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Abstract

Introduction: Cigarette smoking is a major risk factor for cardiovascular disease via acute and chronic mechanisms, some of which remain unclear. One plausible but untested hypothesis concerns cadmium (Cd), a component of cigarette smoke, which is injurious to vascular endothelial cells and is independently associated with cardiovascular disease. To contribute to the formulation of this hypothesis, we performed a meta-analysis of the available data that consisted of cross-sectional studies useful to formulate but not test hypotheses. **Methods:** PubMed and Google Scholar were searched by combining the terms smoking, Cd, correlation, blood, human, and tobacco. Following abstract review, 10 cross-sectional studies were identified. We compared serum Cd levels between smokers and nonsmokers using standardized mean differences (SMDs) as well as correlation coefficients between smoking and Cd. **Results:** The estimated overall random effects SMD in Cd between smokers and nonsmokers was 1.13 (95% confidence interval [CI], .70-1.56) with significant heterogeneity ($Q = 8.6, P < .001$). The estimated overall random effects correlation coefficient between smoking and Cd was .54 (95% CI, .30-.72) with significant heterogeneity ($Q = 71.3, P < .01$). **Conclusions:** Despite major inherent limitations of meta-analyses of cross-sectional studies, we believe that the data contribute to the formulation of the hypothesis that Cd explains, in part, why smokers have an increased risk of cardiovascular disease. Further research, including analytic studies designed a priori are necessary to test the hypothesis.

Keywords

atherosclerosis, cadmium, cardiovascular disease, endothelium, cigarette smoking, meta-analysis

Introduction

Cigarette smoking is a major risk factor for cardiovascular disease via acute and chronic mechanisms, some of which remain unclear.¹ One plausible mechanism is that cadmium (Cd), a component of cigarette smoke, concentrates in the major arterial vessels of the body and exerts a direct toxic effect upon the vascular endothelium.²⁻⁶

In basic research as early as 1985, rats exposed to Cd-enriched cigarette smoke had significantly higher Cd tissue levels when compared to their cage control counterparts.⁷ Since then, basic research has also shown that both cigarette smoke and Cd produce vascular damage.⁸ These mechanisms include vascular plaque inflammation, vasomotor dysfunction, modification of lipids,^{4,9} and delayed or incomplete reendothelialization as a consequence of decreased endothelial cell migration, a process that follows impaired nitric oxide production.⁸ Endothelial cell death has been demonstrated via stress-activated protein kinases (c-Jun N-terminal kinase), p38 mitogen-activated protein kinases, tumor suppressor protein 53 (p53), and B cell lymphoma 2 (bcl2) family member-dependent pathways.^{10,11} Subsequently, vascular endothelial cell damage provides less endothelial cell control to regulate immune cell entry, resulting in increased accumulation

of foam cells in the vessel wall and atherosclerosis. Damaged vascular endothelium can also foster a prothrombotic environment as

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extracellular matrix components are uncovered, which may contribute to thrombus formation.¹²

The National Health and Nutrition Examination Survey (NHANES) includes a random sample of the US population. In 5 such cross-sectional studies, individuals with higher levels of Cd in the blood or urine had increased risks of impaired fasting glucose, diabetes, hypertension, stroke, heart failure, myocardial infarction, and peripheral artery disease.^{13,14-17} To contribute to the formulation of the hypothesis that Cd explains, in part, why cigarette smokers have increased risks of cardiovascular disease, we quantified the difference in serum Cd between smokers and nonsmokers as well as the level of correlation between smoking and serum Cd levels.

Methods

Search Strategy

Article abstracts were located by searching PubMed and Google Scholar using the combination of several key terms including “cadmium,” “smoking,” “correlation,” “blood,” “human,” and “tobacco.” The abstracts were then screened to identify relevant studies that either measured the differences in mean serum Cd levels between smokers and nonsmokers or evaluated the correlation between cigarette smoking and blood serum Cd levels. The inclusion criteria were published observational studies on adults, where serum Cd and smoking status were reported. Studies were excluded if the source of Cd was either occupational or environmental or where patients were either pregnant or lactating women. Occupational and environmental exposure studies were excluded in order to capture the primary effects of smoking on serum Cd without other sources of influence. Due to changes associated with pregnancy and lactation that might affect the relationship of Cd with smoking, studies of pregnant and lactating women were excluded. Studies including population surveys that did not report correlation coefficients or sample variance also had to be excluded. Only studies published after 1981 and reported in English were included.

