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Jane Maddock, Diane J. Berry, Marie-Claude Geoffroy, Chris Power, Elina Hyppönen

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Vitamin D and common mental disorders in mid-life: cross-sectional and prospective findings

AUTHORS: Jane Maddock[1,2], Diane J Berry[1,3], Marie-Claude Geoffroy[1,4], Chris Power[1,5], Elina Hyppönen[1,6]

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NAME OF INSTITUTION WHERE WORK WAS PERFORMED: UCL Institute of Child Health

AUTHOR CONTACT DETAILS: [1]MRC Centre of Epidemiology for Child Health/Centre for Paediatric Epidemiology and Biostatistics, UCL Institute of Child Health, UK.

[2]jane.maddock.10@ucl.ac.uk. [3]diane.berry@ucl.ac.uk. [4]m.geoffroy@ucl.ac.uk. [5]christine.power@ucl.ac.uk. [6]e.hypponen@ucl.ac.uk.

SHORT TITLE: Vitamin D and common mental disorders.

ABBREVIATIONS USED: 25(OH)D (25-Hydroxyvitamin D), CMD (Common mental disorder), CIS-R (Clinical Interview Schedule Revised), MHI-5 (Mental Health Inventory -5) SEP (Socioeconomic Position)

ADDRESS FOR CORRESPONDENCE: Jane Maddock. MRC Centre of Epidemiology for Child Health/Centre for Paediatric Epidemiology and Biostatistics, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH. email: jane.maddock.10@ucl.ac.uk ; Tel. +44 (0)20 7905 2769.

ABSTRACT

Background & Aims:

The relationship between vitamin D and common mental disorders (CMDs) remains unclear. We aimed to determine if behaviours affecting vitamin D concentrations differ between individuals with or without CMDs and evaluate, cross-sectionally and prospectively, the extent to which the association between 25(OH)D and CMDs are explained by these behaviours.

Methods:

Data are from the 1958 British birth cohort (*n*=7,401). Behaviours were ascertained by questionnaire at age 45 years. CMDs (depression, anxiety, panic, phobia) were assessed using the Clinical Interview Schedule-Revised at 45 years and depression using Mental Health Inventory-5 at 50 years.

Results:

Participants with CMDs at 45 years differed from others on some but not all vitamin D related behaviours. There were inverse, cross-sectional associations at 45 years of 25(OH)D with depression and panic, which persisted after adjustment for vitamin D related behaviours (OR=0.57, 95%CI: 0.40,0.81 and OR=0.33, 95%CI: 0.40,0.81, respectively). Association between 25(OH)D and subsequent (50 years) risk of depression was non-linear (*p*=0.01), with lower risk for participants with 25(OH)D between 50 and 85 nmol/l compared with those with lower or higher concentrations.

Conclusion:

This study provides support for an association of low 25(OH)D concentrations with current and subsequent risk of depression in mid-adulthood.

KEYWORDS: 25-Hydroxyvitamin D, vitamin D, mental health, common mental disorders, depressive symptoms, 1958 British birth cohort.

INTRODUCTION

Common mental disorders (CMDs), including depression and anxiety are widespread in the general population and are a leading cause of disability and disease burden worldwide (1). Approximately 450 million individuals globally suffer from mental and behavioural disorders in their lifetime. The aetiology of CMDs is complex and many inter-linking genetic, biological, and environmental factors are likely to be involved (2). In recent years, there has been a growing interest in the role of vitamin D in CMDs.

Vitamin D is a secosteriod prohormone which is obtained mainly through skin synthesis following sun exposure, and to a lesser extent from dietary sources(3). Lifestyle factors are important in determining vitamin D intake. For metabolic activation, vitamin D undergoes two hydroxylation's, firstly to 25-hydroxyvitamin D [25(OH)D, the nutritional indicator for vitamin D status] and secondly to form 1,25-dihdroxyvitamin D, the active hormonal metabolite (3).

An influence of vitamin D on CMDs is biologically plausible. Vitamin D Receptors (VDRs) have been mapped in the human brain and central nervous system, including in key behavioural and emotional regulation sites (4). There is evidence that vitamin D may be involved in the biosynthesis of neurotrophic factors and neurotransmitters (4) and may have neuroprotective, immunomodulatory, antiepileptic and psychotropic effects (5).

While some epidemiological studies have found an association between low 25(OH)D and depression (6, 7), others have not (8, 9). For example, a large US-based study, found that participants with <50nmol/l 25(OH)D had an increased odds ratio of depression compared with those with ≥75nmol/l (7), whereas, no association was found between 25(OH)D concentrations and depressive symptoms in a large population based study in China (8). One randomised controlled trial of vitamin D supplementation in overweight and obese subjects found an improvement in depressive scores (10), while another conducted in postmenopausal women found no effect (11).

Although many studies have focused on depression, the relationship between vitamin D and other CMDs has been neglected. Additionally, little is known about changes in vitamin D related behaviours (e.g. time spent indoors, sun exposure habits, or vitamin D supplements) in those with CMD. Differences in behaviour of those with CMD could explain associations observed for low 25(OH)D concentrations. Furthermore, the temporal association between vitamin D and CMDs remains unclear.

Using information from a large nationwide British birth cohort study, our aim was to evaluate the association between 25(OH)D and CMDs, specifically, 1) to determine if lifestyle factors known to affect 25(OH)D concentrations, differ between people with and without a CMD, 2) to evaluate the extent to which these lifestyle factors may explain the low 25(OH)D concentrations for people with a CMD, and 3) to examine the prospective association between 25(OH)D concentrations and subsequent depressive disorder.

