Manchester Metropolitan University

e-space

Manchester Metropolitan University's Research Repository

Please cite the Published Version

Bradburn, S, McPhee, JS, Bagley, L, Sipila, S, Stenroth, L, Narici, MV, Pääsuke, M, Gapeyeva, H, Osborne, G, Sassano, L, Meskers, CG, Maier, AB, Hogrel, JY, Barnouin, Y, Butler-Browne, G and Murgatroyd, C (2016) Association between osteocalcin and cognitive performance in healthy older adults. Age and ageing, 45 (6). pp. 844-849. ISSN 0002-0729

DOI: https://doi.org/10.1093/ageing/afw137

Publisher: Oxford University Press on behalf of the British Geriatrics Society

Version: Published Version

Downloaded from: https://e-space.mmu.ac.uk/617045/

Usage rights: CC BY-NC Creative Commons: Attribution-Noncommercial 4.0

Additional Information: This is an Open Access article published in Age and Ageing published by Oxford University Press on behalf of the British Geriatrics Society, copyright The Author(s).

Enquiries:
If you have questions about this document, contact openresearch@mmu.ac.uk. Please include the URL of the record in e-space. If you believe that your, or a third party's rights have been compromised through this document please see our Take Down policy (available from https://www.mmu.ac.uk/library/using-the-library/policies-and-guidelines)

Age and Ageing Advance Access published August 11, 2016

Age and Ageing 2016; **0:** 1–6
doi: 10.1093/ageing/afw137

© The Author 2016. Published by Oxford University Press on behalf of the British Geriatrics Society. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Association between osteocalcin and cognitive performance in healthy older adults

Steven Bradburn[1], Jamie S McPhee[1], Liam Bagley[1], Sarianna Sipila[2], Lauri Stenroth[2], Marco Vincenzo Narici[3], Mati Pääsuke[4], Helena Gapeyeva[4], Gabrielle Osborne[5], Lorraine Sassano[5], Carel G. M. Meskers[6], Andrea B. Maier[7,8], Jean-Yves Hogrel[9], Yoann Barnouin[9], Gillian Butler-Browne[9], Chris Murgatroyd[1]

[1]Manchester Metropolitan University, School of Healthcare Science, Manchester, UK
[2]University of Jyväskylä, Gerontology Research Centre, Health Sciences, 40630 Jyväskylä, Finland
[3]University of Nottingham, Faculty of Medicine and Health Sciences, Derby, UK
[4]University of Tartu, Institute of Exercise Biology and Physiotherapy, Tartu, Estonia
[5]Unilever Discover, Colworth Park, Shambrook, Bedford, UK
[6]VU University Medical Center, Rehabilitation Medicine, Amsterdam, The Netherlands
[7]VU University Medical Center, Faculty of Human Movement Sciences, Amsterdam, The Netherlands
[8]Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia
[9]Institut de Myologie, 75634 Paris Cedex 13, France

Address correspondence to: C. Murgatroyd. Email: c.murgatroyd@mmu.ac.uk

Abstract

Introduction: cognitive deterioration and reductions of bone health coincide with increasing age. We examine the relationship between bone composition and plasma markers of bone remodelling with measures of cognitive performance in healthy adults.
Methods: this cross-sectional study included 225 old (52% women, mean age: 74.4 ± 3.3 years) and 134 young (52% women, mean age: 23.4 ± 2.7 years) adult participants from the MyoAge project. Whole body bone mineral density was measured by dual-energy X-ray absorptiometry. Blood analyses included a panel of bone-related peptides (dickkopf-1, osteoprotegerin, osteocalcin (OC), osteopontin, sclerostin, parathyroid hormone and fibroblast growth factor 23), as well as serum calcium and 25-hydroxy vitamin D assays. A selection of cognitive domains (working memory capacity, episodic memory, executive functioning and global cognition) was assessed with a standardised neuropsychological test battery.
Results: adjusting for covariates and multiple testing revealed that plasma OC levels were positively associated with measures of executive functioning ($\beta = 0.444$, $P < 0.001$) and global cognition ($\beta = 0.381$, $P = 0.001$) in the older women.
Discussion: these correlative results demonstrate a positive association between OC, a factor known to regulate bone remodelling, with cognitive performance in older non-demented women. Further work should address possible mechanistic interpretations in humans.

