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ORIGINAL ARTICLE

Ethnic differences in bone mineral density among midlife women in a multi-ethnic Southeast Asian cohort

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Abstract

Summary Chinese Singaporean middle-aged women have significantly lower femoral neck bone mineral density and higher lumbar spine bone mineral density than Malays and Indians, after adjustment for age, body mass index, and height.

Purpose Information regarding mediators of differences in bone mineral density (BMD) among Asian ethnicities are limited. Since the majority of hip fractures are predicted to be from Asia, differences in BMD in Asian ethnicities require further exploration. We compared BMD among the Chinese, Malay, or Indian ethnicities in Singapore, aiming to identify potential mediators for the observed differences.

Methods BMD of 1201 women aged 45–69 years was measured by dual-energy X-ray absorptiometry. We examined the associations between ethnicity and BMD at both sites, before and after adjusting for potential mediators measured using standardized questionnaires and validated performance tests.

Results Chinese women had significantly *lower* femoral neck BMD than Malay and Indian women. Of the more than 20 variables examined, age, body mass index, and height accounted for almost all the observed ethnic differences in femoral neck BMD between Chinese and Malays. However, Indian women still retained 0.047 g/cm^2 (95% CI, 0.024, 0.071) higher femoral neck BMD after adjustment, suggesting that additional factors may contribute to the increased BMD in Indians. Although no crude ethnic differences in lumbar spine BMD were observed, adjusted regression model unmasked ethnic differences, wherein Chinese women had 0.061(95% CI, −0.095, 0.026) and 0.065 (95% CI, −0.091, 0.038) g/cm^2 *higher* lumbar spine BMD compared to Malay and Indian women, respectively.

Conclusion BMD in middle-aged Asian women differ by ethnicity and site. Particular attention should be paid to underweight women of Chinese ethnic origin, who may be at highest risk of osteoporosis at the femoral neck and hence hip fractures.

Keywords Bone mineral density · Ethnic differences · Singapore · Asian · Osteoporosis

Introduction

Hip fractures have devastating consequences, including higher mortality risks, poor quality of life, and depression that can persist up to 10 years [1]. Osteoporosis as identified by bone mineral density (BMD) measurement correlates closely with risk of hip fractures [2]. As a result of abrupt estrogen decline following menopause, women have higher risks of osteoporosis and consequently a 2- to 3-fold increased risk of hip fracture compared to men [3]. Nevertheless, age-standardized incidence rates of hip fracture in women may vary 10- to 200-fold when comparing ethnic groups, countries, and regions [3, 4]. The reasons for these wide variations are unclear [5].

Comparative data on ethnic differences in BMD for midlife women are limited and inconsistent. In the US multicenter

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longitudinal Study of Women's Health Across the Nation [6], ethnicity was significantly associated with changes in hip BMD during the menopause transition, but differences were largely eliminated when adjusted for differences in body weight. Similarly, a UK cohort reported no differences in femoral neck BMD between Indo-Asian and age-matched Caucasian women [7]. However, the largest cohort to date, the National Osteoporosis Risk Assessment (NORA) cohort (197,848 women), found that Black women had lower risk of osteoporosis compared to white and Asian women even after multivariable adjustment (including weight) [8]. Similarly, BMD was observed to be significantly higher in Brazilian Afro-descendant women than in those of Caucasian or Asian descent [9], and Afro-Caribbean women from Tobago and African-American women have been reported to have hip BMD measurements 13–31% higher than those of US Caucasians, who in turn had 4–7% higher BMD than Hong Kong or South Korean women [10], even after adjustment for weight, age, height, and other factors [10]. In a Southeast Asian study, however, age-related decline in bone health indices were uniform among Chinese, Malay, and Indian subjects, and no ethnic differences in bone health were observed [11].

Data from Asia and from its multi-ethnic populations are sparse [10, 12], and little is known about BMD differences among Asian ethnic groups. The majority of the global population resides in Asia, and it is predicted to be a "high risk" region for hip fractures [13]. Singapore is unique in comprising three major Asian ethnic groups (Chinese (75.0%), Malay (13.7%), and Indian (8.7%)) which made up two thirds of the world population, represented in a small, highly urbanized city state [14]. Ethnicity is officially recorded on birth certificates and national identity documents, with inter-ethnic marriage rates relatively low [15]. In the current study, we hypothesized that the differences in BMD exist at the spine and hip among these three ethnic groups in Singapore. We also attempt to identify potential mediators of those differences.

