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## Causal risk and protective factors in rheumatoid arthritis: an update

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## Abstract

The characterization of risk and protective factors in complex diseases such as rheumatoid arthritis (RA) has evolved from epidemiological studies, which test association, to the use of Mendelian randomization approaches, which test direct relationships. Indeed, direct associations with the mucosal origin of RA are retrieved with periodontal disease (*Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* predominantly), interstitial lung involvement, tobacco smoking and air pollutants. Next, factors directly associated with an acquired immune response include genetic factors (HLA DRB1, PTPN22), capacity to produce anti-modified protein antibodies (AMPA), and relatives with a history of autoimmune diseases. Finally, factors can be also classified according to their direct capacity to interfere with the IL-6/CRP/sIL-6R proinflammatory pathway as risk factor (body fat, cardiometabolic factors, type 2 diabetes, depressive syndrome) or either as protective factors by controlling of sIL-6R levels (higher education level, and intelligence). Although some cofounders have been characterized (e.g. vitamin D, physical activity, cancer) the direct association with sex-discrepancy, pregnancy, and infections among other factors remains to be better explored.

**Key words:** rheumatoid arthritis, risk factors, Mendelian's randomization, inflammation, soluble IL-6 receptor

## Introduction

Among non-specific autoimmune diseases (SAD), rheumatoid arthritis (RA) is the most prevalent ranging from 0.5% to 1.0% in the general population (Smolen et al., 2018). As depicted in Figure 1, RA development comprises at least four immune-related stages that begins, in the mucosa of the mouth and/or lung, with an intake by antigen-presenting cells (APC) of neo-epitopes corresponding to peptides post-transcriptionally modified at arginine by citrullinisation or at lysine by carbamylation or acetylation. This leads to a local inflammation and APC migration to the secondary lymphoid organs. Immunization stage takes place in lymphoid organs, which begins 5-10 years before clinical symptoms and involves T and B cells promoted by mucosal APC. This acquired and high-risk immunization step is characterized by the production of autoantibodies targeting mucosal neo-antigens such as anti-citrullinated antibodies (ACPA), anti-carbamylated antibodies (ACarPA), anti-acetylated antibodies (AAPA), all referred as anti-modified protein (AMPA) antibodies. Immunization can be completed by the production of anti-peptidylarginine deiminase (PAD) antibodies, antibody targeting bacteria involved in the neo-antigen process, and rheumatoid factors (RF) that is an anti-immunoglobulin G autoantibody (Renaudineau et al., 2005) (Bettacchioli et al., 2021). Next and following leukocyte recruitment in the joints together with synovial fibrin citrullinisation and fibroblast proliferation, also called fibroblast-like synoviocytes (FLS), an undifferentiated autoimmune pre-clinical arthritis with a synovial inflammation starts (Arleevskaya et al., 2020). Finally, and as RA develops, an uncontrolled systemic inflammatory amplification loop including a dysregulation of the IL-6 signalling pathway leads to joint damage, cartilage destruction, bone erosion and extra-articular manifestations (Alonso et al., 2010) (Simon et al., 2021) (Barturen et al., 2021).

RA is a complex disease and its development includes a long process driven by multiple risk/protective genetic, environmental, and sexual related-factors (Kobayashi et al., 2008) (Brooks et al., 2010). Initially, epidemiological studies were used to identify RA risk and protective factors but it has been more and more evident that such approach is limited due to the risk of confounding effect, reverse causation and various other biases. To circumvent this effect and as an add-on to epidemiological studies, the Mendelian randomization (MR) approach has been developed in order to test the direct relationship from an exposure (risk/protective factor) to an outcome (RA). This can be

performed by using genetic variants robustly and specifically associated with an exposed factor as an instrumental variable. A retro-analysis can be further performed distinguishing causal from bi-directional factors. Another advantage of the MR approach is to link the direct association observed with the immune-related stage of RA development (neoantigen formation, immunization, and chronic inflammatory/clinical activity) as reported in Table 1 and Figure 2. Accordingly, the aim of the present review is to summarize the information regarding risk and protective factors having a direct involvement on RA and establish their contribution according to the immune stage development.

## Material and methods

A selective search of the pubmed database before July 2021 combining keywords related to “rheumatoid arthritis”, “Mendelian randomization”, “risk factors”, “protective factors”, and “meta-analysis” was performed. When specified, odds ratio (OR) and the 95% confidence-interval (IC95) were collected and a p value <0.05 was considered although specified.

## Factors associated with a mucosal origin

According to the mucosal origin hypothesis of RA, a pre-disease stage originates at distal mucosal sites within the oral cavity and lungs, and later spreads to the joints. Such assertion is supported by the report of specific antibodies years before RA development targeting bacterial strains involved in neo-epitope formation, targeting bacterial and host PAD, as well as the detection of AMPA, and RF (Shi et al., 2014).

Periodontal disease is directly associated with RA (Yakob et al., 2011)(Bae and Lee, 2020), and such association is more significant at pre-clinical stage (OR=3.39; IC95: 1.64-7.01) as compared to RA at advanced stage (OR=1.69; IC95: 1.31-2.17) (Qiao et al., 2020). *Porphyromonas gingivalis*, the major periodontal pathogen (OR=6.5; CI95: 1.40-30.21), possess the capacity to citrullinate host proteins via *P. gingivalis* (P)PAD production providing, by this way, the missing link between periodontitis and the development of RA (Jenning et al., 2020)(Shungin et al., 2019). The key role played by *P. gingivalis* on RA is further supported by the detection of IgG, most often IgG2 subclass, against *P. gingivalis* and against PPAD, which are increased at the pre-clinical stage and

associated with ACPA while not with RF (Johansson et al., 2016) (Bello-Gualtero et al., 2016) (Goh et al., 2016) (Maran et al., 1997). Moreover, the anti-bacterial protective variant of TLR4 (rs4986790), suspected first as protective factor for RA but not validated in a meta-analysis, is associated with *P. gingivalis* detection (OR=0.58, CI95: 0.36-0.98) (Sellers et al., 2016) (Lee et al., 2013). A second oral pathogen associated with chronic periodontitis and RA has emerged, *Aggregatibacter actinomycetemcomitans*, due to its capacity to promote in granulocytes host PAD4 hyperactivity and hypercitrullinated protein release in response to the secretion of a leukotoxin A (Konig et al., 2016). The development of IgM antibodies against *A. actinomycetemcomitans* leukotoxin A (AaLtxA) is retrieved with RA at early disease stage (OR=1.012; CI95: 1.007-1.017) and elevated levels are maintained after adjustment with ACPA/RF status, tobacco smoking, sex, and HLA-DRB1 shared epitope (SE) (Gomez-Bañuelos et al., 2020). When present in patients with RA, IgG anti-Aa and/or anti-AaLtxA antibodies, but not IgG anti-Pg antibodies, are associated with a higher prevalence of RF and atherosclerosis in those patients with higher swollen joint counts (Giles et al., 2021). Of note, the increase citrullinisation and PADI2/4 expression observed in gingival tissues from RA patients with periodontitis is imperfectly associated with *P. gingivalis* and *A. actinomycetemcomitans* detection, which suggests other factors implicated in PAD2/4 overexpression and neo-epitope formation (Engström et al., 2018). In Asiatic populations, but not in Caucasians, polymorphisms at PAD4 (rs2240340) and PAD2 (rs1005753) confer a risk to RA with a OR=1.28 (CI95: 1.15-1.42) and OR=0.87 (CI95: 0.77-0.99), respectively (Hua and Huang, 2018) (Too et al., 2012). Other direct associations between periodontitis and RA-related risk factors have been established including tobacco smoking (OR=5.64; CI95: 1.98-16.12), a lower education level (OR=5.02; CI95: 1.25-20.25), and in a lesser extent an elevated body mass index (BMI) (Shungin et al., 2019).

Among patients with RA, 20-60% have interstitial lung abnormality, usually prior to articular manifestations, suggesting a role for the lung in disease progression at early stage (McDermott et al., 2021). Among them an interstitial lung disease (ILD) occurs approximately in 5-10% of them affecting physical functions and with a mortality rate up to 10 fold higher than those without ILD. Anti-CarPA detection rather than ACPA and/or RF is associated with ILD (OR=3.42; CI95: 1.13-10.40) in two case-reports (Castellanos-Moreira et al., 2020) (Zhu et al., 2019). Anti-CarPA detection precedes ILD

and is independent from ILD-RA associated risk factors that took place later such as extensive tobacco smoking (OR=6.06, CI95: 2.72-13.5), inflammation with a CRP > 10mg/L (OR=3.1; CI95: 1.32-7.26), obesity (OR=2.42; CI95: 1.11-5.24), and a lower education levels (Kronzer et al., 2021) (Janssen et al., 2015).

Tobacco smoking is referred to as a direct and main environmental factor associated with RA development with an OR=1.32, IC95: 1.15-.52 (Sugiyama et al., 2010). Using a multivariable analysis approach, the risk to develop RA in smokers remained significant (OR=1.25; CI95: 1.07-1.47) after adjusting with the co-founder factors including BMI, education attainment and alcohol consumption (Qian et al., 2020). A high exposure to tobacco smoke during pregnancy increases the risk of RA at juvenile-onset in girls (OR=2.98; IC95: 0.95-8.78), which is not the case in boys (Jaakkola and Gissler, 2005). Exposition to free crystalline silica represents another air pollutant risk-factor retrieved to be associated with RA development (OR=1.94; CI95: 1.46-2.58), and such association is additive among tobacco smokers seropositive for ACPA and/or RF in men (OR=3.30; CI95: 2.40-4.54) (Morotti et al., 2021) (Sugiyama et al., 2010). The underlying pathways leading to the development of RA within individuals exposed to tobacco smoking and air pollutants is still unclear and several models have been proposed: (i) an impaired innate immune system that relies on the positive association between smoking and *P. gingivalis* (Torrunguang et al., 2020); (ii) an affected adaptive immune response explaining that never smoker RA patients possess elevated protective anti-*P. gingivalis* and anti-PPAD antibody titers (Seror et al., 2015); (iii) a deregulated PAD4 expression in the lung based on the observation that RA patients with ILD have increase PAD4 expression at transcriptional and protein level in bronchoalveolar granulocytes and monocytes among smokers (Samara et al., 2017); (iv) a higher systemic inflammation as retrieved in the elevated tobacco consumption subgroup (Çolak et al., 2019); and (v) an association with RF-positivity (OR=2.35; IC95: 1.64-3.35) independent from ACPA/CarpA status (Sugiyama et al., 2010) (Regueiro et al., 2020). Although all these explanations are plausible, more studies are warranted to elucidate the mechanisms and their interplay.

## **Genetic factors associated with an acquired immune response**

The collection of HLA alleles that contained within the third hyper-variable region of the DR beta-(B)1 chain a conserved amino acid motif (QKRAA) at positions 70-74, known as

SE, corresponds to the main genetic risk factor for RA ranging from OR=2.17 (CI95: 1.94-2.42) for HLA DR1 to OR=4.44 (CI95: 4.02-4.91) for HLA-DR4 (\*04:04) when the SE is associated with a valine residue at position 11 (Delgado-Vega and Anaya, 2007) (Okada et al., 2019). The link between ACPA and HLA-DRB1 is now elucidated through the demonstration that citrullination is mandatory for vimentine peptide binding with the strongest binding retrieved at valine 11 (DR4) and a lesser binding at SE (DR1 and DR4) explaining, when comparing DR4 and DR1 response, that DR4 possess the strongest T-cell response *in vitro* and a severe arthritis in transgenic mice (Becart et al., 2021) (Hill et al., 2003) (Bitoun et al., 2019). Back to humans and when present, HLA-DRB1 valine 11 and SE contribute both and independently to RA disease severity including erosion (OR=2.0; CI95: 1.8-2.2) but not with the formation of rheumatoid nodules (Gorman et al., 2004b) (Gorman et al., 2004a). In addition to HLA-DRB1 SE and valine 11, additional and independent minor loci confer risk for RA and ACPA positivity such as HLA-A, HLA-B including HLA-B\*08 carrying Asp-9 that binds carbamylated peptides (OR=2.0; CI95: 1.53-2.61) (Regueiro et al., 2021), HLA-DPB1, the non-classical HLA-DOA, plus HLA-DQA1 in the Han Chinese population (Okada et al., 2019) (Guo et al., 2019).

The most influential non-HLA RA-risk variant is PTPN22 (rs2476601) that encodes a tyrosine kinase acting as a negative regulator of the antigen receptor and allowing the appearance of auto-reactive T and B cells and defective regulatory T cells. A dichotomy between ACPA positive and negative RA is further retrieved when analyzing non-HLA RA risk factors. The ACPA positive subgroup includes an association with PTPN22 rs2476601 (OR=1.91; IC95: 1.77-2.05) and IL-6R rs12083537, while the ACPA negative subgroup comprises associations with BLK (rs4840565: OR=1.12; CI95: 1.01-1.24), STAT4 (rs10181656: OR=1.04; IC95: 0.93-1.16), and IRF5 (Ruiz-Larrañaga et al., 2016) (Viatte et al., 2016). Genome wide association studies (GWAS) coupled with an epigenetic approach have further implicated genes important for common or cell specific pathways for B cells, CD4 and CD8 T cells, monocytes and natural killer (Li et al., 2020) (Farh et al., 2015).

