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Association between serum concentration of 25-hydroxyvitamin D and the risk of hip arthroplasty for osteoarthritis: result from a prospective cohort study

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SUMMARY

Objectives: There is ongoing debate regarding the optimal serum concentrations of 25-hydroxy-vitamin D for musculoskeletal health, including osteoarthritis (OA). The aim of this prospective cohort study was to determine whether serum 25-hydroxy-vitamin D concentrations were associated with the risk of hip arthroplasty for OA.

Design: This study examined 9135 participants from the Australian Diabetes, Obesity and Lifestyle Study who had serum 25-hydroxy-vitamin D measured in 1999–2000 and were aged ≥40 years at the commencement of arthroplasty data collection. The incidence of hip arthroplasty for OA during 2002–2011 was determined by linking cohort records to the Australian Orthopaedic Association National Joint Replacement Registry.

Results: Over an average 9.1 (standard deviation (SD) 2.7) years of follow-up, 201 hip arthroplasties for OA were identified (males $n = 90$; females $n = 111$). In males, a one-standard-deviation increase in 25-hydroxy-vitamin D was associated with a 25% increased incidence (HR 1.25, 95% CI 1.02–1.56), with a dose response relationship evident by quartiles of 25-hydroxy-vitamin D concentration (P for trend 0.04). These results were independent of age, body mass index (BMI), ethnicity, smoking status, physical activity, season of blood collection, latitude, hypertension and diabetes, area level disadvantage or after excluding those with extreme low 25-hydroxy-vitamin D concentrations. No significant association was observed in women (HR 1.10, 95% CI 0.87, 1.39).

Conclusions: Increasing serum 25-hydroxy-vitamin D concentrations were associated with an increased risk of hip arthroplasty for OA in males, while no significant association was observed in females. The mechanism for the association warrants further investigation.

Introduction

Osteoarthritis (OA) is the most common form of arthritis, causing pain and functional disability. Symptomatic hip OA represents a substantial burden with one in four people developing this condition in their lifetime[1]. The number of years lived with disability for hip OA has increased over the last two decades[2]. Bone is a dynamic tissue undergoing constant remodelling and plays an

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important role in the pathogenesis of OA. Radiographic and biochemical studies have indicated that bone and cartilage pathology are linked in OA[3,4]. Hip geometry is an important risk factor for OA, with subtle bone microarchitectural changes predating radiographic hip OA[5,6].

There is ongoing debate regarding optimal serum concentrations of 25-hydroxy-vitamin D [25(OH)D] for skeletal health[7,8]. Vitamin D plays an essential role in promoting calcium absorption to enable mineralization and promote healthy bones as well as improve lower extremity muscle function and reduce falls risk[9]. Vitamin D also has multiple biological functions in cartilage via vitamin D receptors[10]. While articular cartilage loss is a key feature of OA, OA is now recognised as a disease of the whole joint. The interaction between bone and cartilage is believed to be central to cartilage homoeostasis. Thus vitamin D status might affect the development and progression of hip OA, either directly via its effects on cartilage, or indirectly via its effects on bone[11]. However, the relationship between serum 25(OH)D concentrations and the risk of hip OA is inconclusive[11–14]. While some studies reported that low serum 25(OH)D concentrations were associated with an increased prevalence and incidence of hip OA[11,12], others showed no association[13,14]. The relationship between serum 25(OH)D concentrations and health outcomes may be affected by several factors such as season of blood collection, ageing, latitude, obesity, physical activity, and smoking[15]. The previous studies on vitamin D and OA had a number of limitations which make interpretation of the findings difficult, including small sample sizes[11–13], cross-sectional study design[12], and failure to adjust for important confounders[11,12]. As a result the role of serum 25(OH)D concentrations in the pathogenesis of OA remained unknown. Moreover, these studies have used different methods to define hip OA, such as radiographic hip OA[11,12], clinical examination by physicians[13] or the International Classification of Diseases codes[14]. One method for defining OA is to use arthroplasty, which identifies severe hip OA relevant to symptomatic disease burden and economic impact[16,17]. The aim of this prospective cohort study was to determine whether serum 25(OH)D concentrations were associated with the risk of hip arthroplasty for OA in a large cohort of Australian adults.

