Association between Urine Albumin to Creatinine Ratio and Bone Mineral Density Using Bayesian Approach

Nahome Alemseged, Mohammed Bheser, Kemal Sherefa Oumer,

Department of Health Metrics, University of Washington, Seattle, Washington, USA

Abstract

Studies on the association between urinary albumin to creatinine ratio (ACR) and bone mineral density (BMD) are still controversial. This study investigated the association between ACR and BMD in the general US population using Bayesian approach. This cross-sectional study identified 2007 individuals aged 40 or above years with complete and valid data on urinary albumin to creatinine ratio (ACR), and femoral neck, total femur and lumbar spine BMD from the National Health and Nutrition Examination Survey 2013-2014. ACR was directly measured with established methods. BMDs were measured by Dual-energy X-ray absorptiometry (DXA). After adjusting for multiple covariates, we used Bayesian multiple linear regression to determine the association between ACR and BMD. The results show that the mean age of participants in this study was 54.6 ± 11.3 years; 52.6% of them were female. ACR was negatively associated with BMD at femoral neck and total femur and positively with lumbar spine. After adjusting for covariates, ACR was negatively associated with total femur, but with not femoral neck and lumbar spine BMD. We conclude that ACR was negatively associated with total femur BMD in the general US population. Future studies are warranted to confirm our results.

Keywords: Bone mineral density, Urine Albumin to Creatinine Ratio, Osteoporosis

Background

Osteoporosis and chronic kidney disease (CKD) are public health problems worldwide. Osteoporosis is estimated to affect 200 million people worldwide and cause more than 8.9 million fractures annually [1]. In the United States, an estimated 54 million people have osteoporosis or low bone mass [2]. With increased longevity, the probability of developing osteoporosis over a lifetime has also increased. CKD affects more than 750 million persons worldwide [3]. It affects an estimated 37 million people in the U.S. and millions of others are at increased risk. Osteoporosis and CKD are linked. Osteoporosis is more common in patients with chronic kidney disease (CKD) compared to the general population. Individuals with CKD have 4.4 fold higher risk of osteoporosis fracture than those without CKD [4]. In addition, the association between CKD and reduced BMD and the resulting increased risk of fracture is well recognized [5,4].

Albuminuria, urinary albumin to creatinine ratio (ACR) ≥ 30mg/g in the urine, is a key biomarker for cardiovascular disease and chronic kidney disease [6]. Measurement of ACR is an important tool for both the diagnosis and prognosis of chronic kidney disease. The severity of CKD can be quantified by raised urinary albumin measured by the ACR, which is a marker of kidney damage [7]. A higher level of ACR is associated with reduced bone blood flow, resulting in a decreased rate of bone remodelling and the development of osteoporosis [8]. Also, high ACR level has increased the risk of hip fracture and osteoporosis [9,10].

Several studies have examined the association between urinary albumin to creatinine ratio (ACR) and bone mineral density (BMD) [10-13] . The relationship between renal [12,13]. However, studies on the association are still controversial. As a research question we will try to understand whether this relationship will benefit clinicians in order to enable early screening for osteoporosis and may provide additional information to the health care system and researchers. Investigation on ACR and BMD was really found to be negative in their association.

In addition, there are no studies conducted using Bayesian approach. Therefore, the aim of this study was to investigate the association between ACR and BMD using Bayesian approach in the general US population.

Methods

Study setting and population.

The NHANES is a population-based health examination survey that provides nationally representative cross-sectional data on the health status of the civilian, noninstitutionalized U.S. population from the early 1960s onwards. The participants are selected by a complex probability sampling design, and interviews and examinations are conducted to obtain information on each participant. The NHANES was conducted by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC).

The cross-sectional study was conducted using NHANES data from 2013-2014, we included all participants with complete and valid data on BMD at the femoral neck, total hip and lumbar spine sites and urine albumin to creatinine ratio. We excluded individuals with missing or invalid femoral neck, total femur and lumbar spine BMD. In NHANES 2013-2014, bone scans were administered to eligible survey participants 40 years and older. All participants provided written consent to participate in the NHANES surveys and data collection was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board.

