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Age-related impairments of mobility associated with cobalt and other heavy metals: Data from NHANES 1999-2004

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Abstract

Introduction—Exposure to heavy metals can promote oxidative stress and damage to cellular components, and may accelerate age-related disease and disability.. Physical mobility is a validated biomarker of age-related disability and is predictive of hospitalization and mortality.

Aim—To examine associations between selected heavy metals and impaired lower limb mobility in a representative older human population.

Methods—Data for 1615 adults aged ≥60 years from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004 were used to identify associations between urinary concentrations of 10 metals with self-reported and measured walking impairments (at $p<0.01$). Models were adjusted for confounding factors, including smoking.

Results—In models adjusted for age, sex and ethnicity, elevated levels of cadmium, cobalt and uranium were associated with impairment of the ability to walk a quarter mile. In fully adjusted models, cobalt was the only metal that remained associated: the odds ratio for reporting walking problems with a 1-unit increase in logged cobalt concentration ($\mu g\ L^{-1}$) was 1.43 (95% CI 1.12 to 1.84). Cobalt was also the only metal associated with an increased measured time to walk a 20 foot course ($p=0.008$). In analyses of disease categories to explain the mobility finding, cobalt was associated with physician diagnosed arthritis (1-unit increase OR=1.22 (95% CI 1.00 to 1.49, $p=0.045$).

Conclusions—Low level cobalt exposure, assessed through urinary concentrations of this essential heavy metal may be a risk factor for age-related physical impairments. Independent replication is needed to confirm this association.

Keywords

Cobalt; aging; NHANES; arthritis; gait speed

Interest in the biological effects of heavy metals has increased in recent decades as large amounts of potentially toxic and carcinogenic elements have been released into the

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environment as a result of anthropogenic activities. Whilst improvements in protective legislation have reduced the excessive exposure of both industrial workers and the general population to high concentrations of toxic heavy metals (Christensen, 1995), it is becoming increasingly apparent that prolonged exposure to relatively low concentrations of both essential and non-essential metals may lead to a variety of conditions depending on the route of exposure, metabolism and storage of the specific metal (Hardej and Trombetta 2004).

Detectable levels of a wide range of metals are typically present in over 90% of the normal adult population (CDC 2005). Toxicity arises from the ability of metals to bind to oxygen, nitrogen, and sulfhydryl groups in proteins, resulting in alterations of enzymatic activity that may affect metabolic processes (Hardej and Trombetta 2004). Metals are also associated with the production of reactive oxygen species (ROS) and oxidative stress (Stohs and Bagchi 1995), and in turn with a number of degenerative and immunological disorders. Exposure to different heavy metals can result in damaged or reduced mental and central nervous function, altered blood composition and pathology in lungs, kidneys, liver, and other vital organs. It has been suggested that long-term exposure throughout life may accelerate development of age-related disease and disability including physical, muscular, and neurological degenerative disorders (Barnham and Bush 2008; Domingo 1994; Gallagher et al. In press; Navas-Acien et al. 2005; Uversky et al. 2001). Observing such associations has until now been difficult due to the lack of high-quality population-representative data on exposures, outcomes, and confounding factors.

Here, we access data from the large scale National Health and Nutrition Examination Surveys (NHANES 1999 to 2004) to explore the hypothesis that exposure to low concentrations of heavy metals may be associated with age-related functional impairment. The NHANES surveys assess the health and diet of a representative sample of the population of the United States. This includes biomonitoring for a range of environmental toxins including heavy metals, health outcomes including mobility impairment and many potential confounders. Impaired lower limb mobility (especially difficulty in walking) is a validated biomarker of age-related deterioration in functioning (Hoenig et al. 2006) and is predictive of hospitalization and mortality (Gardener et al. 2006; Hakim et al. 1998). It can be assessed using self-reports of problems with walking or through measured physical performance, e.g. timed walk (gait speed). We examined associations between urinary concentrations of twelve different heavy metals and markers of physical disability in NHANES. For those metals consistently associated with impaired mobility, we explored mechanisms of effect by testing associations with major disease groupings, including cardiovascular and respiratory conditions, stroke, cancer, liver function, thyroid conditions, diabetes, arthritis and asthma.

Methods

Study population

Beginning in the 1960s, the National Centre for Health Statistics (NCHS) has conducted a series of cross-sectional health and nutrition surveys; this became the continuous NHANES in 1999. Each survey has a sample size of around 10000 individuals and using a stratified, multistage probability cluster design, it provides data representing the non-institutionalized U.S. population. Urinary metal analysis was conducted on a one third random subsample of participants aged 6 years and over. Data from the 1999/2000, 2001/2002 and 2003/2004 surveys were combined to provide urinary metal concentrations on 7828 participants. Our study focused on NHANES population aged 60 years and older for which metal concentrations were available for up to 1615 participants. Sample size for each metal is shown in Table 1.

