examined never-smokers and found no relationship between B-Cd and CRP, probably indicating that Cd exposure has no effect until it reaches levels that are generally only seen in smokers. In addition, if there is little support for Cd effects on the arterial wall as the origin of this inflammatory signal, the stronger the findings are that Cd exposure causes human hepatocytes to synthesize the TNF-α and IL-1β which play an important role in the onset of the CRP signalling pathway [81, 110].

Hence, at Cd exposure levels similar to those in humans, there are changes in macrophage fatty acid distributions compatible with changes in immune-modulatory functions. However, it has been difficult to translate these findings of basic mechanisms into consistent observations of proinflammatory effects of Cd on the atherosclerotic process.

**Cadmium and adaptive immune response**

Adaptive immune response is important in plaque formation, lesion stability and rupture (See Supplement Box 8 for background). Cd is taken up by human immune cells; mostly by T- and B-lymphocytes, and to a lesser extent by peripheral monocytes [111].

Cd exposure has been shown to increase circulating oxidized LDL cholesterol in rats [66] and to upregulate heat shock protein expression of endothelial cells from humans and mice [84, 85]. A majority of other studies of adaptive immunity focusing on the splenocytes and thymus suggest that Cd has immunosuppressive effect, but some studies report that Cd exhibits immune-stimulation features [104].
Hence, although several studies have shown that Cd exposure results in oxidative stress, oxidized LDL, and heat shock proteins which have antigenic properties, there is a lack of data on how Cd affects the response from the adaptive immune system.

**Cadmium and prostaglandins**

Prostaglandins have important roles in atherosclerosis (See Supplement Box 7 for background). As summarized by Olszowski et al., several studies have investigated the effect ofCd on COX-2 mRNA protein expression and enzymatic activity [112]. Most of them demonstrated a stimulatory effect of this metal on COX-2 in different experimental models. However, a few reports suggested Cd to exert either inhibitory action or no effect on COX-2. Their own study of human macrophages exposed to 5 nM, 20 nM, 200 nM, and 2 μM of Cd for 48 hours showed that Cd at the highest tested concentrations modulated COX-1 and COX-2 only at the mRNA level [112]. However, the lower tested Cd concentrations appeared to inhibit COX-1 protein expression. No convincing data of Cd effects on prostaglandins have been found.

Hence, Cd exposure seems to affect COX-2 expression, but there is a lack of consistent data regarding effects on the atherosclerotic disease process.

**Cadmium, coagulation and fibrinolysis**

Cd exposure has been shown to induce von Willebrand factor (vWF) expression in vascular endothelial cells in mouse lung and kidney tissues (See Supplement Box 10 for background). *In vitro* analysis showed that 1 μM Cd specifically upregulated vWF mRNA and protein expression in human umbilical vein endothelial cells (HUVECs), indicating that Cd targets vascular endothelial cells even at relatively low concentrations. Since vWF is a key regulator for vascular homeostasis, this may be one mechanism by which Cd can promote atherosclerotic diseases [113].

Fibrinogen is also an acute-phase protein. As such, fibrinogen biosynthesis in hepatocytes is regulated by glucocorticoids and IL-6. The latter, which is produced by fibroblasts, T-cells, endothelial cells, and monocytic cells, stimulates basal levels of fibrinogen production [114]. Cd exposure increases the expression of IL-6 in many cell types [81]. There is some epidemiological indication that plasma fibrinogen levels are increased dose-dependently by Cd exposure in the general population [106].

HUVECs, human fibroblasts, and smooth muscle aortic cells were incubated in cadmium chloride (0.5, 1, or 2 μM) for 24 hours. The results showed that Cd induced plasminogen activator inhibitor type 1 (PAI-1) synthesis and activity in endothelial cells without affecting tissue plasminogen activator (t-PA). Thereby Cd reduced the fibrinolytic activity of t-PA and urinary-PA in vascular endothelial cells [115-117].

Hence, there are several indications that Cd exposure has prothrombotic and anti-fibrinolytic effects which may be important in the later phases of atherosclerotic disease.

**Smoking, cadmium, and atherosclerosis**

The concept that Cd, as a principal toxicant in tobacco smoke, may partially be responsible for the proatherosclerotic effect of smoking, has growing support. Mediation analysis indicated that in smokers, 60 % of the association between current smoking and prevalence...
of carotid plaques was mediated through smoking, whereas about half of the increased risk of incident coronary heart disease in current smokers was mediated via cadmium [42-43]. Data on underlying causes are lacking. But the principle of mediating causes has been exemplified in a recent DNA methylation study in the Strong Heart Study. Mediation analysis supported a biological link for Cd and smoking-associated health effects, including the possibility that Cd is partly responsible for smoking toxicity through epigenetic changes [69].

**Complicated lesions with plaque rupture**

The final stage of the atherosclerotic disease process is when the plaque transforms into a complicated atherosclerotic lesion, with either rupture or erosion, leading to thrombosis and disrupted blood flow. (See Supplement Box 9 for background). There is a scarcity of data on how Cd exposure may be directly involved in this final pathophysiological process. However, there are some clues. In a large population-based prospective study, a proteomics analysis of plasma was performed in never-smokers in order to find proteins associated with B-Cd. Four proteins were identified, validated and found to predict ischemic stroke and/or CHD [118].

The first of these proteins was urokinase plasminogen activator receptor (uPAR), which is mainly expressed on immune cells. Urokinase-type plasminogen activator (uPA) is a protease that by binding to uPAR plays a key role in localized proteolysis and tissue remodelling in diseases such as cancer or atherosclerosis [119]. uPAR is involved in angiogenesis, adhesion, cell migration, proliferation, cell survival, inflammation, and proteolysis. Soluble uPAR has been identified as a biomarker of prevalent and incident atherosclerotic diseases [120-123].

Studies of animal and human plaques showed that uPAR was strongly associated with severe atherosclerosis [124-125]. uPAR and macrophages accumulated within symptomatic plaques, and were co-localized in the unstable parts of the plaque where rupture usually occurs [126-127]. Moreover, B-Cd was correlated with Cd levels and macrophage density in the most unstable parts of such carotid plaques [79, 128], and the occurrence of uPAR and the plasminogen receptor S100A10 were correlated in the same parts of symptomatic carotid plaques [129].

These observational data raise the hypothesis that Cd is involved with the uPA/uPAR/S100A10/annexin A2 complex in plaque tissue degradation and macrophage migration, and may participate in plaque rupture mechanisms. One possibility is that Cd induces uPAR expression, as has been found in human gastric cancer cells mediated by the ERK-1/2, NF-κB, and activator protein-1 signalling pathways [130].

The three other proteins were matrix metalloproteinase-12 (MMP-12); cathepsin L, a lysosomal cysteine protease; and CX3CL1 (fractalkine), a chemokine [118]. All three promote atherosclerosis in mice models, are found in vulnerable and symptomatic plaques in connection with macrophages, and have soluble forms that are associated with prevalent or incident CHD (for detailed information see Supplement). Hypothetically, these proteins may be a link between Cd exposure and ASCVD.

**Complicated lesions with plaque erosion**.

About one-third of cases with myocardial infarctions seem to be caused by thrombi overlying intact, nonruptured atherosclerotic plaques [131]. The underlying pathology is erosion of luminal endothelial cells from smooth muscle and proteoglycan-rich atheromas.
In contrast to plaque ruptures, endothelial erosions tend to occur on thick-capped atherosclerotic plaques with small deep-seated lipid cores and do not have to be associated with inflammation. Eroded plaques are less calcified than ruptured plaques. Risk factors for erosion are smoking and to be a premenopausal woman. Such endothelial erosion may be caused by many mechanisms. Apoptosis of endothelial cells and loss of endothelial contacts with the underlying extracellular matrix are two intimately linked processes which are believed to be important in erosion. Factors promoting endothelial apoptosis include deprivation of growth or survival factors, such as vascular endothelial growth factor, or disruption of cell to cell contacts mediated by VE-cadherin, which interferes with signaling through the mitogen activated protein kinase and c-Akt pathways [132]. The previously mentioned chemokine fractalkine is also known to induce endothelial cell injury [133].

The two intimately linked processes believed to be important in plaque erosion, apoptosis of endothelial cells and loss of endothelial contacts with the underlying extracellular matrix are well-established effect of Cd exposure in experimental and animal studies, as summarized above [82-84]. Female sex and smoking seem to be risk factors for plaque erosion, and these factors are also associated with high Cd exposure in the general population [10]. Fractalkine, a chemokine which is associated with Cd exposure — the chemokine,— is known to induce endothelial cell damage and death and to be expressed in endothelial cells in atheromatous lesions [134].

