

Original Article

# The association between major depressive disorder, use of antidepressants and bone mineral density (BMD) in men

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## Abstract

**Objective:** Both depression and use of antidepressants have been negatively associated with bone mineral density (BMD) but mainly in studies among postmenopausal women. Therefore, the aim of this study was to investigate these relationships in men. **Methods:** Between 2006 and 2011, 928 men (aged 24-98 years) from the Geelong Osteoporosis Study completed a comprehensive questionnaire, clinical measurements and had BMD assessments at the forearm, spine, total hip and total body. Major depressive disorder (MDD) was identified using a structured clinical interview (SCID-I/NP). The cross-sectional associations between BMD and both MDD and antidepressant use were analyzed using multivariable linear regression. **Results:** Of the study population, 84 (9.1%) men had a single MDD episode, 50 (5.4%) had recurrent episodes and 65 (7.0%) were using antidepressants at the time of assessment. Following adjustments, recurrent MDD was associated with lower BMD at the forearm and total body (-6.5%,  $P=0.033$  and -2.5%,  $P=0.033$ , respectively compared to men with no history of MDD), while single MDD episodes were associated with higher BMD at the total hip (+3.4%,  $P=0.030$ ). Antidepressant use was associated with lower BMD only in lower-weight men (<75-110 kg depending on bone site). **Conclusions:** Both depression and use of antidepressants should be taken into account as possible risk factors for osteoporosis in men.

**Keywords:** Antidepressants, Bone Mineral Density, Depression, Osteoporosis, Selective Serotonin Reuptake Inhibitor

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JAP has received grant/research support from the NHMRC, Perpetual, Amgen (Europe) GmBH, BUPA Foundation and Arthritis Australia and has received speaker fees from Amgen and Sanofi Aventis. MB has received grant/research support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier and Woolworths, has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, and served as a consultant to Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck and Servier. LJW received grants from Eli Lilly, Pfizer, The University of Melbourne, Deakin University and NHMRC. All other authors state that they have no conflicts of interest.

The funding providers played no role in the design or conduct of the study; collection, management, analysis, and interpretation of the data; or in preparation, review, or approval of the manuscript.

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Edited by: F. Rauch  
Accepted 6 April 2015

**Abbreviations**

BMD	bone mineral density
GOS	Geelong Osteoporosis Study
MDD	major depressive disorder
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressants
SNRI	serotonin-norepinephrine reuptake inhibitor
AD	antidepressants

**Introduction**

Osteoporosis, a disease characterized by low bone mineral density (BMD) (i.e.  $<-2.5$  standard deviation (SD) from the young adult mean), is a common skeletal disorder with over 75 million people suffering worldwide<sup>1</sup>. It is a silent disorder, expressed mainly in later life, as evidenced by fragility fractures. In people aged 50 years or older, osteoporosis is one of the major health disorders: approximately 7% of men and 22% of women are affected in Europe<sup>1</sup> and similarly, 6% of men and 23% of women in Australia<sup>2</sup>. In the year 2010, approximately 3.5 million osteoporotic fractures occurred in Europe, of which 0.6 million were hip fractures<sup>1</sup>. Hip fracture is the most serious outcome often requiring long-term hospitalization<sup>3</sup>. It can be also a risk factor for poorer health and increased mortality<sup>4,6</sup>. Though women are at an higher risk of osteoporosis and fractures than men, men suffer more serious outcomes, with a 2-fold higher mortality risk after fracture<sup>4,6</sup>.

