Association between Estradiol and Bone Mineral Density in Adults Aged 40-60 years

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Research Article

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Abstract

Background: The purpose of this analysis was to explore the relationship between estradiol and total bone mineral density (BMD) in American adults aged 40 to 60 years.

Methods: We used a cross-sectional study. Data for the study came from the National Health and Nutrition Examination Survey (NHANES) . The study examined data from a sample of the American population.

Results: Data analysis showed a significant association between estradiol levels and total bone mineral density in US adults aged 40 to 60 years. When estradiol levels were below the threshold of 33.3pg/mL, estradiol was positively associated with total BMD in all ethnic groups. There was no significant correlation between estradiol levels above the threshold of 33.3pg/mL. When estradiol levels in men were below the threshold of 40.3pg/mL, estradiol was positively correlated with total BMD. When estradiol levels in women were below the threshold of 25pg/mL, estradiol was positively correlated with total BMD.

Conclusions: In the 40-60 year old population, when estradiol level is at a lower concentration, estradiol level is positively correlated with total BMD. Increasing estradiol level can promote bone health. When estradiol levels are at higher concentrations, changes in estradiol levels may have no significant effect on bone health.

Background

Osteoporosis is a common clinical degenerative disease in adults aged 40–60 years. According to normal physiological changes, after menopause, estrogen levels decrease significantly, and bone mineral density levels decrease accordingly. While, the relationship between estrogen level and osteoporosis in middle-aged and elderly men is often ignored[1].In the traditional view, When estrogen levels are significantly reduced, osteoclast activity increases, bone resorption is greater than femoral formation, resulting in bone loss and osteoporosis.High concentration of estrogen can accelerate the apoptosis of osteoclasts[2, 3], reduce the survival time of osteoclasts and inhibit the differentiation of osteoclasts[4]. But this theory lacks experimentation and research.

Women's bone mineral density seems to be linked to estradiol levels and women's exercise. A study population consisted of 151 female athletes with amenorrhea in Japan showed that BMD was significantly higher in the experimental group than in the untreated group after 12 months of treatment with transdermal estradiol[5]. Another study involving 482 Chinese men with type 2 diabetes found that estradiol levels are important for maintaining bone health, with estradiol concentrations affecting BMD and fracture risk in males[6]. It may be clinically necessary to detect BMD in menopausal women with estrogen deficiency[7]. In addition, a large number of experimental results and clinical evidence have demonstrated a close relationship between estradiol levels and BMD.

Evidence on estradiol and BMD is limited. Osteoporosis in middle-aged people varies by age, sex, race, and country. In addition, estradiol concentration was also affected by age, sex, body composition and other factors affecting BMD. To further investigate, we conducted a cross-sectional study based on an American national population to explore the relationship between estradiol and BMD in US adults aged 40–60 years.

Methods

Study Population

NHANES is a major program of the National Center for Health Statistics (NCHS). This study screened data from the database from 2013 to 2016. This is a stratified, multistage sample. Survey methods and detailed data on the NHANES database can be found at www.cdc.gov/nchs/nhanes/. Study subjects were limited to participants aged 40–60 years (n = 6,005). The NCHS Ethics Review Board approved the actions of NHANES and obtained the written informed consent of all participants.

Study Variables

The main independent variable was estradiol and the main dependent variable was total BMD. Serum estradiol was determined using the same method as the reference method of the National Institute of Standards and Technology (NIST). Estradiol is preformed via isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) method for routine quantitation of estradiol based on the National Institute for Standards and Technology's (NIST) reference method. Dual-energy x-ray absorptiometry (DXA) is the most widely accepted method of measuring body composition. The NHANES DXA examination provides nationally representative data on body composition. The following covariates were included: age, sex, race/ethnicity, level of education, income-poverty ratio, total protein, serum phosphorus, and serum calcium. Detailed information about the data measurement process is available at www.cdc.gov/nchs/nhanes/.

