



Australian Government
Repatriation Medical Authority

REPATRIATION MEDICAL AUTHORITY

STATEMENT OF REASONS

S 196B(9) *VETERANS' ENTITLEMENTS ACT 1986*

**DECISION NOT TO AMEND THE CURRENT BALANCE OF PROBABILITIES
STATEMENT OF PRINCIPLES CONCERNING PSORIASIS
FOLLOWING A REVIEW**

Instrument No. 32 of 2012

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PART I INTRODUCTION

1. The Repatriation Medical Authority (the Authority) pursuant to subsection 196B(9) of the *Veterans' Entitlements Act 1986* (the Act), has decided not to amend Statement of Principles concerning psoriasis, Instrument No. 32 of 2012, following an investigation which was notified in the *Commonwealth of Australia Gazette* on 12 March 2019.
2. Having carried out the investigation as notified, the Authority concluded that the new sound medical-scientific evidence available to it is not sufficient to justify an amendment of the Statement of Principles Instrument No. 32 of 2012, already determined in respect of psoriasis pursuant to subsection 196B(3) of the ACT.

PART II BACKGROUND TO THE INVESTIGATION

1. A request for an investigation into the association between "high stress levels" and psoriasis was received from a veteran on 29 November 2018. The applicant requested the review of the contents of the current balance of probabilities Statement of Principles No. 32 of 2012 to include high stress levels as a cause of a first time flare up. The veteran had read the reasonable hypothesis Statement of Principles for warlike service, and believed that the high stress level factors included there should be considered for peacetime service also.
2. In support of the request, the applicant provided the following:
 - 2.1. Website address <https://www.psoriasis.org/about-psoriasis/causes> for the US National Psoriasis Foundation;
 - 2.2. A letter of recommendation from a dermatologist stating that he believes this is what has caused the applicant's psoriasis initially.
3. On further prompting, the veteran provided the following articles:
 - 3.1. Rousset L, Hailoua B (2018). Stress and psoriasis. *International Journal of Dermatology*, 57(10): 1165-72.
 - 3.2. Ferreira BIRC, Abreu JLPDC, Reis JPGD et al (2016). Psoriasis and associated psychiatric disorders. *The Journal of Clinical and Aesthetic Dermatology*, 9(6): 36-43.
 - 3.3. Leovigildo ES, Mendes AS (2016). Stress level of people with psoriasis at a public hospital. *Anais Brasileiros De Dermatologia*, 91(4): 446-54.
 - 3.4. Kálmán LJ, Gonda X, Kemény L, et al (2014). Psychological and biological background of the correlation between psoriasis and stress. *Orvosi Hetilap*, 155(24): 939-48. [Abstract only. Hungarian language article]
 - 3.5. Manolache L, Petrescu-Seceleanu D (2013). Stress involvement as trigger factor in different skin conditions. *World Journal of Dermatology*, 2(3): 16-26.
 - 3.6. Sathyanarayana Rao TS, Basavaraj KH, Das K (2013). Psychosomatic paradigms in psoriasis: psoriasis, stress and mental health. *Indian Journal of Psychiatry*, 55(4): 313-15.
 - 3.7. Hunter HJ, Griffiths CE, Kleyn CE (2013). Does psychosocial stress play a role in the exacerbation of psoriasis? *The British Journal of Dermatology*, 169(5): 965-74.
 - 3.8. Basavaraj KH, Navya MA, Rashmi R (2011). Stress and quality of life in psoriasis: an update. *International Journal of Dermatology*, 50(7): 783-92.

- 3.9. Heller MM, Lee ES, Koo JY (2011). Stress as an influencing factor in psoriasis. *Skin Therapy Letter*, 16(5): 1-4.
- 3.10. Evers AW, Verhoeven EW, Kraaimaat FW, et al (2010). How stress gets under the skin: cortisol and stress reactivity in psoriasis. *The British Journal of Dermatology*, 163(5): 986-91.
- 3.11. Naldi L, Peli L, Parazzini F, et al (2001). Family history of psoriasis, stressful life events, and recent infectious disease are risk factors for a first episode of acute guttate psoriasis: results of a case-control study. *Journal of the American Academy of Dermatology*, 44: 433-38.
- 3.12. Seville RH (1977). Psoriasis and stress. *The British Journal of Dermatology*, 97(3): 297-302.
4. On 13 February 2019, the Authority considered the request and material provided by the veteran, together with a discussion paper prepared by the Principal Medical Officer. The Authority, under subsection 196B(7A) of the Act, decided to review the contents of the Statement of Principles concerning psoriasis, No. 32 of 2012, determined under s 196B(3) of the Act, to find out if there was new information at the balance of probabilities standard of proof in respect of "stressors" as a factor in psoriasis.
5. The investigation notice was signed by the Chairperson of the Authority on 1 March 2019 and was gazetted in accordance with section 196G of the Act in the *Commonwealth of Australia Gazette* on 12 March 2019. Submissions were invited from persons and organisations wishing to make a submission by 17 May 2019.