Study measures

BMD was measured by dual-energy X-ray absorptiometry (DXA); details of the DXA examination protocol have been published elsewhere [14]. All scans were performed with Hologic Discovery® A densitometers (Hologic, Inc., Bedford, Massachusetts, US) using software APEX v4.0 by trained and certified radiology technologists. Further details of the DXA examination protocol are available in the Body Composition Procedures Manual located on the NHANES website [15].

Urine albumin and creatinine concentrations were measured in one random urine sample. Urine albumin (mg/l) was measured using a solid-phase fluorescent immunoassay [16] and Urine creatinine (mg/dl) was measured by the Jaffe rate method [17]. Urine albumin extraction was estimated as the urinary albumin to creatinine ratio (ACR) in milligrams of albumin per gram of creatinine (mg/g). This method, based on spot urine, yields results comparable to those from a 24-h urine collection [18].

The study covariates included sex, age, smoking, history of hypertension, history of diabetes and race based on the original article's preferences. Body Weight and height were directly measured; other covariates were collected through a structured questionnaire.However, we used BMI due to a combination of height and weight. BMI was calculated as body weight (kg) divided by the square of body height (m^2). Smoking status was classified as a current smoker, former smoker and never smoker.

The race was categorised as Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black or other. We labelled the category as "black and others" because of the original research papers.

Statistical analysis

In the descriptive analysis, continuous variables with a normal distribution were shown as means (SDs); variables with a skewed distribution were shown as medians (inter-quartile ranges (IQR)); and categorical variables were shown as percentages.

Log transformations are often recommended for skewed data. Transformations are applied to accomplish certain objectives, such as ensuring linearity, achieving normality, or stabilising the variance. In this case, we used for exposure, the log transformation of urinary albumin to creatinine ratio (ACR) in the model. The statistical analysis for this study was based on Bayesian multiple linear regression models. Bayesian analysis combines the likelihood (data) with prior knowledge (prior probability) to update information on the parameters to result in a revised probability associated with the parameter (posterior probability).

Bayesian Approach

We used Bayesian multiple linear regression to examine for the association between ACR and BMD at the total femur, femoral neck, and lumbar spine sites without adjusting covariates (1) and after adjusting for covariates (2). We used a likelihood function to assess the probability of the observed data given the model parameters. The likelihood function we used follows a normal distribution and depends on two key parameters: the μ and the δ (standard deviation).

$$B_i \sim \mathrm{N}(\mu_i, \sigma), \qquad \mathrm{i} = \text{Lumbar spine, Total femur, Femoral neck}$$

$$\mu_i = \alpha + \beta_{\mathrm{act}} \cdot \mathrm{act}[i] \ \ldots (1)$$

$$\mu_i = \alpha + \beta_{\mathrm{sex}} \cdot \mathrm{sex}[i] + \beta_{\mathrm{age}} \cdot \mathrm{age}[i] + \beta_{\mathrm{black}} \cdot \mathrm{black}[i] + \beta_{\mathrm{bmi}} \cdot \mathrm{bmi}[i] + \beta_{\mathrm{hyper}} \cdot \mathrm{Hypertension}[i] + \beta_{\mathrm{diab}} \cdot \mathrm{Diabetes}[i] + \beta_{\mathrm{act}} \cdot \mathrm{act}[i] \ \ldots (2)$$

By considering these factors, we aim to accurately capture the relationship between the observed data and the model parameters.

The selection of priors in this Bayesian analysis involves a range of strategies following trial and error methods to strive for a balance between prior beliefs and the evidence provided by the data. After conducting multiple checks and evaluations, we have developed a prior distribution that accurately represents our prior beliefs.

$$\alpha, \beta_{\mathrm{i}} \sim \mathrm{N}(0, 0.1)$$

$$\sigma \sim \mathrm{dexp}(1)$$

$$i = sex, age, smoking, history\ of\ hypertension, history\ of\ diabetes\ and\ race$$

This prior distribution is based on the results of prior predictive checks, which help us assess how well our prior assumptions align with the observed data. The following prior passes a predictive check applied for exposure and controlling covariates. It comes with the well-defined and reliable representation of our initial beliefs.

