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Beyond skin deep: addressing comorbidities in psoriasis

Summary

- Psoriasis is a chronic inflammatory disease that is commonly encountered in primary care and is associated with significant morbidity that extends beyond the skin manifestations.
- Psoriasis is associated with an elevated risk of psoriatic arthritis, cardiovascular disease, obesity, insulin resistance, mental health disorders, certain types of malignancy, inflammatory bowel disease and other immune-related disorders, and hepatic and renal disease.
- Enhanced recognition of these comorbidities may lead to earlier diagnosis and potentially better overall health outcomes.
- Psoriatic nail involvement, severe skin disease and obesity are associated with a greater risk of psoriatic arthritis. Individuals with psoriasis should be routinely screened for psoriatic arthritis to allow for early intervention to improve long term prognosis.
- Life expectancy is reduced in people with psoriasis due to a variety of causes, with cardiovascular disease and malignancy being the most common aetiologies.
- Psoriasis affects several factors that contribute to worsened quality of life and increased risk of depression and anxiety. Effective therapies are now available that have been shown to concurrently improve skin disease, quality of life and psychiatric symptoms.
- As the concordance between psychosocial impact and objective disease severity does not always correlate, it is essential to tailor management strategies specifically to the needs of each individual.
- Cigarette smoking and excess alcohol consumption are among the most important modifiable risk factors that increase the likelihood of psoriasis development and severity of skin disease. This provides a compelling rationale for smoking cessation and limiting alcohol intake in people with psoriasis beyond their traditional harmful health consequences.

Psoriasis is a common condition frequently seen and managed in primary care which has an estimated prevalence in Australia of 2.3–6.6%.¹ While the skin is the most visibly affected organ in psoriasis, there is increasing evidence to support the recognition of psoriasis as a chronic, multisystem inflammatory disorder with many associated

conditions. Acknowledgement and understanding of the relationship between psoriasis and other diseases is important for optimal patient care. Primary care providers and general physicians are well placed to identify and manage these comorbid diseases. Although most patients with psoriasis are managed in primary care, the management of extracutaneous manifestations of psoriasis has yet to be fully explored in this context.

This review provides an updated overview of contemporary knowledge on the burden of comorbid diseases in psoriasis, with a special focus on the role of primary care management. The Box provides a summary of the comorbidities, their strength of association and the role of primary care management. We performed a search of online databases, including PubMed and MEDLINE from 1999 to 2019, and national and international societies were searched for published guidelines. Reference lists and citations of retrieved articles were searched to identify any additional relevant articles. Search terms from the Medical Subject Headings (MeSH) included “psoriasis”; “comorbidity”; “arthritis, psoriatic”; “cardiovascular diseases”; “mental disorders”; “depressive disorder”; “anxiety”; “smoking”; “alcohols”; “quality of life”; “neoplasms”; “autoimmune diseases”; “liver diseases” and “kidney diseases”.

Psoriatic arthritis

Psoriatic arthritis is a form of inflammatory arthritis, with a prevalence between 6% and 41% in people with psoriasis.² Almost all patients with psoriatic arthritis have cutaneous psoriasis. In most people, the skin manifestations precede arthritis, but an estimated 15% of cases present with joint symptoms before or concurrent with skin lesions.²⁴ Psoriatic nail dystrophy has been found to correlate with an almost threefold increase in risk of joint disease.²⁵ The severity of skin disease appears to be associated with an increased risk of psoriatic arthritis; however, the skin and joint manifestations may not be temporally correlated as psoriasis flares do not necessarily precede arthritis flare.²⁶ In addition, obesity was found to be an independent risk factor for the development of psoriatic arthritis in patients with psoriasis, reinforcing the importance of weight reduction in these individuals, who often also have an associated metabolic disorder.²⁶ Psoriatic arthritis can also present with enthesitis (inflammation of the tissue that connects the ligament or tendon to the bone) and dactylitis (“sausage-like” swelling of the digit).²⁷ Dactylitis most commonly affects the feet in an asymmetrical pattern and is associated with worse radiological damage. Unlike other causes of inflammatory arthritis, there is no sex predilection in psoriatic arthritis.²⁸ Nonetheless, sex-related differences have been observed in the clinical phenotypes of psoriatic arthritis. Men are more likely to develop axial disease and radiographic joint damage, while women are more likely to develop severe limitation in function and respond less favourably to tumour necrosis factor- α (TNF- α) inhibitor treatment.²⁹