Materials and methods

The study sample was selected from healthy women aged 45 to 69 years receiving routine gynecological care at the outpatient clinics of the National University Hospital (NUH), Singapore. NUH receives patients from all of Singapore for well-woman checkups and health screenings. Study women were similar to the Singapore's population in terms of ethnicity, education, and employment [14]. We excluded pregnant women, those with terminal or life-threatening conditions and those with physical or mental condition. The size of the cohort was based on a conservative osteoporosis prevalence rate of 6% in our targeted recruitment age groups (45–69 years). We considered the prevalence of osteoporosis reported in Hong Kong (10% in women 50–59 years and 45% in those 60–69 years), Japan (5.3% in women 50–59 years and 13.5% in those 60–69 years), and China (10.75% in postmenopausal women) [1–3]. With a sample size of 1200, and a prevalence rate of 6%, we have adequate (at least 80%) power to detect odds ratios of 1.5 for risk factors of osteoporosis. Eligibility criteria, study protocol, and other methodological features have been described in detail elsewhere [16]. Briefly, out of the 2191 women who were approached, 1201 (54.8%) agreed to participate. This participation rate is commensurate with other midlife women cohorts in the USA [17] and Australia [18]. The study was approved by the Domain Specific Review Board of the National Healthcare Group, Singapore (reference number 2014/00356). All participants provided written informed consent prior to the participation in the study. This study used standardized questionnaires, physical measurements, and validated performance tests to gather information on the following:

Sociodemographic information—for ethnicity/race, participants were asked to self-identify as either "Chinese," "Malay," "Indian," or "Eurasian." Participants could also choose the options "do not know" or "refused to answer." Education levels, marital status, employment status, housing types, and monthly household income were also requested.

Reproductive and menopausal history—we inquired about pregnancies and menopausal status, the latter based on questions on menstrual pattern, hysterectomy, and oophorectomy. Women were categorized as premenopausal if they had menstruated in the past 3 months and reported no change in menstrual frequency in the past 12 months, perimenopausal if they reported recent changes in menstrual frequency or 3 to 11 months of amenorrhea, and postmenopausal if they reported amenorrhea for 12 consecutive months or more.

General health and function—disability assessment was based on the World Health Organization Disability Assessment Schedule (WHODAS) [19], which measures the degree of functional limitation (0 (no disability) to 100 (complete disability)) in six different functioning domains—cognition, mobility, self-care, getting along, life activities, and participation.

Physical activity was assessed using the Global Physical Activity Questionnaire (GPAQ), which measures time spent carrying out moderate physical activities in a typical week [20].

Quality of sleep was determined by the Pittsburgh Sleep Quality Index (PSQI), a self-report of sleep habits in the past month; a score > 5 indicates poor sleep quality [21].

Information on smoking and alcohol, *general medical conditions*, *history of falls* in the previous 12 months, and intake of *calcium and vitamin D supplements* was also obtained.

Anthropometric measurements—duplicate measurements of height, body weight, and waist circumference were measured and averaged. Body mass index (BMI) was computed as

the body weight divided by the height squared (kg/m^2). We used the World Health Organization (WHO) revised classification of BMI for Asians (underweight, < 18.5; normal weight, 18.5–22.9; overweight, 23–27.4; obesity, BMI of 27.5 or more) to categorize the BMI measurements.

Physical performance tests included the Short Physical Performance Battery (SPPB), which assesses lower extremity physical performance status [22]. Handgrip strength was assessed in duplicate and averaged using a JAMAR dynamometer [23].

Participants underwent dual-energy X-ray absorptiometry (DXA) using the Hologic Discovery Wi and Apex software 4.5. Quality control assessments were performed by certified technologists using standard protocols. Daily calibration of the same densitometer was performed using the Hologic spine and hip phantoms before commencing scanning on subjects. The daily phantom plots were reviewed to verify that the spine, hip and whole body phantom BMD, BMC, and area values of the scanner are within normal limits. Short-term in vivo measurement variability was 0.004 g/cm^2 for the lumbar spine and 0.003 g/cm^2 for the femoral neck. None were excluded due to measurement errors. Bone mineral densities of the anteroposterior lumbar spine and femoral neck were assessed and the values expressed as gram per centimeter squared (g/cm^2). The DXA scan also provided total body fat (TBF) percent and visceral adipose tissue area (VAT) as cm^2.

Statistical analysis

Statistical analyses were performed using the SPSS software (Version 22, Chicago, IL, USA). Descriptive results are presented as number and percentage for categorical variables and as mean and standard deviation for continuous variables. For reference groups, we used Chinese for ethnicity and the postmenopausal category for menopausal status. All potential mediators associated with both ethnicity and BMD at femoral neck and lumbar spine at $p < 0.1$ (based on chi-square or ANOVA F tests) were included in the multivariable regression models. In addition, we also considered variables reported in previous studies to affect bone health (physical activity, intake of calcium and vitamin D supplements, smoking, and height) [24]. Multivariable linear regression models were used to examine the relationship of ethnicity to femoral neck BMD and lumbar spine BMD after sequentially adjusting, one at a time, to determine the contribution of potential mediators. 95% confidence intervals were used to assess the variability and statistical significance of all crude and adjusted associations.

