

Smoking and rheumatoid arthritis (RA)

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Key points:

- smoking is a major preventable risk factor for rheumatoid arthritis (RA)¹
- the increased risk due to smoking is dependent both on the amount of smoking and an individual's genetic make-up²
- smoking contributes at least 25% of the population burden of RA and the risk is dose-related, stronger in males and especially strong for anti-citrullinated peptide antibody positive (ACPA+) rheumatoid arthritis³
- the proportion of RA attributable to smoking is similar to that seen for ischaemic heart disease⁴
- heavy smoking - more than 20 pack-years¹ of smoking - approximately doubles the odds of rheumatoid arthritis in both men and women⁵
- people with rheumatoid arthritis have an increased risk of cardiovascular disease⁶, lymphoma and lung cancer⁷, and osteoporosis⁸ compared to the general population and these are also established risk factors of smoking⁹
- smoking can compromise the effectiveness of RA medications^{10 11 12}
- rheumatoid arthritis may be more severe in smokers than in non-smokers¹³
- it may take up to 20 years after smoking cessation to return to baseline risk¹⁴ which is yet another reason to advise young adults not to start smoking.

This specialist briefing is aimed at professionals and policy makers. It reviews the evidence on smoking and an increased risk of developing rheumatoid arthritis (RA), and on how continued smoking can affect both RA severity and the effectiveness of treatments.

¹ One pack year is defined as 20 manufactured cigarettes (one pack) smoked per day for one year.

15 cigarettes a day for 40 years (15/20) x 40 = 30 pack year smoking history.

What is rheumatoid arthritis?

Rheumatoid arthritis (RA) belongs to the group of diseases whereby immune cells attack the body's own tissues. The disease is a result of a complex interplay of genetic factors, environmental influences and infection. Pain and swelling in the finger joints are often the first external symptoms. The underlying inflammation can cause damage to the bone and joint system and as the disease progresses it can also lead to various organ disorders. Prevalence ranges from 0.5-1.5% of the population in industrialised countries¹⁵. The incidence of RA is typically two to three times higher in women than men and the onset, in both women and men, is highest among those in their sixties¹⁶.

How smoking promotes the onset of rheumatoid arthritis

Smoking triggers a reaction in immuno-tolerance which can promote the onset of rheumatoid arthritis. Researchers from the Karolinska Institute in Stockholm¹⁷ have discovered that it increases the risk of rheumatoid arthritis in people who have certain types of antibodies called anti-citrulline antibodies. Citrulline is an amino acid which affects proteins in the body and these proteins, modified with citrulline, are linked to the development of rheumatoid arthritis. In a person with the correct genetic predisposition, chemicals from smoking activate an enzyme called peptidylarginine deiminase type 2, and the activation of this enzyme causes a biochemical change in the body's own proteins. This change is called citrullination. The citrullination causes neoepitopes to form, which the immune system falsely identifies as foreign. These genetically susceptible individuals then form anti-citrullinated protein/peptide antibodies (ACPAs) to fight the altered proteins, which leads to the eventual onset of rheumatoid arthritis, although ACPAs can be present years before the first clinical symptoms of rheumatoid arthritis appear. Essentially, if a person inherits two copies of the genes that most strongly predispose to rheumatoid arthritis, and is a smoker, and is positive for ACPAs, then their risk of developing rheumatoid arthritis is 21 times greater than that of a non-smoker who doesn't have the genes¹⁸. Interestingly, emerging research¹⁹ suggests that changes outwith the joints (such as in the lungs) may be the initiating event of the specific immune response in ACPA positive RA, and this may have implications for smoking.

ACPAs are present in about 70% of RA patients²⁰. That at least 25% of cases of ACPA-positive rheumatoid arthritis, the commonest and most severe

variant of RA, appear to be attributed to smoking illustrates the impact of smoking as a major cause of RA at population level²¹. The smoking attribution to RA is, however, smaller than the smoking attribution to lung cancer, which is estimated to be as high as 90%²², but similar to that seen for ischaemic heart disease²³.

