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ORIGINAL RESEARCH

Associations Between Body Mass Index, WNT16 rs2908004 and Osteoporosis: Findings from Taiwan Biobank

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Purpose: Osteoporosis is a degenerative disease that affects women and men of all races. We studied the association between body mass index (BMI), rs2908004 polymorphism of the WNT16 gene, and osteoporosis using data from Taiwan Biobank (TWB).

Patients and Methods: We analyzed data from 10,942 subjects aged 30 to 70. We defined osteoporosis based on a mean T-score of −2.5 and below in the hip. Body mass index was classified following the guidelines of the Health Promotion Administration. Imputation was carried out using the IMPUTE2 (v2.3.1) program. Multiple logistic regression was used for analysis. The odds ratios (ORs) and 95% confidence interval (CI) for osteoporosis were determined.

Results: In the multivariate regression model, variant rs2908004 had a significant association with osteoporosis. That is, the rs2908004-GA+AA genotype was associated with lower osteoporosis risk than the GG genotype (OR, 0.651; 95% CI = 0.544 to 0.780). Compared to normal-weight, underweight was significantly associated with a higher risk of osteoporosis (OR, 6.517; 95% CI = 4.624 to 9.186) while overweight and obesity were protective (OR, 0.176; 95% CI = 0.140 to 0.221 and 0.057; 95% CI = 0.039 to 0.083, respectively). There was an interaction between rs2908004 and BMI (p = 0.0148). Subgroup analyses (using rs2908004-GG /normal-weight as the reference group) indicated ORs of 7.66 (95% CI = 5.153 to 11.394) in the rs2908004-GG/underweight group and 3.002 (95% CI = 1.509 to 5.974) in the rs2908004-GA+AA/underweight group (95% CI = 1.509 to 5.974). Odds ratios were substantially lower in rs2908004-GG/obese, rs2908004-GG/overweight, GA+AA/normal-weight, rs2908004-GA+AA/overweight, and rs2908004-GA+AA/obese groups, respectively.

Conclusion: According to our study, underweight was associated with an increased risk of osteoporosis irrespective of WNT16 rs2908004 genotypes, while overweight and obesity were associated with a lower risk.

Keywords: bone health, SNP, osteoporosis, anthropometric measures

Introduction

Osteoporosis is a degenerative bone disease that affects men and women of all races. It is more prevalent among older individuals, especially post-menopausal women. The disease may also be classified as primary (postmenopausal or senile osteoporosis) or secondary (a result of other disorders, including chronic exposure to glucocorticoids).[1,2] Taiwan, as well as other parts of Asia, has seen a rapid increase in osteoporosis due to aging populations.[3] By 2011, 25.0% of Taiwanese had osteoporosis, an increase from 17.4% in 2001.[4] In 2050, there may be 212 million people with the disease,[5] and Asia is expected to account for approximately 51.1% of all hip fractures worldwide.[6] Lifestyle choices (diet, inactivity, heavy alcohol intake, cigarette smoking, etc.) and genetic factors are among the factors linked to the development of the disease.[7]

Genetic loci have been reported for bone traits, especially bone mineral density (BMD), which serves as a useful indicator of bone fragility or osteoporosis.[8,9] Ethnicity is well-known as a factor affecting bone mass. According to the findings of Hwang and his team, BMD values are lower in Asians than in other ethnicities despite adjustments for BMI.[3] Unlike other ethnicities, Asians have a lower BMI.[10] Low BMI is associated with osteoporotic fractures, while high BMI

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is believed to enhance BMD.[11] BMD and BMI have strong genetic influences, with heritability ranging from 0.5 to 0.9 and 0.4 to 0.7, respectively.[12–16]

