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Factors associated with vitamin D testing, deficiency, intake and supplementation in patients with chronic pain
Journal of Dietary Supplements, 2018; 15(5):636-648

As the estimated population proportion (P), was unknown we set P = 0.5 and δ, was set as 0.05 with the probability of type-I error being α=0.05. Using, this formula a sample size of 384 was estimated for effect size of 0.5 with 95% CI.

Statistical Analysis

To study the best predictors of described outcomes a common practice is to use a statistical model depending on the type of the variable (for example a linear model if the outcome is continuous). For binary outcomes univariate or multivariate logistic regression is used for estimating odds ratio (Lemeshow, 2013). The multivariate logistic regression allows simultaneous identification of possible risk factors in one model, after adjusting for all predictors. Regular logistic regression estimation is carried out by maximizing the likelihood function. However, when we have many potential predictors and the sample size is small, then there may not be a meaningful way to estimate the coefficients. In order to overcome this, the usual practice is to use stepwise regression. The trouble with stepwise regression is that it uses unconstrained least-square estimation processes, which can either over or underestimate effect sizes. To solve this issue, we used LASSO (Least absolute shrinkage and selection operator). LASSO is a regression technique that allows the selection of variables and estimation simultaneously in order to enhance the accuracy of the prediction and its interpretability (Tibshirani, 1996). LASSO was initially designed for simple linear regression, but was extended for general linear models such as logistic regression (Harrell, 1998). Estimation in LASSO is based on penalizing the likelihood

$$\hat{(\ )} = \text{argmax}(\ (\ ) - \sum_{=1} |\ |)$$

where , is the effect size estimate using maximum likelihood, is the penalty parameter and *p* is the number of covariates in the model. The parameter controls the complexity of the model. In cases where is zero, the estimate will be same as the simple logistic regression. To obtain an optimal value of the penalty parameter we looked at the convergence of the likelihood. For some of the models the penalty value was 0.5, and for others the penalty was 2. The other benefit of using LASSO is it actually specifies the covariates whose effect sizes are exactly zero, thus allowing selection of variables. All the statistical analysis was done in STATA 14.1. The LASSO logits regression were fitted using a special user written program in STATA [http://www.homepages.ucl.ac.uk/~ucakgam/stata.html].

Outcome measures

The outcomes were related to patient reported testing, prescription and consumption of vitamin D supplements. The following information was collected from the participants: i) had they been tested for vitamin D levels; ii) were their test results for vitamin D reported as deficient; iii) which supplements they used for their pain and for other ailments; and iv) which of those supplements were advised by their doctor. All outcome responses are dichotomized and were coded as 1 if Yes and 0 if No.

Independent Variables

The independent variables were the demographic factors of the participants' which included age, gender, country of residence, marital status, education level and employment status. Information regarding participants' pain experience was also collected. Participants were asked 'which of the following describe the characteristics of your pain? The choices given were aching, burning, sharp, pins and needles, throbbing and others. Participants were also asked if their pain was triggered by an injury, options provided were Yes and No. Participants also completed a numerical rating scale (NRS) anchored at left with 0 = no pain and at right with 10 = severe/worst pain in answer to the question 'what's the average severity of your pain?'

RESULTS

The survey was conducted online from 29th August to 24th October 2016. 573 people in total participated however, 108 of these had incomplete information and hence were excluded from the analysis thus giving us a complete sample of 465 participants. All analyses were conducted presuming no participants completed the survey multiple times. Distributions of the demographic characteristics of 465 participants are presented in Table 1.

Table 1 Distribution of the demographic characteristics of the sample

The age of participants ranged from 18 to 90 years, with almost equal number of participants from the age groups between 31- 40 years (22%) and 41-50 years (22%). Most participants were female and about two thirds were from Australia. Among the 465 participants, 57% (n=267 /465) reported that they had been tested for vitamin D and about 40% were aware that they had been diagnosed with vitamin D deficiency. Of those who had been tested for vitamin D, 60% (n= 162/267) were in fact taking vitamin D supplementation.

To identify significant predictors of each outcome a simple logistic regression analysis was performed. In each of these, individual logistic regressions all the factors presumed to be clinically useful for predicting the outcome, were entered simultaneously. In the simple logistic

regression, the factors significant for vitamin D testing were education, country of residence, employment status and gender. The factors that were significant for predicting vitamin D deficiency were gender and mean pain intensity. The factors significant for vitamin D intake were age, gender, employment status, marital status, education and country of residence. All these factors that were entered in logistic regressions were re-entered into the LASSO model. Results from the penalized logistic regression with LASSO suggest that some of the predictors that were initially significant in simple logistic regression were actually not statistically significant after penalizing.