Results

A total of 1201 women were recruited into the study (Table 1). Forty-two women with ethnicities other than that of Singapore's three major ethnic groups were excluded, leaving 1159 Chinese, Malay, or Indian women for subsequent analysis.

Chinese women were older, and consequently a higher proportion of them were postmenopausal, compared to Malay and Indian women (Table 1). Chinese women were more likely to be nulliparous and to own more expensive landed property. They were least likely to have moderate to severe difficulty with daily activities and self-reported the highest physical activity. They slept better and were least likely to report diabetes. Their waist circumference total body fat (TBF) percent and visceral adipose tissue (VAT) area were lower than those in either Malay or Indian women. They were more likely to score high on the physical performance test.

Compared to the Chinese and Indian women, Malay women were younger, less educated and least likely to report ownership of landed properties. They were more likely to be parous and perimenopausal. They reported the highest number of difficulties with daily activities. They were least likely to meet minimum physical activity requirements (> 150 min/week) and more likely to report poor sleep. The highest mean BMI was observed in Malays. They were also more likely to score low or very low on the physical performance test.

Compared to the Chinese and Malays, Indian women were the most educated and were more likely to be premenopausal and report a history of diabetes. They had the highest mean waist circumference, TBF percent, and VAT area. They were least likely to obtain a high score on the physical performance test.

Supplementary Table 1 summarizes the associations between BMD and sociodemographic and clinical variables. Education, menstrual status, diabetes, anthropometric measurements (height, waist circumference, BMI, TBF percent, and VAT area), and handgrip strength were significantly correlated with both femoral neck and lumbar spine BMD. The WHODAS correlated only with femoral neck BMD. Employment, parity, calcium and vitamin D supplement use, and hypertension correlated only with lumbar spine BMD.

Variables that correlated with both ethnicity and BMD (age, education, parity, current menstrual status, BMI, diabetes, WHODAS, and sleep quality) were included in the multivariable regression model. Neither housing type nor the Short Physical Performance Battery was associated with BMD at either site (Supplementary Table 1). Despite non-significant associations with ethnicity and BMD in our study sample, we included physical activity, sleep quality, intake of calcium and vitamin D supplements, smoking, and height in our multivariable models, as they are reported to be significant predictors of BMD [24, 25]. TBF percent, VAT, and waist circumference were excluded from the model, owing to their collinearity with BMI. While years since menopause was significantly associated with BMD, it was comparable among the three ethnic groups (data not shown). Therefore, it was excluded from the model.

Table 1 Sociodemographic and clinical characteristics of the study population, stratified by ethnicity