Keywords: *older people, cognitive decline, ageing, osteocalcin*

Introduction

Cognitive deterioration, including the consequence of neurodegenerative diseases, and reductions of bone health are increasingly evident in older age. Studies have shown relationships between measures of overall bone mineral density (BMD) and the risks of Alzheimer's disease and cognitive decline especially in older women [1, 2]. This raises the possibility that factors related to bone regulation and function may influence cognitive performance.

Bone is a metabolically active tissue and is constantly being remodelled throughout life mainly through the activity of opposing specialised osteoclast and osteoblast cells via secretory peptides and metabolites [3]. For example, differentiated osteoblasts modify and deposit the non-collagenous protein osteocalcin (OC) which, together with minerals,

Downloaded from http://ageing.oxfordjournals.org/ by guest on August 15, 2016

establishes the bone matrix. Conversely, the activation of Dickkopf-1 (DKK1) can instigate osteoclast activation resulting in bone resorption [4].

Since many of these bone-related peptides are secreted into the circulation, there has been growing interest into their influences on the central nervous system [5]. For example, Wnt signalling transduction regulates bone formation, which is prevented through DKK1. This action has been associated with neurodegeneration in Alzheimer's disease [6], whereas the loss of DKK1 has been shown to enhance neurogenesis in mice [7]. Remarkably, bone-derived OC has been shown to cross the blood–brain barrier and influence brain development, cognition and behaviour in mice [8]. A recent human study found a link between lower serum OC levels with microstructural changes and lower cognitive performance, which suggests that these potential neuromodulator mechanisms may also be present in humans [9]. Collectively, these findings suggest that there may be a convergence in mechanisms underlying bone with neurodegeneration and that bone may possess endocrine properties which aid in maintaining cognitive wellbeing.

The majority of observational studies have focussed on BMD measures to characterise bone health [1, 10] and questionnaires for cognitive analysis [10], which provide little mechanistic insight and, in the case of questionnaires, lack sensitivity. Studying biochemical markers of bone remodelling may be a more sensitive analytical approach than radiological BMD measurements to detect subtle preclinical alterations of bone metabolism. For example, Kahl *et al.* [11], investigated various types of depression in women and found elevations of serum markers of bone turnover associated with a relatively mild form of depression, whereas only those with a severe depressed phenotype had reductions in BMD.

Importantly, previous studies have focused on those with clinically-diagnosed neurodegeneration or osteoporosis in the elderly with very few investigating cognitively intact and physiologically healthy subjects. Additionally, since bone remodelling is influenced by ageing and sex, it is also topical to investigate these independently.

This current study evaluated the relationship between BMD and peptides associated with bone remodelling in healthy young and older adults with measures of cognitive performance; specifically working memory capacity, episodic memory, executive functioning and overall performance.

Methods

Participants

MyoAge is a cross-sectional European multi-centre study and the measurements completed in this particular study were collected from centers located in Manchester, UK; Paris, France; Leiden, The Netherlands; Tartu, Estonia and Jyväskylä, Finland. The cohort consisted of young (range: 18–30 years) and relatively healthy older (range: 69–81 years) participants. Those who completed all of the cognitive assessments and had matching plasma samples available (young men, $n = 64$; young women, $n = 70$; old men, $n = 109$; old women, $n = 116$) were used in this study. A detailed description of the exclusion criteria, designed to ensure the selection of healthy participants and to minimise the confounding effect of comorbidity on sarcopenia, has been reported previously [12]. All measurements were performed according to unified standard operating procedures during visits to the local study laboratories. Education levels and lifestyle factors (smoking status, alcohol intake and supplement use) were self-reported. Excessive alcohol was defined as men >21 units/week and women >14 units/week. Supplement usage includes those who reported the use of bisphosphonates, calcium or vitamin D. The local medical ethical committees of the respective institutions approved the study and written informed consent was obtained from all participants.