METHODS

Study population. Participants were from the 1958 birth cohort, consisting of 18,558 people (17,634 from England, Scotland or Wales and 920 immigrants) born in March 1958 and followed from childhood to age 50 years (13). For cross-sectional analyses, data were obtained from a biomedical survey when participants were aged 45 years. **Figure 1** shows the target sample and response for this study. There were 9,377 respondents, of whom 8,302 provided a blood sample. We excluded participants without a 25(OH)D measure (*n* = 711), with no data on CMDs at 45 years (*n* = 30), pregnant women (*n*=1), and participants of non-European ancestry (*n* = 159); leaving 7,401 participants for cross-sectional analyses. For prospective analyses, participants were those with both a 25(OH)D and mental health measurement at age 45 years and with mental health data at 50 years (*n* = 5,966). Ethical approval for the biomedical survey was obtained from South East Multi-centre Research Ethics Committee (ref. 01/1/44).

CMD measures. At age 45 years, CMDs were assessed using the Clinical Interview Schedule Revised (CIS-R) (14). This standardised semi-structured interview was administered by trained survey nurses visiting the participant's home. The presence of depressive, anxiety, panic and phobia symptoms in the past week were assessed on a scale zero to four, with ≥2 symptoms indicating clinically relevant CMD (15).

Depressive symptoms at 50 years were identified using the five question Mental Health Inventory (MHI-5), a paper self-completion questionnaire assessing depressive symptoms in the past four weeks (16). Items were scored on a 6-point scale ranging from "all of the time" to "none of the time." Responses were summed and standardized to a 0-100 scale with lower scores indicating worse mental health (16). While the MHI-5 was designed as a general mental health measure, several studies have shown that it is most appropriate for measuring severe depressive symptoms using a cut-off score ≤52 (17).

25(OH)D measurement. Serum 25(OH)D concentrations were measured using an automated Immunodiagnostic Systems Ltd OCTEIA assay with a Dade-Behring BEP2000 analyser (Dade-Behring, Marburg, Germany) and standardised according to the mean vitamin D external quality assessment scheme (18). For this study, 25(OH)D <25mol/l was chosen to indicate deficiency (19) and 25(OH)D was categorised into the following groups: <25, 25-49, 50-74, 75-99, >100nmol/l.

Covariates. Information on vitamin D-related lifestyle factors was obtained from a self-complete questionnaire at 45 years. Dietary factors include frequency of consumption of oily fish and margarine (weekly and less than weekly) and supplements of cod liver, fish oil or others containing vitamin D (daily and less than daily). Margarine was included as, in the UK, fortification with vitamin D is mandatory (7.05-8.82 µg/100g) (20). Amount of time spent outside during the past month and leisure time spent using the TV or PC (>3 and <3hours per day) were examined along with frequency of sun-cover usage (most of the time and rarely), blistering after sun-burn (often, rarely, sometimes and never) and seeking sun-tan (often, rarely, sometimes and never). BMI (kg/m^2) was derived from measured weight (Tanita solar scales) and height, in light clothes and without shoes taken by a nurse at the participant's home. BMI ≥30 defined obesity (21). Information on physical activity (<2-3 times per month,1 time per week, 2-3 times per week and 4-7 times per week), smoking (never, ex-smoker, 1-19 per day and ≥20 per day) and socioeconomic position (SEP) in adulthood were collected during interviews when participants were 42 years. SEP at birth was based on father's occupation at birth (or at 7 years if missing). SEPs at birth and adulthood were defined using the Registrar General's classification (22), grouped into four categories: professional and managerial (I and II), non-manual (IIInm), manual (IIIm) and unskilled (IV and V). Alcohol intake (classified as non-drinker, light drinker (<7 units per week), moderate (7-14 units per week), heavy (14-21 units per week) and very heavy (>21 units per week)) was self-reported at 45 years and region of residence (Southern England

and Channel Islands (South), Middle England and Wales (Middle), Northern England and Isle of Man (North) and Scotland) at 46 years.

Statistical analyses. To determine if participants with CMD differed from those without on selected characteristics (region, SEP, physical activity, smoking status, alcohol consumption and BMI) and vitamin D-related lifestyles (time outside, watching television or using a computer, using sun-cover (clothing or suncream), blistering after sun-burn, seeking a suntan, consuming oily fish, margarine and vitamin D supplements) we used likelihood ratio tests, adjusting for sex and SEP in adulthood (where appropriate).

25(OH)D was log transformed (ln) to improve approximation of a normal distribution; geometric means are presented for 25(OH)D concentrations.

Multiple logistic regression models were used to assess the association of 25(OH)D categories with the outcomes at 45 years and 50 years. Curvature of the association was assessed by including the quadratic term of 25(OH)D in the model. Logistic regression models were adjusted for: (1) sex and season of blood collection (winter, spring, summer or autumn); (2) sex, season, SEP at birth and adulthood; (3) sex, season, SEP at birth and adulthood and BMI; (4) sex, season, SEP at birth and adulthood, BMI and lifestyles related to CMD (i.e. smoking, physical activity and computer/television leisure time, sun-cover, blistering after sunburn and actively seeking suntan). Models on depression at age 50 used a cut-off of ≤52 and were additionally adjusted for any CMD (i.e. depression, anxiety, panic or phobia) at age 45.

