Original Article

Effects of Lead Exposure on Biomarkers of Thyroid and Renal Function Tests among Panel Beaters in Enugu Metropolis, Nigeria

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ABSTRACT

Background: Occupational lead (Pb) exposure causes multisystem effects at high and sustained low doses. However, there are inconsistencies in the dose–response effects on the thyroid and kidneys. **Aim:** This study aimed to assess the effects of Pb exposure on the biomarkers of thyroid and renal functions among panel beaters in Enugu Metropolis, Nigeria. **Subjects and Methods:** This was a cross-sectional analytical study of 428-panel beaters selected using a multistage sampling technique. Blood lead (BPb), thyroid, and kidney biomarkers were analyzed using atomic absorption spectrometer at 238.3 nm wavelength, enzyme-linked immunosorbent assay, and automated chemistry analyzer, respectively. Analyses were performed using median, mean, Chi-square, correlation, and statistical significance. **Results:** The median BPb levels were 10.0 µg/dl among participants with about half, 211 (49.3%) having BPb within reference levels. Though the mean values of thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), and creatinine (Cr) were within the reference values, the majority of 275 (64.25%) of the participants had non-euthyroid statuses. Significant differences were found in TSH (P = 0.001), thyroid status (P = 0.0129), and estimated glomerular filtration rate (P = 0.00384) between those with BPb within reference level and those with elevated levels. **Conclusion:** Though the mean levels of thyroid hormones and Cr were within their respective reference intervals, there was a preponderance of non-euthyroid status among participants in the present study with the majority of the participants falling within CKD grades 2 and 3.

KEYWORDS: *Creatinine, lead, Nigeria, occupational exposures, thyroid hormones*

INTRODUCTION

Lead (Pb) is among the most commonly used heavy metal that is still prevalent and uncontrolled in many occupational processes in Nigeria.[1,2] Among the sources of Pb exposure is panel beating, a subspecialty of automobile technicians whose occupational practices include repairs, cuttings, soldering, welding, and spray paintings that expose them to Pb poisoning.[3] Panel beaters operate in a workshop where the above-mentioned occupational practices are carried out.[4] Pb poisoning was known to occur following high-dose acute exposures in the past, but with successive preventive measures, most poisonings are due to low-dose chronic exposures.[5] However, there is no recorded level of Pb that is good for the human body, thus no safe level of Pb exposure is known.[6] At varying levels of exposure, Pb interferes with the number of body functions that are multisystemic including thyroid and renal functions.[7]

Thyroid hormones (TH) are necessary for maintaining basic metabolic and neurophysiologic functions of the body through the pituitary–thyroid pathway.[8-10] Thyroid

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stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) are the hormones or biomarkers necessary for the above functions by a complex negative feedback mechanism. The biosynthesis of these hormones depends on their affinity to iodine, selenium, and other trace elements; however, unfortunately, these hormones also have an affinity to certain endocrine disrupting compounds (EDC) including heavy metals (Pb inclusive) causing metabolic disorders from hyper or hypothyroidism.[9,11] Effects of Pb exposure on thyroid physiology have been inconsistent, sometimes contradictory, and without a consensus.[1,10,12,13] It is noted that no dose–response relationship has been found between EDC and thyroid disorders.[11] Pb nephropathy on the other hand could be of glomerular and tubular nature which are detected by many biomarkers of nephrotoxicity but notably are serum creatinine (Cr) and urea. Acute Pb exposure is usually reversible and characterized by the deficient tubular transport mechanism, degenerative changes in tubular epithelium, and Pb protein complexes as nuclear inclusion bodies. In chronic Pb exposure, the irreversible renal disease may occur characterized by glomerular and tubule interstitial changes resulting in hypertension and hyperuricemia.[14] It is equally documented that adverse renal effects may present with mean BPb levels of <5 μg|dl.[15]

According to American Thyroid Association, 12% of people develop thyroid disease in their lifetime with the prevalence of hyperthyroidism ranging from 0.8 to 1.3%, while hypothyroidism is from 0.3 to 4.6%.[16] In the USA, 15% of adults or 37 million people are said to have chronic kidney disease,[17] while in Nigeria, the prevalence ranges from 12.3 to 26%.[18] Occupational Pb exposure studies found that at varying levels of Pb exposures some degrees of health effects are observed in the thyroid and renal systems. At 5–10 μg|dl, there is increased hormone response to stress, at 30–40 μg|dl, there are effects on the hypothalamus–pituitary–thyroid/adrenal axes, and at 40–50 μg|dl and above, there are changes in TH levels. Also from 30–40 μg|dl, there is progressive dysfunction in the kidney and at above 80 μg|dl, nephropathy occurs.[19]