Genetic factors are central but not sufficient to explain the increased risk/protection of several autoimmune diseases among relatives from individuals with RA (Kawai et al., 2020a) (Verma et al., 2019). Accordingly, the common genetic architecture that relates RA with other autoimmune diseases can be subdivided in three sub-groups: a subgroup involving HLA-DRB1 locus as reported with multiple sclerosis and in this case a



protective role is reported (OR 0.82; CI95: 0.77-0.88); a subgroup associated with non-HLA-DRB1 genes such as systemic lupus erythematosus (OR=1.28; CI95: 1.16-1.41), systemic sclerosis (OR=1.32; CI95: 1.13-1.53), primary biliary cirrhosis (OR=1.34; CI95: 1.15-1.56), and psoriasis; and a subgroup involving both HLA-DRB1 and non-HLA genes such as type 1 diabetes (OR=1.10; CI95: 1.04-1.16), and autoimmune thyroiditis (OR 1.34; CI95: 1.20-1.50).

## **IL6/CRP/sIL6R/IL1RA pathway to drive chronic inflammation**

Synovial inflammation characterizes the early stage of RA and is concomitant with the detection of citrullinated fibrin and the influx of leukocytes that comprises granulocytes, monocyte-derived macrophages, CD4+ T cells, and AMPA/RF productive B cells. Pro-inflammatory derived leukocytes produce a high amount of tumor necrosis factor (TNF)- $\alpha$ , IL-1 $\beta$ , and IL-6, which in turn stimulate FLS that play a critical role in the destruction of the joint. Among these pro-inflammatory factors, IL-6 is a pleiotropic cytokine that acts not only on the immune system but also in a large panel of tissues and cells including liver, bone, muscle and neuronal tissue. In liver cells, IL-6 controls acute inflammatory proteins such as C-reactive protein (CRP) and fibrinogen, while inhibiting albumin production.

IL-6 pleiotropic action is possible through a unique pathway that involves three partners: IL-6, IL-6 receptor (IL-6R) that possesses when present at the plasma membrane a short intracytoplasmic portion unable to transduce a signal, and a second receptor gp130 (Figure 3). The latter one, when activated, dimerizes and recruits the Janus kinase (Jak) that results in the phosphorylation of tyrosine residues within gp130 cytoplasmic part that subsequently recruits and phosphorylates the signal transducer and activator of transcription (STAT)3 that can next dimerize to translocate into the nucleus to induce STAT-specific gene expression. IL-6R membrane expression is restricted to leukocytes and hepatocytes, while gp130 is present in all tissues and cells. In the classical and acute inflammatory pathway, IL-6 and membrane bound (m)IL-6R associate with gp130 in an hexameric complex to initiate an intracellular signaling cascade important for B cell differentiation into plasma cells allowing antibody synthesis, for T helper (Th) cell differentiation into Th17 cells and Treg control when associated with TGF- $\beta$ , for CD8 cytotoxic T cell differentiation and promotion of the

acute phase of inflammation through hepatocytes. In the chronic and pro-inflammatory trans-signaling pathway, IL-6 can form a complex with soluble (s)IL-6R and when present at high levels a hexamer complex is formed with membrane gp130 that can transduce IL-6 signal in almost all tissues and cell types. In the joints of RA patients, high levels of IL-6 and sIL-6R are detected resulting from an increase cleavage of membrane bound IL-6R from granulocytes in the acute phase and from monocytes at the chronic phase together with local production of CRP from IL-6/sIL-6R stimulated SFC (Rönnelid et al., 2021) (Jones et al., 1999). Tocilizumab is a humanized anti-IL-6R monoclonal antibody approved in RA that is effective to control both the classical and the trans-signaling pathways (Scheller et al., 2011). Other partners are implicated in the retro-control of the IL-6/CRP pathway such as IL-1RA that controls IL-6 and CRP levels (Interleukin 1 Genetics Consortium, 2015).

When regarding, direct association between RA with IL-6, CRP, sIL-6R, IL-1RA and cellular phosphorylation at Jak/STAT pathway: no association is described with IL-6 levels; a positive association is retrieved with CRP (OR= 1.02; CI95: 1.01-1.03); a lower plasma level of sIL6R is protective for RA (OR= 0.95; CI95: 0.93–0.98) and informative for tocilizumab response (Ligthart et al., 2018a) (Rosa et al., 2019) (Diaz-Torne et al., 2018) (McGowan et al., 2019a); a higher level of IL-1RA protects from RA (OR=0.97; IC95: 0.95-0.99) (Interleukin 1 Genetics Consortium, 2015); and association exists with a negative regulator of the Jak/STAT pathway: SH2B adapter protein 3 (SH2B3) also known as lymphocyte adapter protein (LNK), which is highly express in FLS (Mo et al., 2020). Regarding the association between RA and CRP, discordances are retrieved in the literature and related to the inclusion or not of the HLA locus as instrumental variable (Kawai et al., 2020a) (Klimenta et al., 2019) (Ligthart et al., 2018b) (Prins et al., 2016) (Ling et al., 2016) (van Heemst et al., 2016). Such assertion is further supported by the observation that the valine 11 at HLA-DRB1 represents the strongest genetic factor able to control CRP level and disease activity at swollen levels (not in tender) in a case report study (van Heemst et al., 2016). When regarding other pro-inflammatory drivers (IL-18, IL-2RA, VEGF, TRAIL, IP10, IL-16, HGF, MIF), no direct association is reported with RA (McGowan et al., 2019b).

Interestingly among multiple risk/protective factors associated with RA a bi-directional profile is retrieved when using as main criteria inflammation (CRP) (Figure 3). Accordingly, a group of pro-inflammatory RA risk factors can be established, which

includes the anthropometric factors birth weight, BMI, and body fat (body fat: OR= 1.41; 95%CI 1.09, 1.84) and an altered lung function (Zhao et al., 2021) (Mo et al., 2020) (Kawai et al., 2020b). Again, HLA-DRB1 is retrieved as the main genetic factor to explain the direct association between chronic inflammation in RA with BMI. On the opposite a negative association appears with RA when using low level of sIL-6R as surrogate of anti-inflammatory and protective factor, this includes education factor with a higher education level (OR=0.49; CI95: 0.34-0.69); and cognitive factors with intelligence (OR=0.76; CI95: 0.63-0.91) (Yuan et al., 2021) (Sun et al., 2021) (Sang-Cheol Bae and Lee, 2019a). For the education level and intelligence, the effect is independent and remains after adjusting with BMI and tobacco smoking.

### Co-morbidity factors

The most common comorbidity factors associated with RA are cardiovascular diseases, cancer, osteoporosis, mental health disorders and infections (Dougados et al., 2014) (Arleevskaya et al., 2016) (Arleevskaya et al., 2018). The reciprocal positive relationship between RA, inflammation (IL-6/CRP pathway) and MHC DRB1 locus, as described upstream, is central to explain the direct association retrieved with higher risk of coronary artery disease (OR=1.02; CI95: 1.01-1.03); type 2 diabetes (OR=1.03; CI95: 1.48-1.04); and depressive symptoms; while a lower risk of chronic kidney disease (OR=0.99; CI95: 0.98-1.00) is reported (Corominas et al., 2019) (Rosa et al., 2019) (Kawai et al., 2020b). Such associations are reinforced by the observations that blockade of mIL-6R and sIL-6R in RA patients with tocilizumab prevents coronary heart disease events (Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium et al., 2012), depressive symptoms (Corominas et al., 2019), anemia (Hashimoto et al., 2014), and bone loss (Chen et al., 2017). However when the recombinant form of IL-1RA (anakinra) is used the protective effect on RA is counterbalanced by a higher risk of coronary heart disease (OR= 1.03; IC98: 1.02-1.04), through an increase in cholesterol and triglyceride concentration (Interleukin 1 Genetics Consortium, 2015). The direct association between RA and infections/dysbiosis is more controversial and may result from the inclusion or not of the HLA locus in the analysis (Kawai et al., 2020b) (Kurilshikov et al., 2021). At the opposite, the MR approach has failed to establish a causal link with osteoporosis, vitamin D levels, atrial fibrillation,

ischemic stroke, dyslipidemia, lung and breast cancer (Liu et al., 2021) (Bae and Lee, 2018a) (Kawai et al., 2020b) (Wu et al., 2021) (Ahn et al., 2020) (Jiang et al., 2018). These co-founding effects can be related to the medications used and/or tobacco smoking.

## Nutritional and sexual factors

Nutritional factors are suspected to increase RA risk (Julià et al., 2021) (Hedström et al., 2019) and the MR approaches can help to investigate the causality. A direct and protective association is reported with omega-3/6 polyunsaturated fatty acid (linoleic acid: OR=0.97; CI95: 0.95-0.98) and monounsaturated fatty acids (oleic acid: OR= 0.24; IC95: 0.10-0.59; palmitoleic acid: OR=0.98; IC95: 0.67-0.90), moderate alcohol consumption in some (OR=0.75; CI95: 0.67-0.83) but not all studies (OR=0.80; IC95: 0.54-1.19), and meat reduction (OR=0.81; CI95: 0.76-0.90) (Bae and Lee, 2018b) (Zhao and Schooling, 2019) (Sun et al., 2021). Although RA and disease activity can influence dietary habits, no direct association is reported with the consumption of eggs, sweet, bread, rice, pasta, fruit, legumes, vegetable, coffee and tea (Bae and Lee, 2018b) (Bae and Lee, 2019). Mineral nutrition (calcium, magnesium, iron, copper and zinc) has been also suspected with direct associations retrieved in some but not all MR studies with circulating magnesium (OR=8.94; CI95: 1.06-75.7) and iron (OR=0.79; CI95: 0.65-0.94) (Cheng et al., 2019) (Zhou et al., 2021) (Yuan and Larsson, 2020).

Difference between sexes regarding RA prevalence, activity, disease manifestations and therapeutic responses is likely to involve several mechanisms such as the immunodulatory functions of the sex hormonal factors, the differential regulation of the immune genes encoded on the chromosome X, and the immunomodulation observed during pregnancy that is lost in case of nulliparity. Mechanisms associated with RA improvement during pregnancy are related to a shift from pro-inflammatory cytokine status to an anti-cytokine status. While an elevated level of testosterone is associated with RA development in males (OR=1.69) (Syed et al., 2020), no direct association was retrieved with estrogens and progesterone in women when using as surrogate the three hormonal reproductive factors: age at menarche, age at menopause and age at first birth (Zhu et al., 2021). The sex hormone-binding globulin (SHBG) has been further reported

to be directly associated with RA and more significant in women (OR=1.003; CI95: 1.000-1.007) (Qu et al., 2020).

Miscellaneous associations were further tested by MR in RA to highlight a negative association between life span and telomere length with RA (Chignon et al., 2020) (Zeng et al., 2020), RA reduces the risk of Alzheimer's disease (S.-C. Bae and Lee, 2019), and positive associations are retrieved between multisite chronic pain, magnesium supplementation and RA development (Johnston et al., 2019) (Cheng et al., 2019). Finally, no association is reported with coffee consumption, alcohol intake, attention-deficit/hyperactivity disorder (ADHD), physical activity, blood minerals (Ca<sup>2+</sup>, Zn<sup>+</sup>, Fe<sup>2+</sup> and Cu<sup>+</sup>), the circulating level of growth differentiation factor (GDF)-15 and cellular capacity to glycosylate IgG (Leppert et al., 2021) (Sun et al., 2021) (Ye et al., 2021) (Yarwood et al., 2016) (Renaudineau et al., 1998) (Cheng et al., 2019) (Bae and Lee, 2018a).

## Conclusion

Although preliminary conclusions can be drawn from MR studies conducted in RA presented in this review, several progress have to be taken into consideration in the future studies: the integration of the latest SNPs used as instrumental variables for RA; the use and exclusion of exposure associated SNPs (e.g. HLA DRB1, inflammation...) to better characterize the key pathways; the integration of sex-specificities; and the use of combined mix population not restricted to Caucasians and exposed to different environmental factors. No doubt that in addition to providing an elegant complement to epidemiological studies, the MR approach has started to improve our understanding of the pathophysiology and drug mechanism of action in complex diseases such as RA. Next step is the generalization of this tool for prevention, to optimize treatment strategy, to limit side effects, and for drug repurposing.