Risk factors for low BMD and subsequent fracture include low body mass, previous fracture, female sex and menopause, low calcium and vitamin D intake, smoking, high alcohol consumption, physical inactivity and use of certain medicines such as glucocorticoids, some psychotropics (e.g. antipsychotics) and paracetamol<sup>7-9</sup>. In addition to lifestyle and nutrition, a number of diseases can promote low BMD. For example type 1 diabetes<sup>10</sup>, inflammatory bowel disease<sup>11</sup> and schizophrenia<sup>12</sup> have been linked with reduced BMD. A number of cross-sectional studies have shown this to be true for depression also regardless of gender. A 2.1%<sup>13</sup> and 2.8%<sup>14</sup> lower total hip BMD has been seen among men with clinical depression compared to those without. In addition to clinical depression, also milder depressive symptoms, stress, anxiety and low well-being<sup>15-18</sup> has been shown to affect bone negatively. Furthermore, the use of antidepressants, in particular selective serotonin reuptake inhibitors (SSRI), has also been associated with reduced BMD<sup>19-21</sup> although the mechanism of action is not clearly evidenced. Reduction in bone mass may be attributed to disease and medication related processes and/or modifiable lifestyle factors associated with psychopathology<sup>22</sup>.

In the present study, we investigated the relationship between depression, antidepressant use and BMD in a population based sample of men. We also examined the role of potential confounders in any observed associations.

**Materials and methods***Study design and subjects*

This cross-sectional study examined data collected from men participating in the Geelong Osteoporosis Study (GOS), a large, ongoing, population-based study located in south-eastern Australia<sup>23</sup>. During 2001-2006, 1,540 adult men were randomly recruited from the electoral rolls for the Barwon Statistical Division (response 67%) and 978 of them returned for 5-year follow-up assessments between 2006 and 2011 (response rate 81% of eligible men). Data were collected at one center only, Barwon Health, Geelong. Utilizing data from the 5-year follow-up assessment, participants whose BMD data was available were included to the analyses, resulting in a final sample of 928 men, aged 24-98 years. The study was approved by the Human Research Ethics Committee at Barwon Health and all participants provided written, informed consent.

*Clinical measurements*

Areal BMD (g/cm<sup>2</sup>) was measured at the ultradistal forearm, lumbar spine (posterior-anterior projection, L2-L4), total hip and total body using dual-energy X-ray absorptiometry (DXA; Prodigy Pro). Trained technicians carried out all examinations and performed daily calibrations of the densitometers with equipment-specific phantoms. At the time of DXA, height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively.

*Questionnaire data*

Data on demographic, health, medication and lifestyle factors were obtained. Area-based socio-economic status (SES) was ascertained using Socio-Economic Index For Areas (SEIFA) index scores, based on the Australian Bureau of Statistics Census 2006 data. It was used to derive an Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) score accounting for income, and type of occupation. A low score identifies the most disadvantaged (quintile 1) and a high score the most advantaged (quintile 5).

A lifetime history of MDD was assessed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Non-patient edition; SCID-I/NP)<sup>24</sup> by trained personnel. Participants were divided into three groups: no history of MDD, a single episode or recurrent ( $\geq 2$ ) episodes of MDD.

Medication use was classified as current if used at the time of assessment and categorized into subgroups of antidepressants (including SSRIs, tricyclic antidepressants (TCA) and serotonin-norepinephrine reuptake inhibitors (SNRI)), oral glucocorticoids, gonadal hormones, bisphosphonates, calcium and vitamin D supplements. Habitual physical activity level was classified as active if light or vigorous exercise was performed; otherwise participants were classified as sedentary. Dietary calcium intakes (mg/day) and alcohol consumption were assessed using the validated Cancer Council food frequency questionnaire (FFQ)<sup>25</sup> which considered the participants usual eating habits over the previous 12 months. The

