

Cobalt Exposure in Relation to Cardiovascular Disease in the United States General Population

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Abstract

Cobalt exposure has adverse health effects on the cardiovascular system in occupational and laboratory studies, but these effects have not been assessed in the general population. We aimed to determine whether serum cobalt levels had relationship with the prevalence of cardiovascular disease (CVD) in the general population. Using data from the National Health and Nutrition Examination Survey (NHANES) (2015–2016), we performed the cross-sectional study. We analyzed the baseline characteristics of 3,389 participants (1623 men and 1766 women). Generalized linear models and restricted cubic spline plots curve were undertaken to elucidate the relationship. Stratified subgroup analysis was tested to exclude interaction between different variates and cobalt. Our results showed that the adjusted odds ratios (*ORs*) with 95% confidence intervals (*CI*s) for CVD prevalence across the quartiles of cobalt were 0.94 (0.68, 1.30), 1.58 (1.17, 2.13), and 1.84 (1.37, 2.48) compared with lowest quartile. The restricted cubic spline curve also suggested nonlinear and positive association between cobalt and CVD (*P* for nonlinearity = 0.005). In summary, our cross-sectional results verify that higher cobalt levels are associated with a higher prevalence of cardiovascular disease.

Introduction

Cardiovascular disease (CVD) has caused substantial health and economic burdens around the world (Mozaffarian et al. 2016). The prevalence and control of CVD involve some important risk factors, such as genetic factors, environmental factors, adverse lifestyles and metabolic changes (Bhatnagar 2017; Yu et al. 2016). However, the risks following exposure to heavy metals and the cardiotoxicity of some drugs and devices are often underestimated (Hantson 2019).

Cobalt is a relatively rare magnetic metal element (Barceloux 1999). Studies have shown that heavy metals in environmental pollution can elevate blood pressure and even may cause myocardial toxicity (Wu et al. 2018; Zhang et al. 2016). Environmental cobalt or cobalt added to beer was noted to cause CVD, mainly cardiomyopathy (Milon et al. 1968). Humans can be exposed to cobalt in many ways in daily life, including the use of glass, paint and diet being the main source for the general population, and occupational contact while working in the metal industry (Barceloux 1999; Lauwerys and Lison 1994).

Case studies of severe cardiomyopathy have revealed the association between poisoning cobalt doses and CVD due to the increased use of metal-to-metal (MoM) hip implants in patients undergoing total hip arthroplasty (THA) (Choi et al. 2019; Sanz Pérez et al. 2019). The blood cobalt levels of these patients could reach a fatal dose, as high as 641.6 µg/L (Dahms et al. 2014; Fox et al. 2016). Therefore, serum cobalt levels > 20 µg/L are not allowed in patients given a MoM hip implant (Sanz Pérez et al. 2019), and at > 7 µg/L, clinicians should begin to observe the heart function (Tower 2010).

In addition, cobalt can induce hypoxia in cardiomyocytes (Wang et al. 2019). The mechanism may be that cobalt interferes with the production of ATP by interfering with the synthesis of mitochondrial respiratory chain enzymes (Clyne et al. 2001), and at the same time increases oxidative stress (Akinrinde

et al. 2016; Lewis et al. 1991), which is also involved in the pathophysiology of CVD (Alfatni et al. 2020). However, it is currently uncertain whether the “normal” range of cobalt exposure in the general population has an effect on CVD.

Therefore, based on the National Health and Nutrition Examination Survey (NHANES) providing serum cobalt levels in samples from the United States in 2015–2016, this study was performed to investigate the relationship between cobalt exposure and the prevalence of CVD in the general population.

Materials And Methods

Study population

We used data from the NHANES accessible online for design and procedures through the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) (<https://www.cdc.gov/nchs/nhanes/index.htm>) to estimate the cobalt-related factors of CVD. The data was obtained from the NHANES surveys conducted in the United States population in 2015–2016. Totally 9971 patients were admitted and for whom (n=3442) the serum concentrations were available. We also excluded participants with missing data on CVD (n=49) and those pregnant (n=17). Ultimately, 3389 participants involved in our study as shown in Fig. 1. Additionally, we obtained the permission to use the NHANES data by the National Center for Health Statistics research ethics review board (ERB), as well as signed informed consent from all participants.

Cobalt measurements

Blood samples from the participants were collected after confirming that there was no background contamination. Concentrations of cobalt (micrograms per liter ($\mu\text{g/L}$)) were measured in blood by inductively coupled plasma mass spectrometry (ICP-MS, PerkinElmer/SCIEX model 500; PerkinElmer, Shelton, CT, USA, http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/I06_c_met_hm.pdf) at the Environmental Health Sciences Laboratory of the CDC and the National Center for Environmental Health (NCEH). The normal blood cobalt concentration is defined as $<1 \mu\text{g/L}$ (Samar et al. 2015). The lower limit of detection (LLOD) for cobalt in this study is $0.06 \mu\text{g/L}$. Exposure was divided into weighted quartiles based on the measured distribution of blood cobalt concentration. This study modeled the quartiles of the exposure distribution to assess the potential nonlinear association between cobalt and the target endpoint.

CVD Ascertainment

Statistics on CVD consisted of congestive heart failure (CHF), coronary heart disease (CHD), angina pectoris, heart attack and stroke in this study. The prevalence of the disease was recorded by questionnaire whether the patient had new-onset or pre-existing disease at this time. The diagnosis of CVD included clinical symptoms of the patients (such as shortness of breath, fatigue, exercise intolerance or abrupt onset of chest pain), changes on electrocardiograms (ECG) and serum biomarkers levels (such

as myocardial enzyme and B-type natriuretic peptide (BNP)). For stroke, the diagnosis was based on the patient's recorded signs, symptoms (such as hemiparesis and aphasia), and neuroimaging (CT or MRI) and other diagnostic reports (Folsom et al. 2011).

