Maturitas xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Vitamin D concentration and its association with past, current and future depression in older men: The Health In Men Study

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ARTICLE INFO

Article history:
Received 21 January 2015
Accepted 31 January 2015
Available online xxx

Keywords:
Depression
Vitamin D
Epidemiology
Risk factors
Ageing
Mental health

ABSTRACT

Background: Vitamin D deficiency has been associated with depression in later life, but it remains unclear whether this association is truly causal.
Methods: Observational study examining the retrospective, cross-sectional and prospective associations between vitamin D concentration and depressed mood in a community-derived sample of 3105 older men living in metropolitan Perth, Western Australia. We measured the plasma concentration of 25-hydroxyvitamin D using standard procedures. Past depression was ascertained by direct questioning and through the use of administrative health data linkage. A geriatric depression scale score equal or greater 7/15 established the presence of current depression. Incident depression was established by a patient health questionnaire (PHQ-9) score ≥10 or by administrative health data linkage during the 6-year follow up (range 0.1–10.9 years).
Results: Vitamin D concentration <50 nmol/L was associated with greater odds of current (OR = 1.65, 95% CI = 1.13, 2.42) but not past depression (OR = 1.15, 95% CI = 0.83, 1.58). Of the 2740 men with no past or current history of depression, 81 developed clinically significant symptoms during follow up. The adjusted hazard ratio of incident depression for men with plasma vitamin D <50 nmol/L was 1.03 (95% CI = 0.59, 1.79; adjusted for age, living arrangements, season, and prevalent cardiovascular diseases).
Conclusions: Our results do not support a role for vitamin D in the causation of depression, although a small antidepressant effect of vitamin D cannot be entirely discarded. Large randomised placebo-controlled trials are required to dismiss or establish with certainty the causal link between vitamin D deficiency and depression.

1. Introduction

Q4 Depression is a leading cause of disability worldwide that affects 5–15% of people aged 60 years or older living in the community [1–3]. The causes of depression in later life are likely to be varied and complex [4], with some evidence suggesting that vitamin D deficiency may play some role [5–7].

A recent systematic review summarised the results of fourteen observational studies of 31,424 participants [8]. Four cross-sectional surveys reported data on 3492 older adults [6,9–11] and found a marginally non-significant increase in the risk of depression among those with lowest (<25 or <50 nmol/L) compared with the highest concentration of vitamin D (≥50 or 75 nmol/L). Three cohort studies [12–14] were also available and their results showed that older people in the lowest compared with the highest tertile or quartile of vitamin D concentration experienced an increased hazard of depression over 1–6 years [8]. However, the risk of depression

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http://dx.doi.org/10.1016/j.maturitas.2015.01.016
0378-5122/

was not higher among people with than without vitamin D deficiency (i.e., <50 nmol/L vs ≥50 nmol/L) [8]. Another systematic review reported a near linear inverse association between depression and every 10 ng/ml of vitamin D [25(OH)D] [15]. However, there is limited supportive evidence from randomised controlled trials that raising vitamin D concentrations by means of vitamin D supplementation in efficacious in reducing the severity and prevalence of depression.

Six randomised controlled trials ($n = 1203$) have reported data on depression scores of adults (including older adults) without depression – differences between the groups treated with placebo and with vitamin D were minimal and non-significant [16]. One small trial randomised 42 adults with a major depressive episode to 8 weeks of treatment with 20 mg of fluoxetine plus vitamin D_3 (1500 IU) or 20 mg of fluoxetine plus placebo [17]. Endpoints were available for 40 participants (20 in each treatment group) and showed that people assigned treatment with vitamin D_3 experienced greater decline in depression scores [17]. The authors did not provide information about remission of symptoms.