Article Coding and Study Effects

Articles were coded in duplicate to calculate study effects including the standardized mean difference (SMD) in serum Cd between smokers and nonsmokers, standard deviations, and the correlation coefficient of smoking to serum Cd among smokers and standard deviations. Discrepancies in coding required agreement between the first 2 authors to be considered resolved.

Effect Size and Measure of Homogeneity Analysis

The main variables of this study were Cd levels and cigarette smoking. We first calculated the degree of heterogeneity across the studies and tested its significance using both Cochran Q-statistics and an I^2 value in order to determine the underlying statistical model. In general, when the Q statistic is not significant, the fixed effect model, which assumes that the observed effects are different from the true population value due to

sampling error, is chosen. Otherwise the random effects model, which assumes that study effects are uniquely different regarding sampling error and other differences, is chosen.¹⁸

The SMD in serum Cd between smokers and nonsmokers in each study was calculated by subtracting the mean serum Cd of nonsmokers from smokers and dividing by the pooled standard deviation. In 1 study, the mean and standard deviation for smokers were reported only for subgroups. To obtain a single mean and standard deviation, the sample was recreated using these estimates to randomly generate the subgroups with the *rnorm* function in R.

The Pearson correlation coefficient (r) was based upon the correlation between the number of cigarettes smoked per day and the serum Cd level. Prior to calculating the overall effect size for r , we transformed r to Fisher z and its variance. Following the calculation of the weighted mean effect size, we transformed the Fisher z statistic and its variance back to the r .

An overall summary effect size was estimated for SMD and r by pooling individual effect sizes weighted by the inverse of its associated variance.

Results

Our search yielded 110 abstracts from PubMed and 82 abstracts from Google Scholar of which 40 full texts were then retrieved and more fully evaluated. In all, 10 studies containing 12 independent groups were selected for analysis based upon meeting the inclusion and exclusion criteria (Supplementary Figure 1). In all, 6 studies (and 7 groups) reported mean differences in serum Cd between smokers and nonsmokers. Five studies of smokers reported the Pearson correlation coefficient of their smoking and their serum Cd levels. One study provided information for both the analyses (Table 1).

The Q and I^2 statistics for the 7 SMDs between smokers and nonsmokers were 28.57% and 79%, respectively, with a degree of freedom of 6 ($P < .01$) suggesting we should reject the null hypothesis of homogeneity across studies and determine the average effect size using the random effects model. Under the random effects model, the standardized weighted average mean difference between the groups was 1.13 with a 95% confidence interval (CI) of .70 to 1.56, suggesting a significantly large mean difference in serum Cd levels between smokers and nonsmokers (Figure 1).

The Q and I^2 statistic for 5 correlation coefficients were 71.3% and 94%, respectively, with a degree of freedom of 4 ($P < .01$), suggesting we should reject the null hypothesis of homogeneity across studies and determine the average effect size using the random effects model. Under the random effects model, the weighted average effect size was .54, with a 95% CI of .30 to .72 suggesting a moderate but significant correlation between level of cigarette smoking and serum Cd levels (Figure 1).

