

# Vitamin D Deficiency and Injury Risk During Basic Military Training in the Maltese Armed Forces

Matthew Psaila<sup>1\*</sup>

<sup>1</sup>AFM Medical Centre Luqa Barracks, Luqa, Malta

\*Corresponding author: Matthew Psaila, AFM Medical Centre Luqa Barracks, Luqa, Malta. E-mail: mjpsaila@yahoo.co.uk

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## Abstract

**Background:** Military recruits undertake intense loads of physical training as part of their recruitment to reach a physical level compatible with their line of duties. This training is often conducted over a short time span and complicated by injuries and premature recruit discharge. Identification of risk factors that could decrease the risk of injuries is ideal.

**Objectives:** The present study aimed at correlating pre-recruitment vitamin D levels to injury risk during basic military training in a group of recruits.

**Methods:** A total of 90 recruits commencing their basic military training were invited to participate in the study. The cohort comprised 81 males and 9 females, with a mean age of 22.6. All acute and gradual onset musculoskeletal injuries as well as medical ailments were recorded using the Orchard Sports Injury Classification System. Injuries and medical ailments were analyzed for associations with vitamin D levels. Recruits were grouped according to their serum vitamin D levels into deficient, insufficient, or sufficient as per the Endocrine Society range guidelines.

**Results:** A total of 34 (26.2%) recruits sustained at least 1 injury during the course of their basic military training. Vitamin D level as well as vitamin D status was not associated with injury risk although weak rejection of association with leg injuries and vitamin D insufficiency status was noted ( $P = 0.057$ ). A total of 60% of recruits were identified as being vitamin D deficient or as having insufficient vitamin D levels.

**Conclusions:** Vitamin D deficiency and insufficiency are relatively common in areas with high mean sunlight exposure and should be considered in individuals who might otherwise be at risk. Further studies are recommended in the military using larger populations and possibly focusing on leg injuries.

**Keywords:** Athletic Injuries, Military Personnel, Leg, Vitamin D

## 1. Background

Vitamin D insufficiency may affect over 1 billion people worldwide, with over 77% of Americans considered to have insufficient serum levels of 25-hydroxy vitamin D (1). Serum concentration of 25-hydroxy vitamin D is effected by sunlight exposure and in the absence of exogenous supplementation, explaining the identified variability between different populations (2). Nonetheless, in countries with relatively high mean sunlight exposure, endogenous vitamin D synthesis and bioavailability may be limited by skin pigmentation, clothing, sunscreen use, and excess adiposity (3). Furthermore, sun exposure is being limited even further, as more children are increasingly spending their recreational time indoors. Exogenous intake is limited by few food items that are naturally rich or fortified with vitamin D including oily fish, milk, selected fruit juices, breads, and cereals (4).

The role of vitamin D in skeletal mineralisation through its ability to mediate calcium and phosphate homeostasis has been widely described in the literature

(5). Vitamin D is also an important mediator of muscle function with evidence favouring a common port of interaction between muscular and skeletal tissues (6). Actions of vitamin D on muscle take place via indirect roles through phosphate homeostasis (7) as well as via direct roles through the muscle vitamin D receptors (VDR). Mutations in the VDR were linked with Type 2 muscle fiber atrophy, suggesting that apart from mediating muscle function vitamin D is an essential component of muscle cell life (8). Of note, VDR expression in muscle and bone decreases with age, rendering the musculoskeletal system more sensitive to vitamin D insufficiency (9). In fact, vitamin D supplementation in elderly patients was associated with increased muscle strength and decreased risk of falls (10, 11). Studies on younger individuals are less prevalent (12).

The ensuing muscle weakness from vitamin D insufficiency may potentially lead to an increased injury risk in athletes. To this effect, in a small study of classical ballet dancers, vitamin D supplementation was found to be associated with increased muscle isometric strength as well

as a decreased injury risk (2). Halliday has evaluated college athletes with vitamin D insufficiency and identified increased reports of common infectious illness (common cold, influenza, and gastroenteritis), but not increased injury rates (12). Of note, the action of vitamin D on the immune system and on the musculoskeletal tissue is mediated via different mechanisms.

