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Original article

Genetic influence on bone mineral density for Japanese women: a twin study

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Genetic influence on bone mineral density for Japanese women: a twin study

Abstract

Background

Osteoporosis is a major risk factor for fractures among the elderly. Despite osteoporosis being a significant concern in super-aged societies such as Japan, the heritability of bone mineral density within the Japanese populace remains unexplored. Therefore, we conducted a twin study on Japanese women to determine the extent of genetic and environmental influences on bone mineral density for the Japanese population.

Methods

The bone area ratio of 298 healthy, female Japanese twins (comprising 149 pairs, 136 monozygotic and 13 dizygotic twin pairs) registered in the Osaka University Twin Registry was measured using quantitative ultrasound. Classical twin analysis was employed to ascertain the heritability of bone mineral density.

Results

The heritability of bone mineral density for the entire cohort was 0.51 (95% confidence intervals 0.38 – 0.63). For the subset of subjects younger than 50 years, the effects of menopause were adjusted, and the best-fit model was also found to be the additive genetics and unique environment (AE) model, with a heritability estimate of 0.53 (95% confidence intervals: 0.34 – 0.72).

Conclusions

Compared to women from other countries, Japanese women appear to exhibit relatively lower heritability of bone mineral density. Consequently, environmental factors may exert a more significant influence on osteoporosis in Japanese women compared to women of other races and ethnicities.

Key words: osteoporosis; bone mineral density; bone fractures; heritability; prevention: race and ethnicity

LIST OF ABBREVIATIONS

BAR bone area ratio; BMD bone mineral density; BMI body mass index; DXA dual-energy X-ray absorptiometry; DZ dizygotic; MZ monozygotic; SEM structural equation modelling; CI confidence interval; AIC Akaike information criterion; QUS quantitative ultrasonography.

1. BACKGROUND

Osteoporosis is characterized by low bone mass, concomitant microarchitectural degeneration, and fragility fractures [1]. Bone fractures are the predominant clinical repercussion of osteoporosis. Globally, one in three women [2] over the age of fifty is projected to experience an osteoporotic fracture, particularly prevalent among postmenopausal women [3]. A significant proportion of individuals with osteoporosis-related fractures or at high risk of fracture remain untreated [4]. The substantial healthcare expenditure on osteoporosis [5] underscores its status as a clinical and public health concern, particularly in super-aged societies such as Japan.

Postmenopausal osteoporosis, defined by reduced bone mass and an increased risk of fractures after menopause, represents a significant health concern for women [6, 7]. Contributing factors include smoking, reduced engagement in outdoor activities, advancing age, and a low body mass index (BMI), all of which are closely associated with the onset of postmenopausal osteoporosis [7]. This condition is particularly pertinent in Japan's aging society, where women tend to have a lower BMI compared to their counterparts in other countries [8]. Notably, the prevalence of osteoporosis in women in Japan increases by 10% to 20% with each decade of age after 50 years, trending higher than in men [9, 10]. However, osteoporosis screening and treatment rates remain relatively low, at 0% to 15% varying across districts [11] and approximately 20 to 25% among the eligible population [11, 12], respectively. Although lifestyle interventions and pharmacological treatments are available [13], there remains a lack of data regarding their efficacy and impact, particularly within the Japanese population. Given these constraints, public health interventions, particularly early screening programs, play an equally critical role as therapeutic measures.

Human phenotypes, including bone mass, are influenced by a combination of genetic and environmental factors. Twin studies serve as a valuable tool to distinguish genetic influences from shared environmental factors and adjust for confounding variables [14]. Prior twin studies encompassing diverse races and ethnicities from various regions have indicated that bone mineral density (BMD) exhibits high heritability, with genetic effects accounting for 50% to 90% of the

variance [15-20]. Furthermore, studies on environmental factors such as smoking [21] and dietary habits [21, 22] have been identified to influence bone health. In particular, gut microbiota has been identified as a key factor affected by the environment, which influences bone homeostasis [23-25]. However, no studies up to date have investigated the heritability of BMD within the Japanese population. Given Japan's position at the forefront of aging societies[26], the issues it faces concerning its aging population will hold considerable global relevance. Consequently, we conducted a twin study on Japanese women to ascertain the extent of genetic and environmental influences on BMD within the Japanese population.

2. METHODS

2.1 Subjects

From the Osaka University Twin Registry established by the Center for Twin Research, Osaka University Graduate School of Medicine [27], a total of 298 Japanese female twins (149 pairs), 417 twins (including triplets) were recruited and underwent quantitative ultrasonography (QUS) of the calcaneus. After excluding twins, including males, 136 monozygotic twins (MZ) pairs and 13 dizygotic twins (DZ) pairs were included in the study. Written informed consent was obtained from all twins, including those excluded from this study. The study protocol was approved by the Ethics Committee of Osaka University Graduate School of Medicine (approval numbers 10209 and 696).

