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Association between urinary glyphosate exposure and bone mineral density in adults

Zhenwei Wang, MM[a,b], Hongwei Zhang, MM[c], Weibin Du, MD[a,b], Jintao Hu, MD[d], Renfu Quan, MD[a,b,*]

Abstract

There is very limited evidence linking glyphosate exposure to bone mineral density in adults aged 20 to 59 years in the National Health and Nutrition Examination Survey database. Hence, this study aimed to investigate the correlation between urinary glyphosate concentrations and total bone mineral density (BMD) in adults aged 20 to 59 years. A cross-sectional study was conducted using data from the 2013 to 2016 National Health and Nutrition Examination Survey, which included 594 men (mean age 39.1 years) and 610 women (mean age 40.0 years). In our study, we utilized a weighted multiple regression equation model to investigate the potential correlation between urinary glyphosate concentration and total BMD. Additionally, we conducted a stratified analysis to differentiate between various special populations. Our findings revealed a significant negative association between urinary glyphosate concentration and total BMD across 3 different regression models (Model 1, β [95% CI]: −0.0160 [−0.0200, −0.0120]; Model 2, β [95% CI]: −0.0135 [−0.0172, −0.0098]; Model 3, β [95% CI]: −0.0141 [−0.0178, −0.0104]). However, after stratifying by gender, age, and race, we observed varying conclusions. This study found that urinary glyphosate concentration was negatively associated with total BMD in both men and women when stratified by sex. Additionally, when stratified by age, the negative association was more significant in the 20 to 29 and 50 to 59 year age groups. When stratified by race, a significant negative association was found in races other than Hispanic. Therefore, the impact of glyphosate exposure on BMD should attract more people's attention.

Abbreviations: BMD = bone mineral density, NHANES = National Health and Nutrition Examination Survey.

Keywords: adults, bone mineral density, cross-sectional study, glyphosate, NHANES

1. Introduction

Osteoporosis is a metabolic disease that affects the entire body, characterized by a decrease in bone mass and destruction of bone microarchitecture. This condition is influenced by various factors such as genetics, endocrine changes, diseases, and living environment. Osteoporosis can be classified into 2 types: primary and secondary.[1,2] The prevalence of osteoporosis has been on the rise in recent years, leading to both physical and psychological harm to the affected individuals. Additionally, this trend has placed a significant strain on society, the economy, and overall development.[3] Dual-energy X-ray absorptiometry is a common clinical index used to measure bone mineral density (BMD) for detecting osteoporosis.[4,5] It is also useful in assessing the risk of fragility fractures, tracking changes in the severity of osteoporosis, and evaluating the efficacy of certain habit changes or drugs.[6] As a result, investigating factors that may impact BMD is of great importance for both individual patients and society as a whole.

Glyphosate, an insecticidal herbicide, possesses remarkable characteristics such as high efficiency, low residue, low toxicity, and low selectivity. It is widely used in agricultural production, urban greening, and other fields. With the promotion of glyphosate-tolerant genetically modified crops, their usage is increasing year by year.[7] Various exposure methods such as pharmaceutical production, pharmaceutical spraying, and crop residues have made glyphosate detectable in the urine of at least

ZW and HZ contributed equally to this work.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

[a] Research Institute of Orthopedics, The Affiliated Jiangnan Hospital of Zhejiang Chinese Medical University, Hangzhou, China, [b] Hangzhou Xiaoshan Hospital of Traditional Chinese Medicine, Hangzhou, China, [c] Department of Orthopaedics, Zhoushan Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical University, Zhoushan, China, [d] Orthopedics and Traumatology Department, Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China.

* Correspondence: Renfu Quan, Research Institute of Orthopedics, The Affiliated Jiangnan Hospital of Zhejiang Chinese Medical University, Hangzhou 312001, China (e-mail: quanrenfu@126.com).

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60% of the U.S. population, with a maximum mass concentration of 233 μg/L and an average of 2 to 3 μg/L.[8] Recent research has suggested that the widespread use of glyphosate may contribute to ecological contamination. Le Du-Carrée et al conducted a study that revealed that glyphosate can cause reproductive toxicity in rainbow trout offspring and increase their susceptibility to the hematopoietic necrosis virus.[9] Glyphosate was classified as possibly carcinogenic by the International Agency for Research on Cancer in 2015,[10] with subsequent research revealing its hepatotoxic, nephrotoxic, reproductive toxic, and neurotoxic effects. As such, the impact of glyphosate on human health is a significant concern.[1,9,11,12] However, further research is needed to clarify the mechanistic role of glyphosate in affecting human health.