In the absence of reliable evidence to prove or disprove a causal association between vitamin D deficiency and depression, one may consider biologically plausibility. Vitamin D receptors are expressed in parts of the brain that contribute to the modulation of mood, including the prefrontal cortex, cingulate and hippocampus [18,19]. In addition, the association between vitamin D deficiency and depression may be particularly relevant to older people, as lower circulating concentrations of vitamin D are more frequent in later life independent of latitude [20,21]. Older people are also more prone to reduced synthesis of vitamin D_3 by the skin (age-related and reduced exposure to sunlight) and by less efficient conversion of 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 in the kidneys [20]. Therefore, if vitamin D deficiency is causally related to the onset of depressive symptoms, one might expect depression to be associated with vitamin D deficiency both cross-sectionally and prospectively, but not necessarily retrospectively. Should reverse causality be responsible (i.e., depression causing vitamin D deficiency), then one would expect this association to hold for past and current depression, but not for incident cases.

We designed this study to clarify if the plasma concentration of vitamin D, as measured by 25-hydroxyvitamin D [25(OH)D] is associated with past, current and future depression in later life.

2. Methods

2.1. Study design and setting

This study reports retrospective, cross-sectional and prospective associations between vitamin D concentration and depressed mood in a community-derived sample of older men living in metropolitan Western Australia.

2.2. Participants

The sample consisted of 3105 men aged 71–88 years who donated a fasting blood sample during the second wave of assessments of the Health In Men Study (HIMS) in 2001–2004. Briefly, HIMS is an ongoing cohort study of a random community sample of 12,203 older men recruited between 1996 and 1998 for a study of abdominal aortic aneurysm. An additional third wave of clinical assessments took place in 2008. Details about the study design and cohort have been described elsewhere [22,23].

This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committees of the University of Western Australia and of the Department of Health of Western Australia. Participants provided written informed consent to participate.

2.3. Healthy participant bias

Men who consented to join HIMS were healthier than other eligible men living in the community [23], and those who completed the second assessment had less comorbidities than their surviving counterparts [23,24].

2.4. Outcomes

The primary outcome for this study was the presence of clinically significant depressive symptoms. We used three complementary strategies to identify men with past depression: (i) recorded diagnosis of a depressive episode in the Western Australian Data Linkage System (WADLS) before the date of the assessment (ICD-9 codes 296.2, 296.3, 296.82, 296.90, 298.0 and 311, and ICD-10 codes F32, F33, F34.1 and F38.10) [25,26], (ii) response in the affirmative to the question '*In the last 5 years, have you ever been told for the first time by a doctor that you have depression?*', or (iii) use of an antidepressant at the time of the collection of the blood sample. Past studies have shown that WADLS yields accurate diagnoses for severe mental disorders [27]. We considered that participants showed evidence of current clinically significant symptoms of depression if they scored 7 or more on the 15-item version of the geriatric depression scale (GDS-15) at the time of assessment [28]. During 2008 we asked participants to complete a new assessment that included the patient health questionnaire (PHQ-9), and considered that men with scores greater or equal 10 were experiencing clinically significant symptoms of depression [29,30]. We also used WADLS to monitor death and hospital contacts associated with a diagnosis of depression (as described above) between the collection of blood samples and the 30th September 2012.

We used these data to create two variables: depression group at the time of assessment and incident depression following the assessment. The first variable was rated as 'current' if men had a GDS-15 score ≥7 at the time of assessment, 'past' if they were not depressed at the time of assessment but self-reported or had a recorded WADLS history of depression, and 'never' if they did not have current or past depression. The second variable, incident depression (yes/no), was recorded as present if men were rated as 'never' in the depression group variable (as described above) but scored 10 or more on the PHQ-9 in 2008 or had a WADLS entry indicating the presence of a depressive episode between the collection of blood samples and the 30th September 2012.

2.5. Exposures at study entry

The key explanatory variable for this study was the plasma concentration of 25-hydroxyvitamin D [25(OH)D] at the 2001–2004 assessment for HIMS [31,32]. Fasting blood samples were collected between 8 and 10:30 AM, and the plasma separated from other blood constituents within one hour of collection and stored at −80 °C until assayed. We measured 25(OH)D with the automated "DiaSorin Liaison 25(OH)D total" chemiluminescent immunoassay between 2011 and 2012. The interassay coefficient of variation of the assay was 13.2% at 37.9 nmol/L and 11.3% at 131 nmol/L. We followed Australian guidelines for vitamin D status to group our participants: ≥50 nmol/L (sufficient), 30–49 nmol/L (mild deficiency), <30 nmol/L moderate to severe deficiency [32]. The season at the time of collection of the blood sample was also recorded.