Despite the above-known problems, there are still inconsistencies on the effects of Pb exposure on thyroid functions,[1] likewise the effect on kidney functions is argued by some researchers not to be an early victim of Pb exposure.[14,20] Hence, this study will contribute to existing data on the health effects of Pb exposure on the above systems and the dose–response relationship between Pb levels and the respective biomarkers. This study is, therefore, aimed at assessing the effects of Pb exposure on biomarkers of thyroid and renal functions among panel beaters in Enugu Metropolis, Nigeria.

Methodology

Study location

The study was conducted in Enugu North LGA, located in the Enugu metropolis of Enugu State, Nigeria. The metropolis is made up of three local government areas (LGAs) which are Enugu North, Enugu South, and Enugu East. Enugu North LGA has its headquarters at Okpara Avenue in the heart of the commercial center of Enugu city. It is an urban area inhabited majorly by the Igbos. The LGA has a population of 242,140 and a population density of 5,208/km^2 according to the 2006 National Population Census.[21]

Study design and study participants

The study adopted a cross-sectional study design. The study population included consenting panel beaters and trainees who are 18 years and above, had spent over 1 year on the job with a daily exposure time of 8 h and above, not involved in another job, and having no history of chronic diseases. Individuals with chronic diseases and those not willing to give consent were excluded.

Sampling method

A multistage sampling technique was used to select participants for this study. The first stage was a selection of Enugu North among the three local government areas by simple random sampling using the balloting method.

The second stage involved the selection of two divisions out of the ten divisions in Enugu North LGA by simple random sampling and also by the balloting method. The third stage was a selection of 20 branches out of the 26 branches from the two selected divisions in Enugu North LGA by simple random sampling equally using the balloting method.

This was done using the established organizational structure already in existence among the panel beaters' union whereby the LGA was first divided into divisions, then the divisions were further divided into branches. Lastly, because of the unequal number of panel beaters in the workshops, stratification and proportionate allocation were used to select the required number of panel beaters for the study.

Data collection, blood sampling, and test analysis

These were collected using research assistants who were two resident doctors and two phlebotomists. They were trained for 2 days, 2 h per day on the study objectives and requirements. Data were collected using an interviewer-administered semi-structured

questionnaire. The questionnaire assessed variables like age, years/months spent on current job, number of hours spent daily at work, past medical history, etc., Blood samples were collected under an aseptic procedure in an enclosed well screened area. The desired volume of 2–3 and 6 ml of blood were, respectively, drawn into ethylenediaminetetraacetic acid (EDTA) vacutainer bottles for blood lead (BPb) estimation and plain bottle for thyroid function and Cr tests. The EDTA sample bottles were gently rocked 3–5 times to ensure adequate mixing of blood and prevent blood clots. The samples for BPb estimation were transported immediately to the Project Development Agency Enugu where analysis was done, using the Gio style cold box after each day, accompanied by 5 and 10 ml syringes, bleach, and gloves for maintenance of universal precautions. The blood samples were diluted to 10 ml using deionized water because of accompanying cations and anions. The diluted sample was aspirated by the Buck Scientific Model 210 VGP atomic absorption spectrometer (AAS) via a capillary tube at a wavelength of 283.3 nm for Pb analysis. The blood samples for thyroid function and Cr test were allowed to clot, and serum was separated into plain tubes and stored at −20°C. The samples were thawed before analysis. Thyroid function tests were carried out using enzyme-linked immunosorbent assay (ELISA) method according to the manufacturer's instructions (Monobind Inc., USA), while Cr was analyzed using Roche Cobas C111 fully automated chemistry analyzer, respectively.

Reference intervals were defined according to manufacturers' instructions as follows:
TSH: 0.390–6.160 mIU/ml,
FT4: 0.800–2.000 ng/dl,
FT3: 1.400–4.200 pg/ml,
Cr: 96–140 µmol/l,
BPb: <10 µg/dl.