In this study, a non-informative prior normal distribution assigned to normal prior distribution for the components of where the common choice for μ is zero, and δ is usually chosen to be large enough to be considered as non-informative. The process of obtaining the estimation of regression model parameters with Bayesian approach can be done by using MCMC (Markov Chain Monte Carlo) algorithm. One of the commonly used algorithms in MCMC is Gibbs Sampling. A Gibbs sampler was used to generate a Markov chain Monte Carlo (MCMC) chain of 30,000 samples with a burn-in period of length 10,000 and chains of four. The term convergence of an MCMC algorithm refers to whether the algorithm has reached its equilibrium (target) distribution. Several diagnostic tests have been developed to monitor the convergence of the algorithm such as trace plot, effective sample size, Gelman Rubin. The R package that can be used to Bayesian approach in linear regression model are rethinking and jags. All analysis was run with the R software version 4.2.0.

Results

Baseline characteristics

Baseline characteristics are shown in Table 1. We included 2,007 participants with a mean age of 54.6 ± 11.3 years for our study; 52.6% were women. The average BMI was 28.3 ± 6.1 kg/m^2, and median ACR was 7.50 mg/g (IQR, 4.96, 13.93). The mean BMD for femoral neck, total femur and lumbar spine were 0.79 ± 0.14, 0.95 ± 0.15 and 1.01 ± 0.16 g/cm^2, respectively (Table 1 and Appendix).

Table 1 Baseline characteristics of the study population (N=2007)

Characteristics	Values
Female (n, %)	1055 (52.6)
Age (years)	54.7 (11.3)
Weight (kg)	78.9 (19.7)
Height (cm)	163.6 (10.1)
Body mass index (kg/m^2)	28.32 (6.09)
Race (n, %)	
Mexican American	295 (14.7)
Other Hispanic	202 (10.1)
Non-Hispanic White	777 (38.7)
Non-Hispanic Black	393 (19.6)
Other	340 (16.9)
Smoker	
Current (n, %)	366 (18.2)
Former (n, %)	483 (24.1)
Never (n, %)	1158 (57.7)
History of hypertension (n, %)	808 (40.3)
History of diabetes (n, %)	289 (14.4)
Albumin [a] (mg/l)	7.4 (4.0, 15.4)
Creatinine [a] (mg/dl)	95.0 (54.0, 149.0)
Albumin creatinine ratio [a] (mg/g)	7.50 (4.96, 13.93)
Femoral neck BMD (g/cm^2)	0.79 (0.14)
Total femur (g/cm^2)	0.95 (0.15)
Lumbar spine BMD (g/cm^2)	1.01 (0.16)

Values are means (SD), unless otherwise specified.

[a] Values are shown in medians (interquartile ranges)

Prior Predictive Check

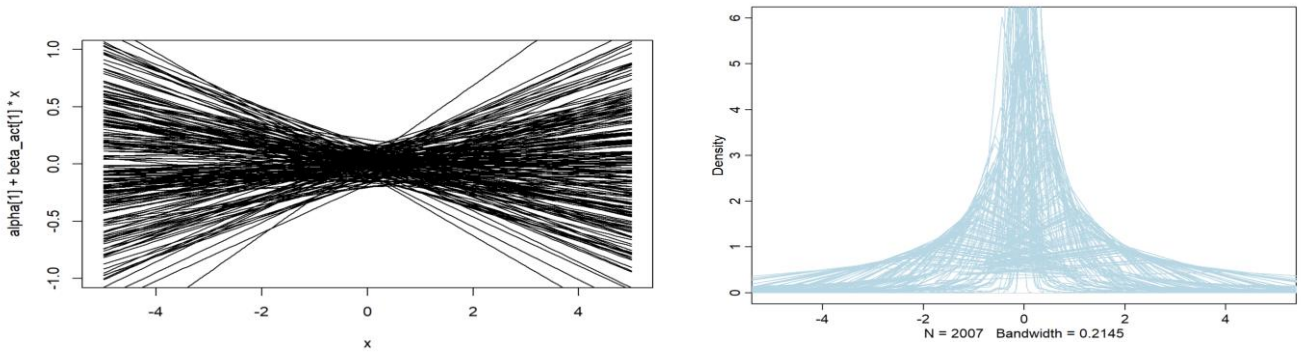

Fig 1 - Prior predictive check Total femur. The same for the other outcomes (see Appendix - Supplementary)

The curve plot of the simulated data of the above prior predictive check is closely centred to zero and density plot shows closer to a normal distribution by following law of large numbers, it suggests that the prior assumptions are reasonable and provide a good fit to the data.