Several loci have been examined for their effect on BMD and osteoporosis, as noted above. Numerous osteoporosis-related phenotypes and fracture risk are influenced by the *Wnt Family Member 16 (WNT16)*, a protein-coding gene that mediates signaling via canonical (known to regulate bone mass) or non-canonical *Wnt* pathways.[9] This gene is located on chromosome 7q31.31 and is considered to play an important role in determining peak bone mass acquisition.[17] Researchers have found that WNT16 has a strong influence on BMD, cortical bone thickness (CBT), fracture risk, and bone strength in humans and mice.[9] Moreover, it has been suggested as a potential therapeutic target for osteoarthritis in a preclinical study.[18] Rs2908004 is one of the variants within the *WNT16* gene that has shown strong associations with BMD phenotypes[19,20] and osteoporotic fractures.[9,21] Researchers previously examined the influence of the WNT16 gene on bone strength measured with ultrasonography and found that the variant rs2908004 was associated with broadband ultrasound attenuation (BUA) measurements in young Spanish individuals.[17] Another study in postmenopausal women has shown that rs2908004 may play a crucial role in osteoporosis pathogenesis, making it an ideal target for future investigations into the genetic basis of fracture risk.[22] However, this SNP was associated with decreased risk of osteoarthritis in women below 60 whose BMI were greater than or equal to 25.[23]

According to other findings,[24] the relationship between WNT16 polymorphisms and osteoporosis risk was determined to be dependent on BMI. Until now, the loci involved in osteoporosis have rarely been evaluated in Taiwan. Thus, we used data from TWB to investigate the association between variant rs2908004, BMI, and osteoporosis risk among Taiwanese adults.

Materials and Methods

Data Resource and Study Population

Taiwan Biobank provided phenotypic and genetic data for this study. The data collection period was between 2016 and 2020. Subjects were between the ages of 30 and 70 and had no history of cancer. During enrollment, all subjects provided written consent. Data from 19,627 subjects were assessed in the current study. Those with osteopenia (ie, total hip T-scores between −1 and −2.5; n = 8680) and those with missing values (n = 5) were excluded from the analysis. Finally, a total of 10,942 subjects were included in the study. This research has been approved by the Institutional Review Board (IRB) of Chung Shan Medical University (CS1-20009). Taiwan Biobank participants had provided written informed consent during enrollment. All methods were performed in accordance with the relevant guidelines and regulations.

SNP Selection, Imputation, and Quality Control

Through literature searches, we identified the variant rs2908004 of the WNT16 gene, which has been associated with osteoporosis in other populations. We used imputed data available in TWB. Two separate customized chips (TWBv1 custom array and TWBv2 custom array) were used for genotyping at Academia Sinica; details about these chips have been described elsewhere.[25,26] IMPUTE2 (v2.3.1) was used to impute data from a subset of individuals genotyped on TWBv1 and TWBv2. The WNT16 rs2908004 variant had an imputation INFO >0.3, minor allele frequency (MAF) greater than 0.01%, Hardy-Weinberg equilibrium (HWE) p-value of $>1.0 \times 10^{-5}$, and a missing rate <5%.

Definition of Osteoporosis and Covariates

Mackay Memorial Hospital performed BMD measurements using the DiscoveryTM QDRTM Bone Densitometry Systems (HOLOGIC) machine. In this study, we defined osteoporosis based on a mean T-score of −2.5 and below in the hip. Body mass index was classified following the guidelines of the Health Promotion Administration. Participants were grouped as follows: normal weight (18.5 kg/m^2 ≤ BMI < 24 kg/m^2), underweight (BMI<18.5 kg/m^2), overweight (24 kg/m^2 ≤ BMI < 27 kg/m^2), and obese (BMI ≥27 kg/m^2).

Statistical Analyses

The analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC, USA) and Plink 1.9. Continuous variables were presented as mean ± standard error (SE) whereas categorical variables were presented as numbers and percentages. Student's *t*-test and Chi-square were used to determine the differences between continuous and categorical variables. The contribution of each variable in the association of BMI and rs2908004 genotypes (GG and GA+AA) with osteoporosis was determined using multiple logistic regression. The odds ratios and 95% CI were determined. Lifestyle habits, such as smoking and drinking alcohol, tea consumption, and exercising, were included in the logistic regression model.