Patients and methods

Study participants

The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study is a national, population-based cohort study of 11,247 people, aged ≥25 years, recruited by a stratified cluster sampling method, involving seven strata (six states and the Northern Territory) and clusters based on census collector districts, during 1999 to 2000[18]. The study was approved by the International Diabetes Institute Ethics Committee and the Monash University Human Research Ethics Committee[18]. All participants gave written informed consent. For the current study, participants were restricted to those aged ≥40 years at the commencement of arthroplasty data collection (January 2002) by the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR), as arthroplasty for the treatment of OA is very uncommon under this age[19]. Of the 11,247 AusDiab participants that attended a biomedical evaluation and provided a fasting blood sample in 1999/2000, a total of 2,112 were excluded as they were aged <40 years or had the first recorded arthroplasty as a revision surgery, leaving 9,135 participants eligible for the current study. The data linkage study was approved by the Alfred Hospital Ethics Committee, the University of Adelaide and Monash University Human Research Ethics Committees.

Demographic, lifestyle factors, and socioeconomic position assessments

Demographic and lifestyle data, including date of birth, gender, ethnicity (Europid vs non-Europid), smoking (current-, ex- or never), and leisure time physical activity (minutes per week), were collected in 1999–2000 by trained interviewers using standardised questionnaires as reported previously[18]. Physical activity was assessed using the Active Australia Survey, which predominantly assesses leisure-time physical activity which includes duration and frequency of walking for recreation or transport; other moderate activity e.g., lawn bowls, golf, and gentle swimming; and vigorous activity e.g., gardening, tennis, jogging, cycling, and keep-fit exercise during the previous week[20]. Total physical activity represents the sum of the time spent walking (if continuous and 10 min or more), the time spent doing other moderate intensity activities, plus the time spent participating in vigorous intensity activity. According to the current public health physical activity guidelines recommendation, participants were categorized as insufficiently active (reporting some moderate- or vigorous-intensity physical activity but less than 150 min in the last week), or sufficiently active (reporting 150 min or more activity at a moderate- or vigorous-intensity level in the last week)[20]. This physical activity measure has been shown to provide acceptable precision [intra-class correlation = 0.59, 95% confidence interval (CI) 0.52 to 0.65] and validity (criterion validity = 0.3) estimates of exercise among adults[20,21]. Data on vitamin D supplement use was not obtained.

Area-level socioeconomic disadvantage was estimated using the Index of Relative Disadvantage code from the Socioeconomic Indexes for Areas (SEIFA). The index was developed by the Australian Bureau of Statistics. This is a summary measure from a group of 20 variables (related to education, income, employment, family composition, housing benefits, car ownership, ethnicity, English language proficiency, residential overcrowding) displaying dimensions of social disadvantage[22]. The index is constructed such that high values reflect areas with high socioeconomic position (relative advantage) and low values reflect areas with low socioeconomic position (relative disadvantage).

Anthropometric and clinical measurements

Height was measured to the nearest 0.5 cm without shoes using a stadiometer. Weight was measured without shoes and in light clothing to the nearest 0.1 kg using a mechanical beam balance. Body mass index (BMI) was calculated as weight in kilogrammes divided by height in metres squared[18]. Blood pressure was measured with Dinamap/mercury sphygmomanometer[18]. Hypertension was defined as systolic and diastolic blood pressure >140/90 mm Hg or current use of antihypertensive medication[18].

Fasting plasma glucose (FPG) and 2-h plasma glucose (2-h PG) were measured with an Olympus AU600 analyzer (Olympus Optical, Tokyo, Japan)[18]. Participants were classified as having known diabetes mellitus if they reported having doctor diagnosed diabetes mellitus and were either taking hypoglycaemic medication or had an FPG ≥7.0 mmol/L or 2-h PG ≥ 11.1 mmol/L. Participants not reporting having diabetes mellitus but who had an FPG ≥7.0 mmol/L or 2-h PG ≥ 11.1 mmol/L were classified as having newly diagnosed diabetes mellitus.