PART III SUBMISSIONS RECEIVED BY THE AUTHORITY PURSUANT TO SECTION 196F

6. Following notification of its investigation, the Authority did not receive any information from persons eligible to make submissions pursuant to section 196F of the Act.

PART IV EVIDENCE/INFORMATION AVAILABLE TO THE REPATRIATION MEDICAL AUTHORITY

7. The following information was available to the Authority:
 - 7.1. The information held by the Authority and obtained during its previous considerations leading to the determination of Statements of Principles concerning psoriasis, Instrument Nos. 31 and 32 of 2012.
 - 7.2. A PubMed literature search for psoriasis AND stress AND psychological yielded 375 articles. A PubMed literature search for psoriasis AND stress AND psychological AND risk yielded 67 articles of which only 28 were more recent than the last RMA investigation (2011).
 - 7.3. Medical or scientific publications as set out in the bibliography attached hereto.
 - 7.4. A briefing paper concerning psoriasis prepared for presentation to the Authority by a Medical Researcher of the Secretariat.

PART V SOUND MEDICAL-SCIENTIFIC EVIDENCE

8. The Statements of Principles are determined on the basis of the available "sound medical-scientific evidence" as defined in section 5AB(2) of the Act which states:

*"Information about a particular kind of injury, disease or death is taken to be **sound medical-scientific evidence** if:*

(a) the information:

- (i) is consistent with material relating to medical science that has been published in a medical or scientific publication and has been, in the opinion of the Repatriation Medical Authority, subjected to a peer review process; or*
- (ii) in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and*

(b) in the case of information about how that kind of injury, disease or death may be caused - meets the applicable criteria for assessing causation currently applied in the field of epidemiology."

PART VI REASONS FOR THE DECISION

9. Category 1A, 1B and 2 stressors are existing factors in the reasonable hypothesis Statement of Principles for psoriasis relating to the clinical onset and clinical worsening of the condition, but there are no stressor factors in the balance of probabilities Statement of Principles for psoriasis. Hence the focus of the current investigation was to determine whether there was sufficient evidence to insert the current reasonable hypothesis stressor factors in the balance of probabilities Statement of Principles for psoriasis.
10. There was only one meta-analysis on the subject of stress and psoriasis. The meta-analysis of one nested case-control study and four case-control studies by Snast et al (2018) found that preceding psychological stress events was significantly strongly positively associated with psoriasis (OR 3.4, 95% CI 1.8-6.4). However there were methodological problems with this meta-analysis, with two of the studies (Manolache et al 2010, and Al'Abadie et al 1994) conflating clinical onset with clinical worsening and disease extension, and the case-control study by Ozden et al (2011) studied a paediatric population rather than an adult population. There was a high heterogeneity in the pooled studies ($I^2=87\%$), and three of the five studies used unmatched controls. The data on the exposure to stressful life events considered stressful life events occurring six months to one year prior to the clinical onset of the psoriasis, but these were based on self-reported memories recalled a long time after the stressful event occurrence, questioning the validity of the self-reported data. The average duration of the disease at the time of the study of Al'Abadie et al (1994) was 16.7 years, and Ozden et al (2011) 3.2 years, which is a long time for memory recall. It is also of note that there were no prospective or cohort studies pooled in this meta-analysis. The only nested case-control study by Huerta et al (2007) was statistically insignificant and related to the different exposure metric of stress disorders rather than the stressful life events which was the title of the meta-analysis. These considerations detract from the suggested strong significant association between stressful life events and psoriasis.
11. An examination of the published literature did not find any cohort studies concerning stressful life events and the clinical onset of psoriasis. There were 16 case-control

studies considering stressful life events and psoriasis, of which 11 were not included in Snast et al (2018) meta-analysis. Twelve out of 16 case-control studies found a significant association between stressful life events and psoriasis with effect sizes between 2.6 and 16.7. The case-control studies considered cases of at least 30 subjects in 12 out the 16 studies, but only five out the 16 studies used matched controls. Only three of the 16 case-control studies used healthy controls with 13 studies using controls who had various different minor skin conditions.