Urinary metals

Urine specimens were collected from the participants after confirmation of no background contamination in collection materials. Urinary concentrations of 12 heavy metals, antimony (Sb), barium (Ba), beryllium (Be), cadmium (Cd), cesium (Cs), cobalt (Co), lead (Pb), molybdenum (Mo), platinum (Pt), thallium (TI), tungsten (W), and uranium (U), were quantified by inductively coupled plasma-mass spectrometry (ICP-MS, PerkinElmer/SCIEX model500; PerkinElmer, Shelton, CT, USA) using published methods (available: http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l06_c_met_hm.pdf. Accessed 01 June 2008) at the Environmental Health Sciences Laboratory of the Centres for Disease Control and Prevention (CDC) and the National Centre for Environmental Health (NCEH). Urine Standard Reference Material 2670 and 2670A from the National Institute of Standards and Technology (Gaithersburg, MD, USA) was used for external calibration and spiked pools prepared at the laboratory were used for internal quality control. Quality control samples included both bench and blind samples. The limits of detection (3× the concentration standard deviation of urine blanks) varied by metal, from 0.004 $\mu g\ L^{-1}$ for uranium to 0.8 $\mu g\ L^{-1}$ for molybdenum (Table 1). Urinary creatinine was determined using an enzymatic reaction measured with a Beckman Synchron CX3 Clinical Analyzer. Detail on the NCHS website (available: http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l16_c_met_creatinine.pdf Accessed 01 June 2008).

Mobility-based health outcomes

i. *Self-reported problem with walking a quarter of a mile*. Participants were asked "By yourself and without using any special equipment, how much difficulty do you have walking for a quarter of a mile [that is about 2 or 3 blocks]?" The respondents could choose from: "no difficulty, some difficult, much difficulty, unable to do, do not do this activity". For regression analysis, participants were categorised as either having difficulty with walking (i.e. some or more difficulty) or no difficulty.

ii. *Measured time to walk a 20-foot course*. The time taken for participants to walk a 20 foot (6.1 m) course (with the aid of a cane if normal) was measured. This outcome was only available in the 1999/2000 and 2001/2002 surveys.

Medical conditions

Participants were asked "Has a doctor or other health professional ever told you that you had …….?" Medical conditions assessed were: angina, myocardial infarction (heart attack), chronic heart failure and chronic health disease were combined as cardiovascular; stroke; cancer, liver conditions; thyroid conditions; diabetes; arthritis; asthma; bronchitis and emphysema were combined. The respondents could choose from: "yes or no".

Statistical analysis and adjustment for potential confounding

All analyses were conducted using Stata SE 9.2. Logistic regression was used to estimate odds ratios of self-reported ability to walk a quarter of a mile (402 m) in relation to logged concentrations ($\mu g\ L^{-1}$) of all urinary metals with >50 % of concentrations above the limits of detection (Table 1), and linear regression to estimate associations between timed walk and logged concentrations of urinary metals. The NHANES survey weights were used to take account of the complex sampling design and adjusted models for the potential confounders described below. Logistic regression was used to estimate odds ratios of a range of clinically diagnosed of medical conditions (as above) associated with cobalt only. Because we were testing for associations with multiple exposures we used a significance level of $p<0.01$.

Regression models were adjusted for potential confounders. Variables included were: race/ethnicity, categorized in five groups based on self-description: Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race (including multi-racial); education, categorized in three groups: less than high school, high school diploma (including GED), and more than high school; annual household income, categorized in three categories of approximately equal size: less than $25,000; $25,000 to $55,000; over $55,000; smoking, categorized, based on self-reported status, as current smoker, ex-smoker, and never-smoker; Body Mass Index (measured weight in kilograms divided by the square of measured height in meters), categorized as underweight (BMI <18.5), recommended weight (BMI 18.5 to 24.9), overweight (BMI 25.0 to 29.9), obese I (BMI 30.0 to 34.9), or obese II (BMI 35.0 or above); alcohol use, categorized, based on self-reported status, on average consumption of alcoholic beverages per day over past 12 months, of 0, 1, 2, 3 to 4, and 5 or more drinks per day; urinary creatinine to account for urine concentration. Due to uncertainties with corrections for creatinine concentrations reported by Barr et al (2005), we have provided models with (model C) and without (model B) adjustment for urinary creatinine. In response to concerns that dietary supplements that contain cobalt may give rise to false positive associations, self-reported use of dietary supplements by NHANES participants was included in the models and the health outcomes were retested, but this did not affect the associations.

Results

Metal concentrations in urine

More than 95% of the sample had detectable concentrations of most metals but not of beryllium (64.4%), platinum (62%), tungsten (35.5%) and uranium (12.4%) (Table 1). The metal with the highest urinary concentration was platinum at 1177.5 $\mu g\ L^{-1}$, with molybdenum, cobalt and cesium all having maximum concentrations in excess of 500 $\mu g\ L^{-1}$ (Table 1). Due to the large proportion of respondents with concentrations of beryllium and platinum below detection limits, these metals were removed from further statistical testing.