Assessment of vitamin D status and dietary calcium intake

Blood samples were stored at −70°C until assayed. As previously reported[23], serum 25(OH)D was measured in the entire AusDiab population at baseline (1999/2000) using the Liaison 25(OH)D TOTAL (Liaison 25OHD) (DiaSorin Inc., Stillwater, MN), a

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direct competitive chemiluminescent immunoassay with an inter-assay coefficient of variation of 7.0% at 45 nmol/L and 6.3% at 93 nmol/L. In 210 samples where fasting serum were not available, fluoride oxalate plasma (fasting plasma n = 190; 2-h plasma post-OGTT n = 20) was used[24]. There was excellent agreement between serum 25(OH)D concentrations collected from both tubes (n = 100): fluoride oxalate plasma 25(OH)D = 0.97 × serum 25(OH)D + 2.5,r^2 = 0.89[24]. Season of blood sampling was divided into: Summer (Dec to Feb), Autumn (Mar to May), Winter (June to Aug) and Spring (Sept to Nov)[25]. The latitude of each blood collection centre was determined using the Google GPS tool (range 12–43°S)[24].

Total energy including dietary calcium intake was assessed using a self-administered validated food frequency questionnaire[20,24]. Nutrient intake was calculated by multiplying the frequency of consumption by standard portion weights, which were then converted into nutrient intakes based on the NUTTAB95 nutrient composition database[20,24]. Dietary calcium intake was adjusted for total energy intake by using the residual method[24].

Identification of incident primary hip arthroplasty

Cases were identified from the AOA NJRR as those who underwent a primary hip arthroplasty. Detailed information is available on prostheses, patient demographics, type and reason for arthroplasty. Data are collected from both public and private hospitals and validated using a sequential multi-level matching process against State and Territory Health Department unit record data[26]. Following the validation process and retrieval of unreported records, the Registry collects an almost complete set of data relating to hip arthroplasty in Australia[26]. Matching of AusDiab participants using first name, surname, date of birth, and gender, to the AOA NJRR in order to identify those who had an arthroplasty performed between 1 January 2002 and 31 December 2011 was performed using U.S. Bureau of the Census Record Linkage Software. This study examined the first hip arthroplasty with a contemporaneous diagnosis of OA, as recorded in the AOA NJRR[27]. If one person had multiple arthroplasties, such as bilateral hip arthroplasties, or both knee and hip arthroplasties, the first recorded procedure was considered the event.

Statistical analysis

Independent (unpaired) samples t-tests (i.e., Student's t-test for independent samples) for continuous variables or chi-squared tests for categorical variables were used to compare the characteristics of the participants with and without hip arthroplasty for OA. Cox proportional hazard regression models were used to estimate the hazard ratio (HR) with 95% CI for the incidence of hip arthroplasty due to OA associated with serum 25(OH)D, with age as the time scale. Follow-up for arthroplasty (calculation of person-time) began at 1 January 2002, and ended at the date of first hip arthroplasty for OA or date of censoring. Participants were censored at either the date of first hip arthroplasty for indications other than OA, the date of death, or end of follow-up (31 December 2011), whichever came first. To test whether associations of serum 25(OH)D with hip arthroplasty risk were modified by sex, obesity, physical activity (sufficient vs insufficient) or age (<65 years vs ≥65 years), interactions were fitted, and tested using the likelihood ratio test. Since an interaction with sex was identified, all analyses were performed for males and females separately, and adjusted for BMI, smoking status, ethnicity, physical activity, season of blood collection and latitude (model 1). Area-level disadvantage, diabetic status and hypertension were additionally adjusted for in model 2. Owing to the importance of calcium in bone health, dietary calcium intake was also adjusted in a separate model with other variables. As walking and gardening are outdoor activities which might affect serum 25(OH)D concentrations, additional modelling was done including walking and gardening time instead of physical activity. Serum 25(OH)D was standardized so that the HRs represent the effect of a one-standard-deviation (SD) difference in 25(OH)D. Serum 25(OH)D was also categorized into gender specific quartiles. The lowest quartile was used as the referent category. Linear association between 25(OH)D and hip arthroplasty risk was examined using the likelihood ratio test. The P-value for trend was calculated by assigning the participants the median value of each serum 25(OH)D category and including this as a continuous variable in the model. To ensure that the result was not driven by extremely low 25(OH)D concentrations, additional analysis was done excluding those with vitamin D deficiency (25(OH)D < 25 nmol/L, n = 276). Death is an event that precludes the assessment of hip arthroplasty for hip OA, i.e., a competing event. To counter this issue we performed competing-risks regression according to the method of Fine and Gray. Tests based on Cox regression methods and Competing-risks regression showed no evidence that underlying assumptions were violated for any analysis. All statistical analyses were performed using Stata 12.0 (StataCorp LP., College Station, TX, USA).