Variable	All ($n = 1201$)	Ethnic comparisons ($n = 1159$)[a]			p
		Chinese ($n = 974$)	Malay ($n = 66$)	Indian ($n = 119$)	
Sociodemographic					
Age at interview in years (mean, SD)	56.3 (6.2)	56.8 (6.2)	53.2 (4.9)	53.9 (5.4)	*< 0.001*
Highest education[b]					*< 0.001*
No formal–primary	169 (14.7)	153 (15.9)	5 (7.6)	11 (9.2)	
Secondary	518 (45.1)	421 (43.7)	47 (71.2)	50 (42.0)	
Pre-university/diploma	234 (20.4)	198 (20.5)	6 (9.1)	30 (25.2)	
Degree or higher	228 (19.8)	192 (19.9)	8 (12.1)	28 (23.5)	
Marital status					0.81
Single/divorced	220 (19.0)	188 (19.3)	12 (18.2)	20 (16.9)	
Married	937 (81.0)	785 (80.7)	54 (81.8)	98 (83.1)	
Employment					0.33
Working	776 (67.1)	649 (66.8)	41 (62.1)	86 (72.3)	
Not working	380 (32.9)	322 (33.2)	25 (37.9)	33 (27.7)	
Housing type					*0.004*
1–3 room apartments	138 (12)	108 (11.1)	11 (16.7)	19 (16.1)	
4–5 room apartments	783 (67.9)	650 (67.1)	52 (78.8)	81 (68.6)	
Landed property[c]	232 (20.1)	211 (21.8)	3 (4.5)	18 (15.3)	
Reproductive and menstrual history					
Parity					*0.001*
Nulliparous	201 (17.3)	176 (18.1)	7 (10.6)	18 (15.1)	
1–2	646 (55.7)	549 (56.4)	26 (39.4)	71 (59.7)	
≥ 3	312 (26.9)	249 (25.5)	33 (50.0)	30 (25.2)	
Current menstrual status					*0.027*
Premenopausal	148 (12.8)	120 (12.3)	8 (12.1)	20 (16.8)	
Perimenopausal	179 (15.4)	138 (14.2)	16 (24.2)	25 (21.0)	
Postmenopausal	832 (71.8)	716 (73.5)	42 (63.6)	74 (62.2)	
General health and function					
WHODAS classification					*< 0.001*
None-mild difficulty (0–24%)	1100 (94.9)	941 (96.6)	55 (83.3)	104 (87.4)	
Moderate-severe difficulty (25–100%)	59 (5.1)	33 (3.4)	11 (16.7)	15 (12.6)	
Self-rated health status					0.31
Poor	52 (4.5)	43 (4.5)	3 (4.5)	6 (5.1)	
Fair	380 (33.2)	326 (33.9)	23 (34.8)	31 (26.3)	
Good	589 (51.4)	489 (50.8)	37 (56.1)	63 (53.4)	
Excellent	125 (10.9)	104 (10.8)	3 (4.5)	18 (15.3)	
Physical activity					
GPAQ (moderate intensity)					*0.003*
< 150 min	459 (40.9)	382 (40.3)	38 (60.3)	39 (34.8)	
> 150 min	664 (59.1)	566 (85.2)	25 (39.7)	73 (65.2)	
Sleep quality (PSQI)					
Good (≤ 5)	702 (60.8)	610 (62.8)	32 (48.5)	60 (50.8)	*0.005*
Poor (> 5)	453 (39.2)	361 (37.2)	34 (51.5)	58 (49.2)	
Lifestyle choices					
Smoking, yes	23 (2.0)	19 (2.0)	1 (1.5)	3 (2.5)	0.88
Alcohol consumption[d]	36 (3.1)	34 (3.5)	0 (0)	2 (1.7)	0.18
Calcium and vitamin D supplements, yes	402 (34.7)	341 (35.0)	21 (31.8)	40 (33.6)	0.84
Past medical history					
Hip fracture[e]	12 (1.0)	9 (0.9)	1 (1.5)	2 (1.7)	0.69

Table 1 (continued)

Variable	All ($n = 1201$)	Ethnic comparisons ($n = 1159$)[a]			p
		Chinese ($n = 974$)	Malay ($n = 66$)	Indian ($n = 119$)	
Stroke	32 (2.8)	29 (3.0)	0 (0)	3 (2.6)	0.35
Deep vein thrombosis	8 (0.7)	6 (0.6)	0 (0)	2 (1.7)	0.30
Heart attack	12 (1.0)	10 (1.0)	1 (1.5)	1 (0.8)	0.90
Angina	21 (1.8)	15 (1.5)	2 (3.0)	4 (3.4)	0.28
Hypertension	337 (29.4)	288 (29.9)	25 (38.5)	24 (20.3)	*0.025*
Diabetes	117 (10.2)	80 (8.3)	10 (15.2)	27 (22.7)	*< 0.001*
Fall in last 12 months	167 (14.5)	145 (15.0)	8 (12.1)	14 (11.8)	0.55
Anthropometric measurements					
Height in cm, mean (SD)	157.2 (5.9)	157.1 (5.8)	156.4 (6.5)	157.7 (6.1)	0.51
Waist circumferences (cm), mean (SD)	81.2 (10.3)	79.7 (9.2)	86.9 (8.8)	90.6 (12.8)	*< 0.001*
Body mass index, mean (SD)	24.1 (4.4)	23.3 (3.8)	28.0 (4.5)	27.8 (5.9)	*< 0.001*
Total body fat percent, mean (SD)	40.2 (5.5)	39.3 (5.1)	44.5 (4.6)	45.3 (5.0)	*< 0.001*
Visceral adipose tissue (cm^2), mean (SD)	116.5 (53.2)	110.3 (50.6)	145.0 (48.1)	145.9 (57.6)	*< 0.001*
Physical performance tests					
Short physical performance battery (SPPB)					*0.021*
High (10–12)	969 (83.6)	829 (85.1)	51 (77.3)	89 (74.8)	
Moderate (7–9)	168 (14.5)	127 (13.0)	13 (19.7)	28 (23.5)	
Low to very low (0–6)	22 (1.9)	18 (1.8)	2 (3.0)	2 (1.7)	
Handgrip strength (kg), mean (SD)	18.1 (5.4)	18.2 (5.3)	17.1(5.6)	18.4 (5.9)	0.22

Data presented as n (%) unless otherwise stated. p values were obtained by chi-square tests for categorical variables and ANOVA for continuous variables

GPAQ global physical activity questionnaire, *WHODAS* WHO disability assessment schedule, *PSQI* Pittsburgh sleep quality index, *DXA* dual-energy X-ray absorptiometry