Conclusions

The results from the mechanistic studies can be merged into a hypothetical summary of the proatherosclerotic effects of Cd exposure (Figure 2). The figure legend gives a more detailed overview of the chain of events over time in the development of atherosclerosis.

Discussion

Four previous meta-analyses have convincingly shown that Cd exposure is associated with CVD [5-8]. The present updated review adds a dose-response analysis. As illustrated in Figure 1, the available evidence indicates that Cd confers increased risk of ASCVD above exposure levels of B-Cd >0.5 µg/L or U-Cd >0.5 µg/g creatinine. At lower exposure levels, there is at present no evidence of increased risk. In addition, there are clear indications that Cd exposure is also associated with asymptomatic atherosclerosis in the carotid and coronary arteries above this threshold.

Smoking is an important confounder, as it is both an important source of high Cd exposure and a potent risk factor. Even if adjustment for smoking does not exclude residual confounding, several studies in never-smoking cohorts have shown associations between Cd and ASCVD, and experimental studies have demonstrated pro-atherosclerotic effects of Cd. Hence, there is strong evidence that Cd causes ASCVD.

A further finding is that that Cd accumulates in atheroprone arterial walls, reaching concentrations corresponding to those in experimental studies that have shown Cd to have proatherosclerotic effects. Considering the well-known cytotoxic effect of Cd, it is no surprise that Cd has dysregulatory effects on most vascular tissues: endothelial cells, smooth muscle cells, immune cells, foam cells, and collagen. Data indicate that Cd is operative both in early atherosclerosis when plaques develop and at late stages when plaques become complicated with rupture or erosion. Furthermore, Cd probably promotes thrombosis and anti-fibrinolysis in the final stage of overt ASCVD. However, as many
mechanisms are hypothetical and data are still scarce, more studies are needed to clarify the details. A still unresolved question is how Cd promotes intraplaque inflammation beyond the capacity to oxidize LDL cholesterol, the prime cause of inflammation in atherosclerosis.

Is Cd a novel risk factor for ASCVD? A pragmatic view is that Cd exposure is a proatherosclerotic causal factor for ASCVD. In never-smokers the major source is diet. In smokers, it seems increasingly plausible that Cd partly mediates the risk of smoking on ASCVD.

Conflict of interest statement
BF and LB have no conflicts of interest.

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References

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1204-22.

2. Levi F, Chatenoud L, Bertuccio P, Lucchini F, Negri E, La Vecchia C. Mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world: an update. *Eur J Cardiovasc Prev Rehabil* 2009;16:333-50.

3. Östgren CJ, Söderberg S, Festin K et al. Systematic Coronary Risk Evaluation estimated risk and prevalent subclinical atherosclerosis in coronary and carotid arteries: A population-based cohort analysis from the Swedish Cardiopulmonary Bioimage Study. *Eur J Prev Cardiol* 2021;28:250-9.

4. Libby P, Pasterkamp G. Requiem for the 'vulnerable plaque'. *Eur Heart J* 2015;36:2984-7.

5. Tellez-Plaza M, Jones MR, Dominguez-Lucas A, Guallar E, Navas-Acien A. Cadmium exposure and clinical cardiovascular disease: a systematic review. *Curr Atheroscler Rep* 2013;15:356.

6. Larsson SC, Wolk A. Urinary cadmium and mortality from all causes, cancer and cardiovascular disease in the general population: systematic review and meta-analysis of cohort studies. *Int J Epidemiol* 2016;45:782-91.

7. Chowdhury R, Ramond A, O’Keeffe LM et al. Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ* 2018;362:k3310.

8. Tinkov AA, Filippini T, Ajsuvakova OP et al. Cadmium and atherosclerosis: a review of toxicological mechanisms and a meta-analysis of epidemiologic studies. *Environ Res* 2018;162:240–60.

9. Åkesson A, Barregard L, Bergdahl IA, Nordberg GF, Nordberg M, Skerfving S. Non-Renal Effects and the Risk Assessment of Environmental Cadmium Exposure. *Environ Health Perspect* 2014;122:431–8.

10. Nordberg GF, Nogawa K, Nordberg M. *Handbook on the toxicology of metals*. Amsterdam: Elsevier, 2015. ISBN 9780444594532.

11. IARC International Agency for Research on Cancer. 2012. Cadmium and cadmium compounds. In Arsenic, metals, fibres, and dusts. Vol.100c. IARC Monographs. WHO Press, Geneva. Available at: [http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-8.pdf](http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-8.pdf)

12. EFSA. EFSA Panel on Contaminants in the Food Chain (CONTAM); Scientific Opinion on Lead in Food. *EFSA Journal* 2010;8:151.

13. World Health Organization. 2011. Evaluation of certain food additives and contaminants. Seventy-third report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva. Available at: [http://www.inchem.org/documents/jecfa/jecmono/v64je01.pdf](http://www.inchem.org/documents/jecfa/jecmono/v64je01.pdf)
14. Akerstrom M, Barregard L, Lundh T, Sallsten G. The relationship between cadmium in kidney and cadmium in urine and blood in an environmentally exposed population. *Toxicol Appl Pharmacol* 2013;268:286–93.

15. Barregard L, Fabricius-Lagging E, Lundh T et al. Cadmium, mercury, and lead in kidney cortex of living kidney donors: Impact of different exposure sources. *Environ Res* 2010;110:47-54.

16. Hecht EM, Arheart K, Lee DJ, Hennekens CH, Hlaing WM. A cross-sectional survey of cadmium biomarkers and cigarette smoking. *Biomarkers* 2016;21:429–35.

17. Barregard L, Sallsten G, Fagerberg B et al. Blood cadmium levels and incident cardiovascular events during follow-up in a population-based cohort of Swedish adults: the Malmo Diet and Cancer Study. *Environ Health Perspect* 2016;124:594–600.

18. Diaz D, Ujueta F, Mansur G, Lamas GA, Navas-Acien A, Arenas IA. Low-Level Cadmium Exposure and Atherosclerosis. *Curr Environ Health Rep* 2021;8:42-53.

19. Sjögren B, Bigert C, Gustavsson P. The Nordic Expert group for criteria documentation of health risks from chemicals. 153. Occupational chemical exposures and cardiovascular disease. *Work and Health* 2020;54:1–428. Available at https://gupea.ub.gu.se/bitstream/2077/66225/1/gupea_2077_66225_1.pdf

20. Kazantzis G, Lam TH, Sullivan KR. Mortality of cadmium-exposed workers. A five-year update. *Scand J Work Environ Health* 1988;14:220-3.

21. Sorahan T, Lister A, Gilthorpe MS, Harrington JM. Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946-92. *Occup Environ Med* 1995;52:804-12.

22. Järup L, Bellander T, Hogstedt C, Spång G. Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. *Occup Environ Med* 1998;55:755-9.

23. Virtanen SV, Notkola V. Socioeconomic inequalities in cardiovascular mortality and the role of work: a register study of Finnish men. *Int J Epidemiol* 2002;31:614-21.

24. Binks K, Doll R, Gillies M et al. Mortality experience of male workers at a UK tin smelter. *Occup Med* (Lond) 2005;55:215-26.

25. Marsh GM, Esmen NA, Buchanich JM, Youk AO. Mortality patterns among workers exposed to arsenic, cadmium, and other substances in a copper smelter. *Am J Ind Med* 2009;52:633-44.

26. Julin B, Bergkvist C, Wolk A, Åkesson A. Cadmium in diet and risk of cardiovascular disease in women. *Epidemiology* 2013;24:880–5.

27. Julin B, Wolk A, Thomas LD, Akesson A. Exposure to cadmium from food and risk of cardiovascular disease in men: A population-based prospective cohort study. *Eur J Epidemiol* 2013;28:837–40.

28. Julin B, Wolk A, Bergkvist L, Bottai M, Akesson A. Dietary cadmium exposure and risk of postmenopausal breast cancer: a population-based prospective cohort study. *Cancer Res* 2012;72:1459-66.
29. Deering KE, Callan AC, Prince RL et al. Low-level cadmium exposure and cardiovascular outcomes in elderly Australian women: A cohort study. *Int J Hyg Environ Health* 2018;221:347-54.

30. Menke A, Muntrer P, Silbergeld EK, Platz EA, Guallar E. Cadmium levels in urine and mortality among U.S. adults. *Environ Health Perspect* 2009;117:190–96.

31. Tellez-Plaza M, Navas-Acien A, Menke A, Crainiceanu CM, Pastor-Barriuso R, Guallar E. Cadmium exposure and all-cause and cardiovascular mortality in the U.S. general population. *Environ Health Perspect* 2012;120:1017–22.

32. Tellez-Plaza M, Guallar E, Howard BV et al. Cadmium exposure and incident cardiovascular disease *Epidemiology* 2013;24:421–29.