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**Table 1:** Risk and protective factors associated with rheumatoid arthritis (RA)

<b>Risk factor</b>	<b>Main mechanism</b>	<b>Meta-analysis</b>	<b>Direct association</b>	<b>References</b>
Periodontitis, interstitial lung disease, tobacco smoking	Mucosal and immune response	Yes	Yes	(Yakob et al., 2011) (Bae and Lee, 2020) (Shungin et al., 2019)(Qian et al., 2020) (Wu et al., 2021) (Sugiyama et al., 2010) (Kronzer et al., 2021) (Çolak et al., 2019)
Autoimmune phenotype (SLE, SSc, PBC, type 1 diabetes), genetic factors (HLA, PTPN22)	Immune response	Yes	Yes	(Kawai et al., 2020b)
Inflammation (CRP, sIL-6R, SH2B3), Coronary artery disease, Type 2 diabetes, systolic blood pressure, chronic kidney disease, BMI, body fat mass,	Inflammation and immune response (MHC) and inflammation	Yes	Yes	(Ligthart et al., 2018b) (Mo et al., 2020) (Kawai et al., 2020b) (Rosa et al., 2019) (Prins et al., 2016) (McGowan et al., 2019b) (Shungin et al., 2019) (Zhao et al., 2021) (Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium et al., 2012) (Sang-Cheol Bae and Lee, 2019b)
High education, intelligence	Anti-inflammatory	Yes	Yes	(Yuan et al., 2021) (Sang-Cheol Bae and Lee, 2019a)
Linoleic and palmitoleic acid, telomere length, elevated testosterone sex hormone binding globulin, Alzheimer's disease, chronic pain, magnesium supplementation	Unknown	Yes	Yes	(Zhao and Schooling, 2019) (Zeng et al., 2020) (Syed et al., 2020) (Qu et al., 2020) (Johnston et al., 2019) (S.-C. Bae and Lee, 2019) (Sun et al., 2021)

LDL & cholesterol level, ischemic stroke, vitamin D, osteoporosis, physical activity, attention deficit/hyperactivity disorder, reproductive factors (age at menarche, menopause, and first birth), GDF-15, IgG N glycosylation, lung & breast cancer, coffee consumption, alcohol intake, blood minerals (Ca <sup>2+</sup> , Fe <sup>2+</sup> , Cu <sup>+</sup> , Zn <sup>+</sup> )	Co-founding factor?	controversial	No	(Kawai et al., 2020b) (Jiang et al., 2018) (Sun et al., 2021) (Liu et al., 2021) (Leppert et al., 2021) (Zhu et al., 2021) (Ye et al., 2021) (Yarwood et al., 2016) (Wu et al., 2021) (Ahn et al., 2020) (Cheng et al., 2019) (Bae and Lee, 2018a) (Bae and Lee, 2018b)
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**Abbreviations:** BMI: body mass index; ILD interstitial lung disease; CAD: Coronary artery disease; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; PBC: primary biliary cirrhosis; MS: multiple sclerosis;

## Figures

**Figure 1:** RA development presents four immune-related stages. First the mucosa stage with an intake by antigen-presenting cells (APC) of neo-epitopes corresponding to peptides post-transcriptionally modified at arginine by citrullinisation or at lysine by carbamylation or acetylation in the mouth and/or lung. Second the immunization stage, following APC migration to the secondary lymphoid organs, that involves T and B cells and leading to the production of anti-modified protein autoantibodies targeting mucosal neo-antigens. This step can be completed by the production of anti-peptidylarginine deiminase (PAD) antibodies, antibody targeting bacteria involved in the neo-antigen process, and rheumatoid factors (RF), an anti-immunoglobulin G autoantibody. Third and joint step corresponding to an autoimmune arthritis with a synovial inflammation, which starts following joint leukocyte recruitment, synovial fibrin citrullinisation and fibroblast-like synoviocyte (FLS) proliferation. Finally in the fourth step a chronic and systemic inflammation takes place involving the pro-inflammatory cytokines (TNF- $\alpha$ , IL-6, IL-1 $\beta$ ) and a dysregulation of the IL-6 signalling pathway to produce joint damage, cartilage destruction, bone erosion and extra-articular manifestations. Abbreviations:

HLA: human leukocyte antigen; ACPA: anti-citrullinated antibodies; aCarP: anti-carbamylated antibodies; aPgA: anti-*Porphyromonas gingivalis* antibodies; AaLtxA: anti-*Aggregatibacter actinomycetemcomitans* leukotoxin A antibodies; PMN= polymorphonuclear granulocyte cells; MLS: macrophage-like synoviocyte; APC: antigen presenting cells.

**Figure 2:** Direct associations between rheumatoid arthritis (RA) development stages and RA-associated risk and protective factors according to Mendelian randomization results. Abbreviations: PD: periodontal disease (*Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*); ILD: interstitial lung disease; HLA-DRB1: human leukocyte antigen human leukocyte antigen DR antigen beta 1 chain; SE: shared epitope at HLA-DRB1; Val11: valine 11 at HLA-DRB1; PTPN22: missense R620W polymorphism at non-receptor type 22 gene; BMI: body mass index; CAD: coronary artery disease; CRP: C-reactive protein; sIL-6R: soluble interleukin-6 receptor.

**Figure 3:** Interleukin-6 exerts its biological activities through two molecules: IL-6R (IL-6 receptor also known as the cluster of differentiation CD126) and gp130 both present in membrane-bound forms or in soluble forms. In the IL-6 classic-signaling pathway (left), IL-6 binds to mIL-6R that recruits gp130 to form a high-affinity functional receptor as observed in lymphocytes and hepatocytes. In the IL-6 trans-signaling pathway (middle), the soluble form of IL-6R (sIL-6R) can bind IL-6 and form in non-immune cells a complex with gp130. Soluble (s)-gp130 (right) is the natural inhibitor of the IL-6/sIL-6R trans-signaling pathway.



## Bibliography

Ahn, C., Lee, S., Park, S.K., 2020. Causal Inference between Rheumatoid Arthritis and Breast Cancer in East Asian and European Population: A Two-Sample Mendelian Randomization. *Cancers* 12, E3272. <https://doi.org/10.3390/cancers12113272>

Alonso, R., Buors, C., Le Dantec, C., Hillion, S., Pers, J.-O., Saraux, A., Montero, E., Marianowski, R., Loisel, S., Devauchelle, V., Youinou, P., Renaudineau, Y., 2010. Aberrant expression of CD6 on B-cell subsets from patients with Sjögren's syndrome. *J. Autoimmun.* 35, 336–341. <https://doi.org/10.1016/j.jaut.2010.07.005>

Arleevskaya, M.I., Albina, S., Larionova, R.V., Gabdoulkhakova, A.G., Lemerle, J., Renaudineau, Y., 2018. Prevalence and Incidence of Upper Respiratory Tract Infection Events Are Elevated Prior to the Development of Rheumatoid Arthritis in First-Degree Relatives. *Front. Immunol.* 9, 2771. <https://doi.org/10.3389/fimmu.2018.02771>

Arleevskaya, M.I., Kravtsova, O.A., Lemerle, J., Renaudineau, Y., Tsubulkin, A.P., 2016. How Rheumatoid Arthritis Can Result from Provocation of the Immune System by Microorganisms and Viruses. *Front. Microbiol.* 7, 1296. <https://doi.org/10.3389/fmicb.2016.01296>

Arleevskaya, M.I., Larionova, R.V., Brooks, W.H., Bettacchioli, E., Renaudineau, Y., 2020. Toll-Like Receptors, Infections, and Rheumatoid Arthritis. *Clin. Rev. Allergy Immunol.* 58, 172–181. <https://doi.org/10.1007/s12016-019-08742-z>

Bae, S.-C., Lee, Y.H., 2020. Causal association between periodontitis and risk of rheumatoid arthritis and systemic lupus erythematosus: a Mendelian randomization. *Z. Rheumatol.* 79, 929–936. <https://doi.org/10.1007/s00393-019-00742-w>

Bae, S.-C., Lee, Y.H., 2019. Alcohol intake and risk of rheumatoid arthritis: a Mendelian randomization study. *Z. Rheumatol.* 78, 791–796. <https://doi.org/10.1007/s00393-018-0537-z>

Bae, S.-C., Lee, Y.H., 2018a. Vitamin D level and risk of systemic lupus erythematosus and rheumatoid arthritis: a Mendelian randomization. *Clin. Rheumatol.* 37, 2415–2421. <https://doi.org/10.1007/s10067-018-4152-9>

Bae, S.-C., Lee, Y.H., 2018b. Coffee consumption and the risk of rheumatoid arthritis and systemic lupus erythematosus: a Mendelian randomization study. *Clin. Rheumatol.* 37, 2875–2879. <https://doi.org/10.1007/s10067-018-4278-9>

Barturen, G., Babaei, S., Català-Moll, F., Martínez-Bueno, M., Makowska, Z., Martorell-Marugán, J., Carmona-Sáez, P., Toro-Domínguez, D., Carnero-Montoro, E., Teruel, M., Kerick, M., Acosta-Herrera, M., Le Lann, L., Jamin, C., Rodríguez-Ubreva, J., García-Gómez, A., Kageyama, J., Buttgereit, A., Hayat, S., Mueller, J., Lesche, R., Hernandez-Fuentes, M., Juarez, M., Rowley, T., White, I., Marañón, C., Gomes Anjos, T., Varela, N., Aguilar-Quesada, R., Garrancho, F.J., López-Berrio, A., Rodriguez Maresca, M., Navarro-Linares, H., Almeida, I., Azevedo, N., Brandão, M., Campar, A., Faria, R., Farinha, F., Marinho, A., Neves, E., Tavares, A., Vasconcelos, C., Trombetta, E., Montanelli, G., Vigone, B., Alvarez-Errico, D., Li, T., Thiagarani, D., Blanco Alonso, R., Corrales Martínez, A., Genre, F., López Mejías, R., Gonzalez-Gay, M.A., Remuzgo, S., Ubilla Garcia, B., Cervera, R., Espinosa, G., Rodríguez-Pintó, I., De Langhe, E., Cremer, J., Lories, R., Belz, D., Hunzelmann, N., Baerlecken, N., Kniesch, K., Witte, T., Lehner, M., Stummvoll, G., Zauner, M., Aguirre-Zamorano, M.A., Barbarroja, N., Castro-Villegas, M.C., Collantes-Estevez, E., de Ramon, E., Díaz Quintero, I., Escudero-Contreras, A., Fernández Roldán, M.C., Jiménez Gómez, Y., Jiménez Moleón, I., Lopez-Pedrerá, R., Ortega-Castro, R., Ortego, N., Raya, E., Artusi, C., Gerosa, M., Meroni, P.L., Schioppo, T., De Groof, A., Ducreux, J., Lauwerys, B., Maudoux, A.-L., Cornec, D., Devauchelle-Pensec, V., Jousse-Joulin, S., Jouve, P.-E., Rouvière, B., Saraux, A., Simon, Q., Alvarez, M., Chizzolini, C., Dufour, A., Wynar, D., Balog, A., Bocskai, M., Deák,

M., Dulic, S., Kádár, G., Kovács, L., Cheng, Q., Gerl, V., Hiepe, F., Khodadadi, L., Thiel, S., de Rinaldis, E., Rao, S., Benschop, R.J., Chamberlain, C., Dow, E.R., Ioannou, Y., Laigle, L., Marovac, J., Wojcik, J., Renaudineau, Y., Borghi, M.O., Frostegård, J., Martín, J., Beretta, L., Ballestar, E., McDonald, F., Pers, J.-O., Alarcón-Riquelme, M.E., 2021. Integrative Analysis Reveals a Molecular Stratification of Systemic Autoimmune Diseases. *Arthritis Rheumatol.* Hoboken NJ 73, 1073–1085. <https://doi.org/10.1002/art.41610>

Becart, S., Whittington, K.B., Prislowsky, A., Rao, N.L., Rosloniec, E.F., 2021. The role of posttranslational modifications in generating neo-epitopes that bind to rheumatoid arthritis-associated HLA-DR alleles and promote autoimmune T cell responses. *PloS One* 16, e0245541. <https://doi.org/10.1371/journal.pone.0245541>

Bello-Gualtero, J.M., Lafaurie, G.I., Hoyos, L.X., Castillo, D.M., De-Avila, J., Munevar, J.C., Unriza, S., Londoño, J., Valle-Oñate, R., Romero-Sánchez, C., 2016. Periodontal Disease in Individuals With a Genetic Risk of Developing Arthritis and Early Rheumatoid Arthritis: A Cross-Sectional Study. *J. Periodontol.* 87, 346–356. <https://doi.org/10.1902/jop.2015.150455>

Bettacchioli, E., Le Gaffric, C., Mazeas, M., Borghi, M.O., Frostegard, J., Barturen, G., Makowska, Z., Babei, S., Lesche, R., PRECISESADS Clinical Consortium, Meroni, P.L., Alarcon-Riquelme, M.E., Renaudineau, Y., 2021. An elevated polyclonal free light chain level reflects a strong interferon signature in patients with systemic autoimmune diseases. *J. Transl. Autoimmun.* 4, 100090. <https://doi.org/10.1016/j.jtauto.2021.100090>

Bitoun, S., Roques, P., Maillere, B., Le Grand, R., Mariette, X., 2019. Valine 11 and phenylalanine 13 have a greater impact on the T-cell response to citrullinated peptides than the 70-74 shared epitope of the DRB1 molecule in macaques. *Ann. Rheum. Dis.* 78, 917–921. <https://doi.org/10.1136/annrheumdis-2019-215114>