We found that ACR was negatively associated with BMD using classical approach at total femur after adjusting for gender, age, race, body mass index, hypertension, diabetes (since their 95% confidence intervals does not contains zero), but with not femoral neck and lumbar spine BMD (Table 2)

Table 2: Linear regression model using classical approaches for BMD and ACR

BMD sites	Estimate	Standard error	95% confidence interval
Femoral neck	-0.0042	0.0023	(-0.0088, 0.0002)
Total femur	**-0.0051**	**0.0023**	**(-0.0097, -0.0005)**
Lumbar spine	0.0024	0.0029	(-0.0032, 0.0081)

Adjusted for gender, age, race, body mass index, hypertension, diabetes

A table 3 shows the posterior mean and 95% credible interval of the regression coefficients of ACR for each site of BMD after adjusting covariates. A 95% Bayesian credible interval provides a range for a parameter such that the probability that the parameter lies in that range is 95%. The credible interval for βj is smaller than the confidence interval using the frequentist approach.

Table 3: Linear regression model using Bayesian approaches for BMD and ACR

BMD sites	Estimate mean	Standard error	95% Posterior credible interval	Effective Sample Size
Femoral neck	-0.0032	0.0026	(-0.0079, 0.0014)	12,522
Total femur	-0.0039	0.0025	(-0.0086, 0.0010)	12,584
Lumbar spine	0.0041	0.0029	(-0.0015, 0.0098)	12,930

Adjusted for gender, age, race, body mass index, hypertension, diabetes (for un- adjusted see appendix - Supplementary)

The Effective Sample Size (ESS) in the context of MCMC for femoral neck is 12.522. A value is the minimum size of a set of posterior samples (taken directly from the posterior), which have the same efficiency (measure of quality) in the posterior density estimation as a given chain of samples obtained from MCMC sampling (Table 3).

Posterior Predictive check

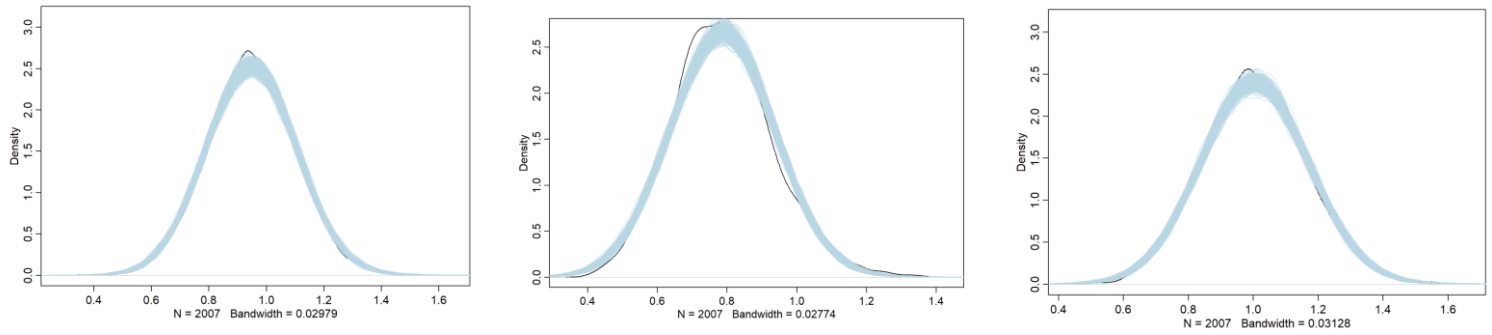

Fig 2 - Posterior predictive check Total femur, lumbar spine, and femoral neck.

When comparing the observed data with the simulated data on a density plot, the above three model densities closely align and overlap, suggesting that the model is consistent with the observed data. This alignment indicates that the model's assumptions and parameters capture the underlying patterns and variability in the data. It implies that the model is a **good fit** for the observed data.