Early treatment of psoriatic arthritis can significantly improve joint and quality of life outcomes and prevent permanent joint damage.³⁰ Even a 6-month delay in rheumatological consultation from symptom onset was found to result in joint erosions

and a greater chance of long term disability.³¹ With a strong emphasis on early diagnosis of psoriatic arthritis, multiple self-administered, questionnaire-based instruments have been developed and validated to screen for psoriatic arthritis.³ Overall, they are moderately accurate in identifying psoriatic arthritis among individuals with psoriasis.³² A recent meta-analysis found that the Early Psoriatic Arthritis Screening Questionnaire (EARP) was the most accurate screening instrument, with the highest sensitivity and specificity.³

Given the significant heterogeneity of psoriatic arthritis, therapeutic response to systemic therapy may be different for skin disease compared with joint disease. For example, while ustekinumab is highly effective in treating cutaneous psoriasis, it is considered less effective than TNF- α inhibitors for psoriatic arthritis.³³ This highlights the importance of multidisciplinary approach in achieving an optimal outcome for patients with psoriasis who have comorbidities.

Primary care management:

- Using validated questionnaire-based screening tools, patients with psoriasis should be screened proactively for psoriatic arthritis and, if appropriate, they should be referred to a rheumatologist. As these screening tools are designed to be self-administered by patients, they can be done routinely while patients are in the waiting room.
- Given that concomitant psoriatic nail change is one of the strongest predictors of psoriatic arthritis,³⁴ patients with psoriasis who have nail involvement should be comprehensively assessed for features of psoriatic arthritis.

Cardiovascular disease

Psoriasis is an independent risk factor for myocardial infarction, stroke and peripheral vascular disease.⁴ Importantly, cardiovascular disease is one of the leading causes of excess death in patients with severe, but not mild, psoriasis.⁴ Although the exact mechanism of this association is unclear, it is likely related to the inflammatory mediators that are important in the pathogenesis of both psoriasis and atherosclerotic diseases.³⁵ Therefore, it is important to identify patients with psoriasis who are at high cardiovascular risk in order to promote early interventions, such as lifestyle and pharmacological modifications. However, about only 15–50% of patients with psoriasis are aware of their increased risk of cardiovascular disease, and an even smaller proportion of these patients (15–25%) are aware of the association with obesity.³⁶ Moreover, many traditional cardiovascular risk assessment calculators have been shown to underestimate the actual cardiovascular and subclinical atherosclerosis risks in patients with psoriatic arthritis.³⁷ This underestimation may result in inadequate optimisation of risk factors in these patients.

Considering the established relationship between psoriasis and cardiovascular disease, it is necessary to ascertain if there are any psoriatic therapies that may reduce the risk for cardiovascular events and mortality. There is some evidence to suggest that methotrexate and TNF- α inhibitors may be associated with a lower risk of cardiovascular events when

compared with other systemic therapies.³⁸ Conversely, no cardioprotective effect was shown for acitretin, cyclosporine or inhibitors of interleukin (IL)-12 and IL-23.³⁹ In fact, hyperlipidaemia is a known adverse effect for both acitretin and cyclosporine. Cyclosporine is also known to cause hypertension, particularly in older patients compared with younger individuals. While the evidence for methotrexate is limited in psoriasis and psoriatic arthritis, in a meta-analysis of observational studies, methotrexate has been shown to decrease the risk of cardiovascular events in patients with rheumatoid arthritis.³⁸ A recent randomised controlled trial demonstrated that methotrexate did not reduce cardiovascular events in patients with stable atherosclerotic disease but without a systemic inflammatory condition.⁴⁰ This may suggest that the reported cardiovascular benefits of methotrexate may apply only to patients with pre-existing inflammatory conditions, such as rheumatoid arthritis and psoriasis.⁴⁰ In addition, TNF- α inhibitor is associated with a lower number of cardiovascular events in patients with psoriasis and/or psoriatic arthritis.³⁸ Nevertheless, these study results need to be interpreted with caution due to the risk of selection bias and confounding effects. TNF- α inhibitor failed to reduce aortic vascular inflammation in two randomised controlled trials, but it improved inflammatory markers, including serum C-reactive protein and glycoprotein acetylation, providing a plausible biological basis of the potential cardiovascular benefits of TNF- α inhibitor.⁴¹ The relationship between TNF- α inhibitor use and congestive cardiac failure is less certain. Studies assessing TNF- α inhibitor use in patients with congestive cardiac failure demonstrated increased mortality compared with the control group.⁴² TNF- α inhibitor is currently not recommended for use in patients with moderate to severe congestive cardiac failure.