Brooks, W.H., Le Dantec, C., Pers, J.-O., Youinou, P., Renaudineau, Y., 2010. Epigenetics and autoimmunity. *J. Autoimmun.* 34, J207-219. <https://doi.org/10.1016/j.jaut.2009.12.006>

Castellanos-Moreira, R., Rodríguez-García, S.C., Gomara, M.J., Ruiz-Esquide, V., Cuervo, A., Casafont-Solé, I., Ramírez, J., Holgado, S., Gómez-Puerta, J.A., Cañete, J.D., Haro, I., Sanmarti, R., 2020. Anti-carbamylated proteins antibody repertoire in rheumatoid arthritis: evidence of a new autoantibody linked to interstitial lung disease. *Ann. Rheum. Dis.* 79, 587–594. <https://doi.org/10.1136/annrheumdis-2019-216709>

Chen, Y.-M., Chen, H.-H., Huang, W.-N., Liao, T.-L., Chen, J.-P., Chao, W.-C., Lin, C.-T., Hung, W.-T., Hsieh, C.-W., Hsieh, T.-Y., Chen, Y.-H., Chen, D.-Y., 2017. Tocilizumab potentially prevents bone loss in patients with anticitrullinated protein antibody-positive rheumatoid arthritis. *PloS One* 12, e0188454. <https://doi.org/10.1371/journal.pone.0188454>

Cheng, W.-W., Zhu, Q., Zhang, H.-Y., 2019. Mineral Nutrition and the Risk of Chronic Diseases: A Mendelian Randomization Study. *Nutrients* 11, E378. <https://doi.org/10.3390/nu11020378>

Chignon, A., Bon-Baret, V., Boulanger, M.-C., Li, Z., Argaud, D., Bossé, Y., Thériault, S., Arsenault, B.J., Mathieu, P., 2020. Single-cell expression and Mendelian randomization analyses identify blood genes associated with lifespan and chronic diseases. *Commun. Biol.* 3, 206. <https://doi.org/10.1038/s42003-020-0937-x>

Çolak, Y., Afzal, S., Lange, P., Nordestgaard, B.G., 2019. Smoking, Systemic Inflammation, and Airflow Limitation: A Mendelian Randomization Analysis of 98 085 Individuals From the General Population. *Nicotine Tob. Res. Off. J. Soc. Res. Nicotine Tob.* 21, 1036–1044. <https://doi.org/10.1093/ntr/nty077>

Corominas, H., Alegre, C., Narváez, J., Fernández-Cid, C.M., Torrente-Segarra, V., Gómez, M.R., Pan, F.M., Morlà, R.M., Martínez, F.J.R., Gómez-Centeno, A., Ares, L.L., Molina, R.G., González-Albo, S.P., Dalmau-Carolà, J., Pérez-García, C., Álvarez, C.B., Ercole, L., Terrance, M.Á., ACT-AXIS Study Group, 2019. Correlation of fatigue with other disease related and psychosocial factors in patients with rheumatoid arthritis treated with tocilizumab: ACT-AXIS study. *Medicine (Baltimore)* 98, e15947. <https://doi.org/10.1097/MD.00000000000015947>

Delgado-Vega, A.M., Anaya, J.-M., 2007. Meta-analysis of HLA-DRB1 polymorphism in Latin American patients with rheumatoid arthritis. *Autoimmun. Rev.* 6, 402–408.

<https://doi.org/10.1016/j.autrev.2006.11.004>

Diaz-Torne, C., Ortiz, M.D.A., Moya, P., Hernandez, M.V., Reina, D., Castellvi, I., De Agustin, J.J., Fuente, D. de la, Corominas, H., Sanmarti, R., Zamora, C., Cantó, E., Vidal, S., 2018. The combination of IL-6 and its soluble receptor is associated with the response of rheumatoid arthritis patients to tocilizumab. *Semin. Arthritis Rheum.* 47, 757–764.

<https://doi.org/10.1016/j.semarthrit.2017.10.022>

Dougados, M., Soubrier, M., Antunez, A., Balint, P., Balsa, A., Buch, M.H., Casado, G., Detert, J., El-Zorkany, B., Emery, P., Hajjaj-Hassouni, N., Harigai, M., Luo, S.-F., Kurucz, R., Maciel, G., Mola, E.M., Montecucco, C.M., McInnes, I., Radner, H., Smolen, J.S., Song, Y.-W., Vonkeman, H.E., Winthrop, K., Kay, J., 2014. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann. Rheum. Dis.* 73, 62–68. <https://doi.org/10.1136/annrheumdis-2013-204223>

Engström, M., Eriksson, K., Lee, L., Hermansson, M., Johansson, A., Nicholas, A.P., Gerasimcik, N., Lundberg, K., Klareskog, L., Catrina, A.I., Yucel-Lindberg, T., 2018. Increased citrullination and expression of peptidylarginine deiminases independently of *P. gingivalis* and *A. actinomycetemcomitans* in gingival tissue of patients with periodontitis. *J. Transl. Med.* 16, 214. <https://doi.org/10.1186/s12967-018-1588-2>

Farh, K.K.-H., Marson, A., Zhu, J., Kleinewietfeld, M., Housley, W.J., Beik, S., Shores, N., Whitton, H., Ryan, R.J.H., Shishkin, A.A., Hatan, M., Carrasco-Alfonso, M.J., Mayer, D., Luckey, C.J., Patsopoulos, N.A., De Jager, P.L., Kuchroo, V.K., Epstein, C.B., Daly, M.J., Hafler, D.A., Bernstein, B.E., 2015. Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature* 518, 337–343.

<https://doi.org/10.1038/nature13835>

Giles, J.T., Reinholdt, J., Andrade, F., König, M.F., 2021. Associations of Antibodies Targeting Periodontal Pathogens With Subclinical Coronary, Carotid, and Peripheral Arterial Atherosclerosis in Rheumatoid Arthritis. *Arthritis Rheumatol.* Hoboken NJ 73, 568–575. <https://doi.org/10.1002/art.41572>

Goh, C.E., Kopp, J., Papapanou, P.N., Molitor, J.A., Demmer, R.T., 2016. Association Between Serum Antibodies to Periodontal Bacteria and Rheumatoid Factor in the Third National Health and Nutrition Examination Survey. *Arthritis Rheumatol.* Hoboken NJ 68, 2384–2393. <https://doi.org/10.1002/art.39724>

Gomez-Bañuelos, E., Johansson, L., König, M.F., Lundquist, A., Paz, M., Buhlin, K., Johansson, A., Rantapää-Dahlqvist, S., Andrade, F., 2020. Exposure to *Aggregatibacter actinomycetemcomitans* before Symptom Onset and the Risk of Evolving to Rheumatoid Arthritis. *J. Clin. Med.* 9, E1906. <https://doi.org/10.3390/jcm9061906>

Gorman, J.D., David-Vaudey, E., Pai, M., Lum, R.F., Criswell, L.A., 2004a. Lack of association of the HLA-DRB1 shared epitope with rheumatoid nodules: an individual patient data meta-analysis of 3,272 Caucasian patients with rheumatoid arthritis. *Arthritis Rheum.* 50, 753–762. <https://doi.org/10.1002/art.20119>

Gorman, J.D., Lum, R.F., Chen, J.J., Suarez-Almazor, M.E., Thomson, G., Criswell, L.A., 2004b. Impact of shared epitope genotype and ethnicity on erosive disease: a meta-analysis of 3,240 rheumatoid arthritis patients. *Arthritis Rheum.* 50, 400–412. <https://doi.org/10.1002/art.20006>

Guo, J., Zhang, T., Cao, H., Li, X., Liang, H., Liu, M., Zou, Y., Zhang, Y., Wang, Y., Sun, X., Hu, F., Du, Y., Mo, X., Liu, Xu, Yang, Y., Yang, Huanjie, Wu, X., Zhang, Xuewu, Jia, H., Jiang, H., Hou, Y., Liu, Xin, Su, Y., Zhang, M., Yang, Huanming, Wang, J., Sun, L., Liu, L., Padyukov, L., Lai, L., Yamamoto, K., Zhang, Xuejun, Klareskog, L., Xu, X., Li, Z., 2019. Sequencing of the MHC region defines HLA-DQA1 as the major genetic risk for seropositive rheumatoid arthritis in Han Chinese population. *Ann. Rheum. Dis.* 78, 773–780. <https://doi.org/10.1136/annrheumdis-2018-214725>

Hashimoto, M., Fujii, T., Hamaguchi, M., Furu, M., Ito, H., Terao, C., Yamamoto, K., Yamamoto, W., Matsuo, T., Mori, M., Ohmura, K., Kawabata, H., Mimori, T., 2014. Increase of hemoglobin levels by anti-IL-6 receptor antibody (tocilizumab) in rheumatoid arthritis. *PloS One* 9, e98202. <https://doi.org/10.1371/journal.pone.0098202>

Hedström, A.K., Hössjer, O., Klareskog, L., Alfredsson, L., 2019. Interplay between alcohol, smoking and HLA genes in RA aetiology. *RMD Open* 5, e000893. <https://doi.org/10.1136/rmdopen-2019-000893>

Hill, J.A., Southwood, S., Sette, A., Jevnikar, A.M., Bell, D.A., Cairns, E., 2003. Cutting edge: the conversion of arginine to citrulline allows for a high-affinity peptide interaction with the rheumatoid arthritis-associated HLA-DRB1\*0401 MHC class II molecule. *J. Immunol. Baltim. Md* 1950 171, 538–541. <https://doi.org/10.4049/jimmunol.171.2.538>

Hua, J., Huang, W., 2018. Peptidylarginine deiminase 4 -104C/T polymorphism and risk of rheumatoid arthritis: A pooled analysis based on different populations. *PloS One* 13, e0193674. <https://doi.org/10.1371/journal.pone.0193674>

Interleukin 1 Genetics Consortium, 2015. Cardiometabolic effects of genetic upregulation of the interleukin 1 receptor antagonist: a Mendelian randomisation analysis. *Lancet Diabetes Endocrinol.* 3, 243–253. [https://doi.org/10.1016/S2213-8587\(15\)00034-0](https://doi.org/10.1016/S2213-8587(15)00034-0)

Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium, Swerdlow, D.I., Holmes, M.V., Kuchenbaecker, K.B., Engmann, J.E.L., Shah, T., Sofat, R., Guo, Y., Chung, C., Peasey, A., Pfister, R., Mooijaart, S.P., Ireland, H.A., Leusink, M., Langenberg, C., Li, K.W., Palmen, J., Howard, P., Cooper, J.A., Drenos, F., Hardy, J., Nalls, M.A., Li, Y.R., Lowe, G., Stewart, M., Bielinski, S.J., Peto, J., Timpson, N.J., Gallacher, J., Dunlop, M., Houlston, R., Tomlinson, I., Tzoulaki, I., Luan, J., Boer, J.M.A., Forouhi, N.G., Onland-Moret, N.C., van der Schouw, Y.T., Schnabel, R.B., Hubacek, J.A., Kubinova, R., Baceviciene, M., Tamosiunas, A., Pajak, A., Topor-Madry, R., Malyutina, S., Baldassarre, D., Sennblad, B., Tremoli, E., de Faire, U., Ferrucci, L., Bandenelli, S., Tanaka, T., Meschia, J.F., Singleton, A., Navis, G., Mateo Leach, I., Bakker, S.J.L., Gansevoort, R.T., Ford, I., Epstein, S.E., Burnett, M.S., Devaney, J.M., Jukema, J.W., Westendorp, R.G.J., Jan de Borst, G., van der Graaf, Y., de Jong, P.A., Mailand-van der Zee, A.-H., Klungel, O.H., de Boer, A., Doevendans, P.A., Stephens, J.W., Eaton, C.B., Robinson, J.G., Manson, J.E., Fowkes, F.G., Frayling, T.M., Price, J.F., Whincup, P.H., Morris, R.W., Lawlor, D.A., Smith, G.D., Ben-Shlomo, Y., Redline, S., Lange, L.A., Kumari, M., Wareham, N.J., Verschuren, W.M.M., Benjamin, E.J., Whittaker, J.C., Hamsten, A., Dudbridge, F., Delaney, J.A.C., Wong, A., Kuh, D., Hardy, R., Castillo, B.A., Connolly, J.J., van der Harst, P., Brunner, E.J., Marmot, M.G., Wassel, C.L., Humphries, S.E., Talmud, P.J., Kivimaki, M., Asselbergs, F.W., Voevoda, M., Bobak, M., Pikhart, H., Wilson, J.G., Hakonarson, H., Reiner, A.P., Keating, B.J., Sattar, N.,

Hingorani, A.D., Casas, J.P., 2012. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet Lond. Engl.* 379, 1214–1224. [https://doi.org/10.1016/S0140-6736\(12\)60110-X](https://doi.org/10.1016/S0140-6736(12)60110-X)

Jaakkola, J.J.K., Gissler, M., 2005. Maternal smoking in pregnancy as a determinant of rheumatoid arthritis and other inflammatory polyarthropathies during the first 7 years of life. *Int. J. Epidemiol.* 34, 664–671. <https://doi.org/10.1093/ije/dyi006>