Dual-energy X-ray absorptiometry

Whole body scans were performed using dual-energy X-ray absorptiometry (DXA) (The Netherlands: Hologic QDR 4500, version 12.4, Hologic Inc., Bedford, MA, USA; Finland: Lunar Prodigy, version enCore 9.30; Estonia: Lunar Prodigy Advanced, version enCore 10.51.006; France: Lunar Prodigy, version enCore 12.30; United Kingdom: Lunar Prodigy Advance, version enCore 10.50.086) to measure whole body BMD. During the measurements, a light cotton shirt was worn by the participants to reduce effects of clothing absorption.

Cognitive assessments

Participants completed the Geriatric Depression Scale (GDS) [13] and the Mini Mental State Examination (MMSE) [14] questionnaires prior to testing to determine their depressive mood and cognitive dysfunction, respectively. Only those who achieved less than 5 points on the GDS and greater than 23 points on the MMSE were included.

Cognitive domains were assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) system (Cambridge Cognition Ltd., UK) in a quiet room free from distractions and overseen by trained experimental staff. The CANTAB system contains standardised assessments that are routinely used in psychological assessment [15]. Each participant performed three tests; Spatial Span, One Touch Stockings of Cambridge and Paired Associate Learning to determine their working memory capacity [16], executive functioning [17] and episodic memory [18] performance, respectively. Each test is discussed in detail in Appendix 1 in the supplementary data on the journal website (http://www.ageing.oxfordjournals.org/).

To standardise performances, each cognitive score was transformed into a *Z*-score based on the young average. A positive score indicates a higher than average performance, relative to the young. The scale in episodic memory score was inverted so a positive score will indicate a better score and vice versa. Additionally, a global cognition score was determined as the sum of the three individual outcomes to represent a combined performance as utilised previously [19].

Downloaded from http://ageing.oxfordjournals.org/ by guest on August 15, 2016

Multiplex immunoassays

Peptides frequently associated with bone metabolism were simultaneously quantified from fasted plasma samples via commercial multiplex immunoassays (MILLIPLEX MAP Human Bone Magnetic Bead Panel, Millipore). The magnetic bead panel was able to simultaneously quantify, Dickkopf-1 (DKK1), osteoprotegerin (OPG), osteocalcin (OC), osteopontin (OPN), sclerostin (SOST), parathyroid hormone (PTH) in a 96-well format. The procedure included an overnight incubation in order to improve assay sensitivity. The sensitivity of each analyte was as follows: 1.4 (DKK1), 1.9 (OPG), 68.5 (OC), 37.7 (OPN), 31.1 (SOST), 1.8 (PTH) and 9.2 (FGF-23) pg/ml. A magnetic plate washer was utilised during the plate washing stages. The plate was processed on a Luminex 200 instrument. Protein concentrations were calculated and analysed with the xPONENT software (Luminex, v.3.1.871).

Serum calcium and 25-hydroxy vitamin D

Serum samples were tested for calcium using a calcium CP reagent on a Horiba ABX Pentra 400 Clinical Chemistry analyser. Serum 25-hydroxy vitamin D (25(OH)D) was determined using an enzyme linked immunosorbent assay (Immunodiagnostic Systems Ltd) according to the manufacturer's instructions. Analysis was conducted at Unilever Discover, Colworth Science Park.

Statistics

All statistical analysis was performed using IBM SPSS Statistics software (v.20). Results were deemed significant at the $P < 0.05$ level, unless otherwise stated. Logarithmic transformation was performed on plasma bone marker data to achieve normality. Continuous data were tested using two-way ANOVA to determine possible age (young or old), sex (men or women) effects and age×sex interactions. Pearson chi-squared tests were performed to determine distribution differences between nominal data. Mann–Whitney *U* tests were performed to determine differences in cognitive performance between age groups.