Missing values for lifestyle and BMI covariates (n = 1,269) were imputed using the multiple imputation chained equations (MICE) in STATA version 12 (23). The regression analyses described above were run on ten imputed datasets. Compared with complete case results, imputed data results had greater precision but were otherwise similar. Mean probabilities of depression at 45 and 50 years over a range of 25(OH)D concentrations were predicted from the multiple regression models using imputed covariates.

159 There were no interactions between sex and 25(OH)D with mental health at age 45
160 or 50 years, therefore combined, sex adjusted analyses are presented. All analyses were
161 conducted using STATA version 12.

RESULTS

Mean 25(OH)D concentrations were found to be slightly higher in men (53.1 nmol/l, 95% CI 52.3 to 53.8) than women (51.2 nmol/l, 95% CI 50.4 to 52.0, p=0.01). Mean 25(OH)D concentrations were also higher in summer/autumn (60.3nmol/l, 95% CI 59.6 to 61.0) than in winter/spring (41.2nmol/l, 95% CI 40.5 to 41.9, p<0.001). For CMDs at 45 years, depression was the most common (8.0%), followed by anxiety (6.8%), phobia (4.1%) and panic (1.5%) (**Table 1**). At age 50 years, 12.2% of participants had depressive symptoms (MHI-5 ≤52) of whom 32.6% also had a CMD at age 45 years. Women were more likely to be affected by CMDs than men (p<0.001).

Table 1 presents descriptive statistics for men and women with CMDs at age 45 years. Participants with a CMD were less physically active and had poorer lifestyle habits than those without a CMD. Individuals with depression, panic and phobia were more likely to be obese (p≤0.04 for all, adjusted for sex) compared with those without a CMD. Participants with depression and anxiety were overrepresented in groups that both rarely exercised and those who exercised most. Participants with CMDs were also more likely than others to smoke heavily (p<0.001 for all) and be in lower SEPs (p≤0.002 for all).

Table 2 presents the cross-sectional association between vitamin D-related lifestyle factors and CMDs at 45 years, controlling for sex and SEP. CMDs were associated with some but not all vitamin D-related lifestyles. Compared to those without CMD, individuals with depression, anxiety and phobia spent more time watching television or using a computer (p≤0.01 for all) and participants with anxiety were less likely to seek a suntan (p=0.017). When participants spent time in the sun, individuals with depression and anxiety were less likely to use sun-cover compared to others (p≤0.02 for all). Blistering after sunburn was more likely in those with depression and panic than in others (p≤0.02 for all).

High 25(OH)D was associated with lower prevalence of depression and panic at 45 years (p_{trend} <0.05, after full adjustment) (Table 3). Following adjustment for SEP, BMI and lifestyle, participants with 25(OH)D ≥75nmol had 43% (95% CI 19% to 60%) lower odds of

depression and 67% (25% to 85%) lower odds of panic compared to those with 25(OH)D <25nmol/l. There was no relationship of 25(OH)D with phobia or anxiety after adjusting for BMI and related lifestyle factors. **Figure 2A** illustrates the predicted probability of having depression at 45 years according to 25(OH)D concentrations.

In analyses of 25(OH)D at 45 years and depression at 50 years, the association was non-linear ($p_{curvature}$ = 0.001, **Figure 2B**). Despite some attenuation after adjustment for BMI and vitamin D-related behaviours, data remained supportive of lower risk of subsequent depression for participants with 25(OH)D between 50 and 85 nmol/l compared to those with lower or higher concentrations ($p_{curvature}$ = 0.016, after full adjustment for CMDs at 45 years BMI, and lifestyle factors).

DISCUSSION

This study used information from a large, nationwide British sample to show that depression and other CMDs in mid-adulthood are associated with some, but not all lifestyles that predispose to low 25(OH)D concentrations. Differences between those with and without a CMD were most notable for sun exposure and indoor lifestyles, however, adjustment for these factors did not fully explain the moderate association observed between vitamin D deficiency and CMDs. A main finding of our study was discovery of the lower odds of having depressive or panic symptoms with 25(OH)D ≥75nmol compared with <25nmol/l, following adjustment for lifestyle factors. 25(OH)D concentrations were also associated with mental health symptoms five years later (at 50 years), with a modest non-linear relationship, even after accounting for baseline CMDs and vitamin D related lifestyles.

Strengths and Limitations.

The association between low 25(OH)D concentrations with depression and panic and the non-linear relationship with subsequent depression observed here could potentially indicate a causal relationship, however methodological limitations should be recognised. Firstly, a systematic bias may have occurred due to participant exclusion and those with internalising and externalising disorders in childhood were underrepresented in the biomedical survey (24). Multiple imputation was used to minimise loss of power due to missing data for covariates, although this may have been offset by the systematic bias. Secondly, the lack of information from diverse ethnic groups may reduce the generalisability of our findings (13). However, the large nationwide sample used suggests that our findings are likely to be broadly representative of the general population of white, British adults (24). Thirdly, while detailed information was collected on vitamin D-related lifestyles, there was a reliance on self-reported data. Despite the lack of a clinical diagnosis of depression and other CMDs, good reliability and validity for the CIS-R has been reported (14) and the instrument is widely used in psychiatric research (14); reliability and validity of the MHI-5 is also well established

(25). However, use of different mental health measures at ages 45 and 50 years may have affected the ability to control for 'baseline' CMDs in prospective analyses. Additionally, although a seasonal trend for CMDs was not observed, the extent to which season, rather than 25(OH)D status alone, affects CMDs remains uncertain. Finally, the aetiology of both CMDs and vitamin D deficiency are complex and their association contains a multitude of confounding factors. Despite the comprehensive adjustments undertaken, we are unable to discount the possibility of residual or unknown confounding.