Statistical Analyses

The estimated values are calculated according to the sample weights of NHANES database. The independent relationship between estradiol and total BMD was investigated using weighted multiple regression analysis. Weighted generalized additive models and smooth curve fittings were employed to address the non-linearity of estradiol and total BMD in the subgroup analyses. The researchers calculated differences between groups using a weighted linear regression model (continuous variables) and a weighted Chi-square test (categorical variables). $P < 0.05$ was considered statistically significant. Empower software was used for data analysis (www.empowerstats.com; X&Y solutions, Inc., Boston MA) and R version 3.4.3 (http://www.R-project.org, The R Foundation).

Results

The description of weighted characteristics is shown in Table 1. There were 4,075 eligible participants in the survey. They were 46.99% male, 53.01% female, 34.58% Non-Hispanic white, 21.84% Non-Hispanic black, 15.75% Mexican American and 27.83% other races. The estradiol data were grouped according to quartile and divided into Q1-Q4 groups. Data was included age, sex, race/ethnicity, income-poverty rate, total protein, total BMD, serum phosphorus and serum calcium. In the fully-adjusted model (Fig. 1-a, Fig. 1-b and Table 2), after controlling for the potential confounders, we observed a significantly positive correlation between estradiol and total BMD in a certain threshold range. The effect of estradiol (PG /mL) on the threshold of total bone mineral density (G /cm2) was analyzed by piecewise linear regression (Table 3). We used smooth curve fittings to find the relationship between estradiol and total BMD, stratified by age, sex, and race/ethnicity (Figs. 2, 3). Estradiol was positively correlated with total BMD in all racial/ethnic populations in men aged 40 to 60 years when estradiol concentration was lower than 40.3pg/mL. In women aged 40–60, estradiol was positively associated with total BMD in all racial/ethnic populations at concentrations below 25pg/mL, but not significantly associated with total BMD at concentrations greater than 25pg/mL.

Table 1
Weighted characteristics of the study population based on estradiol quartiles.

Estradiol (pg/mL)	Total	Q1	Q2	Q3	Q4	P-value
Age(years)	49.8 ± 6.1	50.0 ± 5.9	50.0 ± 5.9	49.9 ± 6.0	46.6 ± 5.0	< 0.0001
Sex(%)						< 0.0001
Male	46.99	9.7	79.2	85.5	17.7	
Female	53.01	90.3	20.8	14.5	82.3	
Race/ethnicity (%)						< 0.0001
Non-Hispanic white	34.6	68.9	64.7	69	60.1	
Non-Hispanic black	21.8	10.2	9	11.4	14.9	
Mexican American	15.8	7.9	10.9	7.1	9.5	
Other race/ethnicity	27.8	13.3	15.3	12.5	15.5	
Level of education (%)						0.0151
Less than high school	22.8	14.8	16.4	13.3	13.0	
High school	21.4	19.2	21.3	23	17.8	
More than high school	55.8	66.1	62.2	63.7	69.2	
Income to poverty ratio	2.7 ± 1.7	3.1 ± 1.7	3.3 ± 1.6	3.4 ± 1.6	3.2 ± 1.7	0.0132
Total protein (g/dL)	7.1 ± 0.5	7.0 ± 0.4	7.0 ± 0.4	7.1 ± 0.4	7.1 ± 0.4	0.0406
Serum calcium (mg/dL)	9.4 ± 0.4	9.4 ± 0.3	9.4 ± 0.4	9.4 ± 0.3	9.3 ± 0.3	< 0.0001
Serum phosphorus (mg/dL)	3.7 ± 0.6	3.9 ± 0.5	3.7 ± 0.6	3.6 ± 0.6	3.7 ± 0.5	< 0.0001
Total BMD (g/cm2)	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	< 0.0001

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. Abbreviation: BMD, bone mineral density.

Table 2
The association between estradiol (pg/mL) and total BMD (g/cm2).