Results

Of the 10,942 participants, 862 had osteoporosis. The average age of those with osteoporosis was 61.606 (SE = 0.268) years and 53.281 (SE = 0.102) years for those without osteoporosis (Table 1). The variant rs2908004 was significantly protective against osteoporosis (GA+AA vs GG genotype: OR, 0.651; 95% CI = 0.543–0.778) as shown in Table 2.

Table 1 Participants' Characteristics

Variables	No Osteoporosis (n =10,080)	Osteoporosis (n = 862)	*p*-value
rs2908004 n, %			<0.0001
GG	6571 (65.19)	636 (73.78)	
GA+AA	3509 (34.81)	226 (26.22)	
BMI categories n, %			
Normal-weight (≥18.5 kg/m^2 to <24 kg/m^2)	3573 (35.45)	617 (71.58)	<0.0001
Underweight (<18.5 kg/m^2)	111 (1.10)	109 (12.65)	
Overweight (≥24 kg/m^2 to <27 kg/m^2)	3345 (33.18)	105 (12.18)	
Obese (≥27 kg/m^2)	3051 (30.27)	31 (3.60)	
Sex n, %			<0.0001
Female	5782 (57.36)	780 (90.49)	
Male	4298 (42.64)	82 (9.51)	
Age (mean±SE), years	53.281 (0.102)	61.618 (0.268)	<0.0001
Smoking n, %			<0.0001
No	7781 (77.19)	806 (93.50)	
Yes	2299 (22.81)	56 (6.50)	
Alcohol intake n, %			<0.0001
No	8764 (86.94)	829 (96.17)	
Yes	1316 (13.06)	33 (3.83)	
Exercise n, %			<0.0001
No	5518 (54.74)	400 (46.40)	
Yes	4562 (45.26)	462 (53.60)	
Tea consumption n, %			<0.0001
No	7541 (74.81)	729 (84.57)	
Yes	2539 (25.19)	133 (15.43)	
Coffee consumption n, %			<0.0001
No	5439 (53.96)	577 (66.94)	
Yes	4641 (46.04)	285 (33.06)	
Vegetarian diet n, %			<0.0001
No	9287 (92.13)	732 (84.92)	
Yes	793 (7.87)	130 (15.08)	
Menopausal status n, % (n = 6562)			<0.0001
No	2775 (47.99)	50 (6.41)	
Yes	3007 (52.01)	730 (93.59)	

Note: GG, GA+AA are the genotypes of rs2908004.
Abbreviations: BMI, body mass index; SE, standard error.

Table 2 Odds Ratios for Osteoporosis Among Study Subjects

Variables	Model 1		
	OR	**95% CI**	***p*-value**
rs2908004			
GG	1		
GA+AA	0.651	0.544–0.780	<0.0001
BMI categories			
Normal-weight	1		
Underweight	6.517	4.624–9.186	<0.0001
Overweight	0.176	0.140–0.221	<0.0001
Obese	0.057	0.039–0.083	<0.0001
Sex			
Women	1		
Men	0.124	0.092–0.167	<0.0001
Age (years)	1.141	1.128–1.154	<0.0001
Smoking			
No	1		
Yes	1.179	0.824–1.686	0.3683
Alcohol intake			
No	1		
Yes	0.732	0.484–1.105	0.1374
Exercise			
No	1		
Yes	0.643	0.541–0.764	<0.0001
Tea consumption			
No	1		
Yes	0.991	0.796–1.234	0.9367
Coffee drinking			
No	1		
Yes	0.728	0.613–0.864	0.0003
Vegetarian diet			
No	1		
Yes	1.665	1.303–2.128	<0.0001
Model 2 (n = 6562)			
Menopausal status			
No	1		
Yes	3.852	2.631–5.640	<0.0001

Notes: Model 1 is the general model; Model 2 shows results based on menopausal status.
Abbreviations: OR, odds ratio; CI, 95% confidence interval.