Associated risk factors for developing rheumatoid arthritis

It is possible that airborne exposures such as silica and other air pollutants may interact with the effects of smoking²⁴; an observed association between exposure to traffic pollution and RA suggests that pollution from traffic in adulthood may be an environmental risk factor for RA. Similarly other lifestyle factors such as alcohol consumption or hormonal factors influencing the risk of RA may interact with smoking^{25 26}. However, smoking has been shown to be a major risk factor for RA in the majority of published studies²⁷.

Rheumatoid arthritis and exposure to second-hand smoke

Currently there is a lack of evidence about an increased risk of developing rheumatoid arthritis from exposure to second-hand smoke. However, cardiovascular disease is the major cause of premature death in people with rheumatoid arthritis²⁸ and chronic exposure to second-hand smoke increases the risk of coronary heart disease²⁹. Research shows that thirty minutes of exposure to second-hand smoke can cause measurable changes to the vascular system, suggesting a mechanism by which second-hand smoke causes disease^{30 31}. Inhaling second-hand smoke causes cancer in non-smokers³² and the US Surgeon General also estimates that living with a smoker increases a non-smoker's chances of developing lung cancer by 20 to 30 per cent²⁹.

Other conditions associated with rheumatoid arthritis

People with rheumatoid arthritis have an increased risk of cardiovascular disease³³, lymphoma and lung cancer³⁴, and osteoporosis³⁵. Pulmonary involvement, the third leading extra-articular (occurring outside the joint) manifestation of RA, is a major cause of morbidity and mortality in people with rheumatoid arthritis³⁶. Pulmonary complications are the presenting manifestation of RA in up to 20% of patients and include airway disease, pleural effusion, pulmonary nodules, and interstitial lung disease (ILD)³⁷.

According to one 2007 best practice guide³⁸ 'the chronic, debilitating, autoimmune nature of RA affects the patient directly or indirectly in almost all organ systems, from cardiovascular problems and infections to depression and gastrointestinal ulcers. On average, the established RA patient has two or more comorbid conditions'. Numerous studies have shown that rheumatoid arthritis (RA) is associated with reduced lifespan and excess mortality^{39 40} and research published in June 2012 reports 'that cardiovascular (CV) risk seems to increase sooner after the RA diagnosis than previously thought. In addition to systematic CV risk assessment, patients with early RA might benefit from being targeted with stricter than conventional CV risk prevention and intervention'⁴¹. As most of the common comorbidities for RA have clear associations with smoking it seems clear that smoking cessation should have a key role to play in improving outcomes for people with rheumatoid arthritis.

Smoking and rheumatoid arthritis medications

People with early rheumatoid arthritis (RA) who smoke are 50% less likely to respond to treatment with two of the most commonly used medications^{42 43}, disease modifying anti-rheumatic drugs (DMARDs) and biologic drugs known as TNF (tumour necrosis factor inhibitors). These drugs are currently first- and second-line agents of choice in early RA treatment. Patients with RA who do not respond to anti-TNF drugs are next considered for treatment with rituximab, a B-cell depleting immunosuppressive drug. Never smokers are 95-100% likely to respond to rituximab compared to a half or less response rate in current smokers⁴⁴.

Smoking cessation for people with rheumatoid arthritis

Smoking has been shown to have an adverse effect on disease progression in people with rheumatoid arthritis^{45 46}. The impact of giving up smoking on on-going rheumatoid arthritis is not yet fully understood but there is a clear link between smoking and cardiovascular disease, which is the major cause of premature death in people with rheumatoid arthritis⁴⁷. Cigarette smoking may adversely influence the severity of RA in a potentially dose dependent fashion⁴⁸. A June 2012 systematic review⁴⁹ has shown that the benefits of smoking cessation are evident in all age groups, including subjects 80 years and older. For those who manage to give up smoking the risk of dying from lung cancer halves within ten years⁵⁰ but the risk of developing rheumatoid arthritis may take twenty years to return to that of a non-smoker⁵¹. Giving up smoking confers both immediate and long-term

health benefits from improved blood pressure and lung function to decreased cancer and stroke risk⁵².