33. Everett CJ, Frithsen IL. Association of urinary cadmium and myocardial infarction *Environ Res* 2008;106:284–86.

34. Lee MS, Park SK, Hu H, Lee S. Cadmium exposure and cardiovascular disease in the 2005 Korea National Health and Nutrition Examination Survey. *Environ Res* 2011;111:171–76.

35. Hecht EM, Arheart KL, Lee DJ, Hennekens CH, Hlaing WM. Interrelation of Cadmium, Smoking, and Cardiovascular Disease (from the National Health and Nutrition Examination Survey). *Am J Cardiol* 2016;118:204-9.

36. Jeong J, Yun SM, Kim M, Koh YH. Association of Blood Cadmium with Cardiovascular Disease in Korea: From the Korea National Health and Nutrition Examination Survey 2008-2013 and 2016. *Int J Environ Res Public Health* 2020;17:6288.

37. Nawrot TS, Van Hecke E, Thijs L et al. Cadmium-related mortality and long-term secular trends in the cadmium body burden of an environmentally exposed population. *Environ Health Perspect* 2008;116:1620–28.

38. Peters JL, Perlstein TS, Perry MJ, McNeely E, Weuve J. Cadmium exposure in association with history of stroke and heart failure. *Environ Res* 2010;110:199–206.

39. Li Q, Nishijo M, Nakagawa H et al. Relationship between urinary cadmium and mortality in habitants of a cadmium-polluted area: A 22-year follow-up study in Japan. *Chin Med J* 2011;124:3504–9.

40. Aoki Y, Brody DJ, Flegal KM, Fakhour THI, Axelrad DA, Parker JD. Blood Lead and Other Metal Biomarkers as Risk Factors for Cardiovascular Disease Mortality. *Medicine* (Baltimore) 2016;95:e2223.

41. Domingo-Relloso A, Grau-Perez M, Briongos-Figuero L et al. The association of urine metals and metal mixtures with cardiovascular incidence in an adult population from Spain: the Hortega Follow-Up Study. *Int J Epidemiol* 2019;48:1839-49.

42. Andersson EM, Fagerberg B, Sallsten G et al. Partial mediation by cadmium exposure of the association between tobacco smoking and atherosclerotic plaques in the carotid artery. *Am J Epidemiol* 2018;187:806–16.
43. Li H, Fagerberg B, Sallsten G et al. Smoking-induced risk of future cardiovascular disease is partly mediated by cadmium in tobacco: Malmö Diet and Cancer Cohort Study. *Environ Health* 2019;18:56.

44. Sears CG, Poulsen AH, Eliot M et al. Urine cadmium and acute myocardial infarction among never smokers in the Danish Diet, Cancer and Health cohort. *Environ Int* 2021;150:106428.

45. Poulsen AH, Sears CG, Harrington JM et al. Urine cadmium and stroke – a case cohort study in Danish never-smokers. *Environ Res* 2021 (in press).

46. Tellez-Plaza M, Navas-Acien A, Crainiceanu CM, Sharrett AR, Guallar E. Cadmium and peripheral arterial disease: gender differences in the 1999-2004 US National Health and Nutrition Examination Survey. *Am J Epidemiol* 2010;172:671–81.

47. Tellez-Plaza M, Guallar E, Fabsitz RR et al. Cadmium exposure and incident peripheral arterial disease. *Circ Cardiovasc Qual Outcomes*. 2013;6:626-33.

48. Fagerberg B, Bergström G, Borén J, Barregard L. Cadmium exposure, intercellular adhesion molecule-1 and peripheral artery disease: a cohort and an experimental study. *BMJ Open* 2013;3:e002489.

49. Zhuang X, Ni A, Liao L et al. Environment-wide association study to identify novel factors associated with peripheral arterial disease: Evidence from the National Health and Nutrition Examination Survey (1999-2004). *Atherosclerosis* 2018;269:172-77.

50. Navas-Acien A, Selvin E, Sharrett AR, Calderon-Aranda E, Silbergeld E, Guallar E. Lead, cadmium, smoking, and increased risk of peripheral arterial disease. *Circulation* 2004;109:3196–3201.

51. Navas-Acien A, Silbergeld EK, Sharrett R, Calderon-Aranda E, Selvin E, Guallar E. Metals in urine and peripheral arterial disease. *Environ Health Perspect* 2005;113:164–69.

52. Ujueta F, Arenas IA, Diaz D et al. Cadmium level and severity of peripheral artery disease in patients with coronary artery disease. *Eur J Prev Cardiol* 2019;26:1456-58.

53. Fagerberg B, Borné Y, Sallsten G et al. Circulating cadmium concentration and risk of aortic aneurysms: A nested case-control study within the Malmö Diet and Cancer cohort. *Atherosclerosis* 2017;261:37-43.

54. Messner B, Knoflach M, Seubert A et al. Cadmium is a novel and independent risk factor for early atherosclerosis mechanisms and in vivo relevance. *Arterioscler Thromb Vasc Biol* 2009;29:1392–8.

55. Fagerberg B, Bergström B, Borén J, Barregard L. Cadmium exposure is accompanied by increased prevalence and future growth of atherosclerotic plaques in 64-year-old women. *J Intern Med* 2012;272:601–10.

56. Fagerberg B, Barregard L, Sallsten G et al. Cadmium exposure and atherosclerotic plaques – results from the Malmö Diet and Cancer study. *Env Res* 2015;136:67–74.
57. Lind PM, Olsén L, Lind L. Circulating levels of metals are related to carotid atherosclerosis in elderly. *Sci Total Environ* 2012;**416**:80-8.

58. Lin CY, Lee HL, Hwang YT et al. Urinary heavy metals, DNA methylation, and subclinical atherosclerosis. *Ecotoxicol Environ Saf* 2020;**204**:111039.

59. Barregard L, Sallsten G, Harari F et al. Cadmium exposure and coronary artery atherosclerosis: a cross-sectional population-based study of Swedish middle-aged adults. *Environ Health Perspect* 2021 (in press).

60. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. *Atherosclerosis* 2012;**220**:128-33.

61. Lamas GA, Navas-Acien A, Mark DB, Lee KL. Heavy metals, cardiovascular disease, and unexpected benefits of chelation therapy. *J Am Coll Cardiol* 2016;**67**:2411–8.

62. Borén J, Williams KJ. The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity. *Curr Opin Lipidol* 2016;**27**:473-83.

63. Fujiwara Y, Tsumura N, Yamamoto C, Kaji T. Differential effects of Cd on proteoglycan synthesis of arterial smooth muscle cells: increase in small dermatan sulfate proteoglycans, biglycan and decorin, in the extracellular matrix at low cell density. *Toxicology* 2002;**170**:89-101.

64. Ohkawara S, Yamamoto C, Fujiwara Y, Sakamoto M, Kaji T. Cd induces the production of high molecular weight heparan sulfate proteoglycan molecules in cultured vascular endothelial cells. *Environ Toxicol Pharmacol* 1997;**3**:187-94.

65. Kijani S, Bergström G, Lindbom M et al. Non-toxic concentrations of Cd accelerate subendothelial retention of atherogenic lipoproteins in humanized atherosclerosis-susceptible mice. *Atherosclerosis* 2017;**263**:E1–E2.

66. Rogalska J, Brzó ska MM, Roszczenko A, Moniuszko-Jakoniuk J. Enhanced zinc consumption prevents cadmium-induced alterations in lipid metabolism in male rats. *Chem Biol Interact* 2009;**177**:142-52.

67. Famurewa AC, Ejezie FE. Polyphenols isolated from virgin coconut oil attenuate cadmium-induced dyslipidemia and oxidative stress due to their antioxidant properties and potential benefits on cardiovascular risk ratios in rats. *Avicenna J Phytomed* 2018;**8**:73-84.

68. Lukkhananan P, Thawonrachat N, Srihirun S et al. Endothelial dysfunction in subjects with chronic cadmium exposure. *J Toxicol Sci* 2015;**40**:605-13.

69. Domingo-Relloso A, Rifo-Campos AL, Haack K et al. Cadmium, Smoking, and Human Blood DNA Methylation Profiles in Adults from the Strong Heart Study. *Environ Health Perspect* 2020;128:67005.

70. González FEM, Ponce-Ruíz N, Rojas-García AE et al. PON1 concentration and high-density lipoprotein characteristics as cardiovascular biomarkers. *Arch Med Sci Atheroscler Dis* 2019;**4**:e47-e54.