A study found that glyphosate caused disruptions in bone metabolism, specifically in calcium and phosphorus levels, as well as hormonal imbalances in Wistar rats. This resulted in thinning and discontinuity of bone trabeculae.[11] However, limited evidence exists linking glyphosate levels to human BMD. To further investigate this, the correlation between urinary glyphosate levels and total BMD in adults aged 20 to 59 years was analyzed using the National Health and Nutrition Examination Survey (NHANES 2013–2016).

2. Materials and methods

2.1. Statement of ethics

The cross-sectional study using the NHANES database was conducted with the approval of the National Center for Health Statistics Research Ethics Review Board, and written consent was obtained from all participants.

2.2. Study population

This study was based on NHANES data collected from 2013 to 2016. A review of previous studies found that most studies on bone mineral density have focused on people aged 20 to 59 years.[12–14] Adolescents are in a critical growth phase, and bones are in the building phase until the age of 20 years. In contrast, people older than 60 years may have more underlying diseases. To minimize confounding factors, we only included participants aged between 20 to 59 years (n = 7746) and excluded those who were younger than 20 years and older than 59 years. After removing missing data on glyphosate (n = 5676) or urinary glyphosate concentrations below the lower limit of detection (0.2 ng/mL) (n = 580), as well as missing data on total BMD (n = 286), our analysis was conducted on a sample size of 1204 individuals. (Fig. 1)

2.3. Study variables

The study aimed to investigate the relationship between urinary glyphosate concentration and total BMD, with urine samples collected from NHANES study participants. The urinary glyphosate concentrations were determined using 200 μl of urine and analyzed through two-dimensional online ion chromatography with tandem mass spectrometry (IC-MS/MS) and isotope dilution quantitative analysis.[15] This study analyzed urinary glyphosate levels in 4738 samples collected between 2013 and 2016. The lower limit of detection was set at 0.2 ng/mL and 76.57% of the samples had glyphosate concentrations at or above this limit. Body composition was assessed using dual-energy X-ray absorptiometry by performing whole-body scans that included the arms, legs, torso, and head. The Hologic Discovery densitometer (Hologic, 95 Inc., Bedford, MA) and APEX version 3.296 software were used to obtain total BMD results. Several covariates are also taken into consideration, including age, gender, race, vigorous recreational activities, smoked at least 100 cigarettes in life, take prescription for cholesterol, use of hormone medication, total testosterone, estradiol, income to poverty ratio, body mass index, blood urea nitrogen, total protein, total cholesterol, serum phosphorus, and serum calcium. And for more information on data measurement, please click here: https://www.cdc.gov/nchs/nhanes/.

2.4. Statistical analysis

All calculations were done using sample weights in accordance with the analysis guidelines provided by NCHS. In

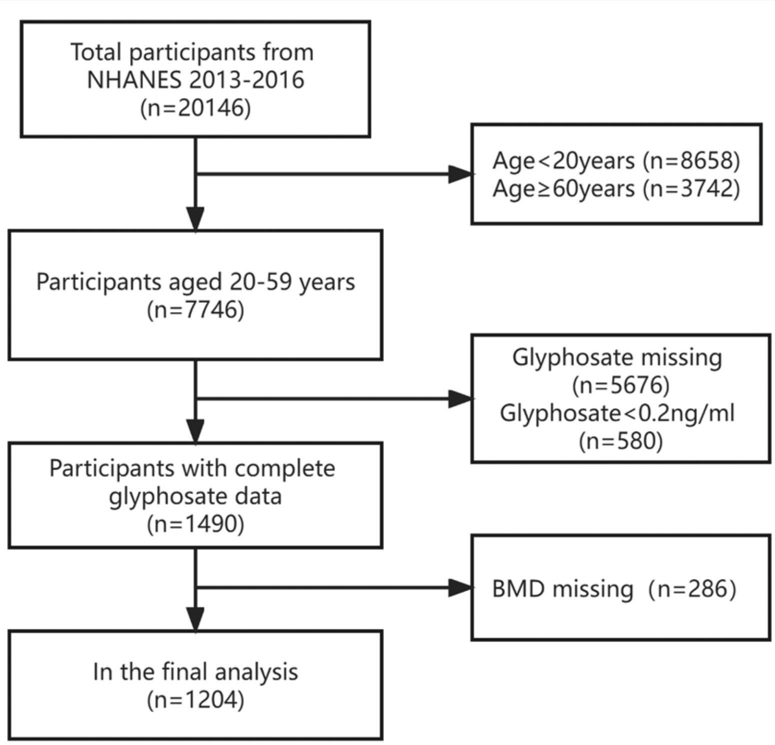

Figure 1. Flow chart of sample selection.