Janssen, K.M.J., de Smit, M.J., Brouwer, E., de Kok, F.A.C., Kraan, J., Altenburg, J., Verheul, M.K., Trouw, L.A., van Winkelhoff, A.J., Vissink, A., Westra, J., 2015. Rheumatoid arthritis-associated autoantibodies in non-rheumatoid arthritis patients with mucosal inflammation: a case-control study. *Arthritis Res. Ther.* 17, 174. <https://doi.org/10.1186/s13075-015-0690-6>

Jenning, M., Marklein, B., Ytterberg, J., Zubarev, R.A., Joshua, V., van Schaardenburg, D., van de Stadt, L., Catrina, A.I., Nonhoff, U., Häupl, T., Konthur, Z., Burmester, G.R., Skriner, K., 2020. Bacterial citrullinated epitopes generated by *Porphyromonas gingivalis* infection—a missing link for ACPA production. *Ann. Rheum. Dis.* 79, 1194–1202. <https://doi.org/10.1136/annrheumdis-2019-216919>

Jiang, X., O'Reilly, P.F., Aschard, H., Hsu, Y.-H., Richards, J.B., Dupuis, J., Ingelsson, E., Karasik, D., Pilz, S., Berry, D., Kestenbaum, B., Zheng, J., Luan, J., Sofianopoulou, E., Streeten, E.A., Albanes, D., Lutsey, P.L., Yao, L., Tang, W., Econs, M.J., Wallaschofski, H., Völzke, H., Zhou, A., Power, C., McCarthy, M.I., Michos, E.D., Boerwinkle, E., Weinstein, S.J., Freedman, N.D., Huang, W.-Y., Van Schoor, N.M., van der Velde, N., Groot, L.C.P.G.M. de, Enneman, A., Cupples, L.A., Booth, S.L., Vasani, R.S., Liu, C.-T., Zhou, Y., Ripatti, S., Ohlsson, C., Vandenput, L., Lorentzon, M., Eriksson, J.G., Shea, M.K., Houston, D.K., Kritchevsky, S.B., Liu, Y., Lohman, K.K., Ferrucci, L., Peacock, M., Gieger, C., Beekman, M., Slagboom, E., Deelen, J., Heemst, D. van, Kleber, M.E., März, W., de Boer, I.H., Wood, A.C., Rotter, J.I., Rich, S.S., Robinson-Cohen, C., den Heijer, M., Jarvelin, M.-R., Cavadino, A., Joshi, P.K., Wilson, J.F., Hayward, C., Lind, L., Michaëlsson, K., Trompet, S., Zillikens, M.C., Uitterlinden, A.G., Rivadeneira, F., Broer, L., Zgaga, L., Campbell, H., Theodoratou, E., Farrington, S.M., Timofeeva, M., Dunlop, M.G., Valdes, A.M., Tikkanen, E., Lehtimäki, T., Lyytikäinen, L.-P., Kähönen, M., Raitakari, O.T., Mikkilä, V., Ikram, M.A., Sattar, N., Jukema, J.W., Wareham, N.J., Langenberg, C., Forouhi, N.G., Gundersen, T.E., Khaw, K.-T., Butterworth, A.S., Danesh, J., Spector, T., Wang, T.J., Hyppönen, E., Kraft, P., Kiel, D.P., 2018. Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. *Nat. Commun.* 9, 260. <https://doi.org/10.1038/s41467-017-02662-2>

Johansson, L., Sherina, N., Kharlamova, N., Potempa, B., Larsson, B., Israelsson, L., Potempa, J., Rantapää-Dahlqvist, S., Lundberg, K., 2016. Erratum to: Concentration of antibodies against *Porphyromonas gingivalis* increased before the onset of symptoms of rheumatoid arthritis. *Arthritis Res. Ther.* 18, 257. <https://doi.org/10.1186/s13075-016-1164-1>

Johnston, K.J.A., Adams, M.J., Nicholl, B.I., Ward, J., Strawbridge, R.J., Ferguson, A., McIntosh, A.M., Bailey, M.E.S., Smith, D.J., 2019. Genome-wide association study of multisite chronic pain in UK Biobank. *PLoS Genet.* 15, e1008164. <https://doi.org/10.1371/journal.pgen.1008164>

Jones, S.A., Novick, D., Horiuchi, S., Yamamoto, N., Szalai, A.J., Fuller, G.M., 1999. C-reactive protein: a physiological activator of interleukin 6 receptor shedding. *J. Exp. Med.* 189, 599–604. <https://doi.org/10.1084/jem.189.3.599>

Julià, A., Martínez-Mateu, S.H., Domènech, E., Cañete, J.D., Ferrándiz, C., Tornero, J., Gisbert, J.P., Fernández-Nebro, A., Daudén, E., Barreiro-de Acosta, M., Pérez, C., Queiró, R.,

López-Longo, F.J., Carazo, J.L.S., Mendoza, J.L., Alpéri, M., Montilla, C., Venegas, J.J.P., Muñoz, F., Castañeda, S., Aterido, A., Lasanta, M.L., Marsal, S., IMID Consortium, 2021. Food groups associated with immune-mediated inflammatory diseases: a Mendelian randomization and disease severity study. *Eur. J. Clin. Nutr.* <https://doi.org/10.1038/s41430-021-00913-6>

Kawai, V.K., Shi, M., Feng, Q., Chung, C.P., Liu, G., Cox, N.J., Jarvik, G.P., Lee, M.T.M., Hebring, S.J., Harley, J.B., Kaufman, K.M., Namjou, B., Larson, E., Gordon, A.S., Roden, D.M., Stein, C.M., Mosley, J.D., eMERGE Investigators, 2020b. Pleiotropy in the Genetic Predisposition to Rheumatoid Arthritis: A Phenome-Wide Association Study and Inverse Variance-Weighted Meta-Analysis. *Arthritis Rheumatol.* Hoboken NJ 72, 1483–1492. <https://doi.org/10.1002/art.41291>

Klimenta, B., Nefic, H., Prodanovic, N., Jadric, R., Hukic, F., 2019. Association of biomarkers of inflammation and HLA-DRB1 gene locus with risk of developing rheumatoid arthritis in females. *Rheumatol. Int.* 39, 2147–2157. <https://doi.org/10.1007/s00296-019-04429-y>

Kobayashi, S., Momohara, S., Kamatani, N., Okamoto, H., 2008. Molecular aspects of rheumatoid arthritis: role of environmental factors. *FEBS J.* 275, 4456–4462. <https://doi.org/10.1111/j.1742-4658.2008.06581.x>

Konig, M.F., Abusleme, L., Reinholdt, J., Palmer, R.J., Teles, R.P., Sampson, K., Rosen, A., Nigrovic, P.A., Sokolove, J., Giles, J.T., Moutsopoulos, N.M., Andrade, F., 2016. *Aggregatibacter actinomycetemcomitans*-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis. *Sci. Transl. Med.* 8, 369ra176. <https://doi.org/10.1126/scitranslmed.aaj1921>

Kronzer, V.L., Huang, W., Dellaripa, P.F., Huang, S., Feathers, V., Lu, B., Iannaccone, C.K., Gill, R.R., Hatabu, H., Nishino, M., Crowson, C.S., Davis, J.M., Weinblatt, M.E., Shadick, N.A., Doyle, T.J., Sparks, J.A., 2021. Lifestyle and Clinical Risk Factors for Incident Rheumatoid Arthritis-associated Interstitial Lung Disease. *J. Rheumatol.* 48, 656–663. <https://doi.org/10.3899/jrheum.200863>

Kurilshikov, A., Medina-Gomez, C., Bacigalupe, R., Radjabzadeh, D., Wang, J., Demirkan, A., Le Roy, C.I., Raygoza Garay, J.A., Finnicum, C.T., Liu, X., Zhernakova, D.V., Bonder, M.J., Hansen, T.H., Frost, F., Rühlemann, M.C., Turpin, W., Moon, J.-Y., Kim, H.-N., Lüll, K., Barkan, E., Shah, S.A., Fornage, M., Szopinska-Tokov, J., Wallen, Z.D., Borisevich, D., Agreus, L., Andreasson, A., Bang, C., Bedrani, L., Bell, J.T., Bisgaard, H., Boehnke, M., Boomsma, D.I., Burk, R.D., Claringbould, A., Croitoru, K., Davies, G.E., van Duijn, C.M., Duijts, L., Falony, G., Fu, J., van der Graaf, A., Hansen, T., Homuth, G., Hughes, D.A., Ijzerman, R.G., Jackson, M.A., Jaddoe, V.W.V., Joossens, M., Jørgensen, T., Keszthelyi, D., Knight, R., Laakso, M., Laudes, M., Launer, L.J., Lieb, W., Lusi, A.J., Masclee, A.A.M., Moll, H.A., Mujagic, Z., Qibin, Q., Rothschild, D., Shin, H., Sørensen, S.J., Steves, C.J., Thorsen, J., Timpson, N.J., Tito, R.Y., Vieira-Silva, S., Völker, U., Völzke, H., Vösa, U., Wade, K.H., Walter, S., Watanabe, K., Weiss, S., Weiss, F.U., Weissbrod, O., Westra, H.-J., Willemsen, G., Payami, H., Jonkers, D.M.A.E., Arias Vasquez, A., de Geus, E.J.C., Meyer, K.A., Stokholm, J., Segal, E., Org, E., Wijmenga, C., Kim, H.-L., Kaplan, R.C., Spector, T.D., Uitterlinden, A.G., Rivadeneira, F., Franke, A., Lerch, M.M., Franke, L., Sanna, S., D'Amato, M., Pedersen, O., Paterson, A.D., Kraaij, R., Raes, J., Zhernakova, A., 2021. Large-scale association analyses identify host factors influencing human gut microbiome composition. *Nat. Genet.* 53, 156–165. <https://doi.org/10.1038/s41588-020-00763-1>

Lee, Y.H., Bae, S.-C., Song, G.G., 2013. Meta-analysis demonstrates association between TLR polymorphisms and rheumatoid arthritis. *Genet. Mol. Res. GMR* 12, 328–334. <https://doi.org/10.4238/2013.February.7.2>

Leppert, B., Riglin, L., Wootton, R.E., Dardani, C., Thapar, Ajay, Staley, J.R., Tilling, K., Davey Smith, G., Thapar, Anita, Stergiakouli, E., 2021. The Effect of Attention Deficit/Hyperactivity Disorder on Physical Health Outcomes: A 2-Sample Mendelian Randomization Study. *Am. J. Epidemiol.* 190, 1047–1055. <https://doi.org/10.1093/aje/kwaa273>

Li, P., Wang, X., Guo, X., Wen, Y., Liu, L., Liang, X., Du, Y., Wu, C., Wang, S., Zhang, F., 2020. Integrative analysis of genome-wide association study and expression quantitative trait loci datasets identified various immune cell-related pathways for rheumatoid arthritis. *Ann. Hum. Genet.* 84, 72–79. <https://doi.org/10.1111/ahg.12351>