Data entry and analysis

The results of the analyses were entered into a spreadsheet for the BPb, TH, and Cr values.

Data were entered and analyzed using Statistical Package for Social Science version 25. Categorical variables were summarized using frequencies and proportions while continuous variables were summarized using mean, standard deviation, median, and interquartile range for skewed data. The BPb were categorized using a cutoff of 10 µg/dl and above as elevated Pb.[22] Association between BPb, TH, and Cr was determined using Pearson's Chi-squared test. The relationship between BPb, TH, and Cr was done using correlation analyses. The level of significance was set at $P < 0.05$.

Ethical considerations

Ethical approval was obtained from the Health Research Ethics Committee of University of Nigeria Teaching Hospital, Ituku Ozalla. (No. NHREC/05/01/200BB—FWA00002458—IRB00002323). Permission was obtained from unions of panel beaters in Enugu State. Informed consent was obtained from participants after study objectives were explained to them.

Results

The overall median BPb level was 10.0 µg/dl among panel beaters with an interquartile range of 0–26 µg/dl, Table 1. Though the mean values of TSH, free T4, free T3 and creatinine were within the reference values, Table 2, a considerable number of participants fell outside the reference values, Table 3, and differences existed in the thyroid statuses. While 153 (35.75%) were found to

Table 1: BPb levels among panel beaters

Parameters	Frequency *n*=428	Percent
BPb		
Median	10.0 µg|dl	
Interquartile range	0-26 µg|dl	
Categories of BPb		
BPb within reference level	211	49.3
Elevated BPb	217	50.7

Table 2: Mean distribution of TSH, FT4, FT3, and Cr among panel beaters

Parameters	Mean	Standard deviation
TSH mIU/ml	4.28	0.38
FT4 ng/dl	0.96	0.04
FT3 pg/ml	2.54	0.07
Cr µmol/l	118.59	2.152

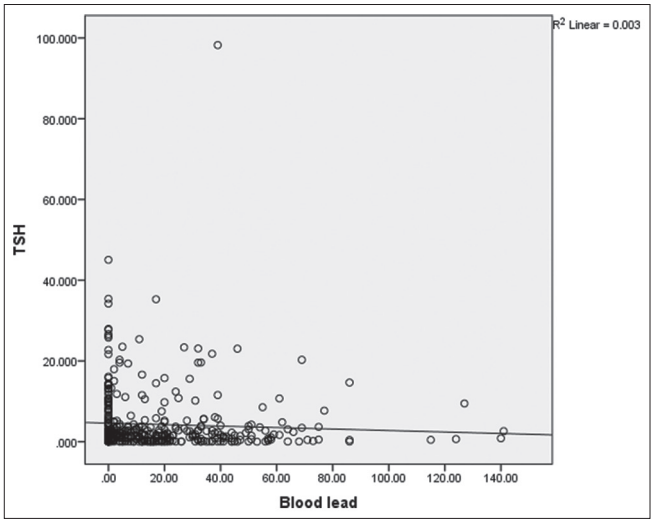

Figure 1: A scatter plot showing the correlation between BPb levels and TSH

Table 3: Distribution of TSH, FT4, FT3, and Cr among panel beaters

Parameters (reference values)	Within reference range Freq (%)	Low Freq (%)	High Freq (%)	Outside reference range; (Low + High) Freq (%)
TSH (0.390-6.160 mIU/ml)	256 (59.8)	97 (22.7)	75 (17.5)	172
FT4 (0.800-2.000 ng/dl)	197 (46.0)	207 (48.4)	24 (5.6)	231
FT3 (1.400-4.200 pg/ml)	289 (67.5)	101 (23.6)	38 (8.9)	139
Cr (96-140 µmol/l)	309 (72.2)	63 (14.7)	56 (13.1)	119