this study, mean ± standard deviation was used to express continuous variables, and *P*-values were calculated using a weighted linear regression model. Categorical variables were presented as percentages and *P* values were calculated using a weighted chi-square test. To assess the independent correlation between urinary glyphosate concentration and total BMD, a weighted multiple regression analysis was performed. Three multiple linear regression models were constructed: model 1, with unadjusted covariates; model 2, adjusted for age, sex, and race; and model 3, adjusted for all covariates listed in Table 1. Interaction and stratified analyses were conducted according to age, gender and race. To resolve the nonlinearity between urinary glyphosate concentration and total BMD, we utilized weighted generalized additive models and smoothed curve fitting. Our analyses were conducted using R (https://www.r-project.org) and EmpowerStats (https://www.empowerstats.net/cn/). Statistical significance was determined by *P* values <.05.

3. Results

Our analysis included 1204 individuals, with 49.27% males and 50.74% females. Age groups were: 20 to 29 years (24.44%), 30 to 39 years (23.23%), 40 to 49 years (26.16%), and 50 to 59 years (26.17%). The largest racial group was non-Hispanic White (63.75%), followed by Mexican American (9.86%), Other Hispanic (7.46%), Non-Hispanic Black (10.53%), and Other Races (8.40%). Table 1 details the weighted sociodemographic and medical characteristics of the participants. The participants were divided into 4 quartiles (Q1–Q4) based on their urinary glyphosate concentration. The table shows that there were significant differences in gender, age, age group, race, vigorous recreational activities, smoked at least 100 cigarettes in life, take prescription for cholesterol, use of hormone medication, total testosterone, estradiol, income to poverty ratio, blood urea nitrogen, total protein, total cholesterol, serum phosphorus, serum calcium and total BMD among the quartiles, as shown in Table 1.

This study utilized multiple regression equations to investigate the correlation between urinary glyphosate levels and total bone mineral density in the population. Table 2 displays the correlation of urinary glyphosate levels with total BMD as a continuous variable. The results indicated a significant negative correlation between urinary glyphosate concentration and total BMD in all 3 models of the multiple regression equations (Model 1, β [95% CI]: −0.0160 [−0.0200, −0.0120]; Model 2, β [95% CI]: −0.0135 [−0.0172, −0.0098]; Model 3. β [95% CI]: −0.0141 [−0.0178, −0.0104]). The negative association between

Table 1

Characteristics of the participants.