Characteristics	All	No MDD	Single MDD	Recurrent MDD	P value <sup>a</sup>
	n=928	n=794	n=84	n=50	
Age (yr)	60.0 (46.3-73.2)	60.9 (47.6-75.1)	51.6 (43.3-64.1)*	55.4 (38.3-64.0)*	<.001
Height (cm)	174.9 (7.2)	174.7 (7.3)	175.3 (6.9)	177.2 (6.4)*	.050
Weight (kg)	84.3 (14.5)	83.9 (14.4)	86.6 (16.5)	87.3 (12.6)	.087
BMD (g/cm <sup>2</sup> )					
Forearm	0.419 (0.064)	0.418 (0.064)	0.435 (0.064)*	0.409 (0.056)	.031
Lumbar spine	1.293 (0.198)	1.298 (0.201)	1.281 (0.191)	1.244 (0.166)	.16
Total hip	1.066 (0.148)	1.062 (0.147)	1.108 (0.154)*	1.058 (0.148)	.027
Total body	1.241 (0.110)	1.239 (0.110)	1.266 (0.115)*	1.230 (0.091)	.088
Calcium intake (mg/day)	934 (366)	923 (354)	958 (441)	1080 (406)*	.015
Alcohol intake (g/day)	12.0 (2.1-28.7)	11.8 (2.1-28.2)	15.1 (2.7-36.1)	17.7 (1.2-37.2)	.20
Socio-economic status					.66
Quintile 1 (lowest)	150 (16.2%)	129 (16.2%)	14 (16.7%)	7 (14.0%)	
Quintile 2	186 (20.0%)	160 (20.2%)	16 (19.0%)	10 (20.0%)	
Quintile 3	179 (19.3%)	160 (20.2%)	12 (14.3%)	7 (14.0%)	
Quintile 4	203 (21.9%)	168 (21.2%)	19 (22.6%)	16 (32.0%)	
Quintile 5	210 (22.6%)	177 (22.3%)	23 (27.4%)	10 (20.0%)	
Smokers (current)	104 (11.3%)	86 (10.9%)	14 (16.9%)	4 (8.0%)	.20
Physically active	660 (71.4%)	570 (72.2%)	58 (69.0%)	32 (64.0%)	.41
Medication (current)					
Antidepressants	65 (7.0%)	38 (4.8%)	13 (15.5%)*	14 (28.0%)*	<.001
SSRI	47 (5.1%)	27 (3.4%)	11 (13.1%)	9 (18.0%)	<.001
TCA	9 (1.0%)	7 (0.9%)	1 (1.2%)	1 (2.0%)	.72
SNRI	9 (1.0%)	4 (0.5%)	1 (1.2%)	4 (8.0%)	<.001
Bisphosphonates	15 (1.6%)	12 (1.5%)	1 (1.2%)	2 (4.0%)	.38
Corticosteroids	10 (1.1%)	9 (1.1%)	1 (1.2%)	0 (0.0%)	.75
Hormone therapy	3 (0.3%)	2 (0.3%)	0 (0.0%)	1 (2.0%)	.093
Calcium/Vitamin D	125 (13.5%)	100 (12.6%)	13 (15.5%)	12 (24.0%)*	.062

Abbreviations: BMD, bone mineral density; MDD, major depressive disorder; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI serotonin reuptake inhibitor; TCA, tricyclic antidepressant. <sup>a</sup>Between MDD status. \*P-value<0.05 compared to men with no MDD (from Pearson chi-square / Anova).

**Table 1.** Characteristics of the study population overall and according to MDD status. Values are given as median (interquartile range), mean (standard deviation) or n (%).

latter was calculated as grams of pure alcohol intake per day (g/day). Current smoking status (no/yes) was self-reported.

### Statistical analyses

Statistical analyses were performed using the SPSS statistical package 19.0 for Windows (SPSS Inc., Chicago, IL, USA). Differences between MDD status groups (no MDD history / single episode / recurrent episodes) were examined using ANOVA for continuous variables and Chi-squared tests (Fisher's Exact Test) for categorical variables.

Univariate and multiple linear regression techniques were used to determine the association between exposure (i.e. history of MDD episodes or use of antidepressants) and outcome (i.e. BMD at the forearm, lumbar spine, total hip or total body). Age, weight, height, smoking, activity level, calcium intake, alcohol intake, socio-economic status, current use of bisphosphonates, corticosteroids, gonadal hormones, calcium or vitamin D supplements were each explored as effect modifiers with MDD episodes and antidepressant use regressed on BMD

at each site and included in the final model if significant ( $p < 0.05$ ).

## Results

### Baseline characteristics

Of the 928 men included in the analyses, 794 (85.6%) had no lifetime history of MDD, 84 (9.1%) had a single MDD episode and 50 (5.4%) had recurrent episodes. Furthermore, 7.0% (65/928) men were currently using antidepressants; 5.1% (47/928) used SSRIs, 1.0% (9/928) TCAs and 1.0% (9/928) SNRIs. Characteristics of the study population are shown in Table 1. Differences were identified across the groups in regards to age, height, BMD (forearm, total hip and total body), nutritional calcium intake and use of antidepressant and calcium/vitamin D supplements; otherwise the groups were similar.