Military recruits undertake intense physical training over relatively short time periods with often little time available for rest and nutrition. Lutz (2012), in a study of female soldiers undertaking basic combat training, identified decreased vitamin D and calcium intake during their training that, coupled with the increased bone turnover, might increase the risk of stress fractures (13). In a recent meta-analysis, the association between low serum vitamin D levels and lower extremity stress fractures in military personnel was described (14). The latter provides evidence for vitamin D supplementation in deficient military personnel. The specific association between vitamin D levels and injury risk during basic military training was, however, not described.

This prospective study aimed at correlating pre-recruitment serum vitamin D levels with injury risk during basic military training in the Maltese armed forces. Correlations will be made to both acute and overuse injuries as well as to common infectious medical illnesses with the aim of identifying at risk recruits who would theoretically benefit from vitamin D supplementation. With the high mean sunlight in the Maltese islands, there exists a general consensus that vitamin D levels are sufficient in most of the population. In fact, Malta enjoys around 3,000 hours of sunshine per year (compared to 1461 hours of sunshine in London), placing it as one of the highest countries in Europe. Because recruits volunteer directly from the general population, the serum levels may be described as representative of the general population and will serve as a reflection of whether the high sunshine hours in Malta result in adequate serum vitamin D levels (15).

## 2. Methods

### 2.1. Participants

A total of 90 recruits scheduled to undertake BMT in April 2016, who were selected after satisfying the criteria for enlistment into the Armed Forces of Malta (AFM), were invited to participate in the proposed research project via a letter that was distributed during their medical screening. Information concerning the proposed study was provided in writing including contact details of the researcher and project supervisor. Interested participants were, then, met

during their medical screening test and given the opportunity to discuss any queries relating to the proposed project.

There were no specific excluding criteria because those applicants unable to undertake BMT secondary to acute or chronic MSK (musculoskeletal) injuries would not satisfy the pre-set medical standards for enlistment in the AFM, and therefore, would have been barred from enlisting as recruits at the initial screening stage. All volunteers for this study were cleared by the medical officers as fit to undertake BMT (basic military training), and by definition, participants were fit to participate in this study. All participants provided a written consent and were specifically informed that they could withdraw from the study at any point of their BMT. Formal permission to undertake this study was granted by the respective head of the AFM's (Armed Forces of Malta) medical section.

### 2.2. Data Collection

Serum 25-hydroxy vitamin D was measured in all recruits during their pre-recruitment medical screening, which as of January 2016 was included as part of the routine blood tests undertaken by recruit applicants. Vitamin D levels were divided into 3 groups: deficient, insufficient, and sufficient as per laboratory's reference values, which are the same as the range guidelines recommended by the endocrine society (16). Blood samples were prepared at the AFM's medical section with the actual testing being performed at Mater Dei hospital's laboratory, which is Malta's general hospital. The time period between the screening blood testing and start of BMT was 6 weeks. Further assessments were performed as follows:

#### 2.2.1. Injury Data

Injuries were defined in accordance with the medical attention definition provided by Clarsen and Bahr (17). These were events characterised by musculoskeletal symptoms (most notably pain) in a body area of interest, which were reported by a recruit to the AFM medical officer, regardless of whether they resulted in time-lost from or modification of BMT. Injuries were subclassified as gradual onset/overuse injuries, developing over a period of time without a single identifiable inciting event, and sudden onset injuries attributable to an instantaneous event (18).

All diagnosed injuries were categorized according to the injured bodily area involved including head/neck, spine, shoulder, upper limb (excluding shoulder), chest, abdomen, pelvis, hip/thigh, knee, leg, ankle, foot, and medical illness (respiratory tract infections and enteric illness). Injuries were coded and recorded according to the orchard sports injury classification system (OSICS) (19). For the purpose of the study, recurrences of the same injury in the

same body area were not recorded. For descriptive analysis, different injuries that were diagnosed in an already injured body area of interest were still recorded. This enabled auditing of the commonest injuries to be diagnosed, allowing comparisons to previous studies conducted on the Maltese military personnel (20). All injuries were reviewed and verified by a military medical officer having a post-graduate level of training in sports and exercise medicine and 6 years of work experience as a team doctor with the national Maltese football team.