	Model1	Model2	Model3
	β(95% CI) P-value	β(95% CI) P-value	β(95% CI) P-value
Estradiol (pg/mL)	0.0001 (0.0001, 0.0002) 0.0001	0.0003 (0.0002, 0.0003) < 0.000001	0.0003 (0.0002, 0.0003) < 0.000001
Estradiol categories			
Q1	0	0	0
Q2	0.0768 (0.0658, 0.0878) < 0.000001	0.0299 (0.0170, 0.0427) 0.000005	0.0237 (0.0103, 0.0371) 0.000542
Q3	0.1102 (0.0993, 0.1210) < 0.000001	0.0572 (0.0441, 0.0703) < 0.000001	0.0534 (0.0396, 0.0671) < 0.000001
Q4	0.0821 (0.0711, 0.0931) < 0.000001	0.0679 (0.0565, 0.0793) < 0.000001	0.0676 (0.0556, 0.0795) < 0.000001
Subgroup analysis stratified by sex			
Men	0.0019 (0.0012, 0.0025) < 0.000001	0.0016 (0.0010, 0.0022) < 0.000001	0.0017 (0.0011, 0.0024) < 0.000001
Women	0.0003 (0.0002, 0.0004) < 0.000001	0.0002 (0.0001, 0.0003) < 0.000001	0.0002 (0.0001, 0.0003) < 0.000001
Subgroup analysis stratified by race/ethnicity			
Non-Hispanic white	0.0001 (0.0000, 0.0002) 0.021392	0.0003 (0.0002, 0.0004) < 0.000001	0.0003 (0.0002, 0.0004) 0.000002
Non-Hispanic black	0.0001 (-0.0000, 0.0003) 0.152722	0.0002 (0.0000, 0.0003) 0.039708	0.0002 (-0.0000, 0.0003) 0.085202
Mexican American	0.0001 (-0.0000, 0.0003) 0.122470	0.0002 (0.0001, 0.0004) 0.004273	0.0002 (0.0000, 0.0004) 0.011490
Other race/ethnicity	0.0002 (0.0000, 0.0003) 0.009624	0.0003 (0.0002, 0.0004) 0.000044	0.0003 (0.0002, 0.0005) 0.000043

Model 1: no covariates were adjusted. Model 2: age, sex, and race/ethnicity were adjusted. Model 3: age, sex, race/ethnicity, education, income poverty ratio, total protein, serum phosphorus and serum calcium were adjusted. In the subgroup analysis stratified by sex and race/ethnicity, the model is not adjusted for sex and race/ethnicity.

Table 3
The threshold effect of estradiol (PG /mL) on total BMD (G /cm2) was analyzed by piecewise linear regression.

Adjusted β (95% CI)P-value	
Males	
Estradiol < 40.3 (pg/mL)	0.0027 (0.0019, 0.0035), < 0.0001
Estradiol > 40.3 (pg/mL)	-0.0015 (− 0.0033, 0.003), 0.0941
Females	
Estradiol < 25 (pg/mL)	0.0029 (0.0021, 0.0036), < 0.0001
Estradiol > 25 (pg/mL)	0.0001 (− 0.0000, 0.001), 0.1813
Total	
Estradiol < 33.3 (pg/mL)	0.0025 (0.0020, 0.0029), < 0.0001
Estradiol > 33.3 (pg/mL)	0.0000 (− 0.0001, 0.0001), 0.6950
Age, sex, race/ethnicity education, income poverty ratio, total protein, serum phosphorus and serum calcium were adjusted in the model.	

Discussion

Reduced BMD can lead to an increased risk of osteoporotic fractures. The relationship between estradiol and bone mineral density has been widely studied and concerned. In a cross-sectional study of 270 women between 40 and 48 years of age, Gerardo Huitrón-Bravo et al. found that when serum estradiol levels were low in premenopausal women, the risk of bone density loss was significantly increased[8]. A study population consisted of 151 female athletes with amenorrhea in Japan showed that BMD was significantly higher in the experimental group than in the untreated group after 12 months of treatment with transdermal estradiol[5]. Another study involving 482 Chinese men with type 2 diabetes found that estradiol levels are important for maintaining bone health, with estradiol concentrations affecting BMD and fracture risk in males[6]. Barbieri et al. proposed a new hypothesis called estrogen threshold hypothesis through research. The research team proved that estradiol levels in the range of 30–45 pg/ml can effectively prevent bone loss, although estradiol sensitivity varies from individual to individual[9]. Kathryn E Ackerman et al. studied the effect of estrogen on BMD in normal-weight young adults in a large number of experiments. The team discussed differences in BMD under different conditions, including no estrogen, physiological dose estrogen, transdermal estrogen administration, and estrogen in combination with oral contraceptives[10, 11]. The institute found that BMD would improve over 12 months with transdermal estradiol administration compared with combined oral contraceptives or no oestrogen.