Interpretation of findings.

Previous studies have mostly focused on depression, with many (6, 7) but not all (8, 9) reporting an inverse association. While most studies have adjusted for factors such as season and BMI, to our knowledge, no previous study includes a comprehensive range of vitamin D related lifestyle factors. Our results suggest that individuals with CMDs are more likely to have lifestyle behaviours associated with reduced 25(OH)D concentrations.

Evidence from laboratory and animal experiments have confirmed a role for vitamin D in brain function, but its role in CMD has been unclear. Mechanisms by which active vitamin D has been proposed to affect brain function are relatively broad and may not be unique to depression. Hence, we examined all available categories of CMD, i.e. depression, anxiety, panic and phobia. The relationship found between 25(OH)D and depression is consistent with the literature and may be due to effects of $1,25(OH)_2D$ on certain neurotransmitters involved in the development of depression e.g. serotonin (5). The association of 25(OH)D with panic is less well documented. The relationship observed in our study may be due to specific biological mechanisms affected by 25(OH)D concentrations, possibly related to the overarching 'physical' symptoms of the disorder. However, a spurious relationship due to low numbers of individuals with symptoms of panic (1.5%) cannot be ruled out. The lack of association of 25(OH)D with anxiety and phobia may point to an aetiology that is independent of an influence of 25(OH)D, or again, may have been unduly dominated by methodological limitations. CMD type specific analyses

might be used to provide insights into possible mechanisms, however, these will need to be interpreted with caution, given limitations of our mental health measures, co-morbidity between symptoms and limited numbers of participants with panic or phobia.

Most past studies on the role of vitamin D in depression have been cross-sectional and our study is one of the few looking at the prospective association. Results from previous prospective studies suggest that, in women, there is an increased risk of depressed mood after 6 years if 25(OH)D was <50nmo/l compared with >50nmol/l at baseline (26). Furthermore, high vitamin D intakes from food and supplements (≥800IU/d) were associated with a lower prevalence of depression and high vitamin D intakes from food (≥400IU/d) reduced the odds of depression after 3 years in 50-79 year-old women (*n* = 81,189) (27). In older men (≥65 years) higher 25(OH)D levels were associated with a lower prevalence of depression, however, after 4 years of follow-up, no beneficial effect of higher 25(OH)D concentrations was observed on the incidence of depression (28). Additionally, a small number of randomised controlled trials have examined the effect of vitamin D supplementation on depression, but with inconsistent results (10, 11), possibly due to methodological differences. Prospective results from our study found that examination of non-linear associations was beneficial to understanding the relationship of 25(OH)D with subsequent depression and provided further evidence for a possible role of vitamin D in the aetiology of depression.

Conclusions

The high burden of mental and behavioural disorders and concurrent high prevalence of vitamin D insufficiency (<75nmol/l) worldwide (29) highlight the potential importance of our findings. Our results suggest that low 25(OH)D is associated with higher prevalence of depression and panic and that 25(OH)D is modestly and non-linearly associated with subsequent depressive symptoms. However, the possibility of thresholds will need to be confirmed. Further prospective and experimental work is required to replicate these findings, clarify causality and establish the most effective 25(OH)D status for maximum benefit.

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STATEMENT OF AUTHORS CONTRIBUTIONS

JM drafted the paper and analysed the data with DJB. All authors contributed to the design, interpretation and critical revision of the manuscript. EH initiated the study and shares the primary responsibility with JM. All authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