The incidence rate for injury was calculated by dividing the total number of injuries by the total number of recruits multiplied by the duration (in days) of BMT. The latter was presented as the incidence rate of injury per 100 days of BMT by multiplying the attained rate by 100. The relative risk of injury in female recruits was identified by dividing the number of injuries in female recruits by the total number of female recruits multiplied by 100. Similarly, the relative risk of injury in male recruits was identified by dividing the number of injuries in male recruits by the total number of male recruits multiplied by 100. The injury risk ratio according to gender was identified by dividing the calculated relative risk in females by the relative risk in male recruits.

### 2.3. Data Analysis

#### 2.3.1. Independent Variables

Independent variables were grouped as demonstrated in Table 1.

#### 2.3.2. Dependent Variables

Presence or absence of injury as well as whether the injury was an acute or overuse injury, denotes the dependant categorical variables in this research. Injuries were subgrouped into body area as described above, allowing direct correlations between injured body area and recruits vitamin D level status.

### 2.4. Statistical Analysis

Data was analyzed using the statistical package for the social sciences (SPSS) statistics software Version 21. All 90 recruits, including prematurely discharged recruits, comprised the final group. In view of the small number of females comprising the group of recruits, no association was made between gender and injury outcomes. Nonetheless, injury risk and injury risk ratio for male and female recruits were calculated. Independent categorical variables were analyzed against injury outcomes using the Chi-square test. The only independent continuous variable, serum vitamin D level, was analyzed using the nonparametric Mann-Whitney U test. All differences were accepted

as being significant when the measured P value was less than 0.05.

### 2.5. Ethical Consideration

Respective permission for conducting this study was obtained from the AFM's principal medical officer. All recruits were consented after being invited to participate by means of a letter that explained that participation was voluntary and that they could withdraw from the study at any stage.

## 3. Results

### 3.1. Demographics

The participants comprised of 81 males and 9 females. In total, 77 recruits completed BMT with 13 recruits, terminating their training prematurely. The total duration of BMT was of 114 days. A total of 38 (42.2%) recruits sustained at least 1 injury during BMT with 32 recruits (35.6%), sustaining at least 1 acute injury and 16 recruits (17.8%), sustaining at least one overuse injury. Ten recruits (11.1%) sustained at least 1 acute and 1 overuse injury. The incidence rate for injury was 0.71 injuries/100 days of BMT. The relative injury of female to male risk ratio was 1.87, indicating that the risk of injury in female recruits was almost twice the risk for male recruits.

### 3.2. Premature Discharge

Four male recruits and 1 female recruit, terminated their training prematurely, representing 5.5% of the total population of recruits, which is slightly lower than the observed rate of 7.9% observed in the preceding recruitment process (20). Four recruits who were discharged prematurely were diagnosed with both musculoskeletal and medical ailments, while only 1 recruit reported medical ailments.

### 3.3. Vitamin D Status

The mean serum vitamin D level was 28.3 ng/mL. With regards to vitamin D status as per range guidelines recommended by the endocrine society, 6.67% (n = 6) of the recruits were identified as vitamin D deficient, 53.3% (n = 48) as vitamin D insufficient, and 40% (n = 36) as vitamin D sufficient.

**Table 1.** Grouping of Independent Variables

Variable	Variable Type	Categories		
Vitamin D status	Categorical	Deficiency	Insufficiency	Sufficiency
Serum vitamin D level	Continuous	Not applicable		

### 3.4. Vitamin D Status and Injury

Pre-recruitment vitamin D deficiency status was not associated with injury risk overall ( $X^2(1) = 0.001$ ,  $P = 0.972$ ), acute ( $X^2(1) = 0.177$ ,  $P = 0.674$ ), or gradual-onset ( $X^2(1) = 0.063$ ,  $P = 0.801$ ) injury during BMT. Pre-recruitment vitamin D insufficiency status was not associated with injury risk overall ( $X^2(1) = 2.229$ ,  $P = 0.135$ ), acute ( $X^2(1) = 1.623$ ,  $P = 0.203$ ), or gradual-onset ( $X^2(1) = 1.157$ ,  $P = 0.282$ ) injury during BMT. Pre-recruitment vitamin D sufficiency status was not associated with injury risk overall ( $X^2(1) = 2.450$ ,  $P = 0.117$ ), acute ( $X^2(1) = 2.415$ ,  $P = 0.120$ ), or gradual-onset ( $X^2(1) = 0.946$ ,  $P = 0.331$ ) injury during BMT.