Participants also completed a health questionnaire that collected information about their age (in years), educational attainment (incomplete vs complete high school education), living

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arrangements (alone vs with others) and smoking (never, past or current). We used standard procedures to measure participants' height (to 0.5 cm) and weight (to 0.2 kg), which provided the basis for the calculation of the body mass index (BMI) in kg/m^2. In addition, we considered that participants had hypertension if their systolic blood pressure was ≥140 mmHg or their diastolic blood pressure was ≥90 mmHg, or if they reported having been advised by their doctor that they had hypertension. The presence of diabetes was ascertained by asking participants if a doctor had ever told them that they had diabetes or if they reported treatment to lower blood sugar. Similarly, men indicated whether a doctor had ever told them that they had had a stroke, or a heart attack or angina (which we considered indicative of the presence of coronary heart disease).

2.6. Study size

The community prevalence of vitamin D deficiency in older people is about 25–30% [21]. Hence, we expected 780 of our 3105 men to be vitamin D deficient. In addition, we have previously found that 4.5% of older men present clinically significant symptoms of depression [33], which would equate to 140 men. With this sample size, the study would have 80% power to declare as significant an odds ratio of 1.7 ($p1 = 0.3$, $p2 = 0.42$; alpha = 5%). We anticipated that the number of men with past depression would be twice as large ($n = 280$), ensuring that a study of this size would have 80% power to declare as significant an odds ratio of at least 1.4 ($p1 = 0.3$, $p2 = 0.38$; alpha = 5%).

2.7. Statistical methods

We used the statistical package Stata/IC 13.1 to manage and analyse the data (StataCorp LP, 2013). Descriptive statistics summarised categorical data as count and proportions (%), and continuous variables as mean, range, and standard deviation of the mean (SD). The median and interquartile range (IQR) were used to describe ranked data, and the Cuzick non-parametric test for trend (z statistic) to examine changes in the concentration of vitamin D across the depression groups. We used the Pearson chi-square statistic (χ^2) to determine the probability that the distribution of exposures among people with past, current and no history of depression could be attributed to chance, and reported the number of degrees of freedom (df) and the probability (p-value) of the associations having arisen as a result of chance. We employed logistic regression to calculate the odds ratio (OR) and respective 95% confidence interval (95% CI) of past and current depression compared with no history of depression for mild and moderately severe vitamin D deficiency (30–49 nmol/L and <30 nmol/L), and multiple logistic regression to adjust the findings for the potential confounding effect of other measured factors. The odds ratio of past and current depression.

The distribution of vitamin D concentration in men with past, current and no past history of depression was examined using a strip plot scattergram, and between group comparisons tested with the Kruskal–Wallis equality of population rank test (χ^2 statistic) followed by two-by-two comparisons with Mann–Whitney tests (z statistic). We estimated the hazard ratio (HR and 95% CI) of novel depression with Cox regression, censoring follow up at the date of diagnosis of depression, death or the 30th September 2012, whichever occurred first. Alpha was set at 0.05 and all tests reported are two-tailed.

3. Results

The mean age of the 3105 participants was 77.0 (SD = 3.6; range = 71.0 to 88.3) years. Table 1 summarises the sociodemographic, lifestyle and clinical characteristics of men with no, past and current history of clinically significant depression. The plasma concentration of 25(OH)D was not the same across the three depression groups ($\chi^2 = 13.50$, df = 2, $p = 0.001$), as men with current depression (median = 60.7 nmol/L, IQR = 47.4, 75.9 nmol/L) displayed significantly lower values than men with no (median = 68.3 nmol/L, IQR = 53.8, 83.2 nmol/L; $z = 3.51$, $p < 0.001$) or with past history of depression (median = 66.5 nmol/L, IQR = 52.9, 79.1 nmol/L; $z = 2.09$, $p = 0.037$). The Cuzick non-parametric test for trend showed that there was a progressive decline in the plasma concentration of vitamin D from amongst those with no depression to past and current depression ($z = -3.57$, $p < 0.001$) (see Fig. 1).