Metals and self-reported problems walking a quarter mile

After adjustment for age, sex and race/ethnicity, logged cadmium, cobalt and uranium concentrations were all significantly associated (at $p<0.01$) with self-reported problems in walking a quarter of a mile (Model, A, Table 2). However, after adjustment for education, income, smoking, BMI and alcohol use, an association at $p<0.01$ remained only for cobalt (OR=1.40; 1.13, 1.72) (Model, B, Table 2). With additional adjustment for urinary creatinine levels (Model C, Table 2), only cobalt ($p<0.01$) remained significant. The odds ratio associated with a 1-unit increase in logged cobalt levels and self-reported problems walking a quarter of a mile was 1.43 (95% CI 1.12 to 1.84, $p = 0.005$).

Metals and time to walk 20 feet

After adjusting for the confounders described above, only cobalt was positively correlated ($p = 0.008$) with a reduction in timed walk (Table 3).

Cobalt and medical conditions

As cobalt was the only heavy metal associated with the mobility outcomes after adjustment for confounders, we examined associations between cobalt and the available major medical condition groupings. Cobalt was associated with arthritis ($p = 0.001$) after adjustment for age, sex and race/ethnicity only (model A). This association survived full adjustment (models C): the odds ratio for a 1-unit increase in logged cobalt levels was 1.22 (95% CI

1.00 – 1.49, p = 0.045, Table 4). This corresponded to an approximately 20% higher urinary cobalt concentration in those with arthritis conditions.

Discussion

Low level heavy metal exposure is common but little has been known about the associations of most heavy metals with aging outcomes. Cadmium and lead have often been recognised as posing toxicological threats to humans and other animals, but far less is known regarding low level exposure to the other heavy metals measured in the NHANES study. We undertook the first large-scale analysis of urinary levels of heavy metals in the general older population of the USA in relation to physical aging outcomes, using the NHANES databases. We examined associations for the ten metals for which most respondents had detectable levels, using a significance level of p<01. In models adjusted for potential confounders including smoking, cobalt was the only metal associated with mobility outcomes. The odds ratio for reported difficulties in walking a quarter of a mile with a 1-unit increase in logged cobalt levels was 1.43 (95% CI 1.12 to 1.84). This association based on self reported difficulties was confirmed with an objective performance measure (timed walk). In an analysis of diseases which may explain the association of cobalt with mobility difficulties, we found an association with physician diagnosis of arthritis (odds ratio 1.22, 95% CI 1.00 – 1.49, p = 0.045).

Most of the heavy metals measured were present in the urine of the vast majority of the population (Table 1). Chronic exposure to various toxic metals is associated with a range of health problems (Hardej and Trombetta 2004). Lead and cadmium in particular have historically been reported to cause toxic effects to many species including humans (Depledge et al. 1994; Domingo 1994). In the present study, these metals, together with antimony, tungsten and uranium, appeared to be associated with self-reported problems with walking a quarter of a mile in the American over 60 population at a p-value of <0.05 (though not at the more stringent significance level of p<0.01 adopted for our analysis). Together with cadmium, low-level concentrations of tungsten and antimony were previously linked to peripheral arterial disease using data from NHANES (Navas-Acien et al. 2005). As noted by Navas-Acien et al. (2005), there is very little information concerning chronic low-level exposure to these heavy metals. Some of the negative impact on walking appears to be due to co-variants accounted for within model B, as the significance of the odds ratios was reduced for all metals after adjusting for these confounders (Table 2). Uncertainties with the validity of correction for creatinine concentrations in widely disparate populations have been reported by Barr et al. (2005), who note significant predictors of urinary creatinine to include age, sex, race/ethnicity, body mass index and fat-free mass. Based on this uncertainty, we have reported results both with and without correction but found only minor differences between models B and C (Tables 2, 3 and 4).

Impaired lower limb mobility is a well established biomarker of age-related decline (Hoenig et al. 2006) and is predictive of hospitalization and mortality. Exposure to toxins that impair mobility may also promote other age-related disorders and reduce life expectancy. Although it was hypothesized that the age-related outcomes used in the present study may be associated with low-level heavy metal concentrations, the associations with cobalt were unexpected as the low concentrations reported were mainly within the reported ‘normal’ range. Over 98% of the over 60s NHANES population had urinary cobalt concentrations within the range 0.04 to 2 $\mu g\ L^{-1}$ reported by Ichikawa (1985) for non-industrially exposed humans. Ohashi et al. (2006) reported a mean urinary cobalt concentration for non-occupationally exposed Japanese women of 0.68 $\mu g\ L^{-1}$ but the authors noted that this was higher than comparable studies. The geometric mean concentration in people aged 60+ in the present study was 0.31 $\mu g\ L^{-1}$ (Table 1). A few individuals in the NHANES population

had very high concentrations (maximum 556.6 μg L^{-1}, Table 1) but no information was available to explain these values. One possibility is leakage from worn orthopaedic joint replacements constructed of cobalt and chrome alloy (Papageorgiou et al. 2007). Excluding individuals with urinary cobalt concentrations greater than 10 μg L^{-1} from the analysis did not change our result i.e linear regression of timed walk and logged concentration produced a β value of 0.34 ($p = 0.006$) in the fully adjusted model (C).