### Univariate and multivariable analyses

In the univariate models, men meeting criteria for a single MDD episode had higher forearm, total hip and total body

BMD/MDD status	Univariate models			Multivariable model 1			Multivariable model 2			Final model		
	B	95% CI	P value	B	95% CI	P value	B	95% CI	P value	B	95% CI	P value
Forearm												
(Constant)	0.418	0.413, 0.422	<.001	0.352	0.323, 0.380	<.001	0.360	0.331, 0.390	<.001	0.475	0.362, 0.587	<.001
Single MDD	<b>0.018</b>	<b>0.003, 0.032</b>	<b>.016</b>	0.009	-0.004, 0.022	.19	0.010	-0.003, 0.024	.15	0.011	-0.003, 0.024	.11
Recurrent MDD	-0.009	-0.027, 0.010	.36	<b>-0.018</b>	<b>-0.035, -0.001</b>	<b>.038</b>	<b>-0.019</b>	<b>-0.036, -0.001</b>	<b>.037</b>	<b>-0.020</b>	<b>-0.038, -0.002</b>	<b>.033</b>
Lumbar spine												
(Constant)	1.298	1.284, 1.311	<.001	0.907	0.812, 1.002	<.001	0.929	0.831, 1.026	<.001	0.608	0.241, 0.974	.001
Single MDD	-0.016	-0.062, 0.029	.48	-0.007	-0.051, 0.037	.75	-0.003	-0.047, 0.042	.91	0.005	-0.040, 0.049	.83
Recurrent MDD	-0.053	-0.110, 0.004	.067	-0.050	-0.106, 0.005	.073	-0.046	-0.103, 0.011	.11	-0.047	-0.106, 0.012	.12
Total hip												
(Constant)	1.062	1.051, 1.072	<.001	0.837	0.770, 0.904	<.001	0.865	0.797, 0.933	<.001	1.262	1.006, 1.517	<.001
Single MDD	<b>0.046</b>	<b>0.012, 0.080</b>	<b>.008</b>	0.029	-0.001, 0.060	.062	<b>0.034</b>	<b>0.003, 0.065</b>	<b>.030</b>	<b>0.034</b>	<b>0.003, 0.064</b>	<b>.030</b>
Recurrent MDD	-0.004	-0.047, 0.039	.85	-0.031	-0.070, 0.007	.11	-0.028	-0.068, 0.011	.16	-0.029	-0.069, 0.012	.17
Total body												
(Constant)	1.239	1.231, 1.247	<.001	0.985	0.940, 1.031	<.001	1.002	0.956, 1.048	<.001	0.945	0.769, 1.120	<.001
Single MDD	<b>0.027</b>	<b>0.002, 0.052</b>	<b>.037</b>	0.012	-0.009, 0.033	.27	0.014	-0.007, 0.035	.19	0.017	-0.004, 0.038	.12
Recurrent MDD	-0.009	-0.040, 0.023	.59	<b>-0.032</b>	<b>-0.059, -0.006</b>	<b>.017</b>	<b>-0.032</b>	<b>-0.059, -0.005</b>	<b>.020</b>	<b>-0.031</b>	<b>-0.059, -0.003</b>	<b>.033</b>

Abbreviations: BMD, bone mineral density; MDD, major depressive disorder. Notes: Multivariable model 1 is adjusted for age and weight. Multivariable model 2 is adjusted for age, weight and current use of antidepressant. Final model is adjusted for age, weight, height, nutritional calcium intake and current use of antidepressants, bisphosphonates and calcium or vitamin D supplements.

**Table 2.** Unadjusted and adjusted linear regression analyses between MDD status and forearm, spine, total body and total hip BMD (g/cm<sup>2</sup>).