Ligthart, S., Vaez, A., Vösa, U., Stathopoulou, M.G., de Vries, P.S., Prins, B.P., Van der Most, P.J., Tanaka, T., Naderi, E., Rose, L.M., Wu, Y., Karlsson, R., Barbalic, M., Lin, H., Pool, R., Zhu, G., Macé, A., Sidore, C., Trompet, S., Mangino, M., Sabater-Lleal, M., Kemp, J.P., Abbasi, A., Kacprowski, T., Verweij, N., Smith, A.V., Huang, T., Marzi, C., Feitosa, M.F., Lohman, K.K., Kleber, M.E., Milanese, Y., Mueller, C., Huq, M., Vlachopoulou, E., Lyytikäinen, L.-P., Oldmeadow, C., Deelen, J., Perola, M., Zhao, J.H., Feenstra, B., LifeLines Cohort Study, Amini, M., CHARGE Inflammation Working Group, Lahti, J., Schraut, K.E., Fornage, M., Suktitipat, B., Chen, W.-M., Li, X., Nutile, T., Malerba, G., Luan, J., Bak, T., Schork, N., Del Greco M, F., Thiering, E., Mahajan, A., Marioni, R.E., Mihailov, E., Eriksson, J., Ozel, A.B., Zhang, W., Nethander, M., Cheng, Y.-C., Aslibekyan, S., Ang, W., Gandin, I., Yengo, L., Portas, L., Kooperberg, C., Hofer, E., Rajan, K.B., Schurmann, C., den Hollander, W., Ahluwalia, T.S., Zhao, J., Draisma, H.H.M., Ford, I., Timpson, N., Teumer, A., Huang, H., Wahl, S., Liu, Y., Huang, J., Uh, H.-W., Geller, F., Joshi, P.K., Yanek, L.R., Trabetti, E., Lehne, B., Vozzi, D., Verbanck, M., Biino, G., Saba, Y., Meulenbelt, I., O'Connell, J.R., Laakso, M., Giulianini, F., Magnusson, P.K.E., Ballantyne, C.M., Hottenga, J.J., Montgomery, G.W., Rivadineira, F., Rueedi, R., Steri, M., Herzig, K.-H., Stott, D.J., Menni, C., Frånberg, M., St Pourcain, B., Felix, S.B., Pers, T.H., Bakker, S.J.L., Kraft, P., Peters, A., Vaidya, D., Delgado, G., Smit, J.H., Großmann, V., Sinisalo, J., Seppälä, I., Williams, S.R., Holliday, E.G., Moed, M., Langenberg, C., Rääkkönen, K., Ding, J., Campbell, H., Sale, M.M., Chen, Y.-D.I., James, A.L., Ruggiero, D., Soranzo, N., Hartman, C.A., Smith, E.N., Berenson, G.S., Fuchsberger, C., Hernandez, D., Tiesler, C.M.T., Giedraitis, V., Liewald, D., Fischer, K., Mellström, D., Larsson, A., Wang, Y., Scott, W.R., Lorentzon, M., Beilby, J., Ryan, K.A., Pennell, C.E., Vuckovic, D., Balkau, B., Concas, M.P., Schmidt, R., Mendes de Leon, C.F., Bottinger, E.P., Kloppenburg, M., Paternoster, L., Boehnke, M., Musk, A.W., Willemsen, G., Evans, D.M., Madden, P.A.F., Kähönen, M., Kutalik, Z., Zoledziewska, M., Karhunen, V., Kritchevsky, S.B., Sattar, N., Lachance, G., Clarke, R., Harris, T.B., Raitakari, O.T., Attia, J.R., van Heemst, D., Kajantie, E., Sorice, R., Gambaro, G., Scott, R.A., Hicks, A.A., Ferrucci, L., Standl, M., Lindgren, C.M., Starr, J.M., Karlsson, M., Lind, L., Li, J.Z., Chambers, J.C., Mori, T.A., de Geus, E.J.C.N., Heath, A.C., Martin, N.G., Auvinen, J., Buckley, B.M., de Craen, A.J.M., Waldenberger, M., Strauch, K., Meitinger, T., Scott, R.J., McEvoy, M., Beekman, M., Bombieri, C., Ridker, P.M., Mohlke, K.L., Pedersen, N.L., Morrison, A.C., Boomsma, D.I., Whitfield, J.B., Strachan, D.P., Hofman, A., Vollenweider, P., Cucca, F., Jarvelin, M.-R., Jukema, J.W., Spector, T.D., Hamsten, A., Zeller, T., Uitterlinden, A.G., Nauck, M., Gudnason, V., Qi, L., Grallert, H., Borecki, I.B., Rotter, J.I., März, W., Wild, P.S., Lokki, M.-L., Boyle, M., Salomaa, V., Melbye, M., Eriksson, J.G., Wilson, J.F., Penninx, B.W.J.H., Becker, D.M., Worrall, B.B., Gibson, G., Krauss, R.M., Ciullo, M., Zaza, G., Wareham, N.J., Oldehinkel, A.J., Palmer, L.J., Murray, S.S., Pramstaller, P.P., Bandinelli, S., Heinrich, J., Ingelsson, E., Deary, I.J., Mägi, R., Vandenput, L., van der Harst, P., Desch, K.C., Kooner, J.S., Ohlsson, C., Hayward, C., Lehtimäki, T., Shuldiner, A.R., Arnett, D.K., Beilin, L.J., Robino, A., Froguel, P., Pirastu, M., Jess, T., Koenig, W., Loos, R.J.F., Evans, D.A., Schmidt, H., Smith, G.D.,

Slagboom, P.E., Eiriksdottir, G., Morris, A.P., Psaty, B.M., Tracy, R.P., Nolte, I.M., Boerwinkle, E., Visvikis-Siest, S., Reiner, A.P., Gross, M., Bis, J.C., Franke, L., Franco, O.H., Benjamin, E.J., Chasman, D.I., Dupuis, J., Snieder, H., Dehghan, A., Alizadeh, B.Z., 2018a. Genome Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders. *Am. J. Hum. Genet.* 103, 691–706. <https://doi.org/10.1016/j.ajhg.2018.09.009>

Ligthart, S., Vaez, A., Vösa, U., Stathopoulou, M.G., de Vries, P.S., Prins, B.P., Van der Most, P.J., Tanaka, T., Naderi, E., Rose, L.M., Wu, Y., Karlsson, R., Barbalic, M., Lin, H., Pool, R., Zhu, G., Macé, A., Sidore, C., Trompet, S., Mangino, M., Sabater-Lleal, M., Kemp, J.P., Abbasi, A., Kacprowski, T., Verweij, N., Smith, A.V., Huang, T., Marzi, C., Feitosa, M.F., Lohman, K.K., Kleber, M.E., Milanese, Y., Mueller, C., Huq, M., Vlachopoulou, E., Lyytikäinen, L.-P., Oldmeadow, C., Deelen, J., Perola, M., Zhao, J.H., Feenstra, B., LifeLines Cohort Study, Amini, M., CHARGE Inflammation Working Group, Lahti, J., Schraut, K.E., Fornage, M., Suktitipat, B., Chen, W.-M., Li, X., Nutile, T., Malerba, G., Luan, J., Bak, T., Schork, N., Del Greco M, F., Thiering, E., Mahajan, A., Marioni, R.E., Mihailov, E., Eriksson, J., Ozel, A.B., Zhang, W., Nethander, M., Cheng, Y.-C., Aslibekyan, S., Ang, W., Gandin, I., Yengo, L., Portas, L., Kooperberg, C., Hofer, E., Rajan, K.B., Schurmann, C., den Hollander, W., Ahluwalia, T.S., Zhao, J., Draisma, H.H.M., Ford, I., Timpson, N., Teumer, A., Huang, H., Wahl, S., Liu, Y., Huang, J., Uh, H.-W., Geller, F., Joshi, P.K., Yanek, L.R., Trabetti, E., Lehne, B., Vozzi, D., Verbanck, M., Biino, G., Saba, Y., Meulenbelt, I., O'Connell, J.R., Laakso, M., Giulianini, F., Magnusson, P.K.E., Ballantyne, C.M., Hottenga, J.J., Montgomery, G.W., Rivadineira, F., Rueedi, R., Steri, M., Herzig, K.-H., Stott, D.J., Menni, C., Frånberg, M., St Pourcain, B., Felix, S.B., Pers, T.H., Bakker, S.J.L., Kraft, P., Peters, A., Vaidya, D., Delgado, G., Smit, J.H., Großmann, V., Sinisalo, J., Seppälä, I., Williams, S.R., Holliday, E.G., Moed, M., Langenberg, C., Rääkkönen, K., Ding, J., Campbell, H., Sale, M.M., Chen, Y.-D.I., James, A.L., Ruggiero, D., Soranzo, N., Hartman, C.A., Smith, E.N., Berenson, G.S., Fuchsberger, C., Hernandez, D., Tiesler, C.M.T., Giedraitis, V., Liewald, D., Fischer, K., Mellström, D., Larsson, A., Wang, Y., Scott, W.R., Lorentzon, M., Beilby, J., Ryan, K.A., Pennell, C.E., Vuckovic, D., Balkau, B., Concas, M.P., Schmidt, R., Mendes de Leon, C.F., Bottinger, E.P., Kloppenburg, M., Paternoster, L., Boehnke, M., Musk, A.W., Willemsen, G., Evans, D.M., Madden, P.A.F., Kähönen, M., Kutalik, Z., Zoledziewska, M., Karhunen, V., Kritchevsky, S.B., Sattar, N., Lachance, G., Clarke, R., Harris, T.B., Raitakari, O.T., Attia, J.R., van Heemst, D., Kajantie, E., Sorice, R., Gambaro, G., Scott, R.A., Hicks, A.A., Ferrucci, L., Standl, M., Lindgren, C.M., Starr, J.M., Karlsson, M., Lind, L., Li, J.Z., Chambers, J.C., Mori, T.A., de Geus, E.J.C.N., Heath, A.C., Martin, N.G., Auvinen, J., Buckley, B.M., de Craen, A.J.M., Waldenberger, M., Strauch, K., Meitinger, T., Scott, R.J., McEvoy, M., Beekman, M., Bombieri, C., Ridker, P.M., Mohlke, K.L., Pedersen, N.L., Morrison, A.C., Boomsma, D.I., Whitfield, J.B., Strachan, D.P., Hofman, A., Vollenweider, P., Cucca, F., Jarvelin, M.-R., Jukema, J.W., Spector, T.D., Hamsten, A., Zeller, T., Uitterlinden, A.G., Nauck, M., Gudnason, V., Qi, L., Grallert, H., Borecki, I.B., Rotter, J.I., März, W., Wild, P.S., Lokki, M.-L., Boyle, M., Salomaa, V., Melbye, M., Eriksson, J.G., Wilson, J.F., Penninx, B.W.J.H., Becker, D.M., Worrall, B.B., Gibson, G., Krauss, R.M., Ciullo, M., Zaza, G., Wareham, N.J., Oldehinkel, A.J., Palmer, L.J., Murray, S.S., Pramstaller, P.P., Bandinelli, S., Heinrich, J., Ingelsson, E., Deary, I.J., Mägi, R., Vandenput, L., van der Harst, P., Desch, K.C., Kooner, J.S., Ohlsson, C., Hayward, C., Lehtimäki, T., Shuldiner, A.R., Arnett, D.K., Beilin, L.J., Robino, A., Froguel, P., Pirastu, M., Jess, T., Koenig, W., Loos, R.J.F., Evans, D.A., Schmidt, H., Smith, G.D., Slagboom, P.E., Eiriksdottir, G., Morris, A.P., Psaty, B.M., Tracy, R.P., Nolte, I.M., Boerwinkle, E., Visvikis-Siest, S., Reiner, A.P., Gross, M., Bis, J.C., Franke, L., Franco, O.H., Benjamin, E.J., Chasman, D.I., Dupuis, J., Snieder, H., Dehghan, A., Alizadeh, B.Z., 2018b.



Genome Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders. *Am. J. Hum. Genet.* 103, 691–706. <https://doi.org/10.1016/j.ajhg.2018.09.009>

Ling, S.F., Viatte, S., Lunt, M., Van Sijl, A.M., Silva-Fernandez, L., Symmons, D.P.M., Young, A., Macgregor, A.J., Barton, A., 2016. HLA-DRB1 Amino Acid Positions 11/13, 71, and 74 Are Associated With Inflammation Level, Disease Activity, and the Health Assessment Questionnaire Score in Patients With Inflammatory Polyarthritis. *Arthritis Rheumatol. Hoboken NJ* 68, 2618–2628. <https://doi.org/10.1002/art.39780>

Liu, Y.-Q., Liu, Y., Chen, Z.-Y., Li, H., Xiao, T., 2021. Rheumatoid arthritis and osteoporosis: a bi-directional Mendelian randomization study. *Aging* 13, 14109–14130. <https://doi.org/10.18632/aging.203029>

Maran, R., Dueymes, M., Le Corre, R., Renaudineau, Y., Shoenfeld, Y., Youinou, P., 1997. IgG subclasses of human autoantibodies. *Ann. Med. Interne (Paris)* 148, 29–38.