Covariates

Participants self-reported the following covariates: age, gender, ethnicity (Mexican American, other Hispanic American, non-Hispanic black, non-Hispanic white, and other races), education level, total energy intake, poverty-income ratio and health behaviors including smoking, alcohol consumption and physical activity, which were collected through online questionnaires (http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm). Hypertension and diabetes mellitus were defined as self-reported diagnoses of these two diseases. Body mass index (BMI in kg/m^2) ≥ 30 was defined as obesity. The concentrations of plasma lipids were publicly available on the NCHS and USDA websites (<https://www.cdc.gov/nchs/nhanes/index.htm>).

Statistical analysis

Continuous variables expressed as the mean (standard deviation, SD), and skewed data expressed as median (quartile range) were analyzed by t-test. Categorical variables presented as numbers (percentages, %) were analyzed by the chi-square test to demonstrated the demographic and health characteristics with CVD and non-CVD. Data on serum cobalt concentration was in log₂-transformation because of its skewed distribution. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and probability value (*P*) were used to evaluate the strength of the associations between variables.

We used a multivariate logistic generalized linear model to determine the relationship between cobalt quartiles and CVD. In model 1, we calculated the OR adjusted for age and gender. Model 2 were adjusted for other potential confounders which included age, gender, education level, ethnicity, BMI, alcohol user, diabetes mellitus and hypertension (Model 2). Based on model 2, the full adjustment was made for poverty-income ratio, energy intake, physical activity, high density and total cholesterol (Model 3).

We also modeled each cobalt quartile as an ordinal variable to test for linear trends. Subgroup analysis was performed to examine whether the effect of cobalt on CVD could be modified by age, gender, physical exercise, diabetes, hypertension and obesity. We used restricted cubic spline regression with 3 knots at the 10th, 50th, and 90th percentages to graph the relationship between cobalt and the prevalence of CVD. The identified nonlinear associations were tested by Wald χ^2 tests (Desquilbet and Mariotti 2010). The interaction between cobalt and stratified covariates in the multiple regression model was tested. We performed all statistical analyzes with R software version 3.6.0, and defined *P* < 0.05 as significant.

Results

Baseline characteristics

The demographic characteristics of the exposure levels in the study population are presented in Table 1. Significant differences were found in age, gender, ethnicity, hypertension, alcohol intake, energy intake, physical activity, high cholesterol and total cholesterol (all $P \leq 0.001$) among the different level of cobalt exposure groups (see Table 1).

Association between cobalt and total CVD

In the fully adjusted model, the ORs (95% CIs) for the CVD prevalence across the cobalt quartiles were 0.94 (0.68, 1.30), 1.58 (1.17, 2.13), and 1.84 (1.37, 2.48) (P for trend < 0.001), compared with the first quartile of cobalt exposure (see Table 2). This characteristic of increased ORs for the prevalence with increased cobalt concentration persisted in the other two adjusted models. Fig.2 shows that the restricted cubic spline plot curve graphs the nonlinear association between cobalt and total CVD (p for nonlinearity = 0.005).

Association between cobalt and individual CVDs

Our data show similar trends in the relationship of cobalt and individual CVDs prevalence. Compared with participants in the lowest quartile, the fully adjusted ORs (95% CIs) of individual CVDs including CHF, CHD, angina pectoris, heart attack and stroke in the highest quartile were 2.03 (1.29-3.22), 1.54 (0.99, 2.41), 1.54 (0.86, 2.82), 2.00 (1.33, 3.04) and 1.35 (0.86, 2.15), respectively (see Table 3).

Stratified associations between cobalt and total CVD

Subgroup analysis stratified by different variates including age, gender, physical exercise, diabetes, hypertension and obesity confirmed a positive association between the total CVD prevalence and cobalt. There was no significant trend towards an association between total CVD and cobalt among participants who were female, younger than 60 years old, or without a history of hypertension and participated in vigorous physical activity. The stratified model of obesity and diabetes also showed that the trend was statistically significant as the cobalt concentration increased and the prevalence of CVD increased (All $P < 0.05$) (Table 4).

Discussion

Our cross-sectional study found a nonlinear positive correlation between cobalt exposure and the prevalence of CVD, and the correlation was associated with the concentration of blood cobalt in the general population.

Previous studies have reported many cases of CVD caused by a cobalt poisoning dose, and suggested that THA patients with higher doses of cobalt presented with more severe CVD (Dahms et al. 2014; Fox et al. 2016; Samar et al. 2015; Sanz Pérez et al. 2019). Due to a lack of data about a possible association between cobalt and CVD in the general population, our research aimed to fill this knowledge gap.

Our results are similar to prior findings in THA patients. A positive correlation between cobalt exposure and the prevalence of CVD existed in both THA patients and the general population. However, a prospective study found no significant differences in cardiac magnetic resonance (CMR) performance in a high blood cobalt group compared to a lower cobalt group among THA patients (Berber et al. 2017). We speculate the reason for this is that the average blood cobalt concentration ($30.0 \pm 29.1 \mu\text{g/L}$) in the high-concentration group in that study was much lower than that among the THA patients with CVD ($\geq 120 \mu\text{g/L}$) (Samar et al. 2015).

For occupational cobalt exposed people, a cross-sectional survey in Belgium found no dose-effect relationship between cobalt exposure and dilated cardiomyopathy by measurement of echocardiography (echo) and ECG (Lantin et al. 2013). Simultaneously, another study, the first follow-up cohort study investigating occupational cobalt exposure, also confirmed no differences in the echo and ECG parameters between exposed and unexposed workers and no differences in the prevalence of myocardial infarction, CHD, or heart failure (Linna et al. 2019).