To determine plasma bone marker relationship with the measures of cognitive functioning, Spearman correlation analysis was initially performed followed by multivariate regression. Factors identified as being significantly associated with cognitive function were investigated further to account for confounders through separate multivariate regression models. Scores of cognitive functioning were set as the dependent variable and the bone markers, as well as potential confounders, were set as the independent variables. To identify confounders, correlations between cognitive scores and physiological measures (height, body mass, body mass index (BMI), BMD, serum calcium and 25(OH)D) were used. A confounder was identified if a relationship existed at the $P < 0.1$ level, as used previously [20]. Following this analysis, BMD, BMI, height and 25(OH)D were all selected as possible confounders to be included in first regression model, along with age, education level and participant location. A second model was also used, which contained Model 1 as well as lifestyle factors (current smoking status, excessive alcohol use and supplement use). The residuals of both regression models were normally distributed as assessed by the Durbin-Watson statistic. Due to multiple testing (four tests), a Bonferroni corrected level of significance of $P < 0.0125$ (0.05/4) was applied for this analysis.

Results

Participant characteristics are presented in Table 1.

As expected, the younger participants performed significantly better on each cognitive test compared with older adults (Figure 1). Men had a better working memory capacity in the older group when compared with women (men median: −1.97; IQR: −1.97 to −1.14; women median: −1.97; IQR: −1.97 to −1.97; $P = 0.017$). No significant differences in

Table 1. Participant characteristics, stratified by physiological, lifestyle and education parameters

Variables	Young		Old		Effects (*P*-value)		
	Men	Women	Men	Women	Age	Sex	Age × Sex
Age, years	23.74 (2.67)	23.05 (2.77)	74.75 (3.35)	74.16 (3.34)	<0.001*	0.063	0.878
Height, m	1.81 (0.06)	1.68 (0.06)	1.74 (0.06)	1.61 (0.07)	<0.001*	<0.001*	0.791
Body mass, kg	75.41 (10.30)	62.90 (9.04)	78.26 (11.10)	65.92 (10.10)	0.009*	<0.001*	0.940
BMI, kg/m^2	23.03 (2.66)	22.27 (2.85)	25.71 (2.96)	25.37 (3.63)	<0.001*	0.103	0.540
BMD, g/cm^2	1.26 (0.10)	1.15 (0.07)	1.19 (0.11)	1.04 (0.10)	<0.001*	<0.001*	0.074
Current smoker, *n* (%)	6 (9.4)	8 (11.4)	7 (6.4)	4 (3.4)	0.045*	0.693	0.173
Excessive alcohol use, *n* (%)	10 (15.6)	5 (7.1)	12 (11)	7 (6)	0.389	0.043*	0.160
Supplement intake, *n* (%)	4 (6.3)	1 (1.4)	14 (12.8)	36 (31)	<0.001*	0.013*	<0.001*
Education, *n* (%)[a]							
Basic school	0 (0)	0 (0)	13 (15.3)	17 (17.9)	<0.001*	0.083	<0.001*
High school	9 (16.4)	5 (8.6)	22 (25.9)	45 (47.4)			
University	46 (83.6)	53 (91.4)	50 (58.8)	33 (34.7)			
MMSE score, median (IQR)	30 (29–30)	30 (29–30)	29 (28–30)	29 (28–30)	<0.001*	0.594	0.508
GDS score, median (IQR)	0 (0–1)	0 (0–1)	1 (0–2)	1 (0–2)	0.002*	0.544	0.356

BMI, body mass index; BMD, bone mineral density; MMSE, Mini Mental State Examination; IQR, interquartile range; GDS, Geriatric Depression Scale. Data are shown as mean (standard deviation), unless otherwise stated. * indicates a significant ($P < 0.05$) effect or interaction.