This article is protected by copyright. All rights reserved.
71. Mackness M, Mackness B. Targeting paraoxonase-1 in atherosclerosis. *Expert Opin Ther Targets* 2013;17:829-37.
72. Wang M, Lang X, Cui S *et al.* Quantitative assessment of the influence of paraoxonase 1 activity and coronary heart disease. *DNA Cell Biol* 2012;31:975-82.
73. Shih DM, Gu L, Xia YR *et al.* Mice lacking serum paraoxonase are susceptible to organophosphate toxicity and atherosclerosis. Nature 1998;394:284-7.
74. Cole TB, LiWF, Richter RJ, Furlong CE, Costa LG. Inhibition of Paraoxonase (PON1) by heavy metals. *Toxicol Sci* 2002;66(Suppl 1):312.
75. Pollack AZ, Sjaarda L, Ahrens KA *et al.* Association of cadmium, lead and mercury with paraoxonase 1 activity in women. *PLoS One* 2014;9:e92152.
76. Hernández AF, Gil F, Leno E, López O, Rodrigo L, Pla A. Interaction between human serum esterases and environmental metal compounds. *Neurotoxicology* 2009;30:628-35.
77. Abu-Hayyeh S, Sian M, Jones KG, Manuel A, Powell JT. Cadmium accumulation in aortas of smokers. *Arterioscler Thromb Vasc Biol* 2001;21:863-7.
78. Egger AE, Grabmann G, Gollmann-Tepeköylü C *et al.* Chemical imaging and assessment of cadmium distribution in the human body. *Metallomics* 2019;11:2010-19.
79. Bergström G, Fagerberg B, Sallsten G, Lundh T, Barregard L. Is cadmium exposure associated with the burden, vulnerability and rupture of human atherosclerotic plaques? *PLoS One* 2015;10:e0121240.
80. Washington B, Williams S, Armstrong P, Mtshali C, Robinson JT, Myles EL. Cadmium toxicity on arterioles vascular smooth muscle cells of spontaneously hypertensive rats. *Int J Environ Res Public Health* 2006;3:323-8.
81. Olszowski T, Baranowska-Bosiacka I, Gutowska I, Chlubek D. Pro-inflammatory properties of cadmium. *Acta Biochim Pol* 2012;59:475-82.
82. Prozialeck WC, Edwards JR, Nebert DW, Woods JM, Barchowsky A, Atchison WD. The vascular system as a target of metal toxicity. *Toxicol Sci* 2008;102:207-18.
83. Messner B, Bernhard D. Cadmium and cardiovascular diseases: cell biology, pathophysiology, and epidemiological relevance. *Biometals* 2010;23:811-22.
84. Knoflach M, Messner B, Shen YH *et al.* Non-toxic cadmium concentrations induce vascular inflammation and promote atherosclerosis. *Circ J* 2011;75:2491-5.
85. Tang L, Su J, Liang P. Modeling cadmium-induced endothelial toxicity using human pluripotent stem cell-derived endothelial cells. *Sci Rep* 2017;7:14811.
86. Tutkun L, Gunduzoz M, Turksoy VA *et al.* Assessment of Endothelial Dysfunction with Methylated Arginines and L-arginine in Cadmium-Exposed People: a Pilot Study. *Clin Lab* 2019;65(10).
87. Martynowicz, H., Skoczynska, A., Wojakowska, A., Turczyn, B.. Serum vasoactive agents in rats poisoned with cadmium. *Int. J Occup Med Environ Health* 2004;17:479–85.

This article is protected by copyright. All rights reserved.
88. Yoopan N, Watcharasit P, Wongsawatkul O, Piyachaturawat P, Satayavivad J. Attenuation of eNOS expression in cadmium-induced hypertensive rats. *Toxicol Lett* 2008;176:157-61.

89. Oliveira TF, Batista PR, Leal MA et al. Chronic Cadmium Exposure Accelerates the Development of Atherosclerosis and Induces Vascular Dysfunction in the Aorta of ApoE-/- Mice. *Biol Trace Elem Res* 2019;187:163-71.

90. Bernhard D, Rossmann A, Henderson B, Kind M, Seubert A, Wick G. Increased serum cadmium and strontium levels in young smokers: effects on arterial endothelial cell gene transcription. *Arterioscler Thromb Vasc Biol* 2006;26:833-8.

91. Fujiwara Y, Honda A, Yamamoto C, Kaji T, Satoh M. DNA microarray analysis of human coronary artery endothelial cells exposed to cadmium. *J Toxicol Sci* 2011;36:141-3.

92. Zhong Q, Li X, Nong Q, Mao B, Pan X. Metabolic Profiling in Association with Vascular Endothelial Cell Dysfunction Following Non-Toxic Cadmium Exposure. *Int J Mol Sci* 2017;18:1905.

93. Park SL, Kim YM, Ahn JH et al. Cadmium stimulates the expression of vascular cell adhesion molecule-1 (VCAM-1) via p38 mitogen-activated protein kinase (MAPK) and JNK activation in cerebrovascular endothelial cells. *J Pharmacol Sci* 2009;110:405-9.

94. Jeong EM, Moon CH, Kim CS et al. Cadmium stimulates the expression of ICAM-1 via NF-kappa B activation in cerebrovascular endothelial cells. *Biochem Biophys Res Commun* 2004;320:887–92.

95. Szuster-Ciesielska A, Lokaj I, Kandefer-Szerszeń M. The influence of cadmium and zinc ions on the interferon and tumor necrosis factor production in bovine aorta endothelial cells. *Toxicology* 2000;145:135-45.

96. Chi JT, Chang HY, Haraldsen G et al. Endothelial cell diversity revealed by global expression profiling. *Proc Natl Acad Sci U S A* 2003;100:10623-8.

97. Subramanyam G, Bhaskar M, Govindappa S. The role of cadmium in induction of atherosclerosis in rabbits. *Indian Heart J* 1992;44:177–180.

98. Meijer GW, Beems RB, Janssen GB, Vaessen HA, Speijers GJ. Cadmium and atherosclerosis in the rabbit: reduced atherogenesis by superseding of iron? *Food Chem Toxicol* 1996;34:611-21.

99. Olszowski T, Gutowska I, Baranowska-Bosiacka I, Łukomska A, Drozd A, Chlubek D. Cadmium Alters the Concentration of Fatty Acids in THP-1 Macrophages. *Biol Trace Elem Res* 2018;182:29-36.

100. Haase H, Ober-Blöbaum JL, Engelhardt G, Hebel S, Rink L. Cadmium ions induce monocytic production of tumor necrosis factor-alpha by inhibiting mitogen activated protein kinase dephosphorylation. *Toxicol Lett* 2010;198:152-8.

101. Yücesoy B, Turhan A, Ure M, Imir T, Karakaya A. Effects of occupational lead and cadmium exposure on some immunoregulatory cytokine levels in man. *Toxicology* 199;123:143-7.

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102. Fujiwara Y, Watanabe S, Kaji T. Promotion of cultured vascular smooth muscle cell proliferation by low levels of cadmium. *Toxicol Lett* 1998;94:175-80.

103. Thyberg J, Hedin U, Sjolund M, Palmberg L, Bottger BA. Regulation of differentiated properties and proliferation of arterial smooth muscle cells. *Arteriosclerosis* 1990;10:966-90.

104. Hossein-Khannazer N, Azizi G, Eslami S et al. The effects of cadmium exposure in the induction of inflammation. *Immunopharmacol Immunotoxicol* 2020;42:1-8.

105. Lee JY, Tokumoto M, Hattori Y, Fujiwara Y, Shimada A, Satoh M. Different Regulation of p53 Expression by Cadmium Exposure in Kidney, Liver, Intestine, Vasculature, and Brain Astrocytes. *Toxicol Res* 2016;32:73-80.

106. Lin YS, Rathod D, Ho WC, Caffrey JJ. Cadmium exposure is associated with elevated blood C-reactive protein and fibrinogen in the U. S. population: the third national health and nutrition examination survey (NHANES III, 1988-1994. *Ann Epidemiol* 2009;19:592-6.

107. Colacino JA, Arthur AE, Ferguson KK, Rozek LS. Dietary antioxidant and anti-inflammatory intake modifies the effect of cadmium exposure on markers of systemic inflammation and oxidative stress. *Environ Res* 2014;131:6-12.

108. Obeng-Gyasi E. Chronic cadmium exposure and cardiovascular disease in adults. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2014;55:726-29.

109. Fagerberg B, Borné Y, Barregard L et al. Cadmium exposure is associated with soluble urokinase plasminogen activator receptor, a circulating marker of inflammation and future cardiovascular disease. *Environ Res* 2017;152:185-91.

110. Li X, Li H, Cai D et al. Chronic oral exposure to cadmium causes liver inflammation by NLRP3 inflammasome activation in pubertal mice. *Food Chem Toxicol* 2021;148:111944.

111. Steffensen IL, Mesna OJ, Andruchow E et al. Cytotoxicity and accumulation of Hg, Ag, Cd, Cu, Pb and Zn in human peripheral T and B lymphocytes and monocytes in vitro. *Gen Pharmacol* 1994;25:1621–1633.