A small study by Rosborg et al (2007), investigating the imbalance of the trace element status, in human tissues and body fluids as a contributing factor for the development of fibromyalgia (a chronic condition that causes fatigue and pain in muscles and ligaments which was included within the arthritis category in NHANES), found increased blood concentrations of trace metals, including cobalt, in those suffering from fibromyalgia. The authors concluded that as both blood and urinary levels were within the normal range, the hypothesis that trace metal abnormalities play a significant role in fibromyalgia was not supported. The present study suggests that their conclusion may have been premature, and 'normal level' exposure to cobalt and its mechanism of toxicity should be considered.

The kinetics of cobalt urinary excretion have been reported to be multiphase with a first stage of rapid elimination, within a day of exposure, and a second phase of slower elimination over the following weeks (Torra et al. 2005). This means that urinary concentrations represent relatively recent exposure. As longer term exposure measures would be less variable, the true associations between cobalt exposure and aging outcomes may be stronger than we have estimated.

Food is the largest potential source of cobalt for the general population and most of the cobalt that is ingested is inorganic (Kim 2006). The occurrence of cobalt in drinking-water is reported to be rare and concentrations low, with ranges from 0.1 to 5 μg L^{-1} (Barceloux 1999). Intake in the US population is estimated to be 5 - 40 μg cobalt day^{-1}, mainly from fish and vegetables which are the richest sources (Kim 2006). Absorption of cobalt in humans via food has been found to be highly variable but was increased among individuals who were iron deficient (Kim 2006). As an essential element, cobalt is found in all tissues and total body burden in humans has been estimated as 1.1 - 1.5 mg, with 0.11 mg in the liver (Kim 2006). Uptake of cobalt can also result from inhalation of airborne particles resulting in deposition in the upper and lower respiratory tract, which can then be absorbed into the blood after dissolution or mechanically transferred to the gastrointestinal tract by mucociliary action and swallowing (Casarett and Doull 1986). This route of uptake is more likely in those working in cobalt-associated industries and those living proximate to industrial emissions. Urinary cobalt concentrations have been reported to correlate positively with occupational exposure to cobalt with 59 - 78 μg L^{-1} in urine from exposed workers. Some bottled mineral waters are marketed for the positive benefits of cobalt and claim to contain up to 100 ppm. Some multi-mineral dietary supplements also contain cobalt. Concerned that such supplements may give rise to false positive associations, self-reported use of dietary supplements by NHANES participants was included in the models and the health outcomes were retested, but this did not affect the associations. Although vitamin B_{12} contains cobalt, this represents only a small fraction of cobalt intake and has previously been found not to influence urinary cobalt concentration (Linnainmaa and Kiilunen 1997).

The physical effects reported following chronic exposure to elevated concentrations of cobalt include cardiac abnormalities and gastrointestinal disturbance. Hard metal lung disease, also known as cobalt lung is associated with inhalation of metallic dusts and there is some evidence for an autoimmune mechanism. In animal studies, exposure to cobalt has shown evidence of carcinogenic activity (NTP 1988) and increased levels of oxidatively damaged DNA bases in the liver, kidney, and lung (Kasprzak et al. 1994) and micronucleus

formation in mouse bone marrow cells (Suzuki et al. 1993). In humans, cobalt has been reported to cause clastogenic effects and sister chromatid exchanges in human lymphocytes (Anard et al. 1997; Andersen 1983). Exposure to soluble cobalt has resulted in increased indices of oxidative stress, diminished levels of reduced glutathione, increased levels of oxidized glutathione, activation of the hexose monophosphate shunt, and free radical-induced DNA damage (Hoet et al. 2002; Kasprzak et al. 1994; Lewis et al. 1991; Zhang et al. 1998). Although, some forms of cobalt can be very reactive in terms of producing ROS (Wang et al. 1993), there is little evidence from previous studies to explain why only cobalt should be more associated with the impairment in age-related outcomes measured than other metals. One possibility is that cobalt is a poor inducer of metallothionein protein which can protect cells from toxic effects (Li et al. 2006). Exposure to cobalt also affects genes that are sensitive to oxidant status, which may lead to the induction of apoptosis through either these genes or other pathways (Kim 2006). Soluble cobalt has been reported to block inorganic calcium channels (Yamatani et al. 1998) which may interfere with neuromuscular transmissions.