### 3.5. Serum Vitamin D Level and Injury

Serum vitamin D level was not associated with injury risk overall ( $U = 937$ ,  $P = 0.676$ ), acute ( $U = 873.5$ ,  $P = 0.645$ ), or gradual-onset ( $U = 506$ ,  $P = 0.363$ ) injury during BMT.

### 3.6. Vitamin D Status and Injured Body Area

Vitamin D status did not alter injury risk in any of the investigated body areas. The respective  $X^2(1)$  and  $P$  values are provided in Table 2. In the absence of documented injuries to the shoulder, chest, abdomen, and pelvis, the respective rows in Table 2 have been left empty.

## 4. Discussion

The interplay between vitamin D deficiency and mitochondrial function has been proposed as a possible mechanism for the correlation between vitamin D deficiency and injury risk, resulting in muscle weakness and imbalance (21). Muscle loss has in fact been shown to be a complication of long-term mitochondrial dysfunction (22). It has been postulated that vitamin D deficiency may interact with mitochondrial function via 2 mechanisms: altered gene expression as well as oxidative stress (21). Oxidative stress is in turn associated with all diseases associated with aging, with vitamin D playing an important role in the expression of mechanisms that maintain oxidation homeostasis (23). The latter could possibly interfere with the body's repair mechanisms and result in delayed or incomplete recovery from musculoskeletal injuries. Furthermore, if vitamin D deficiency interfered with muscle

strength, this also could be an independent risk factor for injury as suggested by Wyon (2).

In the study of MSK injuries in military recruits, differing levels of vitamin D were not significantly associated with injuries. Of note, however, is the weak rejection of statistical significance of vitamin D deficiency status being associated with leg injuries in recruits. The relevance of this study in the Maltese islands relates to the widespread sense of belief that in view of the high average sunlight, vitamin D deficiency is uncommon. However, the results clearly revealed that a considerable number of recruits had deficient or insufficient vitamin D levels. Because recruits apply to enlist in the army from the general population, extrapolations from the obtained vitamin D levels may be made on the general population. The mean serum vitamin D level was, in fact, in the insufficient bracket, as per recommendations by the Endocrine Society. The latter organisation further recommends that exogenous vitamin D supplementation (2,000 IU/day) should be advised to maintain serum levels in excess of 30 ng/mL (16).

With regards to weaknesses of the presented study, having a larger sample size would allow for direct correlations of vitamin D status and acute injury and as well as gradual onset injury risk. In the presented population group, in view of the small sample size, separate correlations could not be made and acute and gradual onset injuries were grouped. Thus, considering the small sample size, it would be of interest to assess the latter association in a larger sample size, especially in view of the high propensity of leg injuries in military recruits (20). Furthermore, although none of the recruits reported supplementation with vitamin D at the commencement of their BMT, the use of multivitamins after the start of the BMT would have potentially introduced bias as it would have improved vitamin D levels in deficient and insufficient recruits.

### 4.1. Conclusion

Vitamin D is an important component of MSK health, being an essential factor in muscle and bone function. Despite the theoretical background for an association with injury risk, no significant association was found in the presented study, however, a weak rejection of a possible association between vitamin D deficiency and injury risk in