We analyzed a larger sample size in our study, allowing us to better generalize the U.S. population. But there are also shortcomings. First, the eligible sample size in the database is still too small. Secondly,

other confounding factors not included in this study may have influenced the results. Women, for example, have biologically higher levels of estradiol than men. Therefore, sex hormone differences during pubertal development in adults aged 40–60 years may be a potential confounding factor that needs to be considered.

Conclusions

In summary, estradiol level and total BMD differed by sex and race, and there are thresholds. When male estradiol level is below the threshold of 40.3pg/mL, estradiol level is positively correlated with total BMD, and increasing estradiol level can promote bone health. When estradiol levels in women fall below the threshold of 25pg/mL, increased estradiol levels contribute to bone health. When female estradiol concentrations are above the threshold of 25pg/mL, increased estradiol levels have little effect on bone health.

Declarations

Ethics approval and consent to participate

The ethics review board of the National Center for Health Statistics approved all NHANES protocols and written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The data are publicly available on the internet for researchers throughout the world. https://www.cdc.gov/nchs/nhanes/

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Nan Wang contributed to the study design and writting the manuscript. Ying Zhang and Chengcheng Huang contributed to data collection and analysis. All authors read and approved the final manuscript.

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Abbreviations

BMD: bone mineral density

NHANES: National Health and Nutrition Examination Survey

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Guidelines

All procedures were performed in accordance with relevant guidelines.

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Figures

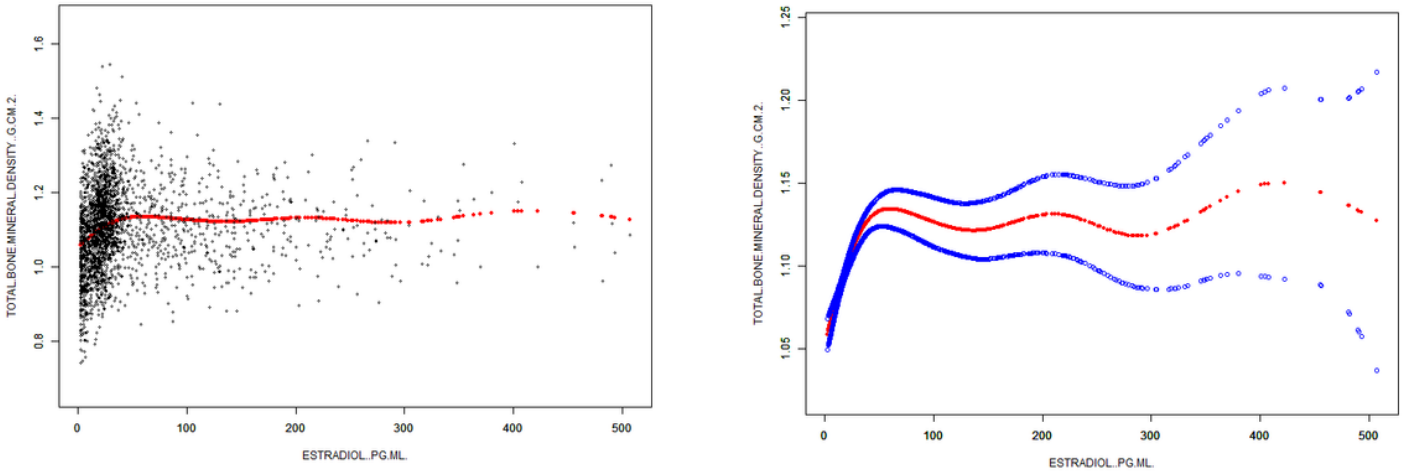

Figure 1

The relationship between estradiol and total BMD. (a) Each black point represents a sample. (b) Solid rad line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit.