J. Maddock, D.J. Berry, M.C. Geoffroy, C. Power, and E. Hyppönen have no conflicts of interest.

Literature cited

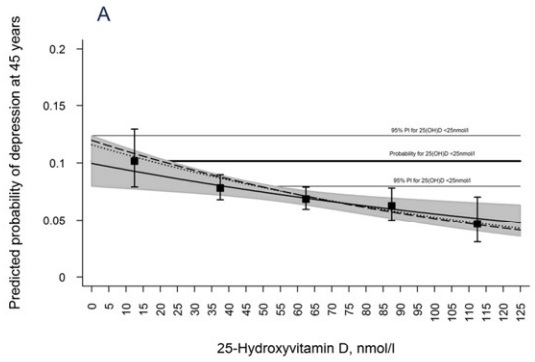
1. Lopez AD. The evolution of the Global Burden of Disease framework for disease, injury and risk factor quantification: developing the evidence base for national, regional and global public health action. Global Health 2005;1(1):5.
2. Ebmeier KP, Donaghey C, Steele JD. Recent developments and current controversies in depression. Lancet 2006;367(9505):153-67.
3. SACN. Update on Vitamin D. In: Scientific Advisory Committee on Nutrition, ed. London, 2007.
4. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. Trends in Endocrinology and Metabolism 2002;13(3):100-5.
5. Kalueff AV, Tuohimaa P. Neurosteroid hormone vitamin D and its utility in clinical nutrition. Curr Opin Clin Nutr 2007;10(1):12-9.
6. Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry 2008;65(5):508-12.
7. Ganji V, Milone C, Cody MM, McCarty F, Wang YT. Serum vitamin D concentrations are related to depression in young adult US population: the Third National Health and Nutrition Examination Survey. IAM 2010;3:29.
8. Pan A, Lu L, Franco OH, Yu Z, Li H, Lin X. Association between depressive symptoms and 25-hydroxyvitamin D in middle-aged and elderly Chinese. J Affect Disord 2009;118(1-3):240-3.
9. Zhao G, Ford ES, Li C, Balluz LS. No associations between serum concentrations of 25-hydroxyvitamin D and parathyroid hormone and depression among US adults. BJN 2010;104(11):1696-702.
10. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. J Intern Med 2008;264(6):599-609.
11. Bertone-Johnson ER, Powers SI, Spangler L, et al. Vitamin D Supplementation and Depression in the Women's Health Initiative Calcium and Vitamin D Trial. Am J Epidemiol 2012.
12. Ismail K, Sloggett A, Stavola BD. Do common mental disorders increase cigarette smoking? Results from five waves of a population-based panel cohort study. Am J Epidemiol 2000;152(7):651.
13. Power C, Elliott J. Cohort profile: 1958 British birth cohort (National Child Development Study). The International Journal of Epidemiology 2006;35(1):34-41.
14. Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. Psychol Med 1992;22(2):465-86.
15. Jenkins R, Meltzer H. The national survey of psychiatric morbidity in Great Britain. Soc Psychiatry Psychiatr Epidemiol 1995;30(1):1-4.
16. Berwick DM, Murphy JM, Goldman PA, Ware JE, Jr., Barsky AJ, Weinstein MC. Performance of a five-item mental health screening test. Med Care 1991;29(2):169-76.
17. Rumpf HJ, Meyer C, Hapke U, John U. Screening for mental health: validity of the MHI-5 using DSM-IV Axis I psychiatric disorders as gold standard. Psychiatry Res 2001;105(3):243-53.
18. Hyppönen E, Turner S, Cumberland P, Power C, Gibb I. Serum 25-hydroxyvitamin D measurement in a large population survey with statistical harmonization of assay variation to an international standard. The Journal of Clinical Endocrinology & Metabolism 2007;92(12):4615-22.
19. Lanham-New SA, Buttriss JL, Miles LM, et al. Proceedings of the Rank Forum on Vitamin D. Br J Nutr 2011;105(1):144-56.
20. Food Standards Agency. Internet: http://www.food.gov.uk/multimedia/pdfs/evm-00-11r.pdf (accessed April 24 2012).

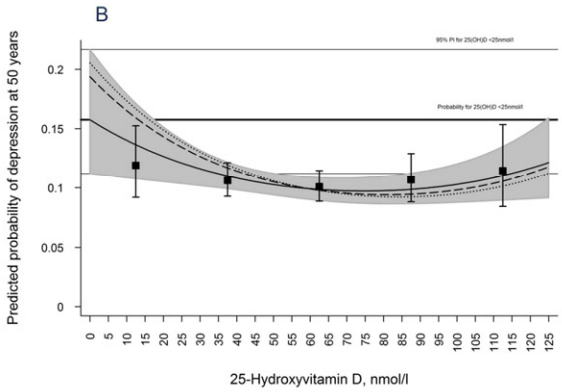
21. National Health Service. Internet: http://www.nhs.uk/Conditions/Obesity/Pages/Diagnosis.aspx (accessed May 1 2012).
22. ONS. September 9. Internet: http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/soc2010-volume-3-ns-sec--rebased-on-soc2010--user-manual/index.html (accessed August 7 2011).
23. Royston P. Multiple imputation of missing values. Stata Journal 2004;4:227-41.
24. Atherton K, Fuller E, Shepherd P, Strachan DP, Power C. Loss and representativeness in a biomedical survey at age 45 years: 1958 British birth cohort. J Epidemiol Community Health 2008;62(3):216-23.
25. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol 1998;51(11):903-12.
26. Milaneschi Y, Shardell M, Corsi AM, et al. Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. J Clin Endocrinol Metab 2010;95(7):3225-33.
27. Bertone-Johnson ER, Powers SI, Spangler L, et al. Vitamin D intake from foods and supplements and depressive symptoms in a diverse population of older women. Am J Clin Nutr 2011;94(4):1104-12.
28. Chan R, Chan D, Woo J, et al. Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. Journal of Affective Disorders 2011;130(1-2):251-9.
29. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357(3):266-81.

FIGURE LEGENDS

FIGURE 1 Number of participants in the 1958 British birth cohort and selection for current study

FIGURE 2 Predicted probability of depression at 45 (**A;** *n = 7,401*) and 50 (**B;** *n = 5,966*) years according to 25(OH)D concentrations at 45. Values are probability (95% Prediction Interval; PI) of having depression at 45 or 50 years for fully adjusted models. *Dot line* (A), adjusted for sex, season and socioeconomic position (SEP). *Dash line* (A) adjusted for sex, season, SEP and BMI *Solid line* (A) adjusted for sex, season, SEP, BMI, smoking, physical activity, TV/PC time, actively seeking suntan, blistering after sun-burn and use of sun-cover. *Dot line* (B)**,** adjusted for sex, season, SEP and presence of any common mental disorder (CMD) at 45 years. *Dash line* (B) adjusted for sex, season, SEP, presence of any CMD at 45 years and BMI. *Solid line* (B) adjusted for sex, season, SEP, presence of any CMD at 45 years, BMI, smoking, physical activity, TV/PC leisure time, actively seeking suntan, blistering after sun-burn and use of sun-cover. Shaded areas show 95% PI for fully adjusted models. 25(OH)D; 25-Hydroxyvitamin D