**Table 2.** Statistical Significance of Injured Anatomical Area and Vitamin D Status

Variables	Vitamin D Deficiency		Vitamin D Insufficiency		Vitamin D Sufficiency	
	X <sup>2</sup> (1)	P value	X <sup>2</sup> (1)	P value	X <sup>2</sup> (1)	P value
Head/neck	0.173	0.678	1.564	0.211	1.129	0.288
Spine	0.077	0.781	0.204	0.652	0.097	0.755
Shoulder	-	-	-	-	-	-
Upper limb	0.085	0.770	0.773	0.379	0.558	0.455
Chest	-	-	-	-	-	-
Abdomen	-	-	-	-	-	-
Pelvis	-	-	-	-	-	-
Hip/thigh	0.000	0.990	0.147	0.702	0.152	0.697
Knee	1.168	0.280	0.564	0.453	0.030	0.863
Leg	3.631	0.057	0.122	0.727	2.037	0.154
Ankle	1.731	0.188	0.573	0.449	2.310	0.129
Foot	0.353	0.552	0.573	0.449	0.204	0.652
Medical illness	0.507	0.477	0.920	0.337	0.354	0.552

the leg was noted. This study also confirmed that despite a high average sunlight exposure, vitamin D deficiency remains a possibility and should be measured in at-risk individuals. Further research in this area would improve the limitations of this study.

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### Footnotes

**Competing Interests:** There are no competing interests to declare.

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### References

- Ogan D, Pritchett K. Vitamin D and the athlete: risks, recommendations, and benefits. *Nutrients*. 2013;**5**(6):1856–68. doi: [10.3390/nu5061856](#). [PubMed: [23760056](#)].
- Wyon MA, Koutedakis Y, Wolman R, Nevill AM, Allen N. The influence of winter vitamin D supplementation on muscle function and injury occurrence in elite ballet dancers: a controlled study. *J Sci Med Sport*. 2014;**17**(1):8–12. doi: [10.1016/j.jsams.2013.03.007](#). [PubMed: [23619160](#)].
- Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr*. 2004;**80**(6 Suppl):1678S–88S. [PubMed: [15585788](#)].
- Holick MF. Vitamin D: a D-Lightful health perspective. *Nutr Rev*. 2008;**66**(10 Suppl 2):S182–94. doi: [10.1111/j.1753-4887.2008.00104.x](#). [PubMed: [18844847](#)].
- Heaney RP. Vitamin D and calcium interactions: functional outcomes. *Am J Clin Nutr*. 2008;**88**(2):541S–4S. [PubMed: [18689398](#)].
- Tagliaferri C, Wittrant Y, Davicco MJ, Walrand S, Coxam V. Muscle and bone, two interconnected tissues. *Ageing Res Rev*. 2015;**21**:55–70. doi: [10.1016/j.arr.2015.03.002](#). [PubMed: [25804855](#)].
- Schubert L, DeLuca HF. Hypophosphatemia is responsible for skeletal muscle weakness of vitamin D deficiency. *Arch Biochem Biophys*. 2010;**500**(2):157–61. doi: [10.1016/j.abb.2010.05.029](#). [PubMed: [20515645](#)].
- Girgis CM, Clifton-Bligh RJ, Hamrick MW, Holick MF, Gunton JE. The roles of vitamin D in skeletal muscle: form, function, and metabolism. *Endocr Rev*. 2013;**34**(1):33–83. doi: [10.1210/er.2012-1012](#). [PubMed: [23169676](#)].
- Montero-Odasso M, Duque G. Vitamin D in the aging musculoskeletal system: an authentic strength preserving hormone. *Mol Aspects Med*. 2005;**26**(3):203–19. doi: [10.1016/j.mam.2005.01.005](#). [PubMed: [15811435](#)].
- Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J Bone Miner Res*. 2003;**18**(2):343–51. doi: [10.1359/jbmr.2003.18.2.343](#). [PubMed: [12568412](#)].
- Girgis CM, Baldock PA, Downes M. Vitamin D, muscle and bone: Integrating effects in development, aging and injury. *Mol Cell Endocrinol*. 2015;**410**:3–10. doi: [10.1016/j.mce.2015.03.020](#). [PubMed: [25837735](#)].
- Halliday TM, Peterson NJ, Thomas JJ, Kleppinger K, Hollis BW, Larson-Meyer DE. Vitamin D status relative to diet, lifestyle, injury, and illness in college athletes. *Med Sci Sports Exerc*. 2011;**43**(2):335–43. doi: [10.1249/MSS.0b013e3181eb9d4d](#). [PubMed: [20543748](#)].
- Lutz LJ, Karl JP, Rood JC, Cable SJ, Williams KW, Young AJ, et al. Vitamin D status, dietary intake, and bone turnover in female Soldiers during military training: a longitudinal study. *J Int Soc Sports Nutr*. 2012;**9**(1):38. doi: [10.1186/1550-2783-9-38](#). [PubMed: [22866974](#)].