112. Olszowski T, Gutowska I, Baranowska-Bosiacka I et al. The Effect of Cadmium on COX-1 and COX-2 Gene, Protein Expression, and Enzymatic Activity in THP-1 Macrophages. *Biol Trace Elem Res*. 2015;165:135-44.

113. Wang X, Dong F, Wang F et al. Low dose cadmium upregulates the expression of von Willebrand factor in endothelial cells. *Toxicol Lett* 2018;290:46-54.

114. Amrani DL. Regulation of fibrinogen biosynthesis: glucocorticoid and interleukin-6 control. *Blood Coagul Fibrinolysis* 1990;1:443-6.

115. Yamamoto, C., Kaji, T., Sakamoto, M., Kozuka, H. Cadmium stimulation of plasminogen activator inhibitor-1 release from human vascular endothelial cells in culture. *Toxicology* 1993;83215–223.

116. Yamamoto, C., Kaji, T., Sakamoto, M., Kozuka, H. Effects of cadmium on the release of tissue plasminogen activator and plasminogen activator inhibitor type 1 from
cultured human vascular smooth muscle cells and fibroblasts. *Toxicology* 1996;106:179–85.

117. Yamamoto C, Kaji T. Induction of Plasminogen Activator Inhibitor Type 1 Synthesis by Cadmium in Human Vascular Endothelial Cells in Culture. *Journal of Health Science* 2002; 48: 55-61 (English abstract).

118. Bornè Y, Fagerberg B, Sallsten G *et al.* Biomarkers of blood cadmium and incidence of cardiovascular events in non-smokers: results from a population-based proteomics study. *Clin Proteomics* 2019;16:21.

119. Preissner KT, Kanse SM, Chavakis T, May AE. The dual role of the urokinase receptor system in pericellular proteolysis and cell adhesion: implications for cardiovascular function. *Basic Res Cardiol* 1999;94:315-21.

120. Desmedt S, Desmedt V, Delanghe JR, Speeckaert R, Speeckaert MM. The intriguing role of soluble urokinase receptor in inflammatory diseases. *Crit Rev Rev Clin Lab Sci* 2017;54:117-33.

121. Sørensen MH, Gerke O, Eugen-Olsen J *et al.* Soluble urokinase plasminogen activator receptor is in contrast to high-sensitive C-reactive protein associated with coronary artery calcifications in healthy middle-aged subjects. *Atherosclerosis* 2014;237:60-6.

122. Eapen DJ, Manocha P, Ghasemzadeh N *et al.* Soluble urokinase plasminogen activator receptor level is an independent predictor of the presence and severity of coronary artery disease and of future adverse events. *J Am Heart Assoc* 2014;3:e001118. Erratum in: *J Am Heart Assoc* 2015;4:e000563.

123. Persson M, Östling G, Smith G *et al.* Soluble urokinase plasminogen activator receptor: a risk factor for carotid plaque, stroke, and coronary artery disease. *Stroke* 2014;45:18-23.

124. Noda-Heiny H, Daugherty A, Sobel BE. Augmented urokinase receptor expression in atheroma. *Arterioscler Thromb Vasc Biol* 1995;15: 37-43.

125. Salame MY, Samani NJ, Masood I, deBono DP. Expression of the plasminogen activator system in the human vascular wall. *Atherosclerosis* 2000;152:19-28.

126. Svensson PA, Olson FJ, Hagg DA *et al.* Urokinase-type plasminogen activator receptor is associated with macrophages and plaque rupture in symptomatic carotid atherosclerosis. *Int J Mol Med* 2008;22:459–64.

127. Edsfeldt A, Nitulescu M, Grufman H *et al.* Soluble urokinase plasminogen activator receptor is associated with inflammation in the vulnerable human atherosclerotic plaque. *Stroke* 2012;43:3305-12.

128. Fagerberg B, Kjell Dahl J, Sallsten G *et al.* Cadmium exposure as measured in blood in relation to macrophage density in symptomatic atherosclerotic plaques from human carotid artery. *Atherosclerosis* 2016;249:209-14.

129. Olson FJ, Sinibon C, Davidsson P, Hulte J, Fagerberg B, Bergström G. Consistent differences in protein distribution along the longitudinal axis in symptomatic carotid atherosclerotic plaques. *Biochem Biophys Res Commun.* 2010;401:574-80.
130. Khoi PN, Xia Y, Lian S et al. Cadmium induces urokinase-type plasminogen activator receptor expression and the cell invasiveness of human gastric cancer cells via the ERK-1/2, NF-kappaB, and AP-1 signaling pathways. *Int J Oncol* 2014;**45**:1760–8.

131. White SJ, Newby AC, Johnson TW. Endothelial erosion of plaques as a substrate for coronary thrombosis. *Thromb Haemost* 2016;**115**:509-19.

132. Dimmeler S, Zeiher AM. Endothelial cell apoptosis in angiogenesis and vessel regression. *Circ Res* 2000; **87**:434–39.

133. Yoneda O, Imai T, Goda S et al. Fractalkine-mediated endothelial cell injury by NK cells. *J Immunol* 2000; **164**:4055-62.

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Figure 1. Schematic illustration of findings in epidemiological studies of atherosclerotic cardiovascular disease when stratified by blood or urinary cadmium. The figure lists the relevant studies per outcome. The sign "+" denotes a statistically significant increase in risk, "(+)" a possible risk (a point estimate above 1.0, but p-value <0.05), and "-" means a null result. The studies are identified by first author, year and number in the reference list. Details behind the classification are tabulated in Table S2 (Supplement).
Figure 2. Hypothetical summary of observed proatherosclerotic effects of cadmium (Cd) exposure in human, animal, and experimental studies. First, Cd causes lipid retention in the subintima by stimulating and modifying the synthesis of proteoglycans (PGs) (1) to better bind and retain low-density lipoprotein (LDL) particles, which also become oxidized (2). At higher exposure levels, Cd also affects the liver and increases the concentration of plasma LDL cholesterol (3). As a further effect of Cd, the endothelium becomes dysfunctional, with impaired NO-related vasodilation (4), later followed by disruption of endothelial cadherin-cadherin bonds, which opens gaps between endothelial cells (ECs) (5). This increases the permeability and allows monocytes (5) to pass into the subintimal space, turn into macrophages, engulf LDL lipoproteins bound to proteoglycans, and differentiate to foam cells. At low concentrations, Cd promotes proliferation of vascular smooth muscle cells (VSMCs) (6), which migrate from the media to the plaque area and strengthen the fibrous cap or turn into foam cells. At higher concentrations, Cd causes death of not only ECs but also VSMCs (7). Increased apoptosis and insufficient removal of apoptotic cells cause expansion of a necrotic core. The synthesis of collagen is also disrupted by Cd (8). Taken, together this contributes to plaque rupture (7). In addition, Cd exposure seems to be associated with increases in urokinase plasminogen activator receptor (uPAR), matrix metalloproteinases-12 (MMP-12), and cathepsin L synthesis (9), which are involved in the degradation of the fibrous cap. The other type of complicated lesion is plaque erosion (7), with damage to the endothelium of the kind that is seen after Cd exposure (7) which may also include effects of fractalkine. Finally, the pro-thrombotic process is stimulated by the Cd-associated increase in vWF and PAI-1 expression and production (10, 11), resulting in an increased risk of a clinical event.
Review of cadmium exposure and smoking-independent effects on atherosclerotic cardiovascular disease in the general population

Cadmium exposure
Food
(Smoking)

ASCVD
Ischemic stroke

Carotid atherosclerosis

Coronary atherosclerosis

Myocardial infarction

Proatherosclerotic effects of cadmium
Mechanism

Peripheral artery disease

Threshold effects of cadmium
Clinical events

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Table 1. Summary of risk estimates presented in four meta-analyses on cadmium (Cd) exposure and cardiovascular disease (CVD), coronary heart disease (CHD), stroke, and peripheral artery disease (PAD) in lower extremities.