Table 4: Association between Pb levels and TH, Cr distributions

Parameters	Lead levels		Statistical test	
	BPb within reference level *n*=211 Freq (%)	Elevated BPb *n*=217 Freq (%)	Chi-square	*P*
TSH status				
Within reference interval	128 (50.0)	128 (50.0)	13.314	0.001*
Low	35 (36.1)	62 (63.9)		
High	48 (64.0)	27 (36.0)		
FT4 status				
Within reference interval	108 (54.8)	89 (45.2)	5.438	0.065
Low	90 (43.5)	117 (56.5)		
High	13 (54.2)	11 (45.8)		
FT3 status				
Within reference interval	131 (45.3)	158 (54.7)	5.722	0.056
Low	59 (58.4)	42 (41.6)		
High	21 (55.3)	17 (44.7)		
Thyroid status				
Euthyroid	81 (38.39)	72 (33.18)	14.448	0.0129*
Hyperthyroid	4 (1.90)	5 (2.30)		
Hypothyroid	8 (3.79)	10 (4.61)		
Secondary hypothyroidism	53 (25.12)	66 (30.42)		
Subclinical hyperthyroidism	29 (13.74) 3	47 (21.66)		
Subclinical hypothyroidism	36 (17.06)	17 (7.83)		
Cr				
Within reference	152 (49.2)	157 (50.8)	3.069	0.215
Low	36 (57.1)	27 (42.9)		
High	23 (41.1)	33 (58.9)		
eGFR (ml/min/1.73 m^2)				
Grade 1 (≥90)	63 (29.86)	37 (17.05)	13.404#	0.00384*
Grade 2 (60-89)	128 (60.66)	142 (65.44)		
Grade 3a (45-59)	18 (8.53)	36 (16.59)		
Grade 3b (30-44)	2 (0.95)	2 (0.92)		

*Significant. #Fischer's exact

Table 5: Correlation between BPb levels, TH, and Cr

Parameters	R (BPb)	*P*
TSH	−0.053	0.275
FT4	−0.094	0.53
FT3	0.007	0.889
Cr	0.080	0.099

be euthyroid, the majority of 275 (64.25%) participants had other thyroid statuses ranging from hyperthyroidism to subclinical hypothyroidism as described in Table 4. Significant differences were found in TSH (P = 0.001), thyroid status (P = 0.0129), and estimated Glomerular Filtration Rate (eGFR) (P = 0.00384) between those with BPb within reference level and those with elevated levels, Table 4. While the majority in both arms fell into CKD grades 1 and 2, a greater proportion of individuals in the BPb elevated arm fell into the moderate Chronic Kidney Disease (CKD) grades 3a and 3b. Differences equally existed in the distribution of FT4, FT3, and Cr statuses between the two groups as described in Table 4, though these were not statistically significant.

Correlation results showed very weak linear relationships between the BPb levels and TH, and also between BPb levels and Cr. These relationships were negative for TSH