Results

Over 9.1 (SD 2.7) years of follow-up, 201 hip arthroplasties for OA were identified (men n = 90; women n = 111). The characteristics of the participants are presented in Table I. Both males and females who received a hip arthroplasty for OA were older, having greater BMI, and more likely to be Europid and hypertensive.

Since sex modified the associations between serum 25(OH)D concentration and hip arthroplasty risk (P = 0.05), men and women were examined separately (Table II). In men, a one SD increase in 25(OH)D was associated with a 25% increased risk of hip arthroplasty for OA (HR 1.25, 95% CI 1.02, 1.56). When the 25(OH)D concentration was examined as quartiles, there was a dose response relationship between increasing quartiles of serum 25(OH)D concentration and the risk of hip arthroplasty for OA (P for trend = 0.04), independent of age, BMI, ethnicity smoking status, physical activity, season of blood collection and latitude, hypertension and diabetes, and socioeconomic position. Adjustment for walking and gardening time instead of physical activity did not change the association (HR 1.25, 95% CI 1.01, 1.54). Additional adjustment for dietary calcium intake did not change the association (data not shown). In contrast, there was no associations between serum 25(OH)D concentration and hip arthroplasty for OA in women (HR 1.10, 95% CI 0.87, 1.39). When we excluded participants with serum 25(OH)D concentrations <25 nmol/L, a one SD increase in 25(OH)D was associated with a 23% increased incidence of hip arthroplasty in men (HR 1.23, 95% CI 1.01, 1.53). The subdistribution hazard ratios derived from competing-risks regression analysis were very similar as the HRs from the Cox regression analysis (data not shown).

Discussion

In this prospective cohort study, higher serum 25(OH)D concentrations predicted an increased risk of hip arthroplasty for OA in males but not in females, independent of age, BMI, smoking status, physical activity, season of blood collection and latitude, comorbidities and socioeconomic position. These results persisted when those with low concentrations of 25(OH)D were excluded.

The data is conflicting regarding the association between serum 25(OH)D concentrations and the risk of hip OA[11–14]. Our findings suggest that serum 25(OH)D concentrations are

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Table I
Baseline characteristics of participants with and without hip OA over the follow-up period