Cobalt has, along with aluminium, copper, iron and manganese, been associated with significant accelerations in the rate of fibril formation that is thought to promote Parkinson's disease via oxidative stress as the molecular mechanism (Uversky et al. 2001). Although their study was performed in-vitro using high levels of metals with low concentrations of α-synuclein, it was suggested that with higher α-synuclein levels much lower concentrations of metals would be required. Furthermore, in a later study (Uversky et al. 2002), synergistic effects between aluminium and pesticides were found. The possibility that cobalt may act synergistically with other environmental contaminants could explain the unexpected association of this metal with all three negative health outcomes at concentrations mainly within the normal range. Some studies have shown synergic effects between cobalt and other metals, primarily copper (Chu and Chow 2002; Cross et al. 2001; Fulladosa et al. 2005; Marr et al. 1998). Insufficient information concerning copper exposure was available within the NHANES data to test for interactivity between cobalt and copper.

In evaluating our results, it should be borne in mind that multiple statistical testing of the ten separate metals could have produced false positive results, although we have reduced this risk by adopting a significance level of $p<0.01$. Our analyses are also based on cross-sectional data, which cannot indicate whether the exposures predate the outcomes studied. It is not clear from our results whether the association between cobalt and the age-related health outcomes reflects a causal relationship or has arisen due to some unmeasured confounder. The large proportion of the NHANES participants with detectable cobalt concentrations and the association with arthritis suggests that cobalt may be a primary factor in the reported mobility impairment, but our findings need independent replication and verification. Although there are several possible mechanisms by which cobalt may affect arthritic conditions, evidence from the literature suggests cobalt is unlikely to be solely responsible. If the cobalt - aging outcomes association proves robust, more work will be needed to explore the mechanisms of effect involved.

Conclusions

Analyses of the NHANES 1999 to 2004 population sample aged ≥60years suggests that higher cobalt concentrations, even when present within the normal range of urinary concentrations, may be associated with age related mobility impairment. This association may be mediated by arthritic conditions. Follow-up studies are required to confirm the findings and explore possible interactive effects between cobalt and other environmental contaminants.

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References

Anard D, KirschVolders M, Elhajouji A, Belpaeme K, Lison D. In vitro genotoxic effects of hard metal particles assessed by alkaline single cell gel and elution assays. Carcinogenesis. 1997; 18(1): 177–184. [PubMed: 9054604]

Andersen O. Effects of Coal Combustion Products and Metal-Compounds on Sister Chromatid Exchange (Sce) in a Macrophagelike Cell-Line. Environmental Health Perspectives. 1983 Jan. 47:239–253. [PubMed: 6337826]

Barceloux DG. Cobalt. Journal of Toxicology-Clinical Toxicology. 1999; 37(2):201–216. [PubMed: 10382556]

Barnham KJ, Bush AI. Metals in Alzheimer's and Parkinson's diseases. Curr Opin Chem Biol. 2008; 12(2):222–228. [PubMed: 18342639]

Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. Urinary creatinine concentrations in the US population: Implications for urinary biologic monitoring measurements. Environmental Health Perspectives. 2005; 113(2):192–200. [PubMed: 15687057]

Casarett, L.; Doull, J. Toxicology: The basic science of poisons. 3. New York, NY: Macmillan Publishing Company; 1986.

CDC. Third National Report on Human Exposure to Environmental Chemicals. Atlanta (GA): CDC; 2005. Centers for Disease Control and Prevention.

Christensen HM. Human exposure to toxic metals: factors influencing interpretation of biomonitoring results. Sci Total Environ. 1995; 166(1):89–135. [PubMed: 7754357]

Chu KW, Chow KL. Synergistic toxicity of multiple heavy metals is revealed by a biological assay using a nematode and its transgenic derivative. Aquat Toxicol. 2002; 61(1-2):53–64. [PubMed: 12297370]

Cross DP, Ramachandran G, Wattenberg EV. Mixtures of nickel and cobalt chlorides induce synergistic cytotoxic effects: Implications for inhalation exposure modeling. Annals of Occupational Hygiene. 2001; 45(5):409–418. [PubMed: 11418091]

Depledge, MH.; Bjerregaard, P.; Weeks, JM. Heavy Metals. Chapter 5. In: Calow, P., editor. Handbook of Ecotoxicology. Vol. 2. Cambridge: Blackwell Publ.; 1994. p. 79-105.