2.2 Bone mass assessment

QUS on the calcaneus was performed on the twins using Tanita CS-800 (Tanita, Tokyo, Japan). This device does not measure BMD itself, but measures the bone area ratio (BAR, %), which was used as an index for bone mass.

2.3 Statistical analysis

Each continuous variable is presented with its mean and standard deviation, and each categorical variable is represented using numbers and percentages. After checking the histogram and independence, the t-test was employed for continuous variables, and the chi-squared test was utilized for categorical variables.

This study employed a univariate ACE model, and the analysis was conducted using the Mets package on R (version 3.6.1). Structural equation modelling (SEM) was employed to calculate heritability [28]. Variability in individual traits can be partitioned into genetic and environmental sources of variance [29]. Classical twin studies use within-twin pair comparisons to account for common genetic and environmental variables, decomposing the variance into additive genetic effects (A), dominant genetic effects (D), shared environmental effects (C), and unique environmental effects (E). This model operates under the assumption that monozygotic pairs share nearly 100% of their genome, and dizygotic pairs share approximately 50% of their genome on average [30]. Furthermore, this model requires all genetic variances to be additive and that environmental covariances and total variances of monozygotic and dizygotic twins are equivalent [20].

By analyzing differences within twin pairs, this method isolates the impact of non-shared environmental influences while controlling common confounding factors [31, 32]. Either the ACE or ADE model is fitted since the classical twin model with twins raised together cannot estimate the (C) and (D) components concurrently [33]. Following a previous study [34], a full model (ACE model) with all latent variables was compared to nested sub-models (AE, CE, and E). Based on the Akaike information criterion (AIC) [35], the best-fit model was selected as the reporting model and was employed to analyze the patients adjusted for age. Interclass correlations were computed for monozygotic (rMZ) and dizygotic (rDZ) twins.

To account for the effects of menopause on the subjects, an additional subgroup was created, and the same analysis as the total group was conducted. A cutoff age of 50 years was used, predicated on previous studies on the age of menopause of Japanese women [36], as the age of menopause was not collected for this analysis.

Statistical analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [37], a graphical user interface for R. A *p*-value of less than 0.05 was considered to indicate a statistically significant difference among groups.

3. RESULTS

Table 1 compares the continuous and categorical variables between the two types of twin zygosity. No significant difference was observed between MZ and DZ in age and BAR.

The results of the univariate twin analysis are shown in Table 2. Intra-twin correlations showed that all models other than the CE model show a stronger correlation between MZ twins than DZ twins. The model with the best fit for the group with all subjects was the AE model, and the heritability estimated for BAR with all subjects included was 0.51 (95% confidence interval (CI): 0.38 – 0.63). For the group of subjects younger than 50 years, the best-fit model to adjust for the effects of menopause was also reported to be the AE model, with a heritability estimate of 0.53 (95% CI: 0.34 – 0.72).

4. DISCUSSION

To the best of our knowledge, our study represents the inaugural report on the heritability of bone mass within the Japanese population. We demonstrated that heritability may account for approximately half of the effects on bone mass in Japanese women, with the remaining variance attributable to environmental factors indicating substantial environmental involvement. Previous studies investigating genetic contributions to bone mineral density have focused exclusively on non-Japanese populations [38, 39]. Our findings will contribute to future research to identify potential factors to prevent the decline of bone mineral density within the Japanese population.

This heritability is lower than that reported in prior studies conducted in Western countries, which report 60% to 80% heritability [15-17, 19, 20], and is even lower than that reported in a previous study from Korea, which reported 50% to 80% heritability [18]. However, these prior studies did not focus mainly on females and included male participants in their analysis. This may

suggest that environmental factors play a significant role in determining bone mass in the Japanese female population, potentially explaining why Japan has a higher prevalence of osteoporosis than other high-income countries [40].

The fact that environmental factors play a pivotal role in determining the bone mass of Japanese women also suggests that interventions to mitigate the effects of such environmental factors may be more effective in Japanese women than in women of other countries. This implies that measures to ameliorate environmental factors that influence osteoporosis, such as physical activity[22], smoking [21], dietary habits [21, 22], as well as gut microbiota [41] may more effectively enhance the bone health of Japanese women than women of other countries. BMI has been presented as an influential determinant of osteoporosis[7, 42]. Japanese women tend to have a lower BMI than other countries [8], which may have contributed to the reduced heritability observed in our study population. Although the smoking rate among Japanese women has been steadily declining over time[43], it remains above the global average [44], presenting the necessity for further initiatives to reduce smoking prevalence. Such actions may also promote bone health among Japanese women. Furthermore, aging itself has been noted to affect bone health [45]. Given that Japanese females are known to have one of the longest healthy and total life expectancies worldwide [46], studies to identify the key factors in preventing osteoporosis should be implemented in the Japanese population, as deaths caused by osteoporotic fractures continue to be underestimated in Japan [47]. However, the extent to which these factors contribute to osteoporosis remains uncertain. For instance, while a higher BMI is positively correlated with BMD [48], a slightly lower BMI has been associated with reduced mortality [49]. Therefore, although low BMD may contribute to increased mortality, it is not the sole determinant, suggesting the involvement of multiple factors. This underscores the need for further research to elucidate the key determinants influencing mortality in individuals with low BMD.