	Hip OA	No hip OA	*P* Value
Male			
Number	90	4052	
Age, years	60.2 (10.2)	56.0 (12.0)	<0.001
Europids, *n* (%)	88 (97.8)	3,647 (90.1)	0.02
Area-level disadvantage (lowest tertile %)	34 (38.6)	1,276 (32.0)	0.33
BMI, kg/m^2	28.6 (3.5)	27.3 (4.1)	0.003
Current/ex-smoker, *n* (%)	9 (11.0)	633 (16.0)	0.18
Physical activity, min/week	250 (263)	316 (304)	0.09
Walking, times/week	3.4 (0.4)	4.0 (0.1)	0.27
Gardening, times/week	1.1 (0.2)	0.8 (0.0)	0.27
Blood collection time, *n* (%)			0.004
Summer (Dec–Feb)	4 (4.4)	457 (11.3)	
Autumn (Mar–May)	35 (38.9)	954 (23.5)	
Winter (June–Aug)	26 (28.9)	1,354 (33.4)	
Spring (Sept–Nov)	25 (27.8)	1,287 (31.8)	
Latitude by region, *n* (%)			0.006
<30°	12 (13.3)	1,058 (26.1)	
30°–35°	39 (43.3)	1,755 (43.3)	
>35°	39 (43.3)	1,239 (30.6)	
Diabetes, *n* (%)	7 (7.8)	477 (11.9)	0.24
Hypertension, *n* (%)	49 (54.5)	1,703 (42.3)	0.02
Dietary calcium, mg/day	904 (364)	919 (340)	0.35
Serum 25(OH)D, nmol/L	71.6 (21.9)	68.6 (24.8)	0.24
Female			
Number	111	4853	
Age, years	62.2 (10.7)	55.6 (12.2)	<0.001
Europids, *n* (%)	107 (96.4)	4,360 (89.9)	0.02
University/Further education, *n* (%)	33 (29.7)	1,470 (30.3)	0.90
Area-level disadvantage (lowest tertile %)	32 (29.1)	1,595 (33.4)	0.64
BMI, kg/m^2	28.0 (5.2)	27.0 (5.5)	0.07
Current/ex-smoker, *n* (%)	16 (14.7)	596 (12.5)	0.50
Physical activity, min/week	218 (265)	223 (282)	0.83
Walking, times/week	2.9 (0.3)	3.4 (0.1)	0.24
Gardening, times/week	0.6 (0.1)	0.5 (0.0)	0.33
Blood collection time, *n* (%)			0.14
Summer (Dec–Feb)	14 (12.6)	560 (11.5)	
Autumn (Mar–May)	35 (31.5)	1,101 (22.7)	
Winter (June–Aug)	32 (28.8)	1,589 (32.7)	
Spring (Sept–Nov)	30 (27.0)	1,603 (33.0)	
Latitude by region, *n* (%)			0.29
<30°	30 (27.0)	1,286 (26.5)	
30°–35°	42 (37.8)	2,156 (44.4)	
>35°	39 (35.1)	1,411 (29.1)	
Diabetes, *n* (%)	9 (8.2)	403 (8.4)	0.93
Hypertension, *n* (%)	54 (48.6)	1,688 (35.0)	0.003
Dietary calcium, mg/day	881 (297)	881 (340)	0.51
Serum 25(OH)D, nmol/L	57.2 (20.6)	57.3 (22.1)	0.96

Data are presented as mean ± SD, or as percentage.

positively associated with risk of hip replacement for OA in men, but not women. The Mini-Finland Health Examination Survey, a 22 year follow-up study of 805 Finnish people including 22 with hip OA[13], and the Health 2000 Survey of Finland, a 10 years follow-up study of 5,274 Finnish people including 45 with hip OA[14], concluded that low concentrations of 25(OH)D do not contribute to the development of hip OA. However, the Health 2000 Survey of Finland found a weak trend (*P* for trend 0.053) for increasing concentration of serum 25(OH)D to be associated with increased risk of hip OA[14]. It is difficult to compare findings across studies because the baseline serum 25(OH)D concentrations in the two Finnish studies were 12–25 nmol/L lower than in our study, and the two Finnish studies had smaller numbers of outcome. Similarly, a recent systematic review found limited or conflicting evidence for an association between concentrations of serum 25(OH)D and the incidence or progression of radiographic hip OA[28]. In contrast, increasing serum concentrations of 25(OH)D were associated with decreased incidence of radiographic hip OA over an average period of 8 years in 237 women from the Study of Osteoporotic Fractures[11]. Similarly, the Osteoporotic Fractures in Men Study, which was a cross-sectional study from six areas of the US, found that men with vitamin D deficiency (≤37.44 nmol/L) were more likely to have radiographic hip OA[12]. However, the participants of these two studies were older (>70 years at baseline) than our population, and the Study of Osteoporotic Fractures did not adjust for season of blood collection[11], which is strongly associated with serum 25(OH)D concentrations.

The finding of an increased risk of hip arthroplasty for OA in men with increasing serum 25(OH)D concentrations, after adjusting for potential confounding, is difficult to explain. We found that men in the highest quartile of serum 25(OH)D concentration were of similar age and socioeconomic position, more physically active, had lower BMI and were less likely to be diabetic and hypertensive than those in the lower quartiles, suggesting they were healthier and more fit for undergoing hip arthroplasty (Supplementary Table 1). Nevertheless, the rate of hip arthroplasty was similar across all the tertiles of the socioeconomic status (2.1% highest, 2.3% middle and 2.3% lowest tertile, $P = 0.90$) and in the diabetic and non-diabetic men (1.5% vs 2.2%, $P = 0.24$), but it was higher in obese men (non-obese vs obese, 1.9% vs 3.2%, $P = 0.02$) and those who were hypertensive (non-hypertensive vs hypertensive, 1.7% vs 2.8%, $P = 0.02$).