Domingo JL. Metal-Induced Developmental Toxicity in Mammals - a Review. Journal of Toxicology and Environmental Health. 1994; 42(2):123–141. [PubMed: 8207750]

Fulladosa E, Murat JC, Villaescusa I. Study on the toxicity of binary equitoxic mixtures of metals using the luminescent bacteria Vibrio fischeri as a biological target. Chemosphere. 2005; 58(5): 551–557. [PubMed: 15620748]

Gallagher C, Kovach J, Meliker J. Urinary Cadmium and Osteoporosis in U.S. Women Age 50 and Older, NHANES 1988-1994 and 1999=2003. Environmental Health Perspectives. In press. 10.1289/ehp.11452

Gardener EA, Huppert FA, Guralnik JM, Melzer D. Middle-aged and mobility-limited - Prevalence of disability and symptom attributions in a national survey. Journal of General Internal Medicine. 2006; 21(10):1091–1096. [PubMed: 16970558]

Hakim AA, Petrovitch H, Burchfiel CM, Ross GW, Rodriguez BL, White LR, et al. Effects of walking on mortality among nonsmoking retired men. New England Journal of Medicine. 1998; 338(2):94–99. [PubMed: 9420340]

Hardej, D.; Trombetta, L. Metals. In: Barile, F., editor. Clinical Toxicology Principles and Mechanisms. Washington, D.C: CRC Press; 2004. p. 295-317.

Hoenig H, Ganesh SP, Taylor DH, Pieper C, Guralnik J, Fried LP. Lower extremity physical performance and use of compensatory strategies for mobility. Journal of the American Geriatrics Society. 2006; 54(2):262–269. [PubMed: 16460377]

Hoet PMH, Roesems G, Demedts MG, Nemery B. Activation of the hexose monophosphate shunt in rat type II pneumocytes as an early marker of oxidative stress caused by cobalt particles. Archives of Toxicology. 2002; 76(1):1–7. [PubMed: 11875618]

Ichikawa Y, Kusaka Y, Goto S. Biological Monitoring of Cobalt Exposure, Based on Cobalt Concentrations in Blood and Urine. International Archives of Occupational and Environmental Health. 1985; 55(4):269–276. [PubMed: 4008051]

Kasprzak KS, Zastawny TH, North SL, Riggs CW, Diwan BA, Rice JM, et al. Oxidative DNA-Base Damage in Renal, Hepatic, and Pulmonary Chromatin of Rats after Intraperitoneal Injection of Cobalt(Ii) Acetate. Chemical Research in Toxicology. 1994; 7(3):329–335. [PubMed: 8075364]

Kim JH. Cobalt and inorganic cobalt compounds. Concise International Chemical Assessment Document 69: World Health Organization. 2006

Lewis CPL, Demedts M, Nemery B. Indexes of Oxidative Stress in Hamster Lung Following Exposure to Cobalt(Ii) Ions - Invivo and Invitro Studies. American Journal of Respiratory Cell and Molecular Biology. 1991; 5(2):163–169. [PubMed: 1892647]

Li Q, Chen HB, Huang X, Costa M. Effects of 12 metal ions on iron regulatory protein 1 (IRP-1) and hypoxia-inducible factor-1 alpha (HIF-1 alpha) and HIF-regulated genes. Toxicol Appl Pharmacol. 2006; 213(3):245–255. [PubMed: 16386771]

Linnainmaa M, Kiilunen M. Urinary cobalt as a measure of exposure in the wet sharpening of hard metal and stellite blades. International Archives of Occupational and Environmental Health. 1997; 69(3):193–200. [PubMed: 9049670]

Marr JCA, Hansen JA, Meyer JS, Cacela D, Podrabsky T, Lipton J, et al. Toxicity of cobalt and copper to rainbow trout: application of a mechanistic model for predicting survival. Aquat Toxicol. 1998; 43(4):225–238.

Navas-Acien A, Silbergeld EK, Sharrett AR, Calderon-Aranda E, Selvin E, Guallar E. Metals in urine and peripheral arterial disease. Environmental Health Perspectives. 2005; 113(2):164–169. [PubMed: 15687053]

Nieboer E, Richardson DHS. The Replacement of the Non-Descript Term Heavy-Metals by a Biologically and Chemically Significant Classification of Metal-Ions. Environmental Pollution Series B-Chemical and Physical. 1980; 1(1):3–26.

NTP. Report on the toxicology and carcinogenesis studies of cobalt sulfate heptahydrate (CAS No. 10026-24-1) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC: United States Department of Health and Human Services, National Institutes of Health, National Toxicology Program (NIH Publication No. 471); 1988.

Ohashi F, Fukui Y, Takada S, Moriguchi J, Ezaki T, Ikeda M. Reference values for cobalt, copper, manganese, and nickel in urine among women of the general population in Japan. International Archives of Occupational and Environmental Health. 2006; 80(2):117–126. [PubMed: 16736192]

Papageorgiou I, Yin ZR, Ladon D, Baird D, Lewis AC, Sood A, et al. Genotoxic effects of particles of surgical cobalt chrome alloy on human cells of different age in vitro. Mutat Res-Fundam Mol Mech Mutagen. 2007; 619(1-2):45–58.