Key messages for people with rheumatoid arthritis:

- smoking causes the body to produce antibodies which are strongly associated with the development of RA
- smoking is a major risk factor for rheumatoid arthritis and heavy smoking more than doubles the risk
- smoking is associated with the most severe kinds of RA
- smoking interferes with many RA medications
- the sooner you quit the better, but it's never too late and it will have immediate health benefits.

Recommendations

Alongside a need for improved awareness of the links between smoking and rheumatoid arthritis, there is a need to develop preventive population strategies similar to those already in place for cancer and heart disease. Information about the benefits of smoking cessation and the health risks of exposure to second-hand smoke should be incorporated into guidelines for the management of rheumatoid arthritis and raised with patients, their families, and carers at every suitable opportunity in the care pathway. There should also be an increase in the number of healthcare professionals trained to deliver brief advice about smoking cessation to people with a diagnosis of rheumatoid arthritis.

Dedicated specialist smoking cessation support should be made available within the hospital/acute setting and integrated with community-based cessation services. According to a May 2012 updated Cochrane Review of interventions for smoking cessation in hospitalised patients⁵³ *'high intensity behavioural interventions that begin during a hospital stay and include at least one month of supportive contact after discharge promote smoking cessation among hospitalised patients. The effect of these interventions was independent of the patient's admitting diagnosis and was found in rehabilitation settings as well as acute care hospitals. There was no evidence of effect for interventions of lower intensity or shorter duration. This update found that adding NRT to intensive counselling significantly increases cessation rates over counselling alone'*. In short, every rheumatology department should reinforce the message that smoking is bad for rheumatoid arthritis and have help available to support people to

stop, including advice, behavioural support and referral pathways on discharge.

Further information and support



The National Rheumatoid Arthritis Society has collaborated with NHS Fife and Pfizer to develop a campaign (leaflet pictured left) to raise awareness of the link between RA and smoking and to encourage people with RA to think twice about smoking. This leaflet and supporting campaign

materials are available from the National Rheumatoid Arthritis Society:

www.nras.org.uk/

Helpline (freephone): 0800 298 7650, weekdays between 9.30am and 4.30pm.

- Arthritis Care: www.arthritiscare.org.uk
Helpline (Freephone): freephone 0808 800 4050, weekdays 10am to 4pm.
- Arthritis Research UK: www.arthritisresearchuk.org/
- Health and Social Care Alliance Scotland: www.alliance-scotland.org.uk
- Arthritis and Musculoskeletal Alliance: <http://arma.uk.net/>

Support to stop smoking

People who smoke have a much better chance of giving up smoking if they get support to do so and there are lots of different ways to find support:

- pharmacies/local chemists are able to provide quit smoking advice and support. Where appropriate, the pharmacist can identify the most suitable form of nicotine replacement therapy (NRT) and some pharmacies run NHS-funded stop smoking services
- through the local doctor's surgery
- phone free to Smokeline on **0800 84 84 84** (8am to 10pm, seven days a week)
- Smokeline advisers provide free advice and information for anyone who wants to stop smoking, or who wants to help someone to quit.

Smokeline also provides information about the free stop smoking services provided by every health board in Scotland

- request stop smoking leaflets, a magazine and a DVD from Smokeline either by calling the helpline, or by texting 'QUIT' to 83434
- visit www.canstopsmoking.com and enter a postcode to find the nearest stop smoking service or use web chat support (8am to 10pm) at www.canstopsmoking.com/Web-Chat

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² Ibid

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