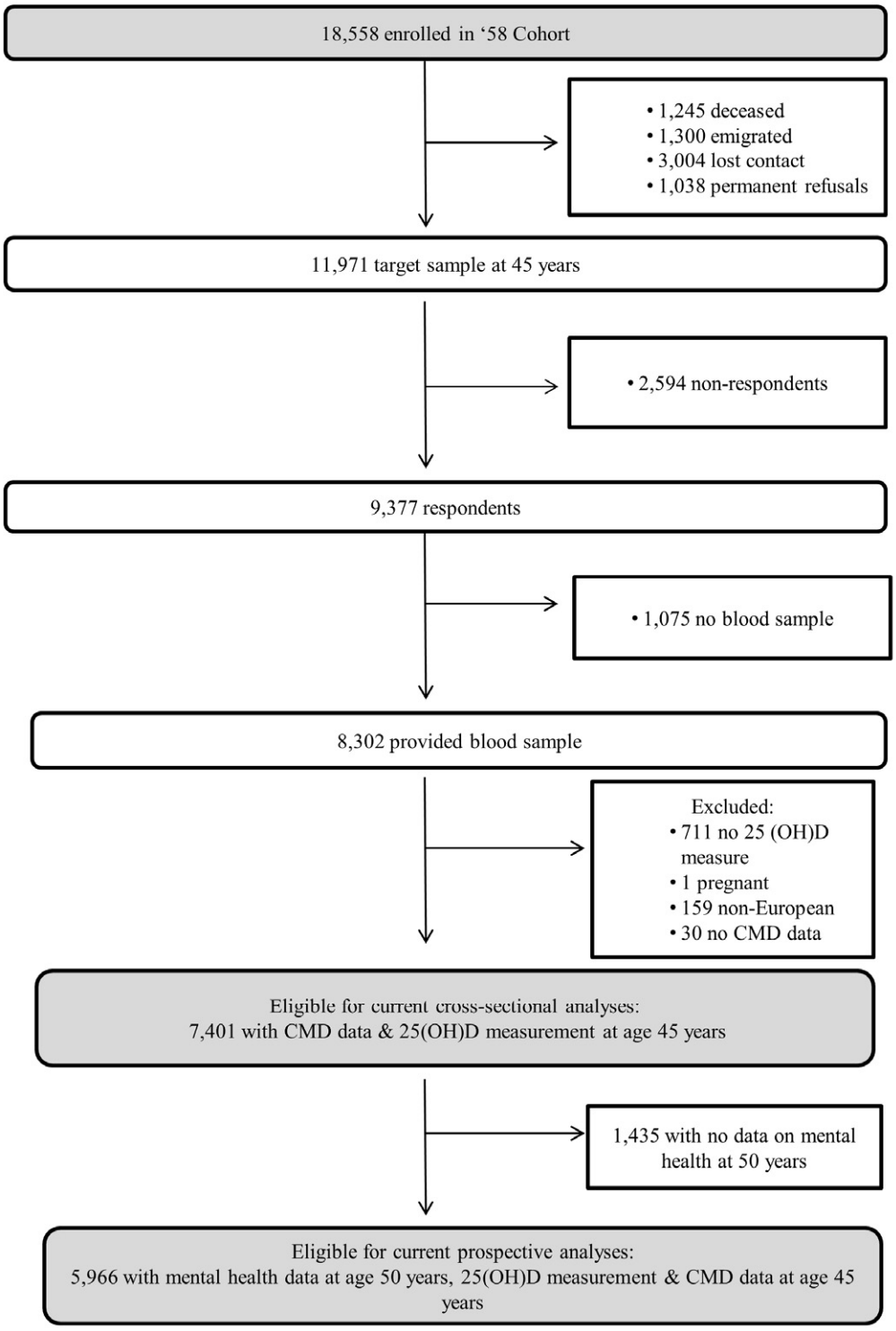

18,558 enrolled in '58 Cohort
• 1,245 deceased
• 1,300 emigrated
• 3,004 lost contact
• 1,038 permanent refusals
11,971 target sample at 45 years
• 2,594 non-respondents
9,377 respondents
• 1,075 no blood sample
8,302 provided blood sample
Excluded:
• 711 no 25 (OH)D measure
• 1 pregnant
• 159 non-European
• 30 no CMD data
Eligible for current cross-sectional analyses:
7,401 with CMD data & 25(OH)D measurement at age 45 years
1,435 with no data on mental health at 50 years
Eligible for current prospective analyses:
5,966 with mental health data at age 50 years, 25(OH)D measurement & CMD data at age 45 years

TABLE 1 Characteristics of participants with common mental disorders (≥2 symptoms)

	Total (*n* = 7,401)	Depression (*n* = 595)	Anxiety (*n*=506)	Panic (*n*=107)	Phobia (*n*=304)
Sex					
Male	3,705	7.0 (259)[a]	5.4 (201)	0.8 (28)	3.1 (114)
Female	3,696	9.1 (336)	8.3 (305)	2.1 (79)	5.1 (190)
Combined	7,401	8.0 (595)	6.8 (506)	1.5 (107)	4.1 (304)
p		0.001	<0.001	<0.001	<0.001
Season					
Winter/spring	2,832	8.1 (228)	6.1 (174)	1.3 (36)	3.8 (108)
Summer/autumn	4,569	8.0 (367)	7.3 (332)	1.6 (71)	4.3 (196)
p †		0.99	0.06	0.30	0.30
Region					
South	2,842	7.4 (211)	6.4 (181)	1.3 (38)	3.7 (105)