BMD/factors	Univariate models			Multivariable model 1			Final model		
	B	95% CI	P value	B	95% CI	P value	B	95% CI	P value
Forearm									
(Constant)	0.419	0.415, 0.424	<.001	0.360	0.331, 0.389	<.001	0.475	0.364, 0.587	<.001
Use of AD	-0.009	-0.026, 0.007	.27	<b>-0.131</b>	<b>-0.224, -0.037</b>	<b>.006</b>	<b>-0.141</b>	<b>-0.233, -0.049</b>	<b>.003</b>
Weight	0.001	0.001, 0.002	<.001	0.001	0.001, 0.001	<.001	0.001	0.001, 0.002	<.001
AD*Weight	-	-	-	0.001	0.000, 0.003	.010	0.002	0.001, 0.003	.003
Lumbar spine									
(Constant)	1.296	1.282, 1.309	<.001	0.924	0.827, 1.021	<.001	0.608	0.241, 0.974	.001
Use of AD	-0.036	-0.086, 0.014	.16	<b>-0.326</b>	<b>-0.622, -0.029</b>	<b>.032</b>	<b>-0.333</b>	<b>-0.627, -0.039</b>	<b>.027</b>
Weight	0.003	0.002, 0.004	<.001	0.003	0.002, 0.004	<.001	0.002	0.001, 0.003	<.001
AD*Weight	-	-	-	0.003	0.000, 0.007	.062	0.004	0.000, 0.007	.043
Total hip									
(Constant)	1.068	1.058, 1.079	<.001	0.868	0.799, 0.936	<.001	1.262	1.006, 1.517	<.001
Use of AD	<b>-0.040</b>	<b>-0.077, -0.002</b>	<b>.039</b>	<b>-0.398</b>	<b>-0.603, -0.194</b>	<b>&lt;.001</b>	<b>-0.414</b>	<b>-0.615, -0.213</b>	<b>&lt;.001</b>
Weight	0.004	0.004, 0.005	<.001	0.004	0.003, 0.004	<.001	0.004	0.003, 0.005	<.001
AD*Weight	-	-	-	0.004	0.002, 0.007	.001	0.004	0.002, 0.007	<.001
Total body									
(Constant)	1.242	1.235, 1.250	<.001	1.001	0.955, 1.048	<.001	0.945	0.769, 1.120	<.001
Use of AD	-0.019	-0.047, 0.009	.18	<b>-0.229</b>	<b>-0.371, -0.087</b>	<b>.002</b>	<b>-0.241</b>	<b>-0.382, -0.101</b>	<b>.001</b>
Weight	0.004	0.004, 0.005	<.001	0.004	0.003, 0.004	<.001	0.004	0.003, 0.004	<.001
AD*Weight	-	-	-	0.002	0.001, 0.004	.004	0.003	0.001, 0.004	.001

Abbreviations: AD, antidepressants (current, no/yes); BMD, bone mineral density. Notes: Multivariable model 1 is adjusted for age and weight. Final model is adjusted for age, weight, height, nutritional calcium intake, MDD status, current use of bisphosphonates and calcium or vitamin D supplements.

**Table 3.** Unadjusted and adjusted linear regression analyses between use of antidepressant and forearm, spine, total body and total hip BMD (g/cm<sup>2</sup>).

BMD (B=0.018, B=0.046 and B=0.027, respectively) compared to men with no history of MDD (Table 2). There was a non-significant trend for men meeting criteria for recurrent MDD to have lower spine BMD (B=-0.053) compared to men with no MDD history.

After age- and weight-adjustments (multivariable model 1), recurrent MDD was significantly associated with lower forearm and total body BMD (B= -0.018 and B= -0.032, respectively) and tended to be associated with spine and total hip BMD (B= -0.050 and B= -0.031, respectively) (Table 2).