[a]Data available in: young men $n = 55$; young women $n = 58$; old men $n = 85$; old women $n = 95$.

Downloaded from http://ageing.oxfordjournals.org/ by guest on August 15, 2016

episodic memory, executive functioning and global cognition were seen between sexes in either young or old groups.

Blood concentrations of the bone-related markers, as well as serum calcium and vitamin D, significantly differed by both age and sex groups. Refer to Appendix 2 in the supplementary data on the journal website (http://www.ageing.oxfordjournals.org/) for the full analysis.

There were no significant associations observed between whole body BMD with episodic memory, working memory, executive functioning or global cognition in young women, young men, old women or old men (data not shown). Furthermore, investigations into serum 25(OH)D and calcium were not significantly associated with any of the measures of cognitive functioning (data not shown).

Initial exploratory analysis between the four measures of cognitive scores and seven plasma markers revealed some sex- and age-specific associations (Table 2). There was no relationship found in the men. There was a negative association between overall cognitive scores and DKK1 in the young women. The old women had a positive association between OC and working memory capacity, executive functioning and global cognition scores.

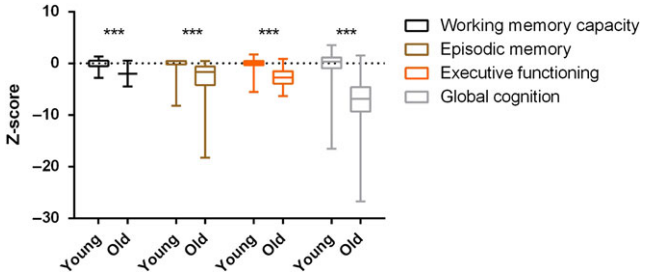

Figure 1. Cognitive performance in the two age groups. Data are shown as median, interquartile range and minimum and maximum. *Z* scores are relative to the young group's average value for each cognitive output. ***$P < 0.001$.

Those significant relationships were analysed further to account for potentially confounding effects of other variables. After adjusting for participant age, country, education level the confounding variables previously highlighted in the preliminary analysis (Model 1) the relationship between DKK1 and global cognition in the young women was no longer significant (Table 3). Despite the association of OC with working memory capacity in the old women, this failed to reach the Bonferroni corrected threshold ($P > 0.0125$). After Model 1 adjustments, significance remained for OC with executive functioning and global cognition in old women even after accounting for multiple comparisons (Table 3). Independently, OC was a significant predictor of executive functioning ($F_{(1,114)} = 5.668$; $P = 0.019$; $R^2 = 0.047$) and global cognition ($F_{(1,114)} = 4.164$; $P = 0.044$; $R^2 = 0.035$) in older women.

A second model (Model 2) was also used, which included the variables in Model 1 as well as supplement intake, current smoking status and excessive alcohol use, which have previously been linked to cognitive decline in the elderly [19]. The relationships between OC with executive functioning and global cognition in old women remained after the adjustment with this model (Table 3).

Discussion

In the present investigation, we identified a relationship between OC and multiple measures of cognitive performance in old women.