Middle	1,920	8.5 (163)	7.7 (148)	1.6 (31)	4.8 (92)
North	1,928	8.5 (163)	6.5 (126)	1.2 (24)	3.7 (72)
Scotland	711	8.2 (58)	7.2 (51)	2.0 (14)	4.9 (35)
p †		0.24	0.54	0.49	0.33
Socioeconomic Position					
prof & managerial-tech	2,998	6.1 (182)	6.1 (183)	0.9 (27)	3.0 (89)
skilled non-manual	1,520	8.8 (133)	7.6 (115)	1.3 (20)	4.3 (66)
skilled & partly-skilled manual	2,309	8.1 (187)	5.9 (136)	1.5 (34)	4.3 (100)
unskilled & other/unknown	574	16.2 (93)	12.5 (72)	4.5(26)	8.5 (49)
p †		<0.001	0.002	<0.001	<0.001
Physical Activity					

<2-3 x per mo	2,393	9.7 (233)	8.4 (200)	1.9 (45)	4.9 (118)
1 x per wk	1,349	6.3 (85)	5.0 (67)	1.0 (13)	2.4 (32)
2-3 x per wk	1,552	7.0 (108)	5.8 (90)	1.1 (17)	3.4 (53)
4-7 x per wk	1,881	7.6 (142)	6.7 (126)	1.5 (28)	4.9 (92)
Missing	226	12.0 (27)	10.2 (23)	1.8 (4)	4.0 (9)
p †		0.006	0.02	0.20	0.86
Smoking status[b]					
Never smoked	3,409	7.0 (240)	6.2 (212)	1.2 (41)	2.8 (94)
Ex-smoker	2,027	7.2 (146)	5.6 (113)	0.9 (19)	3.8 (77)
Smokes 1-19	861	8.4 (72)	8.6 (74)	2.4 (21)	6.3 (54)
Smokes ≥ 20	870	12.8 (111)	9.7 (84)	2.5 (22)	8.1 (70)
Missing	234	11.1 (26)	9.8 (23)	1.7 (4)	3.9 (9)
p †		<0.001	<0.001	<0.001	<0.001
Alcohol consumption					
Non-drinker	457	16.4 (75)	11.6 (53)	4.2 (19)	8.3 (38)

Light <7 units/wk	3,562	8.0 (285)	6.7 (237)	1.4 (51)	4.0 (141)
Moderate 7-14 units/wk	1,852	5.7 (105)	6.0 (111)	0.7 (12)	3.0 (55)
Heavy 14-21 units/wk	827	7.9 (65)	6.8 (56)	1.7 (14)	4.6 (38)
Very heavy >21 units/wk	687	9.2 (63)	7.1 (49)	1.6 (11)	4.5 (31)
Missing	16	12.5 (2)	-	-	6.3 (1)
p †		0.08	0.81	0.51	0.83
BMI, kg/m²					
<30	5,628	7.5 (424)	6.6 (370)	1.3 (71)	3.9 (217)
≥30	1,748	9.5 (166)	7.7 (135)	2.0 (34)	4.9 (86)
Missing	25	20.0 (5)	4.0 (1)	8.0 (2)	4.0 (1)
p †		0.007	0.08	0.03	0.04

[a] Values are presented as percentage (count).

[b] Physical activity and smoking status taken at 42 years.

† P value from likelihood ratio test adjusted for sex, does not include missing covariates.

TABLE 2 Common mental disorders and vitamin D related lifestyle factors at age 45 *(n = 7,401)*[a]

	Participants	>3 h outside/d *(n=2,944)*	>3 h TV/PC/d *(n=2,376)*	Sun-cover most of the time *(n=6,188)*	Often blister after sunburn *(n=129)*	Often actively seek suntan *(n=1,391)*	Vitamin D supplements ≥ daily *(n=1,185)*	Oily fish at least weekly *(n=2,191)*	Margarine at least weekly *(n=4,563)*
Depression									
< 2 symptoms	92.0 (6,806)[b]	39.9 (2,715)	31.7 (2,155)	84.3 (5,740)	1.6 (110)	19.0 (1,292)	16.2 (1,100)	29.9 (2,037)	62.0 (4,216)
≥ 2 symptoms	8.0 (595)	38.5 (229)	37.1 (221)	75.3 (448)	3.2 (19)	16.6 (99)	14. 2 (85)	25.9(154)	58.3 (347)
p[†]		0.88	0.008	<0.001	0.007	0.35	0.48	0.10	0.11
Anxiety									
< 2 symptoms	93.2 (6,895)	39.9 (2,749)	31.8 (2,191)	83.4 (5,783)	1.7 (115)	19.1 (1,315)	16.0 (1,105)	29.5 (2,034)	61.9 (4,268)
≥ 2 symptoms	6.8 (506)	35.5 (195)	36.6 (185)	80.0 (405)	2.8 (14)	15.0 (76)	15.8 (80)	31.0 (157)	58.3 (295)