Rosborg I, Hyllen E, Lidbeck J, Nihlgard B, Gerhardsson L. Trace element pattern in patients with fibromyalgia. Sci Total Environ. 2007; 385:20–27. [PubMed: 17714765]

Stohs SJ, Bagchi D. Oxidative Mechanisms in the Toxicity of Metal-Ions. Free Radical Biology and Medicine. 1995; 18(2):321–336. [PubMed: 7744317]

Suzuki Y, Shimizu H, Nagae Y, Fukumoto M, Okonogi H, Kadokura M. Micronucleus Test and Erythropoiesis - Effect of Cobalt on the Induction of Micronuclei by Mutagens. Environ Mol Mutagen. 1993; 22(2):101–106. [PubMed: 8359151]

Torra M, Fernandez J, Rodamilans M, Navarro AM, Corbella J. Biological monitoring of cobalt exposure: results in a non-exposed population and on workers of a hard metal manufacture. Trace Elem Electrolytes. 2005; 22(3):174–177.

Uversky VN, Li J, Bower K, Fink AL. Synergistic effects of pesticides and metals on the fibrillation of alpha-synuclein: Implications for Parkinson's disease. Neurotoxicology. 2002; 23(4-5):527–536. [PubMed: 12428725]

Uversky VN, Li J, Fink AL. Evidence for a partially folded intermediate in alpha-synuclein fibril formation. Journal of Biological Chemistry. 2001; 276(14):10737–10744. [PubMed: 11152691]

Wang XY, Yokoi I, Liu JK, Mori A. Cobalt(Ii) and Nickel(Ii) Ions as Promoters of Free-Radicals in-Vivo - Detected Directly Using Electron-Spin-Resonance Spectrometry in Circulating Blood in Rats. Archives of Biochemistry and Biophysics. 1993; 306(2):402–406. [PubMed: 8215442]

Yamatani K, Saito K, Ikezawa Y, Ohnuma H, Sugiyama K, Manaka H, et al. Relative contribution of Ca2+-dependent mechanism in glucagon-induced glucose output from the liver. Archives of Biochemistry and Biophysics. 1998; 355(2):175–180. [PubMed: 9675024]

Zhang CG, Cai WQ, Li Y, Huang WQ, Su HC. Quantitative analysis of calcitonin gene-related peptide- and neuropeptide Y-immunoreactive nerve fibers in mesenteric blood vessels of rats irradiated with cobalt-60 gamma rays. Radiation Research. 1998; 149(1):19–26. [PubMed: 9421150]

Abbreviations

NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
CI	Confidence Interval

Table 1

Urinary metals concentrations (μg L^{-1}) in the NHANES 1999 to 2004, aged ≥60 years old.

	Ba	Be	Cd	Co	Cs	Mo	Pb	Pt	Sb	Tl	U	W
Sample size	1557	1615	593	1615	1615	1563	1615	1615	1574	1596	1105	1587
Geometric mean	1.11	0.09	0.39	0.31	4.21	38.87	0.84	0.04	0.10	0.13	0.009	0.06
Percentiles												
5	0.21	0.08	0.08	0.08	1.2	9.0	0.20	0.03	0.05	0.04	0.003	0.02
25	0.59	0.08	0.21	0.19	2.8	22.7	0.50	0.03	0.05	0.08	0.004	0.03
50	1.10	0.09	0.41	0.31	4.5	40.4	0.86	0.03	0.10	0.14	0.007	0.06
75	2.20	0.09	0.70	0.49	6.7	70.7	1.50	0.05	0.14	0.22	0.014	0.10
95	5.90	0.09	1.61	1.07	11.1	151.5	3.30	0.05	0.29	0.38	0.051	0.28
Maximum	81.8	0.2	4.84	556.6	552.1	592.0	31.5	1177.5	5.7	2.8	0.6	4.6
LOD	0.12	0.13	0.06	0.07	0.14	0.80	0.10	0.04	0.04	0.02	0.004	0.04
% < LOD	1.6	64.4	2.4	4.0	4.3	0.1	0.8	62.0	1.5	3.9	12.4	35.5

Abbreviations: LOD = Limit of Detection

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Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for self-reported problems walking quarter of a mile, respondents aged 60+.