| Reference                  | CVD: number of studies, risk estimate | CHD: number of studies, risk estimate | Stroke: number of studies, risk estimate | PAD: number of studies, risk estimate | Comment                                      |
|----------------------------|--------------------------------------|---------------------------------------|------------------------------------------|--------------------------------------|---------------------------------------------|
| Tellez-Plaza et al. 2013a | 6                                    | 7                                     | 5                                       | 3                                    | Cross-sectional and longitudinal biomarker studies |
|                            | 1.36 (1.11–1.66)                     | 1.30 (1.12–1.52)                      | 1.18 (0.86–1.59)                        | 1.49 (1.15–1.92)                     |                                             |
| Larsson and Wolk 2015     | 5                                    | NA                                    | NA                                      | NA                                   | Only CVD mortality and only those based on U-Cd |
|                            | 1.57 (1.27–1.95)                     |                                       |                                         |                                       |                                             |
| Chowdhury et al. 2018     | 6                                    | 5                                     | 3                                       | NA                                   | Only longitudinal biomarker studies         |
|                            | 1.33 (1.09–1.64)                     | 1.29 (0.98–1.71)                      | 1.72 (1.29–2.28)                        |                                       |                                             |
| Tinkov et al. 2018        | 5                                    | 11†                                   | 9                                       | 3                                    | Separate estimates for cross-sectional and longitudinal studies, for B-Cd, U-Cd, and Cd intake |
|                            | B-Cd:1.78 (1.24–2.56)                | CS, B-Cd: 1.59 (1.24–2.04)            | CS, B-Cd: 1.35 (1.17–1.57)              | B-Cd (3): 1.54 (1.00–2.56)            |                                             |
|                            | U-Cd:1.34 (1.07–1.67)                | CS, U-Cd: 1.34 (0.99–1.81)            | CS, U-Cd: 1.44 (0.75–2.74)              | U-Cd (4): 1.97 (0.98–3.94)            |                                             |
|                            |                                       | L, B-Cd: 1.60 (1.21–2.10)             | L, B-Cd: 1.38 (0.56–3.29)               | L, B-Cd: 1.27 (0.85–2.47)             |                                             |
|                            |                                       | L, U-Cd: 1.27 (0.84–1.93)             | L, U-Cd: 1.27 (0.85–2.47)               | Intake: 1.00 (0.88–1.14)             |                                             |
|                            |                                       | Intake: 1.02 (0.87–1.19)              | Intake: 1.00 (0.88–1.14)                |                                       |                                             |

† Including one study on “cardiac disease” (Nawrot et al. 2008), and one study without smoking data (Li et al. 2011).

Note: B-Cd = blood cadmium, CS = cross-sectional studies, L = longitudinal studies, NA = not applicable, U-Cd = urinary cadmium.
Table 2. Epidemiological studies of associations between cadmium (Cd) exposure and coronary heart disease (CHD), including the diagnoses myocardial infarction (MI), acute coronary event (ACE), and ischemic heart disease (IHD).

| Author; study base (ref) | Design (L/CS); follow-up or exam period | Outcome | Measure of Cd exposure, overall GM or median | Numbe r of subject s (cases) | Exposure contrast (highest category vs. reference or using continuous B-Cd or U-Cd) | Findings | Comments |
|--------------------------|------------------------------------------|---------|---------------------------------------------|-----------------------------|--------------------------------------------------------------------------------|---------|----------|
| Biomonitoring studies adjusted for smoking |
| Menke 2009; NHANES, US [30] | L; 1988–1994 to 2000 | CHD mortality | Urine: 0.38 µg/gC (median) | 13958 (367) | U-Cd: ≥0.48 vs. <0.21 µg/gC in men, >0.68 vs. <0.29 in women | HR: men 2.5 (0.9–7.3), women: 0.5 (0.2–0.8) |
| Tellez-Plaza 2012; NHANES, US [31] | L; 1999–2004 to 2006 | IHD mortality | Blood: 0.44 µg/L, Urine: 0.28 µg/gC (GMs) | 8989 (88) | B-Cd: 0.80 vs. 0.22 µg/L U-Cd: 0.57 vs. 0.14 µg/gC | HR: B-Cd 1.7 (0.9–3.4), U-Cd 2.1 (1.1–4.1) |
| Tellez-Plaza 2013; Strong HS, US [32] | L; 1989–1991 to 2008 | CHD, incidence, mortality | Urine: 0.92 µg/gC (median) | 3348 (766) | U-Cd: ≥1.45 (median =2) vs. <0.61 µg/gC | HR: 1.3 (1.1–1.7) for incidence |
| Barregard 2016; MDCS, Sweden; [17] | L; 1991–1994 to 2010 | ACE, incidence | Blood: 0.26 (median) and 0.31 (GM) µg/L | 4745 (328) | B-Cd: >0.5 (median 0.99) vs. <0.17 µg/L | HR: 1.8 (1.2–2.7) |
| Everett 2008; NHANES, US | CS; 1988–1994 | MI, from ECG | Urine: ≥0.65 µg/gC (median) | 4912 (451) | U-Cd: ≥0.88 µg/gC vs. <0.43 µg/g | OR: 1.9 (1.3–2.8) |
| Lee 2011; | CS; IHD, self-reported | Blood: | | 1908 | Continuous | OR: 2.1 | Mean age |

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| Study | Year | Population | Method | Outcome | Measurement | Reference | OR (95% CI) | Notes |
|-------|------|-------------|--------|----------|-------------|-----------|------------|-------|
| KNHANES, ≥20 y, Korea [34] | 2005 | reported | 1.53 µg/L (GM) | (36) | per IQR (0.91 µg/L) per IQR | ≈45y, very few <0.5 µg/L |
| Hecht 2016; NHANES, US [35] | CS; 2003–2012 | MI, self-reported | Blood: 0.27 µg/L (median) | 12511 (663) | B-Cd: >=0.42 vs. <= 0.15 | OR: 1.7 (1.4–2.1) |
| Jeong 2020; KNHANES, 20–59 y, Korea [36] | CS; 2008–2016 | IHD (AMI or angina), self-reported | Blood: 0.89 µg/L (GM) | 10626 (80) | B-Cd: >1.87 (=p90) vs. <1.87 (=below p90) µg/L | OR: 1.1 (0.6–2.2) |
| Tellez-Plaza 2013; Strong HS, US [32] | L; 1989–1991 to 2008 | CHD, incidence, mortality | Urine: not reported | 1145 (243) | U-Cd: ≥1.62 (=p80) vs. <0.55 µg/gC (=p20) | HR: 1.2 (1.0–1.4) |
| Barregard 2016; MDCS, Sweden [17] | L; 1991–1994 to 2010 | ACE, incidence | Blood: 0.20 (median) µg/L | 1782 (111) | B-Cd: >0.5 (median 0.60) vs. <0.17 µg/L (median 0.13) | HR: 2.3 (1.0–5.1) |
| Sears 2020 DHC, Denmark [44] | L; 1993–1997 to 2015 | AMI, incidence | Urine: 0.20 (median) µg/gC | 19394 (809) | U-Cd: Q4 ≥0.32 (median 0.43) vs. Q1 <0.13 µg/gC (median 0.10) | HR: 1.2 (0.9–1.6) |
| Everett 2008 NHANES, US [33] | CS; 1988–1994 | MI, from EKG | Urine: 0.60 (mean) | 2182 (NR) | U-Cd: ≥0.88 µg/gC vs. < 0.43 µg/g | OR: 1.9 (1.1–3.1) |
| Hecht 2016 NHANES, US [35] | CS; 2003–2012 | MI, self-reported | Blood: median NR for | 5963 (185) | B-Cd: >=0.42 vs. <= 0.15 | OR: 1.9 (1.2–3.1) |

**Biomonitoring studies in never-smokers**

| Study | Method | Outcome | Measurement | Reference |
|-------|--------|----------|-------------|-----------|
| Tellez-Plaza 2013; Strong HS, US [32] | CHD, incidence, mortality | Urine: not reported | 1145 (243) |
| Barregard 2016; MDCS, Sweden [17] | ACE, incidence | Blood: 0.20 (median) µg/L | 1782 (111) |
| Sears 2020 DHC, Denmark [44] | AMI, incidence | Urine: 0.20 (median) µg/gC | 19394 (809) |
| Everett 2008 NHANES, US [33] | MI, from EKG | Urine: 0.60 (mean) | 2182 (NR) |
| Hecht 2016 NHANES, US [35] | MI, self-reported | Blood: median NR for | 5963 (185) |
| US [35] | never-smokers | reported uncorrected for dilution |
|---------|---------------|----------------------------------|

Note: B-Cd = blood cadmium, CS = cross-sectional, GM = geometric mean, HR = hazard ratio, IQR = interquartile range, L = longitudinal, OR = odds ratio, U-Cd = urinary cadmium.
Table 3. Epidemiological studies of associations between cadmium (Cd) exposure and stroke.