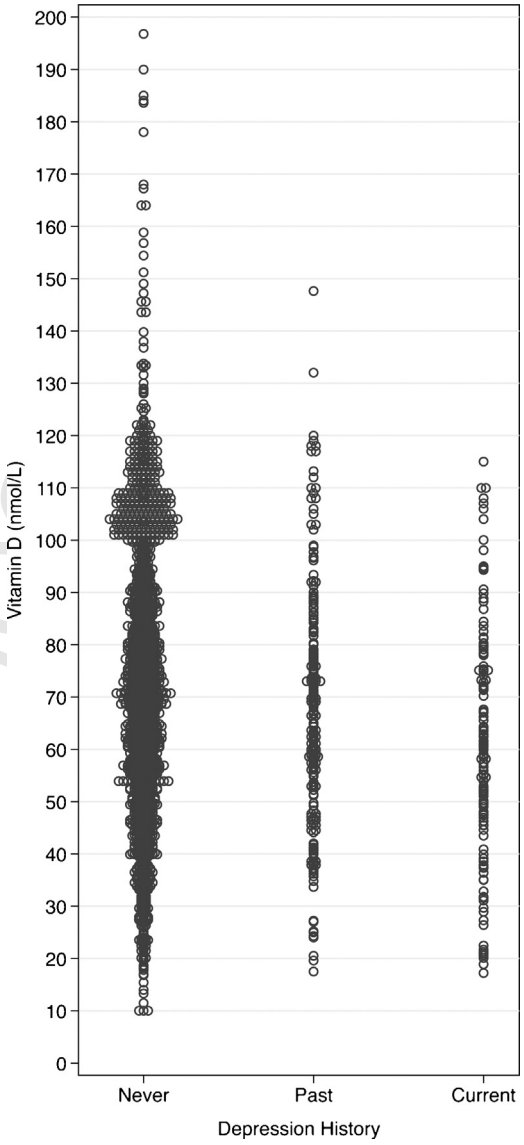

Fig. 1. Scattergram of the serum concentration of vitamin D in older men according to their depression history. The mean concentration (±standard deviation) of 25-hydroxyvitamin D was 69.3 ± 23.2, 67.3 ± 22.6 and 61.6 ± 22.2 nmol/L for men with no, past and current history of depression (Kruskal–Wallis, $\chi^2 = 13.50(2)$, $p = 0.001$). The difference between men with no past history and with current depression retained statistical significance (Mann–Whitney test, $z = 3.51$, $p < 0.001$).

Table 2 summarises the crude and adjusted odds ratio of past and current depression for men with mild and moderately severe vitamin D deficiency compared with those with vitamin D concentration ≥50 nmol/L. Vitamin D concentration <50 nmol/L was associated with greater odds of current (OR = 1.65, 95% CI = 1.13, 2.42) but not past depression (OR = 1.15, 95% CI = 0.83, 1.58).

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Table 1
Q9 Sociodemographic, lifestyle and clinical characteristics of older men according to their history of depression.

		History of depression			χ^2 statistic (df)	*p*-value
		None *N* = 2740 (%)	Past *N* = 230 (%)	Current *N* = 135 (%)		
Age (years)	70–74	1035 (37.8)	72 (31.3)	38 (28.2)	9.94 (4)	**0.041**
	75–79	1184 (43.2)	110 (47.8)	62 (45.9)		
	≥80	521 (19.0)	48 (20.9)	35 (25.9)		
Education (minimal)	High school	1339 (48.9)	115 (50)	54 (40)	4.27 (2)	0.118
Living	Alone	448 (16.4)	50 (21.8)	29 (21.5)	6.52 (2)	**0.038**
Smoking	Never	960 (35.0)	70 (30.4)	33 (24.4)	10.83 (4)	**0.029**
	Past	1660 (60.6)	148 (64.4)	91 (67.4)		
	Current	120 (4.4)	12 (5.2)	11 (8.2)		
Body mass index	Normal	965 (35.3)	80 (34.9)	34 (20.2)	9.09 (6)	0.169
	Underweight	20 (0.7)	2 (0.9)	1 (0.8)		
	Overweight	1384 (50.6)	117 (51.1)	67 (51.5)		
	Obese	367 (13.4)	30 (13.1)	28 (21.5)		
Diabetes		321 (11.7)	30 (13.0)	23 (17.0)	3.67 (2)	0.159
Hypertension		2239 (85.9)	189 (84.8)	115 (87.8)	0.63 (2)	0.731
CHD		690 (26.5)	77 (34.5)	51 (38.9)	15.44 (2)	**<0.001**
Stroke		236 (9.1)	35 (15.7)	32 (24.4)	39.93 (2)	**<0.001**
25(OH)D (nmol/L)	≥50	2184 (79.7)	178 (77.4)	95 (70.4)	14.69 (4)	**0.005**
	30–49	468 (17.1)	43 (18.7)	28 (20.7)		
	<30	88 (3.2)	9 (3.9)	12 (8.9)		