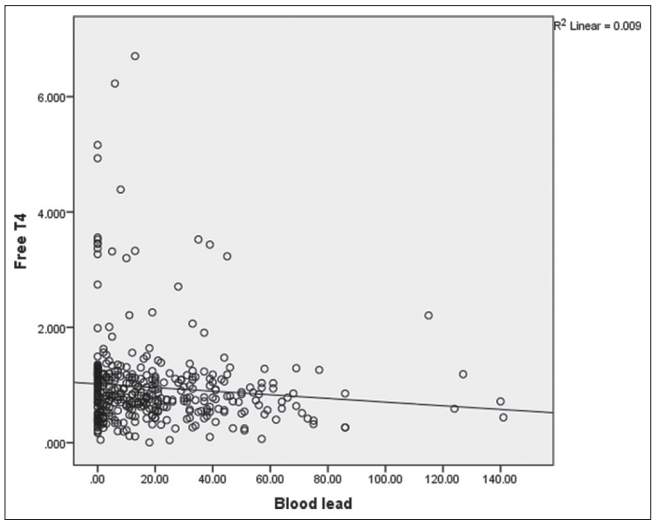

Figure 2: A scatter plot showing the relationship between BPb levels and FT4

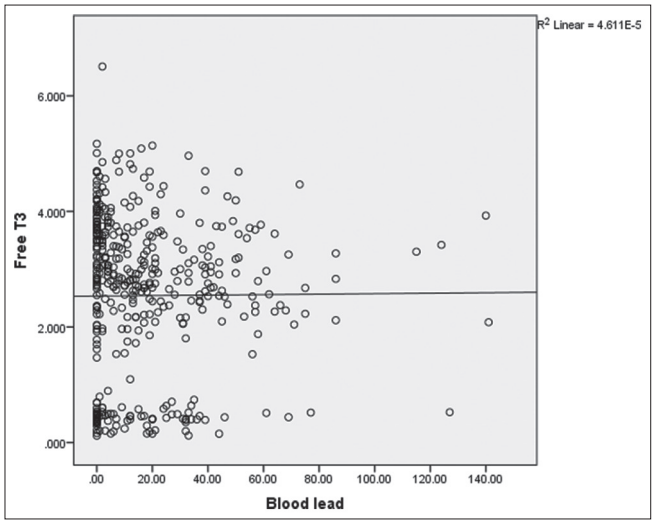

Figure 3: A scatter plot showing the relationship between BPb levels and FT3

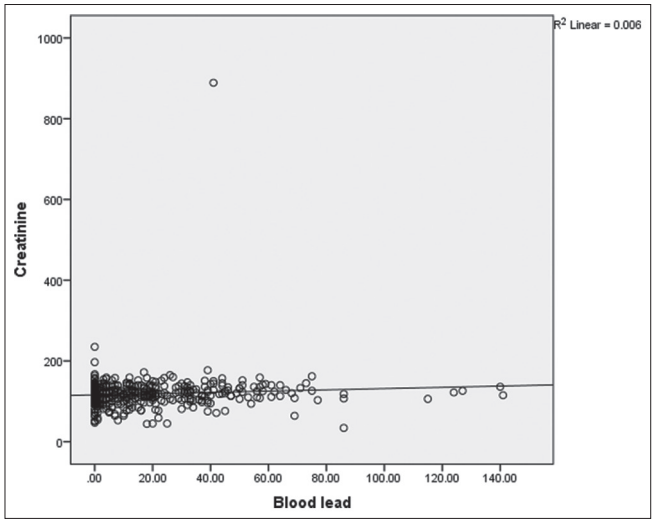

Figure 4: A scatter plot showing the relationship between BPb levels and Cr

and FT4, positive for FT3 and Cr, and not statistically significant, Table 5. The scatter plots showed crowding of TSH, FT4, and Cr values around the normal values of BPb unlike in FT3, Figures 1–4.

Discussion

With progressive and successive preventive measures against occupational and environmental Pb exposures, the consequent health effects from frank poisonings have been reduced.[5] The deleterious nature of Pb has shifted attention to the health effects at lower dose either in acute or chronic exposures and it is noted that there is potential for harm at any level of exposure.[6] These successes had led to continued lowering of occupational Pb exposure levels, currently, occupational Pb exposures are set at 10 µg|dl to mean abnormal Pb exposures or some forms of poisoning and above which the worker should be removed from the source of exposure.[22] This study found that the median BPb level is within the level for abnormal exposure with many of the workers having BPb levels ranging from 0 to 26 µg|dl around the median level. This is supported by about half of workers having elevated BPb levels. This finding agreed with studies in South-East Nigeria, South-South Nigeria, and Iran where the mean BPb levels were at elevated BPb levels of 42.30 µg|dl, 50.37 µg|dl, and 10.59 µg|dl, respectively.[2,23,24] This shows that Pb poisoning is still a prevalent public health problem. The finding, however, differs from that of a study in Southwest, Nigeria in which the mean BPb was 4.4 µg|dl.[25] The difference could be due to the limited sample size used in the Southwest Nigeria study. It should also be noted that the differences in the summary indices through abnormal could be due to the different exposure/occupational sources.

Pb as heavy metal is part of the EDCs, and EDCs have been noted to cause the affectation of hormone systems mainly by interfering with steroid and TH.[26]

In the present study, the relationship between BPb, TSH, and fT4 was noted to be negative, meaning that higher BPb levels were associated with lower TSH and fT4 levels.

This agrees with studies in Iran[12] and Michigan[27] which equally reported lower TSH values in patients with elevated BPb. And equally agrees with studies by Dundar *et al.*[28] which documented a negative correlation between BPb and FT4, and that of Meeker *et al.*[27] which reported a negative relationship between BPb and TSH. This, however, differs from the study by Singh *et al.*[29] which reported a positive relationship between TSH values and elevated BPb levels, and a study in Korea[1] which equally reported higher mean