BMD site	Multivariable model 1			Final model		
	Non-users	Users	diff % <sup>a</sup>	Non-users	Users	diff % <sup>a</sup>
<b>Forearm</b>						
60 kg	0.360	0.289	-19.7	0.266	0.245	-7.9
70 kg	0.370	0.309	-16.5	0.276	0.275	-0.4
80 kg	0.380	0.329	-13.4	0.286	0.305	6.6
90 kg	0.390	0.349	-10.5	0.296	0.335	13.2
100 kg	0.400	0.369	-7.7	0.306	0.365	19.3
110 kg	0.410	0.389	-5.1	0.316	0.395	25.0
<b>Lumbar spine</b>						
60 kg	0.985	0.839	-14.8	1.103	1.010	-8.4
70 kg	1.015	0.899	-11.4	1.123	1.070	-4.7
80 kg	1.045	0.959	-8.2	1.143	1.130	-1.1
90 kg	1.075	1.019	-5.2	1.163	1.190	2.3
100 kg	1.105	1.079	-2.4	1.183	1.250	5.7
110 kg	1.135	1.139	0.4	1.203	1.310	8.9
<b>Total hip</b>						
60 kg	0.989	0.831	-16.0	0.948	0.774	-18.4
70 kg	1.029	0.911	-11.5	0.988	0.854	-13.6
80 kg	1.069	0.991	-7.3	1.028	0.934	-9.1
90 kg	1.109	1.071	-3.4	1.068	1.014	-5.1
100 kg	1.149	1.151	0.2	1.108	1.094	-1.3
110 kg	1.189	1.231	3.5	1.148	1.174	2.3
<b>Total body</b>						
60 kg	1.181	1.072	-9.2	1.120	1.059	-5.4
70 kg	1.221	1.132	-7.3	1.160	1.129	-2.7
80 kg	1.261	1.192	-5.5	1.200	1.199	-0.1
90 kg	1.301	1.252	-3.8	1.240	1.269	2.3
100 kg	1.341	1.312	-2.2	1.280	1.339	4.6
110 kg	1.381	1.372	-0.7	1.320	1.409	6.7

Abbreviations: BMD, bone mineral density. Notes: Multivariable model 1 is adjusted for age and weight. Final model is adjusted for age, weight, height, nutritional calcium intake, MDD status, current use of bisphosphonates and calcium or vitamin D supplements. \* from linear regression; <sup>a</sup> % difference when comparing the BMD of antidepressant users to non-users (calculated as follows  $BMD_{users} - BMD_{non-users} / BMD_{non-users} * 100\%$ ).

**Table 4.** Adjusted calculated\* results according to body weight for antidepressant users and non-users by BMD site (g/cm<sup>2</sup>).

Further adjustment for antidepressant use (multivariable model 2) is shown in Table 2. In the final model, recurrent MDD was associated with lower forearm and total body BMD (B= -0.020 and B= -0.031, respectively) (Table 2), which corresponds to 6.5% lower forearm and 2.5% lower total body BMD than men with no MDD history. Similarly, recurrent MDD tended to be associated with lower spine BMD (B= -0.047, corresponding -4.0%). A single MDD episode was associated with higher adjusted total hip BMD (B=0.034, corresponding +3.4%), but no association was evident for the other sites (Table 2). These models include both antidepressant use and the interaction term between weight and antidepressant use. Still, MDD was independently associated with BMD. There was no significant interaction between antidepressant use and MDD on BMD.

In univariate models, antidepressant users had lower total hip BMD (B= -0.040) than non-users (Table 3). Weight was an effect modifier in the relationship between antidepressant use and BMD (Table 3). In the final models, lower BMD was

associated with antidepressant use in those with lower body weight (<75-110 kg depending on bone site) (Table 4).

## Discussion

Recurrent MDD was associated with lower forearm and total body BMD in the present study in men. In contrast, single MDD was associated with higher BMD at the total hip. Furthermore, use of antidepressants was associated with lower BMD at all measured sites (i.e. forearm, lumbar spine, total hip and total body) among men with low body weight only. These associations were independent of age, anthropometry, socio-economic status, medication and lifestyle factors (i.e. calcium intake, alcohol use, smoking, physical activity).