Primary care management:

- Primary care providers should be aware that traditional cardiovascular risk assessment algorithms developed for use in the general population may underestimate the risk in patients with psoriasis. There is compelling evidence to consider psoriasis as a cardiovascular risk factor in its own right.
- People with psoriasis should be encouraged to engage with their primary care providers to optimise their cardiovascular risk factors according to national guidelines, such as lifestyle modifications (smoking cessation, alcohol counselling and weight reduction).

Obesity and insulin resistance

Psoriasis is associated with several metabolic risk factors, including obesity, type 2 diabetes mellitus, hypertension and dyslipidaemia.^{5,6} These metabolic abnormalities are also more common in patients with greater psoriasis severity than in those with milder disease. The mechanisms underlying this association are complex and multifactorial, involving both genetic and environmental factors. Accumulating evidence suggests that through pro-inflammatory cytokines secreted from white adipocytes, obesity predisposes to the development of psoriasis and worsens existing psoriasis. Weight loss interventions through low-energy diet (800–1000 kcal/day) and gastric bypass were shown to improve

psoriasis outcomes.^{43,44} Surprisingly, gastric banding did not achieve the same antipsoriatic effect, suggesting that the observed discrepancies may be due to factors other than weight loss, such as postoperative hormonal changes.⁴³

It is estimated that for every 10% increase in body surface area affected by psoriasis, there is a 20% additional increase in risk of diabetes development.⁴⁵ Furthermore, patients with concurrent diabetes and psoriasis have a higher risk of developing micro- and macrovascular complications compared with patients with diabetes alone.

Primary care management:

- People with psoriasis should receive routine monitoring of their body mass index, fasting plasma glucose, blood pressure and lipid panel.

Excessive alcohol and tobacco consumption

Beyond its cardiovascular harmful effect, cigarette smoking was found to increase the risk of psoriasis development and the severity of psoriasis.⁷ Smoking has a particularly strong association with the psoriasis variant palmoplantar pustulosis, and smoking cessation was associated with significant clinical improvement in patients with this variant.⁴⁶ With regards to joint disease, there is some controversial evidence surrounding the reverse association of smoking and psoriatic arthritis, often referred to as the “smoking paradox”.⁴⁷ However, rather than being a true association, it is now thought that methodological limitations are likely the main reasons to explain the paradox.⁴⁷

Excess alcohol consumption has been linked with development of psoriasis, more severe skin disease and less favourable response to psoriasis treatment.⁸ Excessive alcohol intake also limits some of the systemic treatment options for psoriasis, such as methotrexate. There is evidence demonstrating that severe psoriasis leads to excess tobacco and alcohol use.⁴⁸ There have been no randomised trials examining whether alcohol abstinence and smoking cessation are effective in treating psoriasis.⁴⁹

Primary care management:

- People with psoriasis should be provided counselling regarding smoking cessation and limiting alcohol intake to improve their overall health.

Psychosocial impact and effect on quality of life

Individuals with psoriasis have been found to have a significantly increased risk of depression and anxiety compared with non-affected individuals.^{9,10} The attributable risk for depression, but not anxiety, is greater in patients with severe than mild psoriasis.⁵⁰ Nevertheless, it is important to recognise that the psychosocial impact experienced by individuals with psoriasis is not always proportional to or predicted by the severity of skin disease.⁵¹ Hence, it should not be assumed that individuals with the same objective severity of psoriasis will exhibit the same level of psychological distress from their condition. There is also evidence to suggest that depression and anxiety are associated with development of atherosclerosis beyond traditional cardiovascular risk factors.⁵²

Although it is uncertain whether psychiatric symptoms associated with psoriasis are related to the elevated inflammatory cytokines or the social impact of psoriasis, several studies have shown that the use of biological therapies in patients with moderate to severe psoriasis results in significant improvement in depression and anxiety scores.⁵³ Biological therapy was found to be associated with a lower incidence of depressive symptoms than conventional systemic therapy and phototherapy.¹⁶ Evidence from these studies suggests that mental health symptoms improve along with the improvement in skin disease.¹⁶