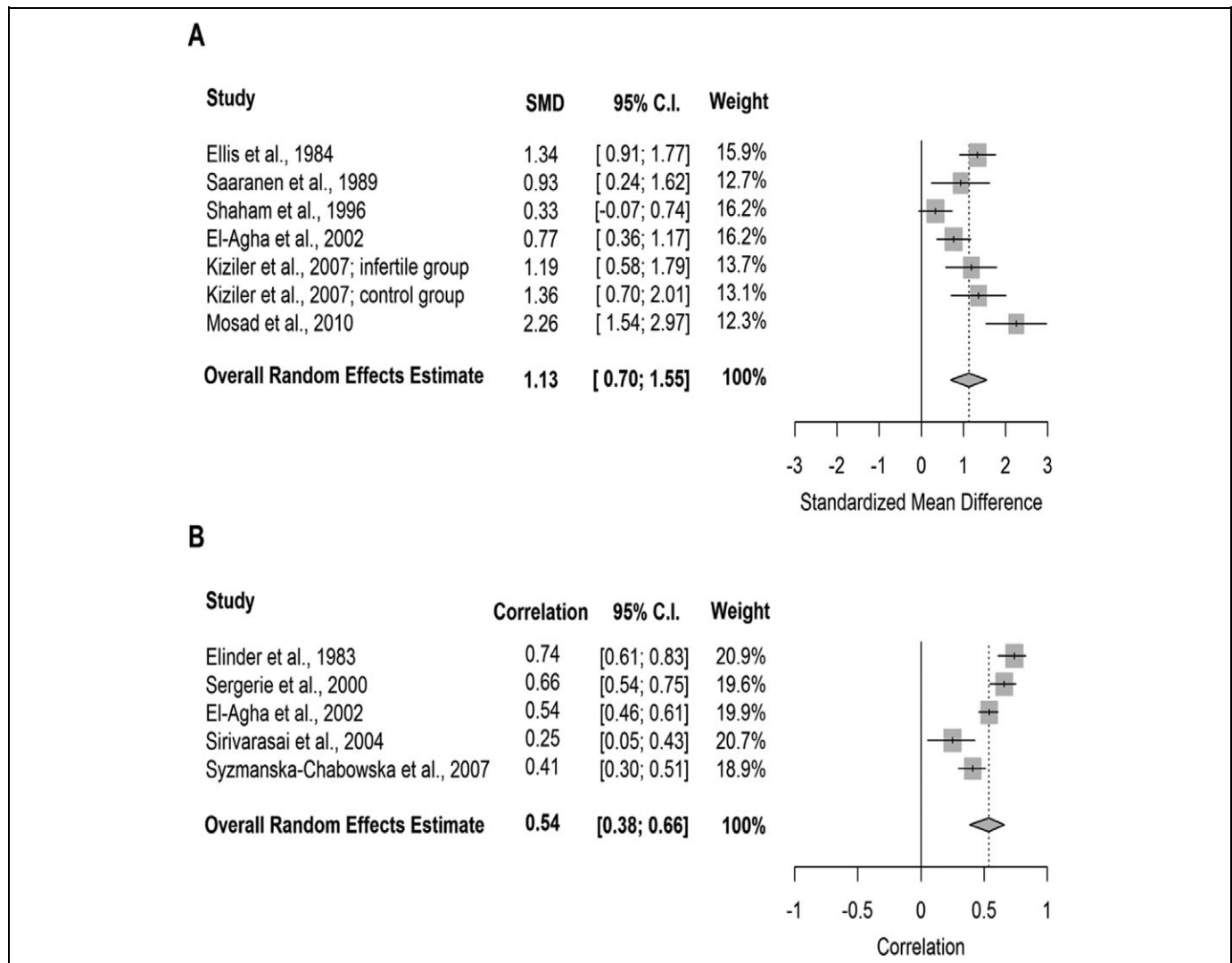
Discussion

In a meta-analysis of cross-sectional studies useful to formulate but not test hypotheses, we found statistically significant

Table 1. Characteristics of Studies Included by Effect Measures.

First Author	Journal	Publication Year	Number of Smokers	Number of Nonsmokers	Age (Mean or Range)	Location
Standardized mean difference						
Ellis ¹⁹	<i>J Clin Pathol</i>	1984	66	41	30-50	United Kingdom
Saaranen ²⁰	<i>Andrologia</i>	1989	16	21	30.5	Finland
Shaham ²¹	<i>J Occup Environ Med</i>	1996	47	50	36.8	Israel
El-Agha ²²	<i>Biol Trace Elem Res</i>	2002	43	61	N/A	Turkey
Kiziler ²³	<i>Biol Trace Elem Res</i>	2007	49	46	40	Turkey
Mosad ²⁴	<i>Curr Eye Res</i>	2010	45	15	53	Egypt
Pearson correlation coefficient						
Elinder ²⁵	<i>Environ Res</i>	1983	337	—	N/A	Sweden
Sergerie ²⁶	<i>Hum Reprod</i>	2000	97	—	27	Canada
El-Agha ²²	<i>Biol Trace Elem Res</i>	2002	119	—	N/A	Turkey
Sirivarasai ²⁷	<i>Asia Pac J Public Health</i>	2004	234	—	41.1	Thailand
Szymańska-Chabowska ²⁸	<i>Int J Occ Med Environ Health</i>	2007	69	—	44	Poland

Abbreviation: N/A, not applicable.