The final model for the prediction of vitamin D deficiency consisted of six predictors: age, gender, country of residence, employment status, mean pain intensity and diagnosis for pain problem. For vitamin D testing additional predictors considered were: education level, pain related to injury, and duration of pain. For, vitamin D intake and doctor advised vitamin D supplementation, characteristics of pain, vitamin D deficiency, and vitamin D testing were considered.

The predictors gender (gender 0= females, 1= males), pain related to injury (No= 0, Yes =1), mean pain intensity (0 = ≤ 5 or 1= ≥ 6 on 11 point numerical scale), duration of pain (0 = <1 year or 1 = > 1 year), vitamin D tested (No= 0, Yes =1) and vitamin D deficient (No= 0, Yes =1) were treated as binary variables. Due to fewer number of cases in each individual category the characteristics of pain were categorized into 3 groups; 0= 1-4 characteristics, 1= 5-8 characteristics and 2= >9 characteristics, which is used as the base category for LASSO. The categorical predictors were re-coded as dummy variables before submitting in the regression.

Outcomes –

Table 2 presents a summary of factors associated with vitamin D testing. The odds ratios (OR) and their CIs suggest that males are half as likely as females to be tested for vitamin D. Similarly, the odds of an individual with chronic pain being tested for vitamin D are 2.3 times higher if they were from Australia, and 0.3 times less likely if they were from New Zealand, than if they were from other countries. In addition, chronic pain patients who were unemployed or on leave due to pain and in part-time employment were twice as likely to be tested for vitamin D. Age, education level, pain related to injury, mean pain intensity of pain and duration of pain were not associated with vitamin D testing.

Table 2 Summary of LASSO for factors associated with vitamin D testing

Table 3 presents a summary of factors associated with vitamin D deficiency. The ORs and CIs suggest that for individuals with chronic pain the odds of being vitamin D deficient are approximately three times higher if they are older than 30 than if they are not. Similarly, the individual with chronic pain who has a mean pain intensity ≥6 on an 11 point NRS are twice as likely to be vitamin D deficient then an individual with chronic pain who has a mean pain intensity ≤5. Gender, country of residence and employment status were not associated with patient reported vitamin D deficiency.

Table 3 Summary of LASSO for factors associated with vitamin D deficiency

Table 4 presents a summary of factors associated with taking vitamin D supplements. The ORs and CIs suggest that individuals with chronic pain aged between 51-60 years are three times more likely to be taking vitamin D supplements than those aged 50 years or younger, and those older than 60 are six times more likely. Not surprisingly, those who had been vitamin D deficient were six times more likely to take vitamin D supplements than those who were not. Gender, country of residence, education level, mean pain intensity, characteristics of pain, duration of pain, pain related to injury and tested for vitamin D were not associated with vitamin D supplement intake.

Table 4 Summary of LASSO for factors associated with intake of vitamin D supplement

Table 5 presents a summary of factors associated with doctor advised vitamin D supplementation. Individuals with chronic pain who were unemployed or on leave due to pain and in part-time employment were 4 times more likely than full-time employed participants to be prescribed vitamin D supplements by their doctor. Not surprisingly, being vitamin D deficient had the largest influence on whether doctors would prescribe vitamin D. Age, gender, country of residence, education level, mean pain intensity, duration of pain and whether pain related to injury were not associated with being prescribed vitamin D supplement. Finally, and surprisingly, whether or not someone had been tested for vitamin D levels was not associated with being prescribed vitamin D supplement.

Table 5 Summary of LASSO for factors associated with doctor advised vitamin D supplement

DISCUSSION

Data from this cross-sectional survey suggests that gender, country of residence and employment status were associated with being tested for vitamin D. Australians were much more likely to be tested for vitamin D than other nationalities. These findings resonate with reports that demonstrate rise in vitamin D testing globally (Australian Governmnet MBS review, 2014; Epling, 2014) and a remarkable 3587% rise in vitamin D testing in Australia over last 10 years (Epling, 2014).