| Author; study base | Design (L/CS); follow-up or exam period | Outcome | Measure of Cd exposure, overall GM or median | Numbe of subject s (cases) | Exposure contrast (highest category vs. reference or using continuous B-Cd or U-Cd) | Findings | Comments |
|--------------------|----------------------------------------|---------|--------------------------------------------|---------------------------|-----------------------------------------------------------------|---------|----------|
| **Biomonitering studies adjusted for smoking** | | | | | | | |
| Nawrot 2008; CadmiBel , Belgium [37] | L; 1988–1994 to 2000 | Stroke mortality | Blood: 1.2 µg/L Urine: 1.1 µg/24h | 956 (21) | Continuous, per doubling of Cd level | Blood: HR 0.8 (0.5–1.5), urine: HR 0.7 (0.6–1.0) | |
| Tellez-Plaza 2013; Strong HS, US [32] | L; 1989–1991 to 2008 | Stroke incidence, mortality | Urine: 0.92 µg/gC (median) | 3348 (244) | U-Cd: Q4 ≥1.45 (median =2) vs. Q1 <0.61 µg/gC | HR: 1.9 (1.2–2.9) for incidence | For ischemic stroke (N=240): HR 1.9 (1.2–3.1) |
| Barregard 2016; MDCS, Sweden; [17] | L; 1991–1994 to 2010 | Stroke incidence | Blood: 0.26 (median) and 0.31 (GM) µg/L | 4583 (294) | B-Cd: >0.5 (median 0.99) vs. <0.17 µg/L | HR: 1.9 (1.3–2.9) | |
| Peters 2010; NHANES, US [38] | CS; 1996–2006 | Stroke, self-reported | Blood: GM 0.42 µg/L | 12049 (492) | Continuous, per 50% increase | OR: 1.4 (1.1–1.7) | |
| Lee 2011; KNHANES , ≥20 y, Korea [34] | CS; 2005 | Stroke, self-reported | Blood: 1.53 µg/L (GM) | 1908 (44) | Continuous, per IQR (0.91 µg/L) | OR: 1.1 (0.8–1.5) per IQR | Mean age ≈45y, very few <0.5 µg/L |
| Hecht 2016; NHANES, | CS; 2003–2012 | Stroke, self-reported | Blood: 0.27 µg/L (median) | 12511 (500) | B-Cd: T3 >about 0.42 vs. T1 | OR: 1.5 (1.1–2.0) | U-Cd in only 1/3, results |
| Study | Country | Cohort |钨含量 | Incidence | Hazard Ratio | OR | Notes |
|-------|---------|---------|------|-----------|--------------|----|-------|
| Jeong 2020; KNHANES, 20–59 y, Korea | US [35] | CS; 2008–2016 | Stroke, self-reported | Blood: 0.89 µg/L (GM) | 10626 (60) | B-Cd >1.87 (=p90) vs. <1.87 (=below p90) µg/L | 2.4 (1.0–5.5) | GMs were 2.4 µg/L for >p90 and 0.8 µg/L for <p90 |
| Tellez-Plaza 2013; Strong HS, US [32] | US | L; 1989–1991 to 2008 | Stroke incidence, mortality | Urine: NR | 1172 (68) | U-Cd ≥1.62 (median =2) vs. <0.55 µg/gC | HR 0.9 (0.5–1.7) for incidence |
| Barregard 2016; MDCS, Sweden [17] | US | L; 1991–1994 to 2010 | Stroke incidence | Blood: 0.20 (median) µg/L | 583 (111) | B-Cd >0.5 (median 0.60) vs. <0.17 (median 13) µg/L | HR 2.2 (1.0–4.8) |
| Poulsen 2021; DHC, Denmark [45] | US | L; 1993–1997 to 2009 | Stroke incidence | Urine: 0.20 (median) µg/gC | 19394 (534) | Q4 U-Cd ≥0.32 (median 0.44) vs. Q1 <0.10 µg/gC | HR: 1.0 (0.8–1.6) |
| Peters 2010; NHANES, US [38] | US | CS; 1996–2006 | Stroke, self-reported | Blood: GM 0.30 µg/L | 5862 (NR) | Continuous, per 50% increase | OR: 1.2 (1.0-1.4) |
| Hecht 2016; NHANES, US [35] | US | CS; 2003–2012 | Stroke, self-reported | Blood: median NR for never-smokers | 5963 (204) | B-Cd >about 0.42 vs. <about 0.15 | OR 1.5 (0.9-2.4) |

Note: B-Cd = blood cadmium, CS = cross-sectional, GM = geometric mean, HR = hazard ratio, IQR = interquartile range, L = longitudinal, OR = odds ratio, U-Cd = urinary cadmium.

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Table 4. Epidemiological studies of associations between cadmium (Cd) exposure and peripheral artery disease.

| Author; study base | Design (L/CS); follow-up or exam period | Outcome | Measure of Cd exposure, overall GM or median | Num. of subject(s) (cases) | Exposure contrast (highest category vs. reference) | Finding(s) | Comments |
|-------------------|----------------------------------------|---------|---------------------------------------------|----------------------------|-------------------------------------------------|-----------|----------|
| **Biomonitoring studies adjusted for smoking** |
| Navas-Acien 2004, 2005; NHANES, US [50-51] | CS; 1999–2000 | ABI <0.9 in ≥1 leg | Blood: 0.50 µg/L, urine: 0.36 µg/L (GMs) | Blood: 2125 (139), urine: 728 (49) | B-Cd: >0.7 vs. ≤0.4 µg/L, U-Cd: 0.67 vs. 0.19 µg/L | OR: B-Cd 2.8 (1.4–5.9), U-Cd 3.1 (1.0–9.6) | U-Cd only in 1/3 |
| Tellez-Plaza 2010; NHANES, US [46] | CS; 1999–2004 | ABI <0.9 in ≥1 leg | Blood: 0.47 µg/L, urine: 0.37 µg/gC (GMs) | Blood: 6456 (468) | B-Cd: ≥0.80 vs. ≤0.22 µg/L, U-Cd: ≥0.69 vs. <0.20 µg/gC | OR: B-Cd 1.8 (0.8–4.1), U-Cd 4.9 (1.6–16) | U-Cd only in 1/3 |
| Tellez-Plaza 2013; Strong HS, US [47] | L; 1989–1991 to 1999 | ABI <0.9 or >1.4 in ≥1 leg | Urine: 0.94 µg/gC (GM and median) | Blood: 2864 (470) | U-Cd: >1.23 vs. ≤0.71 µg/gC (median≈0.5 µg/gC) | HR: 2.0 (1.3–2.8) | |
| Fagerberg 2013; DIWA, Sweden [48] | L; 2001–2003 to 2007–2009 | ABI ≤0.9 in any of 4 leg arteries | Blood: 0.33 µg/L, urine: 0.35 µg/gC (medians) | Blood: 440 (55) | B-Cd: ≥0.44 vs. <0.25 µg/L, U-Cd: ≥0.44 vs. <0.29 µg/gC | OR: B-Cd 2.4 (0.9–6.3), U-Cd 2.5 (1.1–5.8) | |
| Deering 2018; women ≥70 y, Australia [29] | L; 1998–2013 | Hospital registry diagnoses | Urine: 0.18 µg/L (median) | Blood: 1215 (69) | U-Cd: >0.26 vs. <0.12 µg/L | HR: 1.6 (0.8–2.9) | U-Cd uncorrected for dilution |

Biomonitoring studies in never-smokers
| Tellez-Plaza 2010; NHANES, US [46] | CS; 1999–2004 | ABI <0.9 in ≥1 leg | Blood: NR (median ≈ 0.3 µg/L), urine: NR | 5466 (468) | B-Cd: ≥0.80 vs. ≤0.22 µg/L, U-Cd: ≥0.69 vs. <0.20 µg/gC | OR: B-Cd 3.0 (0.6–15), U-Cd 1.7 (0.6–5.0) | In never-smokers, association with B-Cd only in men |
| Tellez-Plaza 2013; Strong HS, US [47] | L; 1989–1991 to 1999 | ABI <0.9 or >1.4 in ≥1 leg | Urine: median =0.9 | 2864 (470) | U-Cd: >1.62 vs. ≤0.55 µg/gC | HR: 1.3 (0.8–1.8) |

Note: ABI = ankle brachial index, B-Cd = blood cadmium, CS = cross-sectional, GM = geometric mean, HR = hazard ratio, L = longitudinal, OR = odds ratio, U-Cd = urinary cadmium.
Table 5. Epidemiological studies of associations between cadmium (Cd) exposure and atherosclerosis in carotid or coronary arteries, or intima-media thickness (IMT) in carotid arteries (cIMT).