12. Only two of the published studies assessed dose-response, with Naldi et al (2001) finding a positive dose-response for Holmes and Rahe life event stress scores greater than 100, and Poikolainen et al (1994) finding no positive dose-response using the area of psoriatic lesions as a metric. Rousset et al (2018) in a review reported that generally there has been no positive dose-response between the severity of psoriasis and the preceding intensity of the psychological stress.
13. Ferreira et al (2016) in a review noted that the direction of the association between psychiatric disorders such as anxiety and depressive disorder and psoriasis is bidirectional.
14. With regard to stressful events and the clinical worsening of psoriasis, there were two prospective studies and five case-control studies. The two prospective studies by Verhoeven et al (2009) and Gaston et al (1987) both reported a significant medium correlation, and three out of the five case-control studies showed a significant association.
15. Overall, the clinical onset and clinical worsening studies were heterogenous. The ascertainment of stressors was subject to recall bias, with the stressors included for up to 12 months prior to the onset of psoriasis which seems excessively long, and were self-reported by the subjects after an average delay of five years in the eight studies that provided this data. Given the substantial delay in the recall of the stressor association, there is the issue of reverse causation, since it is well known that psoriasis is associated with the subsequent development of stress. There was no definite dose-response relationship. The systematic review by Fordham et al (2013) of stress reduction trials in psoriasis found that “due to low quality evidence it is currently insufficient to judge stress reduction interventions as either effective or ineffective”. There was potential confounding due to lack of adjustment in the studies for smoking, injuries, drugs, infections, and being overweight.
16. With regard to the biological mechanism underlying stressful life events and psoriasis, it was suggested that stressful life events may act through direct alterations of the immune system through the hypothalamic-pituitary-adrenal axis, the sympathetic-adrenal-medullary system, or local changes by activated mast cells and nerve related actions; or through indirect alterations of the immune system through behavioural changes in stressed individuals through unhealthy eating, poor sleep hygiene, and greater consumption of alcohol or recreational drugs.

PART VII SUMMARY AND CONCLUSIONS

17. Overall the quantitative evidence available in this investigation showed a significant, strong positive association between preceding psychological stress and psoriasis, but this was substantially weakened by methodological weaknesses in the pooled studies, which included a lack of cohort studies, a long temporal delay between stressors and psoriasis, recall bias due to long delays in obtaining self-reported recollections of the association between stressors and psoriasis, small numbers in the studies, heterogeneity in the studies, and confounding due to use of unmatched controls and lack of sufficient adjustment for all potential confounders such as tobacco smoking, drugs, injuries, infections, and being overweight. There was also insufficient evidence of a positive dose-response, and the stress reduction trials did not provide sufficient evidence of a relieving effect.
18. The Act requires that the same body of evidence be assessed according to two different standards of proof. For assessment under the reasonable hypothesis standard (s 196B(2)) the Act requires that the sound medical-scientific evidence must indicate or point to a causal association between a risk factor and the disease in question. On the other hand, for the balance of probabilities standard (s 196B(3)), the sound medical-scientific evidence must show that it is more probable than not that there is a causal association between a risk factor and the disease. In this matter the distinction between those standards of proof is significant.
19. The available sound medical-scientific evidence indicates or points to a causal association between life stressors and psoriasis, such being sufficient to support a judgement of a possible causal association. The reasonable hypothesis standard is met and the existing reasonable hypothesis Statement of Principles includes factors relating to life stressors.
20. However, as detailed in the reasons set out above, the sound medical-scientific evidence does not show that it is more probable than not that there is a causal association between "stressors" and psoriasis. The available evidence is therefore insufficient to support a judgement of a probable causal association between "stressors" and psoriasis, and the balance of probabilities standard cannot be met. In these circumstances no factor can be included in that Statement of Principles.

PART VIII DECISION NOT TO AMEND INSTRUMENT NO. 32 OF 2012

21. At its meeting on 4 June 2019 the Authority decided not to amend the balance of probabilities Statement of Principles in respect of psoriasis for the purposes of subsections 196B(3) and (8) of the Act as the Authority concluded, for the reasons set out above, that the new sound medical-scientific evidence available to it is not sufficient to justify the inclusion of a factor relating to stressors in the balance of probabilities Statement of Principles already determined in respect of psoriasis.



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Repatriation Medical Authority

21 June 2019

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