For all estimators at each site of BMD, the results show that R−hat approaches one. This indicates there is no common problem when using MCMC, which lacks convergence between chains. (see Appendix - Supplementary)

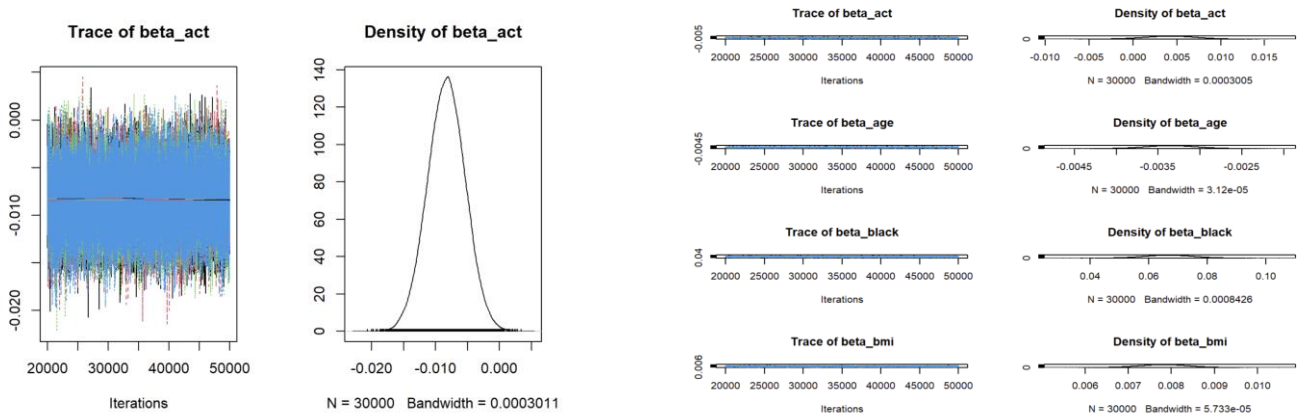

Figure 1: Trace plots of few parameters of Bayesian model using MCMC chains, the other's plot can be found in the Supplementary - appendix.

Each trace plot shows of ae values that the of the relevant parameter took during the run plots the chain in the figures. A trace plot for ACR coefficients at each site of BMD seems like a healthy trace plot. It is highly efficient, converges to its stationary distribution and easy to explore in the same place.

Discussion

Several studies have reported the association between urinary albumin/creatinine ratio (ACR) and bone mineral density (BMD) [10-13]. However, studies on the association between ACR and BMD are still controversial. Therefore, we investigated the association of ACR with BMD in the general US population using Bayesian approach.

Early diagnosis and prevention strategies can improve bone health and reduce the risk of fractures. Assessment of risk factors involves identifying the attributes, characteristics, or exposure of a person who increases the likelihood of osteoporosis. It plays an important role in early detection and prevention techniques. Early diagnosis of osteoporosis by risk assessment could prevent osteoporotic related fractures [19].

The results of the classical multiple linear and Bayesian multiple linear show that the data were well fitted, and the results of both approaches were almost consistent, but almost all parameters in the Bayesian result had small standard errors compared to the corresponding classical model. This is because the Bayesian analysis gives additional solutions as the posterior distribution of the parameters.

We found that ACR was negatively associated with total femur BMD after adjustment for gender, age, BMI, history of hypertension, history of diabetes and race. This result is comparable to that shown in previous studies [10,13]. Similar direction of association has been found in our analysis for the Bayesian multiple regression model we used.

In this study, ACR was positively associated with lumbar spine BMD in the univariate model. However, this association disappeared after adjustment for covariates. A similar study among the general population in Korea, the results showed that ACR was not associated with lumbar spine BMD [12]. Our results showed a negative association between ACR and femoral neck BMD. Also, this association appeared after adjustment for covariates. This is consistent with another population-based study, a study with 5390 women showed that ACR was associated with femoral neck BMD; also this association appeared after adjustment for age, BMI and other covariates [11].

The original articles state that has certain limitations and could not include some covariates due to being incapable of adjusting lifestyle and other factors. Because there were too many missing values in the NHANES 2013–2014 database, and did not account for this as a covariate in their study. Following the articles and due to the absent data, we did not consider osteoporosis factors such as past medical history, including any previous fractures.

Conclusion

ACR was negatively associated with total femur BMD in the general US population. but showed no association with femoral neck and lumbar spine BMD. Future studies are warranted to confirm our results.

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