$p^{\dagger}$		0.89	0.01	0.02	0.09	0.02	0.84	0.56	0.19
Panic									
< 2 symptoms	98.6 (7,294)	39.7 (2,897)	32.0 (2,333)	83.7 (6,105)	1.7 (123)	18.9 (1,378)	16.0 (1,170)	29.5 (2,152)	61.7 (4,503)
≥ 2 symptoms	1.5 (107)	43.9 (47)	40.2 (43)	77.6 (83)	5.6 (6)	12.2 (13)	14.0 (15)	36.5(39)	56.1 (60)
$p^{\dagger}$		0.19	0.07	0.45	0.02	0.07	0.73	0.09	0.57
Phobia									
< 2 symptoms	95.9 (7,097)	39.7 (2,815)	31.5 (2,233)	83.7 (5,938)	1.7 (119)	18.8 (1,331)	16.1 (1,142)	29.6 (2,100)	61.8(4,383)
≥ 2 symptoms	4.1 (304)	42.4 (129)	47.0 (143)	82.2 (250)	3.3 (10)	19.7 (60)	14.1 (43)	29.9 (91)	59.2 (180)
$p^{\dagger}$		0.52	<0.001	0.69	0.08	0.92	0.42	0.85	0.60

[a] N varies according to missing covariates, ranging from 7,243 (supplements and oily fish data missing) to 6,565 (blistering after sunburn data missing).

[b] Values are presented as percentage (count).

† *P* value from likelihood ratio test adjusted for sex and socioeconomic position at adulthood.

TABLE 3 Association between 25(OH) D and common mental disorders at age 45 (n = 7,401)[a,b]

	25- Hydroxyvitamin D, nmol/l					
	<25	25-49.9	50-74.9	75-99.9	≥100	*P*-trend
Depression, % (n)	13.0 (75)	8.8 (222)	7.4 (196)	6.6 (79)	5.0 (23)	
Model 1	1.0	0.64 (0.48, 0.85)[c]	0.50 (0.37, 0.67)	0.43 (0.31, 0.62)	0.32 (0.19, 0.52)	<0.001
Model 2	1.0	0.68 (0.51, 0 .90)	0.55 (0.40, 0.74)	0.47 (0.33, 0.67)	0.34 (0.21, 0.56)	<0.001
Model 3	1.0	0.68 (0.51, 0.91)	0.56 (0.41, 0.76)	0.49 (0.34, 0.70)	0.36 (0.22, 0.60)	<0.001
Model 4	1.0	0.75 (0.56, 1.00)	0.65 (0.48, 0.89)	0.59 (0.41, 0.86)	0.43 (0.26, 0.73)	0.001
Anxiety, % (n)	8.6 (50)	7.2 (180)	6.2 (165)	6.6 (79)	6.9 (32)	
Model 1	1.0	0.80 (0.58, 1.12)	0.64 (0.45, 0.90)	0.67 (0.45, 0.98)	0.68 (0.42, 1.10)	0.03
Model 2	1.0	0.82 (0.59, 1.14)	0.66 (0.47, 0.94)	0.69 (0.47, 1.02)	0.71 (0.44, 1.15)	0.05
Model 3	1.0	0.82 (0.59, 1.15)	0.68 (0.48, 0.96)	0.71 (0.48, 1.05)	0.74 (0.45, 1.20)	0.09
Model 4	1.0	0.94 (0.67, 1.32)	0.85 (0.59, 1.22)	0.97 (0.64, 1.46)	1.03 (0.62, 1.71)	0.98

Panic, % (*n*)	3.3 (19)	1.4 (36)	1.5 (39)	0.8 (9)	0.9 (4)	
Model 1	1.0	0.42 (0.24, 0.75)	0.38 (0.2, 0.68)	0.19 (0.08, 0.43)	0.20 (0.07, 0.62)	<0.001
Model 2	1.0	0.46 (0.26, 0.83)	0.44 (0.24, 0.79)	0.21 (0.09, 0.49)	0.23 (0.08, 0.72)	0.001
Model 3	1.0	0.47 (0.26, 0.84)	0.46 (0.25, 0.85)	0.23 (0.09, 0.54)	0.26 (0.08, 0.81)	0.002
Model 4	1.0	0.53 (0.29, 0.97)	0.59 (0.31, 1.11)	0.32 (0.13, 0.79)	0.39 (0.12, 1.28)	0.048
Phobia, % (*n*)	6.4 (37)	4.2 (105)	4.2 (110)	3.9 (46)	1.3 (6)	
Model 1	1.0	0.62 (0.42, 0.92)	0.57 (0.38, 0.86)	0.52 (0.33, 0.84)	0.17 (0.07, 0.41)	<0.001
Model 2	1.0	0.65 (0.44, 0.96)	0.62 (0.41, 0.92)	0.56 (0.34, 0.90)	0.18 (0.07, 0.44)	<0.001
Model 3	1.0	0.65 (0.44, 0.97)	0.63 (0.42, 0.94)	0.58 (0.36, 0.93)	0.19 (0.08, 0.46)	<0.001
Model 4	1.0	0.75 (0.50, 1.12)	0.81 (0.53, 1.23)	0.77 (0.47, 1.28)	0.25 (0.10, 0.62)	0.052

[a] Multiple imputation used for missing information on covariates.

[b] Model 1 was adjusted for sex & season. Model 2 was adjusted for sex, season & socioeconomic position. Model 3 was adjusted for sex, season & socioeconomic position and Body Mass Index. Model 4 was adjusted for sex, season, socioeconomic position, Body Mass Index, smoking and physical activity, PC/TV leisure time, sun-cover, blistering after sunburn, actively seeking suntan.

[c] Values are presented as Odds Ratio (95% Confidence Interval).