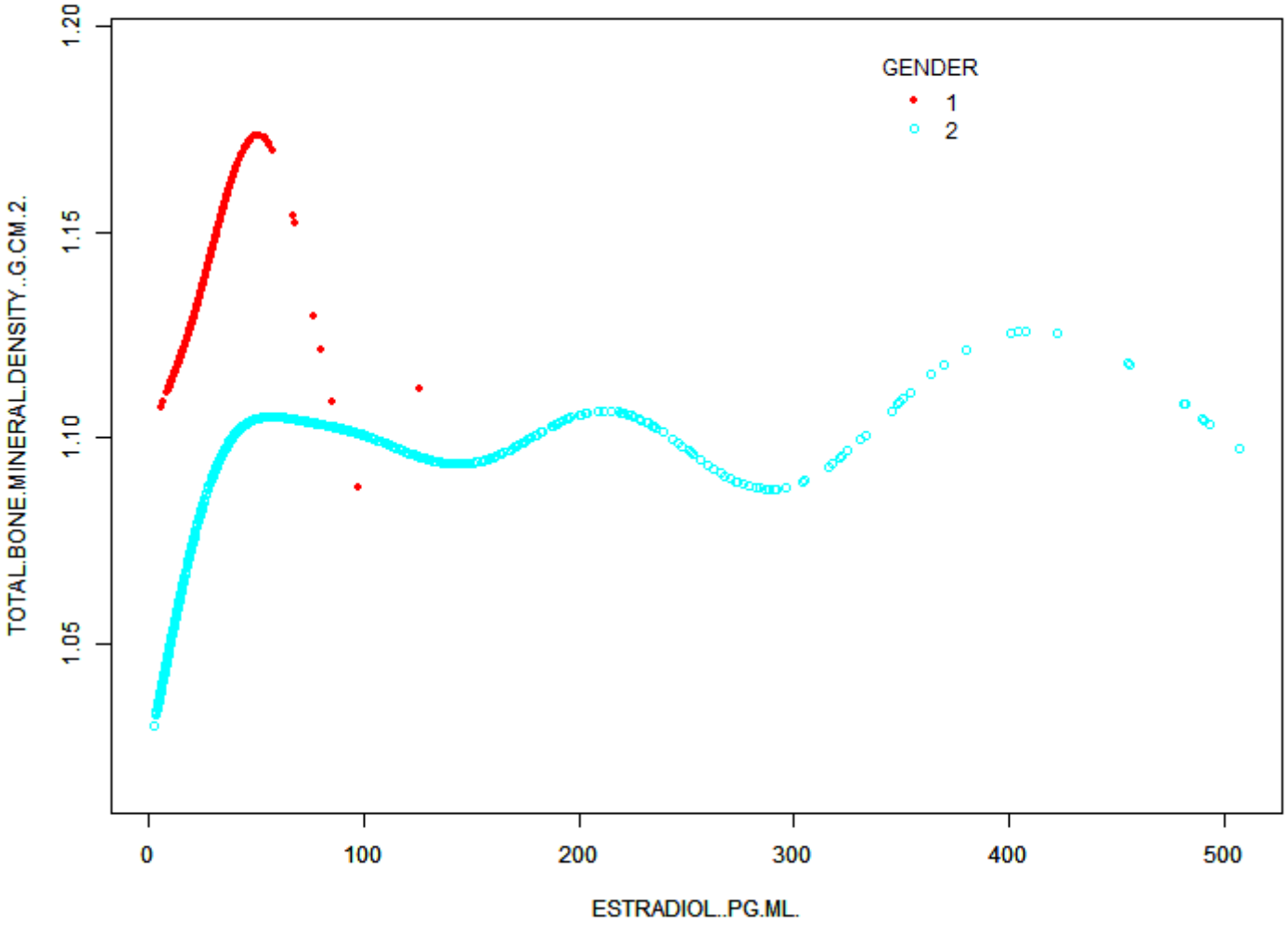

Figure 2

The relationship between estradiol and total BMD stratified by sex.