These results seem to be contrary to our results. However, the occupational population in the Belgium study was significantly younger than the population in our study. Another possible explanation is that it is hard to detect early structural and ECG changes without clinical symptoms in occupational populations. Additionally, regional environmental differences exist between our population and the occupational populations in the two other studies, which can exert an important influence on CVD (Bhatnagar 2017). In addition, the sample sizes of the two other studies are significantly smaller than our study, which may increase the false negative rate. Additionally, our study defined CVD using a questionnaire asking about clinical symptoms rather than using early clinical testing methods.

Furthermore, two specific types of CVD (CHF and heart attack) analyzed in our study show the same trend with cobalt, which is consistent with previous results. CHF results from any functional or structural heart disorder, and it clinically manifests with impaired ventricular filling or ejection of the blood into the systemic circulation (Verbrugge et al. 2013). A previous study explored myocardial specimens of cobalt poisoning patients, and verified a higher cobalt concentration, more cardiac hypertrophy, more interstitial fibrosis in the myocardium and a lower ejection fraction compared with the non-exposed group (Wyles et al. 2017). In addition, as the concentration of cobalt increases, the structure of the heart changes as the left ventricular end-diastolic, end-systolic and the left atrium volume increases (Lodge et al. 2018).

Heart attack, mostly a sudden and fatal occurrence of coronary thrombosis, was estimated to be associated with the serum concentration of cobalt in our study (Murray and Lopez 1997). However, normal coronary angiography has been reported for patients with cobalt poisoning (Samar et al. 2015), and no significant difference was found in serum troponin levels (Berber et al. 2017). Additionally, with the common use of cobalt in drug-eluting stents, no cases of cobalt poisoning have been reported (Kozuma et al. 2019; Romaguera et al. 2014; Sotomi et al. 2018). However, another study has shown significantly increased serum enzymes and low voltages on ECG in patients with cobalt poisoning (Packer 2016). Therefore, there are still controversies about this correlation. This may be due to the rarity

of cases reported so far, so the results are quite different. Therefore, further research and verification in prospective follow-up studies and in animal studies are warranted.

The underlying mechanism of the association of cobalt and CVD is mainly related to mitochondrial respiratory and oxidative stress. Studies use cobalt chloride (CoCl₂), a chemical mimetic of hypoxia, to inhibit mitochondrial function through decreasing ATP production rate in the respiratory chain (Cheng et al. 2017; Chimeh et al. 2018; Clyne et al. 2001; Wang et al. 2019). Ultimately, CoCl₂ constructs hypoxic condition models and decreased cell viability (Sundaram et al. 2018). As the cobalt concentration increasing, mitochondrial dysfunction may contribute to cobalt-induced oxidative stress in macrophages through an increase in reactive oxygen species (ROS) production (Salloum et al. 2018). ROS in most cells, particularly in cardiac cells, are mainly generated from the mitochondria (Assies et al. 2014). Many cell metabolic cascades are linked and modulated by ROS in a complicated pattern, which form the pathogenesis basis of CVD (Cervantes Gracia et al. 2017). In addition, CoCl₂ causes a significant increase in oxidative stress indicators (hydrogen peroxide (H₂O₂) and malondialdehyde (MDA)), an increase in the expression of caspase 8 (apoptosis initiating factor) in the heart, and a significant decrease in glutathione (GSH) (Akinrinde et al. 2016). Therefore, cobalt may eventually lead to CVD by changing the hypoxia state of the respiratory chain and promoting oxidative stress.

The major clinical value of the study is that although the dose of cobalt in our study was rather low, this phenomenon urges us to pay attention to the impact of environmental poisons and heavy metals on CVD. To make primary prevention to reduce it, we need to increase the blood metal detection rate for possibly affected patients.

The current study still has several limitations. Firstly, we used the cross-sectional design of NHANES with a lack of temporality, so causality cannot be determined. Secondly, though the regression model was adjusted for a wide range of covariates, unmeasured confounders correlated to CVD may also play a role. In addition, retrospective bias may exist in this study, as this is a retrospective study and subjects may have a "recall bias" toward some of the relevant results. Thus, the impact of cobalt on CVD in the general population merits further prospective research.

Conclusions

In summary, our findings reveal that elevated serum cobalt levels are nonlinearly and positively associated with a higher prevalence of cardiovascular disease, suggesting that cobalt exposure may be a risk factor for cardiovascular disease. Although the mechanism of cobalt action on CVD is unclear, the current results may contribute to an epidemiological evidence of day-to-day environmental risk factors for cardiovascular disease.

Declarations

Author contributions

X.L.L.: conceptualization, methodology. **S.G.L.**: data curation and project administration. **Q.Q.Z.**: writing-original draft preparation and editing. **X.Y.L** and **X.Z.**: supervision, investigation. **S.S.**: validation. **I.F.C, D.X.G** and **H.F.Z.**: writing-review and editing.

Availability of data and materials

The datasets used and analyzed during the current study are available from https://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm.

Compliance with ethical standards

Ethics approval and consent to participate

The consent form was signed by participants in the survey, and participants consented to storing specimens of their blood for future research. The CDC/NCHS Ethics Review Board approved the NHANES study and gave approval for public dissemination.

Consent for publication Not applicable. There is no individual level data in our publication.