TSH levels among Pb-exposed group compared to the control group. However, it is important to note that the Korean study made use of apparently healthy individuals with no exposure to Pb as the control group, unlike the present study where the comparing arm had been exposed to Pb. The differences seen could equally be from the different sample sizes used in the different studies. Again, the mean BPb level (71.1 μg/dl) in the Korean study is a lot higher than the median level of 10 μg/dl found in the present study. In terms of FT3 and FT4, the Korean study reported that FT3 and FT4 were observed high with high BPb levels. The report on FT3 is in agreement with that of the present study but varies with that of FT4, the difference probably owing to reasons earlier stated. It is equally noteworthy to state that though the present study varied from the study by Singh *et al*[30] in terms of TSH, the values generated by both studies fall within the reference intervals. The non-significant association seen between BPb and FT4, FT3, and TSH in the present study agrees with the study by Mendy *et al.*[30] which equally reported no significant correlation between BPb and TSH, TT3, FT3, and FT4.

The present study reported the preponderance of non-euthyroid status among participants. The majority of these were either in the hypothyroid, secondary hypothyroid, or subclinical hypothyroid states. This is in agreement with other studies by Robins *et al.*[31] and Łasisz *et al.*[32] which reported depressed thyroid indexes consistent with hypothyroidism with occupational exposure to Pb. However, because the TSH levels in this group of individuals varied between high and low levels within reference intervals, it becomes difficult to ascertain the point of the possible effect of Pb on the hypothalamic–pituitary–thyroid axis.

Hyperthyroidism/hyperthyroxinaemia has equally been reported in patients by different authors at different times. Klein *et al.*[33] reported two cases of Pb poisoning secondary to hyperthyroidism. Goldman *et al.*[34] reported the case of a woman with thyrotoxicosis and an elevated BPb level, while Cagin *et al.*[35] reported the case of a patient with a retained bullet who developed Pb poisoning in association with thyrotoxicosis.

The mean serum Cr value from this study was within the reference value. This agrees with previous studies[2,36] which equally documented serum Cr levels within the reference intervals. There was a significant difference in eGFR between participants with elevated BPb and those with BPb within reference intervals, with more individuals in the elevated BPb arm falling into the moderate CKD (grades 3a and 3b). Though the reason for this is not clear, this stage of nephropathy is suggestive of the risk of renal insufficiency. Moreover, the finding of CKD grades 2 and 3 stages in both arms substantiates earlier postulations that the lowest level at which Pb has untoward effects on the renal system is not known.[14]

The present study also noted a weak non-significant correlation between BPb and Cr. This may indicate a possibility that the renal picture seen in the participants may not be solely due to Pb exposure. The relationship between Pb and the biomarkers studied showed a non-significant linear relationship that is very weakly correlated. The non-significant correlation between BPb levels and the biomarkers suggests insufficient evidence to predict the dose–response relationship between the two variables. The correlation was negative for the TSH and FT4 and positive for the FT3 and Cr biomarkers. This means that as BPb levels increases, the TSH and FT4 decreases, while the reverse is for FT3 and Cr. However, the correlation values of the variables are close and crowded to zero in either direction of the relationship. This is also illustrated in the scatter plot in Figures 1-4, where the biomarkers are crowded within normal and early abnormal values of BPb. The slight linearity may be suggestive of abnormal to toxic outcomes of thyroid and renal functions assessed and should provide the basis of consideration for removal of workers from exposure source till BPb or serum levels of biomarkers are brought to normal or acceptable levels. These findings agreed with studies in Egypt, the US, and Poland.[9,37,38]

In light of the above findings, the present study buttresses the public health importance of removing workers from the source of exposure as the BPb levels start to rise above the occupational threshold. It is advocated that these public health preventive measures with other occupational safety measures should be strengthened to continue to keep BPb within the reference levels.

Conclusion

Though the mean levels of TH and Cr were within their respective reference intervals, there was a preponderance of non-euthyroid status among participants in the present study with the majority of the participants falling within CKD grades 2 and 3. These findings, therefore, provide additional evidence of renal and thyroid abnormalities in association with Pb exposure and further buttresses the public health importance of removing workers from the source of exposure as the BPb levels start to rise above the occupational threshold.

Limitations: The study is specific to one area, and, therefore, the findings may not be easily generalized. It is cross-sectional, and the findings are limited to the period of the study. However, the strength lies

in the considerably large number of participants used in the study and being among the first to describe both the renal and thyroid function indices of participants in the study area.

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Conflicts of interest

There are no conflicts of interest.

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