[a] Forty-two subjects excluded as they were not Chinese, Malay, and Indian

[b] 15 subjects refused to disclose their education

[c] Landed property in Singapore refers to residential property where the owner has the title to the land. Landed property in land-scarce Singapore are more expensive than apartments

[d] Consumption of 1–2 units > once a week

[e] In the past 5 years

Mediators of femoral neck BMD

Crude femoral BMD were lowest in Chinese and highest in Indian women (Fig. 1, left bars). Malay and Indian women had 0.065 g/cm^2 and 0.114 g/cm^2 higher femoral neck BMD, respectively, compared to the reference Chinese ($p < 0.001$) (Table 2, model 1). Adjustment for age diminished the association between ethnicity and femoral neck BMD (Table 2, model 2). Additional adjustment for BMI (Table 2, model 3) eliminated the differences between Chinese and Malay women. Indians had higher BMD compared to both Chinese and Malays, even after adjustment for height (Fig. 2, left bars; Table 2, model 4). Indians, but not Malays, had 0.040 (95% CI, 0.015, 0.065) g/cm^2 higher femoral neck BMD compared to the Chinese, even after adjusting for all other mediators (diabetes, physical activity, WHODAS, sleep quality, calcium and vitamin D supplement use, and smoking) in the full multivariable model (Table 4.

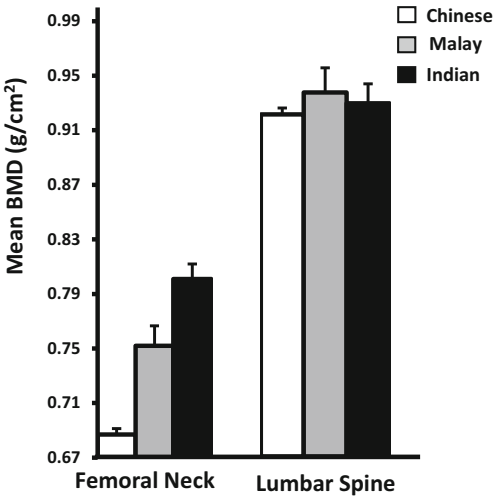

Fig. 1 Crude mean BMD among Chinese, Malay, and Indian women. Data are the mean (± SEM)

Table 2 Femoral neck bone mineral density: multivariate models to evaluate mediators of ethnic differences

	Mean (SD) (g/cm^2)	Model 1 Mean differences (95% CI)	Model 2[a] Mean differences (95% CI)	Model 3[b] Mean differences (95% CI)	Model 4[c] Mean differences (95% CI)
Ethnicity					
Chinese	0.687 (0.133)	Ref	Ref	Ref	Ref
Malay	0.752 (0.118)***	0.065 (0.033, 0.098)***	0.047 (0.015, 0.079)**	− 0.004 (− 0.035, 0.027)	− 0.003 (− 0.034, 0.027)
Indian	0.801 (0.120)***	0.114 (0.089, 0.138)***	0.099 (0.074, 0.123)***	0.050 (0.025, 0.074)***	0.047 (0.024, 0.071)***
Age		–	− 0.005 (− 0.006, − 0.004)***	− 0.005 (− 0.006, − 0.004)***	− 0.005 (− 0.006, − 0.004)***
BMI		–	–	0.011 (0.009, 0.013)***	0.011 (0.009, 0.013)***
Height (m)		–	–	–	0.002 (0.002, 0.003)***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a] Adjusted for age

[b] Adjusted for age and BMI

[c] Adjusted for age, BMI, and height

Mediators of lumbar spine BMD

In contrast to the femoral neck, no ethnic differences were observed in crude lumbar spine BMD (Fig. 1, right bars). Even though age was associated with lower lumbar spine BMD, addition of age alone to the regression model did not unmask any ethnic differences (Table 3, model 2). Strikingly, adjustment for BMI uncovered large and significant ethnic differences, whereby lower lumbar spine BMD was observed for both Malay ($p < 0.001$) and Indian women ($p < 0.001$) compared to Chinese women (Table 3, model 3). Addition of height (associated with higher lumbar spine BMD) to the regression model did not further alter the ethnic differences (Table 3, model 4). Both Malay and Indian women had lower lumbar spine BMD compared to Chinese women after adjustment for age, BMI, and height (Fig. 2, right bars). These differences remained even after adjustment for all the other potential mediators examined (diabetes, parity, physical activity, sleep quality, calcium and vitamin D supplement use, and smoking) (full model, Table 4).