Compared to normal-weight, underweight was significantly associated with a higher risk of osteoporosis (OR, 6.517; 95% CI = 4.624–9.186) while overweight and obesity were protective (OR, 0.176; 95% CI = 0.140–0.221 and 0.057; 95% CI = 0.039–0.083, respectively). Also associated with a lower risk of osteoporosis were male sex, exercise, and coffee consumption. Menopause was strongly associated with osteoporosis (OR, 3.852; 95% CI = 2.631–5.640). There was an interaction between rs2908004 and BMI (p for interaction=0.0148) in the general model that included all individuals. This prompted us to perform subgroup analyses. The ORs for the subgroups defined by the BMI and rs2908004 genotypes are shown in Table 3. Compared to the GG genotype, the OR for osteoporosis in GA+AA individuals was 0.747 (95% CI = 0.608–0.918) for those in the normal-weight group, 0.435 (95% CI = 0.196–0.963) for those in the underweight group, 0.471 (95% CI = 0.285–0.780) for those in the overweight group and 0.307 (95% CI = 0.115–0.818) for obese individuals, respectively. Compared to women, the adjusted OR for osteoporosis was 0.108 (95% CI = 0.075–0.156) in normal-weight, 1.630 (95% CI = 0.559–4.753) in underweight, 0.048 (95% CI = 0.020–

Table 3 ORs for Osteoporosis Among the Different Categories of BMI

Variables	Normal-Weight (n = 4190)			Underweight (n = 220)			Overweight (n = 3450)			Obese (n = 3082)		
	OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
rs2908004												
GG (n = 7207)	1			1			1			1		
GA+AA (n = 3735)	0.747	0.608–0.918	0.0056	0.435	0.196–0.963	0.400	0.471	0.285–0.780	0.0034	0.307	0.115–0.818	0.0182
Sex												
Female (n = 6562)	1			1			1			1		
Male (n = 4380)	0.108	0.075–0.156	<0.0001	1.630	0.559–4.753	0.3708	0.048	0.020–0.119	<0.0001	0.194	0.063–0.598	0.0043
Age (years)	1.138	1.123–1.153	<0.0001	1.137	1.094–1.182	<0.0001	1.155	1.120–1.192	<0.0001	1.165	1.103–1.231	<0.0001

Note: Adjusted for smoking, age, alcohol intake, exercise, tea consumption, coffee consumption, and vegetarian diet.

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Table 4 Estimates of Osteoporosis Odds Ratios Based on rs2908004 Genotype Combinations and BMI Categories

Variables	OR	95% CI	*p*-value
rs2908004-GG/ normal-weight (n = 2752)	1		
rs2908004-GG/ underweight (n = 166)	7.662	5.158–11.410	<0.0001
rs2908004-GG/ overweight (n = 2249)	0.197	0.152–0.256	<0.0001
rs2908004-GG/ obese (n = 2040)	0.071	0.047–0.107	<0.0001
rs2908004-GA+AA/ normal-weight (n = 1438)	0.747	0.608–0.919	0.0057
rs2908004-GA+AA/ underweight (n = 54)	3.007	1.511–5.984	0.0017
rs2908004-GA+AA/overweight (n = 1201)	0.095	0.060–0.150	<0.0001
rs2908004-GA+AA/ obese (n =1042)	0.022	0.009–0.053	<0.0001
Sex			
Female	1		
Male	0.123	0.092–0.166	<0.0001
Age (years)	1.141	1.128–1.153	<0.0001

Note: Adjusted for smoking, age, alcohol intake, exercise, tea consumption, coffee consumption, and vegetarian diet.

