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Causal risk and protective factors in rheumatoid arthritis: A genetic 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-IL6R 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 co-founders 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.

1. 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 [1]. As depicted in Fig. 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 [2,3]. 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 [4]. Finally, and as RA develops, an uncontrolled systemic inflammatory amplification loop including a dysregulation of the IL-6 signaling pathway leads to joint damage, cartilage destruction, bone erosion and extra-articular manifestations [5–7].

RA is a complex disease and its development includes a long process

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driven by multiple risk/protective genetic, environmental, and sexual related-factors [8,9]. 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 Fig. 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.

2. 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.

3. 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 [44].

Periodontal disease is directly associated with RA [10,11], 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) [45]. *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 [12,46]. 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 [47–50]. 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) [51,52]. 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 [53]. 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) [54]. 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 [55]. 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 [56]. 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 [57,58]. 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 extend an elevated body mass index (BMI) [12].

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 [59]. Among them an interstitial lung

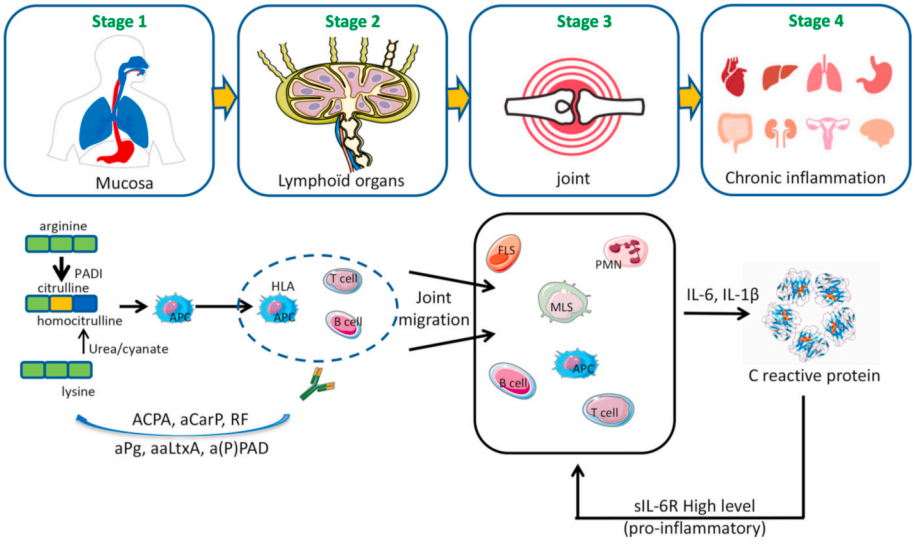

Fig. 1. RA development presents four immune-related stages. First the mucosa stage with an intake by antigen-presenting cells (APC) of neo-epitopes corresponding to peptides post-transcriptionally modified at arginine by citrullinisation or at lysine by carbamylation or acetylation in the mouth and/or 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-α, IL-6, IL-1β) and a dysregulation of the IL-6 signaling 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.

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

Risk factor	Main mechanism	Meta-analysis	Direct association	References
Periodontitis, interstitial lung disease, tobacco smoking	Mucosal and immune response	Yes	Yes	[10–17]
Autoimmune phenotype (SLE, SSc, PBC, type 1 diabetes), genetic factors (HLA, PTPN22)	Immune response	Yes	Yes	[18]
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	[12, 18–26]
High education, intelligence	Anti-inflammatory	Yes	Yes	[26,27]
Linoleic and palmitoleic acid, telomere length, elevated testosteronen sex hormone binding globulin, Alzeimer's disease, chronic pain, magnesium supplementation	Unknown	Yes	Yes	[26, 28–33]
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 (Ca2+, Fe2+, Cu+, Zn+)	Co-founding factor?	controversial	No	[14,18, 33–43]

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.

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 [60,61]. 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 >10 mg/L (OR = 3.1; CI95: 1.32–7.26), obesity (OR = 2.42; CI95: 1.11–5.24), and a lower education levels [16,62].

Tobacco smoking is referred to as a direct and main environmental factor associated with RA development with an OR = 1.32, IC95: 1.15–0.52 [15]. 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 [13]. 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 [63]. 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) [15,64]. 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* [65]; (ii) an affected adaptive immune response explaining that never smoker RA patients possess elevated protective anti-*P. gingivalis* and anti-PPAD antibody titers [66]; (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 [67]; (iv) a higher systemic inflammation as retrieved in the elevated tobacco consumption subgroup [17]; and (v) an association with RF-positivity (OR = 2.35; IC95: 1.64–3.35) independent from ACPA/CarpA status [15,68]. Although all these explanations are plausible, more studies are warranted to elucidate the mechanisms and their interplay.