Glyphosate (ng/mL)	Total	Q1 (0.2–0.314)	Q2 (0.315–0.437)	Q3 (0.439–0.702)	Q4 (0.704–8.21)	*P* value
Age (years)	39.81 ± 11.45	39.94 ± 11.17	39.77 ± 11.33	38.57 ± 11.11	40.98 ± 12.06	<.0001
Age group (%)						<.0001
20–29 years	24.44	23.81	24.63	27.05	22.30	
30–39 years	23.23	23.08	21.91	25.90	22.13	
40–49 years	26.16	25.86	28.74	27.12	22.79	
50–59 years	26.17	27.26	24.72	19.93	32.78	
Gender (%)						<.0001
Men	49.26	42.70	49.91	57.93	47.11	
Women	50.74	57.30	50.09	42.07	52.89	
Race (%)						<.0001
Mexican American	9.86	8.24	11.57	12.05	7.64	
Other Hispanic	7.46	7.42	6.50	8.33	7.66	
Non-Hispanic White	63.75	66.48	65.37	60.15	62.62	
Non-Hispanic Black	10.53	9.43	8.71	11.33	12.88	
Other Race	8.40	8.42	7.87	8.15	9.21	
Vigorous recreational activities (%)						<.0001
Yes	32.84	32.85	38.44	32.19	27.51	
No	67.16	67.15	61.56	67.81	72.49	
Smoked at least 100 cigarettes in life (%)						.0038
Yes	42.47	42.01	43.16	39.17	45.69	
No	57.53	57.99	56.84	60.83	54.31	
Take prescription for cholesterol, (%)						<.0001
Yes	17.21	12.93	16.50	17.59	22.32	
No	82.79	87.07	83.50	82.41	77.68	
Use of hormone medication, (%)						<.0001
Yes	5.22	8.77	4.05	3.17		
No	94.78	91.23	95.95	96.83		
Total testosterone (ng/dL)	218.36 ± 234.14	213.26 ± 242.73	217.95 ± 238.39	238.55 ± 218.23	204.11 ± 233.97	.0007
Estradiol (pg/mL)	44.57 ± 57.60	52.91 ± 67.19	38.98 ± 50.53	43.80 ± 52.41	42.07 ± 57.17	<.0001
Income to poverty ratio	3.00 ± 1.68	3.19 ± 1.61	3.06 ± 1.67	2.98 ± 1.72	2.77 ± 1.68	<.0001
Body mass index (kg/m²)	29.31 ± 6.93	29.14 ± 6.59	29.16 ± 6.67	29.28 ± 6.81	29.71 ± 7.64	.0926
Blood urea nitrogen (mg/dL)	13.05 ± 4.30	13.04 ± 4.82	12.74 ± 3.75	12.81 ± 3.96	13.64 ± 4.50	<.0001
Total protein (g/dL)	7.10 ± 0.44	7.11 ± 0.45	7.11 ± 0.40	7.14 ± 0.43	7.06 ± 0.47	<.0001
Total cholesterol (mg/dL)	196.72 ± 44.58	202.25 ± 53.59	198.65 ± 38.29	193.29 ± 39.61	191.99 ± 43.78	<.0001
Serum phosphorus (mg/dL)	3.77 ± 0.58	3.80 ± 0.59	3.69 ± 0.55	3.79 ± 0.53	3.82 ± 0.64	<.0001
Serum calcium (mg/dL)	9.40 ± 0.41	9.41 ± 0.33	9.46 ± 0.56	9.37 ± 0.33	9.36 ± 0.37	<.0001
Total BMD (g/cm²).	1.11 ± 0.11	1.12 ± 0.10	1.11 ± 0.11	1.10 ± 0.11	1.10 ± 0.11	.0173

Mean ± SD for continuous variables: the *P* value was calculated by the weighted linear regression model. (%) for categorical variables: the *P* value was calculated by the weighted chi-square test.
BMD = bone mineral density.

the 2 variables remained significant ($P < .05$) in the urinary glyphosate concentration quartile group, even after adjusting for all covariates. To better understand the nonlinear relationships, the researchers used weighted generalized summation models and smoothed curve fitting, which is shown in Figures 2 and 3.

The study found a negative association between urinary glyphosate concentrations and total BMD in both men (Model 3, β [95% CI]: −0.0137 [−0.0199, −0.0075]) and women (Model 3, β [95% CI]: −0.0135 [−0.0180, −0.0090]), as well as in most ethnic groups, except for other Hispanic. The analysis was stratified by population age, with ages divided into 4 groups: 20 to 29, 30 to 39, 40 to 49, and 50 to 59 years. After adjusting for all covariates, the negative association between urinary glyphosate concentrations and total BMD was significant for ages

Table 2

The association between glyphosate (ng/mL) and total bone mineral density (g/cm²).

	Model 1, β (95% CI)	Model 2, β (95% CI)	Model 3, β (95% CI)
Glyphosate (ng/mL)	−0.0160 (−0.0200, −0.0120)	−0.0135 (−0.0172, −0.0098)	−0.0141 (−0.0178, −0.0104)
Glyphosate (ng/mL) categories			
Q1(0.2–0.314)	Reference	Reference	Reference
Q2(0.315–0.437)	−0.0054 (−0.0128, 0.0020)	−0.0099 (−0.0167, −0.0030)	−0.0085 (−0.0152, −0.0018)
Q3(0.439–0.702)	−0.0103 (−0.0178, −0.0028)	−0.0228 (−0.0297, −0.0158)	−0.0220 (−0.0228, −0.0151)
Q4(0.704–8.21)	−0.0105 (−0.0181, −0.0030)	−0.0146 (−0.0216, −0.0077)	−0.0129 (−0.0198, −0.0061)
P for trend	.002	<.001	<.001
Stratified by gender			
Men	−0.0159 (−0.0224, −0.0094)	−0.0162 (−0.0226, −0.0098)	−0.0137 (−0.0199, −0.0075)
Women	−0.0133 (−0.0180, −0.0087)	−0.0122 (−0.0167, −0.0077)	−0.0135 (−0.0180, −0.0090)
Stratified by age			
20–29 years	−0.0148 (−0.0253, −0.0042)	−0.0160 (−0.0255, −0.0065)	−0.0211 (−0.0305, −0.0116)
30–39 years	−0.0100 (−0.0210, 0.0010)	−0.0079 (−0.0183, 0.0025)	−0.0083 (−0.0186, 0.0020)
40–49 years	−0.0012 (−0.0127, 0.0102)	0.0007 (−0.0101, 0.0115)	−0.0023 (−0.0133, 0.0086)
50–59 years	−0.0135 (−0.0193, −0.0077)	−0.0148 (−0.0200, −0.0096)	−0.0104 (−0.0154, −0.0053)
Stratified by race			
Mexican American	−0.0287 (−0.0427, −0.0146)	−0.0278 (−0.0413, −0.0143)	−0.0346 (−0.0485, −0.0206)
Other Hispanic	−0.0096 (−0.0280, 0.0088)	−0.0025 (−0.0197, 0.0147)	−0.0067 (−0.0227, 0.0094)
Non-Hispanic White	−0.0144 (−0.0198, −0.0089)	−0.0113 (−0.0164, −0.0062)	−0.0114 (−0.0164, −0.0064)
Non-Hispanic Black	−0.0270 (−0.0406, −0.0135)	−0.0254 (−0.0380, −0.0128)	−0.0325 (−0.0452, −0.0197)
Other race	−0.0291 (−0.0440, −0.0142)	−0.0342 (−0.0485, −0.0200)	−0.0412 (−0.0557, −0.0267)

Model 1: no covariates were adjusted. Model 2: age, gender and race were adjusted. Model 3: age, gender, race, vigorous recreational activities, smoked at least 100 cigarettes in life, take prescription for cholesterol, use of hormone medication, total testosterone, estradiol, income to poverty ratio, body mass index, blood urea nitrogen, total protein, total cholesterol, serum phosphorus, and serum calcium were adjusted. In the subgroup analysis stratified by age, gender and race, the model is not adjusted for age, gender and race, respectively.

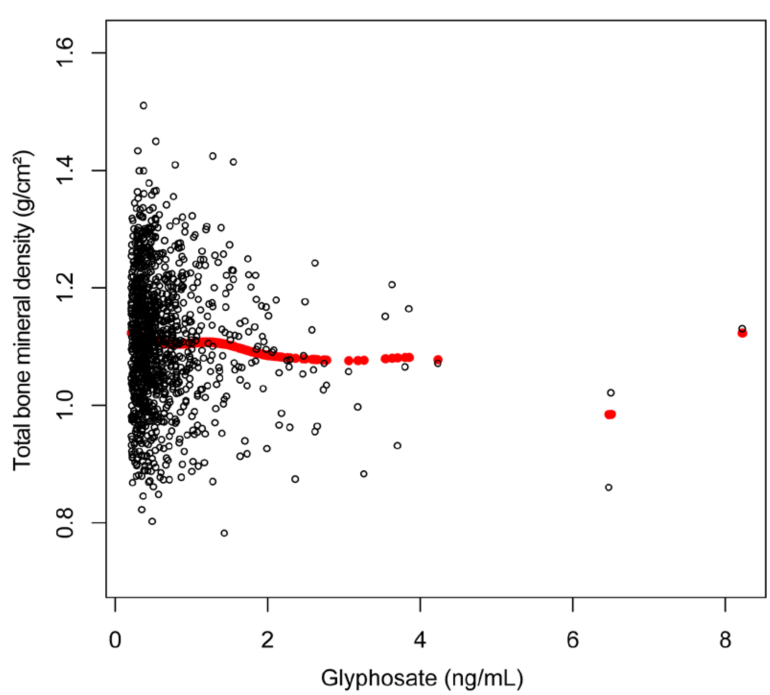

Figure 2. The association between urinary glyphosate concentrations and total BMD. Each black dot represents a sample. Age, gender, race, vigorous recreational activities, smoked at least 100 cigarettes in life, take prescription for cholesterol, use of hormone medication, total testosterone, estradiol, income to poverty ratio, body mass index, blood urea nitrogen, total protein, total cholesterol, serum phosphorus, and serum calcium were adjusted. The red curve is a smooth curve fitting to the scatter diagram, representing the relationship between total BMD and fibrinogen level.

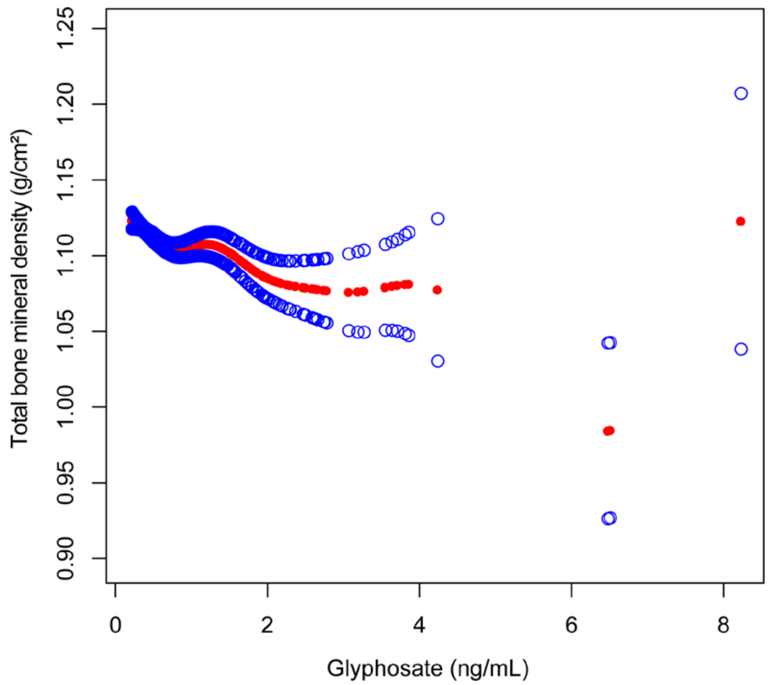

Figure 3. The association between urinary glyphosate concentrations and total BMD. The solid arcs indicate the smoothed curve fit between the variables. The blue bars represent the fitted 95% confidence intervals. Age, gender, race, vigorous recreational activities, smoked at least 100 cigarettes in life, take prescription for cholesterol, use of hormone medication, total testosterone, estradiol, income to poverty ratio, body mass index, blood urea nitrogen, total protein, total cholesterol, serum phosphorus, and serum calcium were adjusted.

20 to 29 (Model 3, β [95% CI]: −0.0211 [−0.0305, −0.0116]) and 50 to 59 years (Model 3, β [95% CI]: −0.0104 [−0.0154, −0.0053]), as shown in Table 2. The study found no significant correlation between urinary glyphosate concentration and total BMD in people aged 30 to 39 years and 40 to 49 years. In the interaction results, it was observed that the correlation between glyphosate and BMD was influenced by age and race (*P* interaction < .05), while it was not influenced by sex (*P* interaction > .05).

4. Discussion

This study presents new epidemiological evidence linking glyphosate exposure to reduced bone mineral density in an American population. Our primary findings suggest that the negative association between urinary glyphosate concentrations and total BMD in adults varied by age and race. Specifically, we found that urinary glyphosate concentration levels were negatively associated with BMD in American populations aged 20 to 29 years and 50 to 59 years. In non-Hispanic Americans, high levels of glyphosate in urine were found to have a significant adverse impact on BMD.

In a study, Geier et al observed a significant negative correlation between glyphosate and total estradiol concentration, as well as a negative trend between glyphosate and total testosterone concentration.[16] Other studies have shown that glyphosate exhibits endocrine disrupting properties by mimicking or blocking androgens or estrogens.[17] Estrogens directly bind to estrogen receptors on osteoblasts, enhancing their differentiation activity, reducing apoptosis, accelerating autophagy, and promoting mineralization and survival.[8] Additionally, estrogen protects the bone by promoting osteoclast apoptosis through signaling pathways, facilitating bone formation, inhibiting osteoclast survival, and reducing bone loss.[18,19] Androgens play a crucial role in regulating bone metabolism through 2 mechanisms. Firstly, they bind to androgen receptors on osteoblasts and osteoclasts, thereby regulating the functions of these cells. Secondly, androgens are converted to estrogens through aromatization, which then regulates bone metabolism via estrogen receptor α.[20] Sex hormones rise rapidly and reach a peak between the ages of 20 and 30, and their decline mainly occurs between the ages of 50 and 60 in men and women.[21,22] Since the sex hormones in these 2 age groups vary greatly, they may be more affected by glyphosate and cause sex hormone disorders in the body, thereby affecting bone density. Our study found that the inverse association between urinary glyphosate levels and BMD was statistically significant in both age groups, further supporting our hypothesis. This suggests that glyphosate may reduce BMD by affecting sex hormone secretion.

A study discovered that glyphosate exposure can disrupt the thyroid system, leading to an imbalance of thyroid hormones and a higher likelihood of hypothyroidism.[23] Glyphosate and other pesticides can have immediate impacts on the hypothalamic–pituitary–thyroid axis, causing sudden changes in thyroid hormone levels.[24] Thyroid hormones can affect osteoblasts and osteoclasts by activating different pathways, including growth hormone/insulin-like growth factor, fibroblast growth factor, parathyroid hormone-related peptide feedback loops, and nuclear factor interleukin-6 activation. This leads to the regulation of bone resorption and bone formation through the induction of osteoclast differentiation factor expression activity.[19] Triiodothyronine binds to receptors in the nucleus of target cells and regulates intramembranous and endochondral ossification, as well as controlling the rate of linear growth, bone maturation, and mineralization in chondrocytes and osteoblasts.[25] Thyroid hormones work together with other endocrine factors like calcitonin and sex hormones to participate in systemic bone metabolic processes such as skeletal growth, development, maturation, bone reconstruction, bone resorption, and calcium and phosphorus metabolism.[26] Glyphosate exposure may also affect BMD by impacting thyroid hormones, which is supported by our research. However, the exact mechanism of how this occurs is still unclear and requires further investigation.

Our study benefits from a US population-based sample that is representative of a diverse range of ethnicities and age groups, allowing for further analysis. However, there are limitations to our study. The cross-sectional design of the study prevents us from determining a causal relationship between urinary glyphosate concentration and total BMD. Also, the NHANES database does not provide comprehensive documentation of daily behaviors, such as dietary habits or occupational exposure, which may influence glyphosate exposure levels. Therefore, it is suggested that future research should investigate the impact of these factors on glyphosate exposure. Second, our study samples were obtained from urine to measure urinary glyphosate concentrations rather than direct measurements of glyphosate exposure doses. While glyphosate has a short half-life in humans, it may still impact urinary glyphosate concentrations due to individual biochemical factors. Additionally, there may be other confounding factors not accounted for in this study that could introduce bias. Therefore, a longitudinal study with a larger sample size is needed to gain a better understanding of the relationship between glyphosate exposure levels and bone health.

5. Conclusion

Our study reveals that the relationship between urinary glyphosate concentration levels and total BMD in adults aged 20 to 59 years is influenced by age and race. Specifically, we found that elevated urinary glyphosate concentration levels had a significant negative impact on bone mass in the 20 to 29 and 50 to 59 age groups. Furthermore, our results indicate that Americans who are not of Hispanic descent are also negatively affected by elevated urinary glyphosate levels in terms of bone mass. Therefore, the impact of glyphosate exposure on human health should attract more people's attention.

Author contributions

Conceptualization: Zhenwei Wang, Hongwei Zhang, Renfu Quan.
Data curation: Zhenwei Wang, Hongwei Zhang.
Formal analysis: Zhenwei Wang, Hongwei Zhang, Weibin Du.
Funding acquisition: Weibin Du, Jintao Hu.
Investigation: Hongwei Zhang, Weibin Du.
Methodology: Hongwei Zhang.
Project administration: Weibin Du, Jintao Hu.
Resources: Weibin Du, Jintao Hu.
Software: Zhenwei Wang.
Supervision: Renfu Quan.
Validation: Jintao Hu, Renfu Quan.
Visualization: Renfu Quan.
Writing – original draft: Zhenwei Wang, Weibin Du.
Writing – review & editing: Zhenwei Wang, Renfu Quan.

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