14. Dao D, Sodhi S, Tabasinejad R, Peterson D, Ayeni OR, Bhandari M, et al. Serum 25-Hydroxyvitamin D Levels and Stress Fractures in Military Personnel: A Systematic Review and Meta-analysis. *Am J Sports Med.* 2015;**43**(8):2064–72. doi: [10.1177/0363546514555971](https://doi.org/10.1177/0363546514555971). [PubMed: [25371440](https://pubmed.ncbi.nlm.nih.gov/25371440/)].
15. Wikipedia . Climate of Malta 2016. [cited 30 Dec]. Available from: [https://en.wikipedia.org/wiki/Climate\\_of\\_Malta](https://en.wikipedia.org/wiki/Climate_of_Malta).
16. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;**96**(7):1911–30. doi: [10.1210/jc.2011-0385](https://doi.org/10.1210/jc.2011-0385). [PubMed: [21646368](https://pubmed.ncbi.nlm.nih.gov/21646368/)].
17. Clarsen B, Bahr R. Matching the choice of injury/illness definition to study setting, purpose and design: one size does not fit all! *Br J Sports Med.* 2014;**48**(7):510–2. doi: [10.1136/bjsports-2013-093297](https://doi.org/10.1136/bjsports-2013-093297). [PubMed: [24620038](https://pubmed.ncbi.nlm.nih.gov/24620038/)].
18. Yang J, Tibbetts AS, Covassin T, Cheng G, Nayar S, Heiden E. Epidemiology of overuse and acute injuries among competitive collegiate athletes. *J Athl Train.* 2012;**47**(2):198–204. doi: [10.4085/1062-6050-47.2.198](https://doi.org/10.4085/1062-6050-47.2.198). [PubMed: [22488286](https://pubmed.ncbi.nlm.nih.gov/22488286/)].
19. Rae K, Orchard J. The Orchard Sports Injury Classification System (OSICS) version 10. *Clin J Sport Med.* 2007;**17**(3):201–4. doi: [10.1097/JSM.0b013e318059b536](https://doi.org/10.1097/JSM.0b013e318059b536). [PubMed: [17513912](https://pubmed.ncbi.nlm.nih.gov/17513912/)].
20. Psaila M, Ranson C. Risk factors for lower leg, ankle and foot injuries during basic military training in the Maltese Armed Forces. *Phys Ther Sport.* 2017;**24**:7–12. doi: [10.1016/j.ptsp.2016.09.004](https://doi.org/10.1016/j.ptsp.2016.09.004). [PubMed: [28038317](https://pubmed.ncbi.nlm.nih.gov/28038317/)].
21. Bouillon R, Verstuyf A. Vitamin D, mitochondria, and muscle. *J Clin Endocrinol Metab.* 2013;**98**(3):961–3. doi: [10.1210/jc.2013-1352](https://doi.org/10.1210/jc.2013-1352). [PubMed: [23472232](https://pubmed.ncbi.nlm.nih.gov/23472232/)].
22. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, D'Hoore A, et al. Mitochondrial fusion, fission, and biogenesis in prolonged critically ill patients. *J Clin Endocrinol Metab.* 2012;**97**(1):E59–64. doi: [10.1210/jc.2011-1760](https://doi.org/10.1210/jc.2011-1760). [PubMed: [22013100](https://pubmed.ncbi.nlm.nih.gov/22013100/)].
23. Eelen G, Verlinden L, Meyer MB, Gijsbers R, Pike JW, Bouillon R, et al. 1,25-Dihydroxyvitamin D3 and the aging-related forkhead box O and sestrin proteins in osteoblasts. *J Steroid Biochem Mol Biol.* 2013;**136**:112–9. doi: [10.1016/j.jsbmb.2012.09.011](https://doi.org/10.1016/j.jsbmb.2012.09.011). [PubMed: [22989484](https://pubmed.ncbi.nlm.nih.gov/22989484/)].