0.119) in overweight, and 0.194 (95% CI = 0.063–0.598) in obese men, respectively. Subgroup analyses (using rs2908004-GG/normal-weight as the reference group) indicated ORs of 7.672 (95% CI = 5.158–11.410) in the rs2908004-GG/underweight group and 3.007 (95% CI = 1.511–5.984) in the rs2908004-GA+AA/underweight group as shown in Table 4. The corresponding ORs (95% CI) were 0.197 (0.152–0.256) in the rs2908004-GG/overweight group, 0.071 (0.047–0.107) in the rs2908004-GG/obese group, 0.747 (0.608–0.919) in the rs2908004-GA+AA/normal-weight group, 0.095 (0.60–0.150) in the rs2908004-GA+AA/overweight group, and 0.022 (0.009–0.053) in the rs2908004-GA+AA/obese group, respectively.

Discussion

In our population-based study, we examined data from 10,942 subjects in TWB and observed that variant rs2908004 had a significant association with osteoporosis. In other words, the rs2908004-GA+AA genotype was associated with lower osteoporosis risk than the GG genotype. Additionally, we found that being underweight was significantly associated with an increased risk of osteoporosis, while overweight and obesity were protective (when compared with normal weight). Once the interaction terms were included in the regression model, our analyses showed a significant interaction between rs2908004 and BMI. When we stratified our model by BMI categories, we found that the GA+AA genotype (compared to the GG) appeared to be protective against osteoporosis regardless of the category. To better understand the association between rs2908004 genotypes, BMI, and osteoporosis, we included a separate model with "rs2908004-GG/normal weight" as the reference group. We found that underweight was associated with an increased risk of osteoporosis both for the GG and GA+AA genotypes, while overweight and obesity were associated with a lower risk.

As far as we know, this is the first study to investigate osteoporosis risk associated with BMI and rs2908004 using TWB. In recent years, underweight has been well-recognized as a risk factor for osteoporosis.[27–29] In a prospective study, the odds ratio associated with osteoporosis in underweight individuals was 7.4 (95% CI 1.3 to 42.5).[30] In the current study, we observed that the OR for osteoporosis was substantially lower among obese individuals. This is an indication that obesity is protective against the disease, even though previous studies have suggested otherwise.[31] Previous data have shown that osteoporosis and obesity are related based on how obesity is defined (ie, based on body mass index or body weight, which makes it protective, or according to the percentage of body fat, which makes it a risk factor).[32] It should be noted that we used BMI to define obesity following the Health Promotion Administration guidelines.

Osteoporosis is also known to be more prevalent in menopausal than in non-menopausal women.[29] In the current study, we found that the odds ratio associated with osteoporosis was 3.852 (95% CI, 2.631 to 5.640) in menopausal women compared to premenopausal women. The increased risk in menopausal women is linked to low estrogen levels, which are associated with bone loss. In contrast, when osteoporosis risk was compared between premenopausal and

postmenopausal women (Supplementary Table 1), we found that the risk was considerably lower for those with GA+AA than for those with GG genotypes.

Our study has some limitations, which need to be acknowledged. To begin with, osteoporosis can either be primary or secondary. This classification was not taken into consideration when analyzing the data. We did not have statistics for patients exposed to glucocorticoids (exogenous or endogenous). Next, our definition of obesity is not based on the percentage of body fat. Finally, the statistical power may not be adequate in light of the imbalanced distribution of the rs2908004 genotypes and BMI. Nevertheless, these findings are preliminary and we hope that future studies with larger sample sizes will provide further clarification.

Our study strength lies in the fact that this is the first study to examine osteoporosis risk associated with BMI and rs2908004 using TWB. We also used an imputed dataset to improve the power of the study or the prediction accuracy of the SNP.

Conclusions

In summary, we found that underweight was associated with increased osteoporosis risk regardless of genotypes associated with WNT16 rs2908004 polymorphism, whereas overweight and obesity were associated with lower risk. In light of the increasing prevalence of osteoporosis, additional studies are necessary to confirm these findings.

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Disclosure

The authors report no conflicts of interest in this work.

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