Table 2. Correlation between cogntive measures and plasma bone markers

Variable	DKK1	OPG	OC	OPN	SOST	PTH	FGF-23[a]
Young men							
Working memory capacity	−0.069	−0.139	0.115	−0.127	0.061	0.027	−0.063
Episodic memory	0.065	0.237	0.078	0.050	0.078	0.181	−0.118
Executive functioning	−0.026	−0.012	−0.018	−0.068	−0.092	0.069	−0.011
Global cognition	−0.034	−0.063	0.042	−0.144	0.002	0.063	−0.077
Young women							
Working memory capacity	−0.208	0.217	−0.173	0.059	−0.149	0.188	0.168
Episodic memory	−0.226	−0.121	0.068	−0.234	0.080	−0.026	0.234
Executive functioning	−0.092	−0.124	0.090	−0.036	−0.057	0.076	−0.040
Global cognition	−0.287*	0.049	−0.069	−0.067	−0.144	0.163	0.095
Old men							
Working memory capacity	−0.094	−0.155	−0.118	0.037	−0.115	0.015	0.109
Episodic memory	−0.041	−0.035	−0.102	−0.022	−0.040	0.071	0.039
Executive functioning	−0.017	0.184	0.050	0.050	0.046	0.000	−0.105
Global cognition	−0.062	0.016	−0.092	−0.023	−0.037	0.037	−0.044
Old women							
Working memory capacity	0.085	0.053	0.256**	0.178	0.117	0.150	−0.145
Episodic memory	−0.101	−0.150	0.147	0.114	−0.030	0.008	−0.021
Executive functioning	−0.127	−0.077	0.252**	0.111	−0.041	−0.002	0.097
Global cognition	−0.107	−0.092	0.245**	0.156	−0.004	0.025	0.031

DKK1, Dickkopf-1; OPG, osteoprotegerin; OC, osteocalcin; OPN, osteopontin; SOST, sclerostin; PTH, parathyroid hormone. Data are shown as Spearman correlation coefficient (*rho*). *$P < 0.05$. **$P < 0.01$.

[a]Some samples were below the lower limit of detection for FGF-23. Data available in: young men, $n = 46$; young women, $n = 58$; old men, $n = 78$; old women, $n = 87$.

Downloaded from http://ageing.oxfordjournals.org/ by guest on August 15, 2016

Table 3. Multivariate regression analysis of bone markers with cognitive functioning

Relationships	Model 1		Model 2	
	β	*P*-value	*β*	*P*-value
Young women				
Global cognition and DKK1	−0.301	0.079	−0.243	0.158
Old women				
Working memory capacity and OC	0.291	0.014	0.274	0.018
Executive functioning and OC	0.433	<0.001*	0.444	<0.001*
Global cognition and OC	0.369	0.001*	0.381	0.001*

β, standardised coefficient; BMI, body mass index; DKK1, Dickkopf-1; OC, osteocalcin. Model 1 included adjustments for age, participant country, education level and those factors which were discovered in the preliminary analysis (whole body BMD, BMI, height, 25(OH)D). Model 2 included Model 1 and lifestyle factors (current smoking status, excessive alcohol use and supplement use).
*Correlation remained significant after accounting for multiple testing via the Bonferroni correction method ($P < 0.0125$).

Comparing cognitive performances between ages indicated that the old had lower working memory capacity, executive functioning capability and episodic memory compared with the young adults. Reductions of most cognitive domains have been noted including memory (episodic, working and verbal), spatial visualisation, processing speed and reasoning [21]. The cause of this phenomenon is yet to be fully elucidated, however, a multifactorial origin is likely to explain this age-related cognitive decline. Additionally, the finding of men having a higher working memory capacity than women is consistent with previous reports [21], which suggests that sex is a determining factor in certain cognitive performances.

When correlating BMD with cognition in the young and older adults we found no associations. Previous structural analysis of bone health with neuropsychological functioning has suggested that lower BMD is associated with lower cognitive performance, particularly in post-menopausal women [2, 10]. Additionally, incidence of Alzheimer's disease is believed to be higher in those with low BMD [1]. These previous studies that associated clinically-diagnosed poor cognition with low BMD contrast with the present findings in healthy older people and it is possible that the association only becomes evident at the later stages of the physiological declines. Analysis of vitamin D and calcium serum levels with relation to cognitive scores suggested no association in the older adults. Despite vitamin D levels being marginally reduced in the older adults reported here, they were still within the optimal reference range (25–80 ng/ml) [22], which may explain the lack of associations in our elderly groups.