However, for several reasons, direct comparison of the results among race and ethnicity is challenging. Firstly, the sample size and equipment of each cohort differ. Studies adjusted for the sample size with similar, ideally identical equipment should be conducted to identify the

differences in heritability and the influential environmental factors. Secondly, some participants may have resided in other countries in the past, which may have influenced the factors that affect osteoporosis, such as dietary habits or physical activity. Although the current residence of the participants is in Japan, we have not been able to obtain information on the past residential history of the patients. Furthermore, although this may be challenging due to various reasons, [50, 51], comparative studies between other races and ethnicities residing in Japan, or Japanese living in different countries would be necessary. Such data would be of immense value in the clinical setting, as this may identify the differences in the clinical features between the local, national patients, compared to the local, non-national patients [52] and patients visiting from abroad for a short term [53].

In addition to research, Japan necessitates amplified efforts to ensure appropriate osteoporosis prevention. Despite Japan's proactive stance in preventing chronic lifestyle diseases through the populational approach of "*Health Japan 21*", the screening rate for osteoporosis among Japanese women aged between 40 and 70 remains low at 4.6% [54]. Dual-energy X-ray absorptiometry (DXA) is the gold standard for detecting osteoporosis, but this necessitates specialized, costly equipment and skilled technicians [55]. A simple, economical screening method is indispensable for a comprehensive populational approach to prevent osteoporosis [56]. Recently, screening methods using chest radiographs have been reported from Japan [56-58], and this may become a viable option, as chest radiographs are routinely obtained in health checkups in Japan.

This study has several limitations. Firstly, the nature of the study limited the participants to a relatively healthy population [59] as the participants were required to come to the recruitment sites for the study. Therefore, less healthy individuals may have been unable to participate in our study. Secondly, our study did not directly measure BMD and used BAR as an alternative obtained from QUS. The use of DXA was not feasible by the unavailability of equipment and ethical concerns regarding radiation exposure to healthy participants. While DXA is widely recognized as the gold standard for osteoporosis diagnosis, QUS has been validated as a reliable method for assessing bone quality [60]. Although there is still not enough evidence to recommend this method

in screening programs over DXA [61], previous studies have identified QUS as a promising alternative for osteoporosis screening. A systematic review has highlighted the utility of QUS in evaluating BMD, particularly among elderly populations [62], and a high correlation between QUS and BMD has been reported in a longitudinal study in Sweden [63], as well as supporting its feasibility for osteoporosis detection among females in the United Kingdom [64]. Additionally, studies conducted in Japan have demonstrated a significant correlation between DXA and QUS measurements in Japanese females [65, 66]. Therefore, although caution is warranted when directly comparing our findings to studies that utilized DXA for BMD measurement in other populations, the quality of the heritability results derived from our twin study should remain broadly comparable. Thirdly, we were not able to obtain thorough basic lifestyle variables and medical histories of the participants, including previous fractures and the use of glucocorticoids, as well as menopausal status. Fourthly, the sample size of this study was smaller than that of several previous studies [15-20], with a relatively limited portion of DZ twins, which may have been a reason for the wide range observed in the 95% CI [67]. This limitation may have also led to an overestimation of heritability relative to the general population due to the differential environmental influences between MZ and DZ twins. Nevertheless, this potential overestimation does not alter our fundamental conclusion that environmental factors play a more significant role in determining bone health among the Japanese population. Furthermore, the small sample size may limit the study's external validity and precision, as it may not fully represent the Japanese population. However, as there are twin studies with a smaller sample size than ours [15, 16, 19], we believe our findings as a twin study are feasible. Fifthly, this study is limited to the Japanese population.

5. CONCLUSION

In conclusion, our study revealed a comparatively lower heritability of bone mass relative to Western nations, as well as an Asian population. This outcome suggests a significant influence of environmental factors on the susceptibility of bone health in Japanese women. Future

investigations into these environmental factors, and interventions to enhance bone health, should be undertaken to prevent osteoporosis effectively.

DECLARATION

Ethics approval and consent to participate

The study protocol and consent forms were approved by the Ethics Committee of Osaka University Graduate School of Medicine (approval numbers 10209 and 696). Written informed consent was obtained from all participants.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to the protection of the personal information of the subjects but are available from the corresponding author on reasonable request.

Author contributions

CH conceptualized, designed, and supervised the study. CH and RT collected and organized the data. SS analyzed the data and drafted the manuscript. KM and KN analyzed and interpreted the data and supervised the study. All authors contributed to the revision of the draft and read and approved the final version of the manuscript. The author's affiliated institution did not contribute to the conceptualization of this manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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