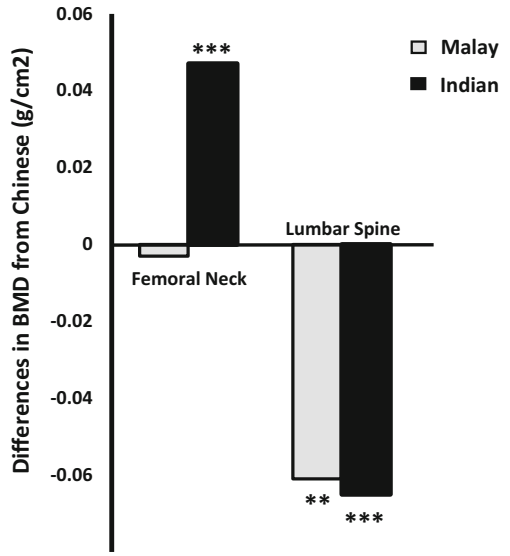

Fig. 2 Linear regression model comparing femoral and lumbar spine BMD of Malays and Indians with reference to Chinese women. BMD were adjusted for age, BMI, and height. **$p < 0.01$, ***$p < 0.001$ comparing Malay and Indian women to Chinese women

Overall, the full multivariate regression models indicate that older age was associated with *lower* BMD, while high body mass index and height were associated with *higher* BMD at both the femoral neck and lumbar spine sites (Table 4). Other factors associated with higher femoral neck BMD were perimenopausal status and diabetes. Higher lumbar spine BMD was also associated with premenopausal and perimenopausal status and with diabetes. Finally, having 1–2 children was associated with lower lumbar spine BMD compared to nulliparity (Table 4).

Discussion

Our study illuminates two novel aspects of BMD in the spine and femoral neck. First, midlife Chinese women have significantly *lower* crude femoral neck BMD than Malay and Indian women (Fig. 1). Of the more than 20 variables examined, age, BMI, and height, accounted for almost all the observed ethnic differences in femoral neck BMD between the Chinese and Malays. However, Indians still retained 0.047 g/cm^2 higher femoral neck BMD after adjustment for these variables, suggesting that other factors contribute to the higher BMD in

Table 3 Lumbar spine bone mineral density: multivariate models to evaluate mediators of ethnic differences

	Mean (SD) (g/cm^2)	Model 1 Mean differences (95% CI)	Model 2[a] Mean differences (95% CI)	Model 3[b] Mean differences (95% CI)	Model 4[c] Mean differences (95% CI)
Ethnicity					
Chinese	0.921 (0.144)	Ref	Ref	Ref	Ref
Malay	0.937 (0.147)	0.016 (− 0.020, 0.053)	− 0.006 (− 0.041, 0.030)	− 0.062 (− 0.096, − 0.027)***	− 0.061 (− 0.095, − 0.026)**
Indian	0.929 (0.156)	0.008 (− 0.020, 0.036)	− 0.009 (− 0.037, 0.018)	− 0.063 (− 0.090, − 0.036)***	− 0.065 (− 0.091, − 0.038)***
Age		–	− 0.006 (− 0.008, − 0.005)***	− 0.006 (− 0.007, − 0.005)***	− 0.006 (− 0.007, − 0.005)***
BMI		–	–	0.012 (0.010, 0.014)***	0.012 (0.010, 0.014)***
Height (m)		–	–	–	0.002 (0.001, 0.003)***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a] Adjusted for age

[b] Adjusted for age and BMI

[c] Adjusted for age, BMI, and height

Indians (Fig. 2). Secondly unlike hip BMD, no crude ethnic differences in lumbar spine BMD were observed (Fig. 1). Nevertheless, adjustment for age, BMI, and height in the regression model unmasked ethnic differences in the lumbar spine, wherein Chinese women had 0.061–0.065 g/cm^2 *higher* lumbar spine BMD compared to Malay and Indian women, respectively (Fig. 2). These findings suggest that ethnicity plays a role in BMD differences and this information would be of value in developing intervention thresholds for osteoporosis treatment.

Crude femoral neck bone density in our midlife cohort of Singaporean women was greatest in those of Indian ancestry, followed by Malays and Chinese. This ethnic ranking in BMD was consistent with the direction of femoral fracture rates in Singapore from 2000 to 2017, wherein Chinese women have 1.4- and 1.9-fold higher age-standardized fractures rates than Malay and Indian women respectively [26]. One well-known protective factor for BMD is body fat. Obese adults have greater BMD than non-obese adults, with thicker bone cortices, higher cortical BMD and tissue mineral density, lower cortical porosity, higher trabecular BMD, and higher trabecular number [27–29]. In our study, 0.011 to 0.012 g/cm^2 of higher BMD can be attributed to BMI at the femoral neck and lumbar spine, respectively (Tables 2 and 3, model 3). In this regard, it is relevant to note that obesity rates increased by 97%, 33%, and 34% in Chinese, Malays, and Indian Singaporeans, respectively, between 1998 and 2010 [30]. Our data suggest that the increasing BMI in Chinese may have narrowed differences in hip fracture rates among the ethnic groups.