| Author; study base | Design (L/CS); follow-up or exam period | Outcome | Measure of Cd exposure, overall GM or median | Number of subjects (cases) | Exposure contrast (highest category vs. reference or using continuous B-Cd or U-Cd) | Findings | Comments |
|-------------------|----------------------------------------|---------|--------------------------------------------|---------------------------|--------------------------------------------------------------------------------|---------|----------|
| Biomonitoring studies adjusted for smoking |
| Messner 2009; ARFY, Austria [54] | CS; 2005 | cIMT | Serum | 195 (20 above the 90% defined as “high”) | Cd levels not reported | OR 6.4 (1.2–33) for “high IMT” in T3 vs. T1 | Female 18–22-year-old students |
| Fagerberg 2012; DIWA, Sweden [55] | CS; 2001–2003, L; 2001–2003 to 2007–2009 | Carotid artery plaque | Blood: 0.34 μg/L, urine: 0.35 μg/gC (medians) | Blood: 599 (262). Urine: 569 (251). | B-Cd: ≥0.56 (median 0.99) vs. <0.23 (median 0.18) μg/L, U-Cd: ≥0.55 (median 0.77) vs. <0.25 (median 0.18) μg/gC | CS OR: B-Cd 2.5 (1.3–4.6), U-Cd 2.5 (1.1–5.8) L OR: B-Cd 1.8 (0.9–4.0), U-Cd 1.6 (0.8–3.6) |
| Lind 2012; PIVUS, Sweden [57] | CS; 2001–2004 | Carotid artery plaque, cIMT | Blood: 0.27 μg/L (median) v with plaque | 943 (616) | B-Cd: Q5 >0.47 vs. Q1 <0.18 μg/L | Adjusted ORs not reported but not significantly different from 1.0, no significant association | 70-year-old men and women |
| Study Details                                    | Data Source | Study Duration | Carotid/CI MT | Blood/Cadmium Concentration | n with IMT       |
|------------------------------------------------|-------------|----------------|--------------|-----------------------------|-----------------|
| Fagerberg 2015, MDCS, Sweden [56]              | CS; 1991–1994 | Carotid artery plaque | Blood: 0.26 µg/L (median) | 4639 (1640) | B-Cd: >0.5 vs. <0.17 µg/L | OR 1.4 (1.1 – 1.7) |
| Deering 2018; women ≥70 y, Australia [29]      | L; 1998–2013 | Carotid artery plaque, CI MT | Urine: 0.18 µg/L (median) | 1219 (472) | U-Cd: >0.26 vs. <0.12 µg/L | HR: 0.6 (0.4–0.8) |
| Lin 2020, Taiwan [58]                          | CS; 2006–2008 | CI MT          | Urine: 0.63 µg/gC (GM) | 736 | Increase in CI MT per unit ln U-Cd | 17 µm increase per unit ln U-Cd (p<0.001) |
| Barregar 2021, SCAPIS, Sweden [59]             | CS; 2013–2018 | CACS           | Blood: 0.25 µg/L (median) | 5295 (2143, CACS >0; 100: 654) | B-Cd: ≥0.39 (median 0.63) vs. <0.16 (median 0.12) µg/L | CACS >0: PR 1.1 (1.0–1.3), CACS ≥100: PR 1.6 (1.3–2.0) |

**Biomonitoring studies in never-smokers**

| Study Details                                    | Data Source | Study Duration | Carotid/CI MT | Blood/Cadmium Concentration | n with IMT       |
|------------------------------------------------|-------------|----------------|--------------|-----------------------------|-----------------|
| Fagerberg 2012, DIWA, Sweden [55]               | CS; 2001–2003 L; 2001–2003 to 2007–2009 | Carotid artery plaque | Blood: 0.34 µg/L | 267 (92) | B-Cd: ≥0.56 vs. <0.23 µg/L | CS: ORs not reported, but not significantly different from 1.0 |
| Fagerberg 2015, MDCS, Sweden [56]               | CS; 1991–1994 | Carotid artery plaque | Blood: 0.20 µg/L (median) | 1851 (551) | B-Cd: >0.23 (median 0.32) vs. <0.16 (median 0.12) µg/L | OR: 0.8 (0.6–1.1) |
| Barregar 2021, SCAPIS, Sweden [59]             | CS; 2013–2018 | CACS           | Blood: 0.24 µg/L (median) | 2446 (848, CACS ≥100: 200) | B-Cd: ≥0.39 (median 0.48) vs. <0.16 (median 0.12) µg/L | CACS >0: PR 1.1 (0.9–1.3), CACS ≥100: PR 1.7 (1.1–2.7) |

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Note: B-Cd = blood cadmium, CACS = coronary artery calcium score, CS = cross-sectional, GM = geometric mean, HR = hazard ratio, L = longitudinal, OR = odds ratio, PR = prevalence ratio, U-Cd = urinary cadmium.

Table 6. Cadmium content in atherosclerosis-prone artery walls.

| Reference | Vascular tissue                              | Cadmium concentration | Comment                                                                 |
|-----------|----------------------------------------------|-----------------------|------------------------------------------------------------------------|
| [77]      | Abdominal aorta, media layer                | 7 µM                  | All subjects were smokers. Intima 35% and adventitia 55% of the Cd concentration in the media. |
| [78]      | Abdominal aorta                             | 1.78 µM               | Total arterial wall.                                                   |
| [79]      | Atherosclerotic plaque in carotid artery    | 0.34 µM (rupture-prone part of plaque) | Symptomatic plaques obtained by carotid endarterectomy. |
Table 7. Summary of studies examining pro-inflammatory gene expression or protein concentration in human endothelial cells after exposure to cadmium (Cd). For comparison, among smoking patients, the average Cd content was 2.5 µM in the intimal layer of the abdominal aorta (Abu-H) and 0.34 µM in symptomatic plaques from carotid arteries (GB), respectively.

| Reference | Type of endothelial cell | Cd exposure | Microarray or ELISA in supernatant (in comparison with controls) |
|-----------|--------------------------|-------------|---------------------------------------------------------------|
| [90]      | Human artery             | 1.5 µmol/L, 24 hours | Upregulated metallothioneins. Downregulated proinflammatory genes: COX-2, CXCL2. Other genes also regulated. |
| [91]      | Human coronary artery    | 10 µmol/L, 12 hours | Upregulated metallothioneins. Downregulated 12 genes not observed in DB. |
| [48]      | Human aorta              | 0.89 µmol/L, 48 hours | No increased expression of ICAM-1, TNF-α, GMCSF, IF-γ, IL-1β, IL-2, IL-6, IL-9, IL-10, or IL-12. |
|           |                          | 4.4 µmol/L, 48 hours | |
| [92]      | HUVECs                   | 1 µmol/L, 48 hours | Increased VCAM-1. |
|           |                          | 5 µmol/L, 48 hours | Increased VCAM-1 and ICAM-1. |
|           |                          | 10 µmol/L, 48 hours | Increased VCAM-1 and ICAM-1. |
| [85]      | Human pluripotent stem cell-derived endothelial cells | ? µmol/L, 24 hours | Upregulation of 722 genes (metallothioneins, heat-shock proteins, DNA-damage inducible proteins). Downregulation of 423 genes. |

Note: COX-2 = cyclooxygenase 2 (the first rate-limiting enzyme in the conversion of arachidonic acid to prostaglandins), CXCL2 = CXC-motif ligand 2 (a powerful neutrophil chemoattractant), GMCSF = granulocyte-macrophage colony-stimulating factor, HUVEC = human umbilical vein endothelial cell, ICAM-1 = intercellular adhesion molecule-1, IF-γ = interferon-γ, IL = interleukin, TNF-α = tumour necrosis factor-α, VCAM-1 = vascular cell adhesion molecule 1.
Table 8. Animal studies of the proatherosclerotic effect of cadmium (Cd).

| Reference | Species, vessel | Cd exposure µmol/L | Weeks | Results (in comparison with controls) |
|-----------|----------------|--------------------|-------|---------------------------------------|
| [97]      | Rabbit, coronary artery | 0.07 mmol/kg/day | 24    | Increased occurrence of atherosclerotic lesions. Decrease in serum cholesterol. |
| [98]      | Rabbit, aorta | 50 (0.4 µmol) µg/kg/day † | 40    | Cholesterol-feeding increased serum cholesterol and atherosclerotic lesions; this was partly counteracted by Cd in a dose-dependent way. |
| [54]      | ApoE−/− mice, aorta | 0.55 mmol/L in drinking water | 12    | Endothelial damage, atherogenic alterations of lipid profiles, accelerated atherosclerotic plaque formation. |
| [84]      | ApoE−/− mice, aorta | 0.55 mmol/L in drinking water | 12    | Increase in atherosclerotic plaque area, immunohistological staining for VCAM-1 and Hsp60, but not significantly for proinflammatory macrophages. |
| [89]      | ApoE−/− mice, aorta | 0.55 mmol/L in drinking water | 4     | Increase in atherosclerotic plaque area, endothelial dysfunction, oxidative stress. |

† Cadmium was added to the diet. The World Health Organization has established a provisional tolerable weekly intake for cadmium at 7 µg/kg of body weight, hence a 50-fold increase in the lowest daily intake group.

Note: Hsp60 = heat shock protein 60 (a protein inducing autoimmune reactions within the vessel wall), VCAM-1 = vascular cell adhesion molecule 1.