Psoriasis affects several factors that contribute to worsened quality of life, including fear of stigmatisation,⁵⁴ impaired social life,⁵⁵ higher rates of unemployment,⁵⁶ and sexual dysfunction.¹³ Genital psoriasis occurs in up to 60% of people with psoriasis; studies also found that sexual disturbance occurred regardless of the presence of genital psoriasis.⁵⁷ Effective systemic therapy has been associated with improved work productivity and lower rates of sexual dysfunction.¹³

Based on these observations, the question emerges whether psoriasis is associated with suicidality at the population level. Two systematic reviews and meta-analyses were published to address this research gap but their conclusions are contradictory.^{11,12} A critical appraisal of these findings deduced that specific recommendations for clinical practice cannot be made based on the low quality of evidence to date.⁵⁸ Clinicians should nevertheless be alert to the warning signs of suicidality.

Primary care management:

- Primary care providers should be aware of the burden of mental health problems in people with psoriasis. They should be screened and managed for depression and anxiety.
- People with moderate to severe psoriasis should be considered for a dermatological assessment, as biological therapy, systemic conventional therapy and phototherapy have all been shown to improve psoriasis and concurrently improve psychiatric symptoms and quality of life.^{15,16}
- Patients should be sensitively asked and provided with validation about the possible impact of psoriasis on their sexual health, social relationships, and employment.

Malignancy

People with psoriasis have been found to have a higher incidence of certain malignancies relative to age-matched controls without psoriasis, including lymphoproliferative disorder (strongest association occurring with cutaneous T-cell lymphoma and Hodgkin lymphoma), non-melanoma skin cancer and malignancies of the gastrointestinal tract, bladder, lung and head and neck.^{17,59} The relative risk of developing cancer increases with the severity of psoriasis, which may be partly explained by the comorbid risk factors of smoking, alcohol use, and obesity.⁵⁹ The higher rates of malignancy are also attributed to the tumour-promoting effects of a chronic systemic inflammatory state.⁶⁰

The elevated risk of non-melanoma skin cancer appears to be associated with the use of cyclosporine, psoralen and ultraviolet A (PUVA), and TNF- α inhibitors.^{17,61} In Australia,

PUVA is now rarely used and largely replaced by narrow-band ultraviolet B (NB-UVB), a safer form of phototherapy without the demonstrated carcinogenic risk of PUVA.⁶² Current evidence suggests that IL-12 and IL-23 inhibition does not appear to increase malignancy risk.⁶³⁻⁶⁵ Acitretin does not increase risk of carcinogenesis and it is also protective against non-melanoma skin cancer and cutaneous T-cell lymphoma.⁶⁵ Based on the high level of evidence to date from the dermatology and rheumatology literature, there is little evidence of an association between non-cutaneous malignancies and systemic immunomodulators for psoriasis.⁶⁶ Optimisation of comorbid, well established risk factors, including obesity, smoking and alcohol use, is more impactful on cancer risk reduction than cessation or avoidance of immunosuppressive therapy for psoriasis.⁶⁷

Primary care management:

- Primary care providers should be cognisant that psoriasis is associated with an increased relative risk of certain cancers. Clinical features suggestive of occult malignancy should be investigated and, if appropriate, referred for further management.
- People with psoriasis should be ensured to be up-to-date with age-appropriate cancer screening.
- Patients who have received more than 100 treatments of PUVA, especially if given in combination with cyclosporine, are recommended to have regular skin cancer surveillance.⁶⁷
- Atypical skin lesions that are not responding to psoriatic treatment should be biopsied or referred for consideration of non-melanoma skin cancer and cutaneous T-cell lymphoma.