Table II
Relationship of serum 25(OH)D concentrations with incidence of hip arthroplasty for OA

	Model 1 hazard ratio (95% CI)	*P*	Model 2 hazard ratio (95% CI)	*P*
Male				
Serum 25(OH)D (per SD)	1.25 (1.02, 1.56)	0.02	1.26 (1.01, 1.56)	0.04
Serum 25(OH)D Quartile				
1 (≤51 nmol/L)	1.00		1.00	
2 (52–65 nmol/L)	2.03 (1.01, 4.03)	0.04	2.02 (1.01, 4.06)	0.05
3 (66–81 nmol/L)	2.18 (1.07, 4.05)	0.03	2.17 (1.08, 4.06)	0.03
4 (≥82 nmol/L)	2.30 (1.09, 4.82)	0.03	2.30 (1.09, 4.82)	0.03
P for trend	0.02		0.04	
Female				
Serum 25(OH)D (per SD)	1.10 (0.87, 1.39)	0.44	1.11 (0.88, 1.41)	0.39
Serum 25(OH)D Quartile				
1 (≤41 nmol/L)	1.00		1.00	
2 (42–54 nmol/L)	1.30 (0.76, 2.23)	0.35	1.21 (0.70, 2.09)	0.50
3 (55–69 mmol/L)	1.10 (0.62, 1.95)	0.75	1.08 (0.61, 1.91)	0.80
4 (≥70 nmol/L)	1.29 (0.71, 2.33)	0.40	1.29 (0.71, 2.34)	0.40
P for trend	0.54		0.49	

Model 1 adjusted for BMI, ethnicity, smoking status, physical activity, season of blood collection and latitude.
Model 2 adjusted for model 1 and hypertension, diabetes, and Area-level disadvantage.

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The mechanism for a positive association between serum 25(OH)D concentrations and risk of end-stage hip OA requiring hip arthroplasty is unclear. Vitamin D is important in regulating calcium homoeostasis by enabling calcium absorption though the small intestine[29] and the vitamin D receptor present in the bone forming osteoblast cells directly affects osteoblast growth and differentiation by stimulating bone formation[30]. Each of these protects against predominantly anabolic state of bone which may result in bone sclerosis or altered hip bone geometry that have a central role in hip OA[31,32].

Another possible mechanism for the positive association between serum 25(OH)D and end-stage hip OA may be mediated through increased bone mineral density (BMD). Serum 25(OH)D (with or without calcium) and BMD are significantly related to one another[33,34]. A recent study showed that increased BMD was associated with cam-type femoroacetabular impingement characterised by a convex deformity of the antero-superior femoral head–neck junction[35]. Cam-type deformity is associated with development of painful degenerative hip disease through chondral injury and eventual cleavage of the cartilage layer[5,35,36]. Both the Chingford study and the Framingham study reported an increase of up to 15% in BMD in patients with OA compared with those without[37,38].

In our study those in the highest quartile of serum 25(OH)D concentration were more active. Thus, the positive association between concentration of serum 25(OH)D and the risk of hip OA may be mediated through physical activity. Physical activity might accelerate “wear and tear” of the hip joints, resulting in joint injury which ultimately will lead to hip OA. Occupational or recreational physical activity has been associated with increased incidence of physician-diagnosed hip OA[39], and prolonged regular sporting activity has been associated with increased risk of hip arthroplasty for OA[40]. We have adjusted for time spent in leisure-time physical activity, or walking and gardening time, indicating our results could not be explained by recreational activity. Our study participants were drawn from the community, thus less likely to be involved in regular sporting activity. However, we do not have detailed occupational activity data which is an important risk factor for hip OA[41], so we were not able to address whether the association we observed was confounded by occupational activity.