	Model A			Model B			Model C		
	OR	***CI***	***n***	***OR***	***CI***	***n***	***OR***	***CI***	***n***
Ba	1.06	(0.94, 1.19)	1349	1.03	(0.89, 0.19)	1307	1.00	(0.86, 1.17)	1307
Cd	1.64	(1.32, 2.05) ***	468	1.40	(1.00, 1.95) *	461	1.45	(0.86, 2.45)	461
Cs	1.07	(0.86, 1.34)	1405	1.13	(0.92, 1.40)	1362	1.04	(0.76, 1.41)	1362
Co	1.47	(1.18, 1.84) ***	1405	1.40	(1.13, 1.72) **	*1362*	1.43	(1.12, 1.84) **	1362
Mo	1.05	(0.90, 1.22)	1355	1.00	(0.84, 1.19)	1312	0.91	(0.73, 1.14)	1312
Pb	1.26	(1.05, 1.50) *	1405	1.18	(0.98, 1.42)	1362	1.14	(0.90, 1.34)	1362
Sb	1.41	(1.08, 1.85) *	1366	1.25	(0.97, 1.62)	1323	1.22	(0.91, 1.64)	1323
Tl	0.98	(0.76, 1.26)	1388	0.98	(0.77, 1.25)	1347	0.84	(0.62, 1.13)	1347
U	1.15	(1.22, 1.77) ***	928	1.35	(1.08, 1.71) *	*891*	1.33	(1.03, 1.71) *	891
W	1.18	(1.02, 1.38) *	1378	1.15	(0.99, 1.34)	1336	1.11	(0.94, 1.32)	1336

Model A: adjusted for age, sex and race/ethnicity. Model B: adjusted for age, sex, race/ethnicity, education, income, smoking, BMI, drinking. Model C: further adjusted by urinary creatinine.

* = significant difference p value ≤ 0.05,

** p ≤ 0.01 and

*** p ≤ 0.001.

Table 3

Linear regression coefficients (β) and 95% confidence intervals (CI) for timed walk over a 20-foot course, respondents aged 60+.

	Model A			Model B			Model C		
	β	***CI***	***n***	***β***	***CI***	***n***	***β***	***CI***	***n***
Ba	0.007	(-0.13, 0.14)	879	-0.012	(-0.16, 0.14)	849	-0.001	(-0.18, 0.18)	849
Cd		No observations			No observations			No observations	
Cs	-0.145	(-0.35, 0.06)	928	-0.101	(-0.31, 0.11)	898	-0.130	(-0.41, 0.15)	849
Co	0.294	(0.07, 0.52) *	928	0.177	(0.02, 0.33) *	898	0.314	(0.09, 0.54) **	898
Mo	0.106	(0.07, 0.28)	882	0.000	(-0.15, 0.15)	852	0.092	(-0.72, 0.26)	852
Pb	-0.048	(-0.20, 0.10)	928	-0.056	(-0.23, 0.12)	898	-0.048	(-0.32, 0.23)	898
Sb	0.099	(-0.16, 0.36)	888	-0.056	(-0.25, 0.13)	858	-0.030	(-0.26, 0.20)	858
Tl	-0.238	(-0.43, -0.04) *	916	-0.176	(-0.35, -0.00) *	887	-0.242	(-0.48, -0.00) *	887
U	-0.007	(-0.23, 0.22)	463	-0.149	(-0.36, (0.06)	436	-0.105	(-0.38, 0.17)	436
W	0.117	(-0.07, 0.31)	903	0.015	(-0.14, 0.17)	873	0.044	(-0.13, 0.22)	873

Coefficient = difference in time to complete course (i.e. higher values = slower speed).

Model A: adjusted for age, sex and race/ethnicity. Model B: adjusted for age, sex, race/ethnicity, education, income, smoking, BMI, drinking. Model C: further adjusted by urinary creatinine.

* = significant difference p value ≤ 0.05,

** p ≤ 0.01 and

*** p ≤ 0.001.

Table 4

Odds ratios (with 95% confidence intervals) of medical conditions associated with cobalt with and without adjustment for creatinine concentrations.

	number of cases (% of total sample)	Odds Ratios (± 95% CI)	
		Unadjusted (model B)	*Adjusted (model C)*
Cardiovascular	349 (22.5)	1.15 (0.97, 1.36)	1.22 (0.98, 1.51)
Stroke	130 (8.1)	1.03 (0.77, 1.36)	1.01 (0.76, 1.36)
Asthma	139 (8.9)	0.98 (0.73, 1.31)	1.11 (0.79, 1.54)
Bronchitis/emphysema	158 (10.2)	0.98 (0.76, 1.28)	0.99 (0.72, 1.37)
Cancer	295 (18.3)	1.13 (0.92, 1.38)	1.16 (0.91, 1.48)
Thyroid	172 (15.6)	0.94 (0.73, 1.21)	0.95 (0.72, 1.27)
Diabetes	208 (19.4)	0.89 (0.73, 1.09)	0.97 (0.79, 1.18)
Liver	53 (3.3)	1.43 (1.03, 1.98)*	1.37 (0.98, 1.90)
Arthritis	758 (47.1)	1.19 (1.00, 1.42)*	1.22 (1.00, 1.49)*

* = significant difference p value ≤ 0.05,

** p ≤ 0.01 and

*** p ≤ 0.001.