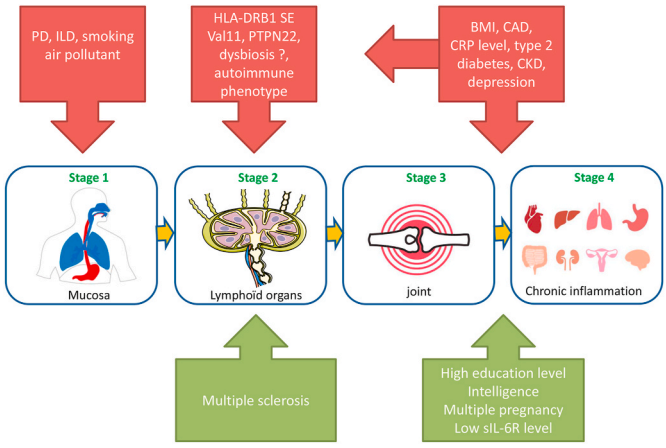

Fig. 2. Direct associations between rheumatoid arthritis (RA) development stages and RA-associated risk and protective factors according to Mendelian randomization results. Abbreviations: PD: periodontal disease (*Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*); ILD: interstitial 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.

4. Genetic factors associated with an acquired immune response

The collection of HLA alleles that contained within the third hypervariable 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 [69,70]. 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 [71–73]. 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 [74,75]. 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) [76], HLA-DPB1, the non-classical HLA-DOA, plus HLA-DQA1 in the Han Chinese population [70,77].

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 autoreactive 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 [78,79]. 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 [80,81].

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) [82]. Accordingly, the common genetic architecture that relies RA with other autoimmune diseases can be subdivided in three subgroups: 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).

5. 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)-α, IL-1β, 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 (Fig. 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 a hexameric complex to initiate an intracellular signaling

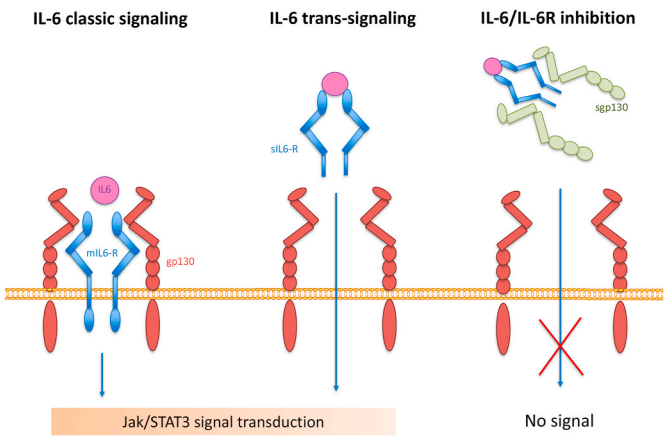

Fig. 3. Interleukin-6 exerts its biological activities through two molecules: IL-6R (IL-6 receptor also known as the cluster of differentiation CD126) and gp130 both present in membrane-bound forms or in soluble forms. In the IL-6 classic-signaling pathway (left), IL-6 binds to mIL-6R that recruits gp130 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.

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-β, 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)sIL-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 [83,84]. 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 [85]. 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 [86].

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 [21,87–89]; a higher level of IL-1RA protects from RA (OR = 0.97; IC95: 0.95–0.99) [86]; 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 [20]. 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) [19,22,90–92]. 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 [92]. When regarding other pro-inflammatory drivers (IL-18, IL-2RA, VEGF, TRAIL, IP10, IL-16, HGF, MIF), no direct association is reported with RA [23].

Interestingly among multiple risk/protective factors associated with RA a bi-directional profile is retrieved when using as main criteria inflammation (CRP) (Fig. 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 [18,20,24]. 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 (0R = 0.76; CI95: 0.63–0.91) [26,27,33]. For the education level and intelligence, the effect is independent and remains after adjusting with BMI and tobacco smoking.

5.1. Co-morbidity factors

The most common comorbidity factors associated with RA are cardiovascular diseases, cancer, osteoporosis, mental health disorders and infections [93–95]. 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 [18,21,96]. 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 [25], depressive symptoms [96], anemia [97], and bone loss [98]. 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 [86]. 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 [18,99]. 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 [14,18,34,35,40,42]. These co-founding effects can be related to the medications used and/or tobacco smoking.

5.2. Nutritional and sexual factors

Nutritional factors are suspected to increase RA risk [100,101] 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) [28,33,43]. 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 [26,43]. 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) [41,102,103].

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) [30], 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 [37]. 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) [31].

Miscellaneous associations were further tested by MR in RA to highlight a negative association between life span and telomere length with RA [29,104], RA reduces the risk of Alzheimer's disease (S.-C. [26], and positive associations are retrieved between multisite chronic pain, magnesium supplementation and RA development [32,41]. Finally, no association is reported with coffee consumption, alcohol intake, attention-deficit/hyperactivity disorder (ADHD), physical activity, blood minerals (Ca2+, Zn+, Fe2+ and Cu+), the circulating level of growth differentiation factor (GDF)-15 and cellular capacity to glycosylate IgG [33,36,38,39,41,42,105].

6. 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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Declaration of competing interest

None.

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