Competing interests

The authors declare that they have no competing interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Akinrinde AS, Oyagbemi AA, Omobowale TO, Asenuga ER, Ajibade TO (2016) Alterations in blood pressure, antioxidant status and caspase 8 expression in cobalt chloride-induced cardio-renal dysfunction are reversed by *Ocimum gratissimum* and gallic acid in Wistar rats *J Trace Elem Med Biol* 36:27-37 <https://doi.org/10.1016/j.jtemb.2016.03.015>

Alfatni A , Riou M, Charles AL, Meyer A, Barnig C, Andres E, Lejay A, Talha S, Geny B (2020) Peripheral Blood Mononuclear Cells and Platelets Mitochondrial Dysfunction, Oxidative Stress, and Circulating mtDNA in Cardiovascular Diseases *J Clin Med* 9 <https://doi.org/10.3390/jcm9020311>

- Assies J, Mocking RJ, Lok A, Ruhé HG, Pouwer F, Schene AH (2014) Effects of oxidative stress on fatty acid- and one-carbon-metabolism in psychiatric and cardiovascular disease comorbidity *Acta Psychiatr Scand* 130:163-180 <https://doi.org/10.1111/acps.12265>
- Barceloux DG (1999) Cobalt J *Toxicol Clin Toxicol* 37:201-206 <https://doi.org/10.1081/clt-100102420>
- Berber R Abdel-Gadir A, Rosmini S, Captur G, Nordin S, Culotta V, Palla L, Kellman P, Lloyd GW, Skinner JA, Moon JC, Manisty C, Hart AJ (2017) Assessing for Cardiotoxicity from Metal-on-Metal Hip Implants with Advanced Multimodality Imaging Techniques *J Bone Joint Surg Am* 99:1827-1835 <https://doi.org/10.2106/jbjs.16.00743>
- Bhatnagar A (2017) Environmental Determinants of Cardiovascular Disease *Circulation research* 121:162-180 <https://doi.org/10.1161/circresaha.117.306458>
- Cervantes Gracia K, Llanas-Cornejo D, Husi H (2017) CVD and Oxidative Stress *J Clin Med* 6 <https://doi.org/10.3390/jcm6020022>
- Cheng CI, Lee YH, Chen PH, Lin YC, Chou MH, Kao YH (2017) Cobalt chloride induces RhoA/ROCK activation and remodeling effect in H9c2 cardiomyoblasts: Involvement of PI3K/Akt and MAPK pathways *Cell Signal* 36:25-33 <https://doi.org/10.1016/j.cellsig.2017.04.013>
- Chimeh U, Zimmerman MA, Gilyazova N, Li PA (2018) B355252, A Novel Small Molecule, Confers Neuroprotection Against Cobalt Chloride Toxicity In Mouse Hippocampal Cells Through Altering Mitochondrial Dynamics And Limiting Autophagy Induction *Int J Med Sci* 15:1384-1396 <https://doi.org/10.7150/ijms.24702>
- Choi HI, Hong JA, Kim MS, Lee SE, Jung SH, Yoon PW, Song JS, Kim JJ (2019) Severe Cardiomyopathy Due to Arthroprosthetic Cobaltism: Report of Two Cases with Different Outcomes *Cardiovasc Toxicol* 19:82-89 <https://doi.org/10.1007/s12012-018-9480-0>
- Clyne N, Hofman-Bang C, Haga Y, Hatori N, Marklund SL, Pehrsson SK, Wibom R (2001) Chronic cobalt exposure affects antioxidants and ATP production in rat myocardium *Scand J Clin Lab Invest* 61:609-614 <https://doi.org/10.1080/003655101753267964>
- Dahms K, Sharkova Y, Heitland P, Pankuweit S, Schaefer JR (2014) Cobalt intoxication diagnosed with the help of Dr House *Lancet* 383:574 [https://doi.org/10.1016/s0140-6736\(14\)60037-4](https://doi.org/10.1016/s0140-6736(14)60037-4)
- Desquilbet L, Mariotti F (2010) Dose-response analyses using restricted cubic spline functions in public health research *Statistics in Medicine* 29:1037-1057 <https://doi.org/10.1002/sim.3841>
- Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD (2011) Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence *J Am Coll Cardiol* 57:1690-1696 <https://doi.org/10.1016/j.jacc.2010.11.041>

- Fox KA, Phillips TM, Yanta JH, Abesamis MG (2016) Fatal cobalt toxicity after total hip arthroplasty revision for fractured ceramic components *Clinical toxicology* (Philadelphia, Pa) 54:874-877
<https://doi.org/10.1080/15563650.2016.1214274>
- Hantson P (2019) Mechanisms of toxic cardiomyopathy *Clinical toxicology* (Philadelphia, Pa) 57:1-9
<https://doi.org/10.1080/15563650.2018.1497172>
- Kozuma K, Shinozaki T, Kozuma K, Kashiwabara K, Oba K, Aoki J, Awata M, Nanasato M, Shiode N, Tanabe K, Yamaguchi J, Kimura T, Matsuyama Y (2019) Impact of Residual Stenosis on the Angiographic Edge Restenosis of a Second-Generation Drug-Eluting Stent *Int Heart J* 60:1050-1060
<https://doi.org/10.1536/ihj.18-717>
- Lantin AC, Vermeulen J, Mallants A, Vanoverschelde JL, Speybroeck N, Swennen B, Hoet P, Lison D (2013) Occupational exposure to cobalt is not associated with incipient signs of dilated cardiomyopathy in a Belgian refinery *Occup Environ Med* 70:386-392 <https://doi.org/10.1136/oemed-2012-100930>
- Lauwerys R, Lison D (1994) Health risks associated with cobalt exposure—an overview *Sci Total Environ* 150:1-6 [https://doi.org/10.1016/0048-9697\(94\)90125-2](https://doi.org/10.1016/0048-9697(94)90125-2)
- Lewis CP, Demedts M, Nemery B (1991) Indices of oxidative stress in hamster lung following exposure to cobalt(II) ions: in vivo and in vitro studies *Am J Respir Cell Mol Biol* 5:163-169
<https://doi.org/10.1165/ajrcmb/5.2.163>
- Linna A Uitti J, Oksa P, Toivio P, Virtanen V, Lindholm H, Halkosaari M, Sauni R (2019) Effects of occupational cobalt exposure on the heart in the production of cobalt and cobalt compounds: a 6-year follow-up *International Archives of Occupational and Environmental Health* 93
<https://doi.org/10.1007/s00420-019-01488-3>
- Lodge F, Khatun R, Lord R, John A, Fraser AG, Yousef Z (2018) Prevalence of subclinical cardiac abnormalities in patients with metal-on-metal hip replacements *Int J Cardiol* 271:274-280
<https://doi.org/10.1016/j.ijcard.2018.05.047>
- Milon H, Morin Y, Bonenfant JL (1968) [Epidemic of myocardosis in beer drinkers. Probable role of cobalt] *Arch Mal Coeur Vaiss* 61:1561-1594
- Mozaffarian D Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB (2016) Executive Summary: Heart Disease and Stroke Statistics—2016 Update: A Report From the American Heart Association *Circulation* 133:447-454 <https://doi.org/10.1161/cir.0000000000000366>