χ^2: Pearson chi-square statistic; df: number of degrees of freedom; CHD: coronary heart disease; 25(OH)D: 25-hydroxyvitamin D.

Table 2
Odds of past and current depression according to the serum concentration of vitamin D.

25(OH)D (nmol/L)	Past depression		Current depression	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
≥50	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
30–49	1.13 (0.80, 1.60)	1.10 (0.78, 1.57)	1.38 (0.89, 2.12)	1.31 (0.84, 2.06)
<30	1.25 (0.62, 2.53)	1.15 (0.56, 2.34)	**3.13 (1.66, 5.93)**	**2.70 (1.39, 5.25)**

OR: odds ratio; 95% CI: 95% confidence interval of the odds ratio.
Variables included in the adjusted models: age group, smoking history, living arrangements, season of collection of blood sample, and past history for coronary heart disease or stroke.
25(OH)D: 25-hydroxyvitamin D.

Eighty-one of the 2740 men without history of depression experienced incident clinically significant depressive symptoms during the subsequent 6.0 years of follow up (SD = 2.2, range = 0.1–10.9 years). There were 996 (36.3%) deaths during this time. Compared with no depression history, past and current depression were associated increased odds of death (OR = 1.58, 95% CI = 1.20, 2.07 and OR = 3.17, 95% CI = 2.21, 4.55). Similarly, men with mild and moderate to severe vitamin D deficiency had higher odds of death during follow up than men with vitamin D ≥50 nmol/L (OR = 1.21, 95% CI = 1.00, 1.46 and OR = 2.01, 95% CI = 1.37, 2.95, respectively). The HR of incident depression among men with vitamin D plasma concentration <50 nmol/L was 1.03 (95% CI = 0.59, 1.79; adjusted for age (in years), living arrangements, season, and prevalent CHD and stroke) compared with men whose plasma concentration of vitamin D was ≥50 nmol/L. Similarly, the adjusted HR of depression for men with plasma concentration of vitamin D between 30–49 nmol/L and <30 nmol/L was 0.97 (95% CI = 0.53, 1.78) and 1.38 (95% CI = 0.43, 4.45), respectively.

4. Discussion

The results of this observational study showed that the plasma concentration of vitamin D among older men decreased progressively from no history of depression to past and then current depression. Moderate to severe vitamin D deficiency was associated with increased risk of current depression, but not past or future depression.

Before discussing the meaning and implications of these findings, we wish to outline the strengths and limitations of our study design. This survey has the merit of having had access to a community-derived sample of older men for whom a wealth of sociodemographic, lifestyle, seasonal and clinical data were available from direct assessment or from contacts with health services [22,26]. This allowed us to adjust our analyses for the potential critical effect of confounding. We also had access to data on past depression obtained from direct questioning and from hospital morbidity data records, which enabled us to investigate if depression (or behaviours associated with depression) was associated with low concentrations of vitamin D. Lastly, we used well established and valid procedures to measure the plasma concentration of vitamin D. We concede, however, that the assessment of vitamin D concentration was limited to one time-point (analyses adjusted for season), and that the diagnosis of 'depression' through WADLS most likely lacks sensitivity (most mild cases of depression are treated in primary care settings). This would lead to a possible misclassification of participants with depression as not depressed and type II error. In addition, our definition of 'clinically significant depression' may not necessarily equate to a diagnosis of major depressive episode according to DSM or ICD criteria, although they have good