Multiple cognitive measures were positively associated with plasma OC levels in older women even after adjusting for confounders in multivariate regression analysis. OC, secreted by osteoblasts, is often used as a marker of bone formation [23] and has been shown to possess endocrine properties such as glucose metabolism [24]. Interestingly, Oury *et al.* [8] demonstrated that bone-derived OC can passively cross the blood–brain barrier, as well as the placenta during pregnancy, to influence neurons in various brain regions including the hippocampus. Specifically, these investigators noted that OC enhanced neurotransmitter synthesis, neurogenesis and measures of spatial learning and memory in mice [8].

From a human clinical perspective, mutations in the *RUNX2* gene, the main regulator of *OC* [25], are known to cause Cleidocranial dysplasia that often presents with cognitive impairments [26]. Furthermore, a recent study on obese and control human subjects found that lower OC was associated with higher BMI and lower cognitive performance together with brain microstructural changes [9]. The authors calculated that serum OC independently explained 10% of the variation in cognitive performance [9]. In this study, we found that plasma OC solely predicted global cognition and executive functioning by 3.5 and 4.7%, respectively. These relatively small effect sizes imply that OC is not the sole mediator in cognitive functioning, which is to be expected considering the complex multifactorial nature of cognitive functioning. Nevertheless, the aforementioned mechanisms linking OC with neuro-modulatory functions in mice [8] and the correlations between numerous cognitive measures in humans, as presented here and elsewhere [9], warrant the need to explore this bone-related peptide further to establish a causal relationship with neuromodulation.

The present study has a number of strengths, particularly with respect to the younger and older cohorts carefully selected to ensure they were healthier than average for their age and they undertook detailed cognitive assessments. The study, however, has several limitations. The cross-sectional design limits a definitive conclusion regarding a cause-and-effect relationship between the plasma markers and cognitive decline, instead we found a correlation rather than causation. We also did not account for variations between the older women in their menstrual status, although they were all post-menopausal, and hormonal influences (such as oestrogen levels) in women as well as thyroid function. These factors may contribute to the lack of associations in males in our analysis; however, further work is needed to investigate this potential sexual dimorphic pattern.

Collectively, the fact that we found no associations between whole body BMD and cognition in our population but, instead, relationships with osteocalcin suggest that the alterations in bone remodelling factors might precede changes in BMD with relation to cognition. Further longitudinal studies investigating bone remodelling proteins, particularly OC, as well as BMD with cognitive performance in older women are needed to elucidate the proposed relationship between bone health and neuromodulation.

Keypoints

- We find no associations between whole body bone mineral density and cognition in a relatively healthy elderly population.
- Plasma levels of osteocalcin associate with measures of executive functioning and cognition in older women.
- Plasma levels of bone remodelling peptides associate with measures of executive functioning and cognition in older women.

Downloaded from http://ageing.oxfordjournals.org/ by guest on August 15, 2016

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Acknowledgement

The authors wish to thank all of the participants and staff for their involvement throughout the MyoAge project.

Conflicts of interest

None declared.

Funding

The MyoAge project was supported by a research grant from the European Union FP7 (223576).

Abbreviations

Dickkopf-1 (DKK1); Osteoprotegerin (OPG); Osteocalcin (OC); Osteopontin (OPN); Sclerostin (SOST); Parathyroid hormone (PTH); 25-Hydroxy vitamin D (25(OH)D); Bone mineral density (BMD).