- Murray CJ, Lopez AD (1997) Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study *Lancet* 349:1436-1442 [https://doi.org/10.1016/s0140-6736\(96\)07495-8](https://doi.org/10.1016/s0140-6736(96)07495-8)
- Packer M (2016) Cobalt Cardiomyopathy: A Critical Reappraisal in Light of a Recent Resurgence *Circ Heart Fail* 9 <https://doi.org/10.1161/circheartfailure.116.003604>
- Romaguera R, Roura G, Gomez-Lara J, Ferreiro JL, Gracida M, Teruel L, de Albert M, Ariza A, Gomez-Hospital JA, Cequier A (2014) Longitudinal deformation of drug-eluting stents: evaluation by multislice computed tomography *J Invasive Cardiol* 26:161-166
- Salloum Z, Lehoux EA, Harper ME, Catelas I (2018) Effects of cobalt and chromium ions on oxidative stress and energy metabolism in macrophages in vitro *J Orthop Res* 36:3178-3187 <https://doi.org/10.1002/jor.24130>
- Samar HY, Doyle M, Williams RB, Yamrozik JA, Bunker M, Biederman RWW, Shah MB (2015) Novel Use of Cardiac Magnetic Resonance Imaging for the Diagnosis of Cobalt Cardiomyopathy *JACC: Cardiovascular Imaging* 8:1231-1232 <https://doi.org/10.1016/j.jcmg.2014.12.016>
- Sanz Pérez MI, Rico Villoras AM, Moreno Velasco A, Bartolomé García S, Campo Loarte J (2019) Heart transplant secondary to cobalt toxicity after hip arthroplasty revision *Hip Int* 29:Np1-np5 <https://doi.org/10.1177/1120700019834793>
- Sotomi Y, Onuma Y, Dijkstra J, Miyazaki Y, Kozuma K, Tanabe K, Popma JJ, de Winter RJ, Serruys PW, Kimura T (2018) Fate of post-procedural malapposition of everolimus-eluting polymeric bioresorbable scaffold and everolimus-eluting cobalt chromium metallic stent in human coronary arteries: sequential assessment with optical coherence tomography in ABSORB Japan trial *Eur Heart J Cardiovasc Imaging* 19:59-66 <https://doi.org/10.1093/ehjci/jew329>
- Sundaram RL, Sali VK, Vasanthi HR (2018) Protective effect of rutin isolated from *Spermococe hispida* against cobalt chloride-induced hypoxic injury in H9c2 cells by inhibiting oxidative stress and inducing apoptosis *Phytomedicine* 51:196-204 <https://doi.org/10.1016/j.phymed.2018.09.229>
- Tower S (2010) Arthroprosthetic cobaltism: identification of the at-risk patient *Alaska Med* 52:28-32
- Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WH, Mullens W (2013) Abdominal contributions to cardiorenal dysfunction in congestive heart failure *J Am Coll Cardiol* 62:485-495 <https://doi.org/10.1016/j.jacc.2013.04.070>
- Wang Q, Lu G, Chen Z (2019) MALAT1 promoted cell proliferation and migration via MALAT1/miR-155/MEF2A pathway in hypoxia of cardiac stem cells *Journal of cellular biochemistry* 120:6384-6394 <https://doi.org/10.1002/jcb.27925>
- Wu W, Jiang S, Zhao Q, Zhang K, Wei X, Zhou T, Liu D, Zhou H, Zeng Q, Cheng L, Miao X, Lu Q (2018) Environmental exposure to metals and the risk of hypertension: A cross-sectional study in China *Environ*

Pollut 233:670-678 <https://doi.org/10.1016/j.envpol.2017.10.111>

Wyles CC, Wright TC, Bois MC, Amin MS, Fayyaz A, Jenkins SM, Wyles SP, Day PL, Murray DL, Trousdale RT, Anavekar NS, Edwards WD, Maleszewski JJ (2017) Myocardial Cobalt Levels Are Elevated in the Setting of Total Hip Arthroplasty *J Bone Joint Surg Am* 99:e118 <https://doi.org/10.2106/jbjs.17.00159>

Yu E, Rimm E, Qi L, Rexrode K, Albert CM, Sun Q, Willett WC, Hu FB, Manson JE (2016) Diet, Lifestyle, Biomarkers, Genetic Factors, and Risk of Cardiovascular Disease in the Nurses' Health Studies *Am J Public Health* 106:1616-1623 <https://doi.org/10.2105/ajph.2016.303316>

Zhang Y, Ji X, Ku T, Li G, Sang N (2016) Heavy metals bound to fine particulate matter from northern China induce season-dependent health risks: A study based on myocardial toxicity *Environ Pollut* 216:380-390 <https://doi.org/10.1016/j.envpol.2016.05.072>