Older people and individuals who reported a mean pain intensity score ≥ 6 on an 11 point NRS were more likely to report vitamin D deficiency. To our knowledge, this is the first time that intensity of self-reported pain has been identified as being associated with vitamin D deficiency. That older people were more likely to report vitamin D deficiency is in line with the association between age and risk of developing vitamin D deficiency (Holick et al., 2011; van Schoor, 2011), which has been attributed to insufficient sun exposure time (Brock, 2004) and decline in the capacity to synthesize vitamin D (Durvasula, 2010). Not surprisingly then, along with diagnosis of vitamin D deficiency, age was associated with taking vitamin D supplements. Supplement usage in general is reported to increase with age (Bailey, 2013; Radimer, 2004; Dickinson, 2014), but not to the levels observed here for vitamin D. Not surprisingly, doctors advised vitamin D supplementation to individuals who were vitamin D deficient, unemployed or on leave due to chronic pain and in part time employment.

To the best of our knowledge, most previous studies have investigated vitamin D deficiency and insufficiency among healthy populations in Australia (Tran et al., 2013), Europe (Sohl et al., 2014) and America (Mitchell 2012). These are findings are important as it highlights factors associated with deficiency, testing, intake and doctor advised supplementation of vitamin D in patients with chronic pain.

That vitamin D deficiency has been proposed as a cause of nonspecific muscular and bone pain (Lyman, 2005) would predict that pain characteristics, intensity and duration would relate to testing, prescribing or taking vitamin D supplementation. We found only a relationship between pain intensity and vitamin D deficiency. Our design does not allow causal attribution, but it is notable that there are biological pathways that could lead from vitamin D deficiency to pain. For example, it is thought that vitamin D deficiency reduces calcium phosphate, which then makes the collagen matrix surrounding the bone rubbery. This can cause pressure on the periosteal covering, which is innervated by sensory fibers (Lyman, 2005). Even slight pressure on the bone can produce pain. In view of this mechanistic plausibility of vitamin D deficiency

to modulate pain levels in patients experiencing chronic pain, it is plausible that it could be one of the reasons for higher mean pain intensity being reported by patients who were vitamin D deficient. Clearly, longitudinal data are required to investigate this possibility.

Our results have practical implications. Identifying several factors associated with a risk of vitamin D deficiency may assist doctors in identifying patients with chronic pain who would more likely benefit from vitamin D supplementation for their chronic pain problem. About 25% of adults worldwide have persistent pain – to test everyone would be expensive and perhaps of limited return. There is clearly merit in identifying pre-test risk factors in those with chronic pain, so as to minimize unnecessary testing.

Study Limitations

Our adherence to CHERRIES recommendations (Eysenbach, 2004) gives us confidence in minimising bias and our online approach allowed us to reach the *a priori* sample size and diversity that was required to fulfil our aims. However, this approach also has clear limitations. We relied on word of mouth, social media networks and promotion through consumer advocates to recruit our sample, a process that might introduce a bias towards sampling within established social media networks and diagnostic groups. That the survey was online clearly limits our sample to those with internet connectivity and engagement, and computer skills. We were also bound by considerations of participant burden (Groves, 2009), which meant that we decided *a priori* on the basis of pilot testing, to not collect information on participants' outdoor activities, sun exposure time and safe sun practices and the type and dosage of vitamin D supplement preferred by the participants. These data might have offered important insights. Finally, any survey is dependent on self-report and little is known about the validity of questions such as those asked here when compared to non-self-report assessment approaches.

CONCLUSION

In summary, the results from the present study examine the associations between vitamin D testing, deficiency, intake and doctor advised vitamin D supplementation in individuals with chronic pain. The simple demographic and pain-related factors, could be used as a guide to identify who may be at risk of vitamin D deficiency, whom to test and when to treat.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all of the study participants who completed the study and the organisations and societies who promoted our survey on their websites.

Declaration of Interest:

MG, SV, and NS declare that they have no conflicts of interest. MNM is funded by John Lynch's NHMRC Australian Fellow funding (ID 478115). GLM has received support from Pfizer, Kaiser Permanente, USA; Workers' Compensation Boards in Australia, North America, and Europe; Agile Physiotherapy, USA; Results Physiotherapy, USA; the International Olympic Committee and the Port Adelaide Football Club, Australia. He receives royalties for books on pain and rehabilitation, including two books that are cited in this article. He receives speaker fees for lectures on pain and rehabilitation. He is supported by a Principal Research Fellowship from the National Health and Medical Research Council of Australia.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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