Inflammatory bowel disease and other immune-mediated diseases

Psoriasis and psoriatic arthritis have been associated with inflammatory bowel disease and several other immune-mediated conditions, including coeliac disease, alopecia areata, vitiligo, rheumatoid arthritis, autoimmune thyroid disease, and systemic sclerosis.^{20,68} Studies demonstrated that psoriasis and inflammatory bowel disease have a significant bidirectional association and share several genetic susceptibility loci.⁶⁹ The prevalence of Crohn disease and ulcerative colitis in patients with psoriasis was 0.7% and 0.5% respectively.⁶⁹ The incidence of Crohn disease and ulcerative colitis was 1.55 and 3.17 per 10 000 person-years among patients with psoriasis respectively.⁷⁰ Several therapies, such as inhibitors of TNF- α and IL-23 are effective in both diseases, highlighting the common immunological mechanisms. Patients with inflammatory bowel disease can paradoxically develop psoriasiform reaction after using TNF- α inhibitors, occurring at an incidence rate of five per 100 person-years.⁷¹ The pathophysiology of this paradoxical skin reaction may be related to a cytokine imbalance and has also been reported to occur in other biologics.⁷² Unlike the link between severe psoriasis and increased risk of psoriatic arthritis and cardiovascular disease, patients with concomitant psoriasis and inflammatory bowel disease were found to have a mild psoriasis phenotype similar to

patients with psoriasis without inflammatory bowel disease.⁷³ Patients with psoriatic arthritis were more likely to have an autoimmune disease than those with only cutaneous disease.²⁰ This may be explained by the greater level of systemic inflammation in patients with psoriatic arthritis compared with those with psoriasis alone.^{20,74}

Primary care management:

- Primary care providers and physicians should be aware of the increased incidence of immune-mediated diseases in people with psoriasis. The clinical features of these disorders should be recognised and suspicious symptoms should be further investigated and referred as deemed appropriate.

Hepatic disease

There appears to be an association between psoriasis and non-alcoholic fatty liver disease.²² The occurrence of non-alcoholic fatty liver disease was greater among patients with psoriatic arthritis and moderate to severe psoriasis compared with mild psoriasis.²² In addition, patients with psoriasis treated with systemic therapy, including methotrexate, were found to have an increased risk of non-alcoholic fatty liver disease to a greater degree than patients with rheumatoid arthritis.⁷⁵

Primary care management:

- People with moderate to severe psoriasis, psoriatic arthritis and/or metabolic syndrome should be monitored for non-alcoholic fatty liver disease.
- Hepatotoxic medications should be used with caution in this at-risk population.

Renal impairment

Even after adjusting for other comorbidities of psoriasis that may negatively affect the kidneys (cardiovascular and metabolic disorders and non-steroidal anti-inflammatory drug use), moderate to severe psoriasis was found to be an independent risk factor for chronic kidney disease.²³ No association was linked with mild psoriasis. While the precise mechanism of this relationship is unclear, possible explanations include accelerated atherosclerotic injury to the kidneys from chronic inflammation in psoriasis and the greater incidence of glomerulonephritis in patients with psoriasis, particularly IgA nephropathy.^{76,77}

Primary care management:

- Nephrotoxic medications should be used with caution in people with moderate to severe psoriasis.
- Impaired renal function may cause accumulation of methotrexate and subsequent myelosuppression. Methotrexate dose reduction is required in patients with glomerular filtration rate (GFR) below 50 mL/min/1.73m² and contraindicated in patients with GFR below 20 mL/min/1.73m².⁷⁸

Conclusion

Given our improved understanding of psoriasis, we should no longer treat psoriasis purely as a skin disease. The chronic inflammatory nature of psoriasis likely contributes to the comorbidities of this complex multisystem disorder. Psoriasis severity is usually associated with the occurrence of most comorbid conditions, warranting greater vigilance when evaluating patients with a more severe clinical phenotype. Given the interdependent relationship between the various comorbidities and psoriasis, effective management of moderate to severe psoriasis is likely to have benefit on comorbidities and overall patient outcome. Primary care providers and general physicians play a crucial role in recognising and managing these comorbid conditions.

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[Insert Box]

Summary of comorbidities in psoriasis, strength of their association and the role of primary care management