Standing height was associated with greater BMD and was a significant positive mediator of ethnic differences in BMD at both the spine and femoral neck, above and beyond the known effect of BMI. The reason remains unclear but may reflect the greater mechanical loading of the skeleton that occurs with taller stature.

Our findings are consistent with reported ethnic disparities in the USA, wherein African-American women had the highest femoral neck BMD, Asian women had the lowest femoral neck BMD, and Caucasians were intermediate [6, 31]. In the US study, adjustment for covariates, including body weight, eliminated crude differences in BMD between Caucasians and Asians, but not between those races and African-Americans, who have about half the prevalence of osteoporosis compared to other races [6, 8]. In our cohort, adjustment for BMI eliminated differences between Chinese and Malays, but not for Indians. Indian women exhibited higher femoral neck BMD in the full multivariate model after adjustment for all variables, suggesting that factors other than those examined contribute to the increased BMD in Indians. Ethnic differences in BMD may reflect differences in peak BMD, rates of bone loss, or both. The former is less likely, in view of the lack of significant differences in peak BMD in both lumbar spine and femoral neck of the three races in Singapore when measured at 20–29 years [12]. Intriguingly, among US ethnic groups, Chinese and Japanese women have the most rapid rates of bone loss in the femoral neck during the menopause [32] and the immediate postmenopausal period [33]. Lower BMD in Chinese Singaporean women may be linked to a faster rate of bone loss compared to Indian and Malay women [12]. Whether genetic factors [34] or other yet unknown dietary, environmental, or behavioral factors [4] contribute to lower femoral neck BMD in Chinese and Malays compared to Indians should be explored in future studies.

Table 4 Full multivariate models of femoral neck and lumbar spine bone mineral density

Variables	Coefficient (95% CI)
LS BMD (g/cm^2)	
Ethnicity	
Chinese	Ref
Malay	−0.050 (−0.085, −0.015)**
Indian	−0.070 (−0.097, −0.043)***
Age	−0.003 (−0.005, −0.001)***
Education[a]	
Degree or higher	Ref
No formal/primary	−0.026 (−0.053, 0.001)
Secondary	−0.004 (−0.025, 0.017)
Pre-university/degree	0.013 (−0.011, 0.037)
Parity[a]	
0	Ref
1–2	−0.033 (−0.054, −0.012)**
≥3	−0.023 (−0.046, 0.001)
Current menstrual status[a]	
Postmenopausal	Ref
Premenopausal	0.078 (0.051, 0.105)***
Perimenopausal	0.046 (0.021, 070)***
BMI	0.012 (0.010, 0.013)***
Height (m)	0.002 (0.001, 0.003)***
Diabetes	0.058 (0.032, 0.084)***
Physical activity	−0.001 (−0.015, 0.016)
WHODAS	−0.024(−0.060, 0.012)
Sleep quality	−0.007 (−0.022, 0.009)
Calcium and vitamin D supplement	−0.013 (−0.029, 0.003)
Smoking	−0.013 (−0.068, 0.042)
FN BMD (g/cm^2)	
Ethnicity	
Chinese	Ref
Malay	0.001 (−0.031, 0.033)
Indian	0.040 (0.015, 0.065)**
Age	−0.003 (−0.005, −0.002)***
Education[a]	
Degree or higher	Ref
No formal/primary	−0.021 (−0.046, 0.003)
Secondary	−0.002 (−0.021, 0.017)
Pre-university/diploma	0.001 (−0.021, 0.023)
Current menstrual status[a]	
Postmenopausal	Ref
Premenopausal	0.025 (0.000, 0.050)
Perimenopausal	0.028 (0.006, 0.051)*
BMI	0.011 (0.009, 0.013)***
Height (m)	0.002 (0.002, 0.003)***
Diabetes	0.032 (0.008, 0.056)*
Physical activity	−0.007 (−0.022, 0.007)
WHODAS	−0.001(−0.034, 0.032)
Sleep quality	0.009 (−0.006, 0.023)
Calcium and vitamin D supplement	−0.006 (−0.021, 0.009)
Smoking	−0.031 (−0.081, 0.020)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a] Compared to reference