Tables

Table 1 Demographic characteristics of different levels of cobalt exposure in the study population

Variable	Overall (n=3389)	≤0.11ug/L (n=977)	>0.11 to ≤0.13ug/L (n=773)	>0.13 to ≤0.17ug/L (n=814)	>0.17ug/L (n=825)	<i>P</i> value
Age, years	59.6 (12.0)	57.1 (11.2)	59.4 (11.4)	61.7 (12.0)	60.5 (13.0)	<0.001
Male, %	1623 (47.9%)	616 (63.1%)	419 (54.2%)	321 (39.4%)	267 (32.4%)	<0.001
Education level, %						0.681
<9th grade	495 (14.6%)	131 (13.4%)	111 (14.4%)	132 (16.2%)	121 (14.7%)	
9–11th grade	415 (12.2%)	126 (12.9%)	99 (12.8%)	96 (11.8%)	94 (11.4%)	
High school	725 (21.4%)	207 (21.2%)	176 (22.8%)	177 (21.7%)	165 (20.0%)	
College	949 (28.0%)	277 (28.4%)	207 (26.8%)	234 (28.7%)	231 (28.0%)	
Graduate	805 (23.8%)	236 (24.2%)	180 (23.3%)	175 (21.5%)	214 (25.9%)	
Ethnicity, %						0.001
Mexican American	578 (17.1%)	167 (17.1%)	141 (18.2%)	122 (15.0%)	148 (17.9%)	
Other Hispanic	466 (13.8%)	130 (13.3%)	117 (15.1%)	119 (14.6%)	100 (12.1%)	
Non-Hispanic White	1173 (34.6%)	319 (32.7%)	252 (32.6%)	299 (36.7%)	303 (36.7%)	
Non-Hispanic Black	707 (20.9%)	239 (24.5%)	153 (19.8%)	138 (17.0%)	177 (21.5%)	
Other race	465 (13.7%)	122 (12.5%)	110 (14.2%)	136 (16.7%)	97 (11.8%)	
Diabetes mellitus, %	707 (20.9%)	195 (20.0%)	157 (20.3%)	170 (20.9%)	185 (22.4%)	0.605
Hypertension, %	1640 (48.4%)	427 (43.7%)	362 (46.8%)	418 (51.4%)	433 (52.5%)	<0.001
Smoker, %	1544 (45.6%)	437 (44.7%)	376 (48.6%)	362 (44.5%)	369 (44.7%)	0.278
Alcohol user, %	2197 (64.8%)	684 (70.0%)	509 (65.8%)	501 (61.5%)	503 (61.0%)	<0.001

Body mass index, kg/m ²	29.9 (6.79)	30.2 (6.61)	29.6 (6.25)	29.7 (7.06)	30.0 (7.20)	0.136
Energy intake (kcal/day)	1930 (747)	2060 (809)	1970 (725)	1850 (737)	1830 (675)	<0.001
Poverty-income ratio	2.33 (1.55)	2.38 (1.56)	2.34 (1.54)	2.32 (1.57)	2.26 (1.52)	0.437
Physical activity						<0.001
Never	2089 (61.6%)	551 (56.4%)	472 (61.1%)	515 (63.3%)	551 (66.8%)	
Moderate	682 (20.1%)	199 (20.4%)	147 (19.0%)	163 (20.0%)	173 (21.0%)	
Vigorous	618 (18.2%)	227 (23.2%)	154 (19.9%)	136 (16.7%)	101 (12.2%)	
High density Cholesterol(mg/dl)	54.7 (18.3)	51.7 (16.1)	54.3 (18.0)	55.7 (19.0)	57.5 (19.7)	<0.001
Total cholesterol(mg/dl)	194 (42.2)	195 (41.2)	197 (43.3)	196 (40.3)	188 (43.8)	<0.001

Data are presented as mean (SD) or n (%).

Table 2 Adjusted odds ratios for associations between cobalt and the prevalence of total CVD

Cobalt	Cases	N	Model 1	Model 2	Model 3
			OR (95% CI)	OR (95% CI)	OR (95% CI)
Q1	109	977	Ref.	Ref.	Ref.
Q2	87	773	0.90 (0.66, 1.23)	0.91 (0.66, 1.25)	0.94 (0.68, 1.30)
Q3	151	814	1.55 (1.17, 2.06)**	1.52 (1.14, 2.04)**	1.58 (1.17, 2.13)**
Q4	175	825	1.97 (1.49, 2.60)***	1.88 (1.41, 2.52)***	1.84 (1.37, 2.48)***
<i>P</i> for trend			<0.001	<0.001	<0.001

Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, education level, ethnicity, diabetes mellitus, smoker, alcohol user, hypertension, body mass index. Model 3 was adjusted for age, gender, education level, ethnicity, diabetes mellitus, smoker, alcohol user, hypertension, body mass index, poverty-income ratio, physical activity, and energy intake, high density cholesterol and total cholesterol. **P* < 0.05, ***P* < 0.01, ****P* < 0.001; CVD, cardiovascular disease; OR, Odd ratio; CI, confidence interval.

Table 3 Adjusted odds ratios for associations between cobalt and individual CVDs

Cobalt	Congestive heart failure	Coronary heart disease	Angina pectoris	Heart attack	Stroke
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Q1	1.00	1.00	1.00	1.00	1.00
Q2	0.93 (0.54, 1.60)	1.20 (0.74, 1.93)	1.28 (0.68, 2.42)	0.83 (0.51, 1.35)	0.97 (0.58, 1.61)
Q3	1.29 (0.79, 2.10)	1.49 (0.95, 2.35)	2.09 (1.20, 3.76)*	1.16 (0.75, 1.81)	1.50 (0.96, 2.38)
Q4	2.03 (1.29, 3.22)**	1.54 (0.99, 2.41)	1.54 (0.86, 2.82)	2.00 (1.33, 3.04)**	1.35 (0.86, 2.15)
<i>P</i> for trend	<0.001	0.066	0.211	<0.001	0.144

Analysis were adjusted for age, gender, education level, ethnicity, diabetes mellitus, smoker, alcohol user, hypertension, body mass index, poverty-income ratio, physical activity, and energy intake, high density cholesterol and total cholesterol. CVD, cardiovascular disease; * $P < 0.05$, ** $P < 0.01$; OR, Odd ratio; CI, confidence interval.

Table 4 Subgroups analysis for the associations of cobalt with the prevalence of total CVD.

	Q1	Q2	Q3	Q4	<i>P</i> for trend	<i>P</i> for interaction
	OR	OR (95% CI)	OR (95% CI)	OR (95% CI)		
Age						0.206
>60 year	1.00	0.97(0.65, 1.46)	1.68(1.16, 2.43)**	2.09(1.46, 3.01)***	<0.001	
≤60 years	1.00	0.92(0.53, 1.62)	1.63(0.96, 2.75)	1.53(0.89, 2.64)	0.070	
Gender						0.386
Male	1.00	1.21(0.80, 1.85)	2.09(1.38, 3.18)**	2.16(1.42, 3.30)***	<0.001	
Female	1.00	0.59(0.34, 1.02)	1.10(0.70, 1.72)	1.48(0.96, 2.28)	0.003	
Diabetes						0.786
Yes	1.00	1.03(0.58, 1.83)	2.38(1.40, 4.03)**	1.73(1.02, 2.94)*	0.023	
No	1.00	0.89(0.60, 1.33)	1.27(0.87, 1.84)	1.80(1.25, 2.59)**	<0.001	
Hypertension						0.345
Yes	1.00	0.93(0.63, 1.38)	1.73(1.21, 2.49)**	2.03(1.42, 2.90)***	<0.001	
No	1.00	0.97(0.54, 1.75)	1.35(0.78, 2.36)	1.45(0.83, 2.52)	0.129	
Obesity						0.304
BMI≥30	1.00	0.89(0.56, 1.42)	1.72(1.12, 2.62)*	1.59(1.04, 2.44)*	0.010	
BMI<30	1.00	0.98(0.61, 1.55)	1.48(0.96, 2.29)	2.15(1.41, 3.30)***	<0.001	
Physical activity						0.993
Never	1.00	0.99(0.65, 1.50)	1.42(0.96, 2.09)	1.74(1.19, 2.54)**	0.001	
Moderate	1.00	0.80(0.35, 1.81)	1.93(0.95, 3.93)	2.75(1.39, 5.43)**	<0.001	
Vigorous	1.00	0.86(0.41, 1.82)	1.65(0.82, 3.35)	1.08(0.49, 2.39)	0.632	

Analyses was adjusted for age, sex, education level, race, diabetes mellitus, smoker, alcohol user, hypertension, body mass index, poverty-income ratio, physical activity, and energy intake, high density cholesterol and total cholesterol when they were not the strata variables. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; OR, Odd ratio; CI, confidence interval.

Figures

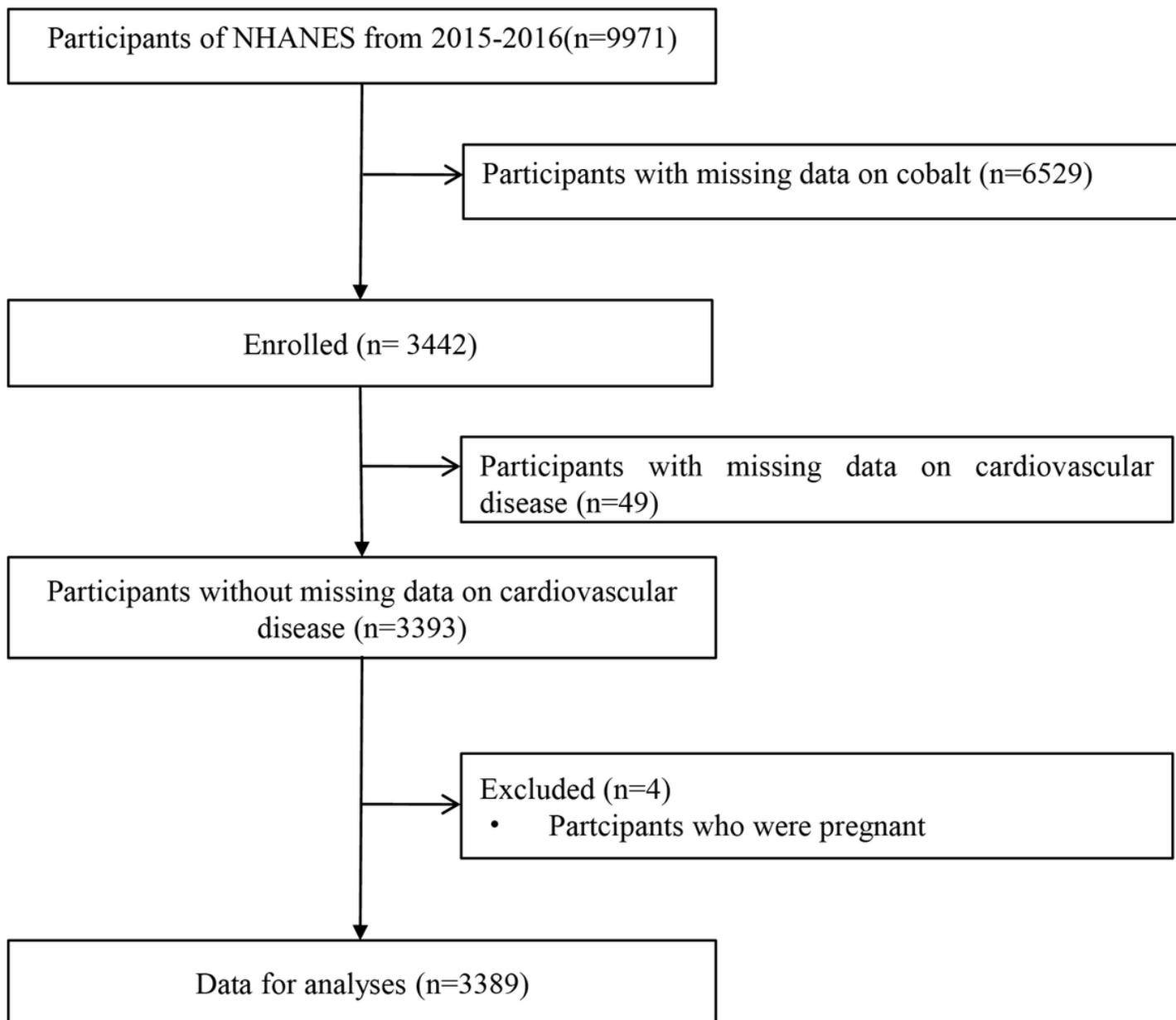


Figure 1

Flow diagram of recruitment in this study; NHANES: National Health and Nutrition Examination Survey

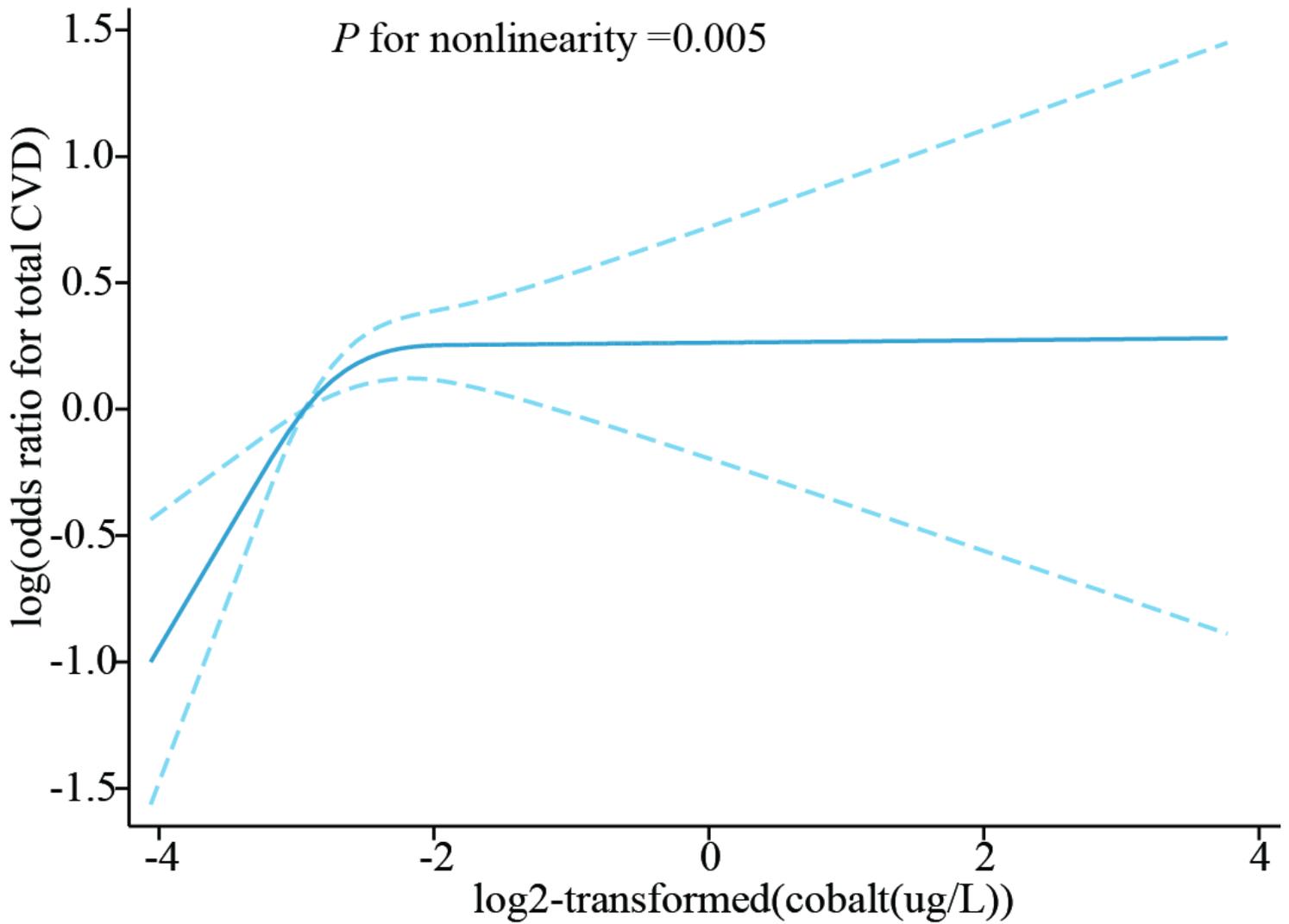


Figure 2

The restricted cubic spline plot of the association between cobalt and the total CVD prevalence; Cobalt is log₂ transformed. The association was adjusted for age, gender, education level, ethnicity, diabetes mellitus, smoker, alcohol user, hypertension, body mass index, poverty-income ratio, physical activity, and energy intake, high density cholesterol and total cholesterol. CVD: cardiovascular disease.