McDermott, G.C., Doyle, T.J., Sparks, J.A., 2021. Interstitial lung disease throughout the rheumatoid arthritis disease course. *Curr. Opin. Rheumatol.* 33, 284–291. <https://doi.org/10.1097/BOR.0000000000000787>

McGowan, L.M., Davey Smith, G., Gaunt, T.R., Richardson, T.G., 2019a. Integrating Mendelian randomization and multiple-trait colocalization to uncover cell-specific inflammatory drivers of autoimmune and atopic disease. *Hum. Mol. Genet.* 28, 3293–3300. <https://doi.org/10.1093/hmg/ddz155>

McGowan, L.M., Davey Smith, G., Gaunt, T.R., Richardson, T.G., 2019b. Integrating Mendelian randomization and multiple-trait colocalization to uncover cell-specific inflammatory drivers of autoimmune and atopic disease. *Hum. Mol. Genet.* 28, 3293–3300. <https://doi.org/10.1093/hmg/ddz155>

Mo, X., Guo, Y., Qian, Q., Fu, M., Zhang, H., 2020. Phosphorylation-related SNPs influence lipid levels and rheumatoid arthritis risk by altering gene expression and plasma protein levels. *Rheumatol. Oxf. Engl.* 59, 889–898. <https://doi.org/10.1093/rheumatology/kez466>

Morotti, A., Sollaku, I., Franceschini, F., Cavazzana, I., Fredi, M., Sala, E., De Palma, G., 2021. Systematic Review and Meta-analysis on the Association of Occupational Exposure to Free Crystalline Silica and Rheumatoid Arthritis. *Clin. Rev. Allergy Immunol.* <https://doi.org/10.1007/s12016-021-08846-5>

Okada, Y., Eyre, S., Suzuki, A., Kochi, Y., Yamamoto, K., 2019. Genetics of rheumatoid arthritis: 2018 status. *Ann. Rheum. Dis.* 78, 446–453. <https://doi.org/10.1136/annrheumdis-2018-213678>

Prins, B.P., Abbasi, A., Wong, A., Vaez, A., Nolte, I., Franceschini, N., Stuart, P.E., Guterriez Achury, J., Mistry, V., Bradfield, J.P., Valdes, A.M., Bras, J., Shatunov, A., PAGE Consortium, International Stroke Genetics Consortium, Systemic Sclerosis consortium, Treat OA consortium, DIAGRAM Consortium, CARDIoGRAMplusC4D Consortium, ALS consortium, International Parkinson's Disease Genomics Consortium, Autism Spectrum Disorder Working Group of the Psychiatric Genomics Consortium, CKDGen consortium, GERAD1 Consortium, International Consortium for Blood Pressure, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Inflammation Working Group of the CHARGE Consortium, Lu, C., Han, B., Raychaudhuri, S., Bevan, S., Mayes, M.D., Tsoi, L.C., Evangelou, E., Nair, R.P., Grant, S.F.A., Polychronakos, C., Radstake, T.R.D., van Heel, D.A., Dunstan, M.L., Wood, N.W., Al-Chalabi, A., Dehghan, A., Hakonarson, H., Markus, H.S., Elder, J.T., Knight, J., Arking, D.E., Spector, T.D., Koeleman, B.P.C., van Duijn, C.M., Martin, J., Morris, A.P., Weersma, R.K., Wijmenga, C., Munroe, P.B., Perry, J.R.B., Pouget, J.G., Jamshidi, Y., Snieder, H., Alizadeh, B.Z., 2016. Investigating the Causal Relationship of C-

Reactive Protein with 32 Complex Somatic and Psychiatric Outcomes: A Large-Scale Cross-Consortium Mendelian Randomization Study. *PLoS Med.* 13, e1001976. <https://doi.org/10.1371/journal.pmed.1001976>

Qian, Y., Zhang, L., Wu, D.J.H., Xie, Z., Wen, C., Mao, Y., 2020. Genetic predisposition to smoking is associated with risk of rheumatoid arthritis: a Mendelian randomization study. *Arthritis Res. Ther.* 22, 44. <https://doi.org/10.1186/s13075-020-2134-1>

Qiao, Y., Wang, Z., Li, Y., Han, Y., Zhou, Y., Cao, X., 2020. Rheumatoid arthritis risk in periodontitis patients: A systematic review and meta-analysis. *Joint Bone Spine* 87, 556–564. <https://doi.org/10.1016/j.jbspin.2020.04.024>

Qu, Z., Huang, J., Yang, F., Hong, J., Wang, W., Yan, S., 2020. Sex hormone-binding globulin and arthritis: a Mendelian randomization study. *Arthritis Res. Ther.* 22, 118. <https://doi.org/10.1186/s13075-020-02202-2>

Regueiro, C., Casares-Marfil, D., Lundberg, K., Knevel, R., Acosta-Herrera, M., Rodriguez-Rodriguez, L., Lopez-Mejias, R., Perez-Pampin, E., Triguero-Martinez, A., Nuño, L., Ferraz-Amaro, I., Rodriguez-Carrio, J., Lopez-Pedreria, R., Robustillo-Villarino, M., Castañeda, S., Remuzgo-Martinez, S., Alperi, M., Alegre-Sancho, J.J., Balsa, A., Gonzalez-Alvaro, I., Mera, A., Fernandez-Gutierrez, B., Gonzalez-Gay, M.A., Trouw, L.A., Grönwall, C., Padyukov, L., Martin, J., Gonzalez, A., 2021. HLA-B\*08 Identified as the Most Prominently Associated Major Histocompatibility Complex Locus for Anti-Carbamylated Protein Antibody-Positive/Anti-Cyclic Citrullinated Peptide-Negative Rheumatoid Arthritis. *Arthritis Rheumatol.* Hoboken NJ 73, 963–969. <https://doi.org/10.1002/art.41630>

Regueiro, C., Rodriguez-Rodriguez, L., Lopez-Mejias, R., Nuño, L., Triguero-Martinez, A., Perez-Pampin, E., Corrales, A., Villalba, A., Lopez-Golan, Y., Abasolo, L., Remuzgo-Martínez, S., Ortiz, A.M., Herranz, E., Martínez-Feito, A., Conde, C., Mera-Varela, A., Balsa, A., Gonzalez-Alvaro, I., González-Gay, M.Á., Fernandez-Gutierrez, B., Gonzalez, A., 2020. A predominant involvement of the triple seropositive patients and others with rheumatoid factor in the association of smoking with rheumatoid arthritis. *Sci. Rep.* 10, 3355. <https://doi.org/10.1038/s41598-020-60305-x>

Renaudineau, Y., Jamin, C., Saraux, A., Youinou, P., 2005. Rheumatoid factor on a daily basis. *Autoimmunity* 38, 11–16. <https://doi.org/10.1080/08916930400022574>

Renaudineau, Y., Saraux, A., Dueymes, M., Le Goff, P., Youinou, P., 1998. Importance of IgG glycosylation in rheumatoid arthritis. *Rev. Rhum. Engl. Ed* 65, 429–433.

Rönnelid, J., Knight, A., Lysholm, J., Manivel, V.A., Sohrabian, A., Larsson, A., Weitoft, T., 2021. High levels of interleukin-6 in rheumatoid arthritis joint fluids can stimulate local production of C-reactive protein resulting in elevated circulating levels. *Joint Bone Spine* 88, 105159. <https://doi.org/10.1016/j.jbspin.2021.105159>

Rosa, M., Chignon, A., Li, Z., Boulanger, M.-C., Arsenault, B.J., Bossé, Y., Thériault, S., Mathieu, P., 2019. A Mendelian randomization study of IL6 signaling in cardiovascular diseases, immune-related disorders and longevity. *NPJ Genomic Med.* 4, 23. <https://doi.org/10.1038/s41525-019-0097-4>

Ruiz-Larrañaga, O., Uribarri, M., Alcaro, M.C., Escorza-Treviño, S., Del Amo, J., Iriando, M., Manzano, C., Migliorini, P., Lóránd, V., Estonba, A., 2016. Genetic variants associated with rheumatoid arthritis patients and serotypes in European populations. *Clin. Exp. Rheumatol.* 34, 236–241.

Samara, K.D., Trachalaki, A., Tsitoura, E., Koutsopoulos, A.V., Lagoudaki, E.D., Lasithiotaki, I., Margaritopoulos, G., Pantelidis, P., Bibaki, E., Sifakas, N.M., Tzanakis, N., Wells, A.U., Antoniou, K.M., 2017. Upregulation of citrullination pathway: From Autoimmune to Idiopathic Lung Fibrosis. *Respir. Res.* 18, 218.

<https://doi.org/10.1186/s12931-017-0692-9>

Scheller, J., Chalaris, A., Schmidt-Arras, D., Rose-John, S., 2011. The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochim. Biophys. Acta* 1813, 878–888. <https://doi.org/10.1016/j.bbamcr.2011.01.034>

Sellers, R.M., Payne, J.B., Yu, F., LeVan, T.D., Walker, C., Mikuls, T.R., 2016. TLR4 Asp299Gly polymorphism may be protective against chronic periodontitis. *J. Periodontal Res.* 51, 203–211. <https://doi.org/10.1111/jre.12299>

Seror, R., Le Gall-David, S., Bonneure-Mallet, M., Schaefferbeke, T., Cantagrel, A., Minet, J., Gottenberg, J.-E., Chanson, P., Ravaud, P., Mariette, X., 2015. Association of Anti-*Porphyromonas gingivalis* Antibody Titers With Nonsmoking Status in Early Rheumatoid Arthritis: Results From the Prospective French Cohort of Patients With Early Rheumatoid Arthritis. *Arthritis Rheumatol.* Hoboken NJ 67, 1729–1737. <https://doi.org/10.1002/art.39118>

Shi, J., van de Stadt, L.A., Levarht, E.W.N., Huizinga, T.W.J., Hamann, D., van Schaardenburg, D., Toes, R.E.M., Trouw, L.A., 2014. Anti-carbamylated protein (anti-CarP) antibodies precede the onset of rheumatoid arthritis. *Ann. Rheum. Dis.* 73, 780–783. <https://doi.org/10.1136/annrheumdis-2013-204154>

Shungin, D., Haworth, S., Divaris, K., Agler, C.S., Kamatani, Y., Keun Lee, M., Grinde, K., Hindy, G., Alaraudanjoki, V., Pesonen, P., Teumer, A., Holtfreter, B., Sakaue, S., Hirata, J., Yu, Y.-H., Ridker, P.M., Giulianini, F., Chasman, D.I., Magnusson, P.K.E., Sudo, T., Okada, Y., Völker, U., Kocher, T., Anttonen, V., Laitala, M.-L., Orho-Melander, M., Sofer, T., Shaffer, J.R., Vieira, A., Marazita, M.L., Kubo, M., Furuichi, Y., North, K.E., Offenbacher, S., Ingelsson, E., Franks, P.W., Timpson, N.J., Johansson, I., 2019. Genome-wide analysis of dental caries and periodontitis combining clinical and self-reported data. *Nat. Commun.* 10, 2773. <https://doi.org/10.1038/s41467-019-10630-1>

Simon, Q., Grasseau, A., Boudigou, M., Le Pottier, L., Bettachioli, E., Cornec, D., Rouvière, B., Jamin, C., Le Lann, L., PRECISESADS Clinical Consortium, PRECISESADS Flow Cytometry Study Group, Borghi, M.O., Aguilar-Quesada, R., Renaudineau, Y., Alarcón-Riquelme, M.E., Pers, J.-O., Hillion, S., 2021. A Proinflammatory Cytokine Network Profile in Th1/Type 1 Effector B Cells Delineates a Common Group of Patients in Four Systemic Autoimmune Diseases. *Arthritis Rheumatol.* Hoboken NJ. <https://doi.org/10.1002/art.41697>

Smolen, J.S., Aletaha, D., Barton, A., Burmester, G.R., Emery, P., Firestein, G.S., Kavanaugh, A., McInnes, I.B., Solomon, D.H., Strand, V., Yamamoto, K., 2018. Rheumatoid arthritis. *Nat. Rev. Dis. Primer* 4, 18001. <https://doi.org/10.1038/nrdp.2018.1>

Sugiyama, D., Nishimura, K., Tamaki, K., Tsuji, G., Nakazawa, T., Morinobu, A., Kumagai, S., 2010. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. *Ann. Rheum. Dis.* 69, 70–81. <https://doi.org/10.1136/ard.2008.096487>

Sun, L., Zhu, J., Ling, Y., Mi, S., Li, Yasong, Wang, T., Li, Yingjun, 2021. Physical activity and the risk of rheumatoid arthritis: evidence from meta-analysis and Mendelian randomization. *Int. J. Epidemiol.* dyab052. <https://doi.org/10.1093/ije/dyab052>

Syed, A.A.S., He, L., Shi, Y., 2020. The Potential Effect of Aberrant Testosterone Levels on Common Diseases: A Mendelian Randomization Study. *Genes* 11, E721. <https://doi.org/10.3390/genes11070721>

Too, C.L., Murad, S., Dhaliwal, J.S., Larsson, P., Jiang, X., Ding, B., Alfredsson, L., Klareskog, L., Padyukov, L., 2012. Polymorphisms in peptidylarginine deiminase associate with rheumatoid arthritis in diverse Asian populations: evidence from MyEIRA study and meta-analysis. *Arthritis Res. Ther.* 14, R250. <https://doi.org/10.1186/ar4093>