We observed striking site-specific differences in BMD between Chinese and Indian women. Unlike in the femoral neck, lumbar spines of Indians were less dense than expected for their BMI compared to Chinese. After adjustment for age, height, and BMI, Chinese women had a *higher* lumbar spine BMD but a *lower* hip BMD than Indian women. Our findings are consistent with those of a cross-sectional study of Singaporean Chinese community-dwelling healthy women aged 29–71 years, in whom osteoporosis was site specific: more frequent in the femoral neck than in the lumbar spine [35]. Site-specific ethnic disparities have also been observed in other populations. In a South African population, femoral neck and total hip BMD were higher, but lumbar spine BMD was lower in black than white women; body composition, lifestyle, and socioeconomic factors contributed differently to BMD in these women [36, 37]. Weight may explain a larger proportion of variance at the femoral neck than at the lumbar spine in Chinese Americans: 16.6 vs 10.5% [27]. Genome-wide association meta-analyses suggest that BMD-associated variants may exert site-specific effects that differ in magnitude of effect in the central versus appendicular skeleton [38]. Intra-population analyses indicate that Chinese and Indians are the most biologically homogeneous and heterogeneous, respectively, of the three Singapore ethnic groups, with 88 of 107 differentiated lipid species driving lipid-level differences between Indians and non-Indians [39]. Whether genetic polymorphisms [34] or other unknown factors affect site-specific ethnic differences should be examined in future studies.

In our study, other factors associated with higher femoral neck BMD were perimenopausal status and diabetes. Higher lumbar spine BMD was also associated with these same factors. Finally, having 1–2 children was associated with lower lumbar spine BMD compared to nulliparity. Although ethnic differences were observed in educational levels, housing type, physical activity, WHODAS, sleep quality, calcium and vitamin D supplement use, and smoking, these variables did not contribute to ethnic differences in BMD in our full multivariable model.

We acknowledge the limitations of possible selection bias inherent in studies based on convenience samples. Unlike the community samples studied in the Study of Women's Health Across the Nation (SWAN) [17], our study women were health-seeking. Nevertheless, the demographics of our study participants were similar to Singapore's general population. For example, 81% were of Chinese ethnic origin (vs 80% in the general population), 40% had postsecondary education (vs 38%), and 67% were employed (vs 60%) [14]. A lower proportion of Malay women compared to the national distribution so caution is recommended in interpreting the result in this ethnic group. However, our findings are consistent with existing literatures [35]. Moreover, the use of areal BMD by DXA scan does not account for skeletal size which could potentially lead to incorrect estimation of low BMD in individuals with smaller bones. However, this concern is

minimized in our regression models by adjusting for age and height as a measure of skeletal size. As DXA does not measure bone quality, it cannot differentiate between cortical and trabecular compartments. Recent studies have reported associations between diet and bone health [40]. We did not include food frequency questionnaires in our data collection. Thus, we cannot exclude residual confounding due to dietary differences across ethnic groups. We did, however, enquire about intake of calcium and vitamin D supplements, which are known to be relevant for osteoporosis. The use of calcium and vitamin D supplements has been controlled for in our statistical models. Our regression approach to assess mediation between ethnicity and BMD ignores the potential for collider stratification bias due to unmeasured (and hence uncontrolled) common causes of the mediators and BMD. As a single-center study, our findings may not be generalizable to other populations or age groups. In particular, they should not be extrapolated to Chinese, Malay, and Indian women living in countries with a higher prevalence of undernutrition or with differences in physical activity. Finally, the variations we observed in bone density are often attributed to differences in genetic and biochemical variables [33, 41], which were not measured in our study.

Despite these limitations, our study has several notable strengths. They include an ethnically diverse sample of midlife Singaporean women comprising three major Asian ethnicities and both pre- and postmenopausal women. Therefore, our cohort is particularly positioned to explore ethnic differences in BMD and the role of their potential mediators. In addition, our cohort captured an important age group to intervene with preventive strategies for age-related bone loss and future fracture, as one in three women over age 50 is at risk for osteoporotic fractures [42]. Our study included an extensive collection of demographic, clinical, and lifestyle variables; use of validated questionnaires and standardized biophysical measurements; and performance assessments. Our study population profile is similar to that of the general Singapore population, and our participation rate (54.8%) is higher than that of many other studies [17, 43]. We are aware of no previous studies on midlife Asian women's bone health.

We found that Chinese women have significantly *lower* femoral neck BMD than Malay and Indian women and that age, BMI, and height accounted for most of the observed differences. Chinese women had *higher* lumbar spine BMD compared to Malay and Indian women, however, after adjustment for age, BMI, and height. Although our findings need to be confirmed by population-based studies with higher numbers of Malays and Indians, the close correspondence of ethnic differences in BMD with actual fracture rates in Singapore [26] suggest the validity of our data. Nevertheless, particular attention should be paid to underweight women of Chinese ethnic origin who are at highest risk of osteoporosis at the femoral neck and hence hip fractures. Incorporation of these marked variations across ethnicities into intervention thresholds for osteoporosis treatment [44] may improve hip fracture rates in Singapore.

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Compliance with ethical standards

The study was approved by the Domain Specific Review Board of the National Healthcare Group, Singapore (Reference Number 2014/00356). All participants provided written informed consent prior to the participation in the study.

Conflicts of interest None.

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