Our study showed a 6.5% decrease in forearm BMD and 2.5% decrease in total body BMD in men with recurrent MDD episodes. Literature shows that a change of 3-6% is required for clinical significance<sup>26</sup>. The present study partly supports



the previous results using data from the GOS showing lower adjusted femoral neck and spine BMD in men with self-reported depression compared to men with no reported history<sup>27</sup>. However, in the current study, we were able to determine the number of episodes of clinically diagnosed MDD and investigate whether this affected the relationship of interest. In general, both clinically diagnosed depression and depressive symptoms have been associated with low BMD among men<sup>13-15,28-30</sup>. Associations have been seen using total hip<sup>13,14</sup>, spine<sup>30</sup> and forearm<sup>15</sup> sites. In contrast to the present study, Wong et al<sup>13</sup> found no association with depression using total body BMD, but akin to the present study, no association with spine BMD was seen either. Charles et al<sup>31</sup> also found no cross-sectional association between BMD and depressive symptoms in men. For most of these studies, the findings were independent of antidepressant use<sup>13,15,28-30</sup> or specifically SSRIs<sup>31</sup>, with the exception of one study of young adults where antidepressant users was not excluded nor antidepressant use statistically controlled for<sup>14</sup>.

In most of the studies among females or both genders pooled, SSRIs have appeared to be negatively associated with BMD<sup>9,19,30,32</sup> but not in all<sup>33</sup>. In contrast, TCAs have been shown to have no effect<sup>32</sup> or even a positive effect on bone<sup>9</sup>. Among men, SSRIs have also been shown to negatively affect bone at different sites in both male adolescents<sup>34</sup> and in older men<sup>21,35</sup>. Similarly, it has been shown that antidepressants have a negative effect on bone in men with low weight<sup>36</sup>. Others have shown no association between any antidepressants<sup>30</sup> and TCA<sup>21,35</sup> use and bone. In our study, we pooled antidepressant use due to power constraints and recognize that if different antidepressant subgroups differentially affect bone, their effect is likely to be diluted. However, in the present study majority (72%) was taking SSRIs, thus, we can assume that possible contradictory results from use of other antidepressants are likely to be small.

The results of the present study support the hypothesis that recurrent episodes of MDD and antidepressants independently have a negative effect on BMD, although the effect of antidepressants was dependent on body weight. It is not clear why single episode MDD in men was positively associated with total hip BMD. It is possibly a spurious finding. However, we do not know the duration or timing of the single episode of depression in these men. It is possible that they may have already had successful treatment for depression in the past without recurrence or the episode may have been short in duration and of mild severity. In addition, the group with no MDD episode may also include participants with sub-threshold depression or prolonged stress without diagnosis and treatment<sup>37</sup>. Moreover, a single-episode of depression may be qualitatively different, being more psychological and related to an adjustment reaction to stressors, as opposed to recurrent depression, which is likely to be more biological and activate neuroprogressive pathways such as inflammation, oxidative stress and apoptosis, which can similarly predispose individuals to osteoporosis<sup>38-40</sup>.

Depression causes chronic stress, which stimulates cortisol and catecholamine (e.g. noradrenaline) secretion resulting in

bone loss<sup>7,40</sup>. Increased levels of bone resorption markers<sup>41,42</sup> and proinflammatory cytokines<sup>43,44</sup> have also been found in association with depression. Studies have shown that bone and immune cells are functionally interconnected<sup>45</sup>. They are derived from same progenitors, share a common microenvironment and are influenced by similar mediators<sup>45</sup>. Activated T cells are the most powerful cells during inflammation which contribute to enhanced osteoclastogenesis both by increasing the production of bone resorbing cytokines and the numbers of osteoclast precursors<sup>45</sup>. Activation of inflammatory markers occurs also in milder depression and in the presence of stress, especially if the effect is prolonged. Low subjective well-being indicated as life dissatisfaction has been longitudinally associated with both lower BMD and greater bone loss in postmenopausal women - independent of severe depression and antidepressant treatment<sup>16</sup>. Among young adults, depressive symptoms in combination with high work-related stress have been associated with lower BMD<sup>17</sup>. Previously, utilizing the present male study population depressive symptoms have been linked with reduced BMD at the lumbar spine and femoral neck<sup>27</sup>. Oxidative stress is another possible mechanism of action. It can impact on bone directly by both promoting osteoclast formation and activity and inhibiting osteoblast differentiation and activity<sup>46</sup>. Finally, various modifiable lifestyle factors linked with depression have physiologic consequences, which in turn are likely to affect bone metabolism<sup>22</sup>.