The reason for the finding that there was detrimental effect of increasing serum 25(OH)D on the incidence of hip OA in males, but not in females, is not clear. However, we found that the concentrations of serum 25(OH)D were significantly different between males and females (mean 68.6 ± 24.8 nmol/L vs 57.3 ± 22.1 nmol/L, $P \leq 0.001$). It is possible that this gender difference in serum 25(OH)D may influence other biochemical or hormonal measures related to bone and/or cartilage health. For instance, sex steroids have been found to be associated with bone geometric structure change in the hip[42]. Besides, there are mutual interaction between vitamin D and estrogenic compounds[43], which might also explain our finding.

The strengths of our study include its prospective design, large sample size, measurement of serum 25(OH)D concentrations in the entire population at baseline, adjustment of season and latitude, and the validation and completeness of AOA NJRR data[26,27]. However, there are a number of limitations. The AusDiab participants were not investigated at baseline for hip OA. It is likely that some participants already had hip OA at baseline. Thus in this study serum 25(OH)D may be a marker of OA incidence, progression, or a marker of being selected for arthroplasty. Serum 25(OH)D was only measured at baseline, which may not reflect long term vitamin D status. We defined OA based on arthroplasty. However, arthroplasty as the treatment of OA may be influenced by a number of factors such as access to health care, socioeconomic status, and patient preference[44], in addition to disease severity. This study was carried out in Australia where there is universal health cover, so access to arthroplasty is available to all. Nevertheless, males with higher serum 25(OH)D concentrations may be more bound to maintain their moving ability and thus have an earlier arthroplasty. Furthermore, we performed the analysis on an age scale and adjusted for BMI, ethnicity, smoking status, physical activity, comorbidity and socioeconomic positioning to counter this issue. We have also compared the rate of hip replacement in different socioeconomic position categories and found no difference (2.1% highest, 2.3% middle and 2.3% lowest tertile, $P = 0.90$). We did not have joint replacement data prior to 2002. This may have resulted in non-differential misclassification of hip replacement, which is likely to bias the results to the null. It is possible that there is residual confounding that can contribute to the concentration of serum 25(OH)D, for example vitamin D supplementation and occupational and sports activities that might have provided alternative explanations of our findings. The results must be taken in context of the whole body of evidence. The findings of this study add to the ongoing debate regarding the optimal serum concentrations of 25(OH)D for joint health after controlling for potential confounders. Nevertheless, our population was community based and so it is unlikely that many of them were engaged in regular sporting activity. Finally, examination of hip arthroplasty for OA was not the primary goal of the AusDiab study.

Owing to a number of limitations, previous observational studies have reported inconclusive findings regarding the association between serum 25(OH)D concentrations and the risk of hip OA[11–14]. The hypothesis that vitamin D has beneficial effect on skeletal health and the results from some observational studies showing vitamin D insufficiency to be associated with a wide variety of disorders such as fractures, cardiovascular disease, and cancer have resulted in the use of widespread vitamin D supplementation[45]. Recent findings from sequential meta-analysis suggest that vitamin D supplementation with or without calcium does not reduce adverse skeletal outcomes in community-dwelling individuals[46]. Our study adds to the ongoing debate regarding the optimal serum concentrations of vitamin D for skeletal health particularly in the setting of widespread vitamin D supplementation.

This study showed that increasing serum 25(OH)D concentrations were associated with an increased risk of hip arthroplasty for OA in males, while no significant association was observed in females. The mechanism underlying the association warrants further investigation.

Authors' contributions

YW and FMC were involved in conception and design of the study. SMH was involved in statistical analysis and interpretation of the data, and drafted the manuscript. YW was involved in cleaning and merging the datasets and interpretation of the data. RMD, AEW and PRE were involved in the interpretation of the data. JES, DJM, RMD and SG were involved in the acquisition of the data. All authors reviewed the manuscript and approved the final manuscript. All authors had full access to all of the data in the study. FMC is the guarantor.

Ethical approval

The AusDiab study was approved by the International Diabetes Institute ethics committee. The current data linkage study was approved by the Alfred Hospital Ethics Committee, and the University of Adelaide and Monash University Human Research Ethics Committees. All participants gave written informed consent.

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Conflict of interest

None declared.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2015.06.006.

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