- Torrunguang, K., Chantarangsu, S., Sura, T., Thienpramuk, L., 2020. Interplay between vitamin D receptor FokI polymorphism and smoking influences *Porphyromonas gingivalis* proportions in subgingival plaque. *J. Clin. Periodontol.* 47, 912–920. <https://doi.org/10.1111/jcpe.13307>
- van Heemst, J., Hensvold, A.H., Jiang, X., van Steenbergen, H., Klareskog, L., Huizinga, T.W.J., van der Helm-van Mil, A., Catrina, A.I., Toes, R.E.M., Lundberg, K., van der Woude, D., 2016. Protective effect of HLA-DRB1\*13 alleles during specific phases in the development of ACPA-positive RA. *Ann. Rheum. Dis.* 75, 1891–1898. <https://doi.org/10.1136/annrheumdis-2015-207802>
- Verma, A., Bang, L., Miller, J.E., Zhang, Yanfei, Lee, M.T.M., Zhang, Yu, Byrska-Bishop, M., Carey, D.J., Ritchie, M.D., Pendergrass, S.A., Kim, D., DiscovEHR Collaboration, 2019. Human-Disease Phenotype Map Derived from PheWAS across 38,682 Individuals. *Am. J. Hum. Genet.* 104, 55–64. <https://doi.org/10.1016/j.ajhg.2018.11.006>
- Viatte, S., Massey, J., Bowes, J., Duffus, K., arcOGEN Consortium, Eyre, S., Barton, A., Worthington, J., 2016. Replication of Associations of Genetic Loci Outside the HLA Region With Susceptibility to Anti-Cyclic Citrullinated Peptide-Negative Rheumatoid Arthritis. *Arthritis Rheumatol.* Hoboken NJ 68, 1603–1613. <https://doi.org/10.1002/art.39619>
- Wu, X., Peng, H., Wen, Y., Cai, X., Li, C., Zhong, R., Huang, Y., Chen, J., Huo, Z., Wang, R., Feng, Y., Ge, F., He, J., Liang, W., 2021. Rheumatoid arthritis and risk of lung cancer: Meta-analysis and Mendelian randomization study. *Semin. Arthritis Rheum.* 51, 565–575. <https://doi.org/10.1016/j.semarthrit.2021.03.015>
- Yakob, M., Söder, B., Meurman, J.H., Jogestrand, T., Nowak, J., Söder, P.-Ö., 2011. *Prevotella nigrescens* and *Porphyromonas gingivalis* are associated with signs of carotid atherosclerosis in subjects with and without periodontitis. *J. Periodontal Res.* 46, 749–755. <https://doi.org/10.1111/j.1600-0765.2011.01398.x>
- Yarwood, A., Viatte, S., Okada, Y., Plenge, R., Yamamoto, K., BRAGGSS, RACI, Barton, A., Symmons, D., Raychaudhuri, S., Klareskog, L., Gregersen, P., Worthington, J., Eyre, S., 2016. Loci associated with N-glycosylation of human IgG are not associated with rheumatoid arthritis: a Mendelian randomisation study. *Ann. Rheum. Dis.* 75, 317–320. <https://doi.org/10.1136/annrheumdis-2014-207210>
- Ye, D., Liu, B., He, Z., Huang, L., Qian, Y., Shao, K., Wen, C., Mao, Y., 2021. Assessing the Associations of Growth Differentiation Factor 15 with Rheumatic Diseases Using Genetic Data. *Clin. Epidemiol.* 13, 245–252. <https://doi.org/10.2147/CLEP.S305024>
- Yuan, S., Larsson, S., 2020. Causal associations of iron status with gout and rheumatoid arthritis, but not with inflammatory bowel disease. *Clin. Nutr. Edinb. Scotl.* 39, 3119–3124. <https://doi.org/10.1016/j.clnu.2020.01.019>
- Yuan, S., Xiong, Y., Michaëlsson, M., Michaëlsson, K., Larsson, S.C., 2021. Genetically predicted education attainment in relation to somatic and mental health. *Sci. Rep.* 11, 4296. <https://doi.org/10.1038/s41598-021-83801-0>
- Zeng, Z., Zhang, W., Qian, Y., Huang, H., Wu, D.J.H., He, Z., Ye, D., Mao, Y., Wen, C., 2020. Association of telomere length with risk of rheumatoid arthritis: a meta-analysis and Mendelian randomization. *Rheumatol. Oxf. Engl.* 59, 940–947. <https://doi.org/10.1093/rheumatology/kez524>
- Zhao, J.V., Schooling, C.M., 2019. Role of linoleic acid in autoimmune disorders: a Mendelian randomisation study. *Ann. Rheum. Dis.* 78, 711–713. <https://doi.org/10.1136/annrheumdis-2018-214519>
- Zhao, S.S., Maglio, C., Hughes, D.M., Cook, J.P., 2021. Body fat composition and risk of rheumatoid arthritis: Mendelian randomisation study. *Arthritis Rheumatol.* Hoboken NJ.

<https://doi.org/10.1002/art.41766>

Zhou, J., Liu, C., Sun, Y., Francis, M., Ryu, M.S., Grider, A., Ye, K., 2021. Genetically predicted circulating levels of copper and zinc are associated with osteoarthritis but not with rheumatoid arthritis. *Osteoarthritis Cartilage* 29, 1029–1035.

<https://doi.org/10.1016/j.joca.2021.02.564>

Zhu, H., Zhao, L.J., Zhou, Y., Chen, Y., 2019. [Significance of anti-carbamylated protein antibodies in patients with rheumatoid arthritis-associated interstitial lung disease]. *Beijing Da Xue Xue Bao* 51, 1003–1007.

Zhu, J., Niu, Z., Alfredsson, L., Klareskog, L., Padyukov, L., Jiang, X., 2021. Age at menarche, age at natural menopause, and risk of rheumatoid arthritis - a Mendelian randomization study. *Arthritis Res. Ther.* 23, 108. <https://doi.org/10.1186/s13075-021-02495-x>

Figure 1

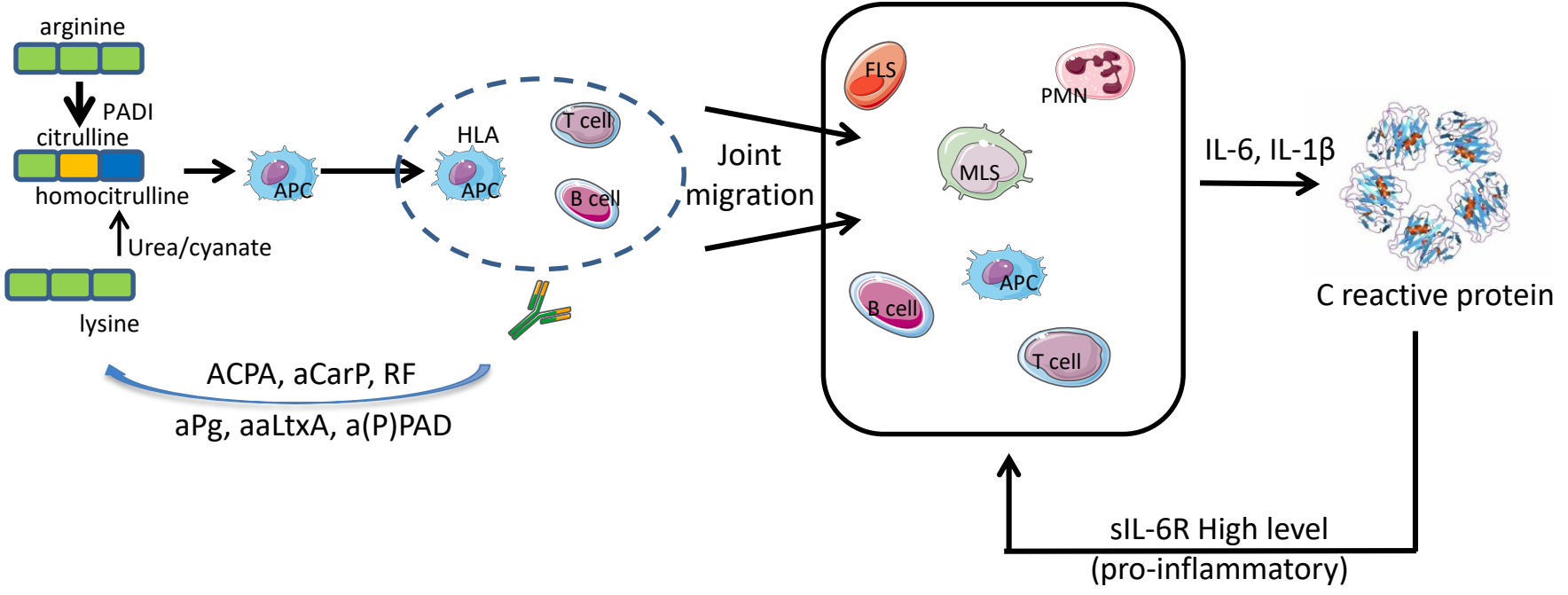
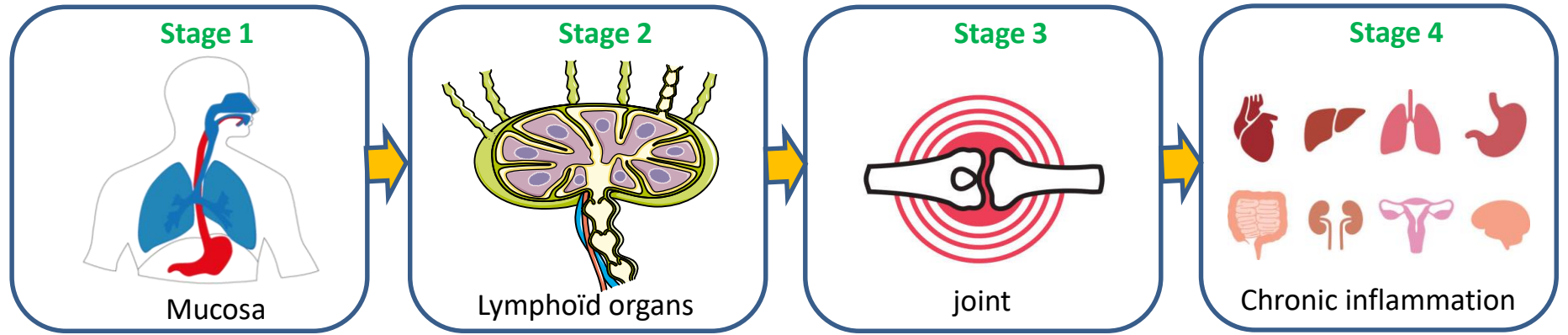
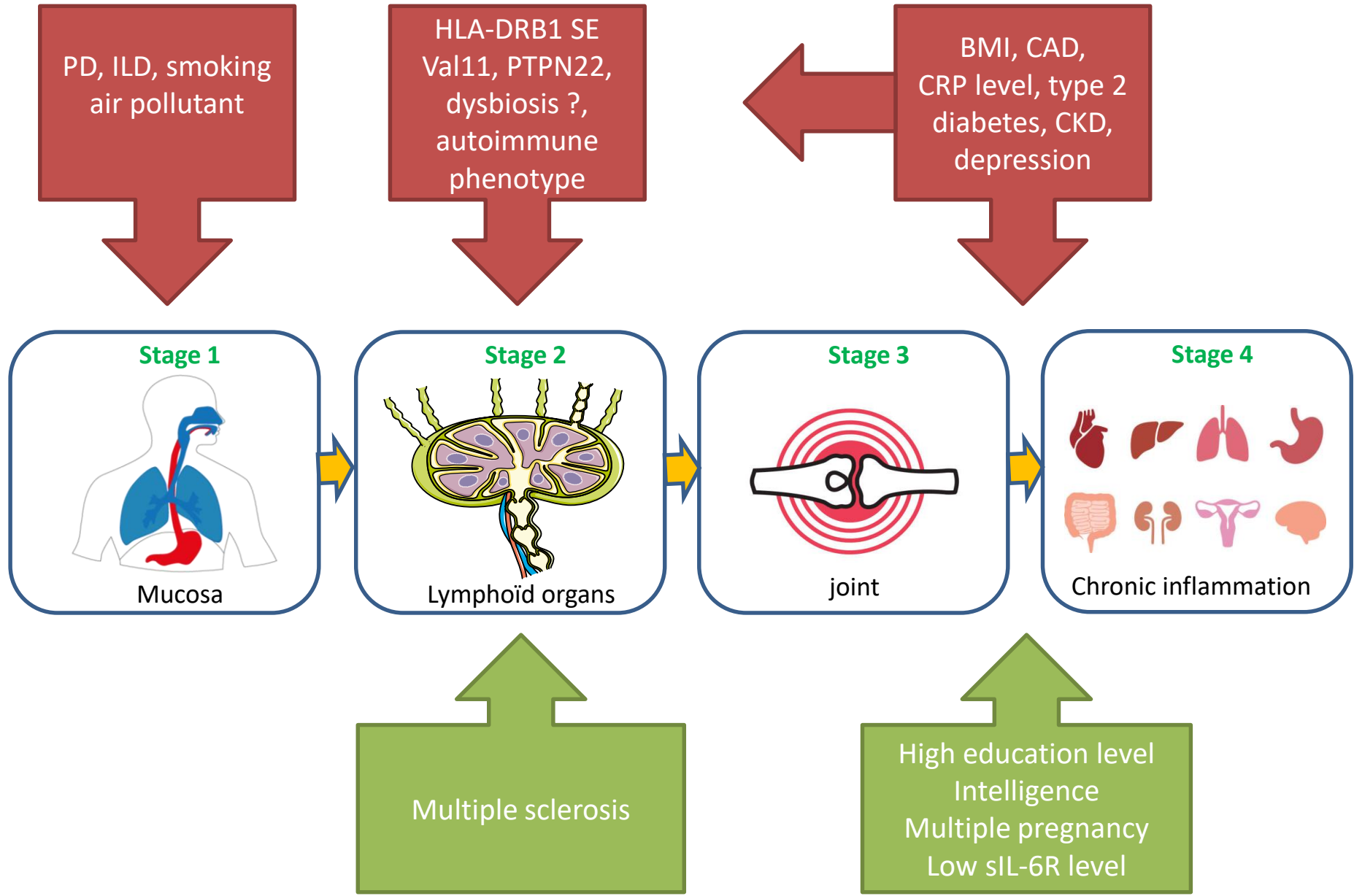


Figure 2



IL-6 classic signaling

IL-6 trans-signaling

IL-6/IL-6R inhibition