In the present study we found that body weight acted as an effect modifier in the association between antidepressant use and BMD. A similar finding was seen in our previous study on the effect of antidepressant use on heel quantitative ultrasound measures in men<sup>36</sup>. The effect of body weight on bone might also be explained by the amount of fat tissue. Adipocytes secrete leptin, which is involved in stimulating food intake and energy expenditure<sup>47</sup>. High leptin concentration has been found to be beneficial to bone mass<sup>48,49</sup>. In addition to indirect effects via the central nervous system<sup>48</sup>, leptin receptors have been found to be expressed in osteoblasts where leptin seems to directly increase proliferation and differentiation<sup>50,51</sup>. However, also differing effects of body fat on bone have been shown. Subcutaneous fat, the main source of leptin and adiponectin, has been shown to be beneficial to bone, whereas visceral fat has been shown to negatively affect bone due to its ability to produce more pro-inflammatory cytokines<sup>52,53</sup>. Serotonin receptors and transporters have also been found to be expressed in adipocytes<sup>54,55</sup>. However, the effect of antidepressants influencing bone metabolism via adipocytes is unclear and both increased<sup>56,57</sup> and decreased<sup>58</sup> or non-changed<sup>57</sup> leptin levels during antidepressant therapy have been seen. Without taking into account the possible effects of antidepressant medication on adipocytes, participants with higher body weight are likely to have more fat tissue with higher concentrations of adipocytes and leptin, which might overshadow the negative effects of antidepressant use on bone. Furthermore, the positive association with BMD in participants with higher weight might also reflect the adaptive effect of load bearing on bone turnover. Finally, there may be other unclear confounding

mechanisms operative between bone, body mass and use of antidepressants. In our cross-sectional study, we did not observe a weight\*MDD interaction on BMD. However, we did not investigate weight change over time.

Strengths of this study include a large population-based sample of men spanning the full adult age range and ability to adjust for several confounding factors. Also, the use of structured diagnostic interviews to determine depression, discriminating between single and recurrent episodes and investigating several BMD sites are further strengths. A limitation is the cross-sectional, observational study design, which does not allow the investigation of causality. We classified participants as current users only if they reported using medication at the time of assessment, which may lead to ignoring users who stopped the use recently or use the medication irregularly. Fracture history had not been considered in the statistical models and we did not account for weight change as a confounding factor in the present study. Furthermore, data on the duration and severity of MDD episodes were not available.

## Conclusions

In conclusion, recurrent MDD was evidenced to have a negative impact on bone. Use of antidepressants was also found to be negatively associated with BMD among men with lower body weight. We found that MDD and antidepressant use were independently associated with BMD; however, separation of these two issues is difficult. In all, prevention of depression, its early detection and appropriate medical care are important issues in the prevention and care of osteoporosis in men. Lastly, these data raise the issue of screening for BMD in at-risk populations.

## Acknowledgements

PHR, JAP, ALS and LJW designed the study. PHR conducted statistical analysis, data interpretation and the writing of the manuscript. JAP, ALS and LJW took part in the statistical analysis. JAP was responsible for the original GOS study design and for the data. JAP, MB, ALS, HK-H, RJH, JMH and LJW contributed to data interpretation and critically revised the manuscript. All authors read and approved the final version of the manuscript.

The GOS is supported by grants from the National Health and Medical Research Council (NHMRC 299831, 628582 and 1009367). PHR received a travel grant and research support from the Saastamoinen Foundation, research support from National Doctoral Programme of Musculoskeletal Disorders and Biomaterials, Finnish Concordia Fund, North Savo Regional Fund of Finnish Cultural Foundation and an EVO grant from Lapland Hospital District. MB is supported by a NHMRC Senior Principal Research Fellowship (1059660). HK-H and RJH received an EVO grant from Lapland Hospital District. JMH is supported by a NHMRC. LJW is supported by a NHMRC Career Development Fellowship (1064272).

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