References

1. Zhou R, Deng J, Zhang M, Zhou H-D, Wang Y-J. Association between bone mineral density and the risk of Alzheimer's disease. J Alzheimers Dis 2011; 24: 101–8.
2. Sohrabi HR, Bates KA, Weinborn M *et al.* Bone mineral density, adiposity, and cognitive functions. Front Aging Neurosci 2015; 7: 16.
3. Raggatt LJ, Partridge NC. Cellular and molecular mechanisms of bone remodeling. J Biol Chem 2010; 285: 25103–8.
4. Pinzone JJ, Hall BM, Thudi NK *et al.* The role of Dickkopf-1 in bone development, homeostasis, and disease. Blood 2009; 113: 517–25.
5. Chamouni A, Schreiweis C, Oury F. Bone, brain & beyond. Rev Endocr Metab Disord 2015; 16: 99–113.
6. Caricasole A, Copani A, Caraci F *et al.* Induction of Dickkopf-1, a negative modulator of the Wnt pathway, is associated with neuronal degeneration in Alzheimer's brain. J Neurosci 2004; 24: 6021–7.
7. Seib DRM, Corsini NS, Ellwanger K *et al.* Loss of Dickkopf-1 restores neurogenesis in old age and counteracts cognitive decline. Cell Stem Cell 2013; 12: 204–14.
8. Oury F, Khrimian L, Denny CA *et al.* Maternal and offspring pools of osteocalcin influence brain development and functions. Cell 2013; 155: 228–241.
9. Puig J, Blasco G, Daunis-I-Estadella J *et al.* Lower serum osteocalcin concentrations are associated with brain microstructural changes and worse cognitive performance. Clin Endocrinol (Oxf) 2016; 84: 756–63.
10. Lee D-Y, Na DL, Seo SW *et al.* Association between cognitive impairment and bone mineral density in postmenopausal women. Menopause 2012; 19: 636–41.
11. Kahl KG, Rudolf S, Stoeckelhuber BM *et al.* Bone mineral density, markers of bone turnover, and cytokines in young women with borderline personality disorder with and without comorbid major depressive disorder. Am J Psychiatry 2005; 162: 168–74.
12. McPhee JS, Hogrel J-Y, Maier AB *et al.* Physiological and functional evaluation of healthy young and older men and women: design of the European MyoAge study. Biogerontology 2013; 14: 325–37.
13. Yesavage JA, Brink TL, Rose TL *et al.* Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res 1982; 17: 37–49.
14. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.
15. Sahakian BJ, Owen AM. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. J R Soc Med 1992; 85: 399–402.
16. Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW. Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 1990; 28: 1021–34.
17. Owen AM, Sahakian BJ, Hodges JR, Summers BA, Polkey CE, Robbins TW. Dopamine-dependent frontostriatal planning deficits in early Parkinson's disease. Neuropsychology 1995; 9: 126–40.
18. Blackwell AD, Sahakian BJ, Vesey R, Semple JM, Robbins TW, Hodges JR. Detecting dementia: novel neuropsychological markers of preclinical Alzheimer's disease. Dement Geriatr Cogn Disord 2004; 17: 42–8.
19. Hagger-Johnson G, Sabia S, Brunner EJ *et al.* Combined impact of smoking and heavy alcohol use on cognitive decline in early old age: Whitehall II prospective cohort study. Br J Psychiatry 2013; 203: 120–5.
20. Baune BT, Ponath G, Golledge J *et al.* Association between IL-8 cytokine and cognitive performance in an elderly general population—The MEMO-Study. Neurobiol Aging 2008; 29: 937–44.
21. Luca CRD, Wood SJ, Anderson V *et al.* Normative data from the CANTAB. I: Development of executive function over the lifespan. J Clin Exp Neuropsychol 2003; 25: 242–54.
22. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. Mayo Clin Proc 2010; 85: 752–8.
23. Lee AJ, Hodges S, Eastell R. Measurement of osteocalcin. Ann Clin Biochem 2000; 37: 432–46.
24. Lee NK, Sowa H, Hinoi E *et al.* Endocrine regulation of energy metabolism by the skeleton. Cell 2007; 130: 456–69.
25. Ducy P, Zhang R, Geoffroy V, Ridall AL, Karsenty G. Osf2/Cbfa1: a transcriptional activator of osteoblast differentiation. Cell 1997; 89: 747–54.
26. Takenouchi T, Sato W, Torii C, Kosaki K. Progressive cognitive decline in an adult patient with cleidocranial dysplasia. Eur J Med Genet 2014; 57: 319–21.

Received 5 February 2016; accepted in revised form 23 May 2016

Downloaded from http://ageing.oxfordjournals.org/ by guest on August 15, 2016