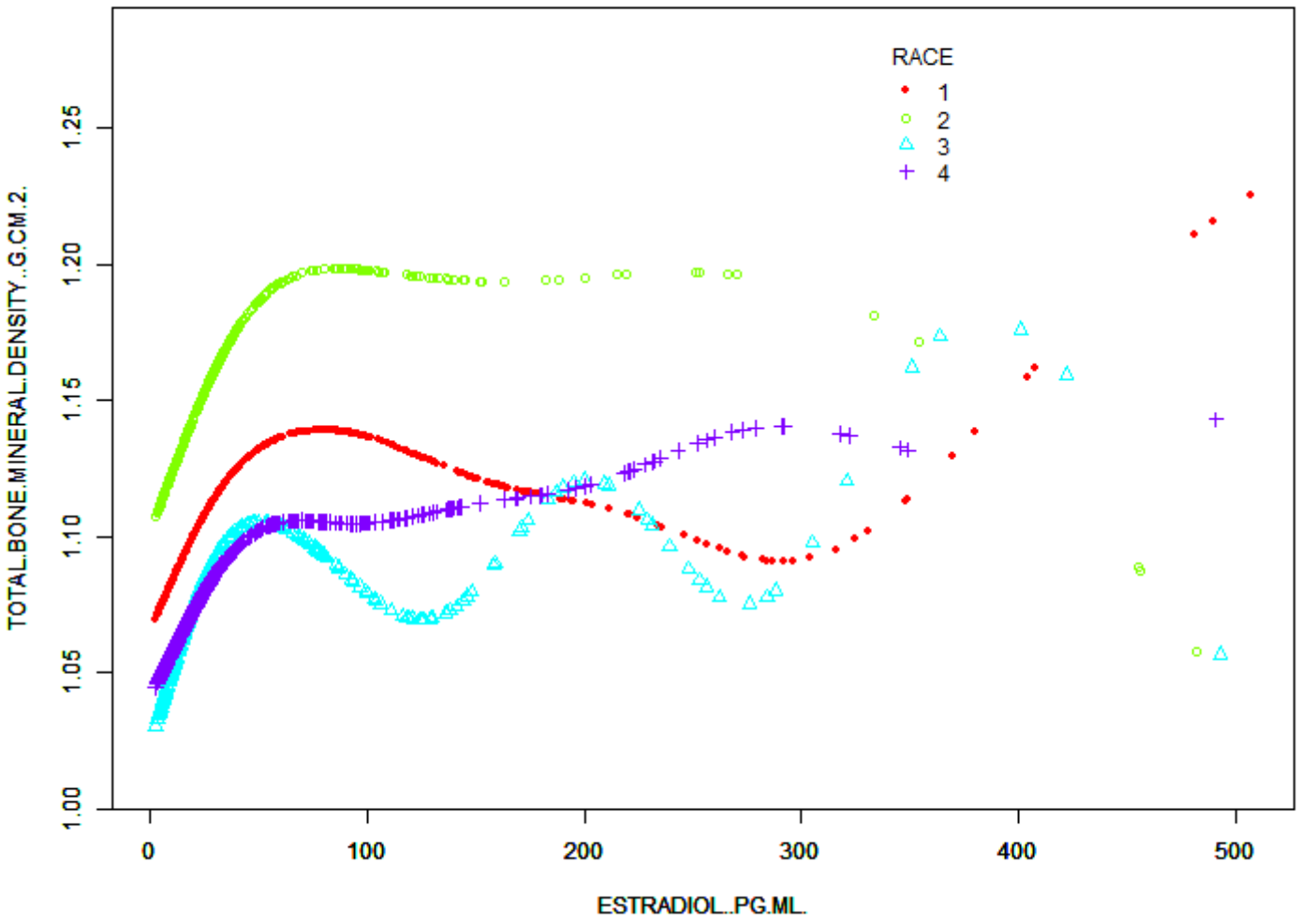

Figure 3

The relationship between estradiol and total BMD stratified by race/ethnicity.