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face validity. We also acknowledge that men who took part in this study were healthier than those who did not participate [23], and this could have reduced the power of the study to detect differences between the groups. Differential loss to follow up is another potential caveat of a longitudinal study such as this, as older people with low vitamin D concentration are at increased risk of death during follow up [34]. Again, the most likely consequence of such a bias would be loss of power. This study was not powered to declare as significant associations between vitamin D and depression associated with small effect sizes. Finally, we acknowledge that the results of this study are limited to men and may not necessarily apply to women.

Taken in context, our findings indicate that vitamin D deficiency is unlike to be an important cause of clinically significant symptoms of depression in older men living in the community. A large Australian study assigned 2258 women older than 70 years to treatment with supplemental vitamin D_3 (500,000 IU orally) or placebo during autumn and winter for 3–5 years [35]. The investigators monitored symptoms of anxiety and depression with the General Health Questionnaire and the 12-item Short Form Health Survey. Treatment with vitamin D had no obvious impact on scores, although floor effects could have contributed to those results. Similarly, Kjaergaard and colleagues randomised 230 adults with vitamin D concentration ≤55 nmol/L to 40,000 IU of vitamin D_3 or placebo per week for 6 months [36]. They found that active treatment had no effect on mood, as measured by the Beck Depression Inventory and the Montgomery-Asberg Depression Rating Scale. In contrast, a randomised placebo-controlled trial of 120 adults with depression and with vitamin D levels <40 nmol/L showed that treatment with a single dose of 150,000 or 300,000 IU of vitamin D improved mood compared with placebo over a three-month period, suggesting that vitamin D may have antidepressant effect among those who are deficient and have depression [37]. However, the trial was not blinded, the concurrent use of antidepressants was not taken into account, and the analyses were not intention to treat [37].

Overall, data from our study and from available trials do not support a role for vitamin D in the causation or treatment of depression. We accept, however, that the quality of available evidence is suboptimal and that a small antidepressant effect of vitamin D is possible. It could also be argued that vitamin D supplementation is safe [38] and that as long as doubt persists about its antidepressant role, its use in clinical practice may be justifiable. However, a recent systematic review of 290 prospective cohort studies and 172 trials investigating the association between vitamin D status and several health outcomes (including depression) concluded that low vitamin D is most likely a marker of ill health, rather than a cause of it [39]. There are also concerns that the use of high dosages of vitamin D may not be as safe as previously thought, with the results of a large randomised placebo-controlled trial of 2256 women older than 70 years concluding that treatment with a high dose of vitamin D increases rather than decreases the risk of falls and fractures [40].

We would suggest that sufficiently powered and well designed randomised placebo-controlled trials are required to dismiss or establish with certainty the causal link between vitamin D deficiency and depression. Until such data are available, health practitioners should refrain from prescribing vitamin D supplementation as an adjunctive or sole treatment of depression.

Contributors

O.P.A. conceived and designed the study. O.P.A., G.J.H., B.B.Y., J.G. and L.F. performed the experiments. O.P.A. analysed the data and drafted the manuscript. O.P.A., G.J.H., B.B.Y., J.G. and L.F. reviewed the manuscript critically and approved its submission to the Journal.

Competing interests

The authors declare they have no competing interests.

Funding

This work was funded through competitive project grants from the National Health and Medical Research Council of Australia (NHMRC), numbers 279408, 379600, 403963, 513823, 540403, 540504, 540405, 634492, 1021416, 1045710 and 1060557. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Ethics

The Human Research Ethics Committees of the Royal Perth Hospital and of the Department of Health of Western Australia approved the research protocol and procedures of the study, which follow the principles of the Declaration of Helsinki. All participants provided written informed consent.

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Please cite this article in press as: Almeida OP, et al. Vitamin D concentration and its association with past, current and future depression in older men: The Health In Men Study. Maturitas (2015), http://dx.doi.org/10.1016/j.maturitas.2015.01.016