Type of comorbidity	Comorbid condition	Strength of association	Primary care management
Arthritis	Psoriatic arthritis, ² prevalence	6–41%	▪ Screen for psoriatic arthritis using a validated questionnaire-based tool³ ▪ Ask and examine patients for inflammatory joint pain, swelling, enthesitis and dactylitis ▪ Early rheumatology referral for suspected psoriatic arthritis
Cardiovascular disease	Cardiovascular mortality, ⁴ RR (95% CI)	1.39 (1.11–1.74)	▪ Screen and manage obesity, diabetes, dyslipidaemia and hypertension as per national guidelines
	Myocardial infarction, ⁴ RR (95% CI)	1.70 (1.32–2.18)	
	Stroke, ⁴ RR (95% CI)	1.56 (1.32–1.84)	
Obesity and insulin resistance	Obesity, ⁵ OR (95% CI)	2.23 (1.63–3.05)	▪ Screen and manage obesity, diabetes, dyslipidaemia and hypertension as per national guidelines
	Type 2 diabetes mellitus, ⁶ OR (95% CI)	1.69 (1.51–1.89)	
Smoking and alcohol	Smoking, ⁷ OR (95% CI)	1.78 (1.52–2.06)	▪ Ask about smoking and alcohol use to every patient with psoriasis
	Alcohol use, ⁸ OR (95% CI)	1.53 (1.16–2.01)	▪ Provide counselling for smoking cessation and moderation of alcohol use with an emphasis on improving overall health as well as reducing severity of psoriasis
Mental health and quality of life	Depression, ⁹ OR (95% CI)	1.57 (1.40–1.76)	▪ Ask and provide validation about possible impact of psoriasis on depression, anxiety, sexual dysfunction and social isolation
	Anxiety, ¹⁰ OR (95% CI)	2.18 (1.68–2.82)	

	Suicidality, ^{11,12} RR (95% CI)	1.26 (0.97–1.64)	Consider referral of patients with moderate to severe psoriasis for consideration of systemic therapy. Improvement in skin scores has been shown to improve both quality of life and psychiatric symptoms^{15,16}
	Suicidality, ^{11,12} OR (95% CI)	1.26 (1.13–1.40)*	
	Sexual dysfunction, ¹³ HR (95% CI)	1.27 (1.11–1.46)	
	Erectile dysfunction, ¹⁴ OR (95% CI)	1.35 (1.29–1.41)	
Malignancy	Squamous cell carcinoma, ¹⁷ SIR (95% CI)	5.3 (2.63–10.71)	- Ensure people with psoriasis have up-to-date age-appropriate cancer screening - Be vigilant of the clinical features suggestive of malignancy; investigate and refer as deemed appropriate - Skin lesions that do not adequately respond to psoriatic treatment should be biopsied or referred for consideration of cutaneous T-cell lymphoma and non-melanoma skin cancer, which can mimic psoriatic plaque
	Basal cell carcinoma, ¹⁷ SIR (95% CI)	2.0 (1.83–2.20)	
	Cutaneous T-cell lymphoma, ¹⁸ RR (95% CI)	4.10 (2.70–6.23)	
	Hodgkin lymphoma, ¹⁷ SIR (95% CI)	1.40 (1.06–1.86)	
	Respiratory tract cancer, ¹⁷ SIR (95% CI)	1.52 (1.35–1.71)	
	Upper gastrointestinal tract cancer, ¹⁷ SIR (95% CI)	3.05 (1.74–5.32)	
Inflammatory bowel disease and other immune-mediated diseases	Crohn disease, ¹⁹ OR (95% CI)	1.70 (1.20–2.40)	Be vigilant of the clinical features of autoimmune diseases and HLA-B27-associated diseases (eg, uveitis, inflammatory bowel disease); investigate and refer as deemed appropriate
	Ulcerative colitis, ¹⁹ OR (95% CI)	1.75 (1.49–2.05)	
	At least one autoimmune disease, ²⁰ OR (95% CI)	1.5 (1.4–1.5)	
	Coeliac disease, ²⁰ OR (95% CI)	2.3 (1.6–3.2)	
	Vitiligo, ²⁰ OR (95% CI)	1.7 (1.4–2.0)	
	Uveitis, ²¹ HR (95% CI)	1.42 (1.23–1.64)	

Liver disease	Non-alcoholic fatty liver disease, ²² OR (95% CI)	2.15 (1.57–2.94)	▪ Monitor for non-alcoholic fatty liver disease in patients with moderate to severe psoriasis and/or psoriatic arthritis ▪ Hepatotoxic medications should be used with caution
	Chronic kidney disease, ²³ RR (95% CI)	1.34 (1.14–1.57)	▪ Nephrotoxic medications should be used with caution
Renal impairment	End-stage renal disease, ²³ RR (95% CI)	1.29 (1.05–1.60)	▪ Dose adjustment is required for methotrexate use in patients with GFR < 50 mL/min/1.73m ²

GFR = glomerular filtration rate; HLA = human leukocyte antigen; HR = hazard ratio; OR = odds ratio; RR = relative risk; SIR = standardised incidence ratio. * See main text for discussion on the conflicting results regarding suicidality risk.