**Figure 1.** Forest plots showing the standardized mean differences in serum cadmium between smokers and nonsmokers (A) and the Pearson correlation coefficients between smoking (cigarettes per day) and serum cadmium levels (B).

differences in the SMDs of Cd between smokers and nonsmokers. We also found correlations with self-reported cigarettes per day in serum Cd among smokers. Among smokers, the overall correlation coefficient of .54 is a moderately large effect. If there is random misclassification of exposure this magnitude is likely to be underestimated.²⁹

These studies were descriptive and therefore useful to formulate hypotheses, so any attempt at summarizing the effect sizes are hypothesis formulating. Further, any meta-analysis, especially of nonrandomized studies, is likely to decrease the role of chance but increase bias and confounding.³⁰ On the other hand, the data sets of 10 independent studies with over 1500 patients were designed to be random samples of local populations. Finally in cross-sectional studies, it is not possible to discern any temporal relationship between the exposure and the outcome. We explored the possibility of publication bias using funnel plots and did not find cogent evidence for either of the 2 separate analyses we conducted (Supplementary Figure 2).

Unexplained variation is apparent in these studies. Mean serum Cd levels for nonsmokers and smokers ranged from .2 to .9 µg/L and from .2 to 4.5 µg/L, respectively. The SMD in serum Cd levels between smokers and nonsmokers also varied with a range of .3 to 2.3. Among smokers, the level of smoking correlated with serum Cd levels across a range of .25 to .74. We were unable to assess possible sources of variation due to the limited number of studies. Several hypothesized sources of variation are possible, most notably gender and age. With respect to gender, under similar conditions of Cd exposure, women tend to have higher urine, blood, and renal Cd levels compared to men owing to decreased iron stores and differences in excretion.³¹ As regards age, the serum Cd levels increase throughout the lifetime of animals and humans.^{13,32-34} In these studies, however, there was insufficient variation in age to assess its possible confounding effects on the observed association.

Other potential sources of variation include varying levels of Cd in different brands of cigarettes, presumably dependent upon the differences in soil content of Cd where the tobacco is grown.³⁵ In general, the soil content of Cd is higher in countries in the far east where industrial processes leech more Cd into nearby agricultural areas.³⁶ The hypothesis of whether tobacco grown in these regions further increases risks of cardiovascular disease has not yet been tested.

It is also plausible that cigarette smokers have different onset of signaling than that of nonsmokers given exposure to Cd. Unfortunately, the studies included in this meta-analysis were all cross-sectional, which precluded our ability to draw inference regarding the onset of smoking or Cd-induced signaling changes that might lead to cardiovascular disease. With respect to differential signaling influences of Cd from smoking versus other sources, the Cd exposure provided by smoking is far greater than that provided by other sources.

Although it is likely that many toxic substances in cigarette smoke contribute to cardiovascular disease,³⁷ few, other than Cd, have the propensity to persist in the vessel wall for decades, initiate endothelial damage, and perpetuate the proinflammatory

and prothrombotic events necessary to accelerate the atherosclerotic process.

Despite the inherent limitations of meta-analyses of cross-sectional studies, we believe that the data contribute to the formulation of the hypothesis that Cd explains, in part, why cigarette smokers have increased risks of cardiovascular disease. Further research, including analytic studies designed a priori are necessary to test the hypothesis as to whether there are valid associations and interrelationships between Cd, cigarette smoking, and cardiovascular disease.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Professor Hennekens reported that he was funded for 5 years by FAU as Principal Investigator of 2 investigator initiated research grants by Bayer; serves as an independent scientist in an advisory role to investigators and sponsors as Chair or Member of Data and Safety Monitoring Boards for Actelion, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, British Heart Foundation, Canadian Institutes of Health Research, Lilly and Sunovion; serves as an independent scientist in an advisory role to the United States (US) Food and Drug Administration (FDA) US NIH, Children's Services Council of Palm Beach County and UpToDate; serves as an independent scientist in an advisory role to legal counsel for Stryker; receives royalties for authorship or editorship of 3 textbooks and as coinventor on patents on inflammatory markers and cardiovascular disease held by Brigham and Women's Hospital; has an investment management relationship with The West-Bacon Group within SunTrust Investment Services who has discretionary investment authority; and does not own any common or preferred stock in any pharmaceutical or medical device company.

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