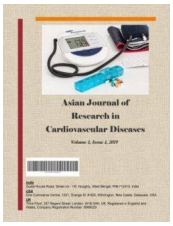

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# Environmental Heavy Metals Exposure: Effects on Development of Heart Failure in Nigeria

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Author ICI designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MNC and NMC designed the study, wrote the protocol managed the analyses of the study. Authors NC and DNJ managed the literature searches, wrote the protocol. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Despite indications that environmental heavy metals; Lead (Pb), Arsenic (As), Cadmium (Cd) and Mercury (Hg) exposure may play important role in the pathogenesis of Cardiovascular diseases and thus heart failure, it has not been investigated in Black-African human population from a developing economy like Nigeria.
**Objective:** The aim of this study is to determine the role of blood Lead, Arsenic, Cadmium and Mercury in development of Heart failure.
**Materials and Methods:** Blood Pb, As, Cd and Hg levels were determined by Atomic Absorption Spectrophotometry (AAS) in 40 patients with heart failure and 40 control subjects.

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**Results:** There were significant increases in Blood Arsenic (0.1082±0.058µg/dl versus 0.0072±0.015µg/dl, p=0.000), Pb (13.17±2.72µg/d versus 9.21±2.12µg/dl, p=0.000) and Cd(0.132±0.054µg/dl versus 0.087±0.029µg/dl, p=0.005) respectively, but no significant difference in blood Hg(0.85±0.55µg/dl versus 0.78±0.16µg/dl, p=0.593) and BMI(28.54±4.99 versus 26.98±3.30, p=0.289) respectively in all patients with heart failure compared to all controls. Comparison of the heavy metals (As, Pb, Cd and Hg) in male patients with heart failure versus female patients with heart failure shows no significant difference(P>0.05) in each case. There was positive correlation of blood Pb with Cd(r=0.474, p=0.036) and Hg( r=0.492, p=0.028) in all patients with heart failure, but there was no significant correlation of blood lead (Pb) with blood As(r=0.088, P=0.712) and BMI (r= -0.104, P=0.490) respectively).
It therefore appears that increases in blood levels of As, Pb and Cd due to environmental exposure may in part contribute to the development of heart failure in this environment. Thus, strict measures should be applied by the policy makers to reduce heavy metals pollution in Nigeria.

*Keywords: Heart failure; heavy metals; environmental exposure; Nigeria.*

## 1. INTRODUCTION

Heart failure is an abnormality of cardiac structure or function leading to failure of the heart to transport oxygen at a rate adequate with the requirements of the metabolizing tissues, and is characterized by pulmonary and systemic congestion [1] thus leading to frequent hospitalizations and shortened life.

Heavy metals include Lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As), which are widely dispersed in the environment, have no established biological functions [2] nor beneficial in humans, but exerts potential environmental and health risks, by causing toxic effects on humans and animals even at low concentrations [3]. *Pb* is ubiquitous, with no known safe blood lead concentration, its exposure causes hypertension, cardiovascular diseases and pre-eclampsia [4-5]. Evidence supports the role of *cadmium* as a cardiovascular disease risk factor, especially for coronary heart disease [6] while epidemiologic studies have related high-chronic *arsenic* exposure to cardiovascular disease, including coronary heart disease, stroke, and peripheral arterial disease [7-8]. Previous studies have reported a correlation of toxic *mercury* exposure with increased risk of hypertension, coronary dysfunction, myocardial infarction and atherosclerosis [9-10]. Ikaraoha *et al*., 2012 [5] have noted that substantial heavy metals environmental exposure lingers in emerging economies such as Nigeria, where existing environmental and industrial policies/regulations are not firmly enforced. Heart failure, hypertension and stroke are Cardiovascular diseases which have been found to be on the increase over the past 20 years in Nigeria [11]. It has been previously reported that out of all the patients presenting with Cardiovascular diseases over a 4-year period of study in South-West Nigeria, heart failure had the highest occurrence [12]. Epidemiologic and investigational evidence supports the role of widespread environmental heavy metals generally and particularly lead and cadmium, in the development of cardiovascular diseases [13] which may include Heart Failure. Despite indications that environmental heavy metals exposure may play important role in the pathogenesis of Cardiac Diseases [14-15] and thus heart failure, it has not been investigated in a Black-African human population and a developing economy like Nigeria, where environmental heavy metal exposure is still substantial. Consequently, this study is intended to bridge this gap in knowledge.

## 2. MATERIALS AND METHODS

### 2.1 Study Design

The sampling, laboratory determinations and data generation lasted from November 2017 to February 2018. The study area is Enugu State University Teaching Hospital (ESUTH), Enugu. Nigeria. ESUTH though at Enugu state, serves also as referral Hospital for patients from Enugu and surrounding states

### 2.2 Study Population

B**y** random sampling 40 patients with heart failure consisting of 20 males and 20 females attending Cardiac Clinic at Enugu State University Teaching Hospital (ESUTH) Enugu were selected for this study. They were age-matched with 20 male and 20 female controls.

### 2.3 Inclusion Criteria for Patients with Heart Failure

List 1: The inclusion criteria for Heart failure are based on at least 2 major clinical criteria, or 1 major clinical criterion with 2 minor clinical criteria [16] It is as follows;

| **Major criteria for the Clinical diagnosis of Heart Failure.** | **Minor criteria for the Clinical diagnosis of Heart Failure** | **Using NYHA functional Classification**, the Stages of heart failure patients selected were; |
|---|---|---|
| Paroxysmal nocturnal dysponea orthopnea, | Ankle edema, | **Class III** characterized by marked limitation in activity due to symptoms, even during less activity, e.g., walking short distances (20-100 m). Comfortable only at rest. |
| Neck-vein distension, | Night cough, | And **Class IV** branded by severe limitations, experiences symptoms even while at rest, and were mostly bedbound patients. |
| Rales, | Dyspnea on exertion, | Also, by **echocardiographic point of view**, heart failure Patients with left ventricular ejection fraction (LVEF) less than 35% were selected. |
| Cardiomegaly on chest x-ray, | Hepatomegaly, | Both diastolic and systolic heart failure patients were selected for this study |
| Acute pulmonary edema, | Pleural effusion, and | |
| S3 gallop, | Vital capacity decreased 1/3 from maximum tachycardia (rate of >120 per minute) | |
| Increased venous pressure >16cm of water, | | |
| Increased Circulation time > 25s, and | | |
| Hepatojugular reflux, | | |

However, N-terminal pro-brain natriuretic peptide (NTproBNP) was not determined for this study.

### 2.3 Exclusion Criteria for Patients with Heart Failure

Exclusion criteria are as follows: patients with other chronic diseases like diabetes mellitus, tuberculosis and hepatitis. Subjects with absence of clinical manifestation of heart disease, and Patients who did not give inform consent for the study.

### 2.4 Sample Collection

After overnight fast, three milliliters of venous blood were collected from each participant, dispensed into lithium heparin specimen container, mixed properly, refrigerated at 4-8$^{o}$C and analyzed within 4 days.

**List 2. The instrumental conditions of each element were as follows**

| s/n | Element | Wavelength (nm) | Slit width (nm) | Lamp current (mA) | Flame Type | Flame Stoichiometry |
|---|---|---|---|---|---|---|
| 1 | Cd | 228.8 | 0.5 | 4.0 | Air-$C_2H_2$ | Oxidizing |
| 2 | As | 193.7 | 0.5 | 5.0 | Air-$C_2H_2$ | Oxidizing |
| 3 | Hg | 253.7 | 0.5 | 5.0 | Air-$C_2H_2$ | Oxidizing |
| 4 | Pb | 283.3 | 0.5 | 5.0 | Air-$C_2H_2$ | Oxidizing |

## 2.5 Methods

Blood Pb, As, Cd and Hg were determined using Atomic absorption spectrophotometer model-200A, (Buck Scientific, East Norwalk, UK.) as previously described by Welz and Sperling [17-20]. The samples were first digested before they were analyzed in duplicates by the instrument employing the AAS methodology and the average reading taken. The standard solutions were repeatedly analyzed to confirmed the method's precision.

## 2.6 Statistical Analysis

IBM SPSS statistic version 21 was employed in Statistical Analysis to determine Mean, standard deviation, student's t-test and correlations for data obtained in this study. Values expressed as Mean ± Standard Deviation were considered statistically significant at $p<0.05$.

## 3. RESULTS

**Blood Heavy Metals and BMI in All Patients with Heart Failure verses All Controls:** There was significant increases in Blood Arsenic (As), lead (Pb) and cadmium (Cd) (p=0.000, p=0.000 and p=0.005 respectively) in all patients with heart failure compared to controls, while there was no significant difference in BMI and blood mercury (p=0.289 and p=0.593 respectively) in all patients with heart failure compared to controls (Table 1).

**Blood Heavy Metals and BMI in Male Patients with Heart Failure verses Male Controls:** There was significant increases in Blood Arsenic (As), lead (Pb) and cadmium (Cd) (p=0.001, p=0.002 and p=0.040 respectively) in male patients with heart failure compared to male control, but there was no significant difference in BMI and blood mercury (p=0.239 and p=0.031 respectively) in male patients with heart failure compared to male controls (Table 2).

**Blood Heavy Metals and BMI in Female Patients with Heart Failure verses Female Controls:** There was significant increases in BMI, blood Arsenic (As), lead (Pb) and cadmium (Cd) (p=0.02, p=0.008, p=0.017 and p=0.010 respectively) in female patients with heart failure compared to female controls, while there was no significant difference in blood mercury (p=0.198) respectively in female patients with heart failure compared to female controls (Table 3).

**Blood Heavy Metals and BMI in Male Patients with Heart Failure verses Female Patients with Heart Failure:** There was significant decrease in BMI (p=0.019) in male patients with heart failure compared to female patients with heart failure, while there was no significant difference in blood Hg, As, Pb, and Cd (p=0.208, p=0.517, p=0.155, and p=0.243 respectively) in male patients with heart failure compared to female patients with heart failure (Table 4).

**Correlation of blood Pb with BMI, Hg, As and Cd in Patients with Heart failure:** There were positive correlation of blood Pb with Cd (r=0.474 & P=0.036) and Hg (r=0.492 &P=0.028) in all patients with heart failure, but there was no significant correlation of blood Pb with BMI (r= -0.104 &P=0.490) and blood As (r=0.088 &P=0.712) respectively (Table 5).

## 4. DISCUSSION

In this present study, blood As, Pb and Cd were significantly increased in all patients with heart failure when compared to controls. In as much as cardiovascular events including coronary heart disease, stroke, and peripheral arterial disease, were found to be associated with lead exposure [4,20] chronic lead exposure has been linked to atherosclerosis and increased cardiovascular mortality in human [21]. Previous epidemiological studies have reported that low level of lead exposure has a graded association with several disease outcomes such as hypertension and peripheral artery disease [22-23].

**Table 1. Blood heavy metals and BMI in all patients with heart failure verses all controls**

| Variables (Mean ± SD) | All Patients with Heart Failure (N=40) | All Controls (n=40) | t-value | p-value |
|---|---|---|---|---|
| Age | 55.36±7.51 | 54.04±6.42 | 0.683 | 0.502 |
| BMI | 28.54±4.99 | 26.98±3.30 | 1.090 | 0.289 |
| Hg(µg/dl) | 0.85±0.55 | 0.78±0.16 | 0.544 | 0.593 |
| As (µg/dl) | 0.1082±0.058 | 0.0072±0.015 | 6.831 | 0.000 |
| Pb (µg/dl) | 13.17±2.72 | 9.21±2.12 | 4.921 | 0.000 |
| Cd (µg/dl) | 0.132±0.054 | 0.087±0.029 | 3.133 | 0.005 |

**Table 2. Blood heavy metals and BMI in male patients with heart failure verses male controls**

| Variables (Mean ± SD) | Male Patients with Heart Failure (N=20) | Male Controls (n=20) | t-value | p-value |
|---|---|---|---|---|
| Age | 54.63±7.64 | 53.90±7.10 | 0.240 | 0.815 |
| BMI | 25.38±3.94 | 27.38±2.30 | -1.262 | 0.239 |
| Hg(µg/dl) | 1.01±0.74 | 0.73±0.09 | 1.161 | 0.276 |
| As (µg/dl) | 0.097±0.061 | 0.010±0.021 | 4.991 | 0.001 |
| Pb (µg/dl) | 14.13±2.20 | 10.29±1.19 | 4.421 | 0.002 |
| Cd (µg/dl) | 0.147±0.073 | 0.083±0.038 | 2.394 | 0.040 |

**Table 3. Blood heavy metals and BMI in female patients with heart failure verses female controls**

| Variables (Mean ± SD) | Female Patients with Heart Failure (N=20) | Female Controls (n=20) | t-value | p-value |
|---|---|---|---|---|
| Age | 56.09 ±7.68 | 54.18± 6.01 | 0.752 | 0.469 |
| BMI | 31.70±3.8 | 26.59±4.17 | 2.827 | 0.02 |
| Hg(µg/dl) | 0.69±0.20 | 0.82±0.20 | -1.388 | 0.198 |
| As (µg/dl) | 0.093±0.084 | 0.003±0.007 | 3.357 | 0.008 |
| Pb (µg/dl) | 12.21±2.95 | 8.12±2.34 | 2.907 | 0.017 |
| Cd (µg/dl) | 0.117±0.018 | 0.092±0.019 | 3.246 | 0.010 |

**Table 4. Blood heavy metals and bmi in male patients with heart failure verses female patients with heart failure**

| Variables (Mean ± SD) | Male Patients with Heart Failure (N=20) | Female Patients with Heart Failure (n=20) | t-value | p-value |
|---|---|---|---|---|
| Age | 54.63±7.64 | 56.09±7.68 | -o.461 | 0.655 |
| BMI | 25.38±3.94 | 31.70±3.85 | -2.841 | 0.019 |
| Hg(µg/dl) | 1.01±0.74 | 0.69±0.20 | 1.356 | 0.208 |
| As (µg/dl) | 0.116±0.057 | 0.100±0.079 | 0.674 | 0.517 |
| Pb (µg/dl) | 14.13±2.20 | 12.21±2.95 | 1.553 | 0.155 |
| Cd (µg/dl) | 0.147±0.073 | 0.117±0.018 | 1.249 | 0.243 |

**Table 5. Correlation of blood Pb with BMI, Hg, as and Cd in patients with heart failure**

| Dependent Variables | No of subjects(n) | r-value | p-value |
|---|---|---|---|
| BMI | 40 | -0.104 | 0.490 |
| Hg | 40 | 0.492 | 0.028 |
| AS | 40 | 0.088 | 0.712 |
| Cd | 40 | 0.474 | 0.036 |

Exposure to heavy metals may lead to heart failure by increasing the production of free radicals and therefore disruptions of intracellular homeostasis [3] and thus promoting oxidative stress, limiting nitric oxide availability, impairing nitric oxide signaling, augmenting adrenergic activity, increasing endothelin production, altering the renin-angiotensin system, raising vasoconstrictor prostaglandins, lowering vasodilator prostaglandins, promoting inflammation, disturbing vascular smooth muscle $Ca^{2+}$ signaling, diminishing endothelium-dependent vasorelaxation, and modifying the vascular response to vasoactive agonists [24].

The endothelium plays a central role in regulation of vascular function, macromolecular permeability, tissue perfusion, blood fluidity, and numerous other vital functions [25]. Therefore, Endothelial damage or dysfunction may result to atherosclerosis, thrombosis, tissue injury, and possibly heart failure [25].

Besides, Pb can cause endothelial injury, delay endothelial repair/growth, suppress proteoglycan production, stimulate vascular smooth muscle cell proliferation and phenotypic transformation [26] reduce tissue plasminogen activator, and raise plasminogen activator inhibitor-1 production [24] Thus, through these and other actions, lead exposure causes hypertension and promotes arteriosclerosis, atherosclerosis, thrombosis, cardiovascular disease, and may be eventually heart failure [24].

In addition, previous report indicates that Pb seems to alter the balance between vasoconstrictive and vasodilatory prostaglandins in a manner that supports development and progression of cardiovascular disease, hypertension in humans [27-28] and may be heart failure.

Our study reveals a significant positive correlation of blood Pb level with Hg and Cd in Patients with Heart Failure. This means that as the blood lead level increase, mercury and cadmium also increase as well. It has been previously reported that lead and other heavy metals in high quantity can cause cardiovascular disease [29].

The exact influence of *cadmium* on the cardiovascular system remains controversial. Previous report show that cadmium may exert effects on the cardiovascular system at extremely low exposure levels [30]. In vitro studies data revealed that low-dose cadmium levels may contribute to the initiation of pathophysiological changes in the arterial endothelial cell gene transcription [31].

Cadmium exposure may stimulate NADPH oxidase 2 (NOX2) expression, inducing superoxide anion production by NADPH oxidase and consequently reducing Nitric oxide (NO) bioavailability, contributing to oxidative stress, notwithstanding enhance nitric oxide synthase (eNOS) expression [32], thus could promote endothelial dysfunction [33], endothelial cell toxicity, apoptosis [34] and damage that might in turn contribute to inflammation, vascular injury and the development of atherosclerosis, rendering the cadmium-induced vascular hyperreactivity to phenylephrine [32] and may consequently lead to heart failure.

Environmental exposure to *Arsenic* contributes substantially in the pathogenesis of vascular endothelial dysfunction by deactivating endothelial nitric oxide synthase, resulting to reduction in the generation and bioavailability of nitric oxide, thus leading to high oxidative stress, and consequentially alters the structure and function of cardiovascular system [35]. Previous report indicates that chronic exposure to arsenic induce cardiovascular pathogenesis by upregulating expression of tumor necrosis factor-alpha, interleukin-1, vascular cell adhesion molecule and vascular endothelial growth factor [35].

Environmental and occupational exposures to inorganic arsenic have been linked to an increased cardiovascular mortality [36-37]. Arsenic has been reported as the main risk factor of a particular peripheral vascular disease called black foot disease in Taiwan, while other forms of peripheral vascular diseases have been linked with arsenic exposure in studies from some other countries [37] Besides, previous reports show arsenic-induced cardiovascular effects including atherosclerosis, coronary heart disease, hypertension and stroke in a dose-dependent manner [38-39].

Environmental exposure to *mercury* upsurges the production of free radicals, reactive oxygen species (ROS), and superoxide anions [40-41]. Mercury binds to thiol (-SH) containing molecules and binds to selenium, forming selenium-mercury complexes, reducing the glutathione peroxidase, catalase, and superoxide dismutase activities due to the absence of selenium in the active site

of these enzymes [40-42]. The increment of ROS and the reduction of antioxidant enzymes activity increase the risk of developing cardiovascular disease [43-44] and may progress to heart failure. Also, Mercury causes toxic effects on the cardiovascular system by inactivation of the paraoxonase, an extracellular antioxidative enzyme related to HDL (high-density lipoprotein) [45-46] which may cause dysfunctional HDL to reduce reverse cholesterol transport. Besides, Paraoxonase functions vitally as an antioxidant of LDL, a process that is actively involved in the pathogenesis of atherosclerosis and as a risk factor for acute myocardial infarction, carotid artery stenosis, coronary heart disease, and cardiovascular disease [47].

Although Our present result shows no significant difference in blood Hg of Patients with heart failure compared to Controls, an earlier report had linked high mercury hair content with an increased development of atherosclerosis and risk of cardiovascular disease [48] Also, it has been documented that Mercury exposure accelerates atherosclerosis both in vivo and in vitro [49].

Previous reports have indicated the role of mercury in the pathogenesis of atherosclerosis, vascular endothelial dysfunction, oxidative stress, inflammation, and dyslipidemia. Mercury can induce atherosclerosis indirectly via increasing the total cholesterol, triglycerides, and LDL-C levels as well as decreasing the HDL-C level [50].

The high blood levels of heavy metals observed among the heart failure patients in this present study may be as a result of various sources of exposure in Nigeria, which are mainly polluted air, drinking water, food and soil in residential areas [51]. These are sequel to industrial, mining, agricultural [52] and domestic activities. Other sources include Lead (PbS) from paints [53]. Leaded gasoline (tetraethyl Pb) in automobiles exhaust which emits Pb halides [54] road side activities and trash incineration [53,55].

There is still lack of information on the blood content of heavy metals in patients with heart failure in Black -African population. Nevertheless, the results presented in this study have considerable public health implications for the general population and particularly for patients with heart failure in this environment. This is because it reveals the importance of As, Cd, Pb and Hg exposure prevention, which may be useful for prevention and management of heart failure. An understanding of the role of heavy metals and its mechanisms in pathogenesis of heart failure can be of great help in controlling this disorder. However, this study has some limitations. We did not consider dietary and occupational exposure of heavy metals in heart failure patients and controls.

## 5. CONCLUSION

Environmental heavy metals exposure may lead to increase in blood levels of As, Pb and Cd which may in part contribute to the development of heart failure in this environment.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

Each participant gave his/her informed consent and approval for this study by signing a consent form after being informed on the procedure and implications of this study using English Language or the local Igbo dialect. Voluntary Participation was ensured; hence, participants could pull out from the study at any stage.

## ETHICAL CONSIDERATION

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Ethical Approval for this Research protocol (Reference No: ESUTHP/C-MAC/RA/034/V/ 11/17) was approved and issued by the Institutional Research